Conduct Problems, Callous-Unemotional Traits and Emotion Processing: Adversity and Diversity, a Functional Neuroimaging Study

Jack Gilgunn

DClinPsy Thesis (Volume 1) 2022

University College London

UCL Doctorate In Clinical Psychology

Thesis Declaration form

Overview

This thesis focused on youths who present with conduct problems (CP), callous-unemotional traits and functional neuroimaging.

Part 1

A narrative review of current neuroimaging literature regarding youths with CP. Firstly, this review outlined general CP related considerations regarding neuroimaging literature and common CP risk factors before summarising structural neuroimaging literature. Functional neuroimaging research was then summarised using neurocognitive domains of functioning: acute threat response, social cognition, cognitive control and reinforcement learning. Findings were discussed with reference to how risk factors and neurocognitive functioning interact to produce behavioural syndromes associated with CP. Future CP related neuroimaging research should focus on domains of functioning and the influence of risk factors on heterogeneity.

Part 2

A functional MRI study that used facial expressions (angry/sad/happy) to investigate neural differences in emotion processing amongst boys with CP split between high and low callous-unemotional (CU) traits, compared to matched controls. Findings highlighted perturbations in limbic, frontal, temporal and medial regions for both high and low CU trait boys compared to controls. CP boys demonstrated specific atypical activation in the amygdala, insula and prefrontal cortex when processing negative facial expressions and were associated with more severe pathological parenting practices than controls. Potential explanations and clinical implications were explored.

Part 3

A critical appraisal of my learning regarding neuroimaging and youths with CP including my perspective from clinical practice. This appraisal focused on the theoretical, diagnostic, research, clinical and narrative implications of transitioning understandings of neural function from a behavioural, damaged and functionally specialised paradigm toward a dimensional, adapted and interrelated paradigm.

Impact statement

Increasingly researchers are conceptualising conduct problems (CP) amongst youths as an interaction between biological predisposition, neuropsychological processes and ecological systems. Neuroimaging research has been employed to provide greater insight into developmental pathways and variation displayed within this heterogenous population. Two specific clusters of youths with CP have been identified based on the presence of callous unemotional (CU) traits/limited prosocial emotions: high CU traits has been linked to proactive aggression, poor empathy and hypo-activity in neural regions associated with threat processing; whereas low CU traits have been linked to reactive aggression and hyper-reactivity in neural regions associated with threat detection. Diversity in neuroimaging findings that focus on this distinction exist and have been suggested the result of unique interactions of specific risk factors and neural adaptation to an adverse developmental environment.

Using facial expressions as an emotional cue, this study aimed to investigate differences in emotion processing, specifically threat (angry), distress (sad) and positive stimuli (happy), amongst CP youth with high CU traits, low CU traits and typically developing boys matched for specific risk factors (IQ, social economic status [SES], & age) permitting the investigation of other risk factors influence (childhood trauma, parenting techniques & general family functioning).

Findings identified that CP boys in general exhibited perturbations in neural regions associated with emotion processing (amygdala) regardless of what emotion was presented with particular deficits in the processing of negative stimuli: angry faces and hypo-activation of the insula; sad faces and hyperactivation of the amygdala and hypothalamus. Further exploration of neural activity based on high vs low CU traits did not support the binary and divergent phenotype previously posited but rather supported the view of a maladaptive, interrelated neural network key to the integration of interoceptive and exteroceptive information required for decision making. The majority of this activity was located in regions associated with emotional resonance, arousal regulation, valence-based processing and face processing. Independent of the matched risk factors as well as self-reported childhood trauma and general family functioning, CP problems were linked to general poor parental monitoring, CPCU- was linked to increased corporal punishment and CPCU+ was linked to increased neglect and inconsistent discipline.

Clinically, our findings support previous findings that CP populations have specific deficits in emotion processing and likely represents specific adaptations to an adverse developmental environment. There is a need for preventative interventions to be developed to avoid the most severe trajectories and would be aided by systematic recording and sharing of risk factors to identify those children at risk of developing CP. These children would benefit from the deriving of neurocognitive profiles based on performance on tasks relating to acute threat response, social cognitive, reinforcement learning and cognitive control. Therefore, situations where dysfunction related latent vulnerability may present can be identified and managed in order to prevent social thinning, maintain social learning and build epistemic trust. This research derived training that was presented to a multi-systemic team that worked with childhood CPs.

Academically, these findings captured variation within a very specific subgroup of youths who present with CP however we continued to witness diversity typical of this population in our findings. We also support the need for greater collaboration of different scientific fields to contribute toward a more holistic understanding of CP.

Contents

Acknowledgements

First and foremost, I would like to thank my tutor and thesis supervisor, Dr Christina Carlisi, for your support and guidance on this project and beyond over the past three years. I have always been able to depend on you to be available and I have continually been struck and fortunate to benefit from your work ethic and positivity. You tirelessly kept me on track, affording me space to make my own mistakes along the way, whilst jumping in to help when I needed you to. Thank you for believing in me, it was sorely needed even if I did not say it. Thank you for the time you have taken in nurturing my academic writing and encouraging me to pursue research more generally. Your patience, attention to detail and ease of working has provided me with an incredible model to take forth into my journey as a researcher, clinician and tutor.

I would also like to thank my clinical supervisors Nadim Ahmed, Graham Jensch and Carly MacDonald. Each progressive experience I had with you has moulded my thinking about how this project translated to the lives of the young people and families we work with. Through your dedication, enthusiasm and creativity, you sparked new ideas and helped me feel more comfortable sitting with the complexity and messiness which we and our communities experience. You have helped me see the social justice of this work and allowed me to bring my authentic self to our clinical roles and this project. It has been a pleasure working with and learning from you.

To my fellow trainees, we made it! Thank you for the being here for this ride and for the continual laughs, inspiration and support you provided along the way. My world has been infinitely bettered by your presence. I cannot wait to see what is in store next for us all.

I would also like to express my gratitude to the young people and their families who took part in this study. Although I never met you, I have looked for you and seen you in the young people I have worked with who have also experienced adversity. You are not the label given to you, you are boys and men who have incredible potential and worth. I will forever be thankful that you had taken the time to help me and I look forward to repaying that debt through my work. Wherever you are on your journey in life, I hope you are flourishing.

Finally, to the difference that made the difference, my family and friends. Seeing so much of myself in this work, you as my community provided me with the safety and scaffolding I needed to become who I am today. Your love, warmth and support from the start was the greatest protective factor I could have ever hoped for. To my Dad, thank you for your example of change and belief in me. To Joe, thank you for always being there next to me, I'm incredibly lucky and proud to have you as my brother. To my mum, your unconditional love, support and dedication is the most valuable thing I have ever had and was the bedrock from which this all was possible. This achievement is as much yours as it is mine.

Part 1: Literature Review

Embedding the Brain: A Narrative Literature Review on How Structural and Functional Neuroimaging Findings Can Inform Developmental and Systems Level Conceptualisations of Conduct Problems.

Abstract

Conduct disorder is an important public health concern impacting perpetrators, victims, and society. Structural and functional neuroimaging has become a common and useful modality for understanding neural correlates of young people that present with conduct problems as part of a complex developmental and etiological process. This narrative review aimed to review current structural and functional neuroimaging research in relation to youths presenting with conduct problems with a particular emphasis on emotion processing. Dysfunctional neurocognitive mechanisms associated with youths with conduct problems were focused on with specific emphasis on how they may contribute toward specific behavioural symptom sets. The most prominent dysfunctional mechanisms were acute threat response, social cognition, cognitive control and reinforcement-based learning systems. Future directions for research were considered with a greater emphasis on studying interrelated neural regions and etiological risk factors in order to better inform interventions and avert long-term negative outcomes.

Introduction

Conduct disorder (CD) has been defined as a collection of behaviours that emerge during childhood which repeatedly violate the rights of others (DSM-V; American Psychological Society 2013). Such behaviours include rule breaking, property damage, theft or physical aggression toward animals or others (Weisz & Kazdin, 2017). The prevalence of children in the general population that would reach threshold for a CD diagnosis is approximately 5%, it is a leading cause of referrals to mental health services (Bevilacqua et al., 2017; Coghill 2013), and is associated with high societal and economic burden (Erskine, 2014). Up to 60% of children diagnosed with CD or oppositional defiant disorder (ODD), a similar condition, go on to develop a mental health disorder in adulthood (Kim-Cohen et al., 2003). Other adult outcomes associated with early onset CD include poor physical health, substance misuse, incarcerations, high rates of criminality and antisocial behaviour (Moffitt, 2018). CD is not considered an episodic disorder and has been described as more closely resembling a personality disorder with up to 50% of individuals going on to develop chronic symptoms, criminal behaviours and receive diagnoses of a personality disorder (Moffitt, 2018).

CD is a highly heterogeneous condition that can often produce seemingly distinct presentations within the population as well as other symptom clusters that are transdiagnostic. Moreover, there is a large variation in trajectory for those diagnosed with a disruptive behaviour disorder (DBD), an umbrella term for CD and ODD, including chronic and remitting symptomology (Odgers et al., 2008; Gutman, Joshi & Schoon, 2019). Attempts to address the heterogeneity within CD has led to categorisation of CD subgroups defined at a behavioural level that includes aggressive versus non-aggressive rule breaking, proactive vs reactive aggression and covert vs overt behaviours. The current categorical approach to CD categorisation fails to utilise dimensional information about underlying pathophysiological, cognitive or affective mechanisms that may result in different behavioural phenotypes (Fairchild et al., 2019; Viding & McCrory 2020). Although alternative dimensional approaches to categorisation have been proposed, such as the National Institute of Mental Health Research Domain Criteria (RDoC; Cuthbert & Insel, 2013), CD categorisation still struggles to delineate between distinct risk profiles or etiologically differentiated groups within this population. With a lack of investigation into how different factors contribute toward different developmental trajectories and underlying mechanisms, potential intervention opportunities are missed.

Conceptualising CD through a developmental understanding of interaction between biological predispositions, neuropsychological processes and ecological systems may provide a more holistic theory regarding how conduct problems develop and then subsequently inform interventions. Most identified risk factors for DBDs are transdiagnostic and individual's trajectories vary widely (Viding & McCrory, 2020). It has been suggested that the organised interactive system of unique genetic risk factors, environmental risk factors and protective factors, over and above those related to general psychopathology, produces variation in the level of impact that specific risk indicators pose; otherwise known as multifinality (Cicchetti & Rogosch, 1996; Hankin et al., 2011). In contrast, multiple and different risk indicator combinations can influence the formation of the same behaviour across different individuals; an example of equifinality (Hyde et al., 2013). Risk factors or predictors of conduct problems reflect one small part of a complex probabilistic and etiological development chain for which there is no complete understanding.

In response, multiple research teams have argued for a biopsychosocial and transactional approach toward understanding CD (Hyde et al., 2013;, Puzzo et al., 2016; Wertz et al., 2019; Nelson & Foell, 2018; Viding & McCrory, 2020). Developing understanding of the dynamic reciprocal influence between one's biological predispositions, including structural and functional brain alterations, and their ecological social systems, moderated by the individual's life experiences, may be key to capturing the

aetiology and development of CD and other DBDs. This integrated approach may highlight how certain individuals are predisposed to present with conduct disorders and how systems may produce and reinforce them (Puzzo et al., 2016). Neurocognitive processes have increasingly become an area of interest in examining CD's etiological development chain, however, when considered in isolation this investigative branch can locate CD aetiology within the child with little consideration as to how this specific phenotype has interacted with and been shaped by their environment (Viding & McCrory, 2020). Neurobiological correlates or dimensional construct performances promote a "biological" nature to the problem which may be incorrectly construed damaged, static and causal (Hyde et al., 2013). Although these observations may be associated with greater risk of conduct problems in aggregate, these factors unlikely generalise to all children, may only be significant in certain contexts and may be a correlate of many different behaviours (Hyde et al., 2013).

An increasing amount of structural and functional neuroimaging techniques have been applied to assist in classifying CD and investigating the underlying mechanisms that are associated with its subgroups. Within CD, structural neuroimaging has been considered a more reliable index of individual differences regarding neurocognitive development (Viding & McCrory, 2020). This accuracy has provided insight into charting CD related heritability as well as reliably associating structural differences to specific behavioural presentations (Ziegler et al., 2019). However, structural imaging in isolation is limited in providing further insight into how neurocognitive function is altered in CD (Viding & McCrory, 2020). Functional neuroimaging research has documented abnormalities increasingly using dimensional neurocognitive processes, such as acute threat response, whilst also identifying specific neurological patterns for categorical CD subtypes (Fairchild et al., 2019; Dugré et al., 2020; Blair et al., 2018). However, functional imaging has been associated with poor reliability, replicability and methodological issues (Viding & McCrory, 2020). Neuroimaging research can be sensitive toward structural heterogeneity within CD populations but provide little insight into the functional consequence whereas functional imaging can provide insight into functional abnormalities but with less consistency (Viding & McCrory, 2020).

The aim of this review is to highlight current structural and functional neuroimaging research in relation to youths presenting with conduct problems with a particular emphasis on emotion processing. Firstly, a brief introduction of considerations relating to the field of study is provided in order to contextualise neuroimaging research. Considering one's behaviour is the result of a complex etiological and developmental process, it is imperative to briefly outline both environmental as well as genetical risk factors that may contribute toward conduct problems.

This paper will examine findings relating to how the brain is structured in these youths and the relationship between neural activity on dimensional neurocognitive processes, as defined by the RDoC, and specific behavioural outcomes associated with conduct problems.

Considerations of Conduct Problems Literature

Definition of Conduct Disorder

Due to high heterogeneity within anti-social populations, researchers have proposed that there are likely multiple conduct disorders rather than a single CD (Viding & McCrory, 2020). This is more consistent with the broader externalising behaviour spectrum of disorders characterised by conduct problems including anti-social personality disorder (ASPD) in adults, CD, ODD, substance misuse disorder and attention deficit and hyperactivity disorder (ADHD; Krueger et al., 2002; Krueger et al., 2005; Kendler et al., 2003). They often share symptoms which has resulted in frequent comparisons among these disorders within clinical research and diagnosis. However much of the findings are

inconsistent and diagnoses can be transient. Even when CD is selected as a singular diagnostic class, the level of heterogeneity of symptoms has led researchers to attempt sub-categorisation based on presenting symptoms like proactive and reactive aggression (Loeber & Stouthamer-loeber, 1998), age of onset of symptoms (Moffitt, 1993), and the presence of specific characteristics such as callous-unemotional/limited prosocial emotions (Frick & Ellis, 1999). Although some subtypes have meaningfully guided research, stratifying heterogeneity across these parameters may lead to divergent findings and measurement error when studying conduct disorders especially if there are subject to different underlying aetiologies (Hyde et al., 2013).

The Adaptive Brain and Important Neural Regions in Conduct Problem Research

A series of interdependent neural networks involved in the integration of interoceptive and exteroceptive information in order to identify future needs for the maintenance of homeostasis and the initiation of allostasis as required is considered the key function of the brain (Steffen, Hedges & Matheson, 2022). This adaptive process involves the production and comparison of predictions based on incoming information and then adjustment to minimise error in favour of adaption and health. This is contrasted to earlier conceptions of brain function based on distinct brain regions that operate mostly independently of each other (Steffen, Hedges & Matheson, 2022). Conceptualising the brain's role in adaptation to factors that disrupt homeostasis, can highlight how the brain may adapt to adverse experiences in order to cope in a non-normative environment but then when exposed to a normative environment those adaptations are then maladaptive and represent a latent vulnerability that presents as distinct pathologies, e.g. conduct problems (McCrory, 2020; Steffen, Hedges & Matheson, 2022). Improper function of specific brain regions and their associated regions can result in impaired adaption and dysregulation.

Amongst CD youths, specific neural regions have been found to have perturbed structural and functional features which have been linked to deficits in neurocognitive and behavioural functioning (Rogers & de Brito, 2015; Dugré et al., 2020). The amygdala is a subcortical region and is considered a connection hub for both subcortical and cortical structures and thus critical for arousal regulation, threat response and learning (Cardinal et al., 2002; Whalen & Phelps, 2009; Hyde et al., 2013). The insula cortex has been linked to the integration of interoceptive states into conscious feelings, empathy, decision making and recognition of distress (Craig, 2009; Decety & Jackson, 2006; Naqvi & Bechara, 2009; Hyde et al., 2013). The anterior cingulate cortex (ACC) is associated with error detection and correction involving salience and cognitive processes (Botvincick, Cohen & Carter, 2004; Bush, Luu & Posner, 2000). The ventral striatum has been linked to reward and motivation (Berridge & Robinson, 2003; Kable & Glimcher, 2007; Hyde et al., 2013). The prefrontal cortex (PFC) has multiple functional and structural distinct areas (Fuster, 2008); the orbitofrontal cortex (OFC) and ventromedial PFC (vmPFC) are regions that integrate information streams from the areas of emotion (amygdala), memory (hippocampus) and executive sensory processing before relaying the processed information the dorsolateral and dorsomedial PFC (dlPFC; dmPFC; Fuster et al., 2001; Wood & Grafman, 2003; Hyde et al., 2013). The amygdala is proposed to relay initial information from sensory and visceromotor inputs to the OFC and vmPFC, regions associated with representation of affective values of reinforcers and decision making (Cardinal et al., 2002; Finger et al., 2011; Kringelback, 2005; Hyde et al., 2013), that in turn relay information to the dmPFC and dlPFC for the execution of planned behaviours, long-terms goals and integration of sensory and working memory related information (Wood & Grafman, 2003; Forbes & Grafman, 2010). The insula cortex, cingulate cortex and frontal regions are elements of an interdependent brain network that are integral to this interoceptive and exteroceptive process (Steffen, Hedges & Matheson, 2022). Insults from risk factors to this network are associated with impaired adaptive function and can result in mental health difficulties.

Age of Onset

The DSM-5 has subdivided CD by age of conduct problem onset: "childhood-onset" (before age 10) and "adolescent-onset". Although an arbitrary distinction, childhood onset of CD symptoms is associated with more severe and chronic problems with behaviour and is suggested to be more strongly influenced by neurodevelopmental influences (Fairchild et al., 2013, Frick & Viding, 2009). Childhood-onset versus adolescent-onset subtypes have been correlated with different aetiological processes and outcomes. Childhood onset has been linked to coercive parenting (Patterson, Reid & Dishion, 1992), difficult temperament (e.g. high negative emotionality, fearlessness), ADHD symptoms (Moffitt, Caspi, Harrington & Milne, 2002) and a chronic and escalating trajectory of behaviour (Shaw & Gross, 2008). On the other hand, adolescent onset is correlated with fewer proximal family risks, less elevated and less chronic trajectory of anti-social behaviour (Moffitt et al., 2002) but higher deviant peer association (Dishion, Paterson, Stoolmiller, & Skinner, 1991). However, despite links between early maltreatment and altered behavioural, physiological and neural changes related to heightened threat reactivity (Hyde et al., 2013), both subtypes have been found to demonstrate lower amygdala, insula and OFC/vmPFC responses to emotional processing (Passamonti et al., 2010).

Callous-Unemotional Traits

A significant subtype of CD is the presence or absence of callous unemotional (CU) traits. Classified as "limited prosocial emotions", the DSM -5 has included CU traits as a distinction in CD's diagnosis criteria and describes them collectively as lack of remorse, empathy, concern about performance and deficient affect (American Psychological Association, 2013). CD with CU traits (CDCU+) represents a specific aetiology and a more severe course of anti-social behaviour (Fairchild et al., 2019). CU traits have been shown to be highly heritable and associated with specific developmental events such as childhood maltreatment and low social economic status (Piotrowska et al., 2015; Viding et al., 2013). CU traits have also been associated with specific neuropsychological deficiencies in recognition of distress cues (Dawel et al., 2012; Schwenck et al., 2012), social cognition (Dotterer et al., 2020), reinforcement-based learning (Hawes et al., 2020), acute threat response (Blair & Zhang, 2020) and resting-state fMRI as well as structural brain abnormalities (Rogers & De Brito, 2015). These deficits have been related to specific behavioural tendencies toward proactive aggression (Fairchild et al., 2019). This is a particularly challenging subgroup due to its associated poorer response to treatment and its predictive qualities of the affective and interpersonal components of ASPD and psychopathy constructs (Frick et al., 2014; Loeber, Burke & Lahey, 2000).

Although there is a clear association between CU traits and poorer outcomes, research is marred with issues relating to conflicting reports of CU traits stability across development (Fontaine, McCrory, Boivin, Moffitt, & Viding, 2011; Fontaine, Rijsdijk, McCrory, & Viding, 2010). Furthermore, efforts to distinguish individuals that persist or desist from CU traits using neurobiological perspectives, largely relating to the amygdala's hypoactivation, is muddied by a lack of consistency in findings (Dugré et al., 2020). CU traits research is also the subject of methodological challenges as CU traits are typically defined as a dichotomy (present/absent) rather than continuous dimension. Moreover, there is a lack of clarity and consensus on the underlying CU construct, which has resulted in the absence of research paradigms/cognitive tasks which appropriately capture behaviours most characteristic of CU traits (Hyde et al., 2013). Collectively this makes interpreting neuroimaging studies more difficult in relation to CU traits.

Sex Differences

Although CD has a prevalence of 3-4% in boys and 1-2% in girls (Polanczyk et al., 2015), far more research is focused on males despite evidence of divergent presentations and underlying mechanisms. A recent review has shown that there is far less known about females relative to males with regard to CD aetiology including heritability, genetic risk and epigenetic mechanisms (Frietag et al., 2018). A recent review of neuroimaging research across five neurocognitive dimensions associated with the antisocial spectrum reported that between 79-95% of included participants were male (Dugré et al., 2020). Neuroimaging research remains unclear regarding whether females have district brain abnormalities and altered brain developmental trajectories in comparison to males. For example, males and females are both associated with a negative correlation between CD symptoms and insula activation when viewing others being harmed (Michalska, Zeffiro & Decety, 2016), however that same study found that females had a stronger negative correlation between CD symptoms and superior temporal sulcus activity compared to males. Furthermore, when measuring responses to emotional facial stimuli, girls were found to have abnormal insula and medial PFC responses (Fairchild, Hagan, Passamonti et al., 2014) whereas boys were only found to have emotion-specific effects relating to angry faces in the CD group (Passamonti, Fairchild, Goodyer et al., 2010). Alegria, Radua and Rubia's (2016) meta-analysis found that males had a more pronounced ACC dysfunction than female counterparts. Further research is needed to investigate sex differences in regard to common or distinct brain activity abnormalities.

Comorbidity

CD's most frequent comorbid psychiatric and developmental disorders are ADHD, ODD, developmental language disorder, dyslexia, anxiety disorders, depression, post-traumatic stress disorder and substance misuse disorders (Groenman, Janssen & Oosterlann, 2017; Bernhard et al., 2018), highlighting that the clinical presentation of CD is often extremely heterogenous and comorbid. Typically, psychosocial treatments first focus on CD followed by specific interventions for the comorbid disorder if it has not improved with first line treatment (Fairchild et al., 2019). Combined evidenced based treatments for CD and mood disorders have produced short- and long-term improvements between 7-13 years old (Weisz et al., 2012; Chorpita et al., 2013) thereby highlighting the possible mechanistic effect of comorbidities. Many neuroimaging papers do not systematically examine comorbid ADHD or ODD thus creating the opportunity for comorbidity to influence results (Fairchild et al., 2019). For example, ADHD has been associated with dysfunction of "cool" cognitive processes such as inhibition & timing in comparison to CD's associated dysfunction in "hot" processes related to motivation and affect (Rubia, 2011). Therefore, when comorbid diagnosis is not controlled for, identified differences associated with the CD group may be because the comorbidity has skewed results, and/or CD and the comorbid disorders' shared biological etiological factors may account for variance, or there may just be genuine specific difference located in CD (Hyde et al., 2013). Clinicians would agree that a diagnosis of CD is purely a phenomenological description of current behaviours that has the possibility to transform to another condition over time (NICE, 2017). However, studies that describe how general or specific their findings are in regard to diagnoses can be helpful in defining shared versus unique aspects to externalising disorders. Moreover, given the extremely high rates of comorbidity among CD populations, it is important to consider what the remaining phenotype represents when controlling for comorbid diagnoses.

Risk Factors for Conduct Problems

Risk factors associated with CD range from proximal factors, like child maltreatment (Hein & Monk, 2017), to increasingly distal factors, such as low social economic status (Farah, 2017), and are thought to impact brain development. Recent twin studies have suggested that environmental risk factors account for 50% of the variance in CD (Latimer et al., 2012; Jaffee, Strait & Odgers, 2012; Meaney,

2010). Prenatal risk factors for foetal brain development and subsequent conduct problems include maternal stress, anxiety, smoking and drug and alcohol use (Popova et al., 2016; Ruisch et al., 2018; MacKinnon et al., 2018; Sandman et al., 2018; Gaysina et al., 2013). The impact of maternal anxiety in the last trimester of pregnancy and moderate alcohol consumption has been linked to increased risk of childhood onset conduct problems but not adolescent onset conduct problems (Barker & Maughan, 2009; Murray et al., 2016). The perinatal period presents yet more risk factors associated with CD including birth complications, malnutrition and increased risk of neurocognitive impairments (Liu, 2011; Liu & Raine, 2006), and the association between heavy metals (e.g. lead) and at risk/clinical samples of children with CD (Marcus, Fulton & Clarke, 2010; Beckley et al., 2017). During childhood, parental discipline that is harsh, coercive and inconsistent, as well as high levels of parental-child conflict and child maltreatment are considered robust risk factors for general CD, childhood-onset CD and CDCU+ for both males and females (Jaffee, Strait & Odgers, 2012; Johnson et al., 2017; Moore et al., 2017; Waller & Hyde, 2017; Kim-Cohen et al., 2006; Norman et al., 2012; Jaffee et al., 2005). Other non-shared and increasingly distal environmental risk factors include deviant peer influence, low social economic status, community violence and poverty (Fairchild et al., 2019). Although each factor increases the risk of conduct disorder developing, a conclusive understanding of how exposure to these external factors translate to neural structural and functional abnormalities and beyond to social interactions associated with conduct problems is yet to be established (Fairchild et al., 2019).

Several studies using twin studies have investigated the influence of genetics alongside shared and non-shared environmental factors. The most comprehensive study estimated that CD heritability is over 50% (Jaffee et al., 2005) and posited that there is no unified construct in terms of genetic architecture for CD. Interestingly, a higher heritability rate of 45-67% has been reported for CDCU+ (Viding, Blair, Moffitt & Plomin, 2005; Moore et al., 2017) suggesting a more distinct genetic influence for more aggressive behavioural presentations of CD (Van Hullee, Waldman & Lahey, 2018; Harden et al., 2015; Moore et al., 2017; Antilla et al., 2018). Conduct problems also seem to be more heritable in males than females. A recent review has summarised both candidate gene and genome-wide association studies focusing on anti-social behaviour stating that serotonergic, dopaminergic and neuroendocrine pathways are implicated in the pathophysiology of CD (Fairchild et al., 2019). However, caution should be taken when considering genetic contribution toward CD symptomology as its impact is not considered stable across time but is suggested to increase between childhood to adolescence (Wesseldijk et al., 2017; Jacobson Prescott & Kendler, 2002; Niv et al., 2013). Polygenic inheritance and genetic heterogeneity across individuals interact with environmental factors across development. For example, a gene responsible for encoding the monoamine oxidase A enzyme, MAOA, has been found to moderate the effect of childhood maltreatment (Caspi et al., 2002; Fairchild et al., 2019). Genetic predispositions of both parents and child calibrates their reactive cognitive and affective functioning when they interact potentially resulting in specific relational constraints like difficulties with attachment and maintaining social relationships with latent consequences (Viding & McCrory, 2019; Bird & Viding, 2014).

Neuroimaging Research

Neuroimaging Techniques

There are several methods currently in use to measure neurobiological activity. Understanding each of their basic properties is important as it underscores the role of contrasts, tasks and stimuli in interpretation of findings. Magnetic resonance imaging (MRI) scanners can sample the entire brain or specific regions to extract information regarding structures or Blood Oxygen Level-Dependent (BOLD) response – a signal that reflects changes in regional blood flow thereby indicating neural activity. Diffusion tensor imaging (DTI) is another MRI technique that estimates the white matter (axonal)

organisation of the brain via quantitative analysis of the magnitude and directionality of water molecules. Structural MRI (sMRI) within experimental designs involves layering multiple BOLD signals taken from participants at a single timepoint enabling an aggregated image to be compared between groups; this is particularly helpful in comparing neural structures and brain anatomy. Within sMRI, surface-based morphometry is a group of brain morphometric techniques that can construct and analyse structural boundaries on the surface of the brain providing information on cortical thickness, surface area, curvature, gyrification and grey matter volume (GMV). Functional MRI (fMRI) collects estimates of the BOLD signal every few seconds typically convolved with an experimental task that enables inferences of neural activity specific to brain areas and task demands and the interaction between these areas. As MRI is not a direct manipulation of brain activity, it is important to note that conclusions from MRI-based neuroimaging cannot be considered strictly casual but are rather correlational thereby limiting the interpretation of results. Furthermore, regarding BOLD signals it is still not clear whether changes represent input or output of the particular brain area.

Structural Neuroimaging

White Matter

The limbic system plays a central role in emotional functioning and its dysfunction is considered a core feature of CD, especially CDCU+. Studies on the integrity of the white matter tracts in the limbic system have identified the uncinate fasciculus (UF) and cingulate as areas of interest in CD (Blair & Zhang, 2020). The UF is a white matter tract that connects the ventromedial/orbital frontal cortex and the amygdala/anterior temporal lobes which are associated with the limbic system and conveying of socio-emotional and memory related information (Von Der Heide et al., 2013; Fairchild et al., 2019). Although adult psychopathy studies have consistently found the UF to have less integrity (reduced fractional anisotropy) in comparison to controls, adolescent CD studies have been less reliable as some reported increased fractional anisotropy whilst others report decreased integrity (Blair & Zhang, 2020). More recent studies have identified less integrity (lower fractional anisotropy and hindrance orientational anisotropy) in the uncinate and cingulum in the preadolescents with high delinquent behaviour/CD (Bolhuis et al., 2019; Gonzalez-Madruga et al., 2020). Interestingly, Gonzalez-Madruga and colleagues (2020) found this effect was moderated by sex; males with CD had significantly lower fractional anisotropy in comparison to healthy male controls which was not reflected in females participants. Furthermore, relative to CDCU-, adolescents with CDCU+ showed reduced diffusivity in the left uncinate fasciculus, bilateral fornix and fronto-occipital fasciculus possibly impacting connectivity between the limbic system and inferior portions of the frontal lobe (vmPFC; Puzzo et al., 2018; Maurer, 2020; Aghajani et al., 2016; Marsh et al., 2008; Bolhuis et al., 2019). This suggests that conduct problems, particularly related to CU traits, are generally associated with lower white matter microstructure integrity in tracts between frontal and temporal lobes which are key regions involved in empathy, decision making, reward processing and emotional regulation.

Grey Matter

Surface based morphometry studies have identified atypical grey matter differences in cortical thickness, gyrification and surface area across different CD subgroups. Smaragdi and colleagues (2017) compared female and male adolescents with matched controls and found that CD was associated with cortical thinning and higher gyrification in the ventromedial prefrontal cortex. Interestingly, CD males showed lower supramarginal gyrus cortical thickness and higher gyrification and surface area in the superior frontal gyrus in comparison to controls whereas females with CD showed the opposite pattern. Budhiraja and colleagues (2019) compared cortical thickness and surface area in young women with a history of CD and found reduced cortical thickness in the brain regions involved in emotion processing

and social interaction independent of comorbid disorders, current mood problems, substance misuse or maltreatment. Child-onset CD displayed a higher number of significant cross-cortical correlations in cortical thickness compared to controls and adolescent-onset participants which remained significant when controlling for IQ and comorbidity (Fairchild et al., 2016). Carlisi (2020) identified that in comparison to adolescent onset and low anti-social groups, those displaying early onset anti-social behaviours had smaller mean surface area and lower mean cortical thickness particularly in frontal and temporal regions associated with executive functioning, affect regulation and motivation. These studies demonstrate that sex, age of onset and general presence of conduct disorder is associated with variation in grey matter structures that have been linked to emotion processing and executive functioning.

Roger and De Brito (2016) conducted a comprehensive meta-analysis into the findings of whole-brain structural MRI studies which examined GMV and found that a number of neural regions associated with the behavioural symptomology of CD youths had reduced GMV. The amygdala is a region considered to be involved in a range of cognitive processes which include empathy, face processing, decision-making, classic aversive conditioning and threat response via the initiation of the hypothalamic pituitary-adrenal axis stress response (Janak & Tye, 2015; Gupta et al., 2011; Hillis, 2014; Gunnar & Quevedo, 2007; Whalen & Phelps, 2009). Consistently youths with conduct problems had been associated with decreased GMV in the left amygdala, particularly for childhood-onset males (Rogers & de Brito, 2015). A more recent voxel-based morphometry and surface-based morphometry investigation also found that grey matter alterations in the fronto-limbic regions, including the amygdala, were more pronounced in those children with CD who had been exposed to childhood maltreatment than CD and controls (Gao et al., 2021). The bilateral anterior insula is part of a neural network that is associated with empathic concern of others (Decety et al., 2009; Mutschler et al., 2013), interoception (Fairchild et al., 2019) and behavioural adjustment during risky decision-making (Clark et al., 2008). Childhood onset CD has also been associated with reduced GMV in the anterior insula and right insula which then extended into the prefrontal cortex and superior temporal gyrus as well as amygdala for childhood onset CD populations. Unsurprisingly, GMV in the anterior insula in male youths with conduct problems was positively correlated with empathy scores and negatively with aggression and lifetime CD symptoms (Rogers & De Brito, 2015; Frick & White, 2008; Blair, 2013; Zhang et al., 2018; 2020). The ventrolateral prefrontal cortex (vlPFC) and vmPFC/OFC are considered key regions in in emotional regulation, response inhibition and decision making (Aron, Robbins & Poldrack, 2004; Ochsner & Gross, 2005; Sakagami & Pan, 2007). Amongst CD youths and ASPD adults, this neural region has a reduced GMV compared to controls leading researchers to suggest that self-regulation processes are compromised in these groups resulting in an increased risk of antisocial and aggressive (Rogers & de Brito, 2015; Raines, Yang & Narr, 2011). Lastly, the putamen/striatum, a key region involved in decision making but also reinforcement learning, has also been found to have a lower reduction in GMV but only within CDCU+ populations (Rogers & De Brito, 2015) which is consistent with findings that striatum volume and CU traits in youths and psychopathy in adults are positively related (Fairchild et al., 2011; Glenn, Raine, Yaralian & Yang, 2010). Although structure and function cannot be directly linked, regions involved in empathy, acute threat processing, interoception, emotional regulation, cognitive control and decision making are smaller in volume and therefore may be linked to behaviours such as reactive or proactive aggression, impulsivity, amoral behaviour and difficulties with learning (Noordermeer et al., 2016; Dugré et al., 2020).

Functional Neuroimaging

Acute Threat Response

The acute threat response system, otherwise known as the defensive survival circuit, involves physiological changes (i.e. endocrine and autonomic nervous systems) and adaptive behaviours (e.g fight, flight or freeze response) that are gradated in relation to proximity of threatening stimuli: the more proximal the threat, the greater the activity within the system and the greater likelihood of aggression will be shown in response (LeDoux, 2015; Blanchard et al., 1977). Typically, youths with conduct problems have reported reduced threat responsiveness in comparison to controls evidenced in reduced amygdala, vmPFC and anterior cingulate responses to threatening stimuli (Hwang et al., 2016a; Stadler et al., 2007; Sterzer et al., 2005). The amygdala is hypothesised to play a central role in emotional reactivity to threat; within CD populations, its hyper-activation amongst low CU trait groups in response to threat, e.g. fearful expressions, has been linked to reactive aggression whereas amygdala hypo-activation is inversely linked with CU traits/decreased empathy (Blair & Zhang, 2020; Blair et al., 2018; Blair, 2016; Hyde et al., 2013; Viding et al., 2012a) although this association is not conclusive (Dugré et al., 2020). Visual threat processing of emotionally salient stimuli, e.g. angry and fearful facial stimuli, for CDCU+ populations has been associated with reduced activity and connectivity between the amygdala-ventral anterior cingulate cortex (Ewbank et al., 2018; Jones et al., 2009; Lozier et al., 2014; Marsh et al., 2008; Viding et al., 2012; White et al., 2012a) whereas for CDCU- populations social threats/provocation has resulted in an elevated amygdala response in comparison to TD controls (Dotterer et al., 2020; Crowe & Blair, 2008; Sebastian et al., 2014;Viding et al., 2012; White et al., 2016) suggesting that the presence of CU traits represents a divergence of threat processing. Interestingly, Hyper-activation of the amygdala amongst CDCU+ youths has been observed but has been associated with historical exposure to trauma (Meffert et al., 2018) therefore highlighting the detrimental developmental effect of childhood maltreatment on threat processing (Blair & Zhang, 2020; Fanti et al., 2020). Furthermore, neural regions that typically act to reappraise threat and link interoceptive states in an inhibitory process, dlPFC and anterior insula respectively, have been observed as hypoactive within CD populations during threat processing (Dugré et al., 2020; Etkin et al., 2015; Hartley & Phelps, 2010; Aupperle Robin & Martin, 2010; Menks et al., 2021; Noordermeer et al., 2016). CD individuals may overestimate the level of social threat/provocation in their environment whilst exhibiting a reduced ability to downregulate their emotional response resulting in an increased likelihood of reactive aggression (Chloe et al., 2015; White et al., 2016b). This overperceived threat may also be linked to the hostile attribution biases toward others seen in CD youths (Dodge et al., 1997, 1995; Lopez-Duran e al., 2009). Conversely, CDCU+ populations may underestimate the level of threat resulting in a reduced emotional response that may then consequently impair their ability to use interoceptive information during empathy-based/moralistic decision making.

Social Cognition

Social cognition relates to behaviours associated with interactions with others and is captured within neuroimaging studies using socially relevant stimuli including faces, voices, and moral decision making to examine affect discrimination, empathy and implicit bias (Gur & Gur, 2015). Social cognition relies upon skills and abilities such as theory of mind and self-reflection (Schurz et al., 2014; Molenberghs et al., 2016), episodic memory (Vargha-Khadem et al., 1997; Tulving & Markowitsch, 1998; Spreng & Mar, 2012) and executive functioning. Cognitive empathy is the representation of intentions and beliefs of other individuals that underpins effective social and communicatory functions (Baron-Cohen et al., 1985; Leslie, 1987) which is not typically impaired in CD populations (Buitelaar et al., 1999) due to appropriate recruitment of neural circuitry (O'Nions et al., 2014; Sebastian et al., 2012). However, more recently studies have found an atypical recruitment of a key neural region, the temporoparietal junction (TPJ) and supramarginal gyrus, when completing social interaction paradigms (Klapwijk et al., 2016; Dong et al., 2016; Bubenzer-Busch et al., 2016; Klapwijk et al., 2016b; van den Bos et al., 2014). Affective empathy involves the representation of emotional states of other individuals and has been found to be impaired within general CD populations (Buitelaar et al., 1999). The amygdala and anterior insula are positively associated with empathic ability and resonance, however they function atypically in CD

populations in comparison to controls (Sebastian et al., 2012). CDCU+ groups demonstrated hypoactivation of the amygdala and insula during affective empathy tasks in comparison to CDCU- and healthy controls (von Polier et al., 2020; Hwang et al., 2016) independent of what emotion was expressed (Sakai et al., 2017; Klaowijk et al., 2016) however additional CD characteristic like impulsiveness and aggression may also explain deficits and require further investigation (Sun et al., 2016). Facial expression processing is based on the understanding that emotional cues have a communicatory function that aids valence-based decision making based upon previous observations of certain emotions (Blair et al., 2018). Amongst typically developing people, the amygdala is particularly responsive to fearful, sad and happy facial expressions, whereas the insula is more responsive to disgust and anger (Fusar-Poli et al., 2009). The amygdala and its interaction with the vmPFC are considered key to the process of valence-based decision making as it is sensitive to expression prediction errors and subsequent social learning (Meffert et al., 2014; Schoenbaum & Roesch, 2005). Amygdala recruitment and amygdala-ventromedial connectivity is atypical within CD populations, especially hypoactive amongst CDCU+ populations (Aghajani et al., 2017; Marsh et al., 2011; 2008), which is reflected in deficits of expression recognition especially for fearful, sad and happy expressions (Blair et al., 2001; Stevens et al., 2001) pervading across vocal tones (Blair et al., 2005; Stevens et al., 2001) and body postures (Munoz, 2009). Decreased amygdala activation in response to distress cues e.g. fear, is specifically linked to increased CU traits and increased risk of instrumental/proactive aggression (Lozier et al., 2014, Thornton et al., 2013; Viding et al., 2012; White et al., 2012). Deficits in recognising distress cues through social stimuli such as facial expressions alongside poor affective and cognitive empathy disrupts valence attribution and aversive conditioning of acts that cause distress (Blair et al., 2018). Consequently, the individual represents amoral/proactive acts less negatively and may therefore contribute toward an increased likelihood of its occurrence.

Cognitive Control

Cognitive control refers to the inhibitory role of executive function during tasks when exposed to interfering stimuli and responses (Miller & Cohen, 2001) typically achieved through the employment of motor and interference inhibition, cognitive flexibility and performance monitoring. Brain regions considered key to cognitive control include the ventrolateral PFC, anterior insula, premotor cortex and cerebellar (Aron et al., 2014; Rae et al., 2014; Nee et al., 2007; Cai et al., 2014). A recent meta-analysis described reduced activation in each of these areas amongst those who experience conduct problems and anti-social behaviours (Dugré et al., 2020). Additional meta-analyses have identified further areas of decreased activation regarding cognitive control amongst anti-social populations including the inferior frontal gyrus, temporal lobe, insula and supplementary motor area (Noordermeer et al., 2016; Blair et al., 2018) and less significantly with areas associated with the default mode network (cingulate cortex and precuneus; Noordermeer et al., 2016). This reflects wider literature that suggests subjects with conduct problems demonstrate deficits in executive functioning, especially in motor and interference inhibition and response selection tasks compared with healthy controls (Seguin et al., 2007; Ogilvie et al., 2011; Morgan & Lilienfeld, 2000; Hobson et al., 2011). Reduced ventrolateral PFC and anterior insula activity has been associated with decreased motor inhibition and decreased motivational/affective processing post task failure respectively (Dugré et al., 2020; Algeria et al., 2016; Fehlbaum et al., 2018; Zeier et al., 2012; Chamberlain et al., 2016). High levels of emotional reactivity and a lack of down regulation processes amongst CD youths are hypothesised to have a performance interfering effect on response control tasks due to their negative correlation with performance when compared to the less emotionally reactive CDCU+ population (Fehlbuam et al., 2018; Hwang et al., 2016; Schiffer et al., 2014; Hiatt et al., 2004; Blair et al., 2006b; Sun et al., 2018). This decreased performance has been attributed to stronger interference by distractor information and increased activity in brain regions sensitive to response conflict (dmPFC; Kerns et al., 2004; Schiffer et al., 2014).

Behaviourally, a dysfunctional response inhibiting neural system may result in an individual who struggles to stop themselves from performing an impulsive yet gratifying antisocial act and then be less able to process the motivational and affective consequences of that action. This behaviour is possibly made more likely through interference of more intense emotion, such as those at high risk of reactive aggression, and/or exacerbating effect of comorbidity e.g. ADHD.

Reinforcement Learning

Reinforcement-based decision making is an interaction between three domains: reward processing, punishment processing and avoidance learning (Fairchild et al., 2019; Blair et al., 2018). Closely aligned to reinforcement-based decision-making, response outcome learning is considered a key cognitive mechanism for behaviour change and involves the striatum providing expectancy information based on prior learning and prediction error signalling during decision making. Prediction error signalling is the level of behavioural discrepancies between expectation and reward/punishment; the higher the discrepancy the more reinforcement learning occurs. The vmPFC is associated with reinforcement expectancies (if the expectancy is positive it is likely to initiate approach behaviour) and functions to represent competing values associated with different responses in conjunction with the dmPFC role of processing conflict in the choice of responses (Blair et al., 2006a). For the optimal decision to be made, attention resources from the lateral frontal and parietal cortices, and response control resources, via inferior frontal cortex and anterior insula cortex are recruited (Blair et al., 2018; Budhani et al., 2007). During avoidance behaviour the anterior insula cortex and dmPFC exhibit greater activity when sub-optimal responses are about to be made and is modulated by expected value of that action processed in the vmPFC (White et al., 2013c; Kuhnen & Knutson, 2005; Blair et al., 2018).

Youths with CD are more likely to be impulsive, seek immediate over delayed rewards and, when actions fail to produce intended outcomes, experience frustration (Blair, 2010; Byrd et al., 2014). Blair and colleagues (2018) argue that youths with CD have a reduced sensitivity/responsiveness to reward in the striatum and vmPFC (Cohn et al., 2015; White et al., 2013; Rubia et al., 2009; Finger et al., 2011; Crowley et al., 2010). This deficit in responsiveness may result in poorer decisions that are less well guided by expectations of reward in relation to punishment. Increased frustration has been associated with increased risk of reactive aggression (Berkowitz, 1993) and has been linked to exposure to harsh parenting (Xu et al., 2009). During reward anticipation, DBD groups with and without CU traits exhibited decreased dorsal ACC activation compared to TD controls. DBD without CU traits exhibited reduced ventral and dorsal striatal activity compared with DBD with CU traits and healthy controls demonstrating reduced anticipatory reward activation (Hawes et al., 2021). Interestingly, during reward receipt, DBDs showed increased activation in the OFC/vmPFC and ventral striatum whilst DBD with CU traits exhibited greater activation in the amygdala (compared to healthy controls) and dorsal ACC (compared to DBD-only). Reduced striatal activity has been linked to ADHD and impulsivity (Plichta & Scheres, 2014) as well as those at risk of developing substance misuse through familial alcoholism or characterisation as a risk taker (Dugré et al., 2020; Heitzeg et al., 2008; Yau et al., 2012; Norman et al., 2011; Schneider et al., 2012; Luijten et al., 2017) whereas striatum hyper-sensitivity has been associated with predatory/proactive aggression in anti-social populations (Xu et al., 2009). These studies suggest that DBD populations exhibit decreased striatum and vmPFC activity resulting in poorer reward expectations as well as irregularities in response to reward receipt which may be linked to adverse outcomes in later life. Critically, the presence of CU traits may make it more likely to experience normal to hyper striatum and vmPFC activity leading to increased risk of proactive aggression as it may be associated with increased reinforcement expectancies.

Dysfunctional punishment processing may result in individuals being less likely to avoid actions/objects associated with undesirable consequences and can also lead to frustration and subsequently aggression

(Blair, 2010; Blair et al., 2018). Typically, when experiencing consequences to actions that were worse than expected, there is associated decreased activity in the striatum and vmPFC (Balleine & O'Doherty, 2010; O'Doherty, 2012). However, within conduct problem populations an inverse response via increased activity in striatum and vmPFC in response to prediction errors to punishment and punishment itself has been observed (White et al., 2013; Finger et al., 2011; Fairchild et al., 2019) as well as reduced activation of the amygdala independent of covariates or CU traits (Byrd et al., 2018). Moreover, decreased activity in areas associated with negative affect regulation (right TPJ & dorsal ACC) and reward expectation (left anterior insula & vmPFC) was also observed in CD populations when losing in a gambling task (Schwench et al., 2017). Collectively, these studies suggest a general abnormal response to punishment specific to CD that involves increased reward, reduced threat and reduced negative affect response compared to healthy controls. Blair and colleagues (2018) have hypothesised this is due to dysfunctional valence-based modulation of dopaminergic prediction error signalling but intact novelty-based modulation that may make punishment positively reinforcing, thereby partly accounting for the ineffectiveness of punishment techniques in behaviour extinction.

A dysfunction in avoidance behaviour amongst youths with CD may present as increased frequency of unwise behavioural choices (Blair et al., 2018). Areas considered key to avoidance behaviour are those involved in cognitive control, which are sensitive to expected value of specific responses, including the anterior insula cortex, dmPFC and caudate (Li et al., 2007; Kuhnen & Knutson, 2005; Casey et al., 2001; Budhani et al., 2007). Youths with conduct problems exhibit less activation of these regions whilst making suboptimal choices during value-based tasks (White et al., 2014; 2013). White and colleagues (2016) identified a relationship between dysfunction in this network and increased antisocial behaviour.

In summary, youths with CD exhibit considerable variation in reward and punishment processing. In regard to reward, CD youth are considered to generally have reduced responsiveness to anticipation of reward and variation in regard to reward receipt. Hypo-sensitive striatum responses may present with individuals who are less able to make accurate predictions of behaviour and therefore make poorer decisions possibly resulting in higher levels of frustration when outcomes are undesirable. This group is considered to be more at risk of substance misuse. Conversely, those that are hyper-sensitive to reward have been linked to more proactive forms of aggression. Interestingly, punishment may be less of a threatening/aversive stimuli amongst CD youths and may actually act as a reward. CD youth are less sensitive to expected outcomes of possible actions which can result in more risky behaviour and a reduction in positive response outcome learning.

Discussion

This review aimed to examine neuroimaging research, particularly fMRI data, which relates to neurocognitive mechanisms that are maladaptive in youths who present with conduct problems. Considering the limitations of categorization based on behavioural symptoms, this paper used dimensional domains of functioning to understand how neurocognitive processes, underpinned by atypical neurobiological structures, contribute toward biased emotion processing and subsequent behavioural symptom sets associated with youths who present with conduct problems. This paper utilised the organisational benefits of research based on CD subtypes, particularly the presence or not of CU traits, to examine differences within this heterogenous population including the risk factors that may moderate or mediated specific symptomology.

Neural regions that are typically engaged in the acute threat response (amygdala, insula & dlPFC) have been associated with reduced GMV and atypical activity amongst youths with conduct problems. Although in general youths with CD displayed reduced threat responsiveness particularly in the amygdala, CD youths with low CU traits have displayed increased amygdala responses relative to

healthy youth (Viding et al., 2012). Increased stimulation in the amygdala has been linked to increased likelihood of reactive aggression in CD youths (Viding et al., 2012) and in animal research (Gregg & Siegel, 2001; Panksepp, 1998). This heightened threat reactivity may be exacerbated by an under-activated neural network that typically function as inhibitors: the insula and dlPFC (Dugré et al., 2020; Etkin et al., 2015; Hartley & Phelps, 2010; Aupperle Robin & Martin, 2010; Menks et al., 2021; Noordermeer et al., 2016). Conversely, amygdala activation is inversely related to CU traits amongst CD populations (Blair & Zhang, 2020; Blair et al., 2018; Blair, 2016; Hyde et al., 2013; Viding et al., 2012; Ewbank et al., 2018; Jones et al., 2009; Lozier et al., 2014; Marsh et al., 2008; White et al., 2012) except for those CDCU+ youths that had been exposed to childhood trauma in response to threat (Meffert et al., 2018; Blair & Zhang, 2020; Fanti et al., 2020). It is therefore plausible that the presence or not of CU traits results in opposing responses to threat except in the presence of childhood maltreatment.

Closely related to acute threat response, neural regions associated with social cognition are considered imperative to providing valence-based information regarding objects/actions in one's environment thereby acting as a modulating influence of current behaviour (Blair et al., 2018; Meffert et al., 2014; Schoenbaum & Roesch, 2005; Aron, Robbins & Poldrack, 2004; Ochsner & Gross, 2005; Sakagami & Pan, 2007). Empathic ability, emotional resonance, facial processing and distress cue processing are positively associated with amygdala and insula activity (Decety et al., 2009; Mutschler et al., 2013; Fairchild et al., 2019) however these regions are also underpinned by reduced GMV amongst youths with CP (Rogers & De Brito, 2015; Zhang et al., 2018; 2020). CD youths in general present with difficulties with affective empathy and facial expression processing, regardless of what emotion is presented, in association with an under reactive amygdala and insula (Sebastian et al., 2012; von Polier et al., 2020; Hwang et al., 2016; Sakai et al., 2017; Klaowijk et al., 2016). The level of maladaptation in this neurocognitive mechanism positively relates to level of CU traits and increased risk of proactive/instrumental aggression (Lozier et al., 2014, Thornton et al., 2013; Viding et al., 2012; White et al., 2012). Poor perception of and emotional resonance with aversive social cues, such as the distress of others, disrupts stimulus-reinforcement learning and development of care-based morality in youth with conduct problems (Harenski et al., 2014; Blair et al., 2018). This may result in individuals representing amoral/proactive aggressive acts less negatively and may therefore contribute toward an increased likelihood of its committal.

Regarding cognitive control and reinforcement learning, the presence of CU traits has been less conclusively linked to specific deficits in comparison to CDCU- peers. Interestingly, CDCU+ groups have performed better on cognitive control tests which researchers have suggested is due to reduced interference of emotional reactivity and therefore response conflict (Fehlbuam et al., 2018; Hwang et al., 2016; Kerns et al., 2004; Schiffer et al., 2014; Hiatt et al., 2004; Blair et al., 2006; Sun et al., 2018). However generally, CD youths have been linked with reduced activity within cognitive control neural regions producing a weaker stop signal during inhibition tasks (Dugré et al., 2020; Noordermeer et al., 2016; Blair et al., 2018) and then lack of affective and motivation processing once suboptimal choices have been made (Dugré et al., 2020; Algeria et al., 2016; Fehlbaum et al., 2018; Zeier et al., 2012; Chamberlain et al., 2016). There is considerable variation in reinforcement research however generally findings have identified a reduced activation of the striatum for reward anticipation and receipt amongst CD youths (Cohn et al., 2015; White et al., 2013; Rubia et al., 2009; Finger et al., 2011; Crowley et al., 2010). Both a reduced inhibition mechanism and poorer sensitivity to expected outcomes have been linked to increase impulsivity and potential for antisocial behaviour (Berkowitz, 1993; Cohn et al., 2015; White et al., 2013; Rubia et al., 2009; Finger et al., 2011; Crowley et al., 2010). These deficits are closely aligned with comorbid disorders of ADHD and substance misuse disorders (Plichta & Scheres, 2014; Dugré et al., 2020; Heitzeg et al., 2008; Yau et al., 2012; Norman et al., 2011; Schneider et al., 2012; Luijten et al., 2017).

Although each of the specific neural regions that contribute toward these neurocognitive processes are interrelated and responsive based on the individual's current homoeostasis need, some research has suggested that specific regions qualify the activation of other regions required for effective emotional processing (Steffen, Hedges & Matheson, 2022). For example, maladaptation in acute threat response and social cognition, specifically for distress cues, possibly represent opposite perturbations of the same neural region (Blair et al., 2018); decreased responding of the acute threat response network is associated with CU traits and proactive aggression, whereas increased responding is associated to heightened threat processing and reactive aggression. This activity is interrelated with vmPFC activity during valence information processing thereby subsequently influencing regions key to other mechanisms like affective empathy, response selection and reinforcement-based decision making. The neural systems outlined in this paper often interact and are compromised resulting in the syndromes that are associated with CD (Blair et al., 2018). Often non-specific but aversive risk factors that disrupt homeostasis during development such as childhood maltreatment, harsh parenting and low SES impacts the brain via adaptation. The adaptation's primary goal is to aid survival but in turn increases heterogeneity of these systems through the process of multifinality and equifinality and require further examination (Viding & McCrory, 2020).

It is worth considering how these interrelated, reciprocal and maladaptive mechanisms influence one's internal world and how this then interacts with their ecological system. The brain functions to integrate information from variety of sources to aid the process of adaption for that specific environment in order to sustain life. The extent of dysfunction, or mis-calibrated adaptation, within a specific neurocognitive domain and their interaction with each other is assumed to increase the risk and variation of conduct problems being exhibited. CP youths may be more at risk of "stress sensitivity'; the increased burden resultant from altered emotional and cognitive functioning (Tottenham & Gabard-Durnam, 2017; McCrory, 2020) e.g. an individual's overestimation of danger when presented with threatening stimuli. Conversely, the reduced emotional reactivity of CDCU+ youths may place them at heightened risk of "stress insensitivity": a process of altered socioemotional and interoceptive neurocognitive processes that directly affect psychological functioning by decreasing the degree of aversion of negative stimuli e.g. poor perception of and emotional resonance with aversive social cues disrupting valence-based decision making. Both processes would likely directly influence the young person's own social experience by increasing the likelihood they act to precipitate the occurrence of stressor events, also known as 'stress generation', thereby influencing and being influenced by their own ecological system (McCrory, 2020). As stress generation continues to rise a gradually accruing set of negative biological, psychological and social outcomes occur for the individual resulting in a high societal burden (McCrory, 2020). It is therefore crucial that the field develops understanding of how risk factors increase likelihood of adaptation in these emotion processing neurocognitive mechanisms as well as our understanding of how interrelated neural activity can contribute toward specific conduct disorder syndromes. By identifying this we may identify what contexts may trigger latent vulnerabilities and therefore guide interventions.

Further Research

Future conduct disorder research should aim to examine the relationship between neurocognitive systems involved in emotion processing and how they contribute toward specific CD syndromes (Blair et al., 2018). Proactive aggression & high CU traits versus reactive aggression & low CU traits, are currently the most consistent symptom sets that are related to atypical function in acute threat response and social cognition neurocognitive domains (distress cues and facial expression processing). These divergent CD syndromes, grouped using the presence or not of CU traits, are hypothesised to be distinguished by reactivity in the amygdala and insula in response to distress and threat salient facial

expressions as sources of exteroceptive and interoceptive information respectively. It would be helpful to examine the activation of the vmPFC of each group under the assumption that its role in valence-based information processing would influence the interrelated regions involved in subsequent processes e.g. decision making or error prediction. In light of multifinality and equifinality, it would be useful to examine the mediating effect of external factors, such as childhood maltreatment, parenting techniques and SES, as well as comorbidities like ADHD and substance misuse disorder to capture their influence on activity. During research design, specific focus should be assigned to ensuring attentional load is low and severity of antisocial behaviour, stimuli type, task instructions and socio-emotional context are adequately defined (Dugré et al., 2020). The participant groups would benefit from being a well-defined homogeneous but representative groups of anti-social subjects (e.g. inclusion of participants with comorbidities) with systematic descriptions of relevant demographic information with the aim to further examine other groups for comparison at a later date.

Conclusions

To summarise, this review examined the current state of emotion processing neuroimaging findings using neurocognitive mechanisms that are considered to be dysfunctional or maladaptive within youths that present with conduct problems. It attempted to contextualise neuroimaging findings by discussing pertinent issues within CP neuroimaging studies including those surrounding diagnosis and comorbidity, and non-specific risk factors that could contribute toward the process of multifinality and equifinality in the development of conduct difficulties and neural adaptation. Underpinned by a general lack of integrity of white matter tracts connecting subcortical limbic areas to frontal areas as well as a general reduced GMV within areas associated with emotion processing, supporting functional neuroimaging research has associated with a range of atypical neurocognitive mechanisms with youths with conduct problems including acute threat response, social cognition, cognitive control and reinforcement learning. Aiming to increase the practical application of neuropsychological findings, neuroimaging and domain of functioning findings were related to specific behavioural symptom sets that are not exclusive to CD however contribute toward the behavioural syndromes associated with it. Although the overall pattern of findings of both structural and functional neuroimaging identify a perturbated neural network that is related to emotion processing, it is remains unclear how interrelated regions work together and what is being assessed specifically. Understanding the interplay of activity within the interrelated neural regions related to emotion processing is key to understanding why specific behaviours are produced. Conceptualising conduct problems through the lens of dysfunctional neurocognitive mechanisms provides greater potential for individualised assessment and intervention within the individual's ecological system.

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Part 2: Empirical Paper

Differences in Emotion Processing Amongst Boys with Conduct Problems and Varying Levels of Callous-Unemotional Traits: A Functional Neuroimaging Study.

Abstract

Aims: Responses to emotional states of others has been linked to two clusters of adolescents with conduct problems (CP): one characterised by low callous-unemotional (CU) traits, hyper-reactivity of the amygdala and reactive aggression; the other with high CU traits, hypo-reactivity of the amygdala and proactive aggression. However, variation in findings exist and this may be linked to a complex interaction of risk factors. This study aims to investigate emotion processing within boys with CP with varying levels of CU traits and associated risk factors.

Method: This current study used functional Magnetic Resonance Imaging (MRI) and facial expressions (angry/sad/happy) to examine neural differences in facial emotion processing among boys who present with CP and high CU traits (CPCU+; n = 27), CP and low CU traits (CPCU-; n = 27) and typically developing peers (TD; n = 25). The participants were matched for socio-economic status, age and IQ. A 3 x 3 design using both whole brain and region of interest (ROI) analyses in the amygdala, insula and medial prefrontal cortex (PFC) was conducted. Demographic and psychological measures were compared across groups.

Results: All results were observed at a suprathreshold of p = 0.001 uncorrected. In response to all emotions combined, whole brain analyses revealed that CPCU+ boys had decreased amygdala activation compared to TD peers whereas CPCU- boys had decreased activation of the right hypothalamus. In response to angry faces, CPCU- boys exhibited hypo-activation in limbic, frontal and temporal regions compared to TD peers and hypoactivation in the dorsolateral PFC compared to CPCU+ peers. In response to sad faces, CPCU+ boys exhibited hypoactivation in the inferior temporal gyrus compared to TD peers and hypoactivation across frontal, temporal and cerebellum regions compared to CPCU- peers whereas CPCU- boys exhibited hyperactivity in the dorsomedial and rostral anterior cingulate cortex compared to TD peers. In response to happy faces, only the CPCU+ group demonstrated hyperactivity in the ventromedial PFC and hypoactivity in the posterior middle temporal gyrus compared to CPCU- peers. Interestingly the combined CP groups compared to TD peers exhibited decreased amygdala activity in response to all emotions combined, increased amygdala responses to sad faces and decreased insula and dorsolateral PFC activation in response to angry faces. Region of interest analyses revealed perturbations in insula and medial PFC activity dependent on specific emotional expressions but not the amygdala. Both CP groups were associated with poor parental monitoring, the CPCU- group was associated with corporal punishment whereas the CPCU+ group was associated with neglect and inconsistent discipline.

Conclusions: Findings did not support the hypothesised binary difference based on level of CU traits but did support a general perturbation of neural regions associated with emotion processing amongst boys with CP, especially for negative emotional stimuli. Diversity in findings reflects the experienced adversity and heterogeneity of the CP population whilst suggesting an interrelated neural system devoted to emotion processing. Further research is needed to combine different fields of research to develop a more holistic explanatory model. Clinical implications were discussed.

Introduction

Despite a continual increase in genetic, environmental and neurocognitive risk factor related research, there are still considerable difficulties in etiologically delineating distinct risk profiles and developmental trajectories for youths who present with conduct problems (CP; Viding & McCrory, 2020). The level of heterogeneity within externalising disorders that present with CP can result in children being diagnosed with the same disorder with little overlap in behavioural symptoms as well as seemingly similar behavioural presentations being the result of differing and unique combinations of underlying mechanisms (Viding & McCrory, 2020; Hyde et al., 2013). In contrast to reductionist behaviour-based categorisation and in support of increasing calls for a holistic and integrated explanatory model, domains of functioning have provided a dimensional conceptualisation of anti-social behaviours and researchers have increasingly sought biological, particularly neural, correlates to inform developmental pathways. Responses to emotional states of others have identified two clusters of youths with CP with seemingly distinct etiological pathways: those high in callous unemotional (CU) traits, hyporesponsive neural activity and proactive aggressive; and those low in CU traits, hyperresponsive neural activity and reactive aggression (Blair et al., 2018). Those youth diagnosed with a conduct disorder continue to be a leading cause of referrals to children's mental health services and are associated with a high societal and economic burden as well as a high comorbidity rate with over half of these children going on to develop chronic symptoms, criminal behaviours and receive a diagnosis of a personality disorder in adulthood (Moffitt, 2018). This paper utilised a dimensional domain of functioning related neuroimaging data, whilst accounting for specific risk factors, to investigate the divergent CP phenotypes, distinguished by high or low CU traits, to develop formulations, prevention and intervention strategies.

Although much research has focused on identifying risk factors that contribute toward CP (Fairchild et al., 2019), it is difficult to assess the impact of each factor as most are also risk factors for other psychopathologies and individual's trajectories vary widely (Viding & McCrory, 2020). An interactive system of genetic risk factors, environmental risk factors and protective factors, beyond those related to general psychopathology, are suggested to produce variation in the influence a specific risk factor(s) has; otherwise known as multifinality (Cicchetti & Rogosch, 1996; Hankin et al., 2011). In contrast, multiple and different risk factor combinations can influence the formation of the same behaviour across different individuals; an example of equifinality (Hyde et al., 2013). Both internal and external risk factors shape neural development to best adapt the child to their environment (Steffen, Hedges & Matheson, 2022). Therefore, CP likely reflects a unique and complex probabilistic and etiological development chain. By not considering risk factors when understanding CP, there is a risk of locating the aetiology within the child rather than how this specific phenotype interacted with and was shaped by their environment (Viding & McCrory, 2020).

Behavioural/trait-based categorisation of CP youths has meaningfully guided research but is limited in capturing heterogeneity across groups leading to divergent findings and possible errors in measurement (Hyde et al., 2013; Viding & McCrory, 2020). For example, CP youths with CU traits or "limited prosocial emotions", a conduct disorder subtype characterised by a lack of remorse, empathy, concern about performance and deficient affect (American Psychological Association, 2013), has been linked to a more severe course of anti-social behaviour and poor responsiveness to interventions compared to CP youths without CU traits (Fairchild et al., 2019). CU traits has been associated with specific genetic influences (Viding, Blair, Moffitt & Plomin, 2005; Moore et al., 2017), developmental events such as childhood maltreatment and environmental factors like low social economic status (SES: Piotrowska et al., 2015; Viding et al., 2013). However, as a clinical and research marker, CU traits lacks utility due to its poor definition as a construct, poor research paradigms, instability and inconsistent

predictive power (Hyde et al., 2013; Viding & McCrrory, 2020; Dery et al., 2019). More recently, dimensional approaches have been introduced to move beyond the limitations of trait/behavioural indicators. The National Institute of Mental Health Research Domain Criteria (RDoC; Cuthbert & Insel, 2013) defines dimensions of functioning and specifies research paradigms designed to probe variation within populations. However, despite this more nuanced form of categorisation, researchers and clinicians still struggle to delineate between distinct risk profiles or etiologically differentiated youths who present with CP.

Building on structural findings (Rogers & De Brito, 2015), functional neuroimaging research has increasingly used the RDoC to document neurocognitive variation and specify patterns for categorical CP subtypes (Fairchild et al., 2019; Dugré et al., 2020; Blair et al., 2018). Four key neurocognitive domains of functioning are consistently implicated in youths with CP: acute threat response, social cognition, cognitive control and reinforcement learning (Dugré et al., 2020). Each of these neurocognitive domains involve processes that are critical for navigating the social world through their ability to effectively process emotion, understand others, make moral judgements and learn from the experiences (Hyde et al., 2013; Forbes & Grafman, 2010). The Adaptive Brain Theory suggests that the brain's key role is to produce adaptive predictions that are critical for balancing current needs and interconnections between homeostasis, emotion, cognition and strong social bonds (Steffen, Hedges & Matheson, 2022). The insula cortex, cingulate cortex and frontal regions are elements of an interdependent brain network that integrates interoceptive and exteroceptive inputs necessary to make those predictions, albeit in relationship to other regions and brain circuits (Steffen, Hedges & Matheson, 2022). Therefore, internal and external factors set the context for brain development and function. Risk factor insults to these areas may cause inadequate or impaired adaptive function resulting in pathological phenotypes (Steffen, Hedges & Matheson, 2022). Neurocognitive domains implicated in CP populations involve social and emotion processing, therefore it is understandable that their perturbed activity may produce behaviours that are highly risky, highly rewarding but yet highly damaging to themselves, others and social norms (Hyde et al., 2013).

The processing of emotionally salient stimuli is essential to being able to adapt to our social world effectively. For CP populations, there is increasing behavioural and neuroimaging data that suggest this group presents with deficits regarding the processing of both positive and negative socio-emotional stimuli. Emotional facial expressions are often used to investigate social cognition and emotion processing (for example, acute threat response). Negative stimuli such as fearful and angry faces are associated with threat (Mancini, Falciati, Maioli & Mirabella, 2020), sad faces are associated with distress (Blair et al., 2018) and happy faces with positive social stimuli. As an emotional cue, facial expressions impart rapid and critical value-based information to the observer based on another individual's reaction to the preceding stimuli (Blair, 2003; Fridlund, 1992). Thus, this information enables modulation of on-going behaviour through social referencing: if the observer's value of a stimulus is based on the elicitation of another's distress or fear, related to their own experience of this emotion, it is considered bad and therefore should be avoided (Blair et al., 2018; Klinnert et al., 1987). The use of facial expressions as social stimuli within neuroimaging studies is extensive and key neural regions that facilitate this process amongst typically developing (TD) populations have been identified (Fusar-Poli et al., 2009). The amygdala, fusiform gyrus and superior temporal cortex are involved in processing facial stimuli regardless of what affect is displayed. However, the anterior insula is particularly responsive to disgust and anger expressions whereas the amygdala has been shown to be sensitive to happy, fearful and sad expressions but not angry (Fusar-Poli et al., 2009). If emotion processing is compromised amongst CP groups, there may be abnormal functioning in the neural regions outlined above.

Acute Threat Response

One key neurocognitive domain of functioning associated with CP is the acute threat response system: an evolutionary survival system dedicated to the detection and response to dangerous and aversive stimuli in the environment. It involves internal physiological changes and adaptive behaviours (e.g. fight, flight or freeze response) that are gradated in relation to proximity of threatening stimuli: the more proximal the threat, the greater the activity and likelihood of aggression will be shown in response (LeDoux, 2015; Blanchard et al., 1977). Generally, youths with CP have reported reduced threat responsiveness in comparison to controls via reduced amygdala, ventral medial prefrontal cortex (vmPFC) and anterior cingulate cortex (ACC) responses to threatening stimuli (Hwang et al., 2016; Stadler et al., 2007; Sterzer et al., 2005).

The amygdala plays a critical function in regulating arousal and emotion through its role in connecting subcortical and cortical structures, this is considered crucial for developmental processes like emotional learning (Hyde et al., 2013; Whalen & Phelps, 2009). More specifically, the amygdala is hypothesised to play a central role in emotional reactivity to threat: the greater the perceived threat, the greater the activation. Interestingly, CP youths with low CU traits (CPCU-) have generally been found to demonstrate amygdala hyper-activation and increased likelihood of reactive aggression in response to threat or social provocation in comparison to peers with elevated CU traits (CPCU+) and TD controls (Blair & Zhang, 2020; Blair et al., 2018; Blair, 2016; Hyde et al., 2013; Viding et al., 2012; Dotterer et al., 2020; Crowe & Blair, 2008; Sebastian et al., 2014; White et al., 2016b). Conversely amygdala hypo-activation has been associated with increased CU traits and decreased empathy as well as connectivity between the amygdala-ventral anterior cingulate cortex (Ewbank et al., 2018; Jones et al., 2009; Lozier et al., 2014; Marsh et al., 2008; Viding et al., 2012; White et al., 2012; Blair & Zhang, 2020; Blair et al., 2018; Blair, 2016; Hyde et al., 2013). However, a recent meta-analysis of youth and adult populations who present with anti-social behaviours did not observe atypical amygdala activation however did observe an inverse relationship with its activation and CU traits (Dugré et al., 2020). Interestingly, hyper-activation of the amygdala amongst CPCU+ youths has also been observed but this has been associated with historical exposure to trauma (Meffert et al., 2018) therefore highlighting the detrimental developmental effect of childhood maltreatment on threat processing (Blair & Zhang, 2020; Fanti et al., 2020). These findings suggest that the presence of CU traits represents a divergence of threat processing.

Neural regions that typically act in an inhibitory fashion in regard to threat reactivity have also been observed to react atypically in response to stimuli. The bilateral anterior insula, an area associated with empathic concern, interoception and behavioural adjustment (Decety et al., 2009; Mutschler et al., 2013; Fairchild et al., 2019; Clark et al., 2008) has been observed to have both a smaller grey matter volume (GMV) and be hypo-active amongst CP youths compared to TD peers in response to threat (Dugré et al., 2020; Noordermeer et al., 2016; Menks et al., 2021). The ACC, a subcortical region associated with the regulation of emotional behaviour as well as response conflict and error monitoring (Bush et al., 2000), has demonstrated functional impairment amongst youths with CP (Gavita, Capris, Bolno & David, 2012). The dorsolateral prefrontal cortex (dlPFC), an area associated with control and regulation of valence of emotional experiences, and vmPFC, an area associated with information integration and extinction of arousal caused by emotional stimuli, have also been observed to be hypo-activated in CP populations (Nejati et al., 2021; Dugré et al., 2020; Etkin et al., 2015; Hartley & Phelps, 2010; Aupperle Robin & Martin, 2010; Menks et al., 2021; Noordermeer et al., 2016). The ventrolateral PFC (vlPFC), an area associated with response modulation in relation to emotion processing (Strum et al., 2016), has been found to have reduced GMV in CP populations (Fairchild et al., 2018). Therefore,

functionally connected regions important for threat detection, emotional resonance, information integration, error monitoring and emotional regulation are atypical in CP populations.

Social Cognition

Social cognition research amongst youths with CP has consistently identified important behavioural and neural atypicalities. Defined as any behaviour associated with interactions with others, social cognition relies upon skills and abilities such as perspective-taking and self-reflection (Schurz et al., 2014; Molenberghs et al., 2016), episodic memory (Vargha-Khadem et al., 1997; Tulving & Markowitsch, 1998; Spreng & Mar, 2012) and executive functioning. Social cognitions are considered imperative to providing valence-based information regarding objects/actions in one's environment, key for adaptive predictions, and therefore likely acts as a modulating influence of current behaviour (Blair et al., 2018; Meffert et al., 2014; Schoenbaum & Roesch, 2005; Aron, Robbins & Poldrack, 2004; Ochsner & Gross, 2005; Sakagami & Pan, 2007).

Empathic ability, emotional resonance, facial processing and distress cue processing are positively associated with amygdala and insula activity (Decety et al., 2009; Mutschler et al., 2013; Fairchild et al., 2019) however these regions are also underpinned by reduced GMV amongst youths with CP (Rogers & De Brito, 2015; Zhang et al., 2018; 2020). CP youths in general present with difficulties with affective empathy and facial expression processing, regardless of what emotion is presented, in association with an under reactive amygdala and insula compared to TD peers (Sebastian et al., 2012; von Polier et al., 2020; Hwang et al., 2016; Sakai et al., 2017; Klaowijk et al., 2016). The amygdala and its interaction with regions of the prefrontal cortex, e.g. vmPFC, are considered key to the process of valence-based decision making as it is sensitive to the expression of prediction errors and subsequent social learning (Meffert et al., 2015; Schoenbaum & Roesch, 2005). Amygdala recruitment and amygdala-ventromedial connectivity is atypical within CD populations in response to social stimuli, especially hypoactive amongst CPCU+ populations (Aghajani et al., 2017; Marsh et al., 2011; 2008), which is reflected in their associated deficits of expression recognition especially for fearful, sad and happy expressions (Blair et al., 2001; Stevens et al., 2001) pervading across vocal tones (Blair et al., 2005; Stevens et al., 2001) and body postures (Muñoz, 2009). The level of dysfunction in social cognition positively relates to level of CU traits and increased risk of proactive/instrumental aggression (Lozier et al., 2014, Thornton et al., 2013; Viding et al., 2012; White et al., 2012). Poor perception of and emotional resonance with aversive social cues, such as the distress of others, has been shown to disrupt subsequent stimulus-reinforcement learning and development of care-based morality in youth with CP (Harenski et al., 2014; Blair et al., 2018).

Dysfunction in both the acute threat response and social cognition systems involves much overlap between neural regions, most notably the amygdala, insula and medial PFC (mPFC), and are arguably part of an interrelated brain network for social communication and social processes (Fonagy & Luyten, 2018). Dysfunction in acute threat response and social cognition, specifically for affective empathy tasks such as processing distress cues, possibly represent opposite perturbations of the same neural region (Blair et al., 2018); decreased responding of the amygdala and anterior insula is associated with CU traits, poorer empathy ability and proactive aggression, whereas increased responding of specifically the amygdala is associated to heightened threat reactivity and reactive aggression. This activity likely co-occurs with other neural regions, particularly the vmPFC during valence information processing, thereby subsequently interacting with other neurocognitive mechanisms like cognitive empathy, response selection and reinforcement-based decision making as well as emotional regulation (Harenski et al., 2014; Blair et al., 2018). The neural systems outlined in this paper are interrelated and often compromised resulting in the specific syndromes that are associated with CP (Blair et al., 2018). Often non-specific risk factors such as childhood maltreatment, harsh parenting and SES may contribute

toward the heterogeneity of these systems through the process of multifinality and equifinality and require further examination (Viding & McCrory, 2020).

Study Aims

This study aimed to further investigate the neural basis of emotion processing, specifically acute threat response and social cognition, in children with CPCU+, in contrast to CPCU- and TD children who were matched for intellectual ability, SES and age. It sought to investigate in particular brain regions that have previously been associated with threat reactivity, empathic ability and inhibitory processes (amygdala, insula and mPFC) through the integration of interoceptive and exteroceptive information to inform adaptive predictions. To realise this aim, the study used a gender recognition task that presented angry, sad and happy facial expressions as emotion stimuli targeting threat, negative/distress and positive emotion processes respectively. It was reasoned that brain regions activated in response to these stimuli would adequately represent the core activations of an emotion processing neural network needed for an effective empathic response.

Based on the previous research discussed above, there were multiple hypotheses for this analysis:

- H1: The combined CP groups will demonstrate different neural responses to the TD group across each facial expression but more specifically negative emotions (sad and angry).
- H2: CPCU+ participants will demonstrate a hypoactivation of neural regions compared to TD group across each facial expression. More specifically, hypo-activation of the amygdala in the CPCU+ group compared to TD and CPCU- groups will be displayed in response to angry faces.
- H3: CPCU- will demonstrate a hyperactivation of neural regions, especially the amygdala, in comparison to TD and CPCU+ groups specifically for angry faces.
- H4: CPCU+ and CPCU- groups will both demonstrate a hypoactivation of the amygdala, insula and mPFC in response to sad and happy faces compared to the TD group.

Based on issues of multifinality and equifinality, exploratory analyses of demographic data will be completed, and any significant findings will be investigated using post hoc tests and discussed in reference to their potential influence on findings.

Methods

Sampling, experimental design and data collection was completed by Sethi and colleagues (2018).

Participants

A community sample of adolescent boys, 11-16 years, were recruited via newspaper advertisements, specialist provision and mainstream schools. For those families that expressed an interest in participating, informed consent was gained and screening questionnaires were administered to both parents and teachers. The screening measures provided demographic information for match controlling purposes (i.e. parent-defined ethnicity, SES, and handedness); information about previous psychiatric or neurological diagnoses; an overall screen for psychopathology; dimensional assessment of CU traits; and a provision of a research diagnosis of current conduct problems.

The measures were selected due to their association with a clinical diagnosis of conduct disorder (Sprafkin & Gadow, 1998). All measures were scored by taking the highest rating from either parent or teacher questionnaire (Piacentini et al., 1992). Current conduct disorder symptomology was assessed using the Child and Adolescent Symptom Inventory-4R (CASI-4R) Conduct Disorder (CASI-CD) subscale (Gadow & Sprakfin, 2009). The Inventory of Callous-Unemotional Traits (ICU) was used to assess CU

traits (Essau et al., 2006). Inclusion within the conduct problem group required that the CASI-CD scale score met the severity cut-off for either the teacher or parent versions (teacher report: cut-off = 3+ [aged 10-12], 4+ [aged 12-14], and 6+ [aged 15-16]; parent report: cut-off = 4+ [aged 10–12] and 3+ [aged 12–16]). Inclusion in the typically developing (TD) group required scores on both measures to be in the normal range, and in the non-clinical range for total difficulties on the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997).

Exclusion criteria for all groups included a previous diagnosis of psychotic or neurological disorder, or current psychiatric medication. Common comorbidities for CP (substance/alcohol abuse, generalised anxiety disorder [GAD], ADHD & depression) were not used as exclusion criteria in order to recruit a representative group of boys with CP. However current parent-reported symptom counts were collected so that their association with findings could be assessed systematically.

Following screening information, 83 participants participated in the fMRI scanning session. Participants were provided with a description of the study that focused on the gender identification task, information regarding emotion processing was omitted. Informed written consent was gained from all participants and their parents. All aspects of the study were approved by University College London Research Ethics Committee (Project ID number: BUCNI-BBK-16-002) and work was conducted in accordance with the Declaration of Helsinki.

One participant (CP) could not tolerate the scanner environment and withdrew from the study before collection of task data. Of the remaining sample that completed scanning (56 CP participants, 26 TD participants), data from three participants (2 CP, 1 TD) were excluded due to poor registration and image artefacts. The remaining participants in the CP group were then assigned to CPCU+ and CPCU- groups based on a median split of their ICU scores. Questionnaire and demographic data for participants are summarised in Table 1.

Psychometric and Questionnaire Measures

During the experimental session, participants completed the Alcohol Use Disorder Identification Test (Babor et al., 2001), the Drug Use Disorder Identification Test (Berman et al., 2005) and the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) whilst parents completed the full CASI-4R (Sprafin & Gadow, 1998). Additional questionnaires were collected including the Childhood Trauma questionnaire (CTQ; Pennebaker & Susman, 1988) child version as a measure of childhood maltreatment; the Alabama Parenting Questionnaire (APQ; Frick, 1991) parent version as measure regarding specific parenting techniques; and the Family Assessment Device (FAD; Epstein, Baldwin & Bishop, 1983) as a measure of general family functioning. Depression, anxiety and ADHD symptoms were collected as part of the SDQ for between-group comparisons. SES was determined as a computation of the primary care givers education and occupation with adjustments for caregivers unable to work due to extraneous circumstances e.g. poor health.

Experimental Task

The fMRI paradigm was a gender recognition task. The tasked used Eckman's (Ekman & Friesen, 1976) photos of three males and three females who displayed happy, sad and angry facial expressions. Specific emotional facial expressions from a single category, e.g. angry, were shown in series of six before showing another series of facial expressions of a different emotion, e.g. sad, and then the last before a rest period. This represents one experimental block and there were six experimental blocks in total. The gender of photos was counter balanced across conditions and the order of emotions within experimental blocks were pseudo-randomised and determined by one of three selected run lists. These lists limited the amount of consecutive repetitions of any one emotion.

Participants were initially presented with the task instructions (duration = 2000ms), followed by a cue cross (duration = 750ms) that alerted the participant that a photo was about to be presented. Next, they viewed a female or male face with a happy, sad or angry facial expression. The duration of the visual stimuli presentation was 2250ms. During this time, participants indicated what gender the person in the photo was (male/female) using a button box. Subsequently, the same facial expression but different person in the photo was shown following the same process a further five times. Following this, the next experimental series of facial expressions was shown. After the three series of facial expressions were shown (18 stimuli in total), a rest period was given (duration = 18000ms) resulting in the total experimental block lasting 72000ms. A further five experimental blocks were displayed with counterbalanced displays of stimuli resulting in a total task duration of 7min 2850ms.

The experimental task was administered using Cogent 2000 (Cogent 2000, Functional Imaging Lab/Institute of Cognitive Neuroscience, UCL, UK). Visual stimuli were displayed on a projector screen in the MRI room.

Scanning

A 5.5-minute three dimensional T1-weighted structural scan and multi-slice T2*-weighted echo planar volumes with blood-oxygen level-dependent contrast was acquired using a Siemens Avanto 1.5 MRI scanner (Siemens Medical, Erlangen, Germany) using a 32-channel birdcage head coil. the echo planar imaging sequence was modified to reduce dropout in the amygdala and orbitofrontal cortex (Weiskopf et al., 2006). Acquisition parameters were as follows: 42 2-mm slices acquired in an ascending trajectory with a 1-mm gap (voxel size = 2 x 2 x 2 mm); TE = 50 ms; slice repetition time = 87 msec, TR = 2300msec; slice tilt 25° ± 5° (TC); flip angle = 90°; field of view = 192 mm; phase oversampling = 12%. A single run was used to acquire 199 volumes of functional data. Normalised pre-scan images were used in analyses.

fMRI Pre-processing

Neuroimaging analyses were conducted using Statistical Parametric Mapping software (SPM version 12; Wellcome Trust Centre for Neuroimaging, UK). For each participant, EPI volumes were realigned to their mean. Then anatomical and EPI images were co-registered using the T1-weighted and mean EPI weighted volumes. The T1 weighted volumes were then segmented to use the resulting deformation fields to normalise subjects' EPI volumes to the MNI template. EPI volumes were resampled to 2 mm3, before being smoothed with a Gaussian Full-Width Half-Maximum kernel of 8mm3. Volumes with abnormal 1^{st} level analysis results were then reviewed manually for excessive motion and rotation artefacts. One participant was excluded due to excessive artefacts.

fMRI Analysis

Statistical parametric mapping is a voxel-based approach that employs classical inference to provide commentary on functionally specialised brain anatomy and responses. Individual conditions ('anger', 'sad', 'happy') were entered into the first level model as regressors of interest and convolved with the haemodynamic response function and its temporal derivative. The trial onset for each participant was coded as the first presentation of the visual stimuli. A high pass filter of 128Hz was used on all data.

Second level analyses of data required individual contrasts to be derived specifically to examine the effects of each emotion on the individual participant. Whole brain analyses were then conducted to determine if neural activation for general emotion processing differed across all experimental groups. This was first achieved by comparing neural activation in response to all emotions of CP boys to TD boys and then subsequently splitting the CP group into CPCU+ and CPCU- groups for further comparisons. Further whole brain analyses then compared the combined CP groups and TD group relative to each

emotion (angry, sad, happy) before then completing additional comparative analyses for TDs, CPCU+ and CPCU- groups relative to one another within each emotional condition.

Based on previous research, the amygdala, insula and mPFC were identified as being key areas involved in acute threat response and social cognition (Dugré et al., 2020; Blair & Zhang, 2020; Sebastian et al., 2012; von Polier et al., 2020; Hwang et al., 2016; Sakai et al., 2017; Klaowijk et al., 2016). Region of interest (ROI) analyses were conducted for each area that compared neural activation between TD, CPCU+ and CPCU- groups in response to the three different emotions using a series of t-tests.

All investigations were first conducted at a conservative threshold of $p<0.05$ FWE corrected but no clusters survived this stringent correction. Therefore, the threshold was lowered to the uncorrected significance threshold of 0.001. All investigations that used a more lenient threshold are indicated and should be interpreted with caution.

Results

Demographics

For a summary of individual factors regarding demographic and psychometric comparisons, please see Table 1.1. Age, handedness and SES were matched across groups. Measures of conduct problems and callous-unemotional traits were significantly elevated in both CPCU+ and CPCU- groups in comparison to TDs, with CPCU+ reporting significantly higher scores than the CPCU- group. Furthermore, both CP groups scored significantly higher than TDs on a measure of hyperactivity (CASI-4R) and did not differ significantly from each other. Although no difference was observed between TD and CPCU- groups, the CPCU+ group reported significantly higher levels of peer problems and less prosocial behaviours in comparison to TD and CPCU- groups. Although no difference was observed between TD and CPCU- groups, the CPCU+ group scored significantly higher on measures of major depression and generalised anxiety compared to the TD group and the CPCU- group. There was no significant difference between any of the groups for alcohol use. The CPCU+ group demonstrated significantly higher drug used compared to TD but not the CPCU- group, however, interestingly, the CPCU- did not differ significantly to the TD group.

In regard to CP risk factors, please see table 1.2. A listwise deletion method was used for between group comparison for the CTQ (n = 4), APQ (n = 3) and FAD (n = 5) due to missing data. There were no significant differences in participant reported childhood trauma or abuse. There was no difference in parental involvement and positive parenting across the groups. The TD group demonstrated significantly better parental monitoring by caregivers in comparison to both CP groups who did not differ from each other. The TD group also experienced significantly less corporal punishment than the CPCU- group however not the CPCU+ group, the CP groups were not significantly different. The CPCU+ group had more severe experiences regarding inconsistent disciplining and emotional neglect than the TD group but did not differ from the CPCU- group.

Table 1

Participant demographic and questionnaire data.

		Mean (SD)						
	Measure	TD	CPCU-	CPCU+	ANOVA	TD vs CPCU-	TD vs CPCU+	CPCU- vs CPCU+
1.1. Individual factors								
	Age	14.39 (1.46)	14.74 (1.623)	14,886 (1.23)	$F(2, 76) = 0.794$, $p = 0.456$	-	-	-
	IQ	91.68 (11.38)	92.52 (12.40)	87.12 (10.98)	$F(2, 76) = 1.678$, $p = 0.194$	-	-	-
	Handedness (L/R)	2/23	4/23	1/26	$\times 2 (2, 79) = 2.097$, $p = 0.350$	-	-	-
	Callous unemotional traits	24.96 (5.52)	34.29 (6.12)	49.22 (5.33)	$F(2, 76) = 121.700$, $p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
	Conduct problems (CASI)	0.08 (0.28)	3.33 (2.02)	6.89 (2.82)	$F(2, 76) = 72.880$, $p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
	Conduct problems (SDQ)	1.00 (1.04)	4.37 (2.29)	7.67 (1.59)	$F(2, 76) = 96.054$, $p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
	Peer problems (SDQ)	2.00 (1.96)	2.93 (1.88)	4.33 (2.51)	$F(2, 76) = 7.88$, $p < 0.01$	$p = 0.269$	$p < 0.001$	$p = 0.047$
	Prosocial behaviours (SDQ)	6.44 (2.04)	5.82 (2.24)	3.89 (1.60)	$F(2, 76) = 11.93$, $p < 0.01$	$p = 0.493$	$p < 0.001$	$p = 0.002$
	Hyperactivity/Impulsivity (CASI)	3.44 (4,68)	9.90 (6.49)	13.41 (6.68)	$F(2, 76) = 18.01$, $p < 0.01$	$p < 0.001$	$p < 0.001$	$p = 0.090$
	Generalised Anxiety (CASI)	4.24 (4.16)	6.70 (3.86)	10.34 (4.76)	$F(2, 76) = 13.43$, $p < 0.01$	$p = 0.102$	$p < 0.001$	$p = 0.007$
	Major Depression (CASI)	3.44 (2.50)	5.78 (4.21)	8.59 (4.97)	$F(2, 76) = 10.51$, $p < 0.01$	$p = 0.102$	$p < 0.001$	$p = 0.034$
	AUDIT	0.52 (1.56)	2.45 (3.86)	1.84 (3.04)	$F(2, 76) = 2.790$, $p = 0.068$	-	-	-
	DUDIT	0.16 (0.80)	2.04 (3.32)	4.04 (6.53)	$F(2, 76) = 5.269$, $p = 0.007$	$p = 0.263$	$p = 0.005$	$p = 0.211$
1.2 Risk factors								
	Emotional abuse (CTQ)	6.49 (0.53)	7.47 (0.52)	7.21 (0.54)	$F(2, 72) = 1.121$, $p = 0.332$	-	-	-
	Physical abuse (CTQ)	5.28 (0.42)	6.23 (0.41)	6.46 (0.42)	$F(2, 72) = 2.253$, $p = 0.112$	-	-	-
	Sexual abuse (CTQ)	5 (0.01)	5.12 (0.01)	5.00 (0.01)	$F(2, 72) = 0.489$, $p = 0.615$	-	-	-
	Physical neglect (CTQ)	9.28 (0.34)	9.56 (0.33)	9.54 (0.35)	$F(2, 72) = 0.211$, $p = 0.811$	-	-	-
	Parental involvement (APQ)	27.68 (0.98)	26.72 (0.98)	26.15 (0.96)	$F(2, 73) = 0.628$, $p = 0.537$	-	-	-
	Positive parenting (APQ)	18.56 (0.63)	18.92 (0.63)	18.73 (0.62)	$F(2, 73) = 0.082$, $p = 0.921$	-	-	-
	Poor monitoring (APQ)	8.60 (1.12)	12.48 (1.12)	13.58 (1.10)	$F(2, 73) = 5.479$, $p = 0.006$	$p = 0.044$	$p = 0.006$	$p = 0.766$
	Emotional neglect (CTQ)	7.18 (2.27)	8.24 (3.60)	10.01 (4.32)	$F(2, 71) = 3.856$, $p = 0.026$	$p = 0.553$	$p = 0.020$	$p = 0.204$
	Corporal punish (APQ)	2.00 (0.32)	3.32 (0.32)	2.65 (0.32)	$F(2, 73) = 4.199$, $p = 0.019$	$p = 0.014$	$p = 0.321$	$p = 0.308$
	Inconsistent discipline (APQ)	7.92 (0.67)	9.96 (0.67)	10.46 (0.65)	$F(2, 73) = 4.143$, $p = 0.020$	$p = 0.083$	$p = 0.021$	$p = 0.853$
	General family functioning (FAD)	3.24 (0.09)	3.16 (0.09)	3.04 (0.09)	$F(2, 71) = 1.161$, $p = 0.319$	-	-	-
	SES	2.853 (1.27)	3.07 (1.17)	3.44 (1.11)	$F(2, 76) = 1.623$, $p = 0.204$	-	-	-

Whole Brain

General Emotion Processing

Whole brain comparisons between the combined CP groups and the TD group for general emotion processing revealed multiple significant clusters. The CP group demonstrated significantly higher activation in the right dorsolateral PFC (dlPFC; figure 1.a) and significant decreased activation in the left and right amygdala compared to the TD group (figure 1.b)

Furthermore, when the CPCU- group was compared to the TD group regarding general emotion processing, the CP group demonstrated increased activation in the right fusiform gyrus and left hippocampus and decreased activation in the right hypothalamus. The CPCU+ was significantly decreased in the left amygdala compared to TD group and there was no difference between CPCU+ and CPCU- groups for general processing of emotions.

At a more stringent threshold of 0.05 FWE corrected, no suprathreshold clusters remained.

Specific Emotions

Anger

During whole brain analyses that investigated neural activity in response to angry faces in comparison to sad and happy faces, multiple effects were observed. The combined CP group demonstrated significantly lower activation in the right insula and left dlPFC compared to the TD group (figure 1.c)

The CPCU- groups compared to TD group demonstrated significantly decreased activation in the bilateral middle temporal gyrus, right globus pallis, right insula, right and left dlPFC, right precentral gyrus, left inferior temporal gyrus par triangularis and left putamen. A significantly increased activation was observed in the right posterior segment of the dlPFC for the CPCU+ group compared to CPCU- group.

At a more stringent threshold of 0.05 FWE corrected, no suprathreshold clusters remained.

Sad

During whole brain analyses that investigated neural activity in response to sad faces compared to happy and angry faces, multiple effects were observed. When comparing the combined CP groups to TD group, the CP group demonstrated increased activation in the right amygdala and left hypothalamus (figure 1.d)

An increase in activation was also observed in the right dmPFC and right rostral ACC when comparing CPCU- to TD boys. The CPCU+ demonstrated a decrease in activation in the right inferior temporal gyrus compared to the TD group. The CPCU+ group also demonstrated decreased activation when compared to CPCU- group in the left dlPFC, right inferior frontal gyrus pars triangularis, right cerebellum and left inferior frontal gyrus orbitalis/ventrolateral PFC (vlPFC).

At a more stringent threshold of 0.05 FWE corrected, no suprathreshold clusters remained.

Happy

During whole brain analyses that investigated neural activity in response to happy faces compared to sad and angry faces, there was a significant increase in activation in the right superior frontal

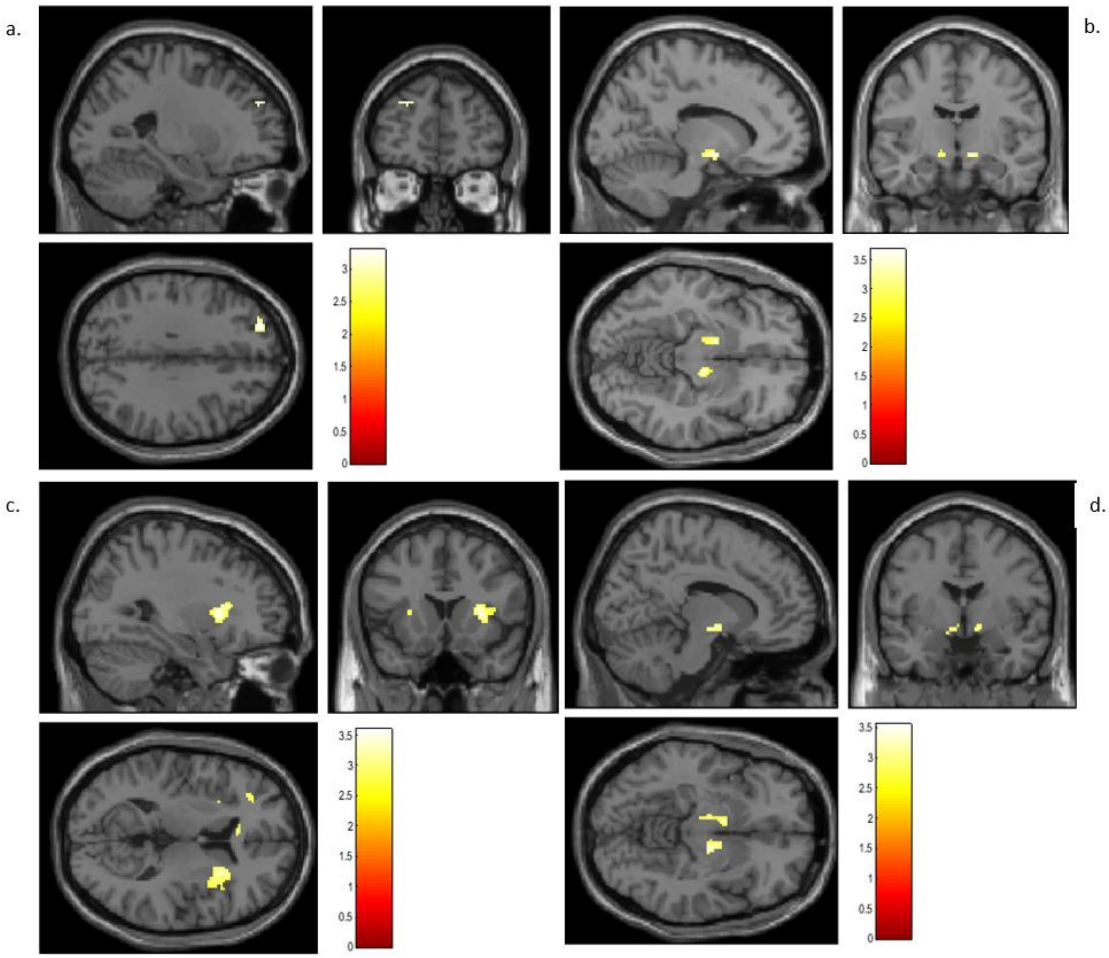
gyrus/vmPFC and significant decrease in the right posterior middle temporal gyrus in the CPCU+ group compared to CPCU- group.

At a more stringent threshold of $p<0.05$ FWE corrected, no suprathreshold clusters remained.

For a summary of activation please see table 2.

Figure 1.

The Combined CP group Compared to TD Group for All Emotions, Angry and Sad Faces.



Note. All activity presented in this figure is at a suprathreshold of 0.005. a. demonstrates the increased activation observed in the dlPFC amongst CP boys compared to TD boys regarding responses to all emotions. b. demonstrates increased activation of the amygdala in response to all emotions in the TD group compared to CP boys. c. demonstrates the increase activity in the insula amongst TD boys compared to CP boys in response to angry faces compared to happy or sad. d. demonstrates increased activation of the amygdala and hypothalamus amongst CP boys compared to TD boys in response to sad faces compared to happy or sad.

Table 2

Between group differences in brain activation

Contrast	All emotions					Angry > happy and sad					Sad > happy & angry					Happy > angry & sad				
	x, y, z	Region	K	*T*	*p*	*x, y, z*	Region	K	*T*	*p*	*x, y, z*	Region	K	*T*	*p*	*x, y, z*	Region	K	*T*	*p*
CP > TD	-24, 48, 32	SFG/dlPFC	2	3.30	= 0.001	-	-	-	-	-	14, -12. -8	r. amygdala	12	3.41	< 0.001	-	-	-	-	-
											-8, -2, -10	l. hypothal	5	3.27	= 0.001					
TD> CP	-12 -4 -8	l. amygdala	13	3.67	< 0.001	30, 14, 6	r. insula	37	3.30	< 0.001	-	-	-	-	-	-	-	-	-	-
	14 -12 -8	r. amygdala	9	3.49	< 0.001	-32, 38, 12	l.MFG/dlPFC	4	3.25	= 0.001										
CPCU- > TD	36, -52, -16	r. FFG	5	3.47	= 0.001	-	-	-	-	-	-14, 48, 8	l. SFG/dmPFC	12	3.80	< 0.001	-	-	-	-	-
	-16, 32, 24	l.hippo	2	3.31	= 0.001						4, 32, 2	r. ros ACC	5	3.50	< 0.001					
TD > CPCU-	10, -2, -8	r. hypothal.	2	3.24	= 0.001	62, 0, -16	r. MTG	19	3.99	< 0.001	-	-	-	-	-	-	-	-	-	-
						8, 6, -4	r. glob. Pal	5	3.41	< 0.001										
						30, 12, 8	r. insula	13	3.40	< 0.001										
						20, 42, 26	r. SFG/dlPFC	11	3.39	< 0.001										
						46, 4, 8	r. PrCG	3	3.29	= 0.001										
						-42, -12, -20	l. ITG	4	3.28	= 0.001										
						-46, -22, -12	l. MTG	7	3.27	= 0.001										
						-14, 58, -10	l. SFG/vmPFC	3	3.15	= 0.001										
						-32, 36, 10	l. IFG tri/vlPFC	1	3.13	= 0.001										
						-26, 14, 8	l. insula	1	3.11	= 0.001										
CPCU+ > TD	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
TD > CPCU+	-14, -8, -6	l. amygdala	9	3.65	< 0.001	-	-	-	-	-	60, -28, -18	r. ITG	16	3.81	< 0.001	-	-	-	-	-
CPCU + > CPCU-	-	-	-	-	-	42, 26, 30	r. MFG/dlPFC	5	3.54	< 0.001	-	-	-	-	-	16, 60. 2	r. SFG/vmPFC	2	3.28	= 0.001
CPCU- > CPCU+	-	-	-	-	-	-	-	-		-	-42, 56, 10	l. MFG/dlPFC	33	3.60	< 0.001	68, -44, -2	r. pos. MTG	1	3.27	= 0.001
											48, 26, 4	r. IFG tri. /vlPFC	19	3.50	< 0.001	66, -46, -4	r. pos. MTG	1	3.27	= 0.001
											60, -24, -18	r.ITG	4	3.40	= 0.001					
											32, -42, -34	r. cerebellum	1	3.35	= 0.001					
											-34, 36, 6	l. IFG orb/vlPFC	2	3.32	= 0.001					

Note. All results are at a threshold of p<0.001, uncorrected. r = right, l = left, dlPFC = dorsolateral prefrontal cortex, FFG = Fusiform gyrus, hippo = hippocampus, hypothal = hypothalamus, MFG = middle frontal gyrus, glob. pal =globus pallidus MTG = middle temporal gyrus, PrCG = precentral gyrus, vmPFC = ventromedial prefrontal cortex, vlPFC = ventrolateral prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, IFG = inferior temporal gyrus, ITG = inferior temporal gyrus, tri = trangularis, orb = orbitalis, pos = posterior, glob. pal =globus pallidus.

ROI Analyses

ROI analyses focused on the amygdala, insula and mPFC. Please see Table 3. for a full summary of significant effects at a suprathreshold of p = 0.001. At a more stringent threshold of 0.05 FWE corrected, no suprathreshold clusters remained.

General Emotion Processing

No voxels survived amygdala and insula ROI analyses of general emotion processing at a threshold of p = 0.001, however, one cluster was significantly increased in the mPFC in the combined CP groups compared to TD group.

Angry

During ROI analyses that investigated activity in response to angry faces in comparison to sad and happy faces, no voxels survived a suprathreshold of 0.001 using the amygdala mask in any group comparison (?). Significant decreases in activation were observed in the insula region when the combined CP group was compared to TD group and in the CPCU- group compared to TD group. There was also a significant decrease in activation in the mPFC for the CPCU- group compared to TD group.

Sad

During ROI analyses that investigated activity in response to sad faces in comparison to angry and happy faces, no voxels survived the use of insula and amygdala masks across all comparisons. A significant increase in activation for the CPCU- group compared to CPCU+ group was observed in the mPFC.

Happy

During ROI analyses that investigated neural activity in response to happy faces compared to sad and angry faces, there were no differences in neural activity in the amygdala, insula and mPFC when comparing CD to TD groups, CPCU- to TD groups, and CPCU+ to TD group.

Table 3

Between Group Differences in Brain Activation Using ROI Masks Across Conditions and Areas at a Suprathreshold of $p = 0.001$

	Region	All emotions				Angry				Sad			
		x, y, z	K	*T*	*p*	x, y, z	K	*T*	*p*	x, y, z	K	*T*	*p*
CP>TD	mPFC	-24, 48, 32	2	3.30	= 0 .001	-	-	-	-	-	-	-	-
TD>CP	Insula	-	-	-	-	32, 14, 4	6	3.38	= 0.001	-	-	-	-
TD>CPCU-	Insula	-	-	-	-	44, 4, 6	1	3.31	= 0.001		-	-	-
	mPFC	-	-	-	-	22, 40, 26	2	3.41	= 0.001		-	-	-
CPCU- >CPCU+	mPFC	-	-	-	-	-	-	-	-	-42, 56, 10	28	3.60	< 0.001

Note. mPFC = medial prefrontal cortex.

Discussion

This study used a gender recognition task with threatening (angry), distressing (sad) and positive (happy) facial expressions to investigate the neural differences in emotion processing, specifically acute threat response and social cognition, in TD, CPCU- and CPCU+ boys. There was a particular interest in investigating areas typically sensitive to threat reactivity (amygdala), emotional resonance (insula) and valence related decision making (mPFC) and their relation to level of CU traits. The sample was matched in age, IQ and SES but also demonstrated no difference in general family functioning, positive parenting and self-reported experiences of childhood trauma.

The findings provided support for the first hypothesis that boys with CP have specific perturbations in neural responses to negative emotion stimuli when compared to TD peers. CP boys demonstrated hypo-activation of the right insula and dlPFC in response to angry faces and interestingly, hyperactivity of the amygdala and hypothalamus in response to sad faces but no difference in the processing of happy faces. When comparing all CP boys to TD peers across all emotions, CPs presented with hypo-activation in the amygdala and hyper-activation in the dlPFC. These results support previous research that posit that the amygdala plays a central role in emotion processing regardless of emotion and that it is under responsive in CP populations (Hyde et al.,2016; Dugré et al., 2020; Sebastian et al., 2012; von Polier et al., 2020; Hwang et al., 2016; Sakai et al., 2017; Klaowijk et al., 2016). In response to angry faces, the hypo-activation of the insula amongst CP boys, an area suggested to be particularly sensitive to angry faces (Fusar-Poli et al., 2009), suggests a lack of resonance and use of interoceptive information with this emotion and coupled with reduced activity in the dlPFC, a region dedicated to emotion based decision making, supports the hypothesis that these regions are interrelated (Blair et al., 2018; Hyde et al., 2013; Cardinal et al., 2002; Fuster, 2001; Stein et al., 2007). Interestingly the hyper-activation of the amygdala and hypothalamus, a region considered key to the expression of emotions and highly correlated to amygdala activity (Kropotov, 2009; Blair et al., 2018), in response to sad faces amongst CP boys perhaps suggests an intact perception of sadness but a lack of corresponding interoceptive information and inhibitory activity without the accompanied observation of increased activity in the insula and PFC regions.

Investigations revealed evidence to partly support the second hypothesis. In comparison to TD peers, CPCU+ boys demonstrated reduced activation in the left amygdala when responses were compared across all emotions and in the right inferior temporal gyrus in response to sad faces but interestingly there was no significant difference in response to angry faces. The hypo-activation of the amygdala supports previous findings that CU traits are inversely related to amygdala responses to emotional stimuli (Aghajani et al., 2017; Marsh et al., 2011; 2008; Blair et al., 2001; Stevens et al., 2001) however this does not explain the lack of difference exhibited in response to threatening stimuli. The hypo-activation of the right inferior temporal gyrus (ITG), an area that has been positively correlated with ability to recognise negative faces (Rosen et al., 2005), supports previous findings that associated CPCU+ populations with reduced activity in the ITG activity (Herpertz et al., 2008). These findings also support wider literature that has identified a reduced amygdala response to distress cues, e.g. sad faces, with regions that are reciprocally activated subsequently being under activated e.g. temporal cortices (Blair et al., 2018; Passamonti et al., 2010; Marsh et al., 2008). This suggests CPCU+ boys have poor perception of exteroceptive inputs and emotional resonance via interoceptive inputs regarding aversive social cues, for example the distress of others. This poor integration of information may impact the ability to produce adaptive predictions subsequently disrupting stimulus-reinforcement learning and development of care-based morality in youth with conduct problems (Harenski et al., 2014; Blair et al., 2018).

The CPCU- group demonstrated increased emotional activity in comparison to TD peers in areas typically observed to be activated during facial processing tasks; the hippocampus (Lopatina et al., 2018), superior temporal gyrus and fusiform gyrus (Fusar-Poli et al., 2009). In response to sad faces, the CPCU- group demonstrated increased activation in the right rostral ACC, an area considered key to regulating emotional behaviour (Bush et al., 2000) and highly correlated with amygdala responses (Bissiere, 2008), as well as the dorsomedial PFC, an area associated with response conflict (Blair et al., 2006). These findings possibly suggest an overactivated emotion regulation system in response to negative emotion stimuli which has historically been linked to behaviours designed to avoid negative affect e.g. substance misuse (Blanchard et al., 2019). Previous research suggested that CU traits represented a divergence in regard to how youths with CP process emotion and that behaviourally, CPCU- youths had a stronger association with reactive aggression (Blair & Zhang, 2020; Blair et al., 2018; Blair, 2016; Hyde et al., 2013; Viding et al., 2012; Dotterer et al., 2020; Crowe & Blair, 2008; Sebastian et al., 2014; White et al., 2016), however, CPCU- youths in this study demonstrated reduced activation compared to TD controls in response to angry faces in regions considered vital for interoceptive processing and empathic ability (insula; Decety et al., 2009; Mutschler et al., 2013; Fairchild et al., 2019), emotion regulation (ventrolateral PFC: Strum et al., 2016), extinction of arousal/integration of information streams (vmPFC; Nejati et al., 2021) and other areas typically associated with motor functions (globus pallidus, middle temporal gyrus and precentral gyrus) with no hyper-activation of the amygdala. These findings do not support the hypothesis that CPCU- boys demonstrate neural hyper-activation to threat but may be the result of biased sampling; although possessing less CU traits than the CPCU+ group and higher than TD peers, the CPCU- group demonstrated characteristics more closely aligned with the presence of CU traits hence the lack of hyperactivity in response to angry faces. This demonstrates the weakness of investigating and treating CU as a dichotomy, present or absent, in favour of its conceptualisation as a continuum of impairment (Viding & McCrory, 2020).

Although not hypothesised, there were specific differences in emotion processing observed between the CPCU+ and CPCU- group. In response to angry faces the CPCU+ group demonstrated more activation in dlPFC, an area associated with control and regulation of valence of emotional experiences (Nejati et al., 2021). This finding is contrary to a recent meta-analysis that found hypo-activation in the dlPFC in response to angry faces amongst CPCU+ youths however the same study found hyper-activation in the dlPFC in response to social cognition tasks (Dugré et al., 2020). This possibly suggests that angry faces failed to activate the acute threat response system and instead engaged regions more closely aligned with social cognition. In response to sad faces, a distress cue, the CPCU- group engaged regions considered central to the processing of negative facial stimuli, the cerebellum (Ferrucci et al., 2012), as well as other regions key to emotional resonance (IFG orbitalis/insula), emotion regulation (vlPFC; Strum et al., 2016) and the control and regulation of valence of emotional experiences (dlPFC). The CPCU+ group demonstrated significantly less activity in these regions which reflects previous findings that positively correlate severity of CU traits and deficits in expression recognition, particularly those related to distress (Blair et al., 2001; Stevens et al., 2001; Dawel et al., 2012; Marsh & Blair, 2008). The lack of activity amongst CPCU+ boys particularly for distress cues possibly reflect a lack of recognition and poorer resonance thereby producing less negative valence during the formation of adaptive predictions. Without this deterrent, it is unsurprising that neural hypo-activation has previously been linked to increased likelihood of proactive antisocial behaviours compared to peers (Blair et al., 2018).

During ROI analyses, there was no observation of hyperactivation or hypoactivation of the amygdala for the CPCU+ group and CPCU- group respectively in comparison to TD peers in response to threat stimuli (angry faces) despite observing divergent amygdala activation in the whole brain analyses. Interestingly the combined CP group, and later CPCU- group, demonstrated reduced activation in the

insula in comparison to TD controls in response to angry stimuli however there was no significant difference in insula activity between CPCU+ and CPCU- groups. This possibly suggests that CU traits modulate insula responses amongst boys with conduct problems; low CU traits are more related to hypo-activation of the insula in response to threat stimuli. Using the mPFC mask, the TD group demonstrated greater activation in this area than the CPCU- group in response to angry faces, whereas the CPCU- group demonstrate increased activation in this area compared to CPCU+ in response to sad faces. This suggests that boys with high CU traits fail to engage inhibitory neural regions associated with response conflict and valence-based processing in response to sad faces whereas CPCU- boys fail to engage these regions in response to angry faces. This reflects a recent meta-analysis finding that the dmPFC was hypoactive in adults with psychopathy (Poeppl et al., 2018). Without this inhibition it is possible that CPCU- boys, because of a maladaptive acute threat response system, may react aggressively when confronted with threat whereas CPCU+ boys may not receive inhibitory, valence-based information in response to distress cues resulting in poor morality-based decision making and proactive aggression.

Considering that interactions, or combinations, of risk factors may produce variation and heterogeneity amongst CP presentations, this study's design controlled for certain risk factors by matching participants on age, IQ, SES and although not intended, general family functioning and child reported childhood trauma. Furthermore, the three groups also represented an increasing severity and significantly different level of CU traits and therefore could be considered a quasi-continuum. Consequently, this enabled greater examination of risk factors associated with specific parenting approaches in relation to CU traits. In support of CPCU+ youths presenting with a more severe course of anti-social behaviour (Fonagy & Luyten, 2018), the CPCU+ group presented with the most severe peer problems, lack of prosocial behaviours as well as general psychopathology (generalised anxiety & major depression) independent of comorbidities such as hyperactivity, drug and alcohol misuse. General CP pathology seemed to be linked to a home environment characterised by a lack of monitoring that may be a reflection of a lack of appropriate social learning as parental involvement was not different across the groups. Child maltreatment or corporal punishment was linked specifically the CPCU- group and although not identified in this sample's neuroimaging findings, maltreatment has been linked to increased psychophysiological processes and amygdala responses linked to the acute threat response (hypothalamic-pituitary-adrenal axis; Fairchild et al., 2019; Hein & Monk, 2018). Furthermore, neglect and inconsistent discipline was linked to higher levels of CU traits and likely reflects a lack of secure attachment and in turn a current and historical lack of opportunity to develop interpersonal skills, most notably mentalization, and epistemic trust (Fonagy & Luyten, 2018). A non-normative developmental environment characterised by neglect, low parental warmth and childhood maltreatment is likely to produce long-term neural adaptations relating to social communication and social learning that historically aided survival possibly via a dose-dependent process.

This study had some limitations that should be considered when interpreting results. Although the head-coil was adapted to prevent dropout in subcortical and PFC regions, the relative weakness of the magnetic field strength of the 1.5T scanner may have resulted in a lack of sensitivity for voxel detection particularly in the subcortical amygdala region (Krasnow et al., 2003). Second, this study was designed to have a low attention load in the scanner environment and angry faces were considered threat related stimuli. However, fMRI tasks thought adequate to identify biomarkers of neural activity have been found to have poor test-retest reliability (Elliot et al., 2020) and there is considerable variation in individuals emotion representation and interpretation (Carlisi et al., 2021). Therefore, it may be that angry faces were misread or did not constitute a sufficient level of proximal threat necessary to activate the acute threat response needed to observe neural differences in the hypothesised regions among the groups. Future studies may rectify this with additional measures of resonance, e.g. skin conductance

and sinus arrhythmia (Munoz, Frick, Kimonis, & Aucoin, 2008; de Wied et al., 2012). Third, in light of a comprehensive meta-analysis into RDoC domains in anti-social populations (Dugré et al., 2020), this study focused on a representative, homogenous sample matched on various measures of individual difference allowing the study of CU traits and the influence of specific parental techniques more accurately, however, this study would benefit from additional indicators of difference or experiences of adversity preferably from the participants developmental history and alternative fields of understanding e.g. genetics. This would help explain the observed diversity in this population and contribute toward the development of a more holistic explanatory model of CP.

Clinical implications

Typically, depending on the developmental stage of the child, recommended interventions move through behavioural, psychosocial and then multi-component treatments with increasing costs and reduced effectiveness (Fairchild et al., 2019). Over time as genetic and neural predispositions interact with the ecological system without intervention, maladaptive neurocognitive development becomes more entrenched/less malleable whilst social capital needed to intervene increasingly thins because of anti-social behaviour (McCrory, 2020). Developing an alternative preventative intervention for those most at risk of developing CP that focuses on a safe home environment, appropriate parenting techniques and the maintenance of the child's social network, as the most important and effective buffer of stress and source of prosocial learning (McCrory, 2020), could offset the more chronic and severe trajectories of anti-social behaviour early in childhood. The following clinical implications and hypotheses for preventative and clinical interventions are based on the current findings however they require further formal systematic testing, ethical considerations and administrative integration.

Firstly, regarding issues related to multifinality, using resources to identify, target and optimise risk factors related to CP would be an apt use of resources. This intervention could be recorded and shared by allied health, social and administrative professionals (Soneson et al., 2022). Secondly, at varying points of child development, indexing of social functioning of at-risk children using the implicated RDoC domains relating to CP could be used to identify neurocognitive maladaptation and derive a unique neurocognitive profile for the individual. Professionals may then question what social scenarios the child may have a latent vulnerability to navigate and use that information to guide an effective model of preventative intervention for that child. Although systematic research is required to identify what that intervention would be, it is likely the most effective would involve being a coordinated systemic intervention across multiple levels of the social network focused primarily on the development of and maintenance of epistemic trust. This would enable the individual to learn from the world more broadly through a series of interpersonal relationships thereby providing the best chance possible for recalibration of domain-level neurocognitive alterations following childhood adversity (McCrory, 2020; Fonagy & Luyten, 2018).

Conclusion

Overall, this study demonstrated that emotion processing, specifically related to threat and distress cues, amongst boys with CP is perturbed and underpinned by dysfunction in a range of interrelated neural regions associated with social communication and threat response. These regions included those associated with interoceptive inputs/emotional resonance (insula), exteroceptive inputs/empathic ability (amygdala) and adaptive predictions and response (dlPFC; vmPFC; vlPFC) as well as supporting neural networks associated with face processing and motor function. These findings support theories regarding an interrelated, diverse and dispersed neural network regarding emotion processing dysfunction rather than localised region specific dysfunction. The hypothesised divergent effect of CU traits on neural and behavioural phenotypes was not found. However, the more severe presentation of

CU traits were associated with increasingly hypo-activity in regions key for social communication and emotion processing, worse functional impairment and severity of child maltreatment via parental practices. This provides support to the understanding of current CP as the result of neural adaptation that once permitted short-term advantage in response to pathological environmental influences but now produce disadvantage through their miscalibration to normative settings and barring of corrective social learning. Clinical practice must focus on preventative practices that focus on maximising the potential for social learning and repairing epistemic trust at various levels of the ecological system whilst research must continue to build a holistic explanatory model for CP.

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Part 3: Critical Appraisal

Introduction

This paper aims to critically reflect and appraise upon the thesis project I have completed as part of my Doctorate in Clinical Psychology. I want this critical reflection to capture the transition in my own understanding and study of youths with conduct problems as well as thoughts in regard to how theory and research translates into clinical practice by focusing on a current shift in research and clinical practice. I will focus on two different models of explanation of neural function, how each influences the practices of categorisation, research implications and clinical teaching and practices. I will also summarise the narratives that this translates to young people and their stakeholders at various levels of the ecological system for both approaches.

Diagnosed, Damaged and Determined

One of the most influential theories used to conceptualise neural function and guide research has been the triune brain theory (Cory, 2000; MacLean, 1990; MacLean, 1998; Panksepp, Moskal, Panksepp & Kroes, 2002; Steffen, Hedges & Matheson, 2022). This theory had taken an evolutionary perspective regard brain development that is based upon the influence of environmental pressures and then how those factors impacted our neural, cognitive and behavioural responses, especially to stress. It posited that three brain regions developed separately and function relatively independently of each other: the basal ganglia and brainstem which were devoted to movement and basic life functions, the limbic system which was related to emotional responses and more complex life e.g. reptiles, and the cortex which was associated with cognition and executive functions most readily associated with humans (Steffen, Hedges & Matheson, 2022). This theory suggests that the human brain has evolved from basic behaviours needed to sustain life, to those driven by emotional responses in response to challenges or threats, and then behaviours based on reason, logic and planning. Recent therapeutic approaches, such as Compassion Focused Therapy (Gilbert, 2010), utilise this theory and conceptualise distress and emotional dysregulation as the result of conflict between “old brain” and “new brain” interactions.

Although there are multiple issues with this theory, the main problem in relation to neuropsychological research and conceptualisations of human distress and emotion dysregulation is that function between brain regions is not independent (Heimer & Van Hoesen, 2006). In response to emotions, neural activity presents in the amygdala and the limbic system alongside activity in the cortex/cortical regions and brain stem (LeDoux, 2012). Although neural regions may highly correlated with specific functions, they are also known to have more than one function and the distinction between functions is not definitive, e.g. emotion and cognition are interrelated functions working concertedly (Steffen, Hedges & Matheson, 2022). Furthermore, using fear research as an example, there is no fear brain circuit that remains dormant and then turns on during a fear response. Rather, there is a certain level of neural activity that influences the processing of incoming information and then it is relative and needs based activity in different brain networks that determines the response. Fear response is not one region simply responding to stimulus but rather an interrelated series of systems that has a pre-stimulus status that then receives, processes and responds depending on current need. This is a complex and highly variable process that does not map on well to singular functional regions and the nominal or ordinal based forms of categorisation that bore from it.

Currently the field of clinical psychology, both in research and academia, is heavily invested in the use of the Diagnostic Statistical Manual (American Psychiatric Association, 2013). Similar to its original intended purpose, the DSM currently is used to establish funding for research and services alike and

uses a series of symptoms to define a syndrome or disorder. If you have enough symptoms to exceed the consensually agreed threshold you may be given a diagnosis. Although this approach has led to the proliferation of bodies of research and support, it is currently marred by a number of issues (Bredstorm, 2017). The most notable in relation to this research, is the abject failure of this approach to capture nuance and heterogeneity within the population of youths who present with conduct problems (Viding & McCrory, 2020). Two children may reach threshold for conduct disorder with completely different presentations and may have completely different developmental pathways that contributed toward the behaviours presentation. The introduction of further subcategories and labels adds confusion due to arbitrary clinical cut-offs, instability and lack of predictive power they pose (Hyde et al., 2013). Furthermore, this approach firmly locates the location of the difficulty within the individual whilst ignoring the pressures, stressors and mechanisms that has resulted in this specific behaviour in this specific moment in their life (Viding & McCrory, 2020). Ultimately this reductionist approach negatively impacts the progression of both research and clinician practice.

The fundamental problems with behavioural categorisation is reflected in research. When researchers attempt to identify mechanisms that are related to the specific presentation, e.g. conduct disorder, they select individuals based on their behavioural symptoms and then try to find the underlying cause. There is a clear circulatory of argument here (Viding & McCrory, 2020). Furthermore, children with conduct disorder are not alike and if we appreciate there are different developmental pathways and expressions of conduct problems, it is much more likely there are conduct disorders rather than one conduct disorder. Prior attempts to stratify the population further in order to capture their heterogeneity and then identify unique causal mechanisms is problematic as the more you control for the various risk factors and common comorbidities the less representative/more homogeneous the sample becomes (Lewinn et al., 2017). As a result, the findings hold less ecological validity and therefore less relevance.

Although anecdotal, my clinical experience working in services with young people who present with conduct disorders/externalising behaviours is that very little of the neuropsychological findings are used in clinical practice and the diagnostic guidance as described by the DSM-5 is almost entirely ignored by clinicians due to their lack of clinical utility however clinical guidelines regarding interventions are adhered to. Services are set up to work with children who already are experiencing the problematic behaviours and negative outcomes associated with conduct problems making the intervention much more reactive in nature and more difficult to produce meaningful change (Fairchild et al., 2019). There is very little specific interventions designed for conduct disorder, or its subtypes, but rather expensive multi-system level interventions that focus on working with various stakeholders who may already hold deterministic views on the child. Meanwhile, there is increasingly less resources available to the young person as a result of their stress sensitivity and social thinning alongside a stigmatising and fixed diagnosis (McCrory, 2020).

Whether the label be conduct disorder, attention deficit and hyperactivity disorder, oppositional defiant disorder or substance misuse disorder, labels are at best a lazy form of clinical formulation and at worst damaging to the individual and systems that interact with them. Beyond clinical diagnoses, research produces equivalent terms such as risk factors (Fairchild et al., 2019), adverse childhood experiences (ACEs; Boullier & Blair, 2018) and biomarkers (Dugré et al., 2020) that are associated with conduct problems. These labels are then communicated to the child, family and school often creating a false, deterministic and biologically based causation and maintenance narrative that is located within the individual. This stands in contrast to the NICE guidelines for best practice that recommend a multi-systemic approach (Fairchild et al., 2019). This can contribute toward feelings of being stuck at various levels of the ecological system and a lack of creative thinking to deal with this complex issue. Lastly,

labels and diagnoses can often be a guise for attributing causation away from those with power to those without it.

Adaptation, Diversity and Dimensions

In contrast to the triune theory, the adaptive brain theory states that the primary function of the brain is to make adaptive models of the external and internal environmental context for the individual through interdependent neural networks (Steffen, Hedges & Matheson, 2022). Specifically it works by integrating interoceptive and exteroceptive information to produce predictions of future needs required to maintain homeostasis and initiate allostasis as needed. This adaptive process involves the production and comparison of predictions based on incoming information and then adjustment to minimise error in favour of adaption and health. This process is a direct result of the evolutionary context our brains developed within that was characterised by limited resources, frequent dangers and a need to balance internal and external needs. Conceptualising the brain as adapted to factors that disrupt homeostasis can highlight how the brain may adapt to adverse experiences in order to cope in a non-normative environment (McCrory, 2020). Importantly, when this adaptation is exposed to a normative environment they may present as maladaptive and represent a latent vulnerability for psychopathologies, e.g. conduct problems (McCrory, 2020; Steffen, Hedges & Matheson, 2022). Improper function of specific brain regions and their associated regions is more the result of a survival adaption than damage. This model better captures heterogeneity observed in this population, based on the principle that adversity produces diversity, but more importantly provides the possibility of future adaptation.

Considering that the brain is a product of adaptation to both internal and external influences, this enables the consideration and inclusion of factors that force adaptations that exist beyond the individual within conceptualisations. It has been suggested that the organised interactive system of unique genetic risk factors, environmental risk factors and protective factors, over and above those related to general psychopathology, produce variation in the level of impact that specific risk indicators pose; otherwise known as multifinality (Cicchetti & Rogosch, 1996; Hankin et al., 2011). In contrast, multiple and different risk indicator combinations can influence the formation of the same behaviour across different individuals; an example of equifinality (Hyde et al., 2013). These convolving factors may cause brain adaptations that then infer a latent vulnerability to psychopathology depending on the context, e.g. conduct problems, and produce differential susceptibility between individuals based on this complex interaction between internal and external influences across the ecological system. As adaptation changes over time, we also know that the influence of certain factors also changes therefore it is important to identify, understand and track difference for those at-risk individuals over time.

As diversity of experience and developmental pathways has greater consideration in this more contemporary theory, forms of tracking the neural adaptation over time is necessary in order to capture the nuance. The Research Doman Criteria (RDoC) uses a dimensional system that integrates psychology, biology and neuroscientific findings based on observable behaviour (Dobrushina et al., 2020). Observed variation within neurocognitive domains of functioning, defined by RDoC and with specific guidance on research paradigms (although not completely agreed), has the potential to capture heterogeneity more effectively and provide a more precise and unique profile of the individual. The RDoC is limited in scope in that it only focuses on the individual rather than how that that variation then interacts with the social world around them. Ultimately, the dimensional approach of the RDoC is imperfect but it is a more precise and useful tool in identifying individual difference than the behaviour-based classification system.

The adaptive brain theory, understandings of latent vulnerability and the RDoC collectively are three mechanisms within neuro and developmental psychology that are promoting diversity when thinking in terms of the child who presents in services and within research. Considering the known range of risk factors and increasing evidence relating to how they can influence development (Fairchild et al., 2019), the field would benefit from greater collaboration between different scientific disciplines in order to progress the current explanatory model (Hyde et al., 2013;, Puzzo et al., 2016; Wertz et al., 2019; Nelson & Foell, 2018; Viding & McCrory, 2020). For example, there has been recent research into the gene x environment interaction which has provided very useful insights into which children are more at risk than others (Caspi et al., 2002). This invitation and inclusion of diversity will then have a subsequent effect on the intervention diversity that can be deployed to adapt the child to their current social context.

Even with the inclusion of the RDoC into the current research landscape, there is much to be desired in regard to optimising change and approaches to research moving forward. Although there are some areas within conduct disorder research that have general support or converging consensus in observed deficits, e.g. emotion processing, there is consistently variation in outcomes and performance. Appreciating that adversity creates diversity invites the complexity into findings rather than viewing this as negative and something that muddies the fields general understanding. With this in mind, it is important to gather a systematic and in-depth developmental history alongside data from agreed and established sets of research paradigms and psychometric measures. The most optimal data would be those that can provide dimensional, precise and reliable understandings of deficits in cognitive/affective functioning to match neuroimaging data (Viding & McCrory, 2020). This history and measures can then be correlated with domain function which is contrasted with the current insensitive psychometric tools available for conduct disorder. Much of the paradigms at present are adapted from experimental psychology and neuroscience, and are developed to minimise between group variation and optimise group effects rather than sensitively and reliably capture individual difference (Elliott et al., 2020). At present these factors limit the ability to relate functional neuroimaging, experimental data and behavioural and clinical outcomes.

As greater focus is paid to diversity to the individual, I believe the field would benefit from greater variation in research methodologies. The current between group analyses are beneficial when comparing distinct groups of people however due to the heterogeneity previously described this is unlikely to be ascertained amongst youths with conduct problems. Furthermore, the approach used in my research used aggregated data across many individuals both in regard to neuroimaging data and psychometric measures and this inherently masks inter-individual variability (Fisher, 2015; Forand, Huibers. & DeRubeis, 2017). It is this inter-individual variability and its relation to multifinality and equifinality factors that is of most clinical use.

Alternative approaches to studying this heterogeneity can take multiple forms. Case studies are recognised as a research design that provides the greatest ecological validity through its in-depth review of new or unclear phenomena whilst 'retaining the holistic and meaningful characteristics of real-life events' (Phelan, 2011). Single case studies help inform practice by highlighting issues in clinical practice in order to develop alternative therapeutic responses (Stickley & Phillip, 2005). As evidence grows regarding neurocognitive deficits, increasingly component studies that administer variations of established treatments or new innovations can be studied in relation to these deficits thereby being central to bridging evidence-based psychosocial interventions and clinical practice (Institute of Medicine, 2015). Another option is to consider mediation studies that look to establish relationships between mediators and outcome at a single time-point, or multiple points to establish directional influence of mediators. If we can find mediators that contribute toward a mechanism of change, defined as factors that explain how interventions translate into events that lead to outcome (Kazdin,

2007), they can identify consistencies across multiple interventions or groups, clarify connections between treatment and outcomes, identify conditions relative to change and give critical information about whom the treatment will aid (Kazdin, 2007). Perhaps most excitingly, moderator studies are being argued as the most adaptive research approach for tailoring practice to the specific and unique characteristics of clients as it produces greater predictors of outcome than specific interventions (Zuroff et al., 2000; Fisher & Boswell, 2016: Kazdin, 2008). Characteristics are captured as moderators which are defined as variables with different levels, e.g. social cognition function, that influences direction between an independent and dependent variable (Kazdin, 2007). Single moderator research has produced inconsistent effects on outcomes (Bohart & Wade, 2013) but if we collapse several weak moderators to produce one strong moderator we can predict differential outcome across treatments (Wallace, Frank, & Kraemer, 2013). The research methodologies we use need to be as diverse as the populations we see.

With advancements in theory, categorisation and future research methodologies, I expect to see corresponding advances in clinical interventions. I expect that interventions will become more preventative and personalised based on greater understanding of the interactive nature of different risk factors and performance on dimensional measures of individuality like the RDoC. This would be in line with wider changes in healthcare such as the introduction of genome sequencing. I also suspect issues relating to comorbidities will reduce as we begin to conceptualise difficulties through a transdiagnostic lens which will be more aligned to changes in wider clinical practice within mental health services through the introduction of transdiagnostic systems like the Power Threat Meaning Framework (Johnstone & Boyle, 2018) however I think this would be bolstered through systematic categorisation and tracking of neurocognitive functioning over time. This could be optimised through the use of age appropriate tasks based on established research paradigms, e.g. neuroeconomic games like the Ultimatum Game, and in various communities across the country. Similar to primary care services, this database could be used for longitudinal and cross-sectional research. With greater personalisation, I expect interventions to become more modular and targeted at specific areas of deficits, with specific capacity for ecological stakeholders to work collaboratively with health care providers through intervention feedback. Ultimately the field and ecological systems that benefit from it will be more fluid and variable in the future and therefore provide greater hope for positive change and adaptation. Inducing this change will require a concerted effort and will of leadership however there seems to be ground swell toward this approach.

This alternative and future approach should also have a profound impact on the narratives our young people experience based on compassion rather than blame. Their behaviours will be viewed more as adaptive as opposed to damaged. It provides more possibility for change based on future adaption and will be more able to capture weaknesses but also their strengths. These narratives could percolate through the wider ecological system and I hope galvanise new creative approaches that are focused on addressing the social injustices that these young people and families are currently exposed to.

Conclusion

Neuroimaging research in relation to youths with conduct problems is extremely exciting however extraordinarily complex. The research field is undergoing a transition away from understandings focused on independent and functionally specialised regions that are damaged toward an interdependent network of neural regions that demonstrate functional pluralism and are the result of adaptions to the internal and external factors. This change is mirrored in movements away from behavioural categorisation toward categorisation based on dimensional domains of functioning and is much better placed to capture the heterogeneity of youths with conduct problems. This is shifting the location of problems from the child toward a more representative but complex interplay of

individualised factors and external experiences that combined to produce a latent vulnerability to conduct problems. This provides very exciting possibilities in regard to research and clinical practice. Specifically for neuroimaging and conduct disorders, this more contemporary understanding of heterogeneity in the population translates to an understandable and even necessary diversity in outcomes. In regard to my own clinical practice with children, families and other stake holders, I look forward to holding a position of hope and variability in future trajectories away from labels that are scientifically meaningless and reductionist yet hold high personal meaning. I recognise that services and stakeholders are invested in this the older system and therefore long-term, concerted effort will be required to facilitate the translation of research to clinical practice.

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