A mechanistic investigation of neuro-cognitive and experiential factors associated with psychiatric vulnerability following childhood maltreatment

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Signed Declaration

I, Mattia Indi Gerin confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

London, September 2018
Abstract

Childhood maltreatment is one of the most potent predictors of future psychopathology. While progress has been made in documenting a number of cognitive and neurobiological mechanisms that might underpin this association, investigations to date have focused on a limited number of domains. The primary aim of this thesis was, therefore, to advance and extend our understanding of the neurocognitive domains that may contribute to increased psychiatric vulnerability following childhood maltreatment.

In the first empirical chapter (Chapter Two), using a model-based fMRI analytic approach and a probabilistic passive-avoidance task, we showed that childhood maltreatment is associated with recalibrations in the neurocomputational processes that underlie reinforcement-based decision-making. These are expected-value representation and prediction-error signalling to reward and punishment cues. In Chapter Three we showed that altered brain responses to threat (in the form of heightened amygdala reactivity) and an increased propensity to experience stressful life events predict future internalising symptoms among individuals with a history of maltreatment. In Chapter Four we found that experiencing maltreatment during childhood is associated with difficulties in imagining specific and detailed possible future scenarios (‘Overgeneral Episodic Future Thinking’). In Chapter Five, a history of maltreatment was linked to deficits in interpersonal problem solving skills – this, in turn, contributed to the association between maltreatment and poor mental health.

The findings of this thesis increase our understanding of how childhood maltreatment impacts neurobiological, cognitive and social functioning in ways that may potentiate subsequent risk of psychopathology. In the longer term, it is hoped that these findings will contribute to the development of screening tools and novel preventative clinical approaches that could foster a resilient outcome for those maltreated individuals at greatest psychiatric vulnerability.
Impact Statement

Childhood maltreatment is a global problem affecting high-, middle- and low-income countries. Despite great efforts, prevention programmes have achieved only a modest reduction in the incidence of abuse and neglect. A large minority of individuals are still exposed to maltreatment during childhood. This represents a major public health concern because maltreatment is a profound developmental insult with long-lasting repercussions in several areas of functioning, including reduced economic productivity, life satisfaction, educational attainment and physical health. Moreover, epidemiological studies indicate that a history of childhood maltreatment may be the single most potent predictor of psychiatric disorder across the lifespan. We still lack, however, a comprehensive understanding regarding how maltreatment shapes neurobiological and cognitive development and what neurocognitive mechanisms underlie the association between maltreatment exposure and subsequent psychopathology.

This thesis – together with extant findings regarding the impact of childhood maltreatment on cognitive, neurobiological and psychosocial development – contributes to the emerging knowledge regarding the neurocognitive recalibrations that follow the experience of abuse and neglect. Such an understanding is essential to refine current clinical and legal definitions of maltreatment, promote sound policy-making and inform the development of more targeted mechanistic models of intervention and prevention. Currently, there is little or no provision for those individuals with maltreatment histories who, despite being at increased risk, do not yet present with a frank psychiatric disorder. The studies presented in this thesis, therefore, by providing further evidence that neurocognitive vulnerabilities are present before the emergence of manifest psychiatric symptoms, contribute to the rationale and motivation to pursue more explicit preventative clinical approaches. They also underscore the importance of creating screening tools that facilitate the identification of those individuals with maltreatment histories who are at increased psychiatric vulnerability.

The work of this thesis has allowed us to increase our understanding of the developmental sequelae of abuse and neglect and, from a conceptual and methodological point of view, it might impact future research in three main ways. First, it highlights the importance of pursuing more longitudinal investigations aimed at examining the prognostic value of maltreatment-related neurocognitive recalibration – the paucity of prospective research has undoubtedly hindered progress.
in the field. Second, it helps demonstrates the viability of novel approaches to
behavioural and neuroimaging data-analysis, including neurocomputational model-
based methods and propensity-score-matching. Third, it shows that it is essential that
we begin to examine alterations in a wider range of cognitive domains and
neurobiological systems that, despite having a well-established link with a number of
psychiatric conditions, have received little if any attention in the childhood
maltreatment literature.

To conclude, the research presented in this thesis is likely to have a number of
implications. In particular, it can inform future studies as well as motivate the
development of preventative clinical approaches for maltreated individuals at
increased psychiatric risk.
Acknowledgments

This doctoral thesis, like any scientific endeavour, is the outcome of a collective effort. First and foremost, I would like to express my heartfelt gratitude to my supervisors, Eamon and Essi. Without their support, guidance, wisdom and inspiring insights, this thesis would have not been possible. I would like to thank also all the members of the lab, the Developmental Risk and Resilience Unit, for their expertise, teamwork-spirit and generosity. A special mention goes to Ruth, my PhD office buddy, Georgia, Molly and Iakovina, for their tireless work, Vanessa, Arjun and Ferdinand, for their mentorship. It has also been a fantastic opportunity to collaborate with Jean-Baptiste. What I have learned from him will accompany me throughout my career.

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AAL = Automated Anatomical Labelling
ABM = Autobiographical Memory
ACC = Anterior Cingulate Cortex
ADHD = Attention Deficit Hyperactivity Disorder
AMT = Autobiographical Memory Test
BOLD = Blood-Oxygen-Level-Dependent
CaRFAX = Capture, Rumination, Functional avoidance, Executive Control
CT = Control Group (i.e. NMT group after PSM)
CTQ = Childhood Trauma Questionnaire
dACC = Dorsal Anterior Cingulate Cortex
dlPFC = Dorso-lateral Prefrontal Cortex
DNS = Duke Neurogenetics Study
DS = Dorsal Striatum
EEG = Electroencephalography
EFT = Episodic Future thinking
EPI = Echo Planar Imaging
EV = Expected Value
fMRI = Functional Magnetic Resonance Imaging
FoV = Field of View
fROI = Functional Defined Region of Interest
FWW = FamilyWise Error
IQ = Intelligence Quotient
IQR = Inter-Quartile Range
LESS = Life Events Scale for Students
lOFC = Lateral Orbito-frontal Cortex
lPC = Lateral Parietal Cortex
lPFC = Lateral Prefrontal Cortex
M-AMT = Modified Autobiographical Memory Test
MASQ = Mood and Anxiety Symptoms Questionnaire
MCC = Mid-Cingulate Cortex
MNI = Montreal Neurological Institute
mOFC = Medial Orbito-frontal Cortex
mPFC = Medial Prefrontal Cortex
MRI = Magnetic Resonance Imaging
Glossary of Abbreviations

MT = Maltreated Group
NMT = Non-Maltreated Group
OEFT = Overgeneral Episodic Future Thinking
OFC = Orbito-frontal Cortex
OGM = Overgeneral Autobiographical Memory
PE = Prediction Error
PET = Positron Emission Tomography
PTSD = Post Traumatic Stress Disorder
PFC = Prefrontal Cortex
PSM = Propensity Score Matching
RM = Relevant Means
ROI = Region of Interest
SEM = Structural Equation Modelling
SES = Socio Economic Status
SDQ = Strength and Difficulties Questionnaires
SDQ Total = Strength and Difficulties Questionnaires Total Score
SDQ Peer = Strength and Difficulties Questionnaires Peer-Problems Subscale
TSCC = Trauma Symptoms Checklist for Children
vACC = Ventral Anterior Cingulate Cortex
vlPFC = Ventro-lateral Prefrontal Cortex
VS = Ventral Striatum
WASI-IQ = Wechsler Abbreviated Scales of Intelligence
WHO = World Health Organisation
**List of Publications**


CHAPTER 1 – General Introduction: Childhood Maltreatment, Latent Vulnerability and The Brain

Childhood maltreatment is a profound developmental insult and one of the most potent predictors of negative outcomes across the lifespan, including reduced economic productivity, educational attainment, life satisfaction and physical health (R. Gilbert, Widom, et al., 2009; Herrenkohl, Klika, Herrenkohl, Russo, & Dee, 2012; Lansford et al., 2002; Widom, Czaja, Bentley, & Johnson, 2012; Zielinski, 2009). Moreover, longitudinal and cross-sectional epidemiological studies suggest that the experience of abuse and neglect during childhood may be the single most potent predictor of poor mental health (Green et al., 2010; Kaplow & Widom, 2007; Ronald C Kessler et al., 2010; Koenen & Widom, 2009; Vachon, Krueger, Rogosch, & Cicchetti, 2015; Widom, DuMont, & Czaja, 2007).

Despite the well-established association between early maltreatment experiences and future psychopathology, we still have an imprecise understanding about the neurocognitive mechanisms underlying this association. This limits the possibility of creating screening tools that could allow us to identify those individuals at increased psychiatric vulnerability and generate preventative clinical interventions which would allow us offset risk trajectories before frank disorders emerge. In other words, a better understanding of how maltreatment impacts neurocognitive functioning has the potential to motivate and inform the development of more timely and effective treatment models.

This introductory chapter is divided into four sections. The first section outlines current definitions of childhood maltreatment, including current limitations in its operationalization and prevalence estimation. In the second section, the evidence for the long-term impact of childhood maltreatment, with particular focus on psychiatric outcomes, are examined. The third section provides a review of extant findings which indicate that childhood maltreatment has a long-lasting impact on several neurocognitive domains. Particular attention is given to the functional magnetic resonance imaging (fMRI) literature. The neuroimaging evidence is discussed within the context of the Theory of Latent Vulnerability. This framework offers a novel theoretical approach that can help us to reconceptualise, from a neurocognitive perspective, how psychiatric risk is potentiated following the experience of
maltreatment. Finally, the four empirical chapter of this thesis are outlined in reference to outstanding questions in the field of maltreatment research.
Chapter 1

1.1. Current Definitions, Measurement and Prevalence of Childhood Maltreatment

1.1.1. What is Childhood Maltreatment?

According to the World Health Organization, childhood maltreatment is defined as “all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child’s health, survival, development or dignity in the context of a relationship of responsibility, trust or power” (Butchart, Putney, Furniss, & Kahane, 2006). Moreover, childhood maltreatment has commonly been subdivided within two main types: act of commission (or threat, often referred to as child abuse) and acts of omission (or deprivation, often referred to as child neglect) (Barnett, Manly, & Cicchetti, 1993; David P. Bernstein et al., 1994, 2003; English & LONGSCAN Investigators, 1997; Leeb, Paulozzi, Melanson, Simon, & Arias, 2008; Radford et al., 2011; Sheridan & McLaughlin, 2014). Within these two main types, four main subtypes have been identified: physical abuse, sexual abuse, emotional abuse (often referred to as emotional maltreatment or psychological abuse) and neglect (often referred to as deprivation, and further subdivided as physical and emotional neglect) (Barnett et al., 1993; David P. Bernstein et al., 1994, 2003; Butchart et al., 2006; Cicchetti & Toth, 2005; Leeb et al., 2008). Moreover, witnessing domestic/intimate partner violence is increasingly recognised not only as a risk factor for childhood maltreatment, but as a subtype of its own right (although it is often categorised within the broader definition of emotional abuse).

1.1.1.1. Physical abuse. This category includes acts such as hitting, kicking, strangling, poisoning, burning, baby-shaking or other physical aggression likely to harm or cause significant damage to a child physical integrity (Leeb et al., 2008). Most physical violence is inflicted within the home with the aim of punishing. For this
reason, any form of corporal punishment is now included in the definition of physical abuse in several countries.

1.1.1.2. Emotional maltreatment. Often referred to as emotional abuse or psychological abuse, it includes acts of commission which involve communicating to children that they are worthless, inadequate, unloved or valued only insofar as they meet the needs of another person (Radford et al., 2011). These include acts such as belittling, intimidating, blaming, terrorising, isolating, degrading and restraining (without causing physical harm). Emotional abuse also includes developmentally or age inappropriate expectations (Barnett et al., 1993). These may include acts of overprotection that may prevent normal social interactions, exploration and learning as well as expectations and the imposition of tasks that are beyond the child’s capabilities and developmental stage. Witnessing domestic/intimate partner violence is also commonly defined as a form of emotional maltreatment.

1.1.1.3. Sexual abuse. According to the World Health Organization (WHO), sexual abuse includes the “involvement of a child in sexual activities that he or she does not fully comprehend, and is unable to give informed consent to, or for which the child is not developmentally prepared, or else that violated the laws or social taboos of society” (Butchart et al., 2006). These activities do not necessarily involve a high level of violence and may involve non-penetrative acts (such as kissing, rubbing, masturbation and touching outside of clothing) as well as penetration (for example oral sex or rape). The definition encompasses also non-contact activities such encouraging children to behave in sexually inappropriate ways and witness sexual activities and watch sexual images. Indeed, not only adult males, but also other children or female adults can be perpetrators of sexual abuse (Leeb et al., 2008).

1.1.1.4. Neglect. This form of maltreatment is often subdivided in emotional and physical neglect. The latter occurs when a caregiver fails to provide adequate clothing,
hygiene, shelter and nutrition (Barnett et al., 1993). A neglectful caregiver does not necessarily live in poverty, according to the World Health Organization (WHO) – physical neglect occurs when there is failure to provide resources that exist or should be available (Butchart et al., 2006). Emotional neglect occurs when a caregiver ignores a child, denies emotional responsiveness and reciprocity, and also when adequate access to mental health care is not provided. Moreover, neglect includes failure to fulfil educational needs and failure to supervise the child’s safety within and outside the home and take into account appropriate emotional and developmental needs (Barnett et al., 1993).

1.1.2. How Is Maltreatment Measured?

Some of the most common prospective/informant measures of maltreatment include the classification methods developed by Kaufmann and colleagues (Kaufman, Jones, Stieglitz, Vitulano, & Mannarino, 1994) and by Cicchetti and colleagues (Barnett et al., 1993; English & LONGSCAN Investigators, 1997). These measures usually entail the retrieval of information about the abuse and neglect from child protection agencies (and when available also from medical reports, clinical observations and parental reports). The retrieved information is then classified within the main maltreatment subtypes and scored on several dimensions, including severity, onset, duration/frequency, number of placements and also perpetrator’s identity.

The most common and best validated measure of self-reported/retrospective measure of childhood maltreatment is the Childhood Trauma Questionnaire – Short Form (CTQ-SF; David P. Bernstein et al., 1994, 2003; David P. Bernstein, Ahluvalia, Pogge, & Handelsman, 1997). This is a short 25-item standardised questionnaire which measures maltreatment severity. It organised around the five maltreatment subtypes: physical abuse, emotional abuse, sexual abuse, physical neglect and emotional neglect.
Despite a growing agreement around the general definition of maltreatment and its subtypes, only a few standardised and validated measures of maltreatment have been developed. Moreover, there are still a number of issues that remain to be addressed and that represent a significant challenge as to how we conceptualise and operationalise the diverse experiences that are encompassed under the ‘umbrella-term’ of childhood maltreatment. For instance, prospective and retrospective measures tend to be poorly correlated, and tend to capture groups of individuals who are largely non-overlapping (Newbury et al., 2018). As a result, there is no general consensus over which method or standardised tool is able to best capture the experience of maltreatment, its subtypes (emotion abuse, neglect, etc.) and its dimensions (severity, frequency, duration and age of onset).

1.1.3 How Common is Childhood Maltreatment?

1.1.3.1. Prospective/informant prevalence estimates. Conceptual differences and intrinsic methodological difficulties briefly described above, as well as heterogeneity in child protection surveillance systems across countries, means that official figures of abuse and neglect can vary greatly across studies (Fallon et al., 2010). In industrialised countries, such as the UK, Canada, and the US, about 1.5-5% of all children are referred to child protection agencies every year, with approximately 1% of children having substantiated experience of abuse and neglect (R. Gilbert, Kemp, et al., 2009; Radford et al., 2011). The rates of substantiated cumulative maltreatment are much higher – for example, in the US 12.5% of individuals have confirmed history of abuse and/or neglect (Wildeman et al., 2014).

A series of meta-analyses of world-wide prevalence indicate that less than 1% of children across the globe every year have substantiated experiences of abuse and/or neglect (Stoltenborgh, Bakermans-Kranenburg, Alink, & Van IJzendoorn, 2012; Stoltenborgh, van IJzendoorn, Euser, & Bakermans-Kranenburg, 2011; Stoltenborgh,
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Bakermans-Kranenburg, & Van Ijzendoorn, 2013). Such heterogeneity in official/prospective estimates across the globe are unlikely to reflect actual prevalence differences across countries. Rather, these may be the result of disparities in the ways that childhood maltreatment is conceptualised, monitored and reported (Fallon et al., 2010; Stoltenborgh, Bakermans-Kranenburg, Alink, & van IJzendoorn, 2015).

1.1.3.2. Retrospective/self-reported prevalence estimates. As pointed out in 1977 by Newberger, the official estimates are likely to be just the tip of the iceberg as they represent a small portion of individuals who have been detected by statutory agencies and for whom it was possible to substantiate the occurrence of abuse and neglect (Newberger, 1977). Compared to official figures, self-reported/retrospective accounts of maltreatment indicate that a much larger proportion of individuals are being exposed to abuse, neglect and domestic violence during childhood. Recent meta-analyses by Stoltenborgh and colleagues, which included hundreds of studies with an overall sample of over 9 million individuals across the world, have helped us gain a more precise estimate (Stoltenborgh et al., 2015). In particular, the researchers have found that about 12.7% of individuals reported having experienced sexual abuse during childhood (Stoltenborgh et al., 2011), 22.6% physical abuse (Stoltenborgh, Bakermans-Kranenburg, van IJzendoorn, & Alink, 2013), 36.3% emotional abuse (Stoltenborgh et al., 2012), 16.3% physical neglect and 18.4% emotional neglect (Stoltenborgh, Bakermans-Kranenburg, & Van Ijzendoorn, 2013). These world-wide estimates are largely in line with a recent study of maltreatment sub-type prevalence carried out in the UK by Radford et al. (2011). The researchers also found that 25.3% of young adults reported having experienced any form of maltreatment during childhood with 14.5% of respondent reporting severe experience of maltreatment perpetrated by a parent or a guardian. Interestingly, these UK self-reported prevalence estimates are equivalent to the afore mentioned cumulative rates of substantiated/prospective maltreatment in the US (Wildeman et al., 2014).
Despite some discrepancies in estimates across studies (for example see a review of 28 studies by Radford et al (2011)), the overall picture that is being portrayed is a similar one. That is, despite great efforts being made to reduce the incidence of abuse and neglect, still a large minority of individuals experience one or more types of maltreatment during childhood (Finkelhor, Ormrod, & Turner, 2007b, 2009; R. Gilbert, Widom, et al., 2009; Lau et al., 2005; Radford, Corral, Bradley, & Fisher, 2013).
1.2. The Long-lasting Impact of Childhood Maltreatment

1.2.1. Physical & Socio-Economic Outcomes

1.2.1.1. Economic burden. The impact of childhood maltreatment has been associated with both individuals and societal costs. At an individual level, after controlling for several confounding variables including socio-economic status, various researchers have found that the experience of childhood abuse and neglect is associated with reduced educational attainment and economic productivity (Currie & Widom, 2010; R. Gilbert, Widom, et al., 2009; Lansford et al., 2002; Thielen et al., 2016; Zielinski, 2009). At a societal level, conservative estimates indicate that in the UK the average lifetime costs of non-fatal maltreatment by a primary caregiver is approximately 89,000 pounds per individual (Conti, Morris, Melnychuk, & Pizzo, 2017). This financial burden includes social care costs, short-term health-related costs as well as costs which results from loss of economic productivity. In 2008, in the United States only, it was estimated the total economic burden of childhood maltreatment was around $124 billions, resulting from increased burden in medical care, loss of productivity, criminal justice, special education and child welfare (Fang, Brown, Florence, & Mercy, 2012).

1.2.1.2. Physical health. Abuse and neglect can lead to proximal negative health outcomes due to direct physical harm and/or malnutrition. Moreover, several prospective and retrospective studies suggest that early experiences of maltreatment can also have an impact on physical health across the lifespan. For instance, both abuse and neglect have been associated with the increased likelihood of contracting viral infections, autoimmune conditions and also cardiovascular diseases (Dube et al., 2009; Norman et al., 2012; Wegman & Stetler, 2009; Widom et al., 2012). In recent years, research have started to elucidate some of the mechanisms and precursor underlying this association. For example, a history of early abuse and neglect has been linked with
higher levels of spontaneous inflammatory/immune responses, telomere-shortening (which suggests increase cellular ageing), increased blood pressure, obesity and also a higher incidence of health-related risky behaviours (Basu, McLaughlin, Misra, & Koenen, 2017; Coimbra, Carvalho, Moretti, Mello, & Belangero, 2017; Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Danese & Tan, 2014; Tyrka et al., 2010).

1.2.2. Mental Health Outcomes

Population attributable risk-assessments indicate that parental maltreatment is likely to account for a large proportion of all psychiatric disorders onsets during childhood, adolescent and adulthood (Green et al., 2010; Ronald C Kessler et al., 2010). These include both internalizing disorders (such as anxiety and depression) and also externalizing disorders (such as conduct problems) (R. Gilbert, Widom, et al., 2009; Lansford et al., 2002). Both prospective and retrospective reports of maltreatment have been shown to be predictive of symptoms levels (Tajima, Herrenkohl, Huang, & Whitney, 2004), although the stronger association seems to be found when abuse and neglect are measured with retrospective self-reports (Newbury et al., 2018). Interestingly, this differential association does not seem to be underpinned by an increased bias in reporting maltreatment among those individuals with higher symptoms levels (Fergusson, Horwood, & Boden, 2011).

1.2.2.1. Internalising disorders. It has been estimated that about a third of all individuals who experience abuse and neglect meet criteria for mood and trauma related disorders by adulthood, even after controlling for several potentially confounding factors (J. Brown, Cohen, Johnson, & Smailes, 1999; Danese et al., 2009; Green et al., 2010; Kearney, Wechsler, Kaur, & Lemos-Miller, 2010; Widom et al., 2007). Some maladaptive outcomes, such as suicide attempts, seem to have an even higher association with early adverse experiences, with upper-bound attributable lifetime estimates of 67% (Dube et al., 2001).
From a clinical perspective, psychiatric patients with internalising disorders with a history of abuse and neglect tend to have unfavourable prognoses, exhibit earlier onsets, more chronic symptoms, greater comorbidity as well as higher relapse risks and poorer responsiveness to evidence-based interventions (Agnew-Blais & Danese, 2016; Harkness & Wildes, 2002; Hovens et al., 2010; Leverich et al., 2002; Nanni, Uher, & Danese, 2012; Post et al., 2015; Teicher & Samson, 2013). In line with this clinical evidence, different neural signatures have been linked with maltreated and non-maltreated individuals which meet diagnostic criteria for the same disorder (M. M. Grant, Cannistraci, Hollon, Gore, & Shelton, 2011; van Harmelen et al., 2013; L. Wang et al., 2014). Overall these findings suggest that, at least in the context of internalizing disorders, psychopathology may be strongly influenced by the exposure of abuse and neglect during childhood. This has led Teicher and Samson (2013) to suggest that psychiatric disorder in the context of maltreatment can be considered as an ecophenotypic subtype; that is a phenotype that has been modified so profoundly by environmental factors (in this case maltreatment) that has evolved into a distinct neurocognitive and clinical variation.

1.2.2.2. Externalising disorders. Individuals who have been abuse and neglected are also more likely of developing a range of externalizing disorders, including conduct, attentional and oppositional-defiant disorders in childhood (Green et al., 2010; Kim-Cohen et al., 2006; Radford et al., 2013). Moreover, among adult and adolescent populations, maltreated individuals have been shown to be at greater risk of developing substance abuse and antisocial personality disorder (Green et al., 2010; Ronald C Kessler et al., 2010; Kim-Cohen et al., 2006; Puettz & McCrory, 2015; Weiler & Widom, 1996). For both man and women, there is also a well-documented association between childhood maltreatment and increased risk of criminal conviction, arrest and violent behaviour during adolescence (Fang & Corso, 2007; Widom, 1989b) and adulthood (Widom, 1989a; Widom & White, 1997).
1.2.2.3. Subclinical symptoms and resilience. Even when maltreated individuals do not meet clinical thresholds for internalizing or externalizing disorders, they usually tend to show elevated symptoms levels (Cicchetti & Toth, 2005; Kearney et al., 2010; Radford et al., 2013). Moreover, growing evidence suggests that even in the absence of a psychiatric diagnosis or heightened elevated symptoms, individuals who suffered abuse and neglect, at a group level, show a series of cognitive and neurobiological alterations which may potentiate the risk of developing mental health problems in the future (McCrory, Gerin, & Viding, 2017; McCrory & Viding, 2015). Despite the robust association between childhood maltreatment and subsequent internalizing and externalizing psychopathology this association is not deterministic and, the majority of individuals who have experienced abuse and neglect have a resilient outcome (e.g. Danese et al., 2009; McGloin & Widom, 2001; Rutter, 2000)
1.3. Neurocognitive Mechanisms Linking Childhood Maltreatment and Psychopathology

Despite the well-established link between childhood maltreatment and several maladaptive outcomes, including increased psychiatric risk, we still lack precision in our mechanistic understanding of this association (McCrory, Gerin, et al., 2017; McCrory & Viding, 2015). This is in part ascribable to both inherent methodological difficulties as well as ontological factors. From an empirical perspective, individual heterogeneity in terms of severity, onset, chronicity and poly-victimisation (i.e. the degree of exposure to multiple maltreatment subtypes), means that childhood maltreatment, as discussed above, can be difficult to define and operationalise. Furthermore, it can be challenging to disentangle the impact of abuse and neglect from that of other co-occurring ecological factors and intrinsic disadvantages, such as lower socio-economic status, higher neighbourhood violence and lower executive functioning (Danese et al., 2017; Zielinski & Bradshaw, 2006).

Moreover, the current nosology within psychiatry, organised around seemingly discrete and “clearer” symptoms categories, has meant that maltreatment research was perceived as less amenable to empirical investigation (McCrory, Gerin, et al., 2017). The focus around mental health has been structured around a medical model that prioritises the investigation of manifest symptoms under the assumption that patients qualifying for the same clinical diagnostic category are comparable (McCrory, Gerin, et al., 2017). This has also led frank psychiatric disorders to receive greater emphasis, with less attention being devoted to the understanding of putative developmental and neurocognitive mechanisms that may be involved in the pathogenesis of mental health problems (McCrory, Gerin, et al., 2017).
1.3.1. The Theory of Latent Vulnerability

The limits of the current symptoms-based diagnostic systems, which is largely agnostic of aetiological factors, are increasingly being recognised (Insel, 2014; Kaufman, Gelernter, Hudziak, Tyrka, & Coplan, 2015; McGorry, 2013). Also, in line with what has been postulated by Cicchetti, Rutter and others more than two decades ago (Cicchetti & Rogosch, 1996; Rutter, 1989), there is now a growing consensus regarding the importance of considering developmental and neurocognitive processes implicated in the pathogenies of a given disorder. Within this framework, McCrory and Viding have proposed the Theory of Latent Vulnerability in an effort to increase the focus on prevention and on the developmental mechanisms associated with the emergence of psychopathology following childhood maltreatment (McCrory, Gerin, et al., 2017; McCrory & Viding, 2015).

According to this theory, the experience of maltreatment leads to a cascade of alterations that can be captured at a neurobiological, genetic, cognitive and behavioural level. However, the biological embedding of early adverse experience (Danese & McEwen, 2012) is believed to be best captured at a neurocognitive level, as this may have the greatest translational potential. In particular, it may help us unveil alterations in cognitive and neurobiological domains that may inform – and be malleable to – intervention.

Crucially, these neurocognitive alterations (for example, reduced expectation/neural signalling of reward, neural sensitisation to threat-related cues or reduced memory specificity for personal events) are not seen as a sign of ‘damage’; rather as an adaptation and system-level recalibration that may confer proximal adaptive value in an early adverse environment (McCrory, Gerin, et al., 2017) . However, such changes may also come at a long-term cost, as they may be no longer adaptive in more normative situations. Furthermore, these alterations are considered to be latent because,
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despite increasing vulnerability to future psychopathology, they may not look like a manifest psychiatric disorder (nor subclinical symptoms) and they are hypothesised to be present despite the absence of overt symptoms (McCrory, Gerin, et al., 2017; McCrory & Viding, 2015).

Finally, these neurocognitive alterations are hypothesised to have two types of possible consequence: i) protracted indirect effects that relate to the child ability to elicit and sustain social support networks with peers and adults, as well as ii) direct and more proximal effects that relate to the child’s processing of the world in a more immediate way that may have an impact on their developmental experience and growth. These direct and indirect effects, are believed to have an impact on socio-emotional functioning which is believed to increase vulnerability to future stressors, thus increasing psychiatric risk (see Figure 1.1 below, taken from McCrory et al., 2017).

In summary, the Theory of Latent Vulnerability aims to capture how early adverse experiences may get under the skin, alter developmental trajectories and recalibrate neurocognitive systems in ways that may embed psychiatric vulnerability and potentiate the likelihood of maladaptive outcomes in the long-run.

McCrory and Viding (2015) proposed that a true maker of latent vulnerability must possess a prognostic value. That is, it should mechanistically explain and predict heightened psychiatric risk among individuals who, following maltreatment exposure, already have an increased propensity to experience mental health difficulties. In particular, the authors proposed that to establish whether maltreatment-related cognitive and neurobiological changes represent a marker of latent vulnerability, empirical evidence must satisfy three core principles (McCrory & Viding, 2015). First, the neurocognitive alterations associated with maltreatment exposure should be present in the absence (or prior to the development) of a manifest psychiatric disorder. Second, they should be predictive, among individuals who were exposed to maltreatment, of
specific psychiatric and socioemotional outcomes (and not simply global functioning).

Third, they should be mechanistically linked to relevant psychiatric conditions known to be common among individuals exposed to maltreatment during childhood. Moreover, in order for maltreatment-related alterations to be considered a sign of adaptation to an early adverse experience (rather than damage), they should be associated with measurable advantages within a neglectful/abusive household.
on protective factors, stress exposure and genotype.

Differential outcomes are shown in relation to mental health risk and resilience depending with both direct and indirect effects on socio-emotional functioning.
Other theoretical frameworks which are often used to conceptualise the impact of childhood maltreatment on subsequent functioning include experience-expectant/dependent and deficit-models of brain development. The young brain’s fast developing organization, structure and function depends on ordinary experience and opportunities that are generally provided within the context of normative caregiving, including age-appropriate opportunities for exploration and stimulation (Greenough, Black, & Wallace, 1987). In other words, a range of domains associated with brain development, such as perception (e.g. hearing and vision) and higher cognitive functions (e.g. language, socio-emotional reasoning) require environmental inputs to develop. Several authors, have conceptualised childhood maltreatment as a violation of species-expectant experiences (McLaughlin, Sheridan, & Nelson, 2017). That is, childhood maltreatment leads to deficits in perceptual, cognitive, emotional and social domains of functioning which accrue via the curtailing of normative and necessary environmental inputs.

Perhaps some of the most compelling evidence for these models come from studies of children who have been institutionalised (Fox, Levitt, & Nelson, 2010; Nelson, Zeanah, & Fox, 2019; Rutter et al., 2007; Rutter, Kumsta, Schlotz, & Sonuga-Barke, 2012). In particular, these studies have shown that early and extreme psychosocial deprivation leads to a plethora of deficits, including alterations in brain function and structure as well as widespread impairments in behavioural and cognitive functioning (Nelson et al., 2019). The deficit model and the experience-expectant/dependent framework are particularly useful when conceptualising the global deficits (and their aetiology) seen in individuals who have experienced gross deprivation and neglect. However, these models are perhaps less precise and useful in capturing more common forms of childhood maltreatment. Abuse and neglect, when occurring in the community, are often characterised by both the presence of normative
environmental inputs as well as experiences that deviate from the species-normal repertoire of caregiving practises.

The theory of latent vulnerability differs in two main ways from the deficit and the experience-expectant/dependent models of maltreatment. First, the former, as described above, conceptualises the neurocognitive changes that occur as a result of childhood maltreatment as a sign of adaptation to early adverse experience rather than damage/deficit. In other words, according to the theory of latent vulnerability, highly plastic neurocognitive systems are believed to adapt to early abusive and neglectful experiences in ways that maximise proximal survival and short-term functioning. For example, heightened reactivity to threat, despite potentiating long-term psychiatric risk, may also improve threat detection. Indeed, it has been shown in laboratory settings that children who have experienced maltreatment have an enhanced ability to recognise threat and hostile social cues in the environment (Pollak & Sinha, 2002). This may represent an adaptive recalibration of the threat system to an environment where either protection from caregivers is inconsistent (e.g. neglect) and/or threat from others may be both extreme and unpredictable (e.g. physical abuse). We currently lack, however, prospective/epidemiological studies which could allow us to track simultaneously the occurrence of adversity over time, the trajectories of neurocognitive developmental and also psychosocial functioning. This kind of evidence is necessary if we are to explore whether maltreatment-related neurocognitive changes represent a form of deficit across contexts (hence, if they are always associated with poorer functioning) or if they can be advantageous in circumscribed early adverse environments. An important first step in this direction is to identify the neurocognitive processes that are both associated with maltreatment exposure and that may be predictive of future functioning – this is indeed one of the aims of this thesis.

Secondly, across these models, there is a differential prediction and emphasis on the type of alterations and outcomes associated with the experience of maltreatment
(e.g. global deficits vs domain-specific recalibrations). The theory of latent vulnerability, for example, focuses on particular neurocognitive process and their impact on specific aspects of functioning. In other words, there is an assumption that some, but not all, neurocognitive systems may recalibrate following maltreatment. These in turn are hypothesised to be linked with a specific set of sequelae. For example, alterations in autobiographical memory following childhood maltreatment are believed to be independent of other cognitive domains (e.g. language development) and to be predictive of depressive, but not anxiety symptoms (McCrory, Puetz, et al., 2017; Valentino, Toth, & Cicchetti, 2009).

To conclude, although it is beyond the scope of the studies presented here to provide definitive evidence for or against either of these models (i.e. theory of latent vulnerability, experience-expectant/dependent brain development, deficit model), it is important to consider the findings of this thesis in relation to these theoretical frameworks, their differential predictive validity and also their falsifiability. Also, despite important nuances and emphasis on different processes, these models are actually in large part complementary as they try to describe how early experiences may affect later development in ways that can increase vulnerability to poor outcome.

1.3.2. A Review of the Functional Neuroimaging Literature of Childhood Maltreatment

In our view task-based functional neuroimaging studies hold great potential in refining our understanding of the neurocognitive alterations associated with maltreatment exposure (McCrory, Gerin, et al., 2017). Moreover, fMRI task-based neuroimaging findings are relevant to a large part of my doctoral work and methodology. Thus, this section will review extant task-based fMRI studies of maltreatment and it is organised around five key domains: threat processing, reward processing, emotion regulation, executive control and autobiographical memory. To
help put these findings into context, for each domain I provide a brief description of the system, its neurocognitive basis, and how it has been implicated in psychiatric disorders. Note that a review of resting-state functional connectivity and structural neuroimaging studies of maltreatment is outside the scope of this chapter (and this thesis). For those readers who may be interested in the latter, there is a recent comprehensive review by Teicher and Samson (2016).

Selected aspects of this review are taken directly from a recent first author accepted/in-press review in Adoption & Fostering (see Appendix 1 for the full manuscript) as well as from a co-authored review published in the Journal of Child Psychology and Psychiatry (McCrory, Gerin, et al., 2017). These reviews have focused on studies with children and adolescents. Here I will expand the discussion to findings from adult studies because these are also relevant to my doctoral work.

In brief, the studies reviewed below support the notion that some individuals with histories of childhood maltreatment, even in the absence of manifest psychiatric disorders, present with changes in brain function across several social, cognitive and emotional domains. Remarkably, these changes are often consistent with the neural signature observed in patients with mood, anxiety and conduct disorders (McCrory, Gerin, et al., 2017).

**1.3.2.1 Threat processing.** Survival is dependent on the ability to detect and respond to dangerous and aversive stimuli in the environment. For this reason, it is not surprising that both animal and human studies have revealed that a large amount of cognitive resources and neurobiological systems are dedicated to threat detection (LeDoux, 2000; Öhman, 2009). Within the central nervous system the amygdala is one of the core structures dedicated to the processing of danger and to the detection of salient information more broadly (LeDoux, 2000; Phelps & LeDoux, 2005). The amygdala is part of an integrated network comprising several cortical and subcortical
brain regions involved in fear conditioning, stress responses and salience detention, such as the hippocampus, the striatum, the anterior insula and the dorsal anterior cingulate cortex (ACC) (Shin & Liberzon, 2010).

*How is altered threat processing implicated in mental health difficulties?* In recent years, neuroimaging findings have shown that alterations in amygdala and anterior insula activation are implicated in several disorders, including posttraumatic stress disorder (PTSD), mood and anxiety disorders (Etkin & Wager, 2007; Kerestes, Davey, Stephanou, Whittle, & Harrison, 2014; Patel, Spreng, Shin, & Girard, 2012), drug addiction (Sripada, Angstadt, McNamara, King, & Phan, 2011) and conduct problems (Viding et al., 2012). Crucially, recent longitudinal studies of healthy individuals exposed to different kinds of environmental stressors have shown that increased baseline neural reactivity to threat is associated not just with current, but also with future symptoms (Admon et al., 2009; Admon, Milad, & Hendler, 2013; Swartz, Knodt, Radtke, & Hariri, 2015).

*Functional neuroimaging studies of threat processing in maltreated children and adolescents.* Animal studies have established a strong link between early adverse experiences (such as early separation from a caregiver, social isolation, or reduced maternal care and sensitivity) and neurophysiological long-lasting alterations in the central and peripheral nervous systems involved in threat processing and stress responses (Caldji et al., 1998; Caldji, Diorio, & Meaney, 2003; Meaney, 2001; Rosenblum et al., 1994). Behavioural and electrophysiological studies with humans also suggest that abuse and neglect are associated with long lasting alterations in threat processing that can be detected as early as infancy. These changes include heightened electrophysiological responses to negative stimuli, and preferential attention and enhanced perceptual ability for threat cues, such as angry or fearful faces (Curtis & Cicchetti, 2013; Pollak & Sinha, 2002; Pollak & Tolley-Schell, 2003; Pollak, Vardi, Putzer Bechner, & Curtin, 2005).
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These behavioural and neurophysiological findings have been extended by a series of recent functional magnetic resonance imaging (fMRI) studies with children and adolescents. These have found a pattern of increased neural response during the processing of threat cues (e.g. angry faces) in the amygdala, and other subcortical neighbouring regions, such as the anterior insula and hippocampus (Maheu et al., 2010; McCrory et al., 2011, 2013; Tottenham et al., 2011). Such neural alterations seem to be shared across individuals with different experiences of early adversity, ranging from severe institutional neglect (Maheu et al., 2010; Silvers et al., 2017; Tottenham et al., 2011), substantiated maltreatment in community settings (Hart, Lim, Mehta, Simmons, et al., 2018; McCrory et al., 2011, 2013) and also less severe experiences of neglect (M. White et al., 2012). Importantly, by using control groups well-matched on demographic variables, these studies suggest that increased threat-related neural responses among maltreated children and adolescents is independent from potentially confounding factors, such as IQ, socioeconomic status, pubertal status and concurrent psychopathology (e.g. Maheu et al., 2010; McCrory et al., 2013). Moreover, by showing that both amygdala and insula hyperactivity have a dose-dependent relationship with the severity / duration of maltreatment (Maheu et al., 2010; McCrory et al., 2011, 2013), these findings point to a pattern of neural calibration directly related to the degree of early adversity. Finally, cross-sectional evidence also suggests that alterations in this system may be associated with higher symptoms levels (Silvers et al., 2017).

Further evidence for the impact of abuse and neglect on threat processing comes from four studies with maltreated children and adolescents (Gee et al., 2013; Lee et al., 2015; Marusak, Martin, Etkin, & Thomason, 2015; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015). The main focus of these studies was to investigate the neural connectivity across brain regions engaged during emotion regulation. As such, these findings will be discussed in greater detail in the affect regulation section below.
However, it is worth noting here that in exploratory analyses of focal activation during threat processing, these studies also found a pattern of increased amygdala reactivity to negative and threatening social cues in maltreated individuals.

*Functional neuroimaging studies of threat processing in adults with a history of maltreatment.* Adults with histories of abuse and neglect also present with a pattern of heightened neural reactivity to threat, suggesting that a history of childhood maltreatment can have a long-lasting impact on the threat-processing system. In two studies with a large community sample, Dannlowski and colleagues (2012, 2013) found that increased amygdala reactivity was positively correlated with self-reported experiences of maltreatment during the conscious detection and also during the pre-attentive presentation of social threat cues and negative affect. These studies were characterized by large sample-sizes and robust methods to control for concurrent psychopathology, factors which make these findings particularly robust.

In another recent study, substantiated experiences of maltreatment during childhood were found to impact the neural processing of threat above and beyond the influence of other aversive circumstances, such as growing up in a high-risk environments and low-income families (Jedd et al., 2015). In particular, a history of maltreatment was associated with increased reactivity in subcortical regions involved in threat processing and stress response, including the basal ganglia. Moreover, the researchers found a pattern of increased functional connectivity between the amygdala and the hippocampus, suggesting potential impairments in threat detection and fear extinction. Edmiston and Blackford (2013) also found that heightened neural reactivity to potential threat was associated with maltreatment exposure during childhood. In particular, adults with maltreatment histories showed increased neural response to novel faces in the hippocampus and in other face-processing temporal regions. Interestingly, converging evidence for maltreatment-related heightened neural responses to threat comes
also from adult studies using other neuroimaging methodologies, such as electroencephalography (EEG) (Sandre, Ethridge, Kim, & Weinberg, 2018).

In recent years, three neuroimaging studies have shown that “risk” genes could moderate the relationship between childhood maltreatment and neural reactivity to threat (Dannlowski et al., 2016; Opmeer et al., 2014; Redlich et al., 2015). In particular, polymorphisms of the neuropeptide Y (NPY), interferon γ (IFNy) and the oxytocin receptor (OXTR) genes have been investigated. These genes, densely expressed in the amygdala, carry information for the production of proteins and neurotransmitters implicated in stress reactivity and mood disorders. Carriers of the riskier genetic variations who were also exposed to maltreatment showed increased amygdala reactivity to threat and negative cues (Dannlowski et al., 2016; Opmeer et al., 2014; Redlich et al., 2015). This is consistent with the notion that some individuals may be more or less genetically susceptible to the impact of early abuse and neglect (Caspi & Moffitt, 2006).

Findings from adult studies investigating psychiatric populations with and without past experiences of abuse and neglect have shed new light on the clinical manifestation of psychopathology in the context maltreatment. Two studies recruited patients with depression (M. M. Grant et al., 2011; van Harmelen et al., 2013). Half of the patients had past experiences of childhood maltreatment while the other half did not. Both studies found that a history of abuse and/or neglect predicted higher neural reactivity to threat in the amygdala compared to healthy controls and to depressed individuals without a history of maltreatment. Furthermore, three recent studies have shown that patients with PTSD, anxiety disorders and substance abuse with a history of maltreatment show greater neural reactivity to threat in the salience network (including the dACC, insula and amygdala) compared to non-maltreated patients (Dean, Kohno, Hellemann, & London, 2014; G A Fonzo et al., 2016; Gregory A Fonzo et al., 2013). Overall, these findings indicate that heightened neural reactivity to threat in the amygdala
and the salience network among maltreated individuals is (at least in part) independent of clinical status.

**Summary.** It has been shown that maltreatment, even among children and adults who are not presenting with overt psychiatric symptomatology, is linked to increased neural reactivity and connectivity during the processing of threat-related social cues. Crucially, this association seems to be directly related to the severity of maltreatment (Dannlowski et al., 2012; Maheu et al., 2010; McCrory et al., 2011; M. White et al., 2012) and it may be augmented by genetic vulnerability (Dannlowski et al., 2016; Opmeer et al., 2014; Redlich et al., 2015). This is consistent with extant animal and human data suggesting that chronic exposure to threat and adverse environments recalibrates the neural system involved in threat and salience detection. It is also consistent with longitudinal studies examining the neurobiological impact of combat exposure on threat-detection (van Wingen, Geuze, Vermetten, & Fernández, 2011). Soldiers after (but not before) deployment show a very similar pattern of neural adaptation to that of children exposed to family violence (McCrory et al., 2011; van Wingen et al., 2011). This suggests that the observed neural changes in maltreated individuals are consistent with a pattern of adaptation rather than a form of ‘damage’. Although such changes may be adaptive in the short-term, the theory of latent vulnerability contends that in the long term their effect is an increased risk of psychopathology following exposure to future stressors. Indeed, increased reactivity of the amygdala and anterior insula to threat have been associated with several psychiatric conditions, including depression, anxiety and PTSD. Thus, it is possible that altered threat processing may increase the risk of future mental health problems. However, longitudinal studies are required to confirm this hypothesis – this will be the focus of the second empirical chapter (Chapter Three).

**1.3.2.2 Reward processing.** Learning which stimuli and actions are associated with attaining rewarding objects, experiences or events is essential to motivate and
guide adaptive decision-making and behaviour. The main network underpinning the processing of reward is the mesocorticolimbic dopaminergic neural pathway. This includes brain-stem regions, such as the ventral tegmental area, which project to basal ganglia nuclei, especially the striatum, and terminate in prefrontal regions, including the orbitofrontal cortex (Clithero & Rangel, 2013; O’Doherty, 2011; Tanaka et al., 2004; Valentin & O’Doherty, 2009).

How is altered reward processing implicated in mental health difficulties?
Neural alterations in the reward system have been associated with suboptimal decision-making and psychopathology, including the emergence and maintenance of anxiety, mood, conduct and substance abuse disorders (Balodis & Potenza, 2015; Eshel & Roiser, 2010; Hartley & Phelps, 2012; Stringaris et al., 2015; S. White et al., 2013; Zhang, Chang, Guo, Zhang, & Wang, 2013). For example, neuroimaging studies have shown that depressed individuals show a consistent pattern of reduced activation in the striatum during reward processing (Forbes & Dahl, 2012; Pizzagalli et al., 2009; Ubl et al., 2015). Interestingly, this predicts not only current but also future clinical status and symptoms level (Bress, Smith, Foti, Klein, & Hajcak, 2012; Morgan, Olino, McMakin, Ryan, & Forbes, 2013; Olino et al., 2014; Telzer, Fuligni, Lieberman, & Galvan, 2014), even in those who were previously “healthy” (Stringaris et al., 2015). Neuroimaging studies suggest that this pattern of blunted neural activation may be associated with difficulties in computing reward anticipation. In the context of depression, this might entail reduced sensitivity to rewards and limited motivational response (i.e. anhedonia) (Gotlib et al., 2010; Stringaris et al., 2015; Ubl et al., 2015); in the context of conduct disorder, this may suggest difficulties in integrating and updating reward (and punishment) information (S. White et al., 2013; S. White, Tyler, Erway, et al., 2016).

Functional neuroimaging studies of reward processing in maltreated children and adolescents. Researchers have been motivated to investigate reward processing in maltreated individuals for two reasons. First, the clinical literature described above
suggests that altered reward processing may be associated not just with current symptoms, but also with the emergence of mental health problems in the future. Secondly, we know that the familial environment experienced by maltreated children is often characterised by the erratic and infrequent availability of rewards.

To date most neuroimaging studies of maltreatment have found reduced activation during reward processing, especially in the striatum and the orbitofrontal cortex (McCrory, Gerin, et al., 2017). This pattern of findings has been found both in individuals who have experienced extreme forms of institutional deprivation (Goff et al., 2013; Mehta et al., 2010) or maltreatment in community settings (Hanson, Hariri, & Williamson, 2015). One study, however, has not found this pattern of blunted reward related response among maltreated individuals (Dennison et al., 2016). Nevertheless, the opposite pattern (i.e. higher neural response to reward) was linked to better future mental health outcomes among individuals with a history of childhood maltreatment. Thus, overall these findings suggest that increased and decreased activation in the striatum may represent, respectively, a marker of resilience and risk to psychopathology among maltreated individuals. In particular, the pattern of lower neural response in maltreated individuals may reflect neural calibration to reduced opportunities for reward-based learning. Such alterations may represent an adaptive regulatory mechanism which reduces disappointment in the context of inconsistent and insensitive parenting (McCrory, Gerin, et al., 2017). However, these neurocognitive alterations may also hamper functioning in more normative situations. For example, they may hinder exploratory behaviour, thus decreasing the opportunities for learning and for motivating the search of alternative sources of reward outside the home environment.

Recently, Harms and colleagues (2017) used an instrumental reward task that required participants to first learn positive (reward) and negative (punishment) stimulus response associations, and then update those pairings once contingencies were shifted by the experimenter. Among a sample of 44 adolescents (22 with documented histories
maltreatment), both reward learning performance and brain activation during learning were correlated with maltreatment exposure. Individuals with maltreatment experience showed poorer performance in punishment avoidance learning, as well as less cognitive flexibility following contingency reversal. Group effects on “re-learning” deficits over the reversal phase of the task were stronger than those in the initial acquisition phase, suggesting that the additional cognitive demands led to further performance decrements among maltreated adolescents. Maltreatment was also associated with reduced reward-related activation in the striatum and ACC during reversal learning. This suggest that maltreatment exposure may lead to alterations in reinforcement-based learning mechanisms. However, computational / model-based approaches are required to more stringently test the hypothesis that reinforcement-based decision-making processes and associative learning are alerted among maltreatment individuals. This will be the focus of the first empirical chapter of this thesis (Chapter Two).

*Functional neuroimaging studies of reward processing in adults with a history of maltreatment.* In line with the child literature, Dillon and colleagues (2009) found that, during the anticipation of rewards, young adults with a history of childhood maltreatment show blunted activation in several reward-processing subcortical regions, including the striatum and globus pallidus (Dillon et al., 2009). However, in this study, the maltreated sample showed higher levels of anhedonia than controls, which may partially account for the observed neural differences because anhedonia has also been linked with reduced striatal activation (Kerestes et al., 2014). In a more recent study, using a large sample of young adults (n = 820), Corral-Frias and colleagues (2015) found that the interaction between maltreatment and reduced activation in the ventral striatum during reward processing was associated with symptoms of anhedonia, as well as alcohol abuse. This suggests that blunted neural response to reward may represent a marker of psychiatric vulnerability among maltreated individuals. However, in this study maltreatment was measured as a continuous variable in a normative group of
young adults. Thus, despite the large sample size, only a relatively small number of individuals actually experienced moderate to severe levels of abuse and neglect. This limits the generalisability of these findings. Notwithstanding the need for further studies with a more representative and better characterised sample of adults with maltreatment histories, the results from these two fMRI studies are nonetheless insightful. In particular, together with the child studies discussed above, they suggest that maltreatment-related recalibrations of the reward processing system are long-lasting and may increase psychiatric risk across the lifespan.

Neurocognitive alteration in the processes underlying reward/value-representation may place individuals who experience maltreatment at an increased risk of developing not only depressive symptoms, but also disorders associated with alterations in action-value representation and reinforcement-based decision-making, such as substance abuse and conduct problems (S. White et al., 2013, 2014; S. White, Tyler, Botkin, et al., 2016). In line with this hypothesis and in the context of the findings from animal models (Everitt & Robbins, 2005; Kosten, Zhang, & Kehoe, 2005), a recent Positron Emission Tomography (PET) study by Oswald and colleagues (2014) found that a history of childhood maltreatment was linked to enhanced neural sensitivity to intravenous amphetamine. In particular, a positive correlation was found with maltreatment severity scores and striatal dopamine response to amphetamine. Such an increased neural response to the reinforcing properties of drugs of abuse can place an individual at a greater susceptibility for developing an addiction (Andersen & Teicher, 2009). More recently, in a fMRI study with a well characterised groups of adults who experienced maltreatment, Birn and colleagues (2017) found that a blunted neural response to the anticipation of reward/punishment was i) associated with a history of maltreatment and ii) was predictive of poorer decision-making and greater risk-taking behaviour (Birn, Roeber, & Pollak, 2017). In a large sample (n = 171) of young adults followed prospectively since birth, Holz and colleagues (2017) also found that
decreased striatal response during reward anticipation was associated with substantiated histories of early adversity (Holz et al., 2017).

No single mechanisms or neurocognitive pathway can be expected to explain entirely the complex association between early maltreatment and future psychiatric disorder. Moreover, longitudinal data is still required to establish any causal relationship between maltreatment-related alteration in the reward processing system and subsequent psychopathology in adults. However, the evidence from the studies reviewed above, together with animal and clinical data (Balodis & Potenza, 2015; Corral-Frias et al., 2015; Everitt & Robbins, 2005; Robinson & Berridge, 2008), suggests that an increased neural sensitivity to drugs of abuse and a decreased response to natural and social rewards, may be one of the mechanisms that place adults with maltreated histories at a greater risk of developing drug addictions (Puetz & McCrory, 2015) conduct disorders and depression (McCrory, Gerin, et al., 2017).

**Summary.** Overall, these findings suggest that a history of childhood maltreatment is associated with a blunted neural response to reward cues, especially in the orbito-striatal network. This neural profile, which may be shaped by familial environments characterised by erratic and infrequent availability of rewards, is also known to be associated with common mental health problems, particularly depression, drug abuse and conduct disorder. Therefore, alterations in reward processing following maltreatment may instantiate vulnerability to future mental health difficulties. Initial longitudinal evidence also suggests that the opposite pattern (i.e. higher levels of neural response to reward) may be a marker of resilience to future psychopathology following maltreatment.

**1.3.2.3 Emotion regulation.** The ability to regulate affect entails the modification of an emotion by producing changes to its intensity, duration or valence (P. M. Cole, Martin, & Dennis, 2004; Eisenberg & Spinrad, 2004; Ochsner et al., 2004).
Various strategies can be used for emotion regulation, such as emotional distancing, suppression, social support, reappraisal and attention modulation, just to mention a few (Koenigsberg et al., 2010; Ochsner, Silvers, & Buhle, 2012). Crucially, such processes may involve explicit effort or occur implicitly and outside conscious awareness (Gyurak, Gross, & Etkin, 2011). A large neural network is linked to affect regulation. Broadly speaking, prefrontal regions are understood to have top-down regulatory control over regions implicated in emotional reactivity, impulsivity and negative affect, such as the amygdala, insula and striatum (Etkin, Büchel, & Gross, 2015; Ochsner et al., 2012). In particular, the ventral anterior cingulate cortex (vACC) and medial prefrontal cortex (mPFC) seem to be more involved in the implicit and automatic regulation of affect, while latero-prefrontal (lPFC) and also latero-parietal (lPC) cortices seem to be necessary for more explicit and volitional forms of emotion regulation (Etkin et al., 2015).

*How is altered emotion regulation implicated in mental health disorders?* Many psychiatric disorders involve altered affect regulation (e.g. anxiety, conduct disorder and depression) (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Mennin, Holaway, Fresco, Moore, & Heimberg, 2007). Moreover, difficulties in emotion regulation have been shown to represent a risk factor for developing future mental health problems among those individuals who have suffered early adversity (Kim-spoon, Cicchetti, & Rogosch, 2013; Kim & Cicchetti, 2010; Shields & Cicchetti, 2001) and/or who do not present with current clinical symptoms (Ehring, Tuschen-Caffier, Schnülle, Fischer, & Gross, 2010; Folk, Zeman, Poon, & Dallaire, 2014; Keenan, 2006; Michl, McLaughlin, Shepherd, & Nolen-Hoeksema, 2013; Wirtz, Hofmann, Riper, & Berking, 2014). As such, this represent a promising putative domain for indexing latent psychiatric vulnerability.

*Functional neuroimaging studies of emotion regulation in children and adolescents exposed to maltreatment.* Three studies of functional connectivity have
reported that maltreated children and adolescents present with atypical connectivity between regulatory frontal regions, such as the vACC and mPFC, and subcortical brain areas, such as the amygdala (Gee et al., 2013; Lee et al., 2015; Marusak et al., 2015). In addition, five studies that investigated focal brain activity have also reported alterations in the same frontal regulatory network, including the mPFC, vACC, dACC and also the IPFC (Elsey et al., 2015; Marusak et al., 2015; McLaughlin et al., 2015; Puetz et al., 2014, 2016). However, despite the fact that these studies have reported altered functioning in a consistent set of brain regions during emotion regulation, the direction of these alterations has been inconsistent (i.e. increased vs. decreased activity and stronger vs. weaker connectivity). These discrepancies are not entirely unexpected given the spectrum of participants recruited in these studies. Participants varied in terms of developmental stage and type of early adversity (e.g. physical abuse, verbal abuse, institutionalisation, neglect in community settings, etc.). Moreover, different emotion regulation paradigms were implemented, with some requiring simple or automatic emotional processing and others requiring more explicit and higher order regulatory efforts.

It has been suggested that these different task demands may be helpful in understanding the differences across studies (McCrory, Gerin, et al., 2017). When a task explicitly requires participants to attend to aversive stimuli or to consciously modulate affective responses (Elsey et al., 2015; McLaughlin et al., 2015) one tends to see a pattern of increased activation in regulatory frontal regions in maltreated individuals that may reflect increased effort. On the other hand, on those tasks where it is possible to shift attention away from the processing of aversive stimuli, maltreated individuals show a pattern of reduced activation and connectivity (Gee et al., 2013; Lee et al., 2015; Puetz et al., 2014, 2016). This pattern of hypo-activation is consistent with the use of avoidant and dissociative regulatory strategies (McCrory, Gerin, et al., 2017) that can often be unhelpful in the longer term and are
associated with increased risk of anxiety, depression, self-harm and PTSD (Bryant & Harvey, 1995; Holahan, Moos, Holahan, Brennan, & Schutte, 2005; Kaplow, Dodge, Amaya-Jackson, & Saxe, 2005; Karstoft, Armour, Elklit, & Solomon, 2015; Wirtz et al., 2014; Yates, Carlson, & Egeland, 2008).

*Functional neuroimaging studies of emotion regulation in adults with a history of maltreatment.* Two recent studies explored implicit emotional processing among adults with histories of childhood abuse and neglect (Mackiewicz Seghete, Kaiser, DePrince, & Banich, 2017; Metz et al., 2018). During the suppression of task-irrelevant emotionally salient information (such as negative affect), a history of childhood maltreatment was associated with reduced recruitment of brain regions supporting task-set maintenance and regulatory control (such as the dlPFC and precuneus), and increased reactivity for task-irrelevant information in medial brain regions, such as the ACC (Mackiewicz Seghete et al., 2017; Metz et al., 2018). This suggests that adults with a history of maltreatment may experience greater difficulties in down-regulating brain response to task-irrelevant affective cues.

Four studies investigated emotion regulation by inducing psychosocial stress. This was done by using very similar experimental paradigms – i.e. during cognitively demanding tasks participants received negative social evaluations (Banihashemi, Sheu, Midei, & Gianaros, 2015; Fan et al., 2014, 2015; Grimm et al., 2014). Moreover, these studies also examined the effect of intranasal oxytocin, a neurohormone which has been shown to modulate stress response. In a study with a small sample of male adults, Fan and colleagues (2014) found that past maltreatment experiences were associated with elevated state anxiety after psychosocial stress induction. This was associated with reduced functional connectivity in the regulatory vACC-amygdala network during rest and deactivation in the vACC during acute psychosocial stress. Notably, the administration of intranasal oxytocin facilitated regulation only among non-maltreated individuals, suggesting that adults with history of abuse and neglect may be less
responsive to the modulatory effect of oxytocin. These findings are consistent and complemented by a more recent study in which Fan and colleagues (2015) found that, during acute psychosocial stress, increased connectivity between the amygdala and the hippocampus was associated with maltreatment exposure. As mentioned above, the hippocampus plays a crucial role in regulating neuroendocrine stress responses. In line with their previous study (i.e. Fan et al., 2014), they also found that maltreated individuals showed a differential pattern of neural (and hormonal) response to the administration of intranasal oxytocin (Fan et al., 2015). Overall, these results are suggestive of maltreatment-related altered sensitivity to hormones important for the down-regulation of stress. This, in turn, may be explained by anomalies in functional connectivity between the amygdala and cortical and subcortical regions important for regulatory responses (such as the vACC and the hippocampus) (Fan et al., 2014, 2015).

Further evidence for the interaction between early negative experiences and altered neural and hormonal regulatory responses comes from two studies by Grimm et al (2014) and Banihashemi et al. (2015). The researchers, in line with the two studies by Fan and colleagues (2014, 2015), found that maltreatment was associated with neural anomalies in similar brain regions (e.g. in the vACC, amygdala and hippocampus) and also with differential responsiveness to neurohormones, such as oxytocin, during the regulation of psychosocial stress. Overall, these adults fMRI studies of maltreatment suggests that exposure to abuse and neglect leads to long-lasting alterations in the neural networks responsible for emotion regulation.

Summary. The neuroimaging studies of affect regulation in maltreated children and adults, despite some heterogeneity, converge and suggest that the network traditionally involved in self-regulatory processes shows a pattern of atypical focal activation and connectivity. Medial frontal regions (e.g. vACC and mPFC) and the lPFC seem to be particularly implicated, as well as the frontolimbic neural network (e.g. amygdala-vACC connectivity). The heterogeneity in the
neurocognitive findings to date probably reflects differences in the type and timing of early adversity, and the specific computations (simply put, explicit vs. implicit) engaged during different emotion regulation tasks. Taken together with the neuroimaging studies of mental health disorders, these findings suggest that neurocognitive alterations in emotion regulation may confer increased psychiatric risk. However, longitudinal studies are still required to test this hypothesis directly.

1.3.2.4 Executive control. Executive control broadly refers to three interrelated cognitive functions: inhibiting (the ability to constrain automatic and dominant responses irrelevant to a given goal), updating (the ability to maintain, monitor and quickly add/delete information), and shifting (the ability to flexibly switch between different tasks) (Miyake et al., 2000). These functions are important for adaptive behaviour and effective decision-making. Neuroimaging studies have found that these functions are underpinned by a central executive network, whose central nodes include the dorsolateral prefrontal cortex (dPFC) and the posterior parietal cortex. Brain areas engaged during error monitoring, such as the dorsal anterior cingulate cortex (dACC) and mid cingulate cortex (MCC), are also involved in executive control functions, in particular error monitoring and updating.

*How is altered executive control implicated in mental health difficulties?* Cross-sectional and longitudinal evidence suggests that alterations in executive control may be involved in the development of depression, anxiety, conduct problems, attention deficit hyperactivity disorder (ADHD), PTSD and psychosis (Campbell & von Stauffenberg, 2009; Cannon et al., 2006; Cortese et al., 2012; L. D. Evans, Kouros, Samanez-Larkin, & Garber, 2015; Parslow & Jorm, 2007; Snyder, 2013; Snyder, Kaiser, Warren, & Heller, 2015; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). The association between atypical executive control and mental health problems may (for example) be mediated by alterations in several cognitive, emotional and social processes which rely
upon executive functions, such as suppression of ruminative thinking, problem solving and regulation of affect (Snyder, Miyake, & Hankin, 2015).

*Functional neuroimaging studies of executive control in maltreated children and adolescents.* Two studies have found that exposure to early adversity is associated with increased activation during tasks requiring executive functions (such as error processing, cognitive shifting and inhibition) in brain areas linked with executive control, including the dACC/MCC and lateral frontal regions (Lim et al., 2015; Mueller et al., 2010). This increased activation among maltreated children may reflect decreased neural efficiency and increased effort to attain the same performance as their non-maltreated peers. Notably, these findings are in line with the neuroimaging clinical literature of several disorders associated with maltreatment, such as anxiety (Basten, Stelzel, & Fiebach, 2011), psychosis (Callicott et al., 2000), depression (Harvey et al., 2005) and ADHD (Cortese et al., 2012).

More recently, in line with the evidence discussed above, two studies have found that during tasks that require sustained attention (Hart et al., 2017) and error-monitoring (Hart, Lim, Mehta, Curtis, et al., 2018), a history of maltreatment was linked, respectively, with reduced connectivity in fronto-parietal attention networks, including hubs such as the dorsolateral prefrontal and parietal regions, and reduced connectivity in fronto-cingulo-striatal regions, including the ACC. The latter, together with the evidence of increased focal activation during error processing, have been suggested to reflect constant monitoring for errors in order to avoid mistakes which, in abusive contexts, can be associated with disproportionate and violent parental responses (Hart, Lim, Mehta, Curtis, et al., 2018).

*Functional neuroimaging studies of executive control in adults with a history of maltreatment.* To date, only one study has investigated executive functioning in healthy adults who experienced childhood maltreatment (Elton et al., 2014). A very
similar stop-signal paradigm to the child studies mentioned above was implemented. However, because a very different analytic approach was adopted the findings across studies are not directly comparable. Rather than measuring focal brain activity, Elton and colleagues (2014) used graph-theory based statistical measures of brain connectivity. Despite these methodological differences, the same brain regions were implicated, namely the dACC and ventro-lateral frontal regions. Moreover, connectivity analyses revealed a sex-dependent effect on the neural inhibitory control network between the inferior prefrontal cortex and the dACC. This suggests that the study of neural connectivity represents an important and complementary venue for investigating brain activity as it can allow us to detect fine-grained alterations associated with the experience of maltreatment and with potentially moderating variables, such as gender. It is important to note, however, that the majority of the sample recruited for this study experienced negative early life events that fall within a normative range. Thus, the generalisations of these findings to adults with more severe experiences of maltreatment is limited at the moment.

Summary. To date, only a few fMRI studies have investigated executive control in maltreated youth and adults. All studies identified a pattern of increased brain activation and altered connectivity in regions involved in executive functions such as inhibition and performance monitoring/updating, including the dACC/MCC and the fronto-lateral cortex. These findings, in conjunction with the clinical neuroimaging literature suggest that neurocognitive alterations in executive control may increase the risk of mental health problems. However, a recent study by Danese and colleagues (Danese et al., 2017) suggests that we should be cautious in assuming a causal link between maltreatment experience and alterations in executive function, as these may instead result from the socioeconomic and genetic factors that commonly co-occur with maltreatment. Indeed, similar limitations may apply to the
other neurocognitive domains of interests. However, to the best of my knowledge, this has not yet been investigated in population-representative birth cohort samples.

1.3.2.5 Autobiographical memory. To date, the neurocognitive investigation of maltreatment has focused on processes that have already been implicated primarily in the adult psychiatric literature. In particular, functional neuroimaging studies have focused around the four systems reviewed above – i.e. threat and rearward processing, affect regulation and executive control. However, there are likely other domains able to capture how vulnerability to psychopathology becomes embedded following the experience of maltreatment. The autobiographical memory (ABM) system may be one such domain. ABM refers to the retrieval of personally experienced events and self-relevant information. Emerging evidence suggests that ABM plays a central role in scaffolding our sense of self, in regulating affect, in thinking about the future, problem solve as well as remain oriented in the present (Conway & Pleydell-Pearce, 2000; Goddard, Dritschel, & Burton, 1996; Hassabis, Kumaran, & Maguire, 2007; Raes et al., 2005; Schacter et al., 2012; Schacter, Addis, & Buckner, 2007; Williams, 2006).

How is altered ABM implicated in mental health difficulties? Given the central role that ABM is thought to play in our ability to regulate emotions and in mitigating the potential negative impact of life stressors and developmental challenges, it is perhaps not surprising that anomalies in this system have been implicated in several psychiatric disorders. A particular phenomenon that has received attention is that of overgeneral autobiographical memory (OGM). This refers to the reduced specificity during the retrieval of autobiographical episodic information. For example, when asked to retrieve a specific memory/event in response to a cue word, some individuals are more inclined to retrieve categorical memories (such as ‘I used to swim twice a week when I lived at my aunt’s house’ or ‘I always scored low grades in math exams’) or memories that are extended in time (i.e. that last longer than a day, such as ‘during my vacation in Spain I went to the beach every day), rather than specific events that
occurred in a specific place and time (such as ‘3 weeks ago, on Monday night, I went to my first ballet class’).

Interestingly, OGM has not only been associated with several psychiatric disorders (Berna et al., 2016; Dalgleish & Werner-Seidler, 2014; Williams et al., 2007), but it has also been shown to predict future symptoms of PTSD and depression in at-risk individuals (Hermans et al., 2008; Kleim & Ehlers, 2008; Rawal & Rice, 2012). These findings are consistent with the hypothesis that OGM may be involved in the aetiology of mood and trauma-related disorders commonly associated with maltreatment.

*Functional neuroimaging studies of executive control in maltreated children and adolescents.* Recent studies have shown that OGM is more common among individuals who have experienced early adversity, including abuse and neglect (Hitchcock, Nixon, & Weber, 2014; Valentino et al., 2009). Moreover, a recent neuroimaging study from our group has shown that, during autobiographical memory retrieval, maltreated youth with substantiated experiences of neglect and abuse show a pattern of reduced hippocampal activation for positive memories (McCrory, Puetz, et al., 2017). Moreover, in line with the notion that maltreated individuals privilege the processing of negative information, increased activation of the amygdala was also found during negative memory retrieval. Notably, this pattern of findings was independent of current diagnostic status or symptoms level, yet it was comparable to that seen in depressed individuals, remitted patients and individuals at higher familial risk of depression (Young, Siegle, Bodurka, & Drevets, 2016). This support the notion that neurocognitive alteration in the autobiographical memory system following the experience of maltreatment may represent a marker of increased risk to future mental health difficulties.
Summary. Behavioural and neuroimaging evidence suggests that alterations in the autobiographical memory system may represent a marker of latent vulnerability to psychopathology among maltreated individuals. In particular, studies have shown that a history of abuse and neglect is associated, at a behavioural level, with a pattern of reduced retrieval specificity (i.e. OGM) which is accompanied, at a neural level, by a pattern of reduced processing of positive memories and increased processing of negative memories. Longitudinal investigations, however, are still required to test if OGM and these neural alterations predict future symptoms among individuals with a history of maltreatment. Furthermore, we still lack precision in our understanding of the mechanisms through which OGM may increase psychiatric risk (e.g. reduced problem solving, future thinking, planning and increased ruminative thinking). Two of these domains (Episodic Future Thinking and Interpersonal Problem Solving) will be the main focus of the last two empirical chapters of this thesis (Chapters Four and Five).

1.3.3. Implications for research and clinical practise

The functional neuroimaging literature suggests that the experience of abuse and neglect can influence the development of specific aspects of cognitive and affective functioning, which may increase vulnerability to future mental health problems. However, there are still common methodological shortcomings that characterise the neuroimaging literature of maltreatment that need to be addressed in future research if stronger causal inferences are to be made. Some of the most common limitations include small sample sizes, the lack of prospective/longitudinal designs and the conflation of severe maltreatment experience with adversity in the normal range. Moreover, it is essential that future studies aim to control for relevant confounding variables, such as IQ, pubertal status, age, gender, socio-economic status and the presence of a frank mental health disorders, which are known to co-occur with the experience of maltreatment – see McCrory et al (2017) for a more comprehensive critique of these methodological concerns. Despite these limitations,
the emerging pattern of findings reviewed here complement and extend those from wider psychological research, indicating for example, increased hypervigilance and compromised emotion regulation skills in maltreated children (Curtis & Cicchetti, 2013; Kim-spoon et al., 2013; Romens & Pollak, 2012).

Two aspects of the findings reviewed here merit particular attention. First, maltreatment-related changes resemble the neurocognitive profile associated with mental health disorders commonly associated with maltreatment, such as anxiety and depression. Second, these alterations are already present before a manifest clinical disorder. As such, they can be considered markers of latent psychiatric vulnerability since they may have prognostic value, but do not reflect overt symptomatology. Another important implication emerging from these findings is that, despite the link with mental health problems, these neurocognitive changes should not be readily interpreted as a sign of ‘damage’. Rather, in line with the Theory of Latent Vulnerability (McCrory, Gerin, et al., 2017; McCrory & Viding, 2015), they may in many instances be understood as the outcome of a complex set of adaptive processes which may confer short-term advantages for the child in the context of abusive and neglectful environments. However, they may equally incur long-term costs as an individual may not be equipped to deal with more normative challenges.

The neurobiological and psychological alterations which can follow experiences of maltreatment can be understood to increase mental health risk, particularly following exposure to future stressors, in both direct and indirect ways (McCrory, Gerin, et al., 2017). Alterations in the way we process our internal and external worlds can have immediate repercussions: this can be understood as the direct effects of latent vulnerability. An example is the established pattern of hypervigilance to threat cues. While helpful to the child in a chaotic or dangerous home environment, such a response may curtail attentional resources available for the processing of other potentially helpful environmental cues, limiting the opportunities
Chapter 1

for learning and developing other cognitive and affective functions. Heightened response of the threat system may also lead to increased stress reactivity and experience of negative emotions – in other words, it serves to potentiate the negative impact of new stressor experiences. In this way, adaptation of the threat system may have ‘real-time’ implications for how the child negotiates their experience inside and outside the home.

In parallel, there are likely to be indirect effects that over time can compromise psychological and social functioning. Alterations of the threat system may undermine a child’s ability to develop positive peer friendships and social support networks which may help buffer their experience of future stressors. It may also lead them to act in ways that increase the likelihood of future stressor exposure, for example, because of relationship breakdown or exclusion from school. This may unfold because heightened threat reactivity serves to increase the likelihood of misinterpreting ambiguous cues, and over-responding to negative cues in ways that lead to more conflictual interactions. Equally, avoidance of threat or aversive cues (both internal and external) via dissociation and cognitive and behavioural strategies, whilst reducing distress in the short-term, may impair the development of important skills, such as the effective detection of threat, in the longer term (e.g. DePrince, 2005).

How can neuroimaging research inform preventative clinical approaches?

Currently (notwithstanding some exceptions), statutory interventions happen mainly at two stages. Once the maltreatment has been substantiated, professionals seeks to ensure safety and the stability of the child’s placement. Then, if an individual meets clinical criteria for a mental health problem, they may be offered treatment from mental health services. However, extant neuroimaging findings are beginning to show that neuro-cognitive vulnerabilities are present before manifest behavioural symptoms emerge. These findings, alongside those indicating a variety of other psychological mediators
between maltreatment and mental health difficulty, provide the motivation and the
rationale to pursue a preventative care approach. In other words, help could be provided
proximate to the detection of maltreatment experience to those most at risk of a
worsening mental health trajectory.

Therefore, the natural next step would be to develop a psychometric tool
designed to screen for latent vulnerability that, as part of a formal assessment process,
could help us to identify those children at most risk for later poor outcome. However,
the degree to which the extant neuroscience findings can shed light on models of
prevention and intervention is much less clear; our view is that the field has not matured
to this point. Rather, in the medium term, systematic neurocognitive research could help
identify specific mechanisms that could be targeted in treatment. Further work is
required, particularly within a longitudinal framework, in order to investigate the degree
to which alterations of the systems reviewed here are implicated in the pathways to
overt psychiatric problems and furthermore, whether they are amenable to change. Such
targeted mechanistic approaches are necessary given that ‘treatments as usual’ (Nanni
et al., 2012) and general parental caring (Rothman & Silverman, 2007) may not be
enough to prevent and ameliorate symptoms among individuals who have suffered early
abuse and neglect. If we are able to accurately delineate which neurocognitive systems
are altered following maltreatment, an important next question is how to promote
adaptive change in these systems or compensatory protective neurocognitive functions
which can foster resilience (McCrorry, Gerin, et al., 2017).

Future studies should systematically investigate the impact of positive
relationships (involving peers, carers and others) and what factors promote the child’s
ability to learn from these (Toth et al, 2013). Positive, predictable and safe relationships
may help shift the child’s expectations of other people and build a foundation of trust.
Repeated interactions within such relationships might create the conditions that could
facilitate recalibration of the threat and reward processing systems. Alternatively, such
relationships could foster the development of compensatory strategies that counteract affective processing biases. However, engaging in a positive, warm, consistent and constructive way with children who have experienced maltreatment can be challenging to their carers. If a child is hypervigilant to threat, less sensitive to reward, and has fewer emotion regulation and executive functioning skills, this can often evoke negative feelings and a sense of inadequacy in those who are trying to meet their needs. We argue that a more comprehensive understanding of the neurocognitive impact of maltreatment can help clinicians and carers to reframe the child’s behaviour and develop strategies that are helpful in ‘unhooking’ them from maladaptive patterns of interaction.

In summary, the acquisition of specific knowledge regarding neurocognitive processes impacted by early adverse experiences can help us understand how children who have been maltreated see the world around them and why they are often more vulnerable to developing mental health problems. In the longer term this knowledge can inform the development of both a screening tool to identify those at most risk and preventative approaches that effectively promote resilience and increase the likelihood of positive outcomes following childhood maltreatment.
1.4. Aims and Structure of The Current Thesis

The functional neuroimaging literature reviewed above, together with experimental/behavioural and epidemiological studies, have allowed us to increment our understanding of how childhood maltreatment and subsequent psychiatric disorder may be linked. Despite the recent increase in the number of investigations, it is clear that this remains still a young field. In particular, there is still great progress to be made both from a methodological perspective – such as the recruitment of larger samples, the implementation of longitudinal designs and of more sophisticated statistical methods – and also from a conceptual point of view – there are promising neurobiological systems and constructs that have received little if any attention. The relative paucity of mechanistic explanations for the association between maltreatment and psychopathology means that we are still poorly equipped to develop novel preventative interventions that can offset risk trajectories before disorder emerge.

Therefore, building on previous empirical findings, the main aim of this doctoral thesis is to contribute to our understanding of the latent neurocognitive and experiential factors responsible for increased psychiatric vulnerability among individuals with maltreatment histories. In particular, we aimed to address four main outstanding questions:

i. Is childhood maltreatment associated with alterations in the neurocomputational processes that underlie reinforcement-based decision-making, including expected value (EV) representation and prediction error (PE) signalling?

ii. Are the well-established maltreatment-related neurocognitive alterations in the threat-processing systems a predictor (on its own or in interaction with stress exposure) of future internalising symptoms?
iii. Is exposure to childhood maltreatment associated with overgeneral EFT (i.e. OEFT), and is this linked to concurrent psychiatric symptoms?

iv. Is exposure to childhood maltreatment linked to deficits in interpersonal problem solving skills, and are such alterations associated with concurrent psychiatric symptoms?

Below I will provide a brief overview of the structure of this thesis and of how each empirical chapter aims to address the four questions outlined above.

1.4.1. Chapter Two – Reinforcement-Based Decision-Making

In the study outlined in the first empirical chapter (Chapter Two), maltreated youth and peers well-matched on demographic variables underwent a probabilistic passive-avoidance task in the MRI scanner. The ability to detect patterns in the environment – contingency detection – is fostered through consistent caretaking and plays a central role in reinforcement-based decision-making and reward/punishment associative learning (Ellis, 2006; Nagai, Asada, & Hosoda, 2006; Reeb-Sutherland, Levitt, & Fox, 2012). The experience of abuse and neglect disrupts the species normative learning environment as a child is exposed to unpredictable and extreme parental affective reactions and also to a paucity and/or inconsistency of primary reinforcers. The main aim of this study was to implement a model-based fMRI analytic approach in order to assess, for the first time, maltreatment-related alterations in the computational components underlying reinforcement-based decision-making and reward processing (Clithero & Rangel, 2013; O’Doherty, Hampton, & Kim, 2007; Rescorla & Wagner, 1972). These are expected value (EV) representation (the reinforcement expectancies associated with a stimulus or action) and prediction-error (PE) signalling (the ability to detect the difference between the expected and actual outcome associated with a stimulus or action). Anomalies in these computations have been linked with disorders commonly associated with maltreatment, such as depression, anxiety, drug abuse and conduct
disorder (Eshel & Roiser, 2010; S. Grant, Contoreggi, & London, 2000; Hartley & Phelps, 2012; Matthys, Vanderschuren, & Schutter, 2012; Schoenbaum, Roesch, & Stalnaker, 2006). It is proposed that alterations in reinforcement-based decision-making represent a promising neurocognitive marker that may allow us to index latent psychiatric vulnerability among individuals with a history of abuse and neglect.

1.4.2. Chapter Three – Threat Reactivity and ‘Stress Generation’

In Chapter Three, the main aim is to explore the contribution of threat-related neural functioning and exposure to major stressful life events in understanding the link between a history of childhood maltreatment and adult internalising symptoms. Although both higher baseline amygdala reactivity to threat and increased likelihood of stress exposure have previously been associated with a history of maltreatment (Dannlowski et al., 2012, 2013; Harkness, Lumley, & Truss, 2008; Hein & Monk, 2016; McCrory et al., 2013; Redlich et al., 2015; van Harmelen et al., 2013; Widom, Czaja, & Dutton, 2008), this is the first longitudinal study to directly test their prognostic value in predicting future internalising symptoms severity. Beside the longitudinal design and the relatively large sample size (199 participants), another methodological strength of this study was the implementation of propensity-score matching. This allowed us to select a non-maltreated control group which was matched to the maltreated group for several potentially confounding characteristics, such as IQ, socio-economic status, ethnicity, and even baseline symptoms levels. As such, this study represents a novel and stringent explorations of the impact of childhood maltreatment on threat neural reactivity and stress exposure and their contribution to increased risk of future depression and anxiety.

1.4.3. Chapter Four – Episodic Future Thinking (EFT)

In Chapter Four, using the well-established modified Autobiographical Memory Test (M-AMT; Williams et al., 1996), the main aim is to investigate (behaviourally) ‘Episodic Future Thinking’ (or EFT) among maltreated youth. EFT refers to the ability to
mentally simulate and generate possible future events that are self-relevant (Addis, Musicaro, Pan, & Schacter, 2010; Atance & O’Neill, 2001; Hassabis et al., 2007). EFT emerges in early childhood and is crucial for several aspects of human behaviour and cognition, including affect regulation, impulse control and problem solving (Schacter, Benoit, & Szpunar, 2017). Its development is supported by sensitive caretaking and by parental verbalisation about the future (Atance, 2008, 2015; Prabhakar, Coughlin, & Ghetti, 2016; Suddendorf, 2017). Individuals who experience childhood maltreatment, however, are often exposed to chaotic and neglectful home environments, often characterised by the lack of social and verbal stimulation (R. Gilbert, Kemp, et al., 2009; Radford et al., 2013). Moreover, the fact that maltreatment leads to long-lasting alterations in a number of cognitive and neurobiological domains closely linked to EFT (such as ABM; McCrory, Puetz, et al., 2017; Valentino et al., 2009), also suggests that a history of childhood abuse and neglect may be detrimental to EFT development. A growing body of evidence shows that alterations in EFT, including difficulties in generating specific episodic future events (known as overgeneral EFT, or OEFT), are linked with mental health problems commonly associated with maltreatment, such as depression, bipolar disorder and PTSD (A. D. Brown et al., 2013; Hallford, Austin, Takano, & Raes, 2018). In this chapter we demonstrate that the investigation of EFT alterations, and in particular of OEFT, has the potential to increase our understanding of the pathogenesis of mental health problems following maltreatment exposure.

1.4.4. Chapter Five – Interpersonal Problem Solving

In Chapter Five, interpersonal problem solving skills are investigated using the Means-End Problem Solving (MEPS) test. In the general population, poor interpersonal problem solving abilities have been linked with the emergence, maintenance and relapse of psychiatric disorders, such as depression, and also with maladaptive psychosocial outcomes (Demirbas, Ilhan, & Dogan, 2012; Khurana & Romer, 2012; Marx, Williams, & Claridge, 1992; Nezu & Ronan, 1988b; Pollock & Williams, 2004; Quiñones, Jurska,
A consistent body of evidence shows that the association between maltreatment and later mental health problems may be mediated by reduced social support and social competence (Benedini, Fagan, & Gibson, 2016; Bolger, Patterson, & Kupersmidt, 1998; Kim & Cicchetti, 2010; Matheson et al., 2017; Raby et al., 2018; Sperry & Widom, 2013; van Harmelen et al., 2017; Widom, Czaja, & Dutton, 2014). It is possible that such poor psychosocial outcomes may be linked to deficits in problem solving abilities. In this chapter, we consider how deficits in interpersonal problem solving skills may represent a promising intermediate mechanism which may allow us to capture how childhood maltreatment is linked to poorer social functioning and subsequent psychiatric risk.

1.4.5. Chapter Six – General Discussion

Chapter Six first provides a concise overview of the background and main theoretical framework of this thesis (i.e. the theory of Latent Vulnerability). The main findings outlined in Chapter Two, Three, Four and Five will also be briefly summarised. Finally, overarching methodological limitations will be discussed, and potential future research directions and clinical implications examined.
The second chapter of this thesis (published in Development and Psychopathology – Gerin et al., 2017 – see Appendix 2 for the full manuscript) explored whether alterations in reinforcement-based decision-making may be associated with increased psychiatric vulnerability in children who have experienced maltreatment. A probabilistic passive avoidance task and a model-based fMRI analytic approach were implemented to assess the neurocomputational components underlying decision-making: i) expected value (EV) representation (the reinforcement expectancies associated with a stimulus or action); and ii) prediction error (PE) signalling (the ability to detect the differences between expected and actual outcomes). There were three main findings. First, the maltreated group (n = 18; mean age = 13), relative to non-maltreated peers (n = 19; mean age = 13), showed decreased activity during EV processing in a widespread network commonly associated with reinforcement expectancies representation, including the striatum (especially the caudate), the orbitofrontal cortex, and medial temporal structures including the hippocampus and insula. Second, consistent with previously reported hyper-responsiveness to negative cues in the context of childhood abuse, the maltreated group showed increased PE signalling in the middle cingulate gyrus, somatosensory cortex, superior temporal gyrus and thalamus. Third, the maltreated group showed increased activity in fronto-dorsal regions and in the putamen during expected value representation. These findings suggest that early adverse environments disrupt the development of decision-making processes, which in turn may compromise psychosocial functioning in ways that increase latent vulnerability to psychiatric disorder.
2.1. Introduction

Maltreatment is one of the most profound insults to normal development and it is strongly associated with several maladaptive outcomes including poor mental and physical health as well as reduced economic productivity across the lifespan. Despite the abundance of evidence linking early adversity with negative outcome, there is a relative paucity of knowledge regarding the mechanisms through which increased psychiatric vulnerability becomes instantiated.

As discussed in detailed in the introductory chapter, the theory of Latent Vulnerability (McCrory, Gerin, et al., 2017; McCrory & Viding, 2015) offers a systems-level approach that places emphasis on the neurocognitive mechanisms that link early adversity to future psychopathology. Briefly, according to this account, childhood maltreatment leads to alterations in several neurobiological and cognitive systems, which are understood as developmental recalibrations to abusive and neglectful environments. Such changes are ‘latent’ insofar as they do not inevitably result in a manifest psychological disorder and can even confer short-term functional advantages within early adverse environments. Yet, in the long-term, they come at a cost as they heighten psychiatric risk.

The majority of neuroimaging studies of childhood maltreatment to date have focused on: i) perceptual/attentional processes, such as threat detection (e.g. Dannlowski et al., 2012, 2013; McCrory et al., 2011, 2013; Tottenham et al., 2011); ii) low-level executive functions, especially response inhibition (Elton et al., 2014; Lim et al., 2015; Mueller et al., 2010), and, more recently, iii) affect regulation (McLaughlin et al., 2015; Puetz et al., 2014, 2016) and iv) reward processing (Dennison et al., 2016; Goff et al., 2013; Hanson et al., 2015; Mehta et al., 2010). A number of consistent findings have emerged from these studies (see McCrory, Gerin, & Viding, 2017, for a recent review). First, in relation to threat processing several studies have reported
increased neural response (particularly in the amygdala) to threat-related cues, such as angry faces. Second, studies of explicit affect regulation and executive control have reported a pattern of increased activation in medial frontal regions, including the superior frontal gyrus and cingulate cortex in individuals who have experienced maltreatment. By contrast, during more implicit regulatory processes maltreatment experience has typically been associated with a pattern of reduced activation in a widespread fronto-limbic network. Thirdly, studies of reward processing have generally reported reduced activation in subcortical reward-related areas, in particular the striatum. These alterations in neural function are consistent with those reported in studies of individuals presenting with common psychiatric disorders (such as anxiety and depression) and may therefore represent markers of latent vulnerability to future psychopathology (McCrory, Gerin, et al., 2017; McCrory & Viding, 2015).

However, in addition to these domains of functioning, it is possible that the neurocognitive processes implicated in how an individual learns from their experience, may also be compromised in children exposed to maltreatment given their frequent exposure to chaotic and unpredictable environments (Cyr et al., 2010; Solomon & George, 1999). In recent years a series of studies have documented how altered reinforcement-based decision-making is implicated in a number of disorders associated with maltreatment, such as anxiety and depression (Eshel & Roiser, 2010; Hartley & Phelps, 2012). This suggests that altered reinforcement-based decision-making may help us index latent vulnerability to psychiatric disorder following childhood maltreatment experience.

2.1.1. Reinforcement-Based Decision-Making and Maltreatment

Evidence from neurodevelopmental sciences, psycholinguistics and even cognitive developmental robotics, suggest that our ability to detect patterns in the environment (i.e. contingency detection) is crucial for the acquisition of a number of
skills, ranging from basic perpetual abilities to higher-order cognitive functions, including language, affect regulation and, relevant to this study, reinforcement-based decision-making (Ellis, 2006; Nagai et al., 2006; Reeb-Sutherland et al., 2012). Despite preliminary findings linking maltreatment to neural changes in the context of reward processing (Dillon et al., 2009; Hanson et al., 2015; Mehta et al., 2010) and outcome monitoring (Lim et al., 2015), no prior study has investigated alterations in the neural systems mediating reinforcement-based decision-making and its computational components.

During normal development, our innate ability for contingency detection is fostered through sensitive caretaking. However, maltreatment experiences disrupt the species normative learning environment as the child is exposed to extreme and erratic parental affective reactions and / or a paucity or inconsistency in the availability of primary reinforcers. In the case of physical maltreatment, punishments are unpredictable and extreme, compromising contingency learning by biasing attention towards negative cues (e.g. McCrory et al., 2011; Shackman, Shackman, & Pollak, 2007). This in turn may limit the resources available for the development of a range of normative cognitive functions (Rogosch, Dackis, & Cicchetti, 2011), and reduce the opportunities necessary for learning by inducing a more avoidant exploratory style (Cicchetti & Doyle, 2016; Cicchetti, Rogosch, & Toth, 2006; Cyr et al., 2010). In the case of physical and emotional neglect, which represent common forms of maltreatment, basic reinforcers, such as food and emotional warmth, are not only less frequent but also less predictable (R. Gilbert, Widom, et al., 2009; Radford et al., 2011). These conditions are likely to contribute to the formation of abnormal expectancies representation of stimulus-outcome (S-O) and responses-outcome (R-O) associations. In other words, it is possible the maltreatment experience leads to alterations in the neurocomputational processes critical for reinforcement-based decision-making.
2.1.2. Neurocomputational Processes of Reinforcement-Based Decision-Making

Behavioural and computational neuroimaging research suggests that at least two processes underlie successful reinforcement-based decision-making: i) *expected value (EV)* representation (i.e. the reinforcement expectancies associated with a stimulus or action), and ii) *prediction error (PE)* signalling (i.e. the ability to detect the difference between the actual from the expected outcome associated with a stimulus or action) (Clithero & Rangel, 2013; O’Doherty et al., 2007; Rescorla & Wagner, 1972).

These two components are highly interdependent: PE signals are thought to alter the EV associated with a stimulus or action while EV representation is directly related to the strength of the PE response to a given outcome. Evidence from computational model-based studies and animal models have shown that these two processes engage overlapping fronto-striatal circuitry with its central nodes in the dorsal (DS) and ventral striatum (VS) and the orbitofrontal cortex (OFC) (Clithero & Rangel, 2013; O’Doherty, 2004, 2011; Tanaka et al., 2004; Valentin & O’Doherty, 2009). Other brain areas implicated in PE and EV signalling include the globus pallidus, thalamus, and medial and lateral temporal regions, such as the hippocampus, insula and superior temporal gyrus (Amiez et al., 2013; Bach et al., 2014; Glimcher, 2011; Zénon et al., 2016). Nodes associated with the salience network have consistently been implicated during PE signalling, including the amygdala, insula and dorsal portions of the cingulate gyrus (Amiez et al., 2013; Garrison, Erdeniz, & Done, 2013; Kosson et al., 2006).

2.1.3. Reinforcement-Based Decision-Making and Psychiatric Disorder

Extant neuroimaging and behavioural data suggest that alterations in the mechanisms underlying reinforcement-based learning and decision-making may contribute to the emergence and the maintenance of psychiatric conditions commonly associated with childhood maltreatment, such as anxiety, depression, conduct problems and substance abuse (Eshel & Roiser, 2010; S. Grant et al., 2000; Hartley & Phelps,
Neuroimaging studies of these disorders have typically reported a pattern of decreased neural activation during reinforcement expectancies representation and outcome anticipation in the orbito-striatal circuitry (Benson, Guyer, Nelson, Pine, & Ernst, 2014; Finger et al., 2011; Forbes et al., 2006, 2009; Galván & Peris, 2014; May, Stewart, Migliorini, Tapert, & Paulus, 2013; Schoenbaum et al., 2006; Smoski et al., 2009; Smoski, Rittenberg, & Dichter, 2011; Stringaris et al., 2015). Reduced neural response in the striatum (especially the caudate), OFC, and also the insula, have also been reported in recent computational fMRI studies of EV and PE representation in anxiety, conduct disorder and addiction (S. White et al., 2013, 2014, 2017; S. White, Tyler, Botkin, et al., 2016; S. White, Tyler, Erway, et al., 2016). This is in line with animal models of early adversity (e.g. Pani, Porcella, & Gessa, 2000) and with neuroimaging data of reward processing with institutionalised individuals (Mehta et al., 2010).

2.1.4. The Current Study

In the current study we examined reinforcement-based decision-making, and its neurocomputational correlates, as a potential candidate system for indexing latent vulnerability among maltreated individuals. In order to investigate maltreatment-related changes in EV and PE neural signalling, children (10-15 years) with and without documented abuse and neglect were presented in the scanner with a probabilistic passive avoidance task. This task has been used previously with individuals of similar age ranges, as well as with patients with psychiatric condition associated with maltreatment (S. White et al., 2013, 2017). Briefly, participants were required to learn what stimuli were associated with a higher probability of winning or losing points and respond to (actively approach) the reward stimuli and withhold the response to (passively avoid) the punishment stimuli.
Chapter 2

A model-based functional-magnetic-resonance-imaging (fMRI) analytic method was implemented to assess the computational processes underlying EV and PE representations. Such an approach offers the opportunity to generate regressors of interest that go beyond stimulus inputs and behavioural responses. This can help uncover hidden functions and variables by showing how the brain implements a particular process (O’Doherty et al., 2007). A model-based approach allowed us to detect with greater sensitivity the neural signal underlying the computations necessary for EV and PE representation.

2.1.5. Hypotheses

We hypothesised that for both approached and avoided stimuli, children with maltreatment experience would show reduced modulation of blood-oxygen-level-dependent (BOLD) responses by EV in four regions of interests (ROIs): the DS and VS striatum, the medial (mOFC) and the lateral (lOFC) orbitofrontal cortex. As noted earlier, this is in line with evidence from studies of reinforcement expectancies representation in those psychiatric disorders associated with maltreatment, with the animal literature of early adversity, and with some preliminary evidence from studies of extreme neglect (e.g. Forbes et al., 2009; Mehta et al., 2010; Smoski et al., 2011; Stringaris et al., 2015; White et al., 2013; White, Geraci, et al., 2016). In addition, consistent with substantial evidence of increased neural activation to negative stimuli and negative feedback among abused and neglected children (e.g. Lim et al., 2015; McCrory et al., 2011; McLaughlin et al., 2015), we hypothesised that children with maltreatment experience would show increased modulation of BOLD responses by PE during punishment feedback in four ROIs: the amygdala, the insula, and the anterior-(ACC) and mid- (MCC) cingulate cortex.

In addition, we conducted a number of exploratory analyses related to PE modulated brain response for reward feedback. Extant data from animal models of early
adversity and from studies of psychiatric conditions associated with maltreatment provide conflicting findings (Anisman & Matheson, 2005; Dillon et al., 2009; Hanson et al., 2015). Some studies suggest no maltreatment-related nor psychiatric-related changes in consummatory behaviour, positive outcomes processing and their related neural signalling in striatal and orbitofrontal regions (Dillon et al., 2009; Mehta et al., 2010; Pryce, Dettling, Spengler, Schnell, & Feldon, 2004; Stringaris et al., 2015; Ubl et al., 2015). On the other hand, other studies report a pattern of decreased neural signalling as well as reduced behavioural response to receiving reward (Gotlib et al., 2010; Hanson et al., 2015; Kalinichev, Easterling, & Holtzman, 2001; Matthews & Robbins, 2003; Willner, 2005).


2.2. Methods

2.2.1. Participants

41 children aged 10-15 years participated in this study: 20 with documented experiences of maltreatment (MT group) recruited via the Social Services Department and 21 with no prior Social Service contact recruited via schools / advertisements (NMT group). In the MT group, information about the severity, nature and duration of maltreatment was obtained through independent ratings by the child’s social worker (n = 16) or adoptive parent (n = 4). The children and their families (or foster carers) were contacted by 12 social workers’ teams in the Borough of Camden, London. Each team was approached during team-meetings to present the research project and the selection criteria. The caseload of each social worker was then reviewed to identify suitable participants. These included children at the edge of care, children in need or in care with substantiated past exposure to childhood abuse and/or neglect. At the time of the study participants were in either a stable foster care placement - as rated on the Kaufman measure of maltreatment (Kaufman et al., 1994) – or in a safe home environment. In particular, 7 children in the MT group were in a foster placement, 4 were adopted (and had previous experience of foster care) and 9 were living with their family/close relatives (of those, 4 were placed in foster care while growing up). Thus, 15 out of 20 participants in the MT group were placed in foster care at some point during childhood. The average number of foster care placements was 1.75 (s.d. 0.86).

For both the MT and NMT groups, the exclusion criteria included the presence of a pervasive developmental disorder, neurological abnormalities, standard MRI contra-indications and an IQ below 70. Two participants from each group were excluded from the final analyses due to movement artefacts leaving a final sample of 37 children (MT group, N=18; NMT group N=19). Consent was obtained from the child’s legal guardian and assent to participate was obtained from all children. Procedures were
approved by University College London (UCL) Research Ethics Committee (0895/002). Participant details of the final sample are reported in Table 2.1 below.

2.2.2. Measures

2.2.2.1. Maltreatment history. History and severity of abuse type (neglect, emotional, sexual and physical abuse and intimate partner violence) was provided by the child’s social worker or the adoptive parent (on the basis of Social Services reports). Severity of each abuse type was rated on a scale from zero (not present) to four (Table 2.2) in line with an established measure of maltreatment (Kaufman et al., 1994). In addition, age of onset and duration of maltreatment by subtype was estimated on the basis of Social Services’ available documentation.
### Table 2.1. Demographics and psychiatric symptomatology of Maltreated (MT) and Non-Maltreated (NMT) participants included in the fMRI analyses.

<table>
<thead>
<tr>
<th>Measures</th>
<th>MT (n=18)</th>
<th>NMT (n=19)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (Female)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>10 (56%)</td>
<td>13 (68%)</td>
<td>.42</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White &amp; White mixed</td>
<td>15 (83%)</td>
<td>13 (68%)</td>
<td>.37</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (11%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1 (6%)</td>
<td>3 (16%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td><strong>SES - Level of Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(beyond secondary)¹</td>
<td>9 (50%)</td>
<td>13 (60%)</td>
<td>.26</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (Years)</strong></td>
<td>13.01</td>
<td>13.15</td>
<td>.75</td>
</tr>
<tr>
<td><strong>Pubertal Status</strong>²</td>
<td>2.06</td>
<td>1.92</td>
<td>.49</td>
</tr>
<tr>
<td><strong>WASI-IQ</strong></td>
<td>108.06</td>
<td>108.84</td>
<td>.87</td>
</tr>
<tr>
<td><strong>TSCC³</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>43.28</td>
<td>43.47</td>
<td>.94</td>
</tr>
<tr>
<td>Depression</td>
<td>45.00</td>
<td>43.05</td>
<td>.42</td>
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<tr>
<td>PTSD</td>
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<td>42.16</td>
<td>.67</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>SDQ-P⁴</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Total Score</td>
<td>11.50</td>
<td>5.42</td>
<td>.01*</td>
</tr>
<tr>
<td>Emotional Symptoms</td>
<td>2.61</td>
<td>1.53</td>
<td>.11</td>
</tr>
<tr>
<td>Conduct Problem</td>
<td>2.72</td>
<td>.84</td>
<td>.103*</td>
</tr>
<tr>
<td>Hyperactivity/Inattention</td>
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<td>2.00</td>
<td>.009*</td>
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<td>1.05</td>
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<tr>
<td>Prosocial Behaviour</td>
<td>7.61</td>
<td>8.27</td>
<td>.42</td>
</tr>
</tbody>
</table>

**Abbreviations:** MT = Maltreated group; NMT = Non-maltreated group; WASI-IQ = 2 IQ-subscale derived from the Wechsler Abbreviated Scales of Intelligence (Wechsler, 1999); SES = Socio-economic-status; TSCC = Trauma Symptom Checklist for Children; SDQ-P = Strength and Difficulties Questionnaire – Parent report. * p<.05; ¹ Completed by caretaker; ² Composite score of self-report and parent rating of Puberty Development Scale (PDS); ³ Three MT and six non-MT participants meet the threshold for underresponsiveness. By excluding those individuals, the scores did not differ across the two groups; ⁴ Missing data for 1 MT.
Table 2.2. Abuse subtype frequency, severity, estimated onset age and duration (in years) in the MT group.

<table>
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<tr>
<th>Abuse Subtype</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
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<tr>
<td>Physical abuse (n=3)</td>
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<tr>
<td>Severity (0-4)</td>
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<td>.58</td>
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<tr>
<td>Mean age at onset</td>
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<td>Mean duration</td>
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</tr>
<tr>
<td>Neglect (n=15)</td>
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</tr>
<tr>
<td>Severity (0-4)</td>
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</tr>
<tr>
<td>Mean age at onset</td>
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<td>Mean duration</td>
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<td>4.52</td>
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<td>Sexual abuse (n=1)</td>
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<td></td>
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<tr>
<td>Severity (0-4)</td>
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<td>-</td>
</tr>
<tr>
<td>Mean age at onset</td>
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<td>-</td>
</tr>
<tr>
<td>Mean duration</td>
<td>.50</td>
<td>-</td>
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<tr>
<td>Emotional abuse (n=17)</td>
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<td></td>
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<tr>
<td>Severity (0-4)</td>
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<td>.77</td>
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<tr>
<td>Mean age at onset</td>
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<td>6.01</td>
<td>4.27</td>
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<tr>
<td>Domestic Violence (n=11)</td>
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<td>Severity (0-4)</td>
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<tr>
<td>Mean age at onset</td>
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<td>3.29</td>
</tr>
<tr>
<td>Mean duration</td>
<td>4.28</td>
<td>3.24</td>
</tr>
</tbody>
</table>

2.2.2.2. Psychiatric symptomatology. The Trauma Symptom Checklist for Children (TSCC), a self-report measure of affective and trauma-related symptomatology was administered to all participants (Table 2.1) (Briere, 1996). The Strengths and Difficulties Questionnaire (SDQ), was completed by parents or caregivers to assess general functioning (Table 2.1) (R. Goodman, 2001).

2.2.2.3. Cognitive ability. Cognitive functioning was assessed using two subscales of the Wechsler Abbreviated Scales of Intelligence (Wechsler, 1997).

2.2.2.4. Behavioural fMRI paradigm. A probabilistic passive avoidance task was administered in the scanner (Figure 2.1) (S. White et al., 2013, 2017). Participants were required to learn what stimuli were associated with a higher chance of winning or losing points. The task consisted of two phases: a decision-phase and a feedback-phase. During the decision-phase participants could either: i) actively approach (by a button press); or ii) passively avoid (by withholding a response) one of four stimuli that were presented for 1500ms. Each stimulus was presented 14 times in total (creating a total of...
56 trials). The stimulus presentation was followed by a randomly jittered fixation cross (0-4000ms). During the feedback-phase one of four outcomes was presented for 1500ms: “you win 50 points”, “you win 10 points”, “you lose 50 points”, “you lose 10 points”. The feedback was probabilistic as the reward and punishment stimuli lead to, respectively, gains and losses 70% of the time. Moreover, one reward stimulus was associated with a higher winning rate (i.e. a maximum gain of 185 points every 10 trials) while the other stimulus had a lower winning rate (a maximum gain of 70 points every 10 trials). Similarly, one punishment stimulus led to worst outcomes (a maximum loss of 185 points every 10 trials) compared to the other (a maximum loss of 70 points over 10 trials). Importantly, the participants could only win or lose points if a stimulus was approached. Thus, avoidance responses led to no feedback presentation and a fixation cross was presented instead (also for 1500ms). The feedback phase was followed by another randomly jittered fixation cross (0-4000ms).
Figure 2.1. The probabilistic passive avoidance task. The figure illustrates the behavioural paradigm used in the scanner. Participants chose to either approach (via a button press) or avoid (by withholding a response) four stimuli presented one at a time. Reinforcement was probabilistic such that over the course of the task two objects would result overall in gains and the other two in losses. (a) Following an approach response (i.e., a button press), a rewarding feedback is received. (b) Following an approach response, a punishing feedback is received. (c) Following an avoidance response (no button press), no feedback is received (i.e., no losses or gains).

2.2.2.5. fMRI data acquisition. All data were acquired on a 1.5 tesla Siemens (Siemens Medical Systems, Erlangen, Germany) Avanto Magnetic Resonance Imaging (MRI) scanner with a 32-channel head coil during 1 run of approximately 7 minutes. A total of 127 T2* weighted echo-planar (EPI) volumes were acquired, covering the whole brain with the following acquisition parameters: slice thickness: 2mm; TR: 85ms; TE: 50ms; FoV: 192 mm x 192 mm²; 35 slices per volume, gap between slices: 1mm; flip angle: 90°). A high-resolution, three-dimensional T1- weighted structural scan was acquired with a magnetization prepared rapid gradient echo sequence. Imaging parameters were: 176 slices; slice thickness = 1 mm; gap between slices = 0.5 mm; echo time = 2730 msec; repetition time = 3.57 msec; FoV = 256m2; matrix size = 256²; voxel size = 1mm³.
2.2.3. Data analysis

2.2.3.1. Behavioural analyses. Behavioural performance on the task was assessed in relation to the number of omission errors (i.e. the number of trials in which reward stimuli were avoided) and the number of commission errors (i.e. the number of trials in which punishment stimuli were approached) as well as the total number of errors (i.e. the sum of omission and commission error). In addition, to test the validity of the behavioural model, we examined whether the EV estimates for each trial predicted behaviour (i.e. approach and avoidance responses).

2.2.3.2. fMRI analyses. Data analyses were conducted using the software package SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8) implemented in Matlab 2015a (The MathWorks Inc., 2012b).

Image preprocessing. After discarding the first 3 volumes of each run to allow for T1 equilibration effects, each participant’s scans were realigned to their own first image using a least squares approach and a 6 parameter (rigid body) spatial transformation. As part of the alignment procedure, we chose a separation estimate of 4mm between the points sampled in the reference image because smaller sampling distances give more accurate results. Before estimating the realignment parameters, we used a 5mm FWHM Gaussian smoothing kernel. When estimating the optimum transformation, images were sampled using a high degree of interpolation (2nd degree B-spline during the estimation and 4th degree B-spline during reslicing). Images were wrapped around the Y axis. To reduce movement-related artefacts, we additionally included the six motion parameters as regressors and an additional regressor to model images that were corrupted due to head motion >1.5 mm and were replaced by interpolations of adjacent images (<10% of participant's data for 9 NMT and 5 MT; no difference between groups, \( p = .22 \)). Images were also visually inspected to assure quality and to detect potential motion artefacts that were not detected during the
automated preprocessing pipeline. Four participants (two in each group) were excluded from the final analyses due to more than 10% of the images being corrupted by head motion > 1.5mm. This left a final sample of 19 NMT and 18 MT (total n=37).

The realigned scans of each participant were co-registered with each participants T1-weighted images. Segmentation was performed using the ICBM tissue probability map. The warping regularisations were set to 1, the warp frequency cut-off was set to 25 to allow deformation to be modelled. The images were then normalised into standard Montreal Neurological Institute (MNI) space using deformation fields from the T1-segmented images by resampling to a voxel size of 3mm³ using non-linear transformations. The resulting images were smoothed with a 6mm Gaussian filter to minimize noise and residual difference in gyral anatomy. A high-pass filter at 128 seconds was also applied to remove low-frequency drifts.

First level (model-based) analysis. Fixed-effects statistics for each individual were calculated by convolving the canonical hemodynamic response function with the box-car functions modelling the four conditions: stimulus approached, stimulus avoided, reward received, punishment received. Furthermore, linear polynomial expansion was applied to the percent signal change at each voxel and time point using the EV and PE estimates as parametric modulators during, respectively, the decision-phase and the feedback-phase. In particular, the behavioural data was used to model the EV and PE for each trial for each participant based on the Rescorla-Wagner (R-W) model of conditioning (O’Doherty et al., 2007; Rescorla & Wagner, 1972). The EV for the first trial of each object was set to 0 and was then updated using the following formula: $EV(t) = EV(t-1) + (\alpha \cdot PE(t-1))$. That is, EV of the current trial (t) equalled the EV of the previous trial (t-1) plus the PE of the previous trial multiplied by the learning rate ($\alpha$). The PE for the current trial equalled the Feedback (F) of the current trial minus the EV of the current trial: $PE(t) = F(t) - EV(t)$. These parameters were then used for the model-based fMRI analyses.
The learning rate ($\alpha$) used to calculate the $EV(t)$ was set to 0.354. This was calculated by taking the average across all individually estimated learning rates via a model-fitting simulation. In particular, a reinforcement-based learning model was fit to the choice data of our participants to determine two free parameters: the learning rate $\alpha$ and the inverse temperature $\beta$ (Averbeck et al., 2013; Costa, Tran, Turchi, & Averbeck, 2014; Lindner et al., 2016). These were estimated through nonlinear optimization by maximizing the likelihood of the actual choices of participants to approach or avoid each stimulus. The probability, $P$, of approaching a stimulus $i$, given its value, $V$, was calculated using the softmax rule:

$$P_i(t) = \frac{e^{\beta V_i(t)}}{1 + e^{\beta V_i(t)}}$$

The log-likelihood was then calculated as follows:

$$LL = \sum_{t=1}^{T} \log [c_k(t)P_i(t) + (1 - c_k(t))(1 - P_i(t))]$$

Where $c_k = 1$ when a participant approached stimulus $i$ in trial $t$ and $c_k = 0$ when a subject avoided stimulus $i$, and $T$ is the total number of trials. The negative log-likelihood was minimized using fminsearch in Matlab. The initial values of $\alpha$ were drawn from the standard uniform distribution on the open interval $(0, 1)$. The initial values of $\beta$ were drawn from the standard uniform distribution. The model fit was repeated 100 times, each time with different initial values for the free parameters drawn from these distributions. The values of the free parameters were set at the value for which the iteration resulted in the minimum log-likelihood. The overall free parameters across the group ($\alpha$ and $\beta$) were then calculated by taking the average across all individually estimated $\alpha$ and $\beta$ parameters. These parameters were then used for all participants.
Second level analysis. Group analyses were conducted using a series of independent samples t-tests by entering the individual statistical parametric maps containing the parameter estimates of the four conditions as fixed effects and an additional ‘subject factor’ for random effects. For the decision-phase, activation in the NMT group was compared to the activation in the MT individuals for: i) the approached stimuli modulated by the EV estimates; ii) the avoided stimuli modulated by the EV estimates. For the feedback-phase, activation in the NMT group was compared to the activation in the MT individuals in relation to: iii) the punishment feedback modulated by the PE value; exploratory analyses were also conducted to examine iv) the reward feedback modulated by the PE value.

Given our a priori hypotheses, small-volume corrected ROI analyses (thresholded at p < .05 corrected for Family Wise Error; FWE) were performed, on the decision-phase data, on the DS, VS, medial-orbitofrontal-cortex (mOFC) and lateral-orbitofrontal-cortex (lOFC). Masks for the mOFC and IOFC were taken from the Automated Anatomic Labelling (AAL) atlas (WFU PickAtlas). The VS and DS masks were created based on the findings by Martinez et al. (2003) on the functional subdivisions of the striatum. For the punishment feedback condition, small volume-corrected ROI analyses (thresholded at p < .05 corrected for Family Wise Error; FWE) were performed in the amygdala, insula, anterior cingulate cortex (ACC) and midcingulate cortex (MCC). Masks for these regions were also taken from the AAL atlas (WFU PickAtlas).

For completeness, whole brain analyses were also conducted, using Monte-Carlo Simulation (3D ClusterSim; Ward, 2000) correcting for multiple comparisons. Cluster-size corrected results are reported (voxel-wise p < .005, ke = 75) corresponding to \( p = .05 \) FWE corrected.
2.3. Results

2.3.1. Behavioural Results

2.3.1.1. Demographics and symptomatology. The MT and NMT groups did not statistically differ in age, gender, pubertal status, ethnicity, socio-economic-status (SES), intelligence (IQ), and self-reported internalising symptomatology – depression, anxiety and PTSD symptoms on the TSCC (Table 2.1). The SDQ revealed difference among the two groups in overall parent-reported functioning, and in relation to the conduct and hyperactivity scales.

2.3.1.2. Behavioural performance. The MT and NMT groups did not differ significantly in task performance at the behavioural level. In particular, they did not differ in relation to number of total (MT Mean = 23.22, SD=8.39; NMT Mean = 23.42, SD = 6.89; t = .08, df = 35, p = .94) omission (MT Mean = 9.89, SD = 4.73; NMT Mean = 9.39, SD = 4.65; t = .33, df = 35, p = .75) and commission errors (MT Mean = 13.83, SD = 5.65; NMT Mean = 13.53, SD = 5.47; t = -.17, df = 35, p = .87).

2.3.1.3. Model validity. To test the validity of the computational model we examined the extent to which the estimated EV predicted participant’s approach and avoidance responses. Consistent with the model, there was a significant relationship between predicted and observed behaviour [average correlation: r = .23; one sample t-test (null r = 0), t = 4.59, df = 36, p < .001]. Moreover, the model was equally predictive of behaviour across groups (t = -.15, df = 35, p = .89).

2.3.2. fMRI Results

2.3.2.1. Main effects in the Non-Maltreated group. Whole-brain main effect analyses were performed within the NMT group in order to ensure that the four conditions (i.e. approach trials, avoidance trials, positive feedback and negative feedback) elicited activation patterns that were comparable to previous studies
As shown in Table 2.3, within-group analyses for the NMT participants revealed that EV representation during the decision-phase for both approached and avoided stimuli recruited, as expected, the fronto-striatal circuitry (e.g. DS, mOFC, IOFC), as well regions, such as the insula and the thalamus, that have also been extensively linked with the processing of outcome expectancies (e.g. Bach et al., 2014; Barkley-Levenson & Galván, 2014; Glimcher, 2011; Kosson et al., 2006; Payzan-LeNestour, Dunne, Bossaerts, & O’Doherty, 2013; Tanaka et al., 2016; Zénon et al., 2016).

However, no activation, modulated by PE, was found for the main effects of reward and punishment feedback conditions within the NMT group. It is worth mentioning that feedback was provided after approach trials only, which amounted to about half (55%) of all the decision-phase trials. Moreover, the feedback trials were further split into reward (57%) and punishment (43%) outcomes. Therefore, limited statistical power likely accounts for the lack of main-effect findings for feedback conditions. For this reason, a more lenient statistical threshold was applied: while maintaining the same p-value (p<.005), the ke (cluster extent) was reduced from 75 to 10, so that significant activation in smaller clusters could be detected (Table 2.4).

With this less stringent threshold, during reward feedback, NMT participants recruited a network that has been previously associated with PE and reward outcome processing, including the superior and middle temporal cortex (especially their posterior sections), and the basal ganglia, including the globus pallidus, claustrum and DS (Carlson, Foti, Mujica-Parodi, Harmon-Jones, & Hajcak, 2011; Garrison et al., 2013; Wunderlich, Rangel, & O’Doherty, 2009). Moreover, during the punishment feedback, areas that have been specifically linked to PE for negative outcomes were also recruited, such as the precentral gyrus, the dACC/MCC and also dorso-medial and dorso-lateral frontal regions, including the dorsal sections of the medial and middle frontal gyrus (Amiez et al., 2013; Garrison et al., 2013).
Chapter 2

To summarise, as expected, the approach and avoidance conditions activated a network that has been previously linked with EV representation and outcome anticipation (Table 2.3). Similarly, (although at a more lenient cluster threshold) the punishment and reward feedbacks elicited brain activity in areas associated with PE signalling (Table 2.4).
Table 2.3. Whole-Brain\(^1\) results for the main-effects of decision type (approach and avoidance) and feedback type (reward and punishment) within the Non-Maltreated (NMT) group.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Brain region</th>
<th>R/L</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>ke</th>
<th>t</th>
<th>Z</th>
</tr>
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<td><strong>Approached Stimuli</strong></td>
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</tr>
<tr>
<td></td>
<td>Globus Pallidus ext. VS, Thalamus</td>
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<td><strong>Punishment Feedback</strong></td>
<td><strong>Modulated PE</strong></td>
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\(^1\)Whole Brain analyses corrected/thresholded at ke=75 \(p<.005\) (equivalent to \(p<.05\) FWE). Abbreviations: R/L = Right/Left; ke = cluster extent; MT = Maltreated group; NMT = Non-Maltreated group; DS = Dorsal striatum; VS = Ventral striatum; mOFC = Medial orbitofrontal cortex; IOFC = Lateral orbitofrontal cortex; BA10 = Brodmann area 10; MTG = Middle temporal gyrus; STG = Superior temporal gyrus; dACC = Dorsal anterior cingulate cortex; vACC = Ventral anterior cingulate cortex; vIPFC = Ventrolateral prefrontal cortex.
### Table 2.4. Whole-Brain results for the main-effects of feedback type within the Non-Maltreated (NMT) group (reduced threshold at ke = 10).

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1Whole Brain analyses corrected/thresholded at ke=10 p<.005.

**Abbreviations:** R/L = Right/Left; ke = cluster extent; MT = Maltreated group; NMT = Non-Maltreated group; DS = Dorsal striatum; MCC = Mid-cingulate cortex; MTG = Middle temporal gyrus; STG = Superior temporal gyrus; dACC = Dorsal anterior cingulate cortex; dmPFC = Dorso-medial prefrontal cortex; dlPFC = Dorso-lateral prefrontal cortex.
2.3.2.2. Decision-phase activation modulated by EV. In line with our hypotheses, the MT group showed reduced modulation of BOLD activity in the DS (in particular in the caudate nucleus), the mOFC and the IOFC as a function of EV when choosing to approach a stimulus (Table 2.5, Figure 2.2). However, contrary to our hypotheses, no statistically different activation was found in the VS (Table 2.5, Figure 2.2).

When choosing to avoid a stimulus, the MT group showed reduced modulation of BOLD activity as a function of EV in all four ROIs (Table 2.5, Figure 2.3). Unexpectedly, the MT group also showed a pattern of increased bilateral modulation as a function of EV in the putamen (DS) when choosing to avoid a stimulus (Table 2.5).

Findings from the whole brain analyses (Table 2.6) were consistent with our ROI analyses, indicating a widespread pattern of reduced EV signalling (for both approach and avoidance responses) and also implicated other brain regions including the globus pallidus and temporal regions, such as the insula and the hippocampus (which have in some previous studies been implicated in the representation of reinforcement expectancies).

Interestingly, the whole-brain data revealed that the MT group showed a pattern of increased activation in fronto-dorsal regions during EV processing for both approached and avoided stimuli (Table 2.6). In particular, the dorsomedial and dorsolateral prefrontal cortex (dmPFC, dLPFC) (e.g. Brodmann Area 9) and the dACC and mid-cingulate cortex (MCC). These unexpected findings were interrogated further in post-hoc analyses reported below.

Finally, covarying for the symptoms/demographic variables for which we found a group difference (i.e. the SDQ conduct problems and hyperactivity/inattention scales or the SDQ total score) did not alter the findings.
2.3.2.3. Feedback phase activation modulated by PE signalling. No group difference in BOLD activity as a function of PE was found during punishment feedback in the four regions of interests (i.e. amygdala, insula, dACC and MCC) (Table 2.5). However, MCC activity modulated by PE fell just above traditional significance threshold level (p = .052, FWE). For completeness whole brain analyses were also conducted (Table 2.6). Increased BOLD response modulated by PE was found among MT individuals in regions associated with PE processing, such as the MCC (which approached significance in the ROI analyses), the thalamus and the superior temporal gyrus (Table 2.6) (Amiez et al., 2013; Garrison et al., 2013). During reward feedback, no difference was found between the two groups (Table 2.6). Covarying for conduct problems and hyperactivity/inattention, and also for overall functioning (i.e. SDQ total score), did not alter the findings.
Figure 2. Peak activation in each region of interest modulated by expected value during approach responses. Error bars represent 95% confidence intervals. *p < .05 corrected for family-wise error. Initial threshold p < .05 uncorrected. DS, dorsal striatum; mOFC, medial orbital frontal cortex; BOLD, blood oxygen level dependent; VS, ventral striatum; lOFC, lateral orbitofrontal cortex.
Chapter 2

Figure 2.3. Peak activation in each region of interest modulated by expected value during avoidance responses. Error bars represent 95% confidence intervals. * p < .05 family-wise error. Initial threshold p < .05 uncorrected. DS, dorsal striatum; mOFC, medial orbital frontal cortex; BOLD, blood oxygen level dependent; MT, maltreatment; VS, ventral striatum; lOFC, lateral orbitofrontal cortex.
Table 2.5. ROI\(^1\) Regions Demonstrating Group-Level Differential BOLD Responses During the Task

**Contrasts for Approached Stimuli Modulated by Expected Value**

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*Contrasts for Punishment Feedback Modulated by Prediction Error*

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\(^1\)ROI analyses corrected at p<.05 FWE. Initial threshold p<.005

**Abbreviations:** R/L = Right/Left; ke = Cluster extent; MT = Maltreated group; NMT = Non-Maltreated group; ROI = Region of interest; DS = Dorsal striatum; VS = Ventral striatum; mOFC = Medial orbitofrontal cortex; IOFC = Lateral orbitofrontal cortex.
### Table 2.6. Whole Brain Regions Demonstrating Group-Level Differential BOLD Responses During the Task

#### Contrasts for Approached Stimuli Modulated by Expected Value

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#### Contrasts for Avoided Stimuli Modulated by Expected Value

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Contrasts for Reward Feedback Modulated by Prediction Error

Contrasts for Punishment Feedback Modulated by Prediction Error

NMT > MT

MT > NMT

Whole Brain analyses corrected/thresholded at ke=75 p<.005 (equivalent to p<.05 FWE).

Abbreviations: R/L = Right/Left; ke = cluster extent; MT = Maltreated group; NMT = Non-Maltreated group; DS = Dorsal striatum; VS = Ventral striatum; mOFC = Medial orbitofrontal cortex; lOFC = Lateral orbitofrontal cortex; dlPFC = Dorsolateral prefrontal cortex; BA9 = Brodmann area 9; MTG = Middle temporal gyrus; STG = Superior temporal gyrus; MTL = Medial temporal lobe; dACC = Dorsal anterior cingulate cortex; MCC = Middle cingulate cortex; PCC = Posterior cingulate cortex.
Chapter 2

2.3.3. Post-hoc Analyses

Three sets of post-hoc analyses were conducted. First, we tested whether the pattern of altered neural activation found among maltreated individuals during EV representation (Table 3) was associated with maltreatment duration and severity. These correlational analyses indicated that within the MT group, maltreatment duration was associated with reduced BOLD activity by EV in the mOFC during approach trials ($r = -46, p = .03$).

Second, we examined whether reduced activation in orbito-striatal regions during EV representation in the MT group (Table 3) was associated with increased psychiatric symptomatology. Previous clinical computational fMRI studies that used the same passive avoidance paradigm implemented here, have found that, during EV processing, patients with anxiety or conduct disorder show a highly comparable neural profile to the MT group in this study (S. White et al., 2013, 2017; S. White, Tyler, Erway, et al., 2016). These clinical studies have consistently reported a pattern of reduced activation, modulated by EV, in the DS (in particular the caudate) and in the medial and lateral orbitofrontal cortices (S. White et al., 2013, 2017; S. White, Tyler, Erway, et al., 2016). Thus, our correlation analyses focused on these two areas (i.e. OFC and DS). Measures of anxiety (using the TSCC anxiety subscale and the SDQ emotional problems subscale) and conduct problems (using the SDQ conduct disorder subscale) were correlated with the peak activation in the lOFC, mOFC and DS (caudate) during EV processing within the MT group. Consistent with prior studies of EV representation with anxiety patients (S. White et al., 2017), reduced EV neural signalling during approach trials in the lOFC ($r = -.60, p = .004$) and in the DS ($r = -.41, p = .04$) was associated with self-reported (TSCC) anxiety symptoms levels within the MT group. Moreover, we found a significant correlation between parental reported measures of emotional problems on the SDQ ($r = -.41, p = .04$) and lOFC activation during avoidance trials.
Finally, post-hoc analyses were performed to interrogate the unexpected whole-brain finding of increased activity, within the MT group, in a large fronto-dorsal cluster during EV representation during both approach and avoidance (Table 4). One interpretation for the observed increased EV neural signalling among MT individuals in fronto-dorsal regions is that it represents an adaptive response, compensating for reduced signalling in areas traditionally associated with EV computations (such as the DS, VS, mOFC, lOFC, insula and hippocampus). In line with this post-hoc hypothesis, we found that MT individuals’ total error rate was negatively correlated with fronto-dorsal activation modulated by EV during both approach (r = -.45, p = .03) and avoidance (r = -.41, p < .05) trials. This suggests that the degree of engagement of this fronto-dorsal network during EV processing contributes to improved behavioural performance on the task. To explore this effect further, the total error rate was then divided into omission and commission error rates. It was found that while the BOLD response by EV in this fronto-dorsal cluster during both approach and avoidance trials was significantly correlated with omission errors (r = -.64, p = .002 and r = -.43, p = .04 respectively), that was not the case for the commission errors (r = -.15, p = .28 and r = -.26, p = .15 respectively).
2.4. Discussion

To our knowledge this is the first study to investigate the extent to which children with documented experiences of childhood maltreatment show alterations in the neural systems engaged with specific computations of reinforcement-based decision-making. We employed a probabilistic passive avoidance task, in combination with a model-based fMRI analytic approach, in order to assess neural responses associated with EV representation and PE signalling for reward and punishment cues. At the behavioural level the children who had experienced maltreatment (MT group) did not differ from a group of non-maltreated (NMT) peers. By contrast, at the neural level the MT group differed from their peers in three main ways. First, the MT group demonstrated a pattern of reduced activity modulated by EV in a network commonly associated with reinforcement expectancies representation, including the orbito-striatal circuitry. Second, during losses, the MT compared to the NMT group showed increased PE signalling in frontal and temporal regions, including the mid-cingulate gyrus and the superior temporal gyrus. Third, the MT group showed increased activity in the putamen and in fronto-dorsal regions during EV representation.

2.4.1. EV Modulated Neural Response

2.4.1.1. Reduced EV modulated neural response in cortico-limbic circuitry. As predicted, maltreatment experience was associated with reduced BOLD response by EV in both approach and avoidance trials in the medial (mOFC) and the lateral (lOFC) orbitofrontal cortex, and in the DS, especially in the caudate nucleus. Reduced response in the VS was also observed, but only in the avoidance trials. Our whole-brain analyses were consistent with these findings, and also implicated the globus pallidus, the subthalamic nucleus, insula and the hippocampus. These regions have been previously shown to be involved in reinforcement expectancy representation in typical individuals.
reduced neural response in these same regions has been reported in studies of psychiatric disorders associated with maltreatment experience including anxiety, conduct disorder and depression (Gotlib et al., 2010; Ubl et al., 2015; S. White et al., 2013, 2017). This pattern of reduced neural response is thought to reflect impairments in the precision of EV representation (S. White et al., 2013, 2017). As such, the findings of the current study may reflect alterations in reinforcement-based decision-making that may in turn confer increased latent vulnerability to psychiatric disorder. Our post-hoc analyses, demonstrating that reduced activation in the caudate and the OFC was related to higher levels of anxiety symptomatology in the MT group, are consistent with this hypothesis. It is also noteworthy that post-hoc analyses indicated a dose-dependent negative association between maltreatment duration and degree of activation in these areas, suggesting that greater maltreatment exposure was associated with more marked neurocognitive alterations.

2.4.1.2. Increased EV modulated neural response in the putamen. During EV processing for avoided stimuli, the MT group showed an unexpected pattern of increased activation relative to the NMT group in the putamen. This may initially appear surprising, given that the MT group also showed a pattern of reduced EV-related signalling in the caudate. However, studies of disorders associated with early adversity, such as depression (see Zhang et al., 2013 for a meta-analysis) and anxiety (S. White et al., 2017), suggest that the caudate (but not the putamen) is less active during outcome anticipation. Moreover, data from a recent study investigating affect processing and regulation, reported that children who have experienced maltreatment also show greater engagement of the putamen (but not the caudate) to negative cues (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015).
The putamen and the caudate are connected to different brain regions and are understood to perform different functions (M. X. Cohen & Frank, 2009; Grahn, Parkinson, & Owen, 2008). The caudate is thought to be crucial for EV representation, including response-outcome (R-O) and stimulus-outcome (S-O) associations, flexible cognition and it underpins goal-directed behaviour (Grahn, Parkinson, & Owen, 2009). By contrast, outcome expectancy is not evaluated in the putamen. Rather, this region has been implicated in less complex and less flexible types of behavioural and cognitive representations, such as habit learning (Devan, Hong, & McDonald, 2011; Grahn et al., 2008). It has been suggested that the putamen may be recruited during the initial phases of reinforcement-based learning, with the caudate becoming more dominant during later stages of instrumental learning (Brovelli, Nazarian, Meunier, & Boussaoud, 2011).

One possible explanation for the pattern of findings in the DS, is that children with experience of maltreatment sustain activation of the putamen throughout the task, unlike their peers who progress to more flexible and complex reinforcement-based representations (indexed by their greater activation of the caudate and other regions involved in higher-order EV processing). For maltreated individuals it may be paramount and more adaptive to learn rapidly (at the expense of more flexible and complex EV processing) which elements in the environment are associated with punishment and should be avoided. The development of more flexible and higher order cognition in relation to reinforcement and contingency learning to negative cues may be less optimal (or even counterproductive) in environments where behavioural responses must be quickly learned to avoid punishment. Future studies are required to investigate this hypothesis by parsing out early from later stages of reinforcement-based learning differences in MT and NMT individuals.

2.4.1.3. Increased EV modulated neural response in the dorso-medial and dorso-lateral frontal cortex. Our whole-brain analyses revealed a pattern of increased activation in an extended dorso-frontal network that includes the dorso-medial (dmPFC)
and dorso-lateral (dIPFC) prefrontal cortex (especially Brodmann Area 9), the dorsal anterior-cingulate-cortex (dACC) and also the middle cingulate cortex (MCC). Although unexpected, this finding is in line with neuroimaging studies of outcome anticipation among depressed children and adolescents (Forbes et al., 2006, 2009). Recent neuroimaging studies of maltreatment have found that despite no differences in task performance, MT children show increased activation in dorso-medial and dorso-lateral prefrontal regions while performing different cognitive functions – e.g. explicit affect regulation (McLaughlin et al., 2015) and response inhibition (Lim et al., 2015). It has been proposed that greater engagement of these regions, involved in effortful control, may represent a compensatory mechanisms as more effort may be required for comparable task performance by children who have experienced maltreatment (McLaughlin et al., 2015).

In the context of this study, the engagement of this dorso-frontal network may similarly represent an adaptive response, compensating for the reduced signalling in brain areas traditionally associated with EV representation (such as the DS, VS, mOFC, lOFC, insula and hippocampus). In line with this potential explanation, our post-hoc correlational analyses indicated that, among maltreated individuals, EV modulated activation in this dorso-frontal network was associated with improved task performance, and in particular with improvement in omission (but not commission) error rate. On this basis we speculate that a tendency for an avoidant response in the MT group (as indexed by increased neural response to punishment) is attenuated by the increased activity found in fronto-dorsal region during EV processing. If this is the case, it suggests that the comparable behavioural performance of the groups may be driven by differential neuro-computational processes. Moreover, it is possible that the pattern of widespread deactivation in fronto-orbital (e.g. mOFC) and striatal regions among individuals with a history of maltreatment may be directly linked to the increased engagement of inhibitory fronto-dorsal areas. Future studies may be able to address this hypothesis.
directly by systematically analysing functional connectivity patterns during reinforcemen
t-based decision-making. It is possible that focal deactivation of the orbito-
striatal network found in this study is part of widespread connectivity alterations in brain regions involved in performance monitoring and reward-based learning (Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004).

2.4.2. PE Modulated Neural Response

2.4.2.1. PE for reward feedback. No group difference was found during PE modulated brain activation to reward. This is in line with a large set of studies that suggests that consummatory (unlike anticipatory) neurocognitive and behavioural processes are not implicated in disorders such as depression (Stringaris et al., 2015; Ubl et al., 2015), nor appear associated with early adverse experiences (Dillon et al., 2009; Mehta et al., 2010; Pryce et al., 2004).

2.4.2.2. PE for punishment feedback. As noted earlier, extant studies on threat-
detection and salience processing among maltreated children and adults have found a consistent pattern of increased activation in several regions implicated in the detection of negative cues (e.g. Dannlowski et al., 2012; McCrory et al., 2011). On this basis, we also expected an increased pattern of PE signalling during punishment feedback in the MT group in four regions: the amygdala, insula, anterior cingulate cortex (ACC) and in the mid-cingulate cortex (MCC). However, no group differences were found in these ROIs. On the other hand, the whole-brain data revealed a widespread pattern of increased activation in frontal, temporal and subcortical areas, including the MCC, the superior temporal gyrus, the post-central gyrus and the thalamus. This network has been extensively implicated in PE error signalling in normative samples (Amiez et al., 2013; Garrison et al., 2013). In addition, these findings are in line with the data from the only study that has investigated (non-computationally) PE in maltreated children (Lim et al., 2015). Maltreatment-related alterations in PE processing for negative information may
therefore be system-specific insofar as they do not overlap with the brain network that is devoted to salience detection and threat-processing (e.g. insula and amygdala). Future studies should test this hypothesis by directly comparing PE and threat-detection signalling in MT and NMT individuals.

2.4.3. Childhood Maltreatment, Decision-Making & Latent Vulnerability

As discussed in the introduction, sensitive caregiving and appropriate parental scaffolding plays an important role in the normative development of contingency detection, which is a *sine qua non* for the acquisition of a number of skills and higher order cognitive functions, including reinforcement-based decision-making (Ellis, 2006; Nagai et al., 2006; Reeb-Sutherland et al., 2012). However, this developmental learning process may be compromised by an impoverished and chaotic environment and by several other aspects associated with the maltreatment experience, such as unpredictable and severe forms of punishment.

It has been shown that an abusive environment can lead to the preferential diversion of attentional resources towards threat-related cues in the environment (McCrorry et al., 2011; Pollak & Tolley-Schell, 2003; Pollak et al., 2005). Early adverse experiences may also contribute to the misattribution of negative valence to social cues in the environment that are actually neutral and non-threatening, in line with a number of psychiatric presentations (Cooney, Atlas, Joormann, Eugene, & Gotlib, 2006; Leppänen, Milders, Bell, Terriere, & Hietanen, 2004). Negative attention and attribution biases may, in turn, contribute to the development of abnormal EV representation in several ways: i) by diverting away the cognitive and attentional resources necessary for normal associative learning (Rogosch et al., 2011); ii) by over-weighting stimulus-outcome (S-O) and response-outcome (R-O) associations in favour of negative information; or iii) by reducing the amount and quality of exploratory behaviour, crucial
for contingency learning and the development of normative EV and PE representations (Cicchetti & Doyle, 2016; Cicchetti et al., 2006).

An alternative view is that physical and emotional neglect, common forms of childhood maltreatment (R. Gilbert, Widom, et al., 2009; Radford et al., 2011), create aberrant environments that distort the development of flexible and contingency-based learning and context-appropriate higher-order representations (e.g. Fonagy, Gergely, Jurist, & Target, 2004; Gergely & Watson, 1999), leading to widespread alterations in EV and PE neural signalling. It is known that these forms of neglect are characterised by environments were primary reinforcers (e.g. food) are less predictable and frequent, and where there is a lack of timely and sensitive positive affective communication and emotional reciprocity.

The ability to envisage the consequences and predict the outcomes associated with a given stimulus or action is crucial for our ability to orient, motivate and flexibly guide behaviour towards specific goals and navigate the environment successfully (O’Doherty, 2004). However, abnormal EV representation can compromise this ability, leading to suboptimal decision-making and maladaptive outcomes, as documented in a number of common psychiatric disorders (Eshel & Roiser, 2010; Hartley & Phelps, 2012; Stringaris et al., 2015; Zhang et al., 2013).

The maltreatment-related neurocomputational alterations found in this study, however, rather than being the result of adaptation and recalibration to an early environment characterised by unpredictable and extreme punishment and/or paucity of reinforcements, may also be the outcome of more global deficits which have accrued due to insufficient environmental inputs during development. Nevertheless, the likelihood that global deficits characterize the current sample of children with a history of maltreatment is low given that these children are comparable with their non-maltreated peers in relation their verbal and non-verbal reasoning skills (i.e. same IQ
tests scores do not suggest the presence of global and domain-unspecific deficits).

Therefore, the evidence presented here is in line with the view that abnormalities in reinforcement-based decision-making may represent one neurocognitive candidate system to index latent vulnerability among individuals who have experienced early adversity. However, future studies are required to investigate the prognostic value of such alterations (e.g., whether they predict increased psychiatric risk in the future), and also to investigate if they contribute to adaptive short-term outcomes in the context of a maltreating household.

2.4.4. Limitations and Conclusions

The current study has a number of limitations. First, this study has a relatively small sample size and the design is cross-sectional in nature. A longitudinal design and larger sample will be necessary to investigate whether maltreatment-related alterations found in reinforcement-based decision-making are associated with future psychiatric disorder. A second limitation pertains to the design of the passive avoidance task employed here. Although a well-validated measure of reinforcement-based decision-making used in a number of prior developmental studies of psychiatric groups, this measure does not allow the parsing of EV processing from motor-output responses during the approached trials. Future neuroimaging investigations, that require the approach (or avoidance) responses to be executed after stimulus presentation, would address this issue directly. Nevertheless, the model-based fMRI analytic approach implemented here allowed the estimated EVs (on a trial-by-trial and individual basis) to be convolved with the BOLD signal, facilitating the partialling out of the brain signal that was unrelated to the representation of reinforcement expectancies. Third, a recent study has shown that maltreatment exposure is more detrimental to the development of executive control functions when it occurs earlier (during infancy) than later in life (during childhood) (Cowell, Cicchetti, Rogosch, & Toth, 2015). Executive control
functions, including working memory, cognitive flexibility and inhibitory control, are central to the computations that underlie reinforcement-based learning and decision-making (e.g. Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). Therefore, an examination of the timing of maltreatment exposure may contribute to a more precise understanding of the neurocomputational mechanisms through which maltreatment interferes with the development of reinforcement-based decision-making. Our post-hoc analyses suggest that greater duration of maltreatment relates to more considerable neurocognitive alterations; however, the heterogeneity and size of the recruited sample did not allow us to systematically investigate the existence of periods during which the effect of early adversity may be particularly potent (i.e. sensitive periods – Knudsen, 2004). This remains an important open question to be addressed in the future.

To conclude, this is the first study to show that childhood maltreatment may be associated with altered neurocomputational EV representation (for both punishment and reward) in a widespread cortico-limbic network that includes the orbitofrontal cortex, the basal ganglia (especially the caudate) and medial temporal regions (i.e. hippocampus and insula). Moreover, in line with an account of increased neural signalling to negative stimuli and feedback in this population, an increased PE modulated brain response during punishment trials was found in several frontal and parietal regions that have been implicated with both PE signalling and with the experiences of abuse and neglect. Consistent with the clinical literature, these neurocognitive alterations may compromise the ability of maltreated individuals to accurately predict the outcomes associated with a given stimulus or action and in turn confer increased latent vulnerability to future psychiatric disorder.
CHAPTER 3 – Heightened Amygdala Reactivity and Increased Stress Generation Predict Internalizing Symptoms in Adults with Childhood Maltreatment

Childhood maltreatment is one of the most potent predictors of future psychopathology, including internalizing disorders. It remains unclear whether heightened amygdala reactivity to threat and elevated stress exposure may be implicated in the pathogenesis and maintenance of internalizing disorders among individuals with a history of childhood maltreatment. In this chapter, using data from a sample of 1144 young adults, we investigated the contribution of baseline threat-related amygdala reactivity and prospective stressful life events to internalizing symptoms severity one year later (on average) in individuals with a history of maltreatment (n=100) and propensity-score-matched non-maltreated peers (n=96). Even after stringently matching for several potentially confounding variables – including baseline internalizing symptoms, socio-economic-status and IQ – maltreatment status predicted increased amygdala reactivity at baseline, elevated post-baseline exposure to major stressful life events and internalizing symptoms at follow-up. We also showed, for the first time, that amygdala reactivity at baseline and also post-baseline exposure to major stressful life events mediated the association between a history of maltreatment and future internalizing symptoms. These findings provide support for the view that maltreatment-related long-lasting recalibrations of the threat processing system may impact mental health functioning by compromising the ability to effectively negotiate everyday challenges ('stress susceptibility'). They also lend compelling support to the view that increased psychiatric risk, in the context of maltreatment, also follows from an increased propensity to experience major stressful life events ('stress generation').
3.1. Introduction

Epidemiological and neurocognitive evidence, described in detail in the introduction chapter of this thesis, suggests that childhood maltreatment is a developmental insult with profound and far-reaching consequences (R. Gilbert, Widom, et al., 2009; Radford et al., 2011) accounting for the emergence of a significant proportion of all psychiatric disorders across the lifespan (Green et al., 2010; Ronald C Kessler et al., 2010). Despite this well-established link between childhood maltreatment and subsequent disorder (Agnew-Blais & Danese, 2016; R. Gilbert, Widom, et al., 2009; Green et al., 2010; Harkness, Wildes, Medicine, Harkness, & Wildes, 2002; Hovens et al., 2010; Ronald C Kessler et al., 2010; Leverich et al., 2002; Nanni et al., 2012; Post et al., 2015; Radford et al., 2011; Teicher & Samson, 2013), we still lack precision in our understanding of the mechanisms and markers underlying increased psychiatric vulnerability (McCrory, Gerin, et al., 2017; McCrory & Viding, 2015). In particular, prospective studies are required to determine whether maltreatment-related neurobiological and cognitive alterations are mechanistically implicated in the emergence of future disorders. The absence of such studies limits the possibility of developing preventative diagnostic tools and clinical interventions to identify and provide support for those maltreated individuals at greatest risk.

It has been proposed that the biological embedding of maltreatment experience is associated with recalibration of several neurocognitive systems (Danese & McEwen, 2012; McCrory & Viding, 2015). These adaptations are postulated to provide proximal benefits for a child in an abusive or neglectful home environment but confer risk (‘latent vulnerability’) for psychopathology, since such adaptations are not thought to be optimized for more normative environments (McCrory & Viding, 2015). Candidate neurocognitive systems include threat processing (McCrory et al., 2011), reward
processing (Gerin et al., 2017; Hanson et al., 2015) and autobiographical memory processing (McCrory, Puetz, et al., 2017). These neurocognitive changes can confer latent vulnerability either directly or indirectly. Direct effects capture how maltreatment-related neurocognitive changes alter the way in which an individual perceives, processes and responds to the social world around them. For example, recalibration of the threat processing system may have a direct effect on psychological functioning by compromising the emotional regulation system (Tottenham & Gabard-Durnam, 2017). This may increase the degree to which everyday challenges burden and tax an individual and/or increase the deleterious impact of major stressful life events (‘stress susceptibility’). Equally, neurocognitive changes can alter how an individual influence their own social experience. Direct effects here capture the way in which an individual may act in ways that precipitate the likelihood of stressor events occurring (‘stress generation’). Indirect effects (not examined in this study), capture how maltreatment-related neurocognitive changes influence how an individual elicits and sustains a network of social support (Gerin, Hanson, Viding, & McCrory, 2018; McCrory, Gerin, et al., 2017).

### 3.1.1. Maltreatment and Threat Reactivity

Several lines of evidence support the view that altered threat processing is associated with internalizing symptomatology. Among groups of adults (not selected based on maltreatment status), it has been reported that amygdala reactivity on its own (Mattson, Hyde, Shaw, Forbes, & Monk, 2016), and in interaction with stress exposure (Admon et al., 2009; McLaughlin, Busso, et al., 2014; Swartz et al., 2015), predicts future internalizing symptomatology several years later. Thus, variability in amygdala reactivity on its own may represent a neural biomarker capable of indexing psychiatric risk; moreover, amygdala reactivity may also potentiate the effects of stressor events. While extant studies have documented an association between childhood maltreatment
experience and increased amygdala reactivity to threat (Dannlowski et al., 2012, 2013; Hein & Monk, 2016; Redlich et al., 2015; van Harmelen et al., 2013) its prognostic value has not previously been investigated. Here, using a longitudinal design and a propensity score matched control group, we aimed to investigate for the first time the potential contribution of baseline threat-related amygdala reactivity to future internalizing psychopathology among individuals with significant childhood maltreatment experiences. In particular, we investigated whether baseline amygdala reactivity on its own (i.e. independently of subsequent major stressful life events) would mediate the association between maltreatment status and increased future internalizing symptoms. In addition, we explored whether baseline amygdala reactivity in interaction with subsequent major stressful life events was associated with increased future internalizing symptoms.

3.1.2. Maltreatment and Stress Generation

Extant findings also suggest that a history of childhood maltreatment is associated with a higher incidence of stressful life events (Finkelhor, Ormrod, & Turner, 2007a, 2007c; Hankin, 2005; Hernandez, Trout, & Liu, 2016; R. T. Liu, Choi, Boland, Mastin, & Alloy, 2013; Uhrlass & Gibb, 2007; Widom et al., 2008), which in turn potentiate psychiatric risk (Espejo et al., 2007; Hammen, Henry, & Daley, 2000; Harkness, Bruce, & Lumley, 2006; Harkness et al., 2008; Hernandez et al., 2016; Kendler, Kuhn, & Prescott, 2004; McLaughlin, Conron, Koenen, & Gilman, 2010; Uhrlass & Gibb, 2007). However, it remains unclear whether these associations are in fact secondary to baseline levels of symptomatology and other co-occurring risk factors, and whether they apply to individuals who have experienced parental maltreatment above clinical thresholds. Previous studies have not concurrently controlled for the impact of several potentially confounding factors such as, socio-economic-status, IQ, ethnicity, age, gender and, crucially, baseline symptom levels. Another common limitation is that a number of previous studies have conflated the
experience of parental childhood maltreatment with other forms of early adversity (e.g. death of parent, severe illness, poverty) and/or have measured maltreatment as a continuous variable, thus including mostly individuals who experienced maltreatment within normative/subclinical ranges. Here, we address these methodological limitations by carefully selecting a group of individuals with significant experiences of self-reported childhood maltreatment and systematically controlling for a set of potentially confounding variables using a propensity score matched control group. This allowed us to test, in the context of stringent controls, whether a history of childhood maltreatment is associated with higher incidence of post-baseline major stressful life events and whether this may explain, in part, the association between childhood maltreatment and future internalizing symptoms. Using the baseline measure of amygdala activation, it was also possible to explore whether amygdala reactivity to threat was associated with increased likelihood of major stressful life events.

3.1.3. Hypotheses

We had two main hypotheses. First, that individual variability in baseline threat-related amygdala reactivity would capture latent vulnerability to future internalizing symptoms either on its own or in interaction with major stressful life events. That is, we investigated whether, in the context of maltreatment, heightened amygdala reactivity was associated with increased future internalizing symptoms generally, or only in the context of major life stressors. Second, we hypothesized that (even after stringent matching for several potentially confounding variables) maltreatment would be associated with an increased likelihood of stressful life events occurring, and that these would in turn partly mediate the association between maltreatment and future symptoms. In an exploratory step we investigated whether individual differences in amygdala response to threat could partly account for any increased likelihood of subsequently experiencing stressful life events.
3.2. Methods

3.2.1. Participants

Participants were young adult college students who were recruited as part of the ongoing Duke Neurogenetics Study (DNS; n=1144). Exclusion criteria included i) medical diagnoses of stroke, diabetes, cancer, chronic kidney or liver disease; ii) use of psychotropic, glucocorticoid, or hypolipidemic medication; iii) lifetime history of psychotic symptoms iv) conditions affecting cerebral blood flow and metabolism (e.g., hypertension); and v) did not meet quality control criteria for functional MRI scanning (see “fMRI analysis” section below for more details).

3.2.1.1. Participants with longitudinal data. Only individuals who had post-baseline assessment of internalizing symptoms and stressful life events were considered for this study (n = 584). Note that previous studies [1] that used a largely overlapping DNS dataset and variables of interests showed that participants who completed follow-up assessment did not differ from participants who did not in relation to several variables of interest and covariates (e.g. age, childhood trauma, baseline measures of stressful life events, amygdala activity and internalizing symptoms). Participants were contacted every 3 months by email to voluntarily fill in a checklist about their current internalizing symptoms and experience of stressful life events since the previous assessment. Because the DNS is an ongoing research project, there is great variability among participants in terms of both the number of post-baseline assessment completed and, as a result, also in the time-interval lapsed between baseline and last post-baseline assessment. Therefore, only up to the first three post-baseline assessments (where available) for each participant were included in order to reduce variability in both the number of assessments and time elapsed between baseline and last follow-up.
3.2.1.2. Maltreated group (MT). In line with studies of childhood maltreatment prevalence (Radford et al., 2011; Stoltenborgh et al., 2015), among the 584 participants with longitudinal available data, after outlier removal (see below for details), a subset of individuals (n=100) reported experiences of significant childhood abuse and/or neglect. This was operationalized as having experienced at least one form of childhood abuse or neglect – i.e. they scored, as established by the Childhood Trauma Questionnaire (CTQ) manual, within or above the “Moderate-Severe” range in one or more maltreatment subtype scales (i.e. emotional neglect ≥ 13, physical abuse ≥ 10, sexual abuse ≥ 8, emotional neglect ≥ 15 and physical neglect ≥ 10). In the MT group 33% experienced emotional abuse, 29% experiences physical abuse, 19% sexual abuse, 32% emotional neglect and 44% physical neglect. Moreover, 41% had experiences more than one maltreatment type. In relation to normative epidemiological data thresholds, all individuals in the MT group had at least one maltreatment subtype CTQ scores above the 90th percentile (C. D. Scher, Stein, Asmundson, Mccreary, & Forde, 2001).

3.2.1.3. Non-Maltreated group (Non-MT). Participants were included in the Non-Maltreated (Non-MT; n=127) group if i) their CTQ total score was below the 50th normative percentile threshold (C. D. Scher et al., 2001) AND ii) if they scored in each CTQ maltreatment subtype scale within the none-or-minimal range (D. P. Bernstein & Fink, 1997). 353 individuals were excluded from further analyses because they reported some experience of childhood maltreatment – thus, could not be included in the Non-MT group – nor did they meet threshold for significant experiences of abuse or neglect.

3.2.1.4. Final sample after Propensity Score Matching (PSM). After Propensity Score Matching (PSM, described in detail below) and outlier removal, all analyses were performed using the Maltreated Group (MT; n=100) and the propensity score-matched Control Group (CT; n=96) – i.e. the Non-MT group after PSM (see below for details).
3.2.1.5. Propensity Score Matching (PSM). The impact of potentially confounding variables can be reduced using Propensity Score Matching (PSM). This comprises a range of statistical approaches that can be applied, prior to any inferential statistical analysis, in order to balance the distribution of covariates across the treatment and control groups (McCaffrey, Ridgeway, & Morral, 2004). When applying PSM, several matching methodologies should be explored to identify which one yields the greatest reduction in distance (i.e. distribution of covariates) between the control and treatment groups (Ho, Imai, King, & Stuart, 2007, 2011; Stuart, 2010). The most common matching procedures rely on exact pairing, weighting or sub-classification (or a combination of those). PSM can be used with a large number of control variables without incurring in model over-fitting issues and multicollinearity, which, in traditional linear regression modelling, can reduce the ability to assess the impact of a predictor variable on the outcome variables (Ho et al., 2011; Stuart, 2010). Crucially for this study, unlike traditional co-varying methods in linear regression, PSM can be used reliably also for variables that are characterized by considerable distribution differences across groups (Pingault, Cote, Petitclerc, Vitaro, & Tremblay, 2015; Rubin, 2002).

The outcome of the matching (i.e. the balance between the two groups post-matching), is often assessed using a standardized mean difference (i.e. effect size) of the propensity score (Ho et al., 2007, 2011). Although there is not a consensus on the cut-off, it has been suggested that value between 0.1 and 0.25 represent acceptable cut-offs for standardized means differences post-matching (Stuart, Lee, & Leacy, 2013). It has also been suggested that standardized mean differences for each variable pre- and post-matching can be interpreted as effect sizes, with values smaller than 0.2 considered a small difference, 0.4 medium and 0.8 large (McCaffrey et al., 2004; Pingault et al., 2015).

The R software package MatchIt (Ho et al., 2011) was used to implement four PSM methods that use different algorithms to match participants. Nearest Matching and Optimal Matching are similar procedure as they use 1:1 matching approach. In Nearest
Matching, for each participant in the maltreated group one or more participants with the closest propensity score (i.e. smallest distance) is selected from the non-maltreated group. In Optimal Matching the 1:1 matching is conducted in such a way to minimize the overall distance between the two groups. Genetic Matching and Full Matching, which enables flexible matching within subclasses by applying weighting, were also explored.

Within the current study, the following potentially confounding variables were selected for the PSM between the MT and Non-MT groups: age, gender, IQ, ethnicity, socio-economic status (measured by parental level of education), and baseline internalizing symptoms – which was assessed by the composite score on the Mood and Anxiety Symptoms Questionnaire (MASQ) (Watson et al., 1995). The outcome of the PSM procedure is described below.

3.2.2. Procedure

3.2.2.1. Baseline assessments.

fMRI paradigm. The neuroimaging protocol included a face-matching paradigm that has been shown to evoke robust (Prather, Bogdan, & Hariri, 2013) and reliable (Manuck, Brown, Forbes, & Hariri, 2007) threat-related amygdala reactivity across a wide range of populations. This task has been described in detail in previous published research from the Duke Neurogenetics Study (Prather et al., 2013; Swartz et al., 2015). Briefly, the paradigm consisted of four task blocks interleaved with five control blocks. A total of four emotion categories were used for each task block: fearful (F), angry (A), surprised (S), and neutral (N), taken from a standardized facial expression set (Ekman & Friesen, 1975). Participants viewed the task blocks in one of four randomly assigned orders as determined by a Latin Square (i.e., FNAS, NFSA, ASFN, SANF). During task blocks, participants viewed a trio of faces and matched one of two faces identical to a target face. Each trial in the task blocks lasted for 4 seconds with a variable interstimulus
interval of 2-6 seconds (mean = 4 seconds), for a total block length of 48 seconds. The experimental blocks were interleaved with sensorimotor control shape-matching blocks, during which six geometric shape trios were presented for 4 seconds with a fixed interstimulus interval of 2 seconds for a total block length of 36 seconds. Each block was preceded by a brief instruction (“Match faces” or “Match shapes”) lasting 2 seconds resulting in a total task time of 390 seconds. In the present study, we restricted analyses to fearful and angry expressions.

*fMRI acquisition.* Participants were scanned using one of two identical General Electric MR570 3T scanners at the Duke-UNC Brain Imaging and Analysis Centre equipped with high power high duty cycle 50mT/m gradients at 200 T/m/s slew rate, and an 8 channel head coil for parallel imaging at high bandwidth up to 1 MHz. Thirty-four interleaved AC-PC aligned axial functional slices were acquired for full-brain coverage using an inverse-spiral pulse sequence to reduce susceptibility artefacts (TR = 2000ms; TE = 30 ms; flip angle = 60°; FoV = 240 mm; 3.75 × 3.75 × 4 mm voxels; interslice skip = 0). Four initial volumes were acquired and discarded to achieve steady state equilibrium. A semi-automated high-order shimming program was used to ensure global field homogeneity. High resolution 3D structural images (TR = 7.7 s; TE; 3.0 ms; flip angle = 12°; voxel size = 0.9 × 0.9 × 4 mm; FoV = 240 mm, interslice skip = 0) were also acquired in 34 axial slices to assist registration of functional data.

*Behavioural measures.* Measures of anxiety and depression were collected using the MASQ (Watson et al., 1995). In line with previous investigations, scores across all four subscales (depression, anxiety, anxious arousal and anhedonia) were summed together to create a total internalizing symptoms score (Swartz et al., 2015). Experience of childhood abuse and neglect were assessed using the Childhood Trauma Questionnaire (David P. Bernstein et al., 1994). This is a retrospective 28-items screening tool which assess five subtypes of maltreatment: emotional, physical and sexual abuse and physical and emotional neglect. Each of the CTQ’s five subscales has
robust internal consistency, test-retest reliability, and convergent validity with a clinician-rated interview of childhood abuse (David P. Bernstein et al., 1994, 2003, 1997). This is one of the best validated self-reported/retrospective measure of childhood abuse and also one of the most commonly implemented in studies of childhood maltreatment (Dannlowski et al., 2012; Hanson, Knodt, Brigidi, & Hariri, 2017; Heleniak, Jenness, Vander Stoep, McCauley, & McLaughlin, 2016; van Harmelen et al., 2013). Moreover, as part of a large battery of demographic information and questionnaires, participants reported their age, gender, ethnicity and socio-economic status (operationalized using the information related to highest parental education achievement by either parent).

3.2.2.2. Longitudinal assessments.

Behavioural measures. Every 3 months participants were invited by email to complete the MASQ. They also reported their experience of major stressful life events since their last assessment (e.g. break-up with partner, death of a good friend, major argument with friend or family member, personal injury, etc.) using the Life Events Scale for Students (LESS) (Clements & Turpin, 1996). If multiple longitudinal assessments were available, the last available MASQ score was selected. For the longitudinal LESS scores, all available post-baseline assessments were used to create a standardized metric of stressful life events per year, which also included a measure of severity of impact. The time-lapsed between baseline and last post-baseline assessment between the MT group (mean = 11.8 months, s.d. = 7.7, min = 1.2, max = 43.9) and the CT group (mean = 11.4 months, s.d. = 7.9, min = 2.7, max = 45.7) was not significantly different $t(197) = -0.37, p = .71$. Moreover, the number of post-baseline assessments was also similar across groups (about half of participants completed two or three post-baseline assessments).
3.2.3. Data Analysis

3.2.3.1. fMRI analysis. The general analytic strategy has been reported in previously published research from the Duke Neurogenetics Study (Nikolova et al., 2014; Swartz et al., 2015). Briefly, Neuroimaging analyses were conducted using the software package SPM8 (www.fil.ion.ucl.ac.uk/spm/software/spm8) implemented in Matlab 2015a (MathWorks Inc.). A standard pre-processing procedure was implemented in line with previously published research from the Duke Neurogenetics Study [e.g. 37,52]. This included head motion corrections (i.e. realigning the images to the first volume in the time series); spatial normalization into standard stereotactic Montreal Neurological Institute (MNI) space using a 12-parameter affine model (final resolution of functional images = 2 mm isotropic voxels); and smoothing with a full width and half maximum 6mm Gaussian filter. Voxel-wise intensities were ratio normalized to the whole-brain global mean signal.

An artefact detection software (ART – www.nitrc.org/projects/artefact_detect) was implemented to create a regressor which assigned lower weighting to i) individuals volumes where scan-to-scan movement was greater than $2^\text{th}$ rotation or 2mm translation, ii) volumes exhibiting significant variation in mean-volume signal intensity (i.e. volumes with mean signal smaller or greater than four standard deviations of the mean signal of all the volumes in the time series). Moreover, only data from participants with the following characteristics were included: i) $\geq 90\%$ coverage of signal within the anatomically-defined bilateral amygdala region of interest, ii) $<5\%$ volumes exceed Artefact detection criteria for motion or signal intensity outliers, and iii) accuracy $\geq 75\%$ on the matching task performed during scanning.

In line with procedures implemented in prior published data from the DNS (Nikolova et al., 2014; Swartz et al., 2015), parameter estimates for each participant were extracted from the functional cluster (i.e. set of contiguous voxels activated at
P<.05, FWE corrected) within the anatomical amygdala (defined structurally by the Automated Anatomical Atlas; AAL). It was hypothesized that our findings would be specific to threat-related amygdala reactivity, thus the analyses focused on the contrast of angry and fearful faces (vs. neutral faces), because each represents a canonical threat stimuli (Prather et al., 2013; Whalen et al., 2009). Left and right amygdala threat-reactivity for our contrast of interest (i.e. angry and fearful faces > neutral faces) was highly correlated (r = 0.81, p < .001). Thus, in order to reduce the number of comparison performed, we averaged the parameter estimates across hemispheres to obtain one mean parameter estimate of amygdala reactivity to threat.

3.2.3.2. Statistical models. All analyses were performed with the propensity score matched data, which included a weighting variable. To assess the relationship between maltreatment status, amygdala reactivity, stressful life events and future internalizing symptoms, a parallel mediation model (with baseline amygdala and post-baseline exposure to stressful life events as mediators) and a moderated mediation model (with baseline amygdala as the mediator and post-baseline exposure to stressful life events as the moderator) were performed in the R package Lavaan (Rosseel, 2012) in combination with Lavaan.Survey (Oberski, 2014).

3.2.3.3. Outlier removal. In order to remove outliers for normally distributed outcome variables (i.e. baseline amygdala reactivity) Tukey’s box-plot Inter-quartile range (IQR) method was implemented, using a multiplier of 2.2, as suggested by simulation estimates by Hoaglin & Iglewixcz (1987) (Hoaglin & Iglewicz, 1987). For non-normally distributed data (i.e. prospective stressful life events and longitudinal internalizing symptoms levels), the ‘adjusted boxplot’ method developed by Hubert & Vandervieren (2008) (Hubert & Vandervieren, 2008) was implemented instead (Seo, 2006). Consequently 12 participants were removed from further analyses (4 belonging to the MT group and 8 to the CT group).
3.3. Results

3.3.1. Propensity Score Matching

Optimal and Nearest Neighbor Matching did not yield satisfactory results as, after matching, the standardized mean difference between the two groups remained almost unchanged (0.32). Moreover, the absolute standardized mean difference after matching was still moderate-to-large for several covariates, such as baseline internalizing symptoms (i.e. > 0.7). Genetic Matching also did not generate satisfactory results because, despite achieving low overall distance reduction between the two groups, it discarded several individuals in the Non-Maltreated (Non-MT) group (ratio of 1 : 0.4).

However, Full Matching achieved satisfactory results. Reduction in the overall standardized mean difference across all covariates was achieved from 0.42 to 0.09 post-matching (Table 3.1); moreover, the standardized mean difference for each variable was below the small effect size threshold (i.e. < 0.2), with absolute values ranging between 0.02 and 0.15. Notably, internalizing symptoms and ethnicity (i.e. the two variables with the largest absolute standardized mean difference before matching) achieved, respectively, a reduction in standardized mean difference from 1.02 to 0.02 and from 0.70 to 0.12. Furthermore, gender and ethnicity, which are the two variables with the largest absolute standardized mean difference post-matching (0.15 and 0.11 respectively), showed only a small and non-significant group difference: the CT group had 7% more females ($X^2(1) = 1.45, p = .29$) and 5.5% more Caucasians than the MT group ($X^2(1) = 0.57, p = .45$) (Table 3.2).

All analyses were performed using the MT group (n=100) and the propensity score-matched CT group (n=96) – i.e. the Non-MT group after propensity score matching.
Table 3.1. Balance in Covariates Before and After Matching between the Maltreated and Non-Maltreated Group/Controls.

<table>
<thead>
<tr>
<th></th>
<th>MT</th>
<th>Non-MT</th>
<th>CT (Non-MT Post Matching)</th>
<th>Before Matching</th>
<th>Post Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance</td>
<td>0.6</td>
<td>0.3</td>
<td>0.6</td>
<td>1.16</td>
<td>-0.00</td>
</tr>
<tr>
<td>Age</td>
<td>19.41</td>
<td>19.79</td>
<td>19.57</td>
<td>-0.21</td>
<td>-0.09</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>63 %</td>
<td>66 %</td>
<td>70 %</td>
<td>-0.06</td>
<td>-0.15</td>
</tr>
<tr>
<td>IQ</td>
<td>119.63</td>
<td>123.16</td>
<td>120.47</td>
<td>-0.31</td>
<td>-0.07</td>
</tr>
<tr>
<td>Ethnicity (Caucasian)</td>
<td>30%</td>
<td>63%</td>
<td>35.5%</td>
<td>-0.70</td>
<td>-0.11</td>
</tr>
<tr>
<td>SES</td>
<td>7.53</td>
<td>7.9</td>
<td>7.36</td>
<td>-0.24</td>
<td>0.09</td>
</tr>
<tr>
<td>Baseline Internalizing symptoms</td>
<td>127.65</td>
<td>100.29</td>
<td>127.07</td>
<td>1.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Absolute Standardized Mean Difference$^2$</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.42</td>
<td>0.09</td>
</tr>
</tbody>
</table>

MT = Maltreated group (n=100), Non-MT = Non-Maltreated group (n=127), CT = Control group (i.e. matched Non-Maltreated individuals; N = 96), IQ = intelligence quotient, SES = socio-economic status (i.e. parent with highest education level). $^1$ Each standardized mean difference is obtained by subtracting the mean in the MT group minus mean in the CT group, divided by the standard deviation in the MT group. $^2$ The average absolute standardized mean difference is the average of the absolute values of standardized mean differences for all covariates.

3.3.1.1. Participants characteristics for matched variables. In addition to inspecting standardized mean difference after PSM, we further tested whether any significant differences remained between the two groups. t-test and chi-square tests revealed that across all propensity score matched variables there were not significant differences between the MT and CT groups (Table 3.2).
### Table 3.2. Mean and standard deviation for propensity score matched variables post-matching.

<table>
<thead>
<tr>
<th></th>
<th>MT Mean (Standard Deviation)</th>
<th>CT (Non-MT Post Matching) Mean (Standard Deviation)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>19.41 (2.33)</td>
<td>19.57 (1.11)</td>
<td>.53</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>63 %</td>
<td>70%</td>
<td>.29</td>
</tr>
<tr>
<td>IQ</td>
<td>119.63 (14.69)</td>
<td>120.47 (8.2)</td>
<td>.63</td>
</tr>
<tr>
<td>Ethnicity (Caucasian)</td>
<td>30 %</td>
<td>35.5 %</td>
<td>.45</td>
</tr>
<tr>
<td>SES</td>
<td>7.53 (1.8)</td>
<td>7.36 (1.82)</td>
<td>.50</td>
</tr>
<tr>
<td>Baseline Internalising symptoms</td>
<td>127.65 (33.02)</td>
<td>127.07 (36.19)</td>
<td>.91</td>
</tr>
</tbody>
</table>

### 3.3.2. Participants Characteristics for Non-matched Variables

This subsection reports variables which were not propensity score matched (i.e. CTQ scores, longitudinal assessments number and time-intervals).

**3.3.2.1. Longitudinal time-interval information.** The time lapsed between baseline and last post-baseline assessment between the MT group (mean = 11.8 months, s.d. = 7.7, min = 1.2, max = 43.9) and the CT group (mean = 11.4 months, s.d. = 7.9, min = 2.7, max = 45.7) was not significantly different $t(197) = -0.37$, $p = .71$.

Moreover, a similar number of individuals – about half – in both the MT (47.5%) and CT (50.6%) had one longitudinal assessment, while the other half of participants in each group had 2 or 3 longitudinal assessments.

**3.3.2.2. CTQ scores.** The MT and the Non-MT individuals, as discussed in the methods section, were selected based on their CTQ scores. Thus, the CTQ total and subscale scores for the MT and CT group (i.e. the Non-MT group post-matching) were statistically significant (Table 3.3). Notably, while the CTQ total score for the MT group was above the 90th percentile of the population normative threshold, the CT group total score was close to the 25th lowest percentile of the population normative threshold (C. D. Scher et al., 2001).
Table 3.3. Mean and standard deviation for CTQ values post-matching.

<table>
<thead>
<tr>
<th>CTQ Total Score</th>
<th>Mean (Standard Deviation)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT</td>
<td>CT (Non-MT Post Matching)</td>
<td></td>
</tr>
<tr>
<td>CTQ Total Score</td>
<td>46.23 (8.58)</td>
<td>25.56 (0.5)</td>
</tr>
<tr>
<td>Physical Abuse</td>
<td>7.97 (3.43)</td>
<td>5.03 (0.17)</td>
</tr>
<tr>
<td>Emotional Abuse</td>
<td>10.60 (4.05)</td>
<td>5.19 (0.39)</td>
</tr>
<tr>
<td>Sexual Abuse</td>
<td>6.24 (2.78)</td>
<td>5 (0)</td>
</tr>
<tr>
<td>Physical Neglect</td>
<td>9.07 (3.15)</td>
<td>5 (0.03)</td>
</tr>
<tr>
<td>Emotional Neglect</td>
<td>12.35 (4.05)</td>
<td>5.34 (0.48)</td>
</tr>
</tbody>
</table>

3.3.3. Maltreatment Status and Future Internalizing Symptoms

Maltreatment status significantly predicted future levels of internalizing symptoms reported on average one year later ($\beta = 16.07$, $\beta_{\text{standardized}} = 0.60$, $p < .001$). The MT and CT group showed a mean internalizing symptom score at follow-up of 118.78 (s.d. = 31.34) and 102.71 (s.d. = 18.71), respectively.

3.3.4. Mediation Analyses

A parallel mediation analysis using structural equation modelling (SEM) was run to explore the role of (i) baseline amygdala reactivity to threat and (ii) post-baseline exposure to stressful life events on future internalizing symptoms severity. As shown in Figure 3.1 (path $a_2$), maltreatment status was associated with higher threat-related baseline amygdala reactivity. Higher baseline amygdala reactivity partially mediated the association between maltreatment status and levels of future internalizing symptoms (Figure 3.1, indirect pathway $a_2 \times b_2$). In other words, the higher levels of symptoms in the MT group followed from increased baseline amygdala reactivity.
Chapter 3

Figure 3.1. Parallel structural equation mediation model depicting how the association between future internalizing symptoms and maltreatment status is partially mediated by both baseline amygdala reactivity to threat and post-baseline exposure to major stressful life events. Note. Coefficient values are standardized; * indicates statistically significant coefficients; the interaction terms (i.e. indirect effects) significance threshold were measured using Monte Carlo test of mediation (MacKinnon, Lockwood, & Williams, 2004).

We also ran an SEM moderated mediation analysis, based on Preacher, Rucker & Hayes (2007) model 3 (Preacher, Rucker, & Hayes, 2007) (the specific path that is moderated is conceptually represented in Figure 3.2). This model tested whether the mediating effect of baseline amygdala reactivity on the relationship between maltreatment status and future internalizing symptoms was conditional on post-baseline exposure to stressful life events. In particular, as depicted in Figure 3.2 below, this model tested whether the pathway from baseline amygdala threat reactivity (the mediator) to future internalizing symptoms was modulated by stressful life events. This analysis revealed that post-baseline exposure to stressful life events did not interact with baseline amygdala reactivity in predicting future symptom levels ($\beta_{\text{standardized}} = 0.05$, $\text{Monte Carlo 95\% CIs LL }=-0.04 \text{ UL}=0.14$). Moreover, the index of moderated mediation, which formally tested if the mediating effect of amygdala on the association between maltreatment status and future symptoms is influenced by exposure to stressful life events, was also non-significant ($\beta_{\text{standardized}} = 0.03$, $\text{Monte Carlo 95\% CIs LL }=-0.03 \text{ UL}=\ldots$)
0.09). That is, in the context of maltreatment, baseline amygdala reactivity was not found to sensitize an individual to the impact of subsequent stressful life events.

![Figure 3.2. Conceptual moderated mediation model depicting the putative moderating effect of post-baseline stressful life events on the mediating effect of baseline amygdala threat reactivity on the association between maltreatment status and future internalizing symptoms.](image)

In the parallel mediation model (Figure 3.1), we also found that maltreatment status predicted higher post-baseline occurrence of stressful life events (path $a_1$ in Figure 3.1). The mean occurrence of these (per year) for the MT and CT groups, respectively, was 4.00 (s.d. = 4.54) and 2.25 (s.d. = 3). A t-test revealed that the average rated impact of each stressful event, however, did not differ between the groups $t(197) = 0.15$, $p = .88$. In other words, individuals in the MT group experienced significantly more stressful events, but the reported impact of individual events did not differ between the groups.

Furthermore, higher post-baseline exposure to stressful life events was found to partially mediate the association between maltreatment status and levels of future internalizing symptoms (Figure 3.1, indirect pathway $a_1 \times b_1$). In other words, the higher levels of symptoms in the MT group followed from increased occurrence of post-baseline exposure to major stressful life events.
Finally, in the parallel mediation model, the covariation term between baseline amygdala reactivity and post-baseline stressful life events (not graphically represented in Figure 3.1) was not statistically significant ($\beta_{\text{standardized}} = -0.09, p = .35$). This suggests that baseline amygdala reactivity was not associated with the occurrence of post-baseline stressful life events.
3.4. Discussion

This study had three main findings. First, we found that the association between maltreatment history and future internalizing symptoms severity was partially explained by higher baseline amygdala reactivity to threat. Second, even in this propensity score matched sample, where baseline symptoms levels and other potentially contributing factors were comparable between the groups, individuals with a history of childhood maltreatment showed a higher incidence of post-baseline stressful life events. This, in turn, partially mediated the relationship between maltreatment status and future internalizing symptoms. Third, a history of childhood maltreatment was found to have a prognostic value for internalizing symptoms that goes above and beyond that of other factors, including baseline symptoms severity.

3.4.1. The Theory of Latent Vulnerability – Threat Reactivity

Several independent research groups have postulated that cognitive and neurobiological alterations in salience detection and threat reactivity may serve as mediators between the experience of childhood maltreatment and the later development of internalizing disorders (Dannlowski et al., 2012; McCrory & Viding, 2015; Pollak & Tolley-Schell, 2003; Shackman et al., 2007). According to the theory of latent vulnerability, maltreatment can lead to a cascade of neurocognitive recalibrations, including changes in threat processing, which may be adaptive in the context of chaotic, dangerous and species-atypical home environments. While helpful in the short-term, these adaptations may be poorly optimized for negotiating more normative environments over the longer term. For example, changes in how an individual responds to threat can curtail opportunities and the resources necessary for developing other affective and cognitive functions. Increased amygdala reactivity, in particular, may entail an increased experience of negative emotions, reduced emotion regulation and hypervigilance.
In this study, the implementation of PSM allowed us to demonstrate that maltreatment experience is associated with increased threat-related amygdala reactivity (Dannlowski et al., 2012; McCrory et al., 2011, 2013) even when accounting for other potentially confounding factors including concurrent internalizing symptom severity and socio-economic status, which have been linked extensively with both maltreatment (Green et al., 2010) and amygdala reactivity (Etkin & Wager, 2007; Gianaros et al., 2008; Hamilton et al., 2012). Moreover, we found that higher baseline amygdala reactivity to threat contributed (independently of major stressful life events) to the association between a history of maltreatment and future internalizing symptoms severity reported on average one year later. These findings provide unique support for the notion that the experience of childhood maltreatment may lead to neurocognitive alterations in threat processing that are not simply epiphenomenal, but rather contribute to psychiatric vulnerability later in life (McCrory & Viding, 2015).

3.4.2. ‘Stress Generation’

In relation to experiential and environmental factors, we found that a higher incidence of stressful life events partly mediated the association between maltreatment status and future internalizing symptoms severity. Again, using PSM we were able to mitigate the effects of potentially confounding factors commonly associated with childhood maltreatment known to increase the likelihood of stressful life experiences including higher internalizing symptomatology (R. T. Liu & Alloy, 2010) and lower IQ (Breslau, Lucia, & Alvarado, 2006). It has been postulated that growing up in an abusive environment can lead to alterations in a number of domains that in the longer term can compromise social and emotional functioning (McCrory, Gerin, et al., 2017). For instance, recent neurocognitive evidence indicate that children exposed to maltreatment show increased susceptibility to psychosocial stressors (Puetz et al., 2014, 2016), reduced affect regulation (McCrory, Gerin, et al., 2017), and increased rejection sensitivity associated with higher likelihood of conflictual interactions.
Moreover, overgeneral autobiographical memory, commonly associated with the experience of abuse and neglect (McCrory, Puetz, et al., 2017; Valentino et al., 2009), is thought to reduce social problem solving ability (Raes et al., 2005; Sutherland & Bryant, 2008). One important implication is that such maladaptive social functioning may not only compromise an individual’s ability to establish and sustain positive relationships that help buffer the impact of future stressor experiences, but also act in ways that might potentiate the generation of stressful life events (e.g. relationship breakdowns, exclusion from school, peer-victimization, and difficulties in the work environment).

This concept of ‘stress generation’ has been well documented in the context of adult depression (Hammen, 1991; R. T. Liu & Alloy, 2010). It will be of interest to explore in future studies, with an appropriate measure, the degree to which these stressor events are interpersonal in nature – as opposed to events like accidents or deaths among family members that are typically not thought to be related to the agency of the individual. We did not find that individual differences in amygdala reactivity to threat were associated with the occurrence of major stressful life events; psychological studies have pointed to the importance of negative inferential styles (R. T. Liu et al., 2013). Future neuroimaging studies will be helpful in establishing which specific neurocognitive processes contribute to the association between maltreatment experience and increased likelihood of stress generation.

3.4.3. Threat Reactivity and Exposure to Major Stressful Life Events

In our exploratory analysis, contrary to what has been observed in previous ‘typical’ samples – i.e. selected blind to maltreatment status, (Admon et al., 2009; McLaughlin, Busso, et al., 2014; Swartz et al., 2015) – we did not find that higher baseline amygdala reactivity interacted with higher stress exposure in accounting for future internalizing symptoms in those with a maltreatment history. That is, amygdala
reactivity was not found to further sensitize individuals with maltreatment histories to the impact of subsequent major stressful life events. In accounting for this null finding, it is important to consider the possibility that different factors are likely to underlie the same endophenotype (increased amygdala reactivity) among those with maltreatment and non-maltreatment histories. While heightened amygdala reactivity in those with non-maltreatment histories is likely to primarily reflect an intrinsic neurobiological risk factor (Admon et al., 2009; McLaughlin, Busso, et al., 2014; Swartz et al., 2015), in individuals with maltreatment histories such heightened reactivity may primarily reflect a neurocognitive response to early stress exposure and adverse experiences (Dannlowski et al., 2012, 2013; Hein & Monk, 2016; McCrory et al., 2011, 2013). Therefore, the way in which amygdala reactivity is implicated in stress sensitization and in the pathogenesis of psychiatric disorders may differ among individuals with and without a history maltreatment. Nonetheless, future studies, with larger sample sizes and greater variation in stress exposure severity are necessary to replicate this finding.

3.4.4. Limitations and Conclusions

Our current analyses feature several strengths including a longitudinal design, a large sample which included a group of individuals with significant experiences of maltreatment and the implementation of PSM for the selection of a tightly matched comparison peer group. However, there are also notable limitations. First, the maltreated and non-maltreated participants consisted of university students; replication would help establish that these findings are evident in other groups within the general population. Nonetheless, the findings reported here are consistent with previous investigations characterized by samples of different educational and socioeconomic backgrounds as well as age. In particular, these prior studies also reported greater symptom severity (J. Brown et al., 1999; Danese et al., 2009; Green et al., 2010; Kearney et al., 2010; Widom et al., 2007), amygdala hyperactivity (Dannlowski et al., 2012, 2013; Hein & Monk, 2016; McCrory et al., 2011; Redlich et al., 2015; van
Harmelen et al., 2013) and increased stress exposure (Finkelhor et al., 2007a, 2007c; Hankin, 2005; Hernandez et al., 2016; R. T. Liu et al., 2013; Uhrlass & Gibb, 2007; Widom et al., 2008) in individuals with childhood maltreatment histories. This suggests that the effects of maltreatment on multiple levels of functioning are pervasive and likely to be consistent across different populations. Second, it has been proposed that childhood maltreatment occurring earlier in life may lead to more profound alterations in amygdala functioning due to region-specific neurodevelopmental trajectories (Tottenham & Gabard-Durnam, 2017; Tottenham & Sheridan, 2009). However, the retrospective/self-reported assessments of maltreatment used in this study did not provide age of onset information. It will be important in future work to investigate the existence of sensitive periods during which the impact of maltreatment on the brain may be particularly potent. Retrospective/self-reported assessments are also poor at capturing maltreatment during infancy or early childhood and may in addition be compromised by the fact that maltreatment exposure is often associated with dissociative/overgeneral cognitive styles (e.g. McCrory, Puetz, et al., 2017) which may lead to under-reports and limited conscious awareness of the experience of abuse and neglect. Finally, the implementation of a functionally defined region of interest (fROI) approach during the neuroimaging analyses may also represent a potential shortcoming. This approach has been criticised in the literature because it may introduce bias in the data (Friston, Rotshtein, Geng, Sterzer, & Henson, 2006; Poldrack, 2007). In particular, some authors have argued that fROIs can inflate the statistical strength of the analyses and increase the likelihood of a type I error because the same data is interrogated twice – i.e. to localise the region in which the hypothesis is tested and also to demonstrate the effect (e.g. a group difference in brain activation) (Friston et al., 2006; Poldrack, 2007). Despite this potential limitation, the implementation of fROIs has theoretical and methodological advantages over other standard analytic procedures (Saxe, Brett, & Kanwisher, 2006). For example, compared to whole-brain analyses – which involve
tens of thousands of voxels, hence tens of thousands of multiple comparisons – the specification of fROIs can result in a large increase in statistical power (Saxe et al., 2006). fROIs also possess some advantages compared to anatomically defined ROIs. The latter method, despite being an effective and widely used approach, often involves the analysis of brain areas whose sub-regions may actually support different functions. This can potentially increase the likelihood of a type II error because the ‘truly’ active voxels within an anatomical ROI may represent a relatively small proportion of the total (Poldrack & Mumford, 2009). Moreover, Saxe and colleague have argued that scientific hypotheses concerning fROIs are often the most unambiguous to provide a rationale for and to test (Saxe et al., 2006). Considering both the strengths and limitations of an fROI approach, Poldrack has argued that the use of fROIs may be particularly suitable for exploratory analyses, for data quality control and for cognitive functions whose underlying neural underpinnings have already been localised with a certain degree of confidence (Poldrack, 2007). The role of the amygdala in the processing of threat/salient information is unequivocal (Phelps & LeDoux, 2005; Sergerie, Chochol, & Armony, 2008). Moreover, its pattern of differential activation in response to threat among individuals with and without a maltreatment history represents a well-established finding (Hein & Monk, 2016; McCrory, Gerin, et al., 2017). Thus, it is unlikely that the implementation of an fROI approach in this study could have introduced bias in the data. Nevertheless, it is paramount that the current findings are replicated in future investigations using different methodological approaches, such as structurally defined ROI.

In conclusion, we found that increased baseline amygdala reactivity to threat partly explains the association between a maltreatment history and future internalizing symptoms. This finding lends support to the view that recalibration of amygdala reactivity to threat increases stress susceptibility in the context of how everyday challenges burden and tax an individual. However, altered amygdala reactivity was not
found to increase sensitivity to major life stressors as measured via a well validated screen of stressful life events. We also provide the most definitive evidence to date that maltreatment status predicts a greater number of stressful life events that in turn are associated with greater internalizing symptoms. These findings powerfully emphasize the way in which latent vulnerability can unfold as a result of stress generation of dependent events, akin to what has been postulated in depression (Hammen, 1991; R. T. Liu & Alloy, 2010). Further work is needed to delineate the neurocognitive and social mechanisms that are associated both with increased stress susceptibility and with increased stress generation following maltreatment. Such work is crucial to inform our understanding of the pathogenesis of psychiatric disorder and guide the development of novel preventative strategies that could offset the likelihood of disorders arising in the first place (McCrory, Gerin, et al., 2017; Teicher & Samson, 2013).
The experience of childhood maltreatment is linked to negative outcomes across the lifespan, including increased risk of psychopathology. Our understanding of the cognitive mechanisms for this well-established association, nevertheless, is still limited. Recent behavioural and neurobiological evidence suggests that alterations in autobiographical memory (ABM) may contribute to increased psychiatry risk following childhood maltreatment. However, a closely related construct, ‘Episodic Future Thinking’ (EFT; the ability to imagine specific, and detailed possible future scenarios) has received little attention. In this chapter, we examined EFT in a group of adolescents (12-17 years) with substantiated experience of maltreatment (n=31) and a group of non-maltreated peers (n=37) well-matched on demographic variables. We found that individuals with histories of childhood maltreatment were able to generate fewer specific episodic future events compared to their peers (Cohen’s d = .6). This pattern of overgeneral EFT (or OEFT) in the general population has been linked to several psychiatric conditions and a number of maladaptive outcomes, including reduced impulse control and social problem-solving skills. The findings of this study suggest that early experiences of abuse and/or neglect may disrupt the development EFT. This, in turn, may compromise future psychosocial functioning and potentiate psychiatric vulnerability.
4.1. Introduction

While alterations in a number of cognitive domains following experiences of childhood maltreatment have been investigated (McCrorry, Gerin, et al., 2017), there are a range of domains that have not yet received empirical attention (McCrorry, Gerin, et al., 2017). One such domain is ‘Episodic Future Thinking’ (EFT- Atance & O’Neill, 2001), also referred to as mental time travel, prospection or scene construction (Addis, Wong, & Schacter, 2007; D. T. Gilbert & Wilson, 2007; Hassabis & Maguire, 2007; Schacter et al., 2007; Suddendorf & Busby, 2005). As discussed in greater detail below, impairments in EFT have been associated with psychopathology. Thus, altered functioning in this domain may represent a potential candidate marker of latent vulnerability to future psychiatric disorder following the experience of abuse and/or neglect.

4.1.1. What is EFT?

EFT refers to the ability to simulate possible personal future scenarios. This is a unique ability that begins to develop in early childhood and is crucial for several aspects of human behaviour and cognition (Schacter et al., 2017). Although compelling evidence suggests that EFT is not simply a direct expression of autobiographical memory (ABM; Klein, 2016; Schacter, Benoit, & Szpunar, 2017), a consistent body of literature suggests that episodic memory and EFT are cognitively, developmentally and neurobiologically related (Addis et al., 2010; Benoit & Schacter, 2015; Coughlin, Lyons, & Ghetti, 2014; Gott & Lah, 2014; Hassabis & Maguire, 2007; Schacter et al., 2012; Spreng, Mar, & Kim, 2009; Q. Wang, Hou, Tang, & Wiprovnick, 2011). For example, EFT and ABM share similar developmental trajectories across the whole lifespan (Addis, Wong, & Schacter, 2008; Coughlin et al., 2014; Q. Wang, Capous, Koh, & Hou, 2014) and are underpinned by very similar neural pathways, including the main hubs of the default mode network (Benoit & Schacter, 2015). Moreover, several
authors have hypothesised that one of the crucial functions of ABM is to store and provide episodic and self-relevant personal knowledge that can be flexibly recombined to project ourselves in time and foresee possible future scenarios (Schacter et al., 2012). In line with this notion, it has been proposed that EFT and ABM are reliant on similar processes, such as mental scene construction, mental simulation, self-projection and perspective taking (Hassabis & Maguire, 2007; Schacter & Addis, 2007). Despite this overlap, EFT differs from ABM both phenomenologically – EFT is more goal-oriented, more positively valence and less vivid (Barsics, Van der Linden, & D’Argembeau, 2016; D’Argembeau & Mathy, 2011) – and cognitively – several studies have shown that executive functioning (S. N. Cole, Morrison, & Conway, 2013) and semantic memory (Irish & Piolino, 2016) play a unique role in shaping EFT (Schacter et al., 2017).

4.1.2. EFT, Social Functioning and Psychopathology

The ability to simulate possible future scenarios has adaptive functional advantages that have primarily been conceptualised around three domains: coping, goal achievement and implementation of intentions (Szpunar, 2010). In relation to coping, empirical findings suggests that the ability to imagine detailed and vivid future episodic events plays an important role in social problem-solving (A. D. Brown et al., 2016; A. D. Brown, Dorfman, Marmar, & Bryant, 2012), in emotion regulation (Barsics et al., 2016; A. D. Brown et al., 2012; D’Argembeau & Van der Linden, 2006) and also in scaffolding a person’s sense of identity and self-efficacy (A. D. Brown et al., 2012; D’Argembeau, Lardi, & van der Linden, 2012). For example, recent evidence suggests that training episodic specificity can have a positive impact on problem-solving abilities and on affective regulatory strategies involving worrisome personal future events (Jing, Madore, & Schacter, 2016).
In relation to both goal-achievement and implementation of intentions, a substantial body of empirical work has shown that EFT is important in predicting hedonistic consequences, in regulating motivational drives and in promoting the generation of personal goals and plans (D. T. Gilbert & Wilson, 2007; Malek, Berna, & D’Argembeau, 2018; Prabhakar et al., 2016; Schacter et al., 2017; Terrett et al., 2016). For example, reduced EFT specificity has been associated with high delay discounting—a consistent bias towards more immediate gratification—which is linked with poorer self-regulation, impulsive decision-making and increased risk of maladaptive behaviours, including substance abuse (Bromberg, Wiehler, & Peters, 2015; Ohmura, Takahashi, Kitamura, & Wehr, 2006; Wiehler, Bromberg, & Peters, 2015). Moreover, in experimental settings, engaging in EFT has been shown to reduce delay discounting in healthy adults and adolescents (Benoit, Gilbert, & Burgess, 2011; Bromberg, Lobatcheva, & Peters, 2017; L. Liu, Feng, Chen, & Li, 2013; Palombo, Keane, & Verfaellie, 2015; Peters & Büchel, 2010). It has also been shown to decrease impulsivity and craving in relation to maladaptive eating, smoking and drinking behaviours (Daniel, Said, Stanton, & Epstein, 2015; Daniel, Stanton, & Epstein, 2013; Dassen, Jansen, Nederkoorn, & Houben, 2016; Snider, LaConte, & Bickel, 2016; Stein et al., 2016; Sze, Stein, Bickel, Paluch, & Epstein, 2017).

One way in which altered EFT has been operationalised is by indexing the degree to which an individual can imagine specific future scenarios. Overgeneral EFT (or OEFT) reflects the degree of difficulty an individual has in generating such specificity, and several studies have used cue words and a number of scoring methods to capture this construct (Hallford et al., 2018). Given the contribution of EFT to several cognitive and behavioural domains, it is perhaps unsurprising that alterations in EFT, and in particular OEFT, have been associated with a number of maladaptive outcomes and psychiatric disorders (Hallford et al., 2018). Since the first investigation of OEFT in 1996 by Williams and colleagues, reduced EFT specificity has been linked to a range of
mental health difficulties, including: internalizing disorders such as depression (Addis, Hach, & Tippett, 2016; Belcher & Kangas, 2014; Hach, Tippett, & Addis, 2014; M. J. King, MacDougall, Ferris, Herdman, & McKinnon, 2011; Williams et al., 1996), PTSD (A. D. Brown et al., 2013; Kleim, Graham, Fihosy, Stott, & Ehlers, 2014), bipolar disorder (M. J. King, Williams, et al., 2011) and schizophrenia (D’Argembeau, Raffard, & Van der Linden, 2008; Lyons, Henry, Rendell, Robinson, & Suddendorf, 2016).

4.1.3. EFT and Childhood Maltreatment

Early childhood represents an important period for the development of EFT. The ability to imagine episodic future events is in place by age 4-5 years, and continues to develop throughout childhood and adolescence (Atance, 2008, 2015; Suddendorf, 2017). Preliminary evidence suggests that sensitive caretaking, and particularly parental verbalisation about the future, play a central role in scaffolding the development of EFT (Atance & O’Neill, 2005; Prabhakar et al., 2016). Individuals who experience childhood maltreatment are often exposed to species-atypical early home and learning environments, characterised by erratic caretaking, unpredictable parental affective reactions and inconsistency in the availability of primary reinforcers and affection. Thus, the experience of abuse and neglect during childhood is likely to cause disruptions to EFT development.

The evidence that maltreatment leads to long-lasting alterations in a number of cognitive and neurobiological domains associated with EFT, lends support to this hypothesis. Firstly, several independent groups of researchers have found that a history of abuse and neglect is associated with reduced ABM specificity (De Decker, Hermans, Raes, & Eelen, 2003; Kuyken & Brewin, 1995; McCrory, Puetz, et al., 2017; Valentino et al., 2009). Moreover, during ABM retrieval, abnormal patterns of brain activation in medial temporal structures, including the hippocampus, have been associated with a history of maltreatment (McCrory, Puetz, et al., 2017). In line with Williams’ CaRFAX
model (Williams, 2006; Williams et al., 2007), it has been proposed that children who have been abused may develop OGM to avoid accessing traumatic or distressing episodic information. This, in turn, may lead to difficulties in accessing the episodic information necessary for generating personal memories and indeed for the generation of specific future events. Secondly, goal-directed/motivated behaviour and reward-based decision-making, which rely on the ability to imagine future events and outcomes with a high degree of specificity (D. T. Gilbert & Wilson, 2007; Prabhakar et al., 2016; Schacter et al., 2017), have been shown to undergo profound and enduring recalibrations as a result of maltreatment exposure (Gerin et al., 2017; Harms et al., 2018). Third, structural and functional neuroimaging studies of childhood maltreatment have consistently found patterns of abnormal activation, connectivity and structure in brain hubs known to support the processes that underlie mental simulation, self-projection and EFT (Benoit & Schacter, 2015; Prabhakar et al., 2016; Stawarczyk & D’Argembeau, 2015). These include medio-prefrontal and medio-temporal cortical regions such as the medial prefrontal cortex and the hippocampus (Herringa et al., 2013; McCrory, Gerin, et al., 2017; Teicher & Samson, 2016). Finally, several disorders commonly associated with childhood abuse and neglect, such as depression and PTSD (Danese et al., 2009; Green et al., 2010; Kearney et al., 2010; Widom et al., 2007), have been associated with deficits in EFT (Addis et al., 2016; A. D. Brown et al., 2013; Williams et al., 1996).

Collectively, the studies presented above suggests that alterations in EFT may represent a promising cognitive construct that may allow us to index latent psychiatric vulnerability among individuals who were exposed to childhood maltreatment (McCrory & Viding, 2015). In particular, maltreatment-related alteration in EFT may be a path through which psychiatric vulnerability may ‘get under the skin’ directly by impacting on-line processing of the world (e.g. by reducing emotion regulation abilities and planning skills, thus increasing the impact of daily stressors) and also indirectly, for
instance by reducing the ability to elicit and sustain social networks and positive peer interactions (e.g. EFT alteration may be linked with deficits in social problem-solving skills, as well as with increased impulsivity, which in turn may lead to maladaptive social behaviours and greater relational difficulties).

4.1.4. The Current Study & Hypotheses

In the current chapter we investigated, for the first time, the possibility that a history of maltreatment is associated with OEFT. Adolescents (12-17 years) with and without documented experience of abuse and neglect responded to a set of positive and negative cue words by generating episodic personal future events. In line with studies of OEFT in psychiatric populations (Hallford et al., 2018; McLaughlin et al., 2015) and studies investigating OGM among adolescents with a history of maltreatment (Valentino et al., 2009), we expected that individuals who experienced childhood maltreatment would show elevated OEFT compared to non-maltreated peers. Moreover, we explored whether OEFT was associated with greater maltreatment severity and elevated psychiatric symptoms.
4.2. Methods

4.2.1. Participants

An initial sample of 73 children and adolescents aged 12-17 years participated in this study: 33 with documented experiences of maltreatment (MT group) recruited via the Social Services Department and 40 peers with no prior Social Service contact recruited via schools / advertisements in the community (NMT group). Consent was obtained from the child’s legal guardian and assent to participate was obtained from all children. Procedures were approved by University College London (UCL) Research Ethics Committee (0895/002). Exclusion criteria included the presence of a pervasive developmental disorder, neurological abnormalities and an IQ below 70. The procedure for removing outliers is described below. Demographic details of the final sample are reported in Table 4.1 (MT = 31, NMT = 37). Detailed information regarding the sample overlap with Chapter Two and Chapter Five can be found in Appendix 3.

4.2.2. Measures

4.2.2.1. Maltreatment history. History and severity of abuse type (neglect, emotional, sexual and physical abuse and intimate partner violence) was provided by the child’s social worker or the adoptive parent (on the basis of Social Services reports). Severity of each abuse type was rated on a scale from zero (not present) to four (Table 4.2) in line with an established measure of maltreatment (Kaufman et al., 1994). In addition, age of onset and duration of maltreatment by subtype was estimated on the basis of Social Services reports.

4.2.2.2. Psychiatric symptomatology. The Strengths and Difficulties Questionnaire (SDQ), was completed by parents or caregiver to assess general functioning and psychopathology (Table 4.2) (R. Goodman, 2001). This is a well
validated measures, with high internal consistency (mean Cronbach α: .73), and good retest stability (mean correlation: 0.62) (R. Goodman, 2001).

4.2.2.3. Cognitive ability. Verbal and non-verbal intelligence was assessed using two subscales of the Wechsler Abbreviated Scales of Intelligence (Wechsler, 1997). Verbal fluency, a measure of executive control, was assessed using the composite score from a phonemic and a semantic fluency task – i.e. participants were required to produce in 60 seconds as many words as possible beginning with the letter ‘s’ (phonemic fluency), and from the category ‘animals’ (semantic fluency) (Benton & Hamsher, 1983; Heller & Dobbs, 1993; Ruff, Light, Parker, & Levin, 1996).

Table 4.1. Demographics and symptomatology of MT and NMT groups included in the analyses.

<table>
<thead>
<tr>
<th>Measures</th>
<th>MT (n= 31)</th>
<th>NMT (n= 37)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>14</td>
<td>23</td>
<td>.16</td>
</tr>
<tr>
<td>%</td>
<td>45.2</td>
<td>62.2</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (Caucasian)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>19</td>
<td>20</td>
<td>.55</td>
</tr>
<tr>
<td>%</td>
<td>61.3</td>
<td>54.1</td>
<td></td>
</tr>
<tr>
<td>SES - Level of Education of parent (% beyond secondary)</td>
<td>14</td>
<td>23</td>
<td>.16</td>
</tr>
<tr>
<td>Mean</td>
<td>14.39</td>
<td>14.94</td>
<td>.13</td>
</tr>
<tr>
<td>SD</td>
<td>1.66</td>
<td>1.24</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent Report2</td>
<td>2.97</td>
<td>3.19</td>
<td>.08</td>
</tr>
<tr>
<td>Self-Report3</td>
<td>2.92</td>
<td>3.12</td>
<td>.16</td>
</tr>
<tr>
<td>WASI-IQ4</td>
<td>106.1</td>
<td>109.7</td>
<td>.24</td>
</tr>
<tr>
<td>Verbal Fluency2</td>
<td>36.90</td>
<td>37.08</td>
<td>.93</td>
</tr>
<tr>
<td>SDQ-P Total Score6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional Symptoms</td>
<td>2.74</td>
<td>2.03</td>
<td>.21</td>
</tr>
<tr>
<td>Conduct Problem</td>
<td>2.07</td>
<td>1.65</td>
<td>.39</td>
</tr>
<tr>
<td>Hyperactivity/Inattention</td>
<td>3.85</td>
<td>2.74</td>
<td>.11</td>
</tr>
<tr>
<td>Peer Relationship Problems</td>
<td>2.11</td>
<td>1.41</td>
<td>.14</td>
</tr>
<tr>
<td>Prosocial Behaviour</td>
<td>7.82</td>
<td>7.71</td>
<td>.84</td>
</tr>
</tbody>
</table>

Abbreviations: MT = Maltreated group; NMT = Non-maltreated group; PDS = Puberty Development Scale; SES = Socio-economic-status; SDQ-P = Strength and Difficulties Questionnaire – Parent report; WASI-IQ = 2 IQ-sub scales derived from the Wechsler Abbreviated Scales of Intelligence.

1 Completed by caretaker; 2 MT = 21, NMT = 29; 3 MT = 28, NMT = 36; 4 MT = 30, NMT = 35; 5 MT = 30, NMT = 30; 6 MT = 27, NMT = 34.
Table 4.2. Abuse subtype severity, estimated onset age and duration (in years) in the MT group.

<table>
<thead>
<tr>
<th>Abuse Subtype</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical abuse (n=3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity (0-4)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>4.7</td>
<td>5.1</td>
</tr>
<tr>
<td>Mean duration</td>
<td>5.3</td>
<td>6.5</td>
</tr>
<tr>
<td>Neglect (n=23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity (0-4)</td>
<td>3.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>3.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Mean duration</td>
<td>5.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Sexual abuse (n=5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity (0-4)</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>5.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Mean duration</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Emotional abuse (n=26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity (0-4)</td>
<td>3.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>3.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Mean duration</td>
<td>6.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Domestic Violence (n=17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity (0-4)</td>
<td>2.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>4.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Mean duration</td>
<td>4.4</td>
<td>3.2</td>
</tr>
</tbody>
</table>

4.2.2.4. EFT. The modified version of the Autobiographical Memory Test (M-AMT; Williams & Broadbent, 1986) was used to assess EFT overgenerality (e.g. Birgit Kleim et al., 2014; Williams et al., 1996). During the M-AMT, 12 word cues (6 positive and 6 negative words) were presented visually and orally in an alternating and pseudorandomised order, to which participants responded with a future related event. Before the beginning of the task, participants were instructed to describe specific, detailed, personal and realistic future scenarios that would not last more than one day and that had not been previously experienced. Following the instructions, all participants had two practise trials during which they received feedback. During the task, participants did not receive any feedback and only up to two general probes were provided – e.g. “can you think of anything else” or “is there anything else you would like to add” – and words such as “specific” or details’ were not used. Each trial lasted a maximum of 60 seconds. All trials were audio-recorded and later transcribed for scoring. Positive and negative cue words were matched for word frequency and
imageability (Rubin & Schulkind, 1997; Williams, Healy, & Ellis, 1999). Frequency characteristics were taken from the English Lexicon Project (Balota et al., 2007). Imageability (and valence) was determined using a 9-point rating scale which was administered to 25 young adults. The 6 positive cue words were: admired, kind, strong, joyful, hopeful, grateful; the 6 negative cue words were: ashamed, disappointed, hate, stressed, insecure, unhappy; the two word cues used during the practise trials were: satisfied and criticised.

**Scoring.** In line with the majority of EFT studies in psychiatric populations (Addis et al., 2016; Hallford et al., 2018; Kleim et al., 2014; Williams et al., 1996) and ABM studies of childhood maltreatment (Valentino et al., 2009), future events were scored as either specific or overgeneral. The overgeneral EFT score for each participant was calculated from the total number of overgeneral responses (min. = 0 max. = 12). Overgeneral future events were defined as scenarios that did not include at least one specific detail that identified them as a distinct episode, or events that lasted for more than one day (known as extended overgeneral future events), or events that reflected a series of repeated future events (known as categorical overgeneral future events) (A. D. Brown et al., 2012; Valentino et al., 2009). In line with standard scoring procedures, if no repose was provided within 1 minute, it was scored as an omission. Omissions counted as overgeneral responses as they suggest difficulties in generating specific future events.

Scoring was carried out blindly (i.e. group/participant identity was unknown) by one experimenter (the author of this thesis). Moreover, a second independent blind rater (a member of staff with an undergraduate degree in psychology) scored a random subset of interviews (19%) in order to determine inter-rater reliability. Intra-class correlations (ICC) were calculated using a two-way random absolute agreement model. An excellent degree of reliability was found. The single measures ICC was .79 [95% CIs LL = .71 UL = .85, F(131,131) = 8.42, p < .001].
Feasibility. EFT is more cognitively demanding than ABM (Coughlin et al., 2014; D’Argembeau & Van der Linden, 2006; Q. Wang et al., 2014) and participants across the lifespan have been shown to consistently produce fewer detailed and specific episodic future events compared to episodic personal memories (Addis et al., 2010, 2008; Coughlin et al., 2014; Madore, Gaesser, & Schacter, 2014; Q. Wang et al., 2014). Possibly for this reason, previous studies with adolescents provided specificity-inducing instructions during each trial – e.g. “tell me the details of one event that is related to…” (Bromberg et al., 2015; Coughlin et al., 2014) – reducing the ecological validity of the task (i.e. how episodic future thoughts emerge in real-life settings). Other studies have tested EFT and ABM in the same experimental testing session, without controlling for the possibility of ‘recasting’ (Addis et al., 2010) entire past events as future ones (Gott & Lah, 2014; Terrett et al., 2013; Q. Wang et al., 2014). Conversely, in this study we provided minimal instructions during each trial, and, in order to reduce potential ‘recasting’, we have not combined the M-AMT with the AMT. Therefore, by using experimental procedures and scoring methods which are in line with adult studies of EFT and developmental studies of ABM (Addis et al., 2016; Kleim et al., 2014; Valentino et al., 2009; Williams et al., 1996), here, were are able to show that the M-AMT is feasible among individuals between 12 to 17 years of age.

4.2.3. Procedure

Demographic information, symptoms questionnaire and psychometric testing were completed by the participant and one parent/carer during an initial home visit. Some participants completed the M-AMT during the same home visit, while others attended a second session at University College London (UCL) campus. The session on campus also involved other behavioural experiments and a brain scan (results reported in the study described in Chapter Two (Gerin et al., 2017) and in other published studies (e.g. Hoffmann et al., 2018; McCrory, Puetz, et al., 2017).
4.2.4. Data-analysis

4.2.4.1. Outliers and missing values. Participants with two or more invalid M-AMT trials due to experimental/technical reasons (e.g. inaudible audio recording) or lack of engagement with the task were excluded from the study. This led 3 NMT and 1 MT to be excluded from further analyses. When only one trial was missing, a replacement-by-mean was performed (for 1 MT and 1 NMT).

In order to remove outliers for normally distributed outcome variables (OEFT scores in the NMT group) Tukey’s box-plot Inter-quartile range (IQR) method was implemented, using a multiplier of 2.2, as suggested by simulation estimates by Hoaglin & Iglewixcz (1987). For non-normally distributed data (i.e. OEFT scores in the MT groups), the ‘adjusted boxplot’ method developed by Hubert & Vandervieren (2008) was implemented instead (Seo, 2006). This led to 1 participant from the MT group to be removed from further analyses. The final sample consisted of 68 participants (31 MT and 37 NMT; Table 4.1).

4.2.4.2. Demographics, cognitive abilities and symptoms. Independent sample t-tests or chi-squared tests were performed to explore whether the MT and NMT groups differed on demographic characteristics (age, gender, pubertal status, socio-economic-status, ethnicity) cognitive abilities (IQ, executive control, including visual and verbal memory and verbal fluency) or symptoms levels/functioning (measured with the SDQ) (Table 4.1).

4.2.4.3. EFT analyses. An independent samples t-test was performed to investigate if MT and NMT groups differed on M-AMT performance (i.e. OEFT total score). Pearson correlations were also performed within the MT group to explore if OEFT was associated with the maltreatment dimensions of severity, onset and duration.

Structural equation modelling (SEM) mediation analyses were performed in the R package Lavaan (Rosseel, 2012) to explore if variability in OEFT could explain (i.e.
mediate) the association between maltreatment status and i) general psychopathology / adjustment (measured with the SDQ total score).
4.3. Results

4.3.1. Demographics, Cognitive Abilities and Symptoms

The two groups did not differ on demographic characteristics, symptom levels, nor on measures of intelligence and verbal fluency (Table 4.1).

4.3.2. EFT

As predicted, we found a significant medium-sized group difference in EFT performance (Table 4.3). In particular, the MT group produced significantly more overgeneral episodic future events compared to the NMT group. This group difference remained significant after removing participants who met clinical threshold on the SDQ total score (i.e. scores equal or above 17; MT = 5, NMT = 4) or after using the SDQ total score as a covariate of no interest \([F (1,58) = 5.86, p = .02]\). Moreover, we found that MT participants, compared to their NMT peers, produced more overgeneral future event to both positive and negative cues. For this reason, we used the composite OEFT total score in further analyses – rather than the positive and negative subscales separately – in order to reduce the number of multiple comparisons.

Table 4.3. Mean Overgeneral Episodic Future Thinking (OEFT) scores in the MT and NMT groups.

<table>
<thead>
<tr>
<th></th>
<th>MT (n=31)</th>
<th>NMT (n=37)</th>
<th>p(^{1})</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td>OEFT Total Score</td>
<td>Mean 8.35</td>
<td>Mean 6.72</td>
<td>.01*</td>
<td>.59</td>
</tr>
<tr>
<td></td>
<td>SD 2.49</td>
<td>SD 3.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OEFT Positive</td>
<td>Mean 4.12</td>
<td>Mean 3.32</td>
<td>.02*</td>
<td>.51</td>
</tr>
<tr>
<td></td>
<td>SD 1.43</td>
<td>SD 1.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OEFT Negative</td>
<td>Mean 4.23</td>
<td>Mean 3.41</td>
<td>.02*</td>
<td>.51</td>
</tr>
<tr>
<td></td>
<td>SD 1.52</td>
<td>SD 1.74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MT = Maltreated group; NMT = Non-maltreated group; OEFT = Overgeneral Episodic Future Thinking. \(^{1}\) One-tailed significance value. * p < .05
4.3.3. EFT and Maltreatment Severity

Within the MT group, correlation analyses revealed no significant association between OEFT total score and maltreatment severity ($r = -.01, p = .93$), onset ($r = .20, p = .29$), or duration ($r = .06, p = .75$).

4.3.4. EFT and SDQ

The mediation model presented Figure 4.1 below shows that increased OEFT did not mediate the association between maltreatment status and SDQ total score. That is, variability in EFT specificity across groups was not found to be linked to variability in symptom levels.

![Figure 4.1](image_url)

*Figure 4.1.* Structural equation mediation model depicting the association between maltreatment status, OEFT and SDQ total score. N = 61 (MT = 27, NMT = 34). Note. Coefficient values are standardized; * indicates statistically significant coefficients; the significance thresholds were measured using bootstrapping.
4.4. Discussion

Difficulties in generating specific, detailed and vivid possible future scenarios (known as OEFT) have been associated with mental health difficulties and a number of maladaptive outcomes, including reduced social problem solving abilities (A. D. Brown et al., 2012). In this study, we investigated for the first time if the experience of childhood maltreatment may disrupt the development of EFT. In line with our hypothesis, we showed that exposure to childhood abuse and/or neglect, independent of symptom levels or clinical status, is associated with increased OEFT. That is, we found that adolescents with substantiated histories of childhood maltreatment were able to generate fewer specific episodic future events compared to well matched non-maltreated peers. However, OEFT was not associated with continuous indexes of maltreatment severity, nor it was found to predict concurrent psychopathology.

Several factors may contribute to the emergence of OEFT among individuals with a history of abuse and neglect. Previous research has shown that exposure to maltreatment during childhood is associated with ABM reduced specificity (i.e. OGM; Aglan, Williams, Pickles, & Hill, 2010; McCrory, Puetz, et al., 2017; Valentino et al., 2009). According to William’s theoretical model, OGM is believed to emerge, in part, as an avoidant coping strategy among individuals who experience abuse and trauma (Williams, 2006; Williams et al., 2007) – avoiding the details of painful or traumatic memories may help reduce distress. However, this functional avoidance may become maladaptive when it is applied inflexibly to all autobiographical memories (Williams et al., 2007). Impaired retrieval and access to detailed personal memories is believed to disrupt the ability to then imagine specific future events (Hassabis & Maguire, 2007; Schacter & Addis, 2007). In fact, the ability to project and imagine the self in the future relies upon the flexible recombination of elements and specific information from past personal episodes (Hassabis & Maguire, 2007; Schacter & Addis, 2007). Therefore, the
well-established impairments in ABM functioning among maltreated individuals may constrain the typical development of future thinking. Furthermore, considering the crucial role of sensitive caretaking in the development of both ABM and EFT (Atance, 2015; Prabhakar et al., 2016; Suddendorf, 2017), exposure to chaotic early-learning environments and neglectful parenting is also likely to contribute to the emergence of OEFT among individuals who experience childhood maltreatment.

This pattern of increased OEFT that we found among maltreated adolescents may represent a marker of latent vulnerability to future psychopathology. As discussed in the introduction, there is a well-established association between OEFT and a range of psychiatric conditions, such as depression and PTSD (Addis et al., 2016; A. D. Brown et al., 2013; Hallford et al., 2018; Kleim et al., 2014; Williams et al., 1996). Moreover, OEFT has been shown to be associated with impairments in a range of cognitive and psycho-social domains, including impulse control, affect regulation, planning and social problem solving (Bromberg et al., 2015; A. D. Brown et al., 2016, 2012; Malek et al., 2018; Prabhakar et al., 2016; Terrett et al., 2016; Wiehler et al., 2015).

Reduced EFT specificity in the MT group, however, was not found to be related to symptom levels (Figure 4.1). Nevertheless, the cross-sectional design of this study does not allow us to determine whether, over time, EFT alterations may still impact social functioning and psychiatric symptomatology. We know from epidemiological studies that psychiatric disorders may not emerge until several years after the experience of abuse and neglect (Green et al., 2010; Ronald C Kessler et al., 2010). According to the theory of Latent Vulnerability (McCrory, Gerin, et al., 2017), cognitive and neurobiological alterations that occur as a result of maltreatment may not have cross-sectional relationship with overt symptoms. Rather, their latent nature entails that maladaptive mental health outcomes may emerge even several years (or decades) after the experience of maltreatment (McCrory, Gerin, et al., 2017; McCrory & Viding,
Chapter 4

2015). In particular, maltreatment-related cognitive recalibrations are hypothesised to have direct effects by changing how an individual perceives, processes and responds to the environment. In addition, these alterations are also thought to have indirect effects, as they cumulatively shape an individual’s social ecology over time. In the context of EFT, reduced EFT specificity may directly increase the degree to which stressors or everyday challenges burden and tax an individual by altering, for instance, social problem solving, affect regulation and impulse control abilities. These alterations, in turn, can also have indirect negative consequences by increasing relational difficulties and by decreasing the ability to elicit social support and sustain peer and family networks, which serve important protective functions (van Harmelen et al., 2017). In particular, investigating the close link between EFT and interpersonal problem solving abilities (A. D. Brown et al., 2016, 2012) may represent a promising intermediary mechanism through which OEFT may instantiate psychiatric vulnerability among maltreated individuals. This will be one of the main aims of the next empirical chapter (Chapter Five).

4.4.1. Limitations and Conclusions

The study presented in this chapter featured several strengths. First, the analyses showed that the group difference in OEFT was independent of concurrent symptomatology or clinical status. Moreover, the demographic similarity of the MT and NMT groups for several potentially confounding factors (e.g. socio-economic status, executive function/verbal ability, IQ and symptom levels), suggests that the observed group difference in OEFT is unlikely to be secondary to the experience of maltreatment. Second, studies that rely solely on self-report/continuous measures of maltreatment tend to recruit individuals with a history of maltreatment that fall within a normative range. This reduces the generalisability (and potential clinical relevance) of the findings to the substantial minority of individuals who experience more severe forms of abuse and neglect. Here, on the other hand, we were able to recruit (with the
support of local child protection agencies) a sample of young individuals with substantiated and severe experiences of maltreatment. Third, in the present study, OEFT was measured with the most widely used and validated test and scoring method for the assessment of episodic specificity in adult, developmental and clinical populations (e.g. Addis et al., 2016; Hallford et al., 2018; Kleim et al., 2014; Valentino et al., 2009; Williams et al., 1996).

There were, however, also notable limitations. First, a longitudinal design would be necessary to investigate whether maltreatment-related alterations in EFT are indeed associated with increased psychiatric risk (hence, if reduced EFT specificity could be considered a marker of latent vulnerability). Second, extant findings suggest that preschool/early childhood years represent an important period for the emergence of EFT. The limited sample of this study (and the large individual variability in maltreatment onset and duration) precludes us from investigating the existence of sensitive periods during which the experience of abuse and neglect may be particularly potent and disruptive for EFT development. Moreover, the large variability in the types of maltreatment experienced in our sample prevents us from exploring whether there were specific effects of maltreatment subtype (e.g. abuse vs neglect) on EFT abilities. Third, if EFT alterations are to be considered a marker of latent psychiatric vulnerability across the lifespan, it is necessary that the increased pattern of OEFT that we found in adolescents, be replicated in research with adults who have histories of childhood maltreatment. Finally, the design of this study does not allow us to rule out the possibility that a third, yet unidentified variable, drives the association between a history of maltreatment and reduced OEFT specificity. ABM represents the generative basis of EFT, and functional avoidance (e.g. cognitive and experiential avoidance) has been found to contribute to reduced ABM specificity (e.g. Debeer et al., 2012; Sumner, 2012). Avoidant coping strategies (in the form of both experiential and cognitive avoidance) have consistently been associated with a history of maltreatment and poorer
outcomes in this group of individuals. It follows that we cannot exclude that the group
difference found in EFT performance is primarily driven by experiential and cognitive
avoidance, rather than a genuine difficulty in generating specific future scenarios.
Future studies could address this issue directly by including a measure of functional
avoidance and use it as a covariate of interest in the SEM analyses.

To conclude, the relative paucity in mechanistic explanations for the well-
established association between childhood maltreatment and later psychopathology (R.
Gilbert, Widom, et al., 2009; Lansford et al., 2002) means that we are still poorly
equipped to target neurocognitive vulnerabilities. For this reason, it is crucial that we
acquire a more detailed understanding of the cognitive processes that are involved in the
pathogenesis and maintenance of psychiatric disorders, and also investigate those
cognitive and affective domains that may be malleable and amenable to psychological
interventions. The evidence presented in this study indicates that alteration in EFT
represents one promising cognitive construct that may allow us to better characterise
latent psychiatric vulnerability among individuals who have experienced childhood
maltreatment. However, future investigations are still required to establish if EFT
maltreatment-related changes may be linked to future psychopathology and to
alterations in related constructs and cognitive domains, such as delay
discounting/impulsivity and interpersonal problem solving. Such work is crucial to
inform our understanding of the pathogenesis of mental health problems following
childhood maltreatment, and to guide the development of preventative strategies
capable of reducing the risk of the emergence (and relapse) of psychiatric disorders.
CHAPTER 5 – Impairments in Interpersonal Problem Solving

Increase Psychiatric Risk and Reduce Psychosocial Adjustment

Among Maltreated Youth

The experience of abuse and neglect leads to maladaptive psychosocial outcomes across the lifespan, such as reduced social support and increased victimisation risk. These, in turn, have been shown to contribute to the emergence of psychopathology, including depression and anxiety (e.g. Sperry & Widom, 2013). It is possible that, as a result of abuse and neglect, individuals with maltreatment histories are less likely to develop the interpersonal skills necessary to support and cultivate positive and stable relationships. In this chapter we investigated interpersonal problem solving skills – and in particular ‘means-end thinking’ – as a potential mechanism underlying increased psychiatric vulnerability following childhood maltreatment. In a sample of adolescents with substantiated experiences of abuse/neglect (n=34) and non-maltreated peers (n=38), we found that a history of maltreatment was linked to poorer social problem solving skills. In particular, individuals exposed to childhood maltreatment generated fewer effective strategies and relevant/concrete steps necessary to solve hypothetical interpersonal problematic situations. This, in turn, was shown to relate to higher psychiatric symptoms. We also showed that reduced ‘Episodic Future Thinking’ (EFT) specificity (or overgeneral EFT; OEFT) contributed to the association between a history of childhood maltreatment and poorer interpersonal problem solving skills. This, in turn, was linked to higher symptom levels. Overall, these findings suggest that deficits in episodic specificity following childhood maltreatment are associated with less effective interpersonal problem solving skills. Over time such a cognitive style and related social difficulties may compromise psychosocial adjustment and mental health functioning. The work presented in this chapter contributes to our understanding of how childhood maltreatment and subsequent psychopathology may be linked and provide targets for future longitudinal investigations aimed at the development of novel preventative clinical approaches.
Chapter 5

5.1. Introduction

The quality of parental care, including sensitive, contingent and consistent caretaking, plays a central role in shaping several aspects of social cognition and behaviour (Belsky & Fearon, 2002; Bottonari, Roberts, Kelly, Kashdan, & Ciesla, 2007; Groh et al., 2014; Reeb-Sutherland et al., 2012). The experience of childhood maltreatment has been shown to be particularly disruptive to psychosocial development (Afifi, Mota, Sareen, & MacMillan, 2017; Benedini et al., 2016; Bolger et al., 1998; Flynn, Cicchetti, & Rogosch, 2014; Kapeleris & Paivio, 2011; Kim & Cicchetti, 2010; A. R. King, 2016; Labella et al., 2018; Matheson et al., 2017; Raby et al., 2018; Sperry & Widom, 2013; van Harmelen et al., 2017; Widom et al., 2014). However, we are still limited in our understanding of the mechanisms that may contribute to this association. Interpersonal problem solving skills represent a promising domain that may allow us to index latent vulnerability to psychiatric disorder and reduced social functioning among adolescents with histories of childhood abuse and neglect.

The introduction section of this chapter is divided into five subsections. First, interpersonal problem solving and interpersonal means-end thinking are defined. Second, the main cognitive and affective processes that are believed to underpin problem solving skills are discussed. In the third subsection we review the evidence linking interpersonal problem solving abilities with psychopathology and psychosocial functioning. In the fourth subsection we explore the direct and indirect evidence suggesting that childhood maltreatment may alter the development of problem solving skills. Finally, the aims and hypothesis of this study are described.

5.1.1. What is Interpersonal Problem Solving?

Problem solving is generally understood to be an explicit, rational and purposeful cognitive and behavioural process aimed at identifying the most effective
strategies/solutions for dealing with problems encountered in daily life, as well as major life events (D’Zurilla & Goldfried, 1971; D’Zurilla, Nezu, & Maydeu-Olivares, 2004; D’Zurilla & Maydeu-Olivares, 1995; Nezu, 1987; Platt & Spivack, 1975a; Spivack, Platt, & Shure, 1976). Problems refer to situations in which effective or adaptive responses and solutions are not immediately apparent or available (D’Zurilla et al., 2004).

Problems can be impersonal (e.g. lost property, financial difficulties) intrapersonal (e.g. physical ailments) as well as interpersonal (e.g. disputes with friends, marital conflicts) (D’Zurilla et al., 2004). Solutions are understood to be cognitive, affective and behavioural coping responses that are the outcome of a problem solving process (D’Zurilla & Maydeu-Olivares, 1995).

D’Zurilla and colleagues, in their Social Problem Solving (SPS) model, delineate an important distinction between two aspects of social problem solving: ‘problem solving skills’ and ‘solution implementation’ (D’Zurilla et al., 2004). The former refers to the cognitive processes required to detect a problem and generate potential strategies and solutions. Solution implementation, on the other hand, refers to the experiential process of executing/applying a strategy. While problem solving skills tend to be generalised, as they can be applied to different situation, solution implementation abilities are context-specific (D’Zurilla et al., 2004). A recent longitudinal study provides support for this notion, whereby showing that problem solving skills and solution implementation abilities – despite some shared variance – were independent predictors of future depressive symptoms (Anderson, Goddard, & Powell, 2011).

According to the Interpersonal Cognitive Problem Solving (ICPS) model by Platt and colleagues, a core component of interpersonal problem solving skills is means-end thinking (Platt & Spivack, 1975a; Spivack et al., 1976). This is the ability to articulate the steps (i.e. relevant means; RM) necessary for problem resolution. Arguably, means-end thinking has been the most influential, validated and widely studied interpersonal problem solving construct, and has been instrumental in guiding
empirical work in the field (D’Zurilla & Maydeu-Olivares, 1995; Marx et al., 1992; Platt & Spivack, 1972; Platt, Spivack, Altman, Altman, & Peizer, 1974; Siegel, Platt, & Peizer, 1976; Williams, Barnhofer, Crane, & Beck, 2005). Means-end thinking, which is the main construct of interest in this chapter, has been operationalised using the Means-End-Problem-Solving test (or MEPS; Platt & Spivack, 1975). In this task, individuals are presented with the beginning and the end of problematic interpersonal situations and are required to articulate the step-by-step strategies that they would enact to achieve a resolution. Performance on this test is usually assessed on the number of means (i.e. concrete and effective steps) that are generated (Quiñones et al., 2015; Williams et al., 2005).

5.1.2. Cognitive and Affective Domains Associated with Interpersonal Problem Solving

Interpersonal problem solving is a multidimensional construct (Nezu, 1987; Nezu & Nezu, 2010), and several cognitive and affective process have been shown to contribute to effective problem solving skills and means-end thinking. Marx, Williams and colleagues proposed that interpersonal problem solving skills rely upon the ability to retrieve formerly successful strategies and to project those onto current and future problematic situations (J. Evans, Williams, O’loughlin, & Howells, 1992; Marx et al., 1992). In particular, both episodic memory retrieval (known as ‘Autobiographical Memory’, or ABM) and ‘Episodic Future Thinking’ (or EFT) are believed to contribute to interpersonal problem solving skills (A. D. Brown et al., 2012; Marx et al., 1992). This is supported by a consistent body of empirical work showing that the ability to generate specific past and future episodic events is associated with better problem solving, including interpersonal means-end thinking (Beaman, Pushkar, Etezadi, Bye, & Conway, 2007; A. D. Brown et al., 2012; J. Evans et al., 1992; Goddard et al., 1996; Goddard, Howlin, Dritschel, & Patel, 2007; Raes et al., 2005; Sutherland & Bryant, 2008; Vandermorris, Sheldon, Winocur, & Moscovitch, 2013; Williams et al., 2005).
Recent studies have also shown that experimentally manipulating EFT and ABM, via a brief episodic specificity induction, enhances problem solving performance among healthy and also depressed adults (Jing et al., 2016; Madore & Schacter, 2014; McFarland, Primosch, Maxson, & Stewart, 2017). Moreover, in a cluster randomised control trial, Werner-Seidler and colleagues (2018) compared Memory Specificity Training (or MEST) to an evidence-based group psychotherapy intervention for depression. Despite comparable symptom reduction in the two treatments groups, only MEST led to a substantial improvement on means-end thinking performance. Similar findings have also been reported among older adults (Leahy, Ridout, Mushtaq, & Holland, 2018). Collectively, the evidence presented above suggests that the ability to retrieve specific personal memories, and to generate detailed episodic future events, contribute to interpersonal problem-solving in both clinical and non-clinical adult populations. However, the association between episodic specificity and social problem solving has not yet been examined in children and adolescents with (and also without) histories of childhood maltreatment.

Another cognitive/affective domain linked to interpersonal problem solving is problem solving orientation (D’Zurilla & Maydeu-Olivares, 1995). This refers to cognitive, affective and behavioural factors that reflect the awareness, beliefs, and expectations relating to an individual’s own ability to resolve a problem (D’Zurilla & Nezu, 1990; D’Zurilla et al., 2004). Problem solving orientation is influenced by existing cognitive schemas, perceived self-efficacy/mastery, self-esteem and approach-avoidance tendencies (D’Zurilla et al., 2004). In particular, high self-efficacy and an internal locus of control are believed to play a central role in motivating an individual to search for, and then make available and apply the skills/knowledge necessary to resolve a problematic situation (Bandura, 1977; Bandura & Locke, 2003; D’Zurilla & Maydeu-Olivares, 1995). Several lines of evidence support this notion. For example, in a longitudinal study, problem solving orientation and self-efficacy were found to predict
the ability to cope with life stressors and successfully negotiate novel developmental challenges (D’Zurilla & Sheedy, 1991). Moreover, in two separate studies, Brown and colleagues showed that experimentally manipulating perceived self-efficacy leads to changes in interpersonal problem solving performance in young adults, and also in patients with PTSD (A. D. Brown et al., 2016, 2012). Interestingly, this effect was in part mediated by increased EFT specificity (A. D. Brown et al., 2012). In other words, higher self-efficacy was shown to facilitate the generation of more specific episodic future events; this, in turn, led to improvements in interpersonal problem solving performance. In line with Williams and colleagues’ Carfax model (Williams, 2006), this could be explained by the fact that higher self-efficacy and self-worth may lessen the impact of processes known to disrupt episodic specificity, such as ruminative thinking and functional avoidance tendencies (A. D. Brown et al., 2016, 2012). Increasing access to detailed representations of past and future events, as discussed above, can then increase interpersonal problem solving skills by facilitating the retrieval of previous successful strategies and information one can use and/or recombine to generate novel effective solutions.

Mentalising (or theory of mind) and executive control are two domains that have also been shown to contribute to effective interpersonal problem-solving. When problems occur in a social setting, the ability to take another person’s perspective into account has been associated with both social competence (Bosacki & Wilde Astington, 2001; Thoma et al., 2013) and interpersonal problem solving abilities (Channon & Crawford, 2010; Channon, Crawford, Orlowska, Parikh, & Thoma, 2014; Thoma et al., 2015). Mentalising, in fact, can contribute to the awareness and ability to detect an interpersonal problem (D’Zurilla & Nezu, 1990; Nezu & Ronan, 1988b), and then promote the generation of solutions and strategies that are socially appropriate (Channon & Crawford, 2010). In terms of executive control, problem solving skills also
require the ability to constrain attention to an external task and to consider, simultaneously, multiple strategies and possible solutions. Neuroimaging and behavioural evidence do indeed suggest that executive control and working memory are associated with problem solving abilities (Addington & Addington, 1999; Channon, 2004; Channon & Crawford, 2010; Ruby, Smallwood, Sackur, & Singer, 2013; Vandermorris et al., 2013), however, only to a modest extent (Marx et al., 1992; Platt & Spivack, 1975a; Siegel et al., 1976; Vandermorris et al., 2013).

To summarise, interpersonal problem solving skills are underpinned by a set of cognitive and affective processes that humans use to facilitate the selection of adaptive coping responses and effective strategies (D’Zurilla et al., 2004). A central component of interpersonal problem solving skills is means-end thinking. This refers to the ability to articulate step-by-step solutions to a problematic situation. Empirical evidence has focused around the contribution of four primary cognitive domains utilised for means-end thinking: episodic specificity, self-efficacy (or mastery), mentalisation (or theory of mind) and executive control.

5.1.3. Interpersonal Problem Solving, Social Functioning and Psychopathology

According to the stress-diathesis model of psychopathology, a disorder emerges due to an interaction between an inherent vulnerability and the exposure to stressful life experiences (Drake, Pillai, & Roth, 2014; Monroe & Simons, 1991; Walker & Diforio, 1997). One factor that may connote greater susceptibility to the impact of stress exposure is reduced interpersonal problem solving skills. Limitations in this ability may mean that an individual is less equipped to deal with novel situations, developmental challenges and interpersonal conflicts (Nezu, 1987; Tse & Bond, 2004). Cross-sectional and also longitudinal evidence do indeed suggests that poor interpersonal problem solving predicts both higher occurrence and increased impact of negative life events (D’Zurilla & Sheedy, 1991; Davila, Hammen, Burge, Paley, & Daley, 1995; S. H.

In line with the notion that interpersonal problem solving skills, and in particular means-end thinking, contribute to the emergence, maintenance and relapse of psychopathology (Thoma et al., 2013), there is a well-established association between poor problem solving and internalising disorders (Anderson et al., 2011; Gotlib & Asarnow, 1979; Haugh, 2006; Kleftaras, 2000; Lyubomirsky & Nolen-Hoeksema, 1995; Marx et al., 1992; Noreen, Whyte, & Dritschel, 2015; Pollock & Williams, 2004; Quiñones et al., 2015; Thoma et al., 2015; Watkins & Baracaia, 2002). Moreover, a large body of cross-sectional data (see Speckens & Hawton, 2005 review) as well as initial longitudinal data (Khurana & Romer, 2012; Quiñones et al., 2015) indicate that problem solving skills deficits are associated with increased risk of suicide among adults and adolescents. Interestingly, the association between interpersonal problem solving skills and internalising symptoms seems to be mediated by difficulties in accessing specific autobiographical memories (or ABM) and personal episodic future events (or EFT) (J. Evans et al., 1992; Goddard et al., 1996; McFarland et al., 2017; Raes et al., 2005; Ridout, Matharu, Sanders, & Wallis, 2015; Williams et al., 2005).

Deficits in interpersonal problem solving skills have not only been associated with depressive symptoms (Thoma et al., 2013), but also with PTSD (Sutherland & Bryant, 2008), conduct problems (Joffe, Dobson, Fine, Marriage, & Haley, 1990), eating disorder (Ridout et al., 2015) and borderline personally disorder (Bray, Barrowclough, & Lobban, 2007; Kehrer & Linehan, 1996). Moreover, among individuals with psychosis, deficits in interpersonal problem solving have been shown to predict future internalising symptoms (Vorontsova et al., 2018). Poor interpersonal problem solving skills also constitute a known risk factor for substance abuse relapse.
(Demirbas et al., 2012; Thoma et al., 2013). Finally, some of the most compelling evidence for the role of interpersonal problem solving in psychiatric disorder comes from studies that have shown that interventions that aim to improve problem solving skills and problem orientation lead to reductions in symptoms (Bell & D’Zurilla, 2009) and risk of relapse (Nezu & Nezu, 2010).

5.1.4. Interpersonal Problem Solving and Childhood Maltreatment

Early contingency detection of socially-relevant associations represents a basic mechanism underlying the emergence of socially oriented behaviours and higher-order social cognitions (Reeb-Sutherland et al., 2012). During development, contingency detection is enabled and potentiated through sensitive parenting (Ellis, 2006; Nagai et al., 2006; Reeb-Sutherland et al., 2012; Tarabulsy, Tessier, & Kappas, 1996). The experience of maltreatment, however, represents an insult to the neurocognitive development of associative learning (Gerin et al., 2017; Harms et al., 2018; Sheridan et al., 2018). Physical/verbal punishments can be extreme and erratic, biasing contingency detection towards negative and threat-related cues (e.g. McCrory et al., 2011; Shackman, Shackman, & Pollak, 2007). A negative/threat bias can limit the availability of resources necessary for the development of a range of socio-cognitive functions (Rogosch et al., 2011) and may also contribute to the formation of a more avoidant exploratory style (Cicchetti & Doyle, 2016; Cicchetti et al., 2006; Cyr et al., 2010). This, in turn, can curtail the opportunities necessary for psychosocial development among individuals with a history of abuse (Cicchetti, Rogosch, Maughan, Toth, & Bruce, 2003; Kim & Cicchetti, 2003). Moreover, parental neglect, by reducing the availability and consistency of basic reinforcers such as emotional warmth and food (R. Gilbert, Widom, et al., 2009; Radford et al., 2011), can also bias the development of contingency learning and expectancies formation, especially in the context of social interactions and interpersonal relations.
Therefore, maltreatment-related alterations in associative learning early in life may perturb the development of affective and social skills. In line with this notion, individuals with a history of childhood maltreatment experience a range of maladaptive interpersonal outcomes across the lifespan. These include reduced perceived social competence by others (Levendosky, Okun, & Parker, 1995; Matheson et al., 2017), romantic functioning (Kapeleris & Paivio, 2011; Labella et al., 2018; Raby et al., 2018), relationship quality (Flynn et al., 2014), likeability by peers (Bolger et al., 1998; A. R. King, 2016), social support (Sperry & Widom, 2013), as well as increased risk of victimisation (Benedini et al., 2016), partner violence (Afifi et al., 2017; Benedini et al., 2016; Widom et al., 2014), peer-rejection (Bolger et al., 1998; Kim & Cicchetti, 2010), and interpersonal conflict (Raby et al., 2018).

Alterations in interpersonal problem solving skills (and the cognitive processes that support these skills) represent one potential explanatory factor underlying poor social functioning among individuals with experiences of childhood abuse and neglect. Indirect evidence in support of this hypothesis comes from studies of maltreatment documenting perturbations in a range of affective, social and cognitive domains believed to underlie effective interpersonal problem solving. For instance, extant findings suggest that maltreated individuals show reduced mentalising abilities and emotional competence (Cicchetti et al., 2003; Kapeleris & Paivio, 2011; O’Reilly & Peterson, 2014; Pears & Fisher, 2005; Shipman & Zeman, 1999; Tarullo, Bruce, & Gunnar, 2007). Thus, in the context of childhood maltreatment, impairments in the ability to read social cues and consider others’ perspectives can have a detrimental effect on the ability to accurately detect problematic interpersonal situations, articulate effective strategies and generate socially adaptive responses (Channon & Crawford, 2010; Channon et al., 2014; Thoma et al., 2015).
Current findings suggest that maltreatment also leads to long-lasting alterations in perceived self-efficacy (Bolger et al., 1998; Cheever & Hardin, 1999; Flynn et al., 2014; Kapeleris & Paivio, 2011; Kim & Cicchetti, 2003; Ryan, Solberg, & Brown, 1996; Sachs-Ericsson, Verona, Joiner, & Preacher, 2006) and in episodic specificity, including the ability to generate detailed descriptions of past (or ABM; De Decker, Hermans, Raes, & Eelen, 2003; Kuyken & Brewin, 1995; McCrory, Puetz, et al., 2017; Valentino et al., 2009) and future events (or EFT; see study in Chapter Four). As discussed above, low self-efficacy and also difficulties in retrieving and recombining detailed episodic information are known to contribute to interpersonal problem solving deficits (Beaman et al., 2007; A. D. Brown et al., 2016, 2012; D’Zurilla & Sheedy, 1991; Goddard et al., 1996, 2007; Marx et al., 1992; Raes et al., 2005; Sutherland & Bryant, 2008; Werner-Seidler et al., 2018; Williams et al., 2005). Therefore, negative self-concept, low self-efficacy and reduced episodic specificity (together with alterations in emotional competence and mentalisation abilities) may underlie poor interpersonal problem solving skills among maltreated individuals.

Only two studies have explored interpersonal problem solving in maltreated individuals. Using peer provocation scenarios in school aged children (8-12 years of age), Levendosky and colleagues (1995) did not find a group difference in the number of solutions generated among maltreated and non-maltreated children. Conversely, in a study with a small sample of pre-schoolers with maltreatment experience (3-6 years of age), Smith and Walden (1999) found that maltreated children generated fewer solutions than non-maltreated peers. The paucity of extant data and the absence of consensus in the reported findings limit our understanding of the impact of childhood maltreatment on social problem solving skills. Furthermore, means-end thinking performance (i.e. the number of relevant and effective steps/means generated to solve a problem) was not examined in these studies, despite its critical role in interpersonal problem solving.
5.1.5. The Current Study & Hypotheses

In the current study we investigated interpersonal problem solving skills (in particular means-end thinking) among adolescents (12-17 years) with and without experiences of abuse and/or neglect. In line with studies of psychosocial competence among maltreated individuals (Bolger et al., 1998; Kim & Cicchetti, 2010; Levendosky et al., 1995; Matheson et al., 2017; Raby et al., 2018; Sperry & Widom, 2013) and of problem solving abilities in psychiatric populations (Nezu, 1987; Thoma et al., 2013), we predicted that a history of childhood maltreatment would be associated with poorer interpersonal means-end thinking performance. Moreover, we hypothesised that i) poorer interpersonal means-end thinking would be associated with higher psychiatric symptoms among maltreated individuals and that ii) maltreatment-related deficits in EFT (reported in the previous chapter) would be linked to poorer interpersonal means-end thinking skills.
5.2. Methods

5.2.1. Participants

An initial sample of 73 children and adolescents aged 12-17 years participated in this study: 35 with documented experience of maltreatment recruited via the Social Services Department (MT group) and 38 peers with no prior Social Service contact recruited via schools / advertisements in the community (NMT group). Consent was obtained from the child’s legal guardian and assent to participate was obtained from all children. Procedures were approved by University College London (UCL) Research Ethics Committee (0895/002). Exclusion criteria included the presence of a pervasive developmental disorder, neurological abnormalities and an IQ below 70. The procedure for removing outliers is described below. Demographic details of the final sample are reported in Table 5.1 (MT = 34, NMT = 38). For more information regarding the recruitment procedure and sample overlap across Chapters Two, Four and see Appendix 3.

5.2.2. Measures

5.2.2.1. Maltreatment history. History and severity of abuse type (neglect, emotional, sexual and physical abuse and intimate partner violence) was provided by the child’s social worker or the adoptive parent (on the basis of Social Services reports). Severity of each abuse type was rated on a scale from zero (not present) to four (Table 5.2) in line with an established measure of maltreatment (Kaufman et al., 1994). In addition, age of onset and duration of maltreatment by subtype was estimated on the basis of Social Services reports.

5.2.2.2. Psychiatric symptomatology. The Strengths and Difficulties Questionnaire (SDQ), was completed by parents or caregivers to assess general functioning and psychopathology (Table 5.2) (R. Goodman, 2001). This is a well
validated measure, with high internal consistency (mean Cronbach α: .73), and good retest stability (mean correlation: 0.62) (R. Goodman, 2001).

5.2.2.3. Cognitive ability. Verbal and non-verbal intelligence was assessed using two subscales of the Wechsler Abbreviated Scales of Intelligence (Wechsler, 1997). Verbal fluency, a measure of executive control, was assessed using the composite score from a phonemic and a semantic fluency task. Participants were required to produce in 60 seconds as many words as possible beginning with the letter ‘s’ (phonemic fluency), and from the category ‘animals’ (semantic fluency) (Benton & Hamsher, 1983; Heller & Dobbs, 1993; Ruff et al., 1996).

Table 5.1. Demographics and symptomatology of MT and NMT groups included in the MEPS analyses.

<table>
<thead>
<tr>
<th>Measures</th>
<th>MT (n= 34)</th>
<th>NMT (n= 38)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female)</td>
<td>16</td>
<td>22</td>
<td>.36</td>
</tr>
<tr>
<td>Ethnicity (Caucasian)</td>
<td>22</td>
<td>21</td>
<td>.42</td>
</tr>
<tr>
<td>SES - Level of Education of parent (% beyond secondary)</td>
<td>12</td>
<td>21</td>
<td>.17</td>
</tr>
<tr>
<td>Mean SD</td>
<td>14.42</td>
<td>14.86</td>
<td>.22</td>
</tr>
<tr>
<td>Age (Years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent Report</td>
<td>3.00</td>
<td>3.14</td>
<td>.21</td>
</tr>
<tr>
<td>Self-Report</td>
<td>2.88</td>
<td>3.08</td>
<td>.18</td>
</tr>
<tr>
<td>WASI-IQ</td>
<td>104.6</td>
<td>110.1</td>
<td>.08</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>37.26</td>
<td>36.68</td>
<td>.79</td>
</tr>
<tr>
<td>SDQ-P Total Score</td>
<td>11.30</td>
<td>7.43</td>
<td>.03*</td>
</tr>
<tr>
<td>Emotional Symptoms</td>
<td>2.97</td>
<td>1.97</td>
<td>.08</td>
</tr>
<tr>
<td>Conduct Problem</td>
<td>2.07</td>
<td>1.54</td>
<td>.29</td>
</tr>
<tr>
<td>Hyperactivity/Inattention</td>
<td>4.20</td>
<td>2.63</td>
<td>.02*</td>
</tr>
<tr>
<td>Peer Relationship Problems</td>
<td>2.07</td>
<td>1.29</td>
<td>.14</td>
</tr>
<tr>
<td>Prosocial Behaviour</td>
<td>7.50</td>
<td>8.06</td>
<td>.08</td>
</tr>
</tbody>
</table>

*Abbreviations: MT = Maltreated group; NMT = Non-maltreated group; PDS = Puberty Development Scale; SES = Socio-economic-status; SDQ-P = Strength and Difficulties Questionnaire – Parent report; WASI-IQ = 2 IQ-subcales derived from the Wechsler Abbreviated Scales of Intelligence. ¹ Completed by caretaker; ² MT = 30, NMT = 37; ³ MT = 21, NMT = 31; ⁴ MT = 31, NMT =37; ⁵ MT = 34, NMT = 37; ⁶ MT =30, NMT = 35. * p < .05.
### Table 5.2. Abuse subtype severity, estimated onset age and duration (in years) in the MT group.

<table>
<thead>
<tr>
<th>Abuse Subtype</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical abuse (n=4)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity (0-4)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>4.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Mean duration</td>
<td>5.2</td>
<td>5.3</td>
</tr>
<tr>
<td><strong>Neglect (n=27)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity (0-4)</td>
<td>3.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>3.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Mean duration</td>
<td>5.2</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Sexual abuse (n=6)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity (0-4)</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>5.7</td>
<td>5.3</td>
</tr>
<tr>
<td>Mean duration</td>
<td>1.9</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Emotional abuse (n=29)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity (0-4)</td>
<td>2.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>3.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Mean duration</td>
<td>6.7</td>
<td>4.8</td>
</tr>
<tr>
<td><strong>Domestic Violence (n=18)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity (0-4)</td>
<td>2.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>4.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Mean duration</td>
<td>4.4</td>
<td>2.9</td>
</tr>
</tbody>
</table>

### 5.2.2.4. EFT.

As already described in detail in Chapter Four, the modified version of the Autobiographical Memory Test (M-AMT; Williams & Broadbent, 1986) was used to assess EFT overgenerality (e.g. Birgit Kleim et al., 2014; Williams et al., 1996). Briefly, during the M-AMT, 12 word cues (6 positive and 6 negative words) were presented visually and orally in an alternating and pseudorandomised order, to which participants responded with a future related event. Before the beginning of the task, participants were instructed to describe specific, detailed, personal and realistic future scenarios that would not last more than one day and that had not been previously experienced. In line with the majority of EFT studies in psychiatric populations (Addis et al., 2016; Hallford et al., 2018; Kleim et al., 2014; Williams et al., 1996) and ABM studies of childhood maltreatment (Valentino et al., 2009), future events were scored as either specific or overgeneral. The overgeneral EFT (OEFT) score for each participant was calculated from the total number of overgeneral responses (i.e. max = 12, min = 0). Overgeneral future events were defined as scenarios that did not include at least one specific detail that identified them as a distinct episode, or events that lasted for more
than one day (known as extended overgeneral future events), or events that reflected a series of repeated future events (known as categorical overgeneral future events) (A. D. Brown et al., 2012; Valentino et al., 2009).

5.2.2.5. Means-end Problem Solving test (MEPS). The MEPS measures the ability to generate and articulate step-by-step strategies necessary for achieving a specific goal in problematic interpersonal situations. Participants are presented with the beginning of a story that describes an interpersonal problem, and then the end of the story that explains the goal/resolution. Participants are assessed on the number of concrete/effective/relevant steps described to resolve the interpersonal problem. The MEPS has good internal consistency (usually > .80) (Platt & Spivack, 1972, 1975a; Platt et al., 1974). Its construct validity has been demonstrated in several studies in which problem solving skills differences were detected across groups varying in psychosocial adjustment (Platt & Spivack, 1972; Platt et al., 1974; Siegel et al., 1976; Thoma et al., 2013). Moreover, recent studies have also shown that interpersonal problem solving skills, measured with the MEPS, is related to real-life problem solving performance (Anderson et al., 2011).

Originally the MEPS consisted of 10 vignettes (Platt & Spivack, 1975a), but subsequent validation studies (Platt & Spivack, 1975b) have indicated that it is possible to burden the participants less and obtain reliable data administering 3-5 vignettes (D’Zurilla et al., 2004; Glazebrook, Townsend, & Sayal, 2015; Hawton, Kingsbury, Steinhardt, James, & Fagg, 1999; Lyubomirsky & Nolen-Hoeksema, 1995; Marx et al., 1992; Oldershaw et al., 2009; Quiñones et al., 2015; Watkins & Moulds, 2005; Werner-Seidler et al., 2018). In this study we also implemented a shortened/modified version of the original MEPS – we administered four interpersonal vignettes related to problems in different social scenarios, including peers/friends, a teacher, moving to a new neighbourhood and leadership/school involvement. Note that, in order to increase the relevance of the problematic situations to our child/adolescent sample, two vignettes
were modified from the original ones: The vignette describing a problem with a teacher was adapted from the original MEPS vignette depicting a problem with a boss/manager at work, and, the vignette about the school meeting was adapted from the original MEPS vignette describing a local community meeting.

The four vignettes were:

You notice that your friends seem to be avoiding you. You want to have friends and be liked. The story ends when your friends like you again.

You had just moved into a new neighbourhood. You want to have friends in the new neighbourhood. The story ends with you having many good friends and feeling at home in the neighbourhood.

You are having trouble getting along with one of your teachers. You are very unhappy about this. The story ends with the teacher liking you.

You are listening to a group of school friends speak about how to make things better in your school. You wanted to say something important and have a chance to be your class representative. The story ends with you being elected leader and presenting a speech.

The presentation order of the vignettes was pseudorandomised, and for each scenario participants had 2 minutes to verbally generate solutions. The vignette describing the interpersonal problem and the resolution was always in front of the participants as they described the solution path. Before the beginning of the task, participants had one practice trial in which an impersonal problematic situation was presented:

You came home after school and found that you had lost your phone. You are very upset about it. The story ends with you finding your phone and you feeling good about it.

The instructions were similar to those implemented in previous studies with adolescents and adults (Glazebrook et al., 2015; Hawton et al., 1999; Oldershaw et al., 2009; Raes et al., 2005; Williams et al., 2005). Participants imagined themselves in the problematic scenarios and generated verbally a detailed step-by-step strategy. During
the practice trial participants received on-line feedback on their performance and were reminded of the importance of generating a detailed step-by-step solution. Conversely, during the actual task, feedback was not provided, and only minimal/general prompting was allowed (e.g. “is there anything else you would like to add”). Responses were audio-recorded and then transcribed.

**Scoring.** In line with standard scoring procedures implemented in studies with adults and adolescents (Glazebrook et al., 2015; Hawton et al., 1999; Kremers, Spinhoven, Van der Does, & Van Dyck, 2006; Marx et al., 1992; Oldershaw et al., 2009; Platt & Spivack, 1975a; Raes et al., 2005) performance was assessed on the total number of **Relevant Means (RM)**, defined as discrete steps taken from the beginning of the story that bring the participant closer to the described problem resolution (Hawton et al., 1999; Kremers et al., 2006; Oldershaw et al., 2009; Platt & Spivack, 1975a). The definition of RM encompassed also: i) the acknowledgment of potential obstacles; ii) recognising that solving problems can require time; iii) the generation of alternative strategies; and also iv) introspective/reflective comments (e.g. realising, deciding, wondering, etc.) (Kremers et al., 2006; Williams et al., 2005). The total number of RM generated across the four vignettes was averaged to generate an individual RM total score. Also, in line with previous studies, RM were broken down into ‘**Active RM**’ (these are relevant steps initiated by the participant) and ‘**Passive RM**’ (these are relevant steps initiated by another person) (Kremers et al., 2006; Oldershaw et al., 2009). Steps lacking detail (e.g. ‘we sorted things out’) with no explanation of how things were resolved, repetitive information, and also descriptions that were irrelevant to the resolution of the problem were not considered as RM; instead, these were scored as **No-Means** (Oldershaw et al., 2009). In line with recent studies, we included an additional **Effectiveness** score. This was rated on a 7-point scale by the experimenter (1 = not at all effective; 7 = extremely effective). The definition of effectiveness was based on that of D’Zurilla and colleagues (D’Zurilla & Goldfried, 1971; D’Zurilla et al.,
2004), who consider a problem-solving strategy to be effective if it maximises positive outcomes and minimises short- and long-term undesirable consequences, both to oneself and others (Kremers et al., 2006; Marx et al., 1992; Oldershaw et al., 2009; Raes et al., 2005; Ridout et al., 2015).

Scoring was carried out blindly (i.e. group/participant’s identity was unknown by the rater – i.e. the author of this PhD thesis). Moreover, a second independent blind rater (a member of staff with an undergraduate degree in psychology) scored a random subset of interviews (16%) in order to determine inter-rater reliability. Intra-class correlations (ICC) for RM total score were calculated using a two-way random absolute agreement model. A good degree of reliability was found – the ICC was .64 [95% CIs LL = .43 UL = .79, F(43,43) = 4.61, p < .001]. Moreover, for Active RM and Passive RM, an excellent degree of reliability was found. The respective ICC was .81 [95% CIs LL = .67 UL = .89, F(43,43) = 9.40, p < .001] and .76 [95% CIs LL = .60 UL = .86, F(43,43) = 7.24, p < .001]. For No-Means, a fair degree of reliability was found with an ICC of .50 [95% CIs LL = .25 UL = .70, F(43,43) = 3.03, p < .001]. Finally, reliability was good for Effectiveness scores – ICC was .62 [95% CIs LL = .41 UL = .78, F(43,43) = 4.32, p < .001].

5.2.3. Procedure

Demographic information, symptoms questionnaire and psychometric testing were completed by the participant and one parent/carer during an initial home visit. Some participants completed the MEPS and the M-AMT during the same home visit, while others attended a second session at University College London’s (UCL) campus. The session at UCL also involved other behavioural experiments and a brain scan – the outcome of these are reported in Chapter Two of this thesis (i.e. Gerin et al., 2017) and in other published studies (e.g. Hoffmann et al., 2018; McCrory, Puetz, et al., 2017).
5.2.4. Data-analysis

5.2.4.1. Outliers and missing values. There were no missing data points. In order to remove outliers for normally distributed outcome variables Tukey’s box-plot Inter-quartile range (IQR) method was implemented, using a multiplier of 2.2, as suggested by simulation estimates by Hoaglin & Iglewicz (1987) (Hoaglin & Iglewicz, 1987). For non-normally distributed data the ‘adjusted boxplot’ method developed by Hubert & Vandervieren (2008) (Hubert & Vandervieren, 2008) was implemented instead (Seo, 2006). This required 1 participant from the MT group to be removed from further analyses. The final sample consisted of 72 participants (34 MT and 38 NMT; Table 5.1).

5.2.4.2. Demographics, cognitive abilities and symptoms. Independent sample t-tests or chi-squared tests, as appropriate, were performed to explore whether the MT and NMT groups differed on demographic characteristics (age, gender, pubertal status, socio-economic-status, ethnicity) cognitive abilities (IQ, executive control, including visual and verbal memory and verbal fluency) or symptom levels/functioning (measured with the SDQ) (Table 5.1).

5.2.4.3. EFT analyses. These analyses are already reported in Chapter Four on a largely overlapping, yet slightly bigger, sample – i.e. there were more participants with available EFT data only (MT= 31 ; NMT = 37 ) than participants with both EFT and MEPS data (MT= 29 ; NMT = 35) – see Appendix 3 for more details on sample overlap. Note that despite the slightly smaller sample of participants with both EFT and MEPS data, group difference remained unchanged. That is, participants in the MT group generated significantly more overgeneral future events (i.e. higher OEFT scores) than the NMT group.

5.2.4.4. MEPS analyses. An independent samples t-test was performed to investigate if MT and NMT groups differed on interpersonal problem solving
skills/means-end thinking (i.e. RM total score). Pearson’s correlations were also performed, within the MT group only, to explore if performance on the MEPS was associated with the maltreatment dimensions of severity, onset and duration.

Structural equation modelling (SEM) mediation models, implemented in the R package Lavaan (Rosseel, 2012), explored: i) if variability in MEPS performance could explain (i.e. mediate) the association between maltreatment status and general psychopathology (measured with the SDQ total score); and ii) if variability in EFT specificity (i.e. the mediator) contributed to group difference in MEPS performance.
5.3. Results

5.3.1. Demographics, Cognitive Abilities and Symptoms

The groups did not differ on demographic characteristics nor on measures of intelligence and verbal fluency/executive control – however IQ difference across groups approached statistical significance (i.e. \(p = .08\)) (Table 5.1). We found a significant group difference in overall symptom levels, as shown by higher SDQ total scores among adolescents with a history of maltreatment compared to their non-maltreated peers. In particular, the subscales scores revealed that participants in the MT group, on average, had significantly more hyperactivity/inattention symptoms. Moreover, the group difference on the emotional symptoms subscale approached statistical significance (i.e. \(p = .08\)).

5.3.2. EFT

As described in detail in Chapter Four, individuals with a history of maltreatment, on average, generated more overgeneral future events (i.e. higher OEFT scores).

5.3.3. MEPS

We found a large (i.e. Cohen’s \(d = .94\)) and significant group difference on RM total score (Table 5.3). Compared to their peers, participants with a history of childhood maltreatment generated fewer concrete steps (or RM) to move from the interpersonal problem situation towards the solution. This group difference remained significant after removing participants who met clinical threshold on the SDQ total score (i.e. scores equal or above 17; MT = 7, NMT = 4) or after using the SDQ total score as a covariate of no interest \(F (1,62) = 17.19, p < .001\]. This suggests that group difference on the RM total score was independent of clinical status or symptom levels. As mentioned above, the MT and NMT groups showed a significant difference on i) the
hyperactivity/inattention symptoms subscale and, also approached significance (p = .08) on ii) the emotional symptoms SDQ subscale and iii) IQ. Thus, we also modelled these three variables as covariates of no interest. Again, the outcome was unchanged – maltreatment status still predicted poorer interpersonal problem solving skills [F (1,60) = 13.57, p < .001]. Participants with a history of maltreatment, compared to their non-maltreated peers, generated both fewer active and passive RM (Table 5.3). Therefore, the composite RM total score – rather than the passive and active RM subscores – was used in further analyses to reduce the number of multiple comparisons. The effectiveness scores, in line with the RM scores, revealed that individuals with a history of maltreatment generated less effective interpersonal problem solving strategies (Table 5.3). Finally, group status did not predict the number of No-Means (Table 5.3). That is, the number of irrelevant or unspecific information/steps that were generated was comparable across the MT and NMT groups.

**Table 5.3.** Mean MEPS scores in the MT and NMT groups.

<table>
<thead>
<tr>
<th></th>
<th>MT (n=34)</th>
<th>NMT (n=38)</th>
<th>p</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>RM Total Score</td>
<td>2.11</td>
<td>1.55</td>
<td>3.61</td>
<td>1.67</td>
</tr>
<tr>
<td>Active RM</td>
<td>1.76</td>
<td>1.27</td>
<td>2.70</td>
<td>1.18</td>
</tr>
<tr>
<td>Passive RM</td>
<td>.27</td>
<td>.38</td>
<td>.56</td>
<td>.70</td>
</tr>
<tr>
<td>No-means</td>
<td>1.57</td>
<td>1.25</td>
<td>1.44</td>
<td>2.10</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>2.65</td>
<td>1.17</td>
<td>3.80</td>
<td>1.33</td>
</tr>
</tbody>
</table>

*Abbreviations:* MT = Maltreated group; NMT = Non-maltreated group; MEPS = Means-end Problem Solving; RM = Relevant Means. ¹ One-tailed t-test. * p < .05; ** p < .01; *** p < .001.
5.3.4. MEPS and Maltreatment Severity

Within the MT group, correlation analyses revealed no significant association between RM total score and continuous measures of maltreatment severity (r = -0.02, p = .92), onset (r = .01, p = .95), or duration (r = -0.22, p = .24).

5.3.5. MEPS and SDQ

As hypothesised, the mediation model (Figure 5.1) shows that lower RM total score partially mediated the association between maltreatment status and higher SDQ total score (i.e. indirect pathways $a_1 \times b_1$). In other words, higher symptom levels as a result of childhood maltreatment was associated with poorer interpersonal problem solving skills.

![Figure 5.1. Structural equation mediation model depicting the association between maltreatment status, Relevant Means (RM) total score and Strength and Difficulties Questionnaire (SDQ) total score; n = 65 (MT = 30, NMT = 35). Note. Coefficient values are standardized; Significance thresholds were measured using bootstrapping; * Statistically significant coefficients.]

5.3.6. MEPS and EFT

A Pearson’s correlation test was used to investigate if, in line with adult studies, among typically developing adolescents (i.e. the NMT group only) EFT specificity was associated to interpersonal problem solving skills. We found a moderate/strong significant correlation (r = .57, p < .001, n = 35) between OEFT and RM scores.
other words, among non-maltreated adolescents EFT specificity was linked to interpersonal problem solving skills.

The mediation model presented in Figure 5.2 below shows that higher OEFT partially mediated the association between maltreatment status and lower RM total score (i.e. indirect pathway $a_1 \times b_1$). In other words, poorer interpersonal problem solving skills in the MT group were associated with reduced EFT specificity.

**Figure 5.2.** Structural equation mediation model depicting the association between maltreatment status, Overgeneral Episodic Future Thinking (OEFT) and Relevant Means (RM) total score; n = 64 (MT = 29, NMT = 35). Note. Coefficient values are standardized; Significance thresholds were measured using bootstrapping; * Statistically significant coefficients.

### 5.3.7. Post-hoc Analyses: MEPS, EFT and SDQ

Following the significant mediations above – i.e. the indirect pathways $a_1 \times b_1$ in Figure 5.1 and Figure 5.2 – we decided to run a post-hoc serial mediation model to test if reduced EFT specificity following maltreatment was linked to higher symptoms by decreasing interpersonal problem solving ability (i.e. MT $\rightarrow$ EFT $\rightarrow$ RM $\rightarrow$ SDQ; serial indirect pathway $a_1 \times d_{21} \times b_1$ in Figure 5.3. below). The serial mediation model (Figure 5.3) indicated that, in line with the mediation model presented in Figure 5.2, higher OEFT partially mediated the association between maltreatment status and lower RM total score (i.e. indirect pathway $a_1 \times d_{21}$; Figure 5.3). This, in turn, was shown to contribute to SDQ total score (serial indirect pathway $a_1 \times d_{21} \times b_1$; Figure 5.3). In other words, these post-hoc analyses suggest that reduced EFT specificity in the MT group
may contribute to poorer interpersonal problem solving skills and that this was associated with higher symptom levels. However, note that the strength of the estimate of the serial indirect effect was rather small (0.07). This suggests that the serial mediation, although significant, explains only a very modest portion of the association between a history of maltreatment and increased psychiatric risk.

Figure 5.3. Structural equation serial mediation model depicting the association between maltreatment status, Overgeneral Episodic Future Thinking (OEFT), Relevant Means (RM) total score, and Strength and Difficulties Questionnaire (SDQ) total score; n = 58 (MT = 25, NMT = 33). Note. Coefficient values are standardized; Significance thresholds were measured using bootstrapping; * Statistically significant coefficients; ' The total model estimate fell short of statistical significance.
5.4. Discussion

In this chapter we investigated the impact of childhood maltreatment on interpersonal problem solving skills in children and adolescents with substantiated experience of abuse and/or neglect and well matched non-maltreated peers. In particular, using the MEPS test, we measured two specific dimensions of interpersonal problem solving skills – means-end thinking and overall problem solving effectiveness.

There were four main findings: i) children and adolescents with a history of maltreatment, compared to their non-maltreated peers, generated less relevant steps (or RM) and effective strategies when articulating solutions to interpersonal problematic situations. Importantly, this group difference was independent of clinical status and cognitive/verbal abilities; ii) deficits in interpersonal problem solving skills contributed to the association between a history of childhood maltreatment and elevated symptom levels (Figure 5.1); iii) reduced EFT specificity (i.e. higher OEFT scores) contributed to the association between a history of childhood maltreatment and poorer interpersonal problem solving skills (Figure 5.2); iv) this, in turn, was linked to higher symptom levels (Figure 5.3). In other words, maltreatment-related alteration in future thinking specificity was linked to poorer interpersonal problem solving performance which, in turn, was associated with poorer mental health.

5.4.1. Latent Vulnerability and Interpersonal Problem Solving

Despite there being a well-established link between a history of childhood maltreatment and several maladaptive psychosocial and psychiatric outcomes (Benedini et al., 2016; Bolger et al., 1998; R. Gilbert, Widom, et al., 2009; Kapeleris & Paivio, 2011; Kim & Cicchetti, 2010; Labella et al., 2018; Raby et al., 2018; Sperry & Widom, 2013), we still lack a precise understanding of the mechanisms that underpin this association. According to the theory of Latent Vulnerability, exposure to childhood
maltreatment leads to a range of neurocognitive recalibrations which, although potentially adaptive in the short-term, can increase the risk of mental health difficulties across the lifespan (McCrory & Viding, 2015). Latent vulnerabilities can be indexed in low-level cognitive processes – such as salience/threat detection (Hart, Lim, Mehta, Simmons, et al., 2018; McCrory et al., 2011), response inhibition (Mueller et al., 2010), expected value representations (Gerin et al., 2017; Mehta et al., 2010) and error signalling (Hart, Lim, Mehta, Curtis, et al., 2018; Lim et al., 2015); and also in higher-order cognitive domains – such as ABM (McCrory, Puetz, et al., 2017), EFT (e.g. Chapter Four) and emotion regulation (McLaughlin et al., 2015). These recalibrations or alterations are thought to instantiate psychiatric risk in direct ways (for example, by increasing stress susceptibility), and also indirectly by altering the social ecology of an individual over time (for example, by reducing the ability to form and sustain social support networks).

In this study we investigated interpersonal problem solving skills as a candidate maker of latent vulnerability following childhood maltreatment. Extant findings suggest that interpersonal problem solving skills, and in particular means-end thinking, are linked to concurrent mental health difficulties (Bray et al., 2007; Kehrer & Linehan, 1996; Marx et al., 1992; Raes et al., 2005; Sutherland & Bryant, 2008), and have been found to also predict future symptom levels, risk of relapse and psychosocial adjustment (Demirbas et al., 2012; Khurana & Romer, 2012; Nezu & Ronan, 1988b; Quiñones et al., 2015; Thoma et al., 2013; Vorontsova et al., 2018). Despite this, interpersonal problem solving has received little attention in the context of childhood maltreatment. Thus, the findings of this study shed new light on our understanding of how childhood maltreatment and subsequent maladaptive outcomes might be linked. In particular, we were able to show, for the first time, that adolescents who experience childhood maltreatment have poorer interpersonal problem solving skills compared to their non-
maltreated peers. Additionally, we found that these alterations were associated with greater psychiatric symptomatology.

5.4.2. Interpersonal Problem Solving Skills Development Following Childhood Maltreatment

Several developmental factors may account for poorer interpersonal problem solving skills following the experience of abuse and/or neglect during childhood. The findings presented here (Figure 5.2) suggest that maltreatment-related alterations in the ability to imagine specific personal future scenarios (i.e. OEFT) represent one potential cognitive mechanism. This is consistent with the notion that ABM and EFT support interpersonal problem solving, respectively, by retrieving formerly successful strategies and flexibly recombining them to meet the needs of current and future problematic situations (A. D. Brown et al., 2012; J. Evans et al., 1992; Marx et al., 1992; Schacter et al., 2007). Indeed, extant studies with adult samples (with and without concurrent psychiatric diagnoses) show that episodic specificity, both for personal memories (ABM) and imagined future events (EFT), contribute to problem solving skills performance (Beaman et al., 2007; A. D. Brown et al., 2012; J. Evans et al., 1992; Goddard et al., 1996, 2007; Jing et al., 2016; Madore & Schacter, 2014; McFarland et al., 2017; Raes et al., 2005; Sutherland & Bryant, 2008; Vandermorris et al., 2013; Werner-Seidler et al., 2018; Williams et al., 2005). Moreover, here we showed for the first time that variability in EFT specificity was linked to individual differences in interpersonal problem solving skills also in typically developing/non-maltreated adolescents. Therefore, reduced EFT specificity (i.e. OEFT) following maltreatment may also impact problem solving skills by constraining the ability to generate detailed and relevant step-by-step solutions to interpersonal problems and conflicts. Interestingly, post-hoc analyses revealed that OEFT not only contributed directly to poorer interpersonal problem solving skills in maltreated individuals, but it also predicted, indirectly, higher psychiatric symptoms (Figure 5.3).
There may be other affective and cognitive processes, not investigated in this study, that contribute to interpersonal problem solving deficits among individuals exposed to childhood maltreatment. Mentalising abilities and emotional competence, for example, have been shown to underlie effective problem solving skills, whereby facilitating the detection of interpersonal problems and the generation of socially appropriate solutions (Channon & Crawford, 2010; Channon et al., 2014; Thoma et al., 2015). A consistent body of literature suggests that the experience of abuse and neglect can compromise the development of both mentalisation and emotional competence (Cicchetti et al., 2003; Kapeleris & Paivio, 2011; O’Reilly & Peterson, 2014; Pears & Fisher, 2005; Shipman & Zeman, 1999; Tarullo et al., 2007). Thus, deficits in these two domains may also contribute to reduced interpersonal problem solving skills among maltreated individuals. However, this remains an open question to be addressed in future research.

Reduced self-efficacy/mastery and negative problem solving orientation (i.e. feelings of hopelessness and negative cognitions associated with problem solving) may also underlie impairments in interpersonal means-end thinking among maltreated individuals. High self-worth and mastery contribute to interpersonal problem solving by facilitating the cognitive representation of desirable interpersonal outcomes and solutions that are consistent with positive self-views (e.g. being liked by friends and teachers, being able to have a leadership role in school, etc.). Extant findings indeed suggests that a sense of self-efficacy/mastery, self-worth and an internal locus of control underpin the motivation necessary to detect interpersonal problems, generate effective strategies and implement them (Bandura, 1977; Bandura & Locke, 2003; A. D. Brown et al., 2012; D’Zurilla & Sheedy, 1991; D ’Zurilla & Maydeu-Olivares, 1995). The experience of maltreatment, however, by promoting an avoidant exploratory style (Cicchetti & Doyle, 2016; Hankin, 2005), can curtail the opportunities necessary for developing a high sense of mastery and self-worth (Kim & Cicchetti, 2003; Thielen et
Moreover, maltreatment-related threat-detection and hostile attribution biases (Dodge, Pettit, Bates, & Valente, 1995; McCrory et al., 2011; Shackman et al., 2007; Taylor & Alden, 2005) can promote the development of negative self-perceptions. These maladaptive outcomes can be further amplified by other social and non-social factors associated with maltreatment, which increase the likelihood of failure in several developmental and socially salient tasks (Kim & Cicchetti, 2004). These include difficulties in forming secure and rewarding attachment relations, adaptation in school, academic performance, as well as socio-economic attainment (Currie & Widom, 2010; Kim & Cicchetti, 2004; Thielen et al., 2016). This can reduce self-worth and expectations regarding one’s ability to produce desired social outcomes. Indeed, a consistent body of evidence suggests that the experience of abuse and neglect play a role in the formation of low self-worth and social self-efficacy (Bolger et al., 1998; Cheever & Hardin, 1999; Flynn et al., 2014; Kapeleris & Paivio, 2011; Kim & Cicchetti, 2003, 2004; Ryan et al., 1996; Sachs-Ericsson et al., 2006). Hence, it is possible that negative problem solving orientation, and in particular reduced self-efficacy, also contribute to the observed deficits in interpersonal problem solving skills following childhood maltreatment.

5.4.3. Limitations and Conclusions

The research presented in this chapter is limited in a number of respects. First, interpersonal problem solving, to be considered a latent psychiatric risk factor among maltreated individuals, should have prognostic value. Thus, one outstanding empirical question is whether maltreatment-related alterations in interpersonal problem solving skills predict not only current but also future symptoms and psychosocial functioning. This could not be investigated within the cross-sectional design of this study. A longitudinal design, moreover, would also allow us to draw stronger conclusions regarding the contribution of EFT specificity on effective means-end thinking. Second, this study did not examine whether variability in self-efficacy/mastery and self-esteem
contributed to the association between EFT overgenerality, reduced interpersonal problem solving performance and a history of childhood maltreatment. This may represent a potential confounding factor (A. D. Brown et al., 2012). However, it is worth noting that performance across the two groups on other tasks that may also be influenced by perceived self-efficacy and motivation (e.g. verbal fluency and IQ test) was comparable. Thus, it is unlikely that the observed group difference in problem solving could be explained solely by variability in self-efficacy. It would, however, be interesting in the future to systemically investigate the extent to which perceived social self-efficacy/mastery may impact episodic and means-end thinking in maltreated adolescents. Third, it remains unclear whether the impact of childhood maltreatment on interpersonal problem solving is especially potent during certain developmental stages. Interpersonal means-end thinking, and social cognition more broadly, rely on medial and lateral prefrontal brain regions (Blakemore & Choudhury, 2006; Channon, 2004; Channon & Crawford, 2010; Hanten et al., 2011; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). These brain areas, during late childhood and adolescence are particularly sensitive/vulnerable to environmental inputs/insults (Blakemore, 2012; Fuhrmann, Knoll, & Blakemore, 2015) as they undergo profound transformation which continues till early adulthood (Giedd et al., 2015; Gogtay et al., 2004). Therefore, it is possible that abuse and neglect occurring in late childhood/adolescence, compared to earlier exposure, may be particularly detrimental to the development of interpersonal problem solving skills. However, a larger sample of individuals with a wider range of maltreatment experiences would be required to address this important question. Finally, as already mentioned in the limitations section of Chapter 4, within the current design it is not possible to rule out that the link between maltreatment exposure and OEFT may be attributed to an avoidant cognitive style. The former is in fact common among individuals with a history of abuse and neglect (Baer & Martinez, 2006; Cicchetti & Doyle, 2016; Cohen et al., 2017; Rosenthal et al., 2005) and it is known to contribute
to deficits in ABM, which is thought to represent the generative basis of both EFT and interpersonal problem solving skills (Williams, 2006). Moreover, cognitive and experiential avoidance seem to be particularly detrimental to problem solving skills (D’Zurilla, Chang, Nottingham, & Faccini, 1998; Dugas, Letarte, Rhéaume, Freeston, & Ladouceur, 1995). Therefore, it is possible that the association found between EFT, reduced ability to generate effective problem solving strategies and childhood maltreatment may be explained by cognitive and experiential avoidance. In other words, the reduced ability to generate step-by-step strategies to resolve interpersonal problems among maltreated individuals cannot conclusively be attributed to a genuine difficulty in problem solving skills. It is possible that an avoidant behavioural and cognitive style towards problem solving may account for the findings of this study. Therefore, it is important that future empirical investigations of problem solving skills, EFT and early adversity control for the potential confounding role of functional avoidance. As the latter is malleable to intervention, this may increase the clinical relevance of these findings.

Despite these limitations, this study has also several strengths. First, we recruited children and adolescents with substantiated experience of maltreatment. This allowed us to include individuals who may otherwise under-report and/or not be explicitly aware of past experiences of maltreatment (e.g. if maltreatment occurred in the first three years of life). Moreover, studies of childhood abuse and neglect which rely on self-reported and continuous measures tend to primarily recruit individuals with maltreatment experiences that fall within a normative range. Conversely, our findings can be generalised to those individuals who experience more severe forms of abuse and neglect which warrant the involvement of child protection agencies. Second, we used a well validated and reliable measure of interpersonal cognitive problem solving skills, the MEPS, developed by Platt, Spivak and colleagues (D’Zurilla et al., 2004; Platt & Spivack, 1972, 1975a; Platt et al., 1974; Siegel et al., 1976; Spivack et al., 1976). The
MEPS has considerable advantages compared to other common measures, such as the
csocial problem solving inventory (SPSI; D’Zurilla & Nezu, 1990), which rely on self-
reports and self-assessments of problem solving abilities. Together with blinded
scoring, this allowed us to objectively measure interpersonal means-end thinking.
Third, SEM mediations analyses, unlike traditional regression methods, can
simultaneously evaluate multiple factors in one model. This allowed us to test specific
pathways and detect complex associations among several variables (e.g. maltreatment
status, EFT scores, MEPS scores and symptoms scores). Finally, the comparability of
the MT and NMT participants on several pertinent demographic (pubertal status, age,
socio-economic status, etc) and cognitive (verbal fluency/executive control and IQ)
variables suggests that the observed group difference on interpersonal problem solving
skills performance was not epiphenomenal (i.e. attributable to cooccurring group
difference in other domains). Moreover, co-varying for symptom levels and re-running
the analyses without the participants who met clinical thresholds gave greater
confidence to the conclusion that the differences observed in interpersonal problem
solving were not solely driven by concurrent psychopathology.

To conclude, we showed that poorer interpersonal problem solving skills was
associated with increased psychiatric vulnerability following childhood maltreatment.
Moreover, we showed that reduced EFT specificity (i.e. OEFT) was linked to
interpersonal problem solving deficits in maltreated individuals. These novel findings
increase our current understanding of the way in which exposure to childhood
maltreatment heightens the risk of maladaptive psychiatric and psychosocial outcomes.
This work can inform the development of screening tools that could allow us to detect
those maltreated individuals at increased psychiatric risk. Deficits in both episodic
specificity and interpersonal problem solving abilities are amenable to targeted
psychological intervention (Bell & D’Zurilla, 2009; Leahy et al., 2018; Nezu & Nezu,
2010; Werner-Seidler et al., 2018). Thus, the findings from this study may also be
relevant in the context of preventative approaches aimed at offsetting the likelihood of developing mental health difficulties following childhood maltreatment.
CHAPTER 6 – General Discussion

The findings presented in this thesis suggest that childhood maltreatment is associated with: i) alterations in the neurocomputational processes that underlie successful reinforcement-based decision-making (Chapter Two); ii) heightened amygdala reactivity to threat and increased likelihood of exposure to major stressful life events – factors that, in turn, predicted higher future internalising symptoms (Chapter Three); iii) alterations in ‘Episodic Future Thinking’ (EFT) – the ability to imagine specific, and detailed possible future scenarios (Chapter Four); iv) deficits in interpersonal problem solving skills – that, in turn, were associated with higher symptom levels (Chapter Five). Overall, these findings increase our understanding of how childhood maltreatment impacts cognitive, social and neurobiological functioning in ways that may potentiate future psychiatric vulnerability. In the longer term, they may also motivate and contribute to the development of screening tools and novel preventative treatment approaches.

This final chapter is divided in three main sections. The first concisely revisits the wider context and the overarching theoretical framework of this thesis – i.e. the theory of Latent Vulnerability. The second section summarises the main empirical questions and the findings from each chapter. Finally, several methodological limitations are considered, and potential future research directions and clinical implications are examined.
6.1. Background Context and Theoretical Framework

6.1.1. Childhood Maltreatment and Mental Health Outcomes

Childhood maltreatment – including emotional, physical, and sexual abuse, exposure to domestic violence and neglect – is experienced by a large minority of individuals (R. Gilbert, Kemp, et al., 2009; Radford et al., 2011). As discussed in detail in Chapter One, these adverse early experiences have been associated with maladaptive outcomes across the life span, including reduced economic productivity, academic attainment and poorer physical health (Currie & Widom, 2010; R. Gilbert, Widom, et al., 2009). Moreover, childhood maltreatment represents one of the most potent predictors of future psychopathology (Green et al., 2010; Ronald C Kessler et al., 2010; McLaughlin et al., 2010) and reduced psychosocial adjustment (Afifi et al., 2017; Benedini et al., 2016; Kim & Cicchetti, 2010; Raby et al., 2018; Widom et al., 2014, 2008). Notably, the experience of maltreatment has also been associated with earlier symptoms onsets, greater comorbidity, chronicity, severity and higher relapse rates (Agnew-Blais & Danese, 2016; Harkness & Wildes, 2002; Hovens et al., 2010; Leverich et al., 2002; Nanni et al., 2012; Post et al., 2015; Teicher & Samson, 2013). Moreover, psychiatric patients with maltreatment histories are less responsive to current evidence-based interventions (Agnew-Blais & Danese, 2016; Harkness & Wildes, 2002; Hovens et al., 2010; Leverich et al., 2002; Nanni et al., 2012; Post et al., 2015; Teicher & Samson, 2013). Despite the well-established link between a history of childhood maltreatment and future psychopathology, we still lack comprehensive mechanistic neurocognitive explanations for this association. This restricts our understanding of the pathogenesis of mental health problems in the context of childhood maltreatment. It also hinders the development of novel and more effective preventative models of intervention that could offset risk trajectories and decrease the likelihood of mental
health problems from emerging in the first place (McCrory, Gerin, et al., 2017; Teicher & Samson, 2013).

6.1.2. The Theory of Latent Vulnerability

The theory of Latent Vulnerability offers a useful framework that can help us to reconceptualise our understanding of how childhood maltreatment and subsequent maladaptive outcomes might be linked (McCrory & Viding, 2015). According to this theory, the experience of maltreatment leads to a cascade of neurocognitive changes. These represent adaptive responses which may confer short-term functional advantages in atypical early environments. In other words, maltreatment-related neurocognitive alterations are not understood as a sign of ‘damage’. Rather, they are seen as system-level recalibrations that can confer proximal adaptive value in environments characterised by inconsistent, harsh and neglectful caregiving (Gerin et al., 2018). However, such adaptations may also incur a longer-term cost as an individual may then be poorly equipped to negotiate more normative tasks and challenges (McCrory, Gerin, et al., 2017).

Another important tenet of this theory is that these maltreatment-related neurocognitive alterations are ‘latent’. That is, despite increasing psychiatric risk, they are often phenomenologically different from manifest symptoms; that is, they are not just subclinical symptoms. In other words, they may be present despite the absence of overt symptoms and are not deterministically linked with the emergence of a mental health problems. These latent vulnerabilities can have direct maladaptive effects acting in a proximal fashion to alter how an individual perceives, processes and responses to the environment (for example by reducing the ability to represent reinforcement expectancies or by increasing emotional reactivity to threat cues). There can also be, however, more protracted indirect effects, acting in a distal fashion to alter an individual’s social ecology. Neurocognitive adaptations that lead (for example) to
changes in associative learning, mentalizing abilities or interpersonal problem solving, may potentiate psychiatric risk by compromising the ability of the individual to elicit social support and then nurture and sustain positive and stable relationships (Sperry & Widom, 2013; van Harmelen et al., 2017).

In summary, according to the theory of Latent Vulnerability, childhood maltreatment leads to long-lasting cognitive and neurobiological recalibrations that potentiate psychiatric vulnerability and cumulatively increase the risk of maladaptive psychosocial outcomes. Indexing these latent vulnerabilities represent an important empirical endeavor with both clinical and theoretical implications for the field of developmental and adult psychopathology.
6.2. Aims and Main Findings

6.2.1. Research Questions

As discussed in detail in Chapter One, maltreatment has been associated with neurocognitive recalibrations across several domains, including reward processing, threat processing, autobiographical memory, affect regulation, executive functioning as well as in higher-order socio-cognitive domains, such mentalising abilities (Cicchetti et al., 2003; McCrory, Gerin, et al., 2017; O’Reilly & Peterson, 2014). These findings have provided incremental advances in our understanding of the developmental pathways and mechanisms that may be responsible for increased psychiatric vulnerability following childhood maltreatment. Notwithstanding this recent proliferation in neurocognitive studies, this is still a nascent field of research. The first functional neuroimaging investigations of abuse and neglect in community settings, for instance, were published less than a decade ago (Dannlowski et al., 2012; McCrory et al., 2011). There is still significant methodological and conceptual progress to be made. For example, despite the well-established association between maltreatment exposure and heightened neural reactivity to threat cues (Hein & Monk, 2016), its prognostic value has not actually yet been investigated. Moreover, neurobiological systems and cognitive constructs linked to the pathogenesis of mental health problems – such as reinforcement-based decision-making, Episodic Future Thinking (EFT) and interpersonal problem solving – have received scarcely any attention in the maltreatment literature.

Therefore, building on previous research, the primary aim of this doctoral thesis has been to contribute to our understanding of the latent neurobiological, cognitive and experiential factors responsible for increased psychiatric risk following maltreatment exposure. In particular, as already discussed in Chapter One, we aimed to address four main outstanding empirical questions:
i. Is childhood maltreatment associated with alterations in the neurocomputational processes that underlie reinforcement-based decision-making, including expected value (EV) representation and prediction error (PE) signalling?

ii. Are the well-established maltreatment-related neurocognitive alterations in the threat-processing systems a predictor (on its own or in interaction with stress exposure) of future internalising symptoms?

iii. Is exposure to childhood maltreatment associated with overgeneral EFT (i.e. OEFT), and is this linked to concurrent psychiatric symptoms?

iv. Is exposure to childhood maltreatment linked to deficits in interpersonal problem solving skills, and are such alterations associated with concurrent psychiatric symptoms?

6.2.2. Summary of the main findings

This section provides a concise summary of the main findings presented in this thesis and highlights their relevance for our understanding of how the experience of maltreatment during childhood may instantiate increased psychiatric vulnerability.

6.2.2.1. Chapter Two. Using a probabilistic passive avoidance task and a model-based fMRI analytic approach, we investigated the impact of maltreatment exposure on reinforcement-based decision-making. In particular, we focused our analyses on two neurocomputational components, expected value representation (EV; the reinforcement expectancies associated with a stimulus or action) and prediction error signalling (PE; the ability to detect the differences between expected and actual outcomes). At the neurocomputational level, children who had experienced maltreatment (n = 18; mean age = 13) differed from their non-maltreated peers (n = 19; mean age = 13) in three main ways. First, maltreatment exposure was linked to decreased activity during EV representation in a widespread network (including the orbitofrontal cortex, the striatum, insula and hippocampus) commonly associated with reinforcement expectancies.
Second, consistent with previously reported increased neural reactivity to negative cues in the context of childhood abuse, the maltreated group showed increased PE signalling in the middle cingulate gyrus, somatosensory cortex, superior temporal gyrus and thalamus. Third, the maltreated group showed increased activity in fronto-dorsal regions and in the putamen during EV representation. Consistent with the clinical literature, the pattern of neurocognitive alterations found in this study suggest that maltreatment experiences may compromise the development of associative learning and reward/punishment processing. This, in turn, may compromise psychosocial functioning and potentiate future psychiatric risk.

6.2.2.2. Chapter Three. Here we examined the contribution of both baseline amygdala reactivity and prospective stress exposure to future internalising symptoms in young adults with a history of maltreatment (n = 100; mean age = 19) and propensity-score-matched non-maltreated peers (n = 96; mean age = 19). The study had two main findings. First, the association between a history of maltreatment and higher future internalising symptoms was partially explained by increased baseline amygdala reactivity to threat. Second, even in this propensity score matched sample, where baseline symptoms levels and other potentially contributing factors were comparable between the two groups, individuals with a history of childhood maltreatment experienced more stressful life events post-baseline. This, in turn, partially mediated the relationship between maltreatment status and higher future internalising symptoms. These findings lend compelling support to the view that recalibration of amygdala reactivity to threat following maltreatment exposure represents a latent vulnerability factor to future psychopathology. They also provide evidence for the role of ‘stress generation’ (i.e. the increased propensity to experience major stressful life events) in the pathogenesis of internalising disorders.
6.2.2.3. **Chapter Four.** Difficulties in generating specific and detailed hypothetical future events (known as overgeneral ‘Episodic Future Thinking’, or OEFT) and episodic memories (known as overgeneral autobiographical memory, or OGM) have been linked to increased psychiatric risk and a number of maladaptive psychosocial outcomes (Hallford et al., 2018; Hitchcock et al., 2014; Ono, Devilly, & Shum, 2016; Sumner, Griffith, & Mineka, 2010). Extant behavioural and neurobiological evidence suggest that alterations in autobiographical memory (ABM) processing, including OGM, may be linked to a history of abuse and/or neglect (McCrory, Puetz, et al., 2017; Valentino et al., 2009). Conversely, alterations in EFT have not yet been examined in the context of childhood maltreatment. In Chapter Four, we investigated OEFT in a group of children and adolescents with substantiated experiences of maltreatment (n = 31, mean age = 14) and a group of well-matched non-maltreated peers (n = 37, mean age = 14). We found that, independently of concurrent symptom levels or clinical status, maltreatment was linked to difficulties in generating specific episodic future events. This pattern of increased OEFT may therefore contribute to the emerge of future mental health problems and psychosocial difficulties also among individuals with a history of childhood abuse and/or neglect.

6.2.2.4. **Chapter Five.** In this study we investigated interpersonal problem solving skills, and in particular means-end thinking, among children and adolescents exposed to maltreatment (n = 34; mean age = 14). There were two main findings. First, compared to their non-maltreated peers (n = 38; mean age = 14), maltreated individuals generated less relevant steps and effective strategies when articulating solutions to interpersonal problematic situations. This, in turn, contributed to the association between a history of maltreatment and elevated symptom levels. Second, we also found that EFT overgenerality mediated the association between a history of childhood maltreatment and poorer interpersonal problem solving skills. Interestingly, this was then linked to higher symptom levels. These findings suggest that maltreatment-related
deficits in episodic specificity are associated with less effective interpersonal problem solving strategies. Over time, such a cognitive style and related interpersonal difficulties may compromise psychosocial and mental health functioning.
6.3. Clinical and Research Implications

6.3.1. General Limitations and Future Directions

The studies presented in this thesis feature several strengths and contribute to the growing knowledge regarding the impact of childhood maltreatment on neurocognitive and psychosocial development. However, as highlighted in each empirical chapter, there were also a number of shortcomings. Here, we consider a number of limitations as well as their implications for the interpretation of the findings and for future research.

6.3.1.1. Gender Differences. Maltreatment-related maladaptive outcomes and neurocognitive adaptations are often comparable between males and females (e.g. Shields & Cicchetti, 2001), however, there is also growing empirical support for the presence of gender-specific alterations across neural, social and cognitive domains (Alto, Handley, Rogosch, Cicchetti, & Toth, 2018; Cullerton-Sen et al., 2008; Hyman, Garcia, & Sinha, 2006; Kelly et al., 2015, 2016; Lansford et al., 2002). This underscores the importance of developing gender-informed research and intervention approaches (Cullerton-Sen et al., 2008; Thompson, Kingree, & Desai, 2004).

Extant data indicate that there are gender differences (in the general population) in the cognitive and neurobiological processes investigated in this thesis, including associative learning (Ding et al., 2017; Lighthall et al., 2012; Spreckelmeyer et al., 2009), threat processing (McClure et al., 2004) and also in interpersonal problem solving (D’Zurilla, Chang, et al., 1998; D’Zurilla, Maydeu-Olivares, & Kant, 1998). Therefore, it is plausible that the impact that maltreatment has on these domains can vary across males and females. Unfortunately, the size of our adolescent and adult samples did not allow us to systematically examine the potentially moderating role of gender among individuals with maltreatment histories. This remains an outstanding question that future studies should endeavour to address, as it may have important
repercussions for the generalisability, interpretation and practical implications of our findings.

6.3.1.2. Maltreatment Dimensions. Sheridan and McLaughlin (McLaughlin, Sheridan, & Lambert, 2014; McLaughlin et al., 2017; Sheridan & McLaughlin, 2014) argue that the consequences of deprivation-related experiences (such as physical and emotional neglect) should differ, in part, from that of abuse-related experiences (such as physical, emotional and sexual abuse). In particular, they argue that abuse-related experiences (unlike deprivation) should have their greatest impact on low-level processes, such as threat detection, and on the development of limbic brain regions, such as the amygdala (Sheridan & McLaughlin, 2014). Conversely, deprivation-related experiences are thought to impact more complex cognitive functions. Preliminary evidence suggests, for example, that deprivation (but not abuse/threat exposure) impacts working memory and the neural systems underlying executive functioning (Sheridan, Peverill, Finn, & McLaughlin, 2017).

According to this framework, some of the domains investigated in this thesis, such as threat-processing (Chapter Three), are more likely to undergo recalibrations following abuse exposure; while associative learning (Chapter Two), future thinking (Chapter Four) and interpersonal problem solving (Chapter Five) may undergo greater changes following neglect and deprivation. Examining the unique impact of different forms of maltreatment on neurocognitive development, however, remains a general challenge for the field because abuse and neglect often co-occur (R. C. Kessler, Davis, & Kendler, 1997; Ronald C Kessler et al., 2010; McLaughlin et al., 2012). This was indeed the case also for our samples of maltreated individuals – i.e. the majority of them were exposed to multiple forms of maltreatment while growing up. Thus, much larger samples (in which a sufficient number of individuals experience only one type of maltreatment) are required to disentangle the differential effects that abuse and neglect can have on the neurobiological and cognitive processes investigated in this thesis.
Increasing our knowledge of this would not only help us to better understand how maltreatment ‘gets under the skin’, but it may also inform the development of psychosocial interventions capable of targeting individual needs and specific vulnerabilities.

6.3.1.3. Age of Onset and Duration. Another inherent methodological challenge in the field (and this thesis) relates to the investigation of putative sensitive periods during which the effect of childhood maltreatment may be particularly potent (Knudsen, 2004). Several factors conspire against our ability to ascertain with precision age of onset, maltreatment duration and their impact on later functioning. First, due to legal/safe-guarding consequences and desirability biases, caregivers are usually reluctant to disclose information regarding abusive/neglectful parenting. Second, self-reports are not always a reliable source of information regarding age of onset because maltreatment often commences before an individual is able to form explicit memories of the events, particularly those that occur during infancy; moreover, dissociative and overgeneral cognitive styles, commonly linked to childhood trauma and abuse (e.g. Valentino et al., 2009), may interfere with the accurate recall of maltreatment-related memories. Third, even when objective and accurate reports are available, due to the interrelatedness of age of onset and duration (as well as maltreatment severity) it is often difficult to disentangle the unique impact of these domains on subsequent neurocognitive alterations and functioning (e.g. earlier age of onset is usually associated with longer and also more severe experiences of maltreatment). For these reasons, researchers are often compelled to rely only on approximate estimates of onset and duration (Barnett et al., 1993; Kaufman et al., 1994). Indeed, difficulties in operationalising these maltreatment dimensions was also an overarching limitation of this thesis. For example, when precise information regarding the age of onset was not available, social services’ referral dates were used instead. Therefore, any reported correlation (Chapter Two), or the lack thereof (Chapter Four and Five), between age of
maltreatment onset (and/or duration) and neurocognitive recalibrations should be interpreted with caution.

6.3.1.4. Longitudinal Design. In order to identify biological and cognitive markers that can allow us to predict future psychiatric risk, one must first establish what neurocognitive domains and processes become altered following maltreatment exposure. In the general population (i.e. among individuals non-selected based on maltreatment status), deficits in associative learning, EFT and interpersonal problem solving have been linked to maladaptive psychosocial outcomes (D. T. Gilbert & Wilson, 2007; Malek et al., 2018; Prabhakar et al., 2016; Schacter et al., 2017; Terrett et al., 2016) and future symptomatology (Khurana & Romer, 2012; Nezu & Ronan, 1988a; Quiñones et al., 2015; Stringaris et al., 2015). We have shown in this thesis that a history of abuse and/or neglect is also associated with similar patterns of neurobiological and cognitive recalibration across these domains – respectively in Chapters Two, Four and Five. The cross-sectional design of these studies, however, limits the scope of causal inference that can be made; yet they provide the motivation and rationale to investigate to what extent these maltreatment-related alterations represent a marker of latent vulnerability to future psychopathology.

It essential that more studies investigate the prognostic value of maltreatment-related neurocognitive alterations. For example, in Chapter There we showed that heightened baseline amygdala reactivity to threat following maltreatment contributes to future internalising symptoms. Notably, the longitudinal design of this study allowed us to provide the most compelling evidence to date regarding the role of neurocognitive alterations in threat-processing in predicting future psychiatric risk among maltreated individuals. A longitudinal design would also be required to established if maltreatment-related recalibrations in associative learning, EFT and interpersonal problem solving contribute to the emergence of future psychopathology.
6.3.1.5. Attachment. The ability to establish a secure relationship with the primary caregivers represents an essential task during development (Belsky & Fearon, 2008; Cicchetti & Doyle, 2016). This is believed to shape internal cognitive schemas and to foster a positive and trusting outlook toward caregivers, the self and the social environment more broadly (Belsky & Fearon, 2002). For these reasons, the quality of attachment formed in infancy is thought to influence subsequent adjustment and functioning across the life span. For example, insecure or disorganised attachment styles have been shown to predict higher internalising and externalising symptoms (Fearon, Bakermans-Kranenburg, van IJzendoorn, Lapsley, & Roisman, 2010; Groh, Roisman, van IJzendoorn, Bakermans-Kranenburg, & Fearon, 2012; Hankin, Kassel, & Abela, 2005; Riggs et al., 2007) as well as poorer psychosocial competence (Groh et al., 2014).

Attachment quality is influenced primarily by the home environment, and in particular by parenting practices (e.g. Bokhorst et al., 2003). In line with this, extant studies have consistently found that exposure to childhood maltreatment represents a robust predictor of both insecure and disorganised attachment (Baer & Martinez, 2006; Cyr et al., 2010; Lee Raby, Labella, Martin, Carlson, & Roisman, 2017; Lo, Chan, & Ip, 2017; Oshri, Sutton, Clay-Warner, & Miller, 2015; Roisman et al., 2017; Unger & De Luca, 2014; van Hoof, van Lang, Speekenbrink, van IJzendoorn, & Vermeiren, 2015). Interestingly, variability in attachment style have been found to mediate the relationship between a history of maltreatment and concurrent (L. J. Cohen et al., 2017; Hocking, Simons, & Surette, 2016; Jardin, Venta, Newlin, Ibarra, & Sharp, 2017) and also future mental health outcomes (Widom, Czaja, Kozakowski, & Chauhan, 2018). However, among maltreated individuals, we still lack a precise understanding of the mechanisms underlying the modulating effect of attachment style on subsequent symptoms. It is possible, for example, that the presence of secure and positive relationships mitigate the negative effects of maltreatment on emerging neurocognitive systems (Cicchetti & Doyle, 2016). An alternative explanation is that attachment security buffers an
individual against the negative impact of existing maltreatment-related neurocognitive recalibrations. Thus, future studies should examine if attachment security: i) influences the extent to which childhood maltreatment leads to alterations in the neurocognitive domains investigated in this thesis; ii) promotes their normalisation where such neurocognitive recalibrations already occurred; iii) mitigates their impact on future mental health outcomes. Addressing these questions might have important implications for research, as well as for models of treatment and prevention – in fact attachment, despite being a stable construct, is amenable to change and psychosocial interventions (e.g. Joseph, O’Connor, Briskman, Maughan, & Scott, 2014).

6.3.1.6. Summary. There were a number of shortcomings in the studies presented in this thesis. These included the lack of a systematic examination regarding the presence of sensitive periods, of different maltreatment types and of gender-specific effects on neurocognitive development. The implementation of longitudinal study designs, moreover, would increase the causal inference that can be drawn from the findings presented in Chapter Two, Four and Five. In particular, prospective data would allow us to investigate the extent to which maltreatment-related neurocognitive alterations are precursors of future psychiatric symptoms. Finally, the examination of higher-order constructs, such as attachment, would allow us to increase the clinical relevance and impact of the findings.

6.3.2. Clinical Implications

It has long been acknowledged that empirical investigation of the developmental sequela of childhood abuse and neglect is important in improving legal and clinical definitions of maltreatment and informing good policy-making (Cicchetti & Doyle, 2016). However, in recent years the inherent value in developing a comprehensive mechanistic understanding of the impact of childhood maltreatment has been increasingly recognised (Cicchetti, 2016; Danese & McEwen, 2012; Kaufman et al., 2016).
2015; McCrory & Viding, 2015). Such an approach has the potential to provide a theoretically informed model of how early adversity shapes development through transactional processes that over time influence a range of developmental outcomes. Understanding of such processes is necessary if we are to develop novel preventative clinical approaches that could reduce psychiatric risk (Cicchetti & Doyle, 2016; McCrory, Gerin, et al., 2017) as well as improve our existing models of intervention.

6.3.2.1. Neurocognitive Recalibrations as Precursors of Psychiatric Symptoms. Two aspects of the findings of this thesis merit particular attention from clinical and conceptual perspectives. First, the reported patterns of maltreatment-related alterations were comparable to cognitive and neurobiological profiles of psychiatric disorders commonly associated with the experience of abuse and neglect, such as anxiety and depression. Second, these recalibrations were present even in the absence of a manifest psychiatric disorder. Thus, the findings of this thesis suggest that maltreatment exposure leads to neurocognitive changes that do not reflect overt symptomatology, yet they may be responsible for increased psychiatric vulnerability. For example, in the longitudinal study described in Chapter Three, we showed that heightened neural threat reactivity in young adults with a history of maltreatment was independent of concurrent internalising symptom levels, yet it predicted future symptom severity.

6.3.2.2. The Adaptive Value of Neurocognitive Recalibrations. In line with one of the central tenets of the theory of Latent Vulnerability, another implication that emerges from the findings of this thesis is that maltreatment-related alterations should not be interpreted necessarily as a sign of ‘damage’ (McCrory, Gerin, et al., 2017; McCrory & Viding, 2015). Rather, they might result from a complex set of processes which may confer short-term advantages in the context of neglectful, abusive and unpredictable environments. For example, reduced reward-related neural signalling in maltreated individuals (Chapter Two) may reflect recalibration to environments characterised by scarcity and inconsistency in primary reinforcers (such as food and
emotional warmth). This may represent an adaptive response for regulating affect and reduce disappointment in the context of neglectful parenting practices (McCrory, Gerin, et al., 2017). However, this neurocognitive recalibration may be maladaptive in species-expectant environments. Similarly, devoting a greater amount of cognitive and neurobiological resources to the processing of threat-related information (as shown in Chapter Three) may also represent an adaptive strategy in the context of chaotic and dangerous home environments. However, this may restrain and divert attentional resources away from the processing of other potentially helpful information, limiting the opportunities for learning and developing other cognitive and social skills (McCrory & Viding, 2015). Moreover, this may also increase emotional reactivity and stress susceptibility. In other words, these neurocognitive recalibrations may have conferred functional short-term advantages in the context of maltreatment; yet they may increase psychiatric vulnerability as they may be no longer adaptive in specie-typical environments.

6.3.2.3. Direct and Indirect Pathways. Maltreatment-related alterations in associative learning, threat processing, future thinking and interpersonal problem solving, can have immediate repercussions in the way an individual processes information about the self and the surrounding environment. These can be understood as the direct effects of latent vulnerability (Gerin et al., 2018). For example, reduced signalling to reward predicting cues (Chapter Two) may reduce the motivation and behavioural responses necessary to seek activities and social interactions that foster our sense of self-efficacy, self-identity and psychological well-being. Difficulties in envisioning future negative outcomes associated with certain actions or stimuli (Chapter Two and Four) may increase impulsivity and the propensity of experiencing stressful life events. Moreover, patterns of increased reactivity to threat cues (Chapter Three) and reduced problem-solving skills (Chapter Five) may increase the extent to which everyday challenges burden and tax an individual. These represent some
examples of how maltreatment-related cognitive and neurobiological adaptations may have ‘real-time’ implications for how an individual may negotiate and navigate the social environment.

However, neurocognitive alterations following maltreatment exposure can also have indirect cumulative negative consequences which impact an individual’s social ecology over time. For example, reduced EFT specificity and interpersonal problem solving abilities (Chapter Four and Five) may instantiate psychiatric vulnerability by increasing difficulties with peers and adults. Furthermore, heightened threat reactivity may also serve to increase the likelihood of misinterpreting ambiguous cues, and over-responding to negative cues in ways that lead to more conflictual interactions. As these relational difficulties unfold across the lifespan, negative effects accrue in the form of a reduced ability to elicit social support and sustain protective family and peer networks. Such interpersonal relationships serve an important function in promoting resilient outcomes, buffering the individual against the impact of stressful life events (van Harmelen et al., 2017). Indeed, decreased social support has been shown to be a mechanism through which maltreated individuals are at greater risk of developing future mental health problem (Sperry & Widom, 2013). Therefore, preventative interventions aimed at decreasing the risk of subsequent psychopathology following maltreatment exposure should target cognitive and neurobiological processes that may contribute to increased psychiatric vulnerability in direct and more immediate ways as well as through protracted and indirect trajectories.

6.3.2.4. Preventative Clinical Approaches. Perhaps the most important implication of our findings is that they contribute to the emerging knowledge regarding the neurocognitive alterations that follow the experience of abuse and neglect during childhood. In particular, by providing further evidence that neurocognitive vulnerabilities are present before frank disorders emerge, they
contribute to the motivation and rationale to pursue more explicit preventative
clinical approaches (McCrory, Gerin, et al., 2017; McCrory & Viding, 2015).

Despite some exceptions, current models of interventions are generally
provided at two levels. At the level of social care, once the maltreatment has been
established, the priority is to ensure the child’s safety, which can entail, in extremo
ratio, even the removal of the child from their home. Then, at the level of mental health
service provision, an individual with a history of maltreatment may be offered treatment
if criteria for a psychiatric disorder are met. There is almost no provision, however, for
those individuals with a history of maltreatment who do not present yet with a frank
psychiatric disorder. The studies presented in this thesis, together with extant findings
regarding the neurocognitive sequelae of childhood maltreatment, suggest that
psychological care should be provided for those individuals a greater risk before they
experience a worsening in their mental health.

A next step would be the development of a screening tool cable of capturing
these latent neurocognitive vulnerabilities. This could form part of routine
assessments and would allow us to detect those individuals with maltreatment
histories that, without being overly symptomatic, are at increased risk for later
psychopathology. However, such an ambition remains untested. Further
neurocognitive informed research is necessary to provide a more comprehensive and
detailed understating of the socio-cognitive and neurobiological processes implicated
in the pathogenies of psychiatric disorders among maltreated individuals. In the
medium-long term, maltreatment research could also contribute to the identification
of specific neurocognitive processes that could be targeted during preventative
interventions. In particular, further longitudinal research is necessary to establish the
extent to which alterations in the processes investigated in this thesis, alongside a
variety of other potential mediators, contribute to future mental health difficulties, and
whether they might be amenable to change. Such targeted mechanistic approaches to
prevention and intervention are necessary, considering that current forms of clinical (e.g. Nanni et al., 2012) and general parental care (e.g. Rothman & Silverman, 2007) may not be sufficient to prevent and/or ameliorate mental health difficulties among individuals with a history of childhood maltreatment.

6.3.3. Conclusions

In summary, the present thesis set out to investigate alterations in brain functioning and cognitive processes which may increase psychiatric vulnerability following exposure to childhood maltreatment. In the first empirical chapter (Chapter Two), we showed that a history of childhood abuse and/or neglect is associated with neural alterations in the brain network that underlies associative learning. In particular, we found alterations in the neurocomputational processes that support reinforcement-based decision-making – i.e. expected value representation and prediction error signalling. Notably, the reported pattern of neurocognitive alterations was consistent to those found in individuals with psychiatric disorders commonly associated with maltreatment, such as anxiety and depression. Thus, recalibrations in the neurocomputational process that underlie associative learning represent promising markers of latent psychiatric risk among maltreated individuals. In the second empirical chapter (Chapter Three), we showed that heightened amygdala reactivity to threat and an increased propensity to experience stressful life events among individuals with a history of maltreatment was independent of co-occurring risk factors (such as concurrent symptoms and socioeconomic status). Importantly, we also showed, for the first time, that increased baseline amygdala reactivity to threat among maltreated individuals contributed to future internalising psychopathology. This is consistent with the view that exposure to childhood abuse and neglect lead to functional recalibration of neural systems in ways that increase vulnerability to future mental health difficulties. In the last two empirical chapters we showed that a history of childhood maltreatment is linked to deficits in two domains that have received little attention in the maltreatment
literature – Episodic Future Thinking (EFT) and interpersonal problem solving skills. In particular, we found that maltreatment was associated with reduced EFT specificity (or Overgeneral EFT; OEFT) and with difficulties in generating the relevant steps necessary to solve interpersonal difficult situations (known as means-end thinking).

In conclusion, this thesis contributes to our current knowledge regarding the neurobiological processes and cognitive domains impacted by exposure to childhood maltreatment. This improves our understanding of how childhood abuse and neglect may be associated with increased risk of future psychopathology. In the longer term, it is hoped that these findings will provide the foundation for the development of screening tools and novel preventative clinical approaches that could promote a resilient outcome among those maltreated individuals at greatest psychiatric risk.
References


References

*Current Biology, 24*(5), 541–547. doi:10.1016/j.cub.2014.01.046


References


References

doi:10.1097/00004583-199703000-00012


References


References


References


References


Danese, A., Moffitt, T. E., Arseneault, L., Bleiberg, B. A., Dinardo, P. B., Gandelman,


References


References

doi:10.1037/0021-843X.104.4.632

doi:10.5665/sleep.3916

doi:10.1001/jama.286.24.3089


doi:10.1016/j.psychresns.2012.11.009

doi:10.1037/a0019010


References

*Nature Reviews Neuroscience, 16*(11), 693–700. doi:10.1038/nrn4044


References


Fuhrmann, D., Knoll, L., & Blakemore, S. L. (2015). Adolescence as a sensitive period...


References

Social Cognitive and Affective Neuroscience, 3(2), 91–96.
doi:10.1093/scan/nsn003

doi:10.1038/npp.2014.236


References


242


References


References

Mediators of the Relation between Childhood Psychological Maltreatment and Adult Love Relationships. *Journal of Aggression, Maltreatment & Trauma*, 20(6), 617–635. doi:10.1080/10926771.2011.595764


References


References


References


doi:10.1080/10926771.2016.1121188


Klein, S. B. (2016). Autonoetic consciousness: Reconsidering the role of episodic


References

*Psychopathology*, 29(2), 347–363. doi:10.1017/S0954579417000037


Matthys, W., Vanderschuren, L. J. M. J., & Schutter, D. J. L. G. (2012). The neurobiology of oppositional defiant disorder and conduct disorder: Altered


References


References


Oldershaw, A., Grima, E., Jollant, F., Richards, C., Simic, M., Taylor, L., & Schmidt,


Palombo, D. J., Keane, M. M., & Verfaellie, M. (2015). The medial temporal lobes are
References


doi:10.1093/scan/nsp011


doi:10.1037/0012-1649.38.5.784


doi:10.1037/0021-843X.112.3.323


doi:10.1111/cdev.13033
References


References

*Development and Psychopathology, 29*(2), 337–345. doi:10.1017/S0954579417000025


Word Association Test: Reliability and updated norms. *Archives of Clinical


Rutter, M., Beckett, C., Castle, J., Colvert, E., Kreppner, J., Mehta, M., … Sonuga-
of findings from a UK longitudinal study of Romanian adoptees. *European
doi:10.1080/17405620701401846

Rutter, M., Kumsta, R., Schlotz, W., & Sonuga-Barke, E. (2012). Longitudinal Studies
Using a “Natural Experiment” Design: The Case of Adoptees From Romanian
Institutions. *Journal of the American Academy of Child & Adolescent Psychiatry,
51*(8), 762–770. doi:10.1016/J.JAAC.2012.05.011

empirical findings, and policy implications. In J. P. Shonkoff & S. J. Meisels
(Eds.), *Handbook of Early Childhood Intervention* (2nd ed., pp. 651–682). New
York, NY, US: Cambridge University Press.
doi:10.1017/CBO9780511529320.030

attachment, and career search self-efficacy among community college students.
*Journal of Counseling Psychology, 43*(1), 84–89. doi:10.1037/0022-0167.43.1.84
References


References

580–585. doi:10.1016/j.tics.2014.09.001


References


memory as a predictor of the course of depression: A meta-analysis. *Behaviour Research and Therapy, 48*(7), 614–625. doi:10.1016/j.brat.2010.03.013


References

doi:10.1037/0033-2909.120.1.25


Tottenham, N., & Sheridan, M. A. (2009). A review of adversity, the amygdala and the
References


striatum during instrumental learning with juice and money reward in the human brain. *Journal of Neurophysiology, 102*(6), 3384–3391. doi:10.1152/jn.91195.2008


References


References


References

*Archives of General Psychiatry, 64*(1), 49–56. doi:10.1001/archpsyc.64.1.49


doi:10.1002/cbm.191


doi:10.1037/0021-843X.114.3.421

Williams, M. J., Barnhofer, T., Crane, C., Herman, D., Raes, F., Watkins, E., &


References


Appendices

Appendix 1 – Accepted/In-press Manuscript in *Adoption and Fostering*

A review of childhood maltreatment, latent vulnerability and the brain:

**Implications for clinical practice and prevention**

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**Abstract**

There is a well-established association between childhood maltreatment and later poor mental health and increasing recognition that we need to find ways to support children following such experiences to improve long-term outcomes. We suggest that the rationale for such a preventative approach is directly informed by the emerging findings from the field of functional neuroimaging. Here, we review the evidence from four neurocognitive systems: threat processing, reward processing, emotion regulation and executive control. We briefly summarise what is known about each system, review the evidence that altered functioning is implicated in common mental health problems, and describe how the functioning of each system is altered following maltreatment. Across domains, these neurocognitive alterations following child maltreatment are in line with those seen in adults presenting with mental health problems, yet most maltreated children studied do not have a presenting ‘disorder’. This suggests that these neurocognitive alterations may potentiate the risk of future psychopathology. We discuss this possibility in the context of the theory of Latent Vulnerability (McCrory & Viding 2015). According to this model, children may respond to early adverse environments in ways that are potentially adaptive in the short term but which create vulnerability to future mental health problems in the long term. We also consider the clinical implications of the neuroimaging evidence - in particular, the growing need for a more preventative clinical approach.

**Keywords:** Child abuse; maltreatment; mental health; functional magnetic resonance imaging; resilience
Introduction

Childhood maltreatment, including physical, emotional, sexual abuse and neglect, are relatively common forms of adversity. Each year, in high income countries about 1% of children are referred to child protection services (Radford et al., 2011). However, the official rates of substantiated maltreatment seem to be just the tip of the iceberg. Self-reported measures suggest a much larger proportion of individuals experience abuse, neglect or are exposed to domestic violence during childhood (Gilbert et al., 2009; Radford et al., 2011). These negative early life experiences are associated with a wide range of negative outcomes, including reduced economical productivity, educational attainment and physical health (Gilbert et al., 2009; Lansford et al., 2002; Widom et al., 2012). Moreover, recent longitudinal work suggests that childhood maltreatment is one of the most potent predictors of poor mental-health across the lifespan (Koenen and Widom, 2009; Vachon et al., 2015; Widom et al., 2007). Population-attributable risk assessments from large cross-cultural studies, which assume the existence of a direct causal link between childhood maltreatment and future psychopathology, estimate that abuse and neglect account for a large proportion of psychological disorders onset during childhood and also adulthood (Green et al., 2010; Kessler et al., 2010).

Despite the well-established association between childhood maltreatment and increased risk for psychopathology (Gilbert et al., 2009; Vachon et al., 2015), we do not know enough about the neurocognitive mechanisms by which increased vulnerability becomes embedded. Nor do we have a detailed understanding about what factors may promote resilience (Rutter, 2000, 2012). We need to better understand how maltreatment alters psychological and neurobiological functioning in ways that increase risk of mental health problems. Equally, we need to understand the intrinsic and extrinsic individual characteristics that can promote a positive outcome despite early adversity. These gaps in our understanding leaves clinicians and professionals that work within child protection services without adequate resources and knowledge that would allow them to identify and provide
support for those individuals most likely to develop mental health difficulties in the future (McCrory et al., 2017). Service provision in the U.K. has been primarily organised around a medical diagnostic model which assumes that individuals with similar clinical presentation are comparable. The evidence suggests that this is not the case (Nanni et al., 2012; Teicher and Samson, 2013). Moreover, the systemic, attachment, social and educational needs of children are often not dealt with holistically alongside symptom presentation. Such an approach has limited the scope for clinicians to develop an understanding of how disorders emerge and unfold across development within complex systems. Although we know a lot about the risk and resilience factors associated with mental health problems, we still have a limited understanding of the mechanisms that shape how they develop following childhood maltreatment. In addition, the differences across disciplines have led to the compartmentalization of knowledge. We argue that there is a growing need for researchers, clinicians, parents, foster-carers, children and social workers to work more collaboratively if progress is to be made.

*The Theory of Latent Vulnerability*

In an effort to shift the focus on prevention and the developmental mechanisms associated with the emergence of mental health problems following childhood maltreatment, McCrory and Viding have proposed the theory of Latent Vulnerability (McCrory et al., 2017; McCrory and Viding, 2015). This theory offers a system-level approach that places emphasis on the neurocognitive mechanisms that link childhood maltreatment to subsequent mental health problems (see Figure 1 for a graphical illustration of the Latent Vulnerability model). According to this account, childhood maltreatment leads to measurable alterations that can be characterised at neurobiological and cognitive levels. These changes can be understood as developmental recalibrations to negative early experiences; in other words, they are not necessarily seen as signs of ‘damage’. Rather, such changes may, in many instances, be adaptive within the context of maltreatment and confer short-term functional advantages (for example, faster detection of threat or reduced expectation of
reward. However, such alterations are also thought to incur long-term costs (e.g. increased risk of psychological problem or revictimization) as an individual may not be optimised to cope with the demands of more normative environments, such as school or a stable foster placement. Importantly, maltreatment related patterns of adaptation are understood to be ‘latent’ as they may appear before the emergence of a mental health problems and are not necessarily manifest symptoms or precursors of any future condition.

The theory of Latent Vulnerability focuses on maltreatment-related neurocognitive processes that increase, non-deterministically, the risk of future difficulties. In doing so, it complements a wider research literature demonstrating that a variety of maltreatment-related emotional states (such as shame), self and other representations (such as abuse-related self-blame), and psychological states (such as dissociation) also confer risk for future difficulties (e.g. Feiring and Cleland, 2007; Feiring and Taska, 2005; Hanson, 2016; Yates et al., 2008). By focussing attention on the maltreatment-related processes and alterations that precede the emergence of more overt difficulties, this framework has the potential to increase the application of research to practice. First, a systematic investigation of the neurocognitive processes associated with increased vulnerability may help inform the development of a screening tool that could be used by frontline practitioners to identify those individuals at most risk of developing later mental health problems. Second, understanding the processes that instantiate increased vulnerability may inform the development of interventions that most effectively help to prevent maltreated children developing subsequent mental health difficulties. Third, this understanding provides a clear rationale for rethinking service design and delivery, with a much greater focus on the prevention of mental health problems.

[Figure 1]

**Functional magnetic resonance imaging studies of childhood maltreatment**
This review explores changes to neurocognitive processes that may increase risk of mental health problems following maltreatment experience. There is a wide range of methods and paradigms that have been used to investigate the neurobiological impact of childhood maltreatment. These include the measurement of neuroendocrine stress and inflammatory responses (e.g. Alink et al., 2012; Coelho et al., 2014), the detection of neuroanatomical changes via Structural Magnetic Resonance Imaging (sMRI) and Diffusion Tensor Imaging (DTI) (Kelly et al., 2015; Puetz et al., 2017), as well as functional brain alterations, using electroencephalography (EEG) (Curtis and Cicchetti, 2013) and Functional Magnetic Resonance Imaging (fMRI). In our view task-based fMRI has the greatest potential to help refine our understanding of the underlying neurocognitive differences in processing that may not be otherwise detectable, with more direct implications for practice (e.g. Gerin et al., 2017; McCrory et al., 2013). Therefore, in order to focus this paper, we will confine our consideration to fMRI findings, reviewing all extant fMRI studies of children and adolescents with histories of maltreatment relating to four key areas: threat processing, reward processing, emotion regulation and executive control - we refer readers to McCrory et al (2017) for a more comprehensive review and methodological critique of the literature. To help put these findings into context, we first provide a brief description of each system and then summarise how each has been implicated in common mental health difficulties before considering the evidence from studies of maltreatment or adverse early life experience.

In brief, the studies discussed here support the notion that some individuals with histories of childhood maltreatment, even in the absence of manifest clinical symptoms, may present with changes in brain function across several cognitive, social and emotional domains. These changes are often consistent with neural signature observed in individuals with anxiety, depression and conduct problems (McCrory et al., 2017).

1. Threat Processing
What is threat processing? Survival is dependent on the ability to detect and respond to dangerous and aversive stimuli in the environment. For this reason, it is not surprising that both animal and human studies have revealed that a large amount of cognitive resources and neurobiological systems are dedicated to threat detection (Ledoux, 2000; Öhman, 2009). Within the central nervous system the amygdala is one of the core structures dedicated to the processing of danger and to the detection of salient information more broadly (Ledoux, 2000; Phelps and LeDoux, 2005). The amygdala is part of an integrated network comprising several cortical and subcortical brain regions involved in fear conditioning, stress responses and salience detection, such as the hippocampus, the striatum, the anterior insula and the dorsal anterior cingulate cortex (ACC) (Shin and Liberzon, 2010).

How is altered threat processing implicated in mental health difficulties? In recent years, neuroimaging findings have shown that alterations in amygdala and anterior insula activation are implicated in several disorders, including posttraumatic stress disorder (PTSD), mood and anxiety disorders (Etkin and Wager, 2007; Kerestes et al., 2014; Patel et al., 2012), drug addiction (Sripada et al., 2011) and conduct problems (Viding et al., 2012). Crucially, recent longitudinal studies of healthy individuals exposed to different kinds of environmental stressors have shown that baseline hyper-responsiveness (i.e. increased responsiveness) to threat in the brain is associated not just with current, but also with future symptoms (Admon et al., 2009, 2013; Swartz et al., 2015).

Functional neuroimaging studies of threat processing in maltreated children and adolescents. Animal studies have established a strong link between early adverse experiences (such as early separation from a caregiver, social isolation, or reduced maternal care and sensitivity) and neurophysiological long lasting alterations in the central and peripheral nervous systems involved in threat processing and stress responses (Caldji et al., 1998, 2003; Meaney, 2001; Rosenblum et al., 1994). Behavioural and electrophysiological studies with humans also
suggest that abuse and neglect are associated with long lasting alterations in threat processing that can be detected as early as infancy. These changes include heightened electrophysiological responses to negative stimuli, and preferential attention and enhanced perceptual ability for threat cues, such as angry or fearful faces (Curtis and Cicchetti, 2013; Pollak et al., 2005; Pollak and Sinha, 2002; Pollak and Tolley-Schell, 2003).

These behavioural and neurophysiological findings have been extended by a series of recent functional magnetic resonance imaging (fMRI) studies with children and adolescents. These have found a pattern of increased neural response during the processing of threat cues (e.g. angry faces) in the amygdala, and other subcortical neighbouring regions, such as the anterior insula and hippocampus (Maheu et al., 2010; McCrory et al., 2011, 2013; Tottenham et al., 2011). Such neural alterations seem to be shared across individuals with different experiences of early adversity, ranging from severe institutional neglect (Maheu et al., 2010; Tottenham et al., 2011), substantiated maltreatment in community settings (McCrory et al., 2011, 2013) and also less severe experiences of neglect (White et al., 2012). Importantly, by using well matched control groups, these studies suggest that increased threat-related neural responses among maltreated children and adolescents is independent from potentially confounding factors, such as IQ, socioeconomic status, pubertal status and concurrent psychopathology (e.g. Maheu et al., 2010; McCrory et al., 2013). Moreover, by showing that both amygdala and insula hyperactivity have a dose-dependent relationship with the severity/duration of maltreatment (Maheu et al., 2010; McCrory et al., 2011, 2013), these findings point to a pattern of neural calibration directly related to the degree of early adversity. Finally, it is worth noting that a similar pattern of findings comes from studies with adults with a history of childhood maltreatment, suggesting that abuse and neglect can have a long-lasting impact on the threat-processing system (e.g. Dannlowski et al., 2012).
Appendix 1

Summary. It has been shown that different forms of early adversity alter the neural reactivity of the threat system, especially amygdala activation, even in children and adolescents who are not presenting with overt psychiatric symptomatology. Crucially, this association seems to be directly related to the severity of maltreatment (Maheu et al., 2010; McCrory et al., 2011; White et al., 2012). Interestingly, similar findings have been reported in adults who experienced maltreatment during childhood (see Hein & Monk, 2016), suggesting that such alterations can be long lasting. Given that hyper-responsiveness of the amygdala and anterior insula have been associated with several psychiatric conditions, including depression, anxiety and PTSD, it is possible that altered threat processing may increase the risk of future mental health problems. However, longitudinal studies are required to confirm this hypothesis. Ways in which this risk might become instantiated are discussed in the clinical implications section below.

2. Reward Processing

What is reward processing? Learning which stimuli and actions are associated with attaining rewarding objects, experiences or events is essential to motivate and guide adaptive decision-making and behaviour. The main network underpinning the processing of reward is the mesocorticolimbic dopaminergic neural pathway. This includes brain-stem regions, such as the ventral tegmental area, which project to basal ganglia nuclei, especially the striatum, and terminate in prefrontal regions, including the orbitofrontal cortex (Clithero and Rangel, 2013; O’Doherty, 2011; Tanaka et al., 2016; Valentin and O’Doherty, 2009).

How is altered reward processing implicated in mental health difficulties? Neural alterations in the reward system have been associated with suboptimal decision-making and psychological distress, such as the emergence and maintenance of anxiety, mood, conduct and substance abuse disorders (Balodis and Potenza, 2015; Eshel and Roiser, 2010; Hartley and Phelps, 2012; Stringaris et al., 2015; White et al., 2013; Zhang et al., 2013). For example, neuroimaging findings show a consistent pattern of reduced activation in the striatum during reward processing among depressed
individuals (Forbes and Dahl, 2012; Pizzagalli et al., 2009; Ubl et al., 2015). Interestingly, this predicts not only current but also future clinical status and symptoms level (Bress et al., 2012; Morgan et al., 2013; Olino et al., 2014; Telzer et al., 2014), even in those who were previously “healthy” (Stringaris et al., 2015). Neuroimaging studies suggest that this pattern of blunted neural activation may be associated with difficulties in computing reward anticipation and detecting differences between expected and actual rewards (prediction-error signalling). In the context of depression, this might entail reduced sensitivity to rewards and limited motivational response (i.e. anhedonia) (Gotlib et al., 2010; Stringaris et al., 2015; Ubl et al., 2015); in the context of conduct disorder, this may suggest difficulties in integrating and updating reward (and punishment) information (White et al., 2013, 2016).

Functional neuroimaging studies of reward processing in maltreated children and adolescents. Researchers have been motivated to investigate reward processing in maltreated individuals for two reasons. First, the clinical literature described above suggests that altered reward processing may be associated not just with current symptoms, but also with the development of mental health problems. Secondly, we know that the familial environment experienced by maltreated children is often characterised by the erratic and infrequent availability of rewards. To date most neuroimaging studies of maltreatment have found reduced activation during reward processing, especially in the striatum and the orbitofrontal cortex (McCrory et al., 2017). This pattern of findings has been found both in individuals who have experienced extreme forms of institutional deprivation (Goff et al., 2013; Mehta et al., 2010) or maltreatment in community settings, especially neglect (Gerin et al., 2017; Hanson et al., 2015). Notably, this pattern of findings remains even after controlling for the presence of overt psychological disorders or symptoms severity for conditions commonly associated with blunted reward-related neural response, such as depression (e.g. Gerin et al 2017). Dennison et al., (2016) did not find this effect but nevertheless found that higher neural response to reward was linked to better future mental health outcomes. Overall these findings suggest that increased / decreased activation in the striatum
may represent a marker of resilience / risk to psychopathology. In particular, the pattern of lower neural response in maltreated individuals may reflect neural calibration to reduced opportunities for reward-based learning. Such alterations may represent an adaptive regulatory mechanism which reduces disappointment in the context of inconsistent and insensitive parenting (McCory et al., 2017). However, these neurocognitive alterations may also hamper functioning in more normative situations. For example, they may hinder exploratory behaviour, thus decreasing the opportunities for learning and for motivating the search of alternative sources of reward outside the home environment.

Summary. Overall, these findings suggest that maltreatment - especially neglect and institutional deprivation - is associated with a blunted neural response to reward cues in the orbito-striatal network. This neural profile, which may be shaped by familial environments characterised by erratic and infrequent availability of rewards, is also known to be associated with common mental health problems, particularly depression and conduct disorder. Therefore, alterations in reward processing following maltreatment may represent a potential neurocognitive vulnerability to mental health difficulties. Initial longitudinal evidence also suggests that higher levels of neural response in this network may be a marker of resilience to future psychopathology.

3. Emotion Regulation

What is emotion regulation? The ability to regulate affect entails the modification of an emotion by producing changes to its intensity, duration or valence (Cole et al., 2004; Eisenberg and Spinrad, 2004; Ochsner et al., 2004). Various strategies can be used for emotion regulation, such as emotional distancing, suppression, social support, reappraisal and attention modulation, just to mention a few (Koenigsberg et al., 2010; Ochsner et al., 2012). Crucially, such processes may involve explicit effort or occur implicitly and outside conscious awareness (Gyurak et al., 2011). A large neural network is linked to affect regulation. Broadly speaking, prefrontal regions are understood to have top-down regulatory control over regions implicated in emotional reactivity, impulsivity and
negative affect, such as the amygdala, insula, striatum and the dorsal anterior cingulate cortex (dACC) (Etkin et al., 2015; Ochsner et al., 2012). In particular, the ventral anterior cingulate cortex (vACC) and medial prefrontal cortex (mPFC) seem to be more involved in the implicit and automatic regulation of affect, while latero-prefrontal (LPFC) and also latero-parietal (IPC) cortices seem to be necessary for more explicit and volitional forms of emotion regulation (Etkin et al., 2015).

*How is altered emotion regulation implicated in mental health disorders? Many psychological difficulties involve altered affect regulation (e.g. anxiety, conduct disorder and depression) (Aldao et al., 2010; Mennin et al., 2007). Moreover, difficulties in emotion regulation have been shown to represent a risk factor for developing mental health problems in the future among those individuals who have suffered early adversity (Kim-Spoon et al., 2013; Kim and Cicchetti, 2010; Shields and Cicchetti, 2001) and/or who do not present with current clinical symptoms (Ehring et al., 2010; Folk et al., 2014; Keenan, 2006; Michl et al., 2013; Wirtz et al., 2014).*

*Functional neuroimaging studies of emotion regulation in children and adolescents exposed to maltreatment. Three studies of functional connectivity have reported that maltreated children and adolescents present with atypical connectivity between regulatory frontal regions (such as vACC and mPFC) and subcortical brain areas, such as the amygdala (Gee et al., 2013; Lee et al., 2015; Marusak et al., 2015). In addition, five studies that investigated focal brain activity have also reported alterations in the same frontal regulatory network, including the mPFC, vACC, dACC and also the LPFC (Elsey et al., 2015; Marusak et al., 2015; McLaughlin et al., 2015; Puetz et al., 2014, 2016). However, despite the fact that these studies have reported altered functioning in a consistent set of brain regions during emotion regulation, the direction of these alterations has been inconsistent (i.e. increased vs. decreased activity and stronger vs. weaker connectivity). These discrepancies are not entirely unexpected given the spectrum of participants recruited in these studies. Participants varied in terms of developmental stage and type of early adversity (e.g. physical abuse, verbal abuse, institutionalisation, neglect in community settings, etc.).*
Moreover, different emotion regulation paradigms were implemented, with some requiring simple or automatic emotional processing and others requiring more explicit and higher order regulatory demands. It has been suggested that these different task demands may be helpful in understanding the differences across studies (McCrorry et al., 2017). When a task explicitly requires participants to attend to aversive stimuli or to consciously modulate affective responses (Elsey et al., 2015; McLaughlin et al., 2015) one tends to see a pattern of increased activation in regulatory frontal regions in maltreated individuals that may reflect increased effort. On the other hand, on those tasks where it is possible to shift attention away from the processing of aversive stimuli, maltreated individuals show a pattern of reduced activation and connectivity (Gee et al., 2013; Lee et al., 2015; Puetz et al., 2014, 2016). This pattern of hypo-activation is consistent with the use of avoidant and dissociative regulatory strategies (McCrorry et al., 2017) that can often be unhelpful in the longer term and are associated with increased risk of anxiety, depression, self-harm and PTSD (Bryant and Harvey, 1995; Holahan et al., 2005; Kaplow et al., 2005; Karstoft et al., 2015; Wirtz et al., 2014; Yates et al., 2008).

Summary. Overall, the neuroimaging studies of emotion regulation in maltreated children and adolescents suggest that the network traditionally involved in self-regulatory processes shows a pattern of atypical focal activation and connectivity. Medial frontal regions (e.g. vACC and mPFC) and the IPFC seem to be particularly implicated, as well as the frontolimbic neural network (e.g. amygdala-vACC connectivity). Taken together with the neuroimaging studies of mental health disorders, these findings suggest that emotion regulation processing changes may confer risk. However, longitudinal studies are still required to test this hypothesis directly. The heterogeneity in the neurocognitive findings to date probably reflects differences in the type and timing of early adversity, and the specific computations (simply put, explicit vs. implicit) engaged during different emotion regulation tasks.

4. Executive Control
What is executive control? Executive control broadly refers to three interrelated cognitive functions: inhibiting (the ability to constrain automatic and dominant responses irrelevant to a given goal), updating (the ability to maintain, monitor and quickly add/delete information), and shifting (the ability to flexibly switch between different tasks) (Miyake et al., 2000). These functions are important for adaptive behaviour and effective decision-making. Neuroimaging studies have found that these functions are underpinned by a central executive network, whose central nodes include the dorsolateral prefrontal cortex (dPFC) and posterior parietal cortex. Brain areas engaged during error monitoring, such as the dACC and mid cingulate cortex (MCC), are also involved in executive control functions.

How is altered executive control implicated in mental health difficulties? Cross-sectional and longitudinal evidence suggests that alterations in executive control may be involved in the development of depression, anxiety, conduct problems, ADHD, PTSD and psychosis (Campbell and von Stauffenberg, 2009; Cannon et al., 2006; Cortese et al., 2012; Evans et al., 2015; Parslow and Jorm, 2007; Snyder, 2013; Snyder, Kaiser, et al., 2015; Willcutt et al., 2005). The association between atypical executive control and mental health problems may (for example) be mediated by alterations in several cognitive, emotional and social processes which rely upon executive functions, such as suppression of ruminative thinking, problem solving and regulation of affect (Snyder, Miyake, et al., 2015).

Functional neuroimaging studies of executive control in maltreated children and adolescents. Two studies have found that exposure to early adversity is associated with increased activation during tasks requiring executive functions (such as error processing, cognitive shifting and inhibition) in brain areas linked with executive control, including the dACC/MCC and lateral frontal regions (Lim et al., 2015; Mueller et al., 2010). This increased activation may reflect decreased neural efficiency and increased effort to attain the same performance as their non-maltreated peers. Notably, these findings are in line with the neuroimaging clinical literature of
several disorders associated with maltreatment, such as anxiety (Basten et al., 2011), psychosis (Callicott et al., 2000), depression (Harvey et al., 2005) and ADHD (Cortese et al., 2012).

**Summary.** To date, two fMRI studies have investigated executive control in maltreated youth (Lim et al., 2015; Mueller et al., 2010). Both studies identified a pattern of increased brain activation in regions involved in executive functions such as inhibition and performance monitoring/updating, including the dACC/MCC and the fronto-lateral cortex. These findings, in conjunction with the clinical neuroimaging literature suggest that neurocognitive alterations in executive control may increase the risk of mental health problems. However, a recent study by Danese and colleagues (Danese et al., 2017) suggests that we should be cautious in assuming a causal link between maltreatment experience and alterations in executive function, as these may instead result from the socioeconomic and genetic factors that commonly co-occur with maltreatment. Indeed, similar limitations may apply to the other neurocognitive domains of interests. However, to the best of our knowledge, this has not yet been investigated in population-representative birth cohort samples.

**Conclusions: Clinical Implications**

The functional neuroimaging literature suggests that the experience of abuse and neglect can influence the development of specific aspects of cognitive and affective functioning, which may increase vulnerability to future mental health problems. However, there are still common methodological shortcomings that characterise the neuroimaging literature of maltreatment that need to be addressed in future research if stronger causal inferences are to be made. Some of the most common limitations include small sample sizes, the lack of prospective/longitudinal designs and the conflation of severe maltreatment experience with adversity in the normal range. Moreover, it is essential that future studies aim to control for relevant confounding variables, such as IQ, pubertal status, age, gender, socio-economic status and the presence of a frank mental health disorders, which are known to co-occur with the experience of maltreatment.
- see McCrory et al (2017) for a more comprehensive critique of these methodological concerns.

Despite these limitations, the emerging pattern of findings reviewed here complement and extend those from wider psychological research, indicating for example, increased hypervigilance and compromised emotion regulation skills in maltreated children (Curtis and Cicchetti, 2013; Kim-Spoon et al., 2013; Romens and Pollak, 2012).

From a clinical perspective, two aspects of the findings we have reviewed merit particular attention. First, maltreatment-related changes resemble the neurocognitive profile associated with mental health disorders commonly associated with maltreatment, such as anxiety and depression. Second, these alterations are already present before a manifest clinical disorder. As such, they can be considered markers of latent psychiatric vulnerability since they may have prognostic value, but do not reflect overt symptomatology. Another important implication emerging from these findings is that, despite the link with mental health problems, these neurocognitive changes should not be readily interpreted as a sign of ‘damage’. Rather, in line with the theory of Latent Vulnerability (McCrory et al., 2017; McCrory and Viding, 2015), they may in many instances be understood as the outcome of a complex set of adaptive processes which may confer short-term advantages for the child in the context of abusive and neglectful environments. However, they may equally incur long-term costs as an individual may not be equipped to deal with more normative challenges.

The neurobiological and psychological alterations which can follow experiences of maltreatment can be understood to increase mental health risk, particularly following exposure to future stressors, in both direct and indirect ways (McCrory et al., 2017). Alterations in the way we process our internal and external worlds can have immediate repercussions: this can be understood as the direct effects of latent vulnerability. An example is the established pattern of hypervigilance to threat cues. While helpful to the child in a chaotic or dangerous home environment, such a response may curtail attentional resources available for the processing of
other potentially helpful environmental cues, limiting the opportunities for learning and developing other cognitive and affective functions. Heightened response of the threat system may also lead to increased stress reactivity and experience of negative emotions – in other words, it serves to potentiate the negative impact of new stressor experiences. In this way, adaptation of the threat system may have ‘real-time’ implications for how the child negotiates their experience inside and outside the home.

In parallel, there are likely to be indirect effects that over time can compromise psychological and social functioning. Alterations of the threat system may undermine a child’s ability to develop positive peer friendships and social support networks which may help buffer their experience of future stressors. It may also lead them to act in ways that increase the likelihood of future stressor exposure, for example, because of relationship breakdown or exclusion from school. This may unfold because heightened threat reactivity serves to increase the likelihood of misinterpreting ambiguous cues, and over-responding to negative cues in ways that lead to more conflictual interactions. Equally, avoidance of threat or aversive cues (both internal and external) via dissociation and cognitive and behavioural strategies, whilst reducing distress in the short-term, may impair the development of important skills, such as the effective detection of threat, in the longer term (e.g. DePrince, 2005).

*When and how to intervene?*

Currently (notwithstanding some exceptions), statutory interventions happen mainly at two stages. Once the maltreatment has been substantiated, professionals seek to ensure safety and the stability of the child’s placement. Then, if an individual meets clinical criteria for a mental health problem, they may be offered treatment from mental health services. However, extant neuroimaging findings are beginning to show that neuro-cognitive vulnerabilities are present before manifest behavioural symptoms emerge. These findings, alongside those indicating a variety of other psychological mediators between maltreatment and mental health difficulty, provide the motivation
and the rationale to pursue a preventative care approach. In other words, help could be provided proximate to the detection of maltreatment experience to those most at risk of a worsening mental health trajectory.

Therefore, the natural next step would be to seek to develop a psychometric tool designed to screen for latent vulnerability that could help as part of a formal assessment process, identify those children at most risk for later poor outcome. However, the degree to which the extant neuroscience findings can shed light on models of prevention and intervention is much less clear; our view is that the field has not matured to this point. Rather, in the medium term we would hope that systematic neurocognitive research could help identify specific mechanisms that could be targeted in treatment. Further work is required, particularly within a longitudinal framework, in order to investigate the degree to which alterations of the systems reviewed here are implicated in the pathways to overt mental health problems and furthermore, whether they are amenable to change. Such targeted mechanistic approaches are necessary given that ‘treatments as usual’ (Nanni et al., 2012) and general parental caring (Rothman and Silverman, 2007) may not be enough to prevent and ameliorate symptoms among individuals who have suffered early abuse and neglect. If we are able to accurately delineate which neurocognitive systems are altered following maltreatment, an important next question is how to promote adaptive change in these systems or compensatory protective neurocognitive functions which can foster resilience (McCrory et al., 2017).

Future studies should systematically investigate the impact of a variety of positive relationships (involving peers, carers and others) and what factors promote the child’s ability to learn from these (Toth et al., 2013). Positive, predictable and safe relationships may help shift the child’s expectations of other people and build a foundation of trust. Repeated interactions within such relationships might create the conditions that could facilitate recalibration of the threat and reward processing systems. Alternatively, such relationships could foster development of compensatory strategies that counteract the affective processing biases. However, engaging in a
positive, warm, consistent and constructive way with children who have experienced maltreatment can be challenging to their carers. If a child is hypervigilant to threat, less sensitive to reward, and has fewer emotion regulation and executive functioning skills, this can often evoke negative feelings and a sense of inadequacy in those who are trying to meet their needs. We argue that a more comprehensive understanding of the neurocognitive impact of maltreatment can help clinicians and carers to reframe the child’s behaviour and develop strategies that are helpful in ‘unhooking’ them from maladaptive patterns of interaction. Building positive peer cultures and harnessing the potential of digital technology are also important areas for future research and innovation. In relation to technology, certain apps can support self-reflection and emotion regulation, and can enable connections with supportive peers and others - this being especially useful if young people are experiencing isolation or ostracism elsewhere (McGeeney and Hanson, 2017).

One key factor that may be important in fostering recalibration of the neurocognitive systems impacted by maltreatment through relational experiences is the development of epistemic trust. This is the ability to use others to acquire new knowledge about the internal and external world – a capacity that has typically been compromised during maltreatment (i.e. the child comes to mistrust information from adults, closing down the ability to learn from others and the cultural world) (Fonagy and Allison, 2014). Children and adults privilege information from a trusted person in guiding their everyday interactions with others and participation in life. In other words, a foundation of epistemic trust with a caregiver can help promote positive interactions that facilitate the acquisition of new knowledge. In developing such carer- and peer-group approaches, it may be useful to draw on the knowledge surrounding a variety of evidence-based interpersonally focused therapies that apply an understanding of epistemic trust (Toth et al., 2013).

There are also other promising approaches that more directly target some of the neurocognitive alterations reviewed in this paper. For example, DePrince et al (2015) found that a 12 session ‘risk detection/executive functioning’ group intervention with maltreated adolescents, which
included teaching mindfulness, problem-solving and accurate threat detection, led to nearly 5-fold
decrease in reports of sexual victimization in the following six months. It will be important to
establish what precise neurocognitive mechanisms underpinned the improved outcome for the
maltreated adolescents with this approach. More broadly, it may be fruitful to review techniques
and approaches that have been developed in the context of treatment for manifest disorders and
consider how these might be adopted or incorporated within a preventative model designed to
enhance resilience. Dialectical Behavioural Therapy (DBT) for example, comprises a number of
elements addressing emotion regulation, tolerating distress and improving interpersonal skills that
may be extremely useful to consider.

As a final note, the ethical implications of any preventative strategy must be carefully
considered in order to minimize risk of stigmatization. How will deviation from normative
development be explained and understood? How will individuals (who have been exposed to abuse
and neglect) be screened? And how will they be engaged as active partners in any process of seeking
and receiving support or help? Should this help be framed as promoting a resilient outcome? These,
and other important issues, will require collaborative engagement with the young people and their
families as active participants and careful consideration by professionals. In our view, such a
collaborative approach has a greater chance of not only being more ethically grounded, but also of
having greater efficacy in enabling and promoting agency and empowerment.

In summary, the acquisition of specific knowledge regarding neurocognitive processes
impacted by early adverse experiences can help us understand how children who have been
maltreated see the world around them and why they are often more vulnerable to developing
mental health problems. In the longer term this knowledge can inform the development of both a
screening tool to identify those at most high risk and preventative approaches that effectively
promote resilience and increase the likelihood of positive outcomes following childhood
maltreatment.
References


Bryant R a and Harvey AG (1995) Avoidant coping style and post-traumatic stress following motor
vehicle accidents. *Behaviour research and therapy* 33(6): 631–635. DOI: 10.1016/0005-7967(94)00093-Y.


Appendix 1


Appendix 1


Hein TC and Monk CS (2016) Research Review: Neural response to threat in children, adolescents,


Kim-Spoon J, Cicchetti D and Rogosch FA (2013) A Longitudinal Study of Emotion Regulation,


Appendix 1

753–62. DOI: 10.1016/j.jaac.2015.06.010.


Snyder HR (2013) Major depressive disorder is associated with broad impairments on 
neuropsychological measures of executive function: a meta-analysis and review. Psychological 

Snyder HR, Miyake A and Hankin BL (2015) Advancing understanding of executive function 
impairments and psychopathology: bridging the gap between clinical and cognitive 

broad impairments in executive function: A meta-analysis. Clinical Psychological Science 3(2): 


and Depression in Adolescence: Dimensionality, Specificity, and Longitudinal Predictions in a 
Community-Based Sample. The American Journal of Psychiatry 172(12): 1215–23. DOI:


recruits cortico-basal ganglia loops. In: Behavioral Economics of Preferences, Choices, and 
Happiness, pp. 593–616. DOI: 10.1007/978-4-431-55402-8_22.

Teicher MH and Samson JA (2013) Childhood maltreatment and psychopathology: A case for 
ecophenotypic variants as clinically and neurobiologically distinct subtypes. The American


White S, Pope K, Sinclair S, et al. (2013) Disrupted expected value and prediction error signaling in


Appendix 2 – Published Manuscript in *Development and Psychopathology*

A neurocomputational investigation of reinforcement-based decision making as a candidate latent vulnerability mechanism in maltreated children

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Abstract

Alleviations in reinforcement-based decision making may be associated with increased psychiatric vulnerability in children who have experienced maltreatment. A probabilistic passive avoidance task and a model-based functional magnetic resonance imaging analytic approach were implemented to assess the neurocomputational components underlying decision making: (a) reinforcement expectancies (the representation of the outcomes associated with a stimulus) and (b) prediction error signaling the ability to detect the differences between expected and actual outcomes. There were three main findings. First, the maltreated group (n = 18; mean age = 13), relative to nonmaltreated peers (n = 19; mean age = 13), showed decreased activity during expected value processing in a widespread network commonly associated with reinforcement expectancies representation, including the striatum (especially the caudate), the orbitofrontal cortex, and medial temporal structures including the hippocampus and insula. Second, consistent with previously reported greater responsivity to negative cues in the context of childhood abuse, the maltreated group showed increased prediction error signaling in the middle cingulate gyrus, somatosensory cortex, superior temporal gyri, and thalamus. Third, the maltreated group showed increased activity in frontostriatal regions and in the putamen during expected value representation. These findings suggest that early adverse environments disrupt the development of decision-making processes, which in turn may compromise psychosocial functioning in ways that increase latent vulnerability to psychiatric disorder.

Childhood maltreatment encompasses various early adverse experiences, including physical and emotional neglect, emotional, physical, and sexual abuse, as well as witnessing domestic violence. Maltreatment is one of the most profound insults to normal development, and it is strongly associated with several maladaptive outcomes including poor mental and physical health as well as reduced economic productivity across the life span (Gilbert et al., 2009; Lansford et al., 2002; Widom, 2004; Bentley, & Johnson, 2012). It is noteworthy that individuals with a psychiatric disorder who have experienced childhood maltreatment show higher rates of comorbidity and symptom severity (Gogus, Timpano, Sachs-Ericsson, Keough, & Ricard, 2010; Teicher & Samson, 2013) and are less likely to respond to treatment (Nanni, Uher, & Danese, 2012). Furthermore, epidemiological data have estimated that childhood abuse and neglect account for up to 45% of the risk of childhood-onset psychiatric disorders and for approximately 30% of adult and adolescent-onset disorders (Green et al., 2010). In line with these findings, population-attributable risk assessments from large cross-cultural data sets have indicated that eradicating childhood abuse and neglect could reduce the occurrence of childhood-onset psychopathology by more than 50% (Kessler et al., 2010).

The Theory of Latent Vulnerability

Despite the abundance of evidence linking early adversity with negative outcome, there is a relative paucity of knowledge regarding the mechanisms through which increased psychiatric vulnerability becomes instantiated. The theory of latent vulnerability (McCory & Viding, 2015; McCory, Gerin, & Viding, 2017) offers a systems-level approach that places emphasis on the neurocognitive mechanisms that link early adversity to future psychopathology. According to this account, childhood maltreatment leads to alterations in several neurobiological and cognitive systems, which are understood as developmental recalibrations to abusive and neglectful environments. Such changes are “latent” insofar as they do not inevitably result in a manifest psychological disorder and can even confer short-term functional advantages within early adverse environments. Yet, in the long-term, they come at a cost as they heighten psychiatric risk.

The majority of neuroimaging studies of childhood abuse and neglect have focused on (a) perceptual/attentional pro-
cesses, such as threat detection (e.g., Durnlovski et al., 2012, 2013; McCrory et al., 2011, 2013; Tottenham et al., 2011); (b) low-level executive functions, especially response inhibition (Elton et al., 2014; Lim et al., 2015; Mueller et al., 2010); and, more recently, (c) affect regulation (McLaughlin, Pepperill, Gold, Alves, & Sheridan, 2015; Paetz et al., 2014, 2016) and (d) reward processing (Dennison et al., 2016; Goff et al., 2013; Hanson, Harrit, & Williamson, 2015; Mehta et al., 2010). A number of consistent findings have emerged from these studies (see McCrory et al., 2017, for a recent review).

First, in relation to threat processing, several studies have reported increased neural response (particularly in the amygdala) to threat-related cues, such as angry faces. Second, studies of explicit affect regulation and executive control have reported a pattern of increased activation in medial frontal regions, including the superior frontal gyrus and cingulate cortex in individuals who have experienced maltreatment. By contrast, during more implicit regulatory processes, maltreatment experience has typically been associated with a pattern of reduced activation in a widespread frontolimbic network. Third, studies of reward processing have generally reported reduced activation in subcortical reward-related areas, in particular the striatum. These alterations in neural function are consistent with those reported in studies of individuals presenting with common psychiatric disorders (such as anxiety and depression) and may therefore represent markers of latent vulnerability to future psychopathology (McCrory et al., 2017; McCrory & Vidang, 2015).

However, in addition to these domains of functioning, it is possible that the neurocognitive processes implicated in how an individual learns from his or her experiences, may also be compromised in children exposed to maltreatment given their frequent exposure to chaotic and unpredictable environments (Cyr et al., 2010; Solomon & George, 1999). In recent years, a series of studies have documented how altered reinforcement-based decision making is implicated in a number of disorders associated with maltreatment, such as anxiety and depression (Eishel & Roiser, 2010; Hartley & Phelps, 2012). This suggests that altered reinforcement-based decision making may index latent vulnerability to psychiatric disorder following childhood maltreatment experience.

Reinforcement-Based Decision Making and Maltreatment

Evidence from neurodevelopmental sciences, psycholinguistics and even cognitive developmental robotics, suggest that our ability to detect patterns in the environment (i.e., contingency detection) is crucial for the acquisition of a number of skills, ranging from basic perceptual abilities to higher order cognitive functions, including language, affect regulation, and relevant to this study, reinforcement-based decision making (Ellis, 2006; Nagaï, Asada, & Hosoda, 2006; Reeb-Sutherland, Levitt, & Fox, 2012). Despite preliminary findings linking maltreatment to neural changes in the context of reward processing (Dillon et al., 2009; Hanson et al., 2015) and outcome monitoring (Lim et al., 2015), no prior study has investigated alterations in the neural systems mediating reinforcement-based decision making and its computational components in maltreated individuals.

During normal development, our innate ability for contingency detection is fostered through sensitive caretaking. However, maltreatment experiences disrupt the species normative learning environment as the child is exposed to extreme and erratic parental affective reactions and/or a paucity or inconsistency in the availability of primary reinforcers. In the case of physical maltreatment, punishments are unpredictable and extreme, compromising contingency learning by biasing attention toward negative cues (e.g., McCrory et al., 2011; Shackman, Shackman, & Pollak, 2007). This in turn may limit the resources available (allostatic load) for the development of a range of normative cognitive functions (Rogosch, Dackis, & Cicchetti, 2011), and reduce the opportunities necessary for learning by inducing a more avoidant exploratory style (Cicchetti & Doyle, 2016; Cicchetti, Rogosch, & Toth, 2006; Cyr et al., 2010). In the case of physical and emotional neglect, which represent common forms of maltreatment, basic reinforcers, such as food and emotional warmth, are not only less frequent but also less predictable (Gilbert et al., 2009; Radford, Corral, Bradley, & Fisher, 2011). These conditions are likely to contribute to the formation of abnormal expectancies representation of stimulus-outcome (S-O) and responses-outcome (R-O) associations. In other words, it is possible that maltreatment experience leads to alterations in the neurocomputational processes critical for reinforcement-based decision making.

Neurocomputational Processes of Reinforcement-Based Decision Making

Behavioral and computational neuroimaging research suggests that at least two processes underlie successful reinforcement-based decision making: (a) expected value (EV) representation (i.e., the reinforcement expectancies associated with a stimulus or action) and (b) prediction error (PE, i.e., the ability to detect the difference between the actual from the expected outcome associated with a stimulus or action; Clithero & Rangel, 2013; O’Doherty, Hampton, & Kim, 2007; Rescorla & Wagner, 1972).

These two components are highly interdependent: PE signals are thought to alter the EV associated with a stimulus or action while EV representation is directly related to the strength of the PE response to a given outcome. Evidence from computational model-based studies and animal models have shown that these two processes engage overlapping frontostriatal circuitry with its central nodes in the dorsal striatum (DS) and ventral striatum (VS) and the orbitofrontal cortex (OFC; Clithero & Rangel, 2013; O’Doherty, 2011; O’Doherty et al., 2004; Tanaka et al., 2016; Valentin & O’Doherty, 2009). Other brain areas implicated in PE and EV signaling include the globus pallidus, thalamus, and medial and lateral temporal regions, such as the hippocampus.
insula, and superior temporal gyrus (Amiez et al., 2013; Bach et al., 2014; Glümers, 2011; Zénón et al., 2016). Nodes associated with the salience network have consistently been implicated during PE signaling, including the amygdala, insula, and dorsal portions of the cingulate gyrus (Amiez et al., 2013; Garrison, Eideniz, & Done, 2013; Kosson et al., 2006).

**Reinforcement-Based Decision Making and Psychiatric Disorder**

Extant neuroimaging and behavioral data suggest that alterations in the mechanisms underlying reinforcement-based learning and decision making may contribute to the emergence and maintenance of psychiatric conditions commonly associated with childhood maltreatment, such as anxiety, depression, conduct problems, and substance abuse (Eshel & Roiser, 2010; Grant, Costoroggi, & London, 2000; Hartley & Phelps, 2012; Masters, Vanderschuren, & Schutte, 2012; Schoenbaum, Roesch, & Stalnaker, 2006). Neuroimaging studies of these disorders have typically reported a pattern of decreased neural activation during reinforcement expectancies representation and outcome anticipation in the orbitofrontal circuitry (Benson, Guyer, Nelson, Pine, & Ernst, 2014; Figner et al., 2011; Forbes et al., 2006, 2009; Galván & Peris, 2014; May, Stewart, Migliorini, Tapert, & Paulus, 2013; Schoenbaum et al., 2006; Smoski et al., 2009; Smoski, Rittenberg, & Dichter, 2011; Stringaris et al., 2015). Reduced neural response in the striatum (especially the caudate), OFC, and the insula have also been reported in recent computational functional magnetic resonance imaging (fMRI) studies of EV and PE representation in anxiety, conduct disorder, and addiction (White et al., 2013, 2014, 2017; White, Tyler, Botkin, et al., 2016; White, Tyler, Erway, et al., 2016). This is in line with animal models of early adversity (e.g., Pan, Porcella, & Gessa, 2000) and with neuroimaging data of reward processing with institutionalized individuals (Mehta et al., 2010).

**Hypotheses**

In the current study, we examined reinforcement-based decision making, and its neurocomputational correlates, as a potential candidate system for indexing latent vulnerability among maltreated individuals. In order to investigate maltreatment-related changes in EV and PE neural signaling, children (10–15 years) with and without documented abuse and neglect were presented in the scanner with a probabilistic passive avoidance task. This task has been used previously with individuals of similar age ranges, as well as with patients with psychiatric condition associated with maltreatment (White et al., 2013, 2017). Briefly, participants were required to learn what stimuli were associated with a higher probability of winning or losing points, and respond to (actively approach) the reward stimuli and withhold the response to (passively avoid) the punishment stimuli.

A model-based fMRI analytic method was implemented to assess the computational processes underlying EV and PE representations. Such an approach offers the opportunity to generate regressors of interest that go beyond stimulus inputs and behavioral responses. This can help uncover hidden functions and variables by showing how the brain implements a particular process (O’Doherty et al., 2007). A model-based approach allowed us to detect with greater sensitivity the neural signal underlying the computations necessary for EV and PE representation.

We hypothesized that for both approached and avoided stimuli, children with maltreatment experience would show reduced modulation of blood oxygen level dependent (BOLD) responses by EV in four regions of interest (ROIs): the DS and VS striatum, the medial OFC (mOFC), and the lateral OFC (lOFC). As noted earlier, this is in line with evidence from studies of reinforcement expectancies representation in those psychiatric disorders associated with maltreatment, with the animal literature of early adversity, and with some preliminary evidence from studies of extreme neglect (e.g., Forbes et al., 2009; Mehta et al., 2010; Smoski et al., 2011; Stringaris et al., 2015; White et al., 2013, 2017). In addition, consistent with substantial evidence of increased neural activation to negative stimuli and negative feedback among abused and neglected children (e.g., Lim et al., 2015; McCroby et al., 2011; McLaughlin et al., 2015), we hypothesized that children with maltreatment experience would show increased modulation of BOLD responses by PE during punishment feedback in four ROIs: the amygdala, the insula, and the anterior cingulate cortex (ACC) and midcingulate cortex (MCC).

In addition, we conducted a number of exploratory analyses related to PE modulated brain response for reward feedback. Extant data from animal models of early adversity and from studies of psychiatric conditions associated with maltreatment provide conflicting findings (Anisman & Matheson, 2005; Dillon et al., 2009; Hanson et al., 2015). Some studies suggest no maltreatment-related nor psychiatric-related changes in consummatory behavior, positive outcomes processing, and their related neural signaling in striatal and orbitofrontal regions (Dillon et al., 2009; Mehta et al., 2019; Pryce, Dettling, Spengler, Schnell, & Field, 2004; Stringaris et al., 2015; Uhl et al., 2015). In contrast, other studies report a pattern of decreased neural signaling as well as reduced behavioral response to receiving reward (Gotlib et al., 2010; Hanson et al., 2015; Kalinichev, Easterling, & Holtzman, 2001; Matthews & Robbins, 2003; Wilher, 2005).

**Methods**

**Participants**

Forty-one children aged 10–15 years participated in this study. 20 with a documented experience of maltreatment (MT group) recruited via a Social Services Department and 21 with no prior Social Service contact recruited via
schools/advertisements (NMT group). Exclusion criteria included the presence of a pervasive developmental disorder, neurological abnormalities, standard MRI contraindications, and an IQ below 70. Two participants from each group were excluded from the final analyses due to movement artifacts leaving a final sample of 37 children (MT group, N = 18; NMT group N = 19). Consent was obtained from the child’s legal guardian, and assent to participate was obtained from all children. Procedures were approved by University College London Research Ethics Committee (0895/002). Participant details of the final sample are reported in Table 1.

Measures

Malformation history. History and severity of abuse type (neglect, emotional, sexual, and physical abuse and intimate partner violence) was provided by the child’s social worker or the adoptive parent (based on the basis of Social Services reports). Severity of each abuse type was rated on a scale from 0 (not present) to 4 (Table 2) in line with an established measure of maltreatment (Kauffman, Jones, Stieglitz, Vitulano, & Manarino, 1994). In addition, age of onset and duration of maltreatment by subtype was estimated on the basis of the file information.

Psychiatric symptomatology. The Trauma Symptom Checklist for Children (TSCC), a self-report measure of affective and trauma-related symptomatology was administered to all participants (Table 1; Briere, 1996). The Strengths and Difficulties Questionnaire (SDQ) was completed by parents or caregiver to assess general functioning (Table 1; Goodman, 1997).

Cognitive ability. Cognitive functioning was assessed using two subscales of the Wechsler Abbreviated Scales of Intelligence (Wechsler, 1997).

Table 1. Demographics and psychiatric symptomatology of MT and NMT participants included in the functional magnetic resonance analyses

<table>
<thead>
<tr>
<th>Measures</th>
<th>MT (n = 18)</th>
<th>NMT (n = 19)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Gender (female)</td>
<td>10 (56%)</td>
<td>13 (68%)</td>
<td>.42</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>.37</td>
</tr>
<tr>
<td>White &amp; White mixed</td>
<td>15 (83%)</td>
<td>13 (68%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (11%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1 (6%)</td>
<td>2 (11%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
<td></td>
</tr>
<tr>
<td>SES education level (beyond secondary)</td>
<td>9 (50%)</td>
<td>13 (60%)</td>
<td>.26</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>13.01</td>
<td>13.15</td>
<td>.75</td>
</tr>
<tr>
<td>SDW-IQ</td>
<td>108.06</td>
<td>108.84</td>
<td>.87</td>
</tr>
<tr>
<td>TSCC Anxiety</td>
<td>43.28</td>
<td>43.47</td>
<td>.94</td>
</tr>
<tr>
<td>TSCC Depression</td>
<td>45.80</td>
<td>43.05</td>
<td>.42</td>
</tr>
<tr>
<td>TSCC PTSD</td>
<td>43.61</td>
<td>42.16</td>
<td>.67</td>
</tr>
<tr>
<td>Met clinical threshold</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>SDQ-P total score</td>
<td>11.50</td>
<td>5.42</td>
<td>.01</td>
</tr>
<tr>
<td>Emotional symptoms</td>
<td>2.61</td>
<td>1.53</td>
<td>.11</td>
</tr>
<tr>
<td>Conduct problem</td>
<td>2.72</td>
<td>0.84</td>
<td>.17</td>
</tr>
<tr>
<td>Hyperactivity/Inattention</td>
<td>4.28</td>
<td>2.00</td>
<td>.009</td>
</tr>
<tr>
<td>Peer relationship</td>
<td>1.89</td>
<td>1.05</td>
<td>.13</td>
</tr>
<tr>
<td>Prosocial behavior</td>
<td>7.61</td>
<td>8.27</td>
<td>.42</td>
</tr>
</tbody>
</table>

Note: MT, maltreated group; NMT, nonmaltreated group; SES, socioeconomic status; WASH-IQ, Wechsler Abbreviated Scales of Intelligence, two IQ subscales (Wechsler, 1999); TSCC, Trauma Symptom Checklist for Children; SDQ-P, Strength and Difficulties Questionnaire—Parent report.

*Completed by caretaker.

* Composite score of self-report and parent rating of Puberty Development Scale.

**Three MT and six non-MT participants met the threshold for underresponsiveness. By excluding those individuals, the scores did not differ across the two groups.

*Missing data for 1 MT.

*p < .05.
Appendix 2

Table 2. Abuse subtype frequency, severity, estimated onset age and duration (years) in the MT group

<table>
<thead>
<tr>
<th>Abuse Subtype</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical abuse (n = 3)</td>
<td>1.02</td>
<td>1.78</td>
</tr>
<tr>
<td>Severity (0–4)</td>
<td>0.33</td>
<td>0.58</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>6.9</td>
<td>5.12</td>
</tr>
<tr>
<td>Mean duration</td>
<td>3.40</td>
<td>1.12</td>
</tr>
<tr>
<td>Neglect (n = 15)</td>
<td>1.22</td>
<td>3.57</td>
</tr>
<tr>
<td>Severity (0–4)</td>
<td>5.39</td>
<td>4.52</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>2.00</td>
<td>—</td>
</tr>
<tr>
<td>Mean duration</td>
<td>0.72</td>
<td>—</td>
</tr>
<tr>
<td>Sexual abuse (n = 1)</td>
<td>5.00</td>
<td>—</td>
</tr>
<tr>
<td>Severity (0–4)</td>
<td>0.50</td>
<td>—</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>2.71</td>
<td>0.77</td>
</tr>
<tr>
<td>Mean duration</td>
<td>1.51</td>
<td>2.87</td>
</tr>
<tr>
<td>Emotional abuse (n = 17)</td>
<td>2.31</td>
<td>1.12</td>
</tr>
<tr>
<td>Severity (0–4)</td>
<td>6.01</td>
<td>4.27</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>1.64</td>
<td>1.12</td>
</tr>
<tr>
<td>Mean duration</td>
<td>3.29</td>
<td>—</td>
</tr>
<tr>
<td>Domestic violence (n = 11)</td>
<td>4.28</td>
<td>3.24</td>
</tr>
</tbody>
</table>

The stimulus presentation was followed by a randomly jittered fixation cross (0–4000 ms). During the feedback phase one of four outcomes was presented for 1500 ms: “you win 50 points,” “you win 10 points,” “you lose 50 points,” or “you lose 10 points.” The feedback was probabilistic as the reward and punishment stimuli led to, respectively, gains and losses 70% of the time. Moreover, one reward stimulus was associated with a higher winning rate (i.e., a maximum gain of 185 points every 10 trials) while the other stimulus had a lower winning rate (a maximum gain of 70 points every 10 trials). Similarly, one punishment stimulus led to worst outcomes (a maximum loss of 185 points every 10 trials) compared to the other (a maximum loss of 70 points over 10 trials). The participants could only win or lose points if a stimulus was approached. Thus, avoidance responses led to no feedback presentation and a fixation cross was presented instead (also for 1500 ms). The feedback phase was followed by another randomly jittered fixation cross (0–4000 ms).

The behavioral data was used to model the EV and PE for each trial for each participant based on the Rescorl–Wagner model of conditioning (O’Doherty et al., 2007; Rescorla & Wagner, 1972). The EV for the first trial of each object was set to 0 and was then updated using the following formula:

\[ \text{EV}_t = \text{EV}_{t-1} + (\alpha \times \text{PE}_{t-1}) \]

In this formula the EV of the current trial \(t\) equaled the EV of the previous trial \((t – 1)\) plus the PE of the previous trial multiplied by the learning rate \(\alpha\). The learning rate was set to 0.354, calculated by taking the average across all individually estimated learning rates via a model-fitting simulation (see the online-only supplementary material for a description of the model-fitting procedure). The PE for the current trial equaled the feedback \(F\) of the current trial minus the EV

Behavioral fMRI paradigm. A probabilistic passive avoidance task was administered in the scanner (Figure 1; White et al., 2013, 2017). Participants were required to learn what stimuli were associated with a higher chance of winning or losing points. The task consisted of two phases: a decision phase and a feedback phase. During the decision-phase participants could either (a) actively approach (by a button press) or avoid (by withholding a response) one of four stimuli that were presented for 1500 ms. Each stimulus was presented 14 times in total (creating a total of 56 trials),

![Figure 1](image-url)
of the current trial: \( PE_{i0} = F_{i0} - EV_{i0} \). These parameters were then used for the model-based fMRI analyses (described below).

**fMRI data acquisition.** All data were acquired on a 1.5 Tesla Siemens Avanto (Siemens Medical Systems, Erlangen, Germany) MRI scanner with a 32-channel head coil during 1 run of approximately 7 min. A total of 127 T2-weighted echo-planar volumes were acquired, covering the whole brain with the following acquisition parameters: slice thickness = 2 mm; repetition time = 85 ms; echo time = 50 ms; field of view = 192 mm \( \times \) 192 mm; 35 slices per volume, gap between slices = 1 mm; flip angle = 90°. A high-resolution, three-dimensional T1-weighted structural scan was acquired with a magnetization prepared rapid gradient echo sequence. Imaging parameters were as follows: 176 slices; slice thickness = 1 mm; gap between slices = 0.5 mm; echo time = 27.30 ms; repetition time = 3.57 ms; field of view = 256 mm; matrix size = 256\(^2\); voxel size = 1 mm\(^3\).

**Data analysis**

**Behavioral analyses.** Behavioral performance on the task was assessed in relation to the number of omission errors (i.e., the number of trials in which reward stimuli were avoided) and the number of commission errors (i.e., the number of trials in which punishment stimuli were approached) as well as the total number of errors (i.e., the sum of omission and commission errors). In addition, to test the validity of the behavioral model, we examined whether the EV estimates for each trial predicted behavior (i.e., approach and avoidance responses).

**fMRI analyses.** Data analyses were conducted using the software package SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) implemented in Matlab 2015a (MathWorks Inc.).

**Image preprocessing.** After discarding the first three volumes of each run to allow for T1 equilibration effects, each participant’s scans were realigned to the first image. Four participants (two in each group) were excluded from the final analyses due to more than 10% of the images being corrupted by head motion greater than 1.5 mm. This left a final sample of 19 NMT and 18 MT (N = 37). Data were normalized into MNI space using deformation fields from T1 scan segmentation at a voxel size of 3 mm\(^3\). The resulting images were smoothed with a 6-mm Gaussian filter and high-pass filtered at 128 Hz.

**First-level analysis.** Fixed-effects statistics for each individual were calculated by convolving the canonical hemodynamic response function with the box-car functions modeling the four conditions: stimulus approached, stimulus avoided, reward received, and punishment received. To reduce movement-related artifacts, we included the six motion parameters as regressors and an additional regressor to model images that were corrupted due to head motion >1.5 mm and were replaced by interpolations of adjacent images (<10% of participant’s data for 9 NMT and 5 MT; no difference between groups, \( p = .22 \)). Furthermore, linear polynomial expansion was applied to the percent signal change at each voxel and time point using the EV and PE estimates as parametric modulators during, respectively, the decision phase and the feedback phase.

**Second-level analysis.** Group analyses were conducted using a series of independent samples \( t \) tests by entering the individual statistical parametric maps containing the parameter estimates of the four conditions as fixed effects and an additional “subject factor” for random effects. For the decision phase, activation in the NMT group was compared to the activation in the MT individuals for the approached stimuli modulated by the EV estimates and the avoided stimuli modulated by the EV estimates. For the feedback phase, activation in the NMT group was compared to the activation in the MT individuals in relation to the punishment feedback modulated by the PE value, and exploratory analyses were also conducted to examine the reward feedback modulated by the PE value.

Given our a priori hypotheses, small-volume corrected ROI analyses (thresholded at \( p < .05 \) corrected for family-wise error [FWE]) were performed, on the decision phase data, on the DS, VS, mOFC, and IOFC. Masks for the mOFC and IOFC were taken from the AAL atlas (WFU PickAtlas). The VS and DS masks were created based on the findings by Martinez et al. (2003) on the functional subdivisions of the striatum. For the punishment feedback condition, small volume-corrected ROI analyses (thresholded at \( p < .05 \), corrected for FWE) were performed in the amygdala, insula, ACC, and MCC. Masks for these regions were also taken from the AAL atlas (WFU PickAtlas).

For completeness, whole-brain analyses were also conducted, using Monte Carlo Simulation (3D ClusterSim; Ward, 2000) correcting for multiple comparisons. Cluster-size corrected results are reported (voxelwise \( p < .005 \), \( ke = 75 \)) corresponding to \( p = .05 \) FWE corrected.

**Results**

**Behavioral results**

**Demographics and symptomatology.** The MT and NMT groups did not statistically differ in age, gender, pubertal status, ethnicity, socioeconomic status, intelligence (IQ), and affective symptomatology (i.e., depression, anxiety, and posttraumatic stress disorder; Table 1). The SDQ revealed difference among the two groups in overall functioning, and in relation to the conduct and hyperactivity scales.

**Behavioral performance.** The MT and NMT groups did not differ significantly in task performance at the behavioral level. In particular, they did not differ in relation to number
Appendix 2

of total (MT $M = 23.22$, $SD = 8.39$; NMT $M = 23.42$, $SD = 6.89$; $t = 0.08$, $df = 35$, $p = .94$), omission (MT $M = 9.89$, $SD = 4.73$; NMT $M = 9.39$, $SD = 4.65$; $t = .33$, $df = 35$, $p = .75$), and commission errors (MT $M = 13.83$, $SD = 5.65$; NMT $M = 13.53$, $SD = 5.47$; $t = -.017$, $df = 35$, $p = .87$).

Model validity. To test the validity of the computational model, we examined the extent to which the estimated EV predicted participant’s approach and avoidance responses. Consistent with the model, there was a significant relationship between predicted and observed behavior; average correlation: $r = .23$; one sample $t$ test (null $r = 0$), $t = 4.59$, $df = 36$, $p < .001$. Moreover, the model was equally predictive of behavior across groups ($r = -.015$, $df = 35$, $p = .89$).

fMRI results

Main effects in the nonmaltreated group. Whole-brain main effect analyses were performed within the NMT group in order to ensure that the four conditions (i.e., approach trials, avoidance trials, positive feedback, and negative feedback) elicited activation patterns that were comparable to previous studies. As expected, the approach and avoidance conditions activated a network that has been previously linked with EV representation and outcome expectation (see online-only supplementary Table S.1). Similarly (although at a more lenient cluster threshold), the punishment and reward feedbacks elicited brain activity in areas associated with PE signaling (see online-only supplementary Table S.2).

Decision phase activation modulated by EV. In line with our hypotheses, the MT group showed reduced modulation of BOLD activity in the DS (in particular in the caudate nucleus), the mOFC, and the IOFC as a function of EV when choosing to approach a stimulus (Table 3, Figure 2). However, contrary to our hypotheses, no statistically different activation was found in the VS (Table 3, Figure 2).

When choosing to avoid a stimulus, the MT group showed reduced modulation of BOLD activity as a function of EV in all four ROIs (Table 3, Figure 3). Unexpectedly, the MT group also showed a pattern of increased bilateral modulation as a function of EV in the putamen (DS) when choosing to avoid a stimulus (Table 3).

Findings from the whole-brain analyses (Table 4) were consistent with our ROI analyses, indicating a widespread pattern of reduced EV signaling (for both approach and avoidance responses) and also implicated other brain regions including the globus pallidus and temporal regions, such as the insula and the hippocampus (which have in some previous studies been implicated in the representation of reinforcement expectancies).

The whole-brain data revealed that the MT group showed a pattern of increased activation in frontodorsal regions during EV processing for both approached and avoided stimuli (Table 4). In particular, the dorsomedial and dorsolateral prefrontal cortex (dmPFC, dIPFC; e.g., Brodmann area 9) and the dACC and MCC were implicated. These unexpected findings were interrogated further in post hoc analyses reported below.

Feedback-phase activation modulated by PE signaling. No group difference in BOLD activity as a function of PE was found during punishment feedback in the four ROIs (i.e., amygdala, insula, dACC, and MCC; Table 3). However, MCC activity modulated by PE fell just above traditional significance threshold level ($p = .052$, FWE). For completeness, whole-brain analyses were also conducted (Table 4). Increased BOLD response modulated by PE was found among MT individuals in regions associated with PE processing, such as the MCC (which approached significance in the ROI analyses), the thalamus, and the superior temporal gyrus (Table 4; Amiez et al., 2013; Garrison et al., 2013). During reward feedback, no difference was found between the two groups (Table 4).

Post hoc analyses

Three sets of post hoc analyses were conducted. First, we tested whether the pattern of altered neural activation found among maltreated individuals during EV representation (Table 3) was associated with maltreatment duration and severity. These correlational analyses indicated that within the MT group, maltreatment duration was associated with reduced BOLD activity by EV in the mOFC during approach trials ($r = -.46$, $p = .03$).

Second, we examined whether reduced activation in orbitostriatal regions during EV representation in the MT group (Table 3) was associated with increased psychiatric symptomatology. Previous clinical computational fMRI studies that used the same passive avoidance paradigm implemented here have found that patients with anxiety and with conduct disorder show a highly comparable neural profile to the MT group in this study during EV processing (White et al., 2013, 2017; White, Tyler, Erway, et al., 2016). These clinical studies have consistently reported a pattern of reduced activation, modulated by EV, in the DS (in particular the caudate) and in the medial and lateral orbitofrontal cortices (White et al., 2013, 2017; White, Tyler, Erway, et al., 2016). Thus, our correlational analyses focused on these two areas (i.e., OFC and DS). Measures of anxiety (using the TSCC anxiety subscale and the SDQ emotional problems subscale) and conduct problems (using the SDQ conduct disorder subscale) were correlated with the peak activation in the IOFC, mOFC, and DS (caudate) during EV processing within the MT group. Consistent with prior studies of EV representation with anxiety patients (White et al., 2017), reduced EV neural signaling during approach trials in the IOFC ($r = -.60$, $p = .004$) and in the DS ($r = -.41$, $p = .04$) was associated with self-reported (TSCC) anxiety symptoms levels within the MT group. Moreover, we found a significant correlation between parental-reported measures of emotional problems on the SDQ ($r = -.41$, $p = .04$) and IOFC activation during avoidance trials.
Table 3. Regions of interest demonstrating group-level differential blood oxygen level dependent responses during the task

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*Note:* The region of interest analyses were corrected at *p < .05* for family-wise error and at *p < .005* for the initial threshold. R/L, right/left; kw, cluster extent; NMT, nonmaltreated group; MT, maltreated group; DS, dorsal striatum; VS, ventral striatum; mOFC, medial orbitofrontal cortex; IOFC, lateral orbitofrontal cortex.

Finally, post hoc analyses were performed to interrogate the unexpected whole-brain finding of increased activity, within the MT group, in a large frontodorsal cluster during EV representation during both approach and avoidance (Table 4). One interpretation for the observed increased EV neural signaling among MT individuals in frontodorsal regions is that it represents an adaptive response, compensating for reduced signaling in areas traditionally associated with EV computations (such as the DS, VS, mOFC, IOFC, insula, and hippocampus). In line with this post hoc hypothesis, we found that MT individuals’ total error rate was negatively correlated with frontodorsal activation modulated by EV during
Figure 2. (Color online) Peak activation in each region of interest modulated by expected value during approach responses. Error bars represent 95% confidence intervals. *p < .05 corrected for family-wise error. Initial threshold p < .05 uncorrected. DS, dorsal striatum; mOFC, medial orbital frontal cortex; BOLD, blood oxygen level dependent; MT, maltreatment; VS, ventral striatum; IOFC, lateral orbitofrontal cortex.
Figure 3. (Color online) Peak activation in each region of interest modulated by expected value during avoidance responses. Error bars represent 95% confidence intervals. *p < .05 family-wise error. Initial threshold p < .05 uncorrected. DS, dorsal striatum; mOFC, medial orbital frontal cortex; BOLD, blood oxygen level dependent; MT, maltreatment; VS, ventral striatum; IOFC, lateral orbitofrontal cortex.
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| Note: | Whole brain analyses corrected/thresholded at kE = 75, p < .005 (equivalent to p < .05 family-wise error). R/L, right/left; kE, cluster extent; NMT, non-maltreated group; MT, maltreated group; DS, dorsal striatum; VS, ventral striatum; mOF C, medial orbitofrontal cortex; IOFC, lateral orbitofrontal cortex; dlPFC, dorsolateral prefrontal cortex; BA9, Brodmann area 9; MTG, middle temporal gyrus; STG, superior temporal gyrus; MTL, medial temporal lobe; dACC, dorsal anterior cingulate cortex; MCC, middle cingulate cortex; PCC, posterior cingulate cortex. |

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both approach ($r = -0.45, p = .03$) and avoidance ($r = -0.41, p < .05$). This suggests that the degree of engagement of this frontodorsal network during EV processing contributes to improved behavioral performance on the task. To explore this effect further, the total error rate was then divided into omission and commission error rates. It was found that while the BOLD response by EV in this frontodorsal cluster during both approach and avoidance trials was significantly correlated with omission errors ($r = -0.64, p = .002$ and $r = -0.43, p = .04$, respectively), that was not the case for the commission errors ($r = -0.15, p = .28$ and $r = -0.26, p = .15$, respectively).

**Discussion**

To our knowledge, this is the first study to investigate the extent to which children with documented experiences of childhood maltreatment show alterations in the neural systems engaged with specific computations of reinforcement-based decision making. We employed a probabilistic passive avoidance task, in combination with a model-based fMRI analytic approach, in order to assess neural responses associated with EV representation and PE processing for reward and punishment cues. At the behavioral level, the children who had experienced maltreatment (MT group) did not differ from a group of nonmaltreated (NMT) peers. By contrast, at the neural level, the MT group differed from their peers in three main ways. First, the MT group demonstrated a pattern of reduced activity modulated by EV in a network commonly associated with reinforcement expectancies representation, including the orbitostriatal circuitry. Second, during losses, the MT compared to the NMT group showed increased PE signaling in frontal and temporal regions, including the mid-cingulate gyrus and the superior temporal gyrus. Third, the MT group showed increased activity in the putamen and in frontodorsal regions during EV representation.

**EV modulated neural response**

*Reduced EV modulated neural response in corticostriatal circuitry.* As predicted, maltreatment experience was associated with reduced BOLD response by EV in both approach and avoidance trials in the mOFC and the IOFC, and in the DS, especially in the caudate nucleus. Reduced response in the VS was also observed, but only in the avoidance trials. Our whole-brain analyses were consistent with these findings, and also implicated the globus pallidus, the subthalamic nucleus, insula, and the hippocampus. These regions have been previously shown to be involved in reinforcement expectancy representation in typical individuals (e.g., Bach et al., 2014; Glimcher, 2011; Kosson et al., 2006; Zénon et al., 2016); reduced neural response in these same regions has been reported in studies of psychiatric disorders associated with maltreatment experience, including anxiety, conduct disorder, and depression (Gotlib et al., 2010; Ubl et al., 2015; White et al., 2013, 2017). This pattern of reduced neural response is thought to reflect impairments in the precision of EV representation (White et al., 2013, 2017). As such, the findings of the current study may reflect alterations in reinforcement-based decision making that may in turn confer increased latent vulnerability to psychiatric disorder. Our post hoc analyses, demonstrating that reduced activation in the caudate and the OFC was related to higher levels of anxiety symptomatology in the MT group, are consistent with this hypothesis. It is also noteworthy that post hoc analyses indicated a dose-dependent negative association between maltreatment duration and degree of activation in these areas, suggesting that greater maltreatment exposure was associated with more marked neurocognitive alterations.

*Increased EV modulated neural response in the putamen.* During EV processing for avoided stimuli, the MT group showed an unexpected pattern of increased activation relative to the NMT group in the putamen. This may initially appear surprising, given that the MT group also showed a pattern of reduced EV-related signaling in the caudate. However, studies of disorders associated with early adversity, such as depression (see Zhang, Chang, Guo, Zhang, & Wang, 2013, for a meta-analysis) and anxiety (e.g., White et al., 2017), suggest that the caudate (but not the putamen) is less active during outcome anticipation. Moreover, data from a recent study investigating affect processing and regulation reported that children who have experienced maltreatment also show greater engagement of the putamen (but not the caudate) to negative cues (McLaughlin et al., 2015).

The putamen and the caudate are connected to different brain regions and are understood to perform different functions (Cohen & Frank, 2009; Grahn, Parkinson, & Owen, 2008). The caudate is thought to be crucial for EV representation, including R-O and S-O associations, flexible cognition, and it underpins goal-directed behavior (Grahn, Parkinson, & Owen, 2009). By contrast, outcome expectancy is not evaluated in the putamen. Rather, this region has been implicated in less complex and less flexible types of behavioral and cognitive representations, such as habit learning (Devan, Hong, & McDonald, 2011; Grahn et al., 2008). It has been suggested that the putamen may be recruited during the initial phases of reinforcement-based learning, with the caudate becoming more dominant during later stages of instrumental learning (Brovelli, Nazarian, Meunier, & Boussaud, 2011).

One possible explanation for the pattern of findings in the DS is that children with experience of maltreatment sustain activation of the putamen throughout the task, unlike their peers who progress to more flexible and complex reinforcement-based representations (indexed by their greater activation of the caudate and other regions involved in higher order EV processing). For maltreated individuals, it may be paramount and more adaptive to learn rapidly (at the expense of more flexible and complex EV processing) which elements in the environment are associated with punishment and should be avoided. The development of more flexible and higher order cognition in relation to reinforcement and con-
Appendix 2

Multidimensional, decision making, and latent vulnerability

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tingency learning to negative cues may be less optimal (or even counterproductive) in environments where behavioral responses must be quickly learned to avoid punishment. Future studies are required to investigate this hypothesis by parsing out early from later stages of reinforcement-based learning differences in MT and NMT individuals.

Increased EV modulated neural response in the dorsomedial and dorsolateral frontal cortex. Our whole-brain analyses revealed a pattern of increased activation in an extended dorsofrontal network that includes the dmPFC and dlPFC prefrontal cortex (especially Brodmann Area 9), the dorsal anterior cingulate cortex (dACC) and also the MCC, which was unexpected, but which is in line with studies investigating outcome anticipation among depressed children and adolescents (Forbes et al., 2006, 2009). Recent neuroimaging studies of maltreatment have found that despite no differences in task performance, MT children show increased activation in dorsomedial and dorsolateral prefrontal regions while performing different cognitive functions (e.g., explicit affect regulation; McLaughlin et al., 2015) and response inhibition (Lim et al., 2015). It has been proposed that greater engagement of these regions involved in effortful control may represent a compensatory mechanism as more effort may be required for comparable task performance by children who have experienced maltreatment (McLaughlin et al., 2015).

In the context of this study, the engagement of this dorsofrontal network may similarly represent an adaptive response, compensating for the reduced signaling in brain areas traditionally associated with EV representation (such as the DS, VS, mOFC, IFOC, insula, and hippocampus). In line with this potential explanation, our post hoc correlational analyses indicated that, among maltreated individuals, EV modulated activation in this dorsofrontal network was associated with improved task performance, and in particular with improvement in omission (but not commission) error rate. On this basis, we speculate that a tendency for an avoidant response in the MT group (as indexed by increased neural response to punishment) is attenuated by the increased activity found in the frontodorsal region during EV processing. If this is the case, it suggests that the comparable behavioral performance of the groups may be driven by different neurocomputational processes.

PE-modulated neural response

PE for reward feedback. No group difference was found during PE-modulated brain activation to reward. This is in line with a large set of studies that suggests that compensatory (unlike anticipatory) neurocognitive and behavioral processes are not implicated in disorders such as depression (Stringaris et al., 2015; Ubl et al., 2015), nor appear associated with early adverse experiences (Dillon et al., 2009; Mehta et al., 2010; Pryce et al., 2004).

PE for punishment feedback. As noted earlier, extant studies on threat-detection and salience processing among maltreated children and adults have found a consistent pattern of increased activation in several regions implicated in the detection of negative cues (e.g., Damasio et al., 2012; McCrory et al., 2011). On this basis, we also expected an increased pattern of PE signaling during punishment feedback in the MT group in four regions: the amygdala, insula, ACC, and MCC. However, no group differences were found in these ROIs. In contrast, the whole-brain data revealed a widespread pattern of increased activation in frontal, temporal, and subcortical areas, including the MCC, the superior temporal gyrus, the postcentral gyrus, and the thalamus. This network has been extensively implicated in PE error signaling in normative samples (Amiez et al., 2013; Garrison et al., 2013). In addition, these findings are in line with the data from the only study that has investigated (noncomputationally) PE in maltreated children (Lim et al., 2015). Maltreatment-related alterations in PE processing for negative information may therefore be system specific insofar as they do not overlap with the brain network that is devoted to salience detection and threat processing (e.g., insula and amygdala). Future studies should test this hypothesis by directly comparing PE and threat-detection signaling in MT and NMT individuals.

Childhood maltreatment, decision making, and latent vulnerability

As discussed above, sensitive caregiving and appropriate parental scaffolding plays an important role in the normative development of contingency detection, which is a sine qua non for the acquisition of a number of skills and higher order cognitive functions, including reinforcement-based decision making (Ellis, 2006; Nagai et al., 2006; Reeb-Sutherland et al., 2012). However, this developmental learning process may be compromised by an impoverished and chaotic learning environment and by several other aspects associated with the maltreatment experience, such as unpredictable and severe forms of punishment.

It has been shown that an abusive environment can lead to the preferential diversion of attentional resources toward threat-related cues in the environment (McCrory et al., 2011; Pollak & Tolley-Schell, 2003; Pollak, Vardi, Putzker, Becherer, & Curtin, 2005). Early adverse experiences may also contribute to the misattribution of negative valence to social cues in the environment that are actually neutral and non-threatening, in line with a number of psychiatric presentations (Cooney, Atlas, Joormann, Eugène, & Gollib, 2006; Leppinen, Milders, Bell, Tierriere, & Hietanen, 2004). Negative attention and attribution biases may, in turn, contribute to the development of abnormal EV representation in several ways: (a) by diverting away the cognitive and attentional resources necessary for normal contingency-based learning (Rogosch et al., 2011); (b) by outweighing S-O and R-O associations in favor of negative information; or (c) by reducing the amount and quality of exploratory behavior, crucial for contingency learning and the development of normative EV
and PE representations (Cicchetti & Doyle, 2016; Cicchetti et al., 2006).

An alternative view is that physical and emotional neglect, common forms of childhood maltreatment (Gilbert et al., 2009; Radford et al., 2011), create aberrant environments that distort the development of flexible and contingency-based learning and context-appropriate higher order representations (e.g., Fonagy, Gergely, Jurist, & Target, 2004; Gergely & Watson, 1999), leading to widespread alterations in EV and PE neural signaling. It is known that these forms of neglect are characterized by environments were primary reinforcers (e.g., food) are less predictable and frequent, and where there is a lack of timely and sensitive positive affective communication and emotional reciprocity.

The ability to envisage the consequences and predict the outcomes associated with a given stimulus or action is crucial for our ability to orient, motivate, and flexibly guide behavior toward specifics goals and navigate the environment successfully (O’Doherty et al., 2004). However, abnormal EV representation can compromise this ability; leading to suboptimal decision making and maladaptive outcomes, as documented in a number of common psychiatric disorders (Eshel & Roi ser, 2010; Hartley & Phelps, 2012; Stringaris et al., 2015; Zhang et al., 2013). Therefore, the evidence presented here suggests that abnormalities in reinforcement-based decision making may represent a promising neurocognitive candidate system to index increased psychiatric risk among individuals who have experienced early adversity.

Limitations and conclusions

The current study has a number of limitations. First, this study has a relatively small sample size and the design is cross-sectional in nature. A longitudinal design and larger sample will be necessary to investigate whether maltreatment-related alterations found in reinforcement-based decision making are associated with future psychiatric vulnerability. A second limitation pertains to the design of the passive avoidance task employed here. Although a well-validated measure of reinforcement-based decision making used in a number of prior developmental studies of psychiatric groups, this measure does not allow the parsing of EV processing from motor-output responses during the approached trials. Future neuroimaging investigations, which require the approach (or avoidance) responses to be executed after stimulus presentation, would address this issue directly. Nevertheless, the model-based IMRI analytic approach implemented here allowed the estimated EVs (on a trial-by-trial and individual basis) to be convolved with the BOLD signal, facilitating the partialing out of the brain signal that was unrelated to the representation of reinforcement expectancies. Third, a recent study has shown that maltreatment exposure is more detrimental to the development of executive control functions when it occurs earlier (during infancy) than later in life (during childhood; Cowell, Cicchetti, Rogosch, & Toth, 2015). Executive control functions, including working memory, cognitive flexibility, and inhibitory control, are central to the computations that underlie reinforcement-based learning and decision making (e.g., Räderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). Therefore, an examination of the timing of maltreatment exposure may contribute to a more precise understanding of the neurocomputational mechanisms through which maltreatment interferes with the development of reinforcement-based decision making. Our post hoc analyses suggest that greater duration of maltreatment relates to more considerable neurocognitive alterations; however, the heterogeneity and sample size of the recruited sample did not allow us to systematically investigate the existence of periods during which the effect of early adversity may be particularly potent (i.e., sensitive periods; Knudsen, 2004). This remains an important open question to be addressed in the future.

To conclude, this is the first study to show that childhood maltreatment may be associated with altered neurocomputational EV representation (for both punishment and reward) in a widespread corticolimbic network that includes the orbitofrontal cortex, the basal ganglia (especially the caudate), and medial temporal regions (i.e., hippocampus and insula). Moreover, in line with an account of increased neural signaling to negative stimuli and feedback in this population, an increased PE-modulated brain response during punishment trials was found in several frontal and parietal regions that have been implicated with both PE signaling and with the experiences of abuse and neglect. Consistent with the clinical literature, these neurocognitive alterations may compromise the ability of maltreated individuals to accurately predict the outcomes associated with a given stimulus or action and in turn confer increased latent vulnerability to future psychiatric disorder.

Supplementary Material

To view the supplementary material for this article, please visit https://doi.org/10.1017/S095457941700133X.

References

Appendix 3 – Participant Recruitment and Overlap Across Studies

Participant Recruitment and Inclusion Criteria

Participants in Chapters Two, Four and Five were part of a larger sample of young children and adolescents recruited as part of a longitudinal study funded by the UK Economic and Social Research Council (ESRC) Grant ES/K005723/1 (Professor Eamon J McCrory [Principal Investigator] and Professor Essi Viding). In total, 132 children and adolescents took part in this study. 62 individuals had documented experiences of maltreatment (MT group) and were recruited via the Social Services Department. 70 peers with no prior Social Service contact (i.e. the non-maltreated group; or NMT group) were recruited via schools / advertisements in the community. Data for this longitudinal sample was collected at baseline (T1) between July 2013 and August 2014 and, two years later, at follow-up (T2). Consent was obtained from the child’s legal guardian and assent to participate was obtained from all children/adolescents. Procedures were approved by University College London (UCL) Research Ethics Committee (0895/002). Exclusion criteria included the presence of a pervasive developmental disorder, neurological abnormalities and an IQ below 70.

Participants in Chapter 2, Chapter 4 and Chapter 5.

Chapter Two. From the total sample described above (n = 132), 41 participants (MT = 20; NMT = 21) aged 10-15 years took part in the neuroimaging study described in Chapter Two (i.e. a model-based fMRI study of reinforcement-based decision-making). The neuroimaging data was collected at T1 for 33 participants (MT =16; NMT =17) and at T2 for 8 participants (MT = 4; NMT = 4). After two participants from each group were excluded due to movement artefacts, a final sample of 37 participants (MT = 18; NMT = 19) were included in the analyses.
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Chapter Four. From the total sample described above (n = 132), 73 children and adolescents (MT = 33; NMT = 40) aged 12-17 years took part in the behavioural ‘Episodic Future Thinking’ (EFT) study described in Chapter Four. All data for this study was collected at T2 only. After outliers and participants with invalid/missing trials were removed, 68 participants (MT = 31; NMT = 37) were included in the EFT analyses.

Chapter Five. From the total sample described above (n = 132), 73 children and adolescents (MT = 33; NMT = 40) aged 12-17 years took part in the interpersonal problem solving study described in Chapter Five. Interpersonal problem solving skills were measured using the Means-end Problem Solving (MEPS) test. All data for this study was collected at T2 only. After outliers were removed, 72 participants (MT = 34, NMT = 38) were included in the MEPS analyses.

Sample Overlap

There were varying degrees of sample overlap between Chapters Two, Four and Five: i) 26 participants (MT = 11; NMT = 15) were included in both the neuroimaging analyses described in Chapter Two and the EFT analyses described in Chapter Four; ii) 28 participants (MT = 14; NMT = 14) were included in both the neuroimaging analyses described in Chapter Two and the MEPS analyses described in Chapter Five; iii) Note that 25 participants (MT = 11; NMT = 14) were included in the neuroimaging, EFT and MEPS analyses (i.e. 25 participants took part in all three studies described in Chapters Two, Four and Five); iv) 64 participants (MT = 29; NMT = 35) were included in both EFT and MEPS analyses described, respectively, in Chapters Four and Five.