Risk for Eating Disorders and Neuropsychological Functioning: Developing Risk Models

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I, Radha Kothari, 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.

Signed_____

Date_____

Abstract

Introduction

Evidence suggests that diagnosis of an eating disorder (ED) is associated with differential cognitive functioning. Whether differences are present prior to onset, possibly affecting risk status for development of an ED, or whether differences are a consequence of secondary features of the disorder such as low nutritional intake, is not conclusive. One method of investigating cognitive functioning prior to onset of a disorder is to investigate cognitive functioning in those that are at high risk of developing that disorder. Studies have shown that first-degree relatives of probands are at higher risk of developing an ED than the general population.

Methods

This is the first study to investigate intelligence, global cognition, executive functioning, social communication and emotion recognition of children at high risk of developing an ED, in comparison to children who are not, in a large community sample. High risk status of children was defined in two ways: (i) maternal self-report diagnosis of an ED during pregnancy; (ii) maternal lifetime ED behavioural phenotype.

Results

Children at high risk for ED demonstrated superior intellectual functioning and working memory; but inferior attentional capacity, social communication and emotion recognition. Profile of children at high risk differed according to type of maternal ED. There was also some evidence of maternal behavioural phenotype being a better predictor of children's functioning than maternal self-report of ED diagnosis.

Discussion

Results suggest that the differences observed in children at high risk are putative intermediate phenotypes for ED, possibly affecting risk status for development. Findings are extremely important: both in relation to the identification of vulnerable individuals (and therefore preventative efforts); and in furthering our

understanding of which neuropsychological profiles are linked to susceptibility for ED. Also, use of a lifetime behavioural ED phenotype may provide the homogeneity required for research investigating intermediate phenotypes and genetic correlates of ED.

Dedicated to my wonderful father,
an incredible man without whom this, and so many other things in this world, would never have been possible.

Acknowledgements

Doing a PhD is a lesson in independence and self- responsibility; however the last three years would have been very different without the help of my supervisors, Nadia Micali and Janet Treasure. Working with such experts in the field has been an honour. I would like to give special thanks to my first supervisor Nadia Micali, who has taught me more about the real world of research than any text book could have. Her trust in my knowledge and ideas, her guidance in my areas of weakness, and her belief in my potential, has made my PhD experience a perfect combination of freedom and challenge.

Working with the Avon Longitudinal Study of Parents and Children has been a privilege, one which I will always be thankful for. Not only is the study a staggering resource, but it is managed and run by an incredible team of staff. I would like to express particular gratitude to Kate Northstone, whose help and patience have been invaluable. I am also especially grateful to over one thousand women who agreed to be interviewed, took the time to speak with me about difficult times in their lives, and often thanked me for the opportunity to do so. The resilience and strength of the women I spoke with is admirable, and their continued desire to help future generations an inspiration.

Doing a PhD can be an all absorbing experience at times, leaving little time or space for anything else. I would like to thank my friends and family, not only for their continued support, but also for accepting my absence from their lives. I would particularly like to thank my mother, who has always had more faith in my abilities than anyone else in the world; my best friend Sarah, who somehow always manages to make me feel sane; and my partner Jonny, whose love, support and belief in me is a luxury I too often take for granted. Most importantly I am grateful to my father, who passed away before the completion of this thesis. No one in this world has had a bigger influence on who I have become. His love and care for others transcended all boundaries, and he taught me that there was nothing more important in life than helping others (except for listening to really good music).

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List of Abbreviations

ED = Eating Disorder(s)

AN = Anorexia Nervosa

BN = Bulimia Nervosa

EDNOS = Eating Disorder Not Otherwise Specified

AN-R = Anorexia Nervosa – Restricting Subtype

AN-BP = Anorexia Nervosa – Binge/Purge Subtype

BN-R = Bulimia Nervosa – Restricting Subtype

BN-P = Bulimia Nervosa – Purging Subtype

DSM = Diagnostic and Statistical Manual for Mental Disorders

WISC = Wechsler Intelligence Scale for Children

WAIS = Wechsler Adult Intelligence Scale

ASD = Autism Spectrum Disorder(s)

OCD = Obsessive Compulsive Disorder

SCID = Structured Clinical Interview for DSM

TEA-Ch = Tests of Everyday Attention for Children

SCDC = Social and Communication Disorders Checklist

DANVA = Diagnostic Analysis of Non-Verbal Accuracy

Dissemination

Publications

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Conference Presentations

"Risk for Eating Disorders and Neurocognitive Functioning: Developing risk models" *British Association for Behavioural & Cognitive Psychotherapies Conference 2011*.

"The Cognitive Profile of Individuals with Eating Disorders: Risk, Maintenance and Obstacles to Recovery" *Student Run Self Help Conference 2011*.

"The Neuropsychological Profile of Children at High Risk of Developing an Eating Disorder: Moving Away from Diagnostic Categories and Towards Observable Phenotypes" *The 11th London International Eating Disorders Conference 2013.*

Conference Posters

"The Neurocognitive Profile of Children at High Risk of Developing an Eating Disorder" *The Eating Disorder Research Society Conference 2011.*

"How Common are Eating Disorder Behaviours?" *ALSPAC Researchfest 2012.*

Candidates Contribution

Data on maternal self-report ED diagnosis, children's cognitive development, and socio-demographic data, were collected as part of the ALSPAC study. Proposals to gain access to the relevant data were written and submitted by Radha Kothari. The data on maternal lifetime ED behaviours were collected via in depth diagnostic interviews. Radha Kothari made the relevant changes to the research version of the Structured Clinical Interview for DSM Disorders – Fourth Edition (SCID-IV) (First, Spitzer, Gibbon, & Williams, 2002), and designed the study protocol for conducting the interviews. Radha Kothari also devised the training package, and trained two other interviewers who conducted 253 interviews between them; while Radha conducted the other 890. The coding methods and database for the results were designed by Radha Kothari, and she entered the majority of the data. Radha Kothari conducted all of the data analyses under the guidance of her supervisors, Nadia Micali and Janet Treasure.

Chapter One

General Introduction

1.1 Chapter Overview

The aim of this thesis is to investigate neuropsychological functioning and social cognition in children at high risk of developing an eating disorder (ED), to explore whether the differences observed in ED individuals are also present in the first degree relatives of probands. High risk status in children is determined by presence of a maternal ED, and this has been defined in two ways: (i) maternal self-report diagnosis of an ED; and (ii) maternal ED behaviours over lifetime. This chapter provides an overview of ED psychopathology, diagnosis, and prevalence; examining the limitations of current diagnostic criteria. It then goes on to provide reasoning for use of the two different definitions of "high-risk" in this thesis.

1.2 An Overview of Anorexia Nervosa, Bulimia Nervosa, and Eating Disorder Not Otherwise Specified

Anorexia Nervosa

The core psychopathology of anorexia nervosa (AN) is the exaggerated value, and distorted perception of one's own body shape and weight; which not only leads to an obsessive drive for thinness, but also leads to a non-acceptance or denial of one's own dangerously low weight. Many develop a habit of exercising excessively. Individuals with AN may also employ purging behaviours such as vomiting, or excessive use of laxatives and/or diuretics, to keep their weight low. For some, an occasional "loss of control" over fasting/restricting behaviours can lead to a binge, where a large quantity of food is consumed in a short period of time ("American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)," 2000).

Onset of AN is typically in mid to late adolescence (Attia, 2009); though age of onset appears to be decreasing (Favaro, Caregaro, Tenconi, Bosello, & Santonastaso, 2009), and the recognition of cases with onset in childhood is increasing for both girls and boys (Madden, Morris, Zurynski, Kohn, & Elliot, 2009). In their population based study, Hudson and colleagues found the mean age of onset for AN to be 18.9 years old (Hudson, Hiripi, Pope, & Kessler, 2007); though a recent investigation of a large representative sample of adolescents in the United States reports a median age of onset for AN of 12.3 years old, earlier than previous estimates (Swanson, Crow, Le Grange, Swendsen, & Merikangas, 2011). This estimate can only be generalized to adolescent populations however. Early onset has been associated with comparatively worse personality disturbance, higher body dissatisfaction, and a fear of maturity (Abbate-Daga, et al., 2007); making early intervention strategies a priority.

Presentation of AN is often accompanied by other psychological symptoms such as depression, anxiety, obsessionality, and compulsivity (Attia, 2009); however these symptoms have also been observed in non-ED patients with restricted calorie intake and substantial weight loss (Keys, Brozek, Henschel, Mickelsen, & Taylor, 1950), making it possible that such symptoms are secondary to the disorder itself. In addition, research shows that patients who report additional psychological symptoms prior to onset of AN often experience a worsening in their severity during the illness, and an improvement with weight restoration (Meehan, Loeb, Roberto, & Attia, 2006). A high percentage of patients with AN also suffer from comorbid psychiatric disorders such as mood disorders, anxiety disorders, obsessive-compulsive disorder, and substance use disorders (Salbach-Andrae, et al., 2008); making diagnosis difficult and treatment challenging.

A diagnosis of AN according to the Diagnostic and Statistical Manual of Mental Disorders (fourth edition – revised; DSM-IV-TR) criteria requires: (i) Maintenance of a body weight that is less than 85% of normal weight for that particular age and height; (ii) Intense fear of fatness and gaining weight; (iii) disturbed experience of one's own body shape and/or denial of one's own low weight; and (iv) amenorrhea for a minimum of three consecutive months. Accompanying behaviours may

include excessive exercise; vomiting; excessive use of laxatives, diuretics or other weight suppressants; and episodes of bingeing. Individuals with AN can fall into one of two sub-types according to these accompanying behaviours: those that engage in bingeing and/or purging behaviours are considered have the binge-purge subtype of AN (AN-BP); while individuals who maintain their low weight mainly through food restriction are considered to have the restricting subtype of AN (AN-R). Diagnostic categories are updated over time however, and it is worth noting that proposals for the new DSM-V include the criterion regarding amenorrhea being removed, and criterion (i) being reviewed (Wilfley, Bishop, Wilson, & Agras, 2007).

Bulimia Nervosa

Bulimia Nervosa (BN) is characterized by episodes of bingeing accompanied by compensatory behaviours (such as vomiting or the misuse of laxatives), and an overvaluation of weight and shape. Due to this combination of bingeing and weight loss behaviours, individuals suffering from BN are generally at a normal weight. Onset of BN is typically reported to be later than AN. Mean age of onset in a large population based study was found to be 19.7 years old (Hudson, Hiripi, Pope, et al., 2007); though research suggests that the age of onset may be decreasing (Favaro, et al., 2009). A recent study investigating a large representative population of adolescents in the United States reported median age of onset to be 12.4 years old, though this finding can only be generalized to other adolescent populations (Swanson, et al., 2011). Individuals with BN often suffer from comorbid psychiatric disorders such as anxiety disorders, mood disorders, and substance abuse disorders (e.g. Hudson, 2007; Keel, Mitchell, Miller, Davis, & Crow, 1999). A generally accepted characteristic of BN is increased impulsivity; and this can be seen in the variety of additional problems that are associated with BN such as sexual promiscuity, excessive drinking, drug abuse, and shoplifting (e.g. Polivy & Herman, 2002).

For a diagnosis of BN according to the DSM-IV-TR, the following criteria must be met: (i) Recurrent episodes of bingeing in which individuals experience a lack of control over their own eating and consume large amounts of food in a short period of time; (ii) The presence of compensatory behaviours such as purging (vomiting and/or excessive use of laxatives, diuretics, weight loss pills), fasting, or excessive exercising; (iii) A self-evaluation that is overly dependent on one's weight and shape; and (iv) Currently, episodes of bingeing and compensatory behaviours must occur at least twice a week for a minimum of three months. It is worth noting however that the new DSM-V criteria are likely to change the minimum frequency to once a week (Wilfley, et al., 2007). Two subtypes of BN exist which reflect the differences in the compensatory behaviours that are employed. Individuals who purge are diagnosed with the purging subtype of BN (BN-P); while individuals who use fasting or excessive exercising are diagnosed with the non-purging subtype (BN-NP).

Eating Disorder Not Otherwise Specified/Atypical AN and BN

While AN and BN are defined by specific criteria, Eating Disorder Not Otherwise Specified (EDNOS) is a broad and heterogeneous diagnosis which defines presentations of ED that are of clinical significance, but do not meet criteria for AN or BN. The range of possible criteria that can be met for a diagnosis of EDNOS has led to this category becoming more commonly diagnosed than both AN and BN(e.g. Fairburn & Bohn, 2005a; Fairburn, et al., 2007). However, the heterogeneous nature of the EDNOS category has led to a paucity of research regarding individuals with this diagnosis; and this in turn leads to a continued lack of clarity regarding the effectiveness of criteria for this diagnosis. A substantial subgroup of individuals in the EDNOS category will have previously met full criteria for AN or BN, or will do in the future (Milos, Spindler, Schnyder, & Fairburn, 2005), which raises questions about the clinical utility of this diagnosis. Many of the proposed changes to the upcoming DSM-V aim to reduce the number of cases in this "not otherwise specified" group. Binge Eating Disorder (BED) is likely to become a separate diagnosis, while diagnostic criteria for AN and BN are to be relaxed as described above. There has also been some discussion over the clinical utility of creating a separate diagnosis of Purging Disorder, to define individuals who purge

in the absence of bingeing episodes (e.g. Binford & le Grange, 2005; Keel & Striegel-Moore, 2009); however it seems unlikely that a separate category for this sub-group will be in the DSM-V.

Currently the DSM-IV provides seven examples of possible situations in which a diagnosis of EDNOS is appropriate: (1) All criteria for AN are met, except for amenorrhea; (2) All criteria for AN are met, except that despite substantial weight loss the individuals current weight does not meet criteria of less than 85% of expected weight; (3) All criteria for BN are met, except that the frequency of bingeing and compensatory behaviours is less than twice a week, or that duration is less than three months; (4) The individual regularly engages in inappropriate compensatory behaviours after the consumption of a small or normal quantity of food (in the absence of a bingeing episode), often referred to as purging disorder; (5) The individual starves themselves but does not lose weight; (6) Repeated chewing and spitting out of large quantities of food without swallowing; (7) Recurrent episodes of bingeing (at least twice a week for six months) in the absence of compensatory behaviours, referred to as Binge Eating Disorder (BED).

1.3 Prevalence

Estimating the prevalence of ED in the general population is difficult. Due to the rarity of the disorders, and the tendency of affected individuals to deny or conceal their illness, community studies can be expensive and ineffective. Many epidemiological studies use medical and psychiatric records to estimate prevalence; however resulting figures are likely to be an underestimate as not all individuals with an ED will be diagnosed or treated. The lifetime prevalence (proportion of people who have had an ED at any point in their lifetime) of AN, BN, and EDNOS are briefly described below.

Anorexia Nervosa

A diagnosis of AN requires the presence of amenorrhea for a minimum of three months. Due to the questionable nature of this diagnostic criteria, and proposed changes for the DSM-V criteria, prevalence studies often investigate and report the prevalence of AN (fulfilling all criteria) and 'broad AN' (meeting all criteria except amenorrhea). Three recent studies have employed population based cohort studies of twins and found prevalence of lifetime AN and broad AN to be 1.2% - 2.2% and 2.4 % - 4.3% respectively (Bulik, et al., 2006; Keski-Rahkonen, et al., 2006; Wade, Bergin, Tiggemann, Bulik, & Fairburn, 2006); while two large population studies in Europe and the United States found that the lifetime prevalence of AN in adult women was 0.9% (Hudson, Hiripi, Pope, et al., 2007; Preti, et al., 2009). Another large study in the U.S. found that lifetime prevalence of AN in female adolescents between 13 and 18 years of age was 0.3% (Swanson, et al., 2011), though this estimate can only be generalized to other adolescent populations.

The prevalence of AN in male samples has been less well investigated, though recent evidence suggests that the previous female to male ratio of 10:1 (Hoek & van Hoeken, 2003), may underestimate the true number of cases in males (Smink, van Hoeken, & Hoek, 2012). In a Finnish cohort of twins prevalence of lifetime AN in men was found to be 0.24% (Raevuori, et al., 2009). In contrast, a study of adolescents in the United States found prevalence of lifetime AN in adolescent males to be 0.3%; the same as prevalence in adolescent females (Hudson, Hiripi, Pope Jr, & Kessler, 2007). It is thought that AN is more frequently detected in females than in males (Striegel-Moore, Franko, & Ach, 2006), and that prevalence of AN in males is higher than estimated (Smink, et al., 2012).

Bulimia Nervosa

Recent studies report lifetime prevalence of BN to be between 0.9% and 2.9% (Smink, et al., 2012; Swanson, et al., 2011; Wade, et al., 2006). Studies investigating the lifetime prevalence of BN when relaxing the symptom frequency to once a week rather than twice a week, as has been proposed for the upcoming DSM-V guidelines, provide estimates of 1.6% to 2.3% (Keski-Rahkonen, et al., 2009; Trace,

et al., 2011). With regard to BN in males, a review by Smink and colleagues reported lifetime prevalence of BN in adults to be between 0.1% and 0.5% in Europe and the United States (Smink, et al., 2012). Lifetime prevalence of BN in male adolescents in the United States, between the ages of 13 and 18 years old, has also been reported to be 0.5% (Swanson, et al., 2011).

Eating Disorder Not Otherwise Specified

The heterogeneous nature of the EDNOS category makes estimating prevalence difficult, and many of the standard clinical interviews used for assessment do not cover all possible behavioural expressions of this diagnostic group (i.e. purging disorder). A study investigating prevalence of ED in a large sample of female students between the ages of 12 and 23, found that prevalence of EDNOS was 2.37%; in comparison to 0.39% for AN, and 0.30% for BN (Machado, Machado, Gonçalves, & Hoek, 2007). This finding supports literature suggesting that that the majority of individuals diagnosed with an ED are diagnosed with EDNOS rather than AN or BN (e.g. Fairburn & Bohn, 2005b; Fairburn, et al., 2007); a problem that is being addressed in modifications to ED diagnostic criteria for the DSM-V.

Prevalence of BED specifically has been more extensively studied due to the comparative clarity of diagnostic criterion and homogeneous presentation. In a large population study of six European countries, lifetime prevalence was found to be 1.9% for women, and 0.3% for men (Preti, 2009). A population study of adults in the United States found higher prevalence: 3.5% in women and 2.0% in men; however the duration criteria used in this study was three months, as proposed for new DSM-V guidelines, rather than the duration of six months that is required by the DSM-IV (Hudson, Hiripi, Pope Jr, et al., 2007). A higher prevalence of BED was also found in a large Swedish sample of adult female twins when using proposed DSM-V criteria (0.35%), in comparison to DSM-IV criteria (0.17%)(Trace, et al., 2011).

Sub-threshold ED Behaviours

It is commonly accepted that ED symptoms are present for between 6 and 24 months prior to clinical diagnosis (Lena, Fiocco, & Leyenaar, 2004). In a population

sample of middle and high school students, 16.0% of girls and 15.4% of boys reported binge eating, self-induced vomiting, laxative use, and/or excessive exercise, though none of them met the full diagnostic criteria for an ED (Ackard, Fulkerson, & Neumark-Sztainer, 2007). In addition, Hay and colleagues investigated prevalence of ED behaviours using population surveys from South Australia between 1995 and 2005; they reported a two-fold increase in the prevalence of bingeing, purging, and fasting in both males and females, indicating an increase in the prevalence of ED behaviours (Hay, 2008). It could be argued that these clinically severe symptoms are more important than full diagnosis with regard to intervention. A recent longitudinal study that followed a community sample of adolescent girls found that sub-threshold EDs were more prevalent than threshold EDs; and sub-threshold cases frequently progressed to full threshold (Stice, Marti, Shaw, & Jaconis, 2009). Another study found that 2.5% - 2.9% of girls who met partial or asymptomatic diagnostic criteria went on to develop a full/partial ED over a three year follow-up (Taylor, et al., 2003).

1.4 Limitations of Diagnostic Criteria with Regard to Research

The diagnostic groups of AN, BN and EDNOS may not be effective for research regarding nosology and etiology; or in the search for genetic biomarkers. Concerns have been raised regarding the definition of particular diagnostic terms, such as "refusal" and "weight phobia," and the lack of empirical evidence for the use of such criterion (Hebebrand, Casper, Treasure, & Schweiger, 2004). In addition, the phenotypic expression of BN is very similar to that of AN-BP; however, the combination of bingeing and weight control behaviours means that individuals suffering from BN are generally at a normal weight. It has been suggested that the two diagnoses may only be distinguished by an ability to suppress weight to less that 85% of what would be expected (Polivy & Herman, 2002). Two particular concerns regarding the use of ED diagnoses in research are: (i) the heterogeneity of patients diagnosed with EDNOS, which has been discussed above; and (ii) the instability of specific ED diagnoses over time (i.e. cross over between AN/BN/EDNOS).

A high percentage of patients migrate between ED types (AN, BN, EDNOS/Atypical) (e.g. Eddy, et al., 2008; Fairburn & Harrison, 2003; Milos, et al., 2005), raising questions about the distinctiveness of the different ED diagnoses and highlighting problems with the validity of the DSM-IV classifications. Evidence suggests that while cross-over from AN-R to AN-BP or BN is common, cross-over in the other direction is more rare (Eddy, et al., 2008; Milos, et al., 2005; Tenconi, Lunardi, Zanetti, Santonastaso, & Favaro, 2006); indicating a possible evidence based distinction between AN-R and other ED diagnoses.

As stated earlier, the majority of ED patients fall into the category of EDNOS (e.g. Nicholls, Chater, & Lask, 2000; Turner & Bryant-Waugh, 2004). Many of these individuals will have previously been diagnosed with AN or BN but no longer fulfill all criteria for these diagnoses (Milos, et al., 2005). It is questionable whether these individuals should be given the different diagnosis of EDNOS, or whether their change in symptoms should be considered part of the natural course of AN/BN. A recent longitudinal study investigated the type of EDNOS presentations that followed an initial diagnosis of AN or BN, and found that EDNOS presentations resembled initial diagnosis at intake (Eddy, et al., 2010). Women with an intake diagnosis of AN-R were unlikely to develop symptoms of bingeing and purging when diagnosed with EDNOS; while women with an initial diagnosis of AN-BP or BN developed presentations that were mainly characterized by bingeing and purging. In addition, from a diagnosis of EDNOS women were just as likely to return to a full syndrome diagnosis (AN/BN) as they were to achieve recovery. Another important observation was that for women who no longer met criteria for AN-R or AN-BP it was generally due to an increase in weight. This study highlights the lack of distinction between ED diagnoses, and questions whether a step towards recovery, or a slight change in weight or symptom frequency, should require reclassification into a different diagnosis.

The considerable overlap of features between the different ED diagnoses, and the frequency of cross-over between these diagnoses, led Fairburn and Bohn to propose a “transdiagnostic” approach to ED classification (Fairburn & Bohn,

2005a). The authors suggest that a category of "mixed eating disorders" is established, encompassing AN, BN and EDNOS. They argue the case that the similarities between these disorders are more important than the differences; and that this approach would highlight the differences between the common traits of ED and traits associated with other psychiatric disorders, emphasizing the peculiar nature of the disorder. Though this approach has clear advantages, it may prove problematic with regard to research. The heterogeneity of existing ED diagnoses is already proving to be problematic when investigating the etiology and nosology of the disorders, and one overall group of ED may only make these investigations more difficult.

1.5 The Evidence Based Classification of ED Sub-groups

There have been several studies attempting to empirically define ED phenotypes using latent class analysis, one of which revealed four distinct groups: (i) a group that resembled restricting AN; (ii) a group of individuals diagnosed with either AN or BN that employed multiple methods of purging; (iii) a group diagnosed with AN that did not exhibit obsessive-compulsive features; and (iv) a group diagnosed with BN that only used vomiting to purge (Keel, et al., 2004). More recently, Mazzeo and colleagues also highlighted the importance of classifying ED at the symptom level (Mazzeo, et al., 2009). In their twin study investigating specific BN symptoms they found that while vomiting was very strongly influenced by additive genetic factors, other symptoms such as over concern with weight and shape were less heritable.

As has been highlighted above, ED diagnoses are not stable over the course of illness and cross-over between different diagnostic categories is common. Despite the fact that this cross-over is driven by fluctuations in symptoms and weight, there has only been one study investigating the course and trajectory of specific ED symptoms/behaviours over time (Lavender, et al., 2011). Lavender and colleagues were the first to conduct a large prospective study following the longitudinal trajectory of specific ED behaviours (Lavender, et al., 2011). Their results showed

that most individuals, who followed a trajectory of "persistently low weight", also followed trajectories of "non-binge eating" and "non-purging"; resembling the syndrome of AN-R. They also found that women who followed a trajectory of "fluctuating weight" also followed trajectories of decreasing or persistent binge eating and purging. The authors suggest that this pattern is characteristic of those individuals who frequently move between a diagnosis of AN-BP, BN, and possible even AN-R; highlighting the lack of distinction between these ED diagnoses.

Anderluh and colleagues have previously suggested that a solution to the instability of ED diagnosis could be to classify individuals according to lifetime ED symptoms (Anderluh, Tchanturia, Rabe-Hesketh, Collier, & Treasure, 2009). They investigated this possibility and found that the four most common lifetime diagnostic categories, based on retrospective reporting, were: (i) Restricting subtype (no bingeing or purging present); (ii) Purging subtype (vomiting or other purging behaviours present); (iii) Binge/Purge subtype (bingeing and purging behaviours present; and (iv) Bingeing subtype (bingeing present without purging). They also found that: a longer duration of underweight status; longer episodes of severe restriction; episodes of excessive exercising; and shorter durations of bingeing; were associated with perfectionism and rigidity.

The most recent version of cognitive behavioural therapy was designed to be adapted for specific sets of symptoms (Fairburn, Cooper, & Shafran, 2003). Investigation into the trajectory and associated characteristics of specific ED symptoms could inform such treatment programs in the future. Identifying predictors of symptom trajectories could also improve knowledge of the etiology of ED, and help clarify the boundaries between ED diagnoses and subtypes; as well as inform the development of interventions that may encourage movement to decreasing symptomatology(Lavender, et al., 2011).

1.6 Interim Conclusion

For the studies in this thesis, two different methods have been used to define high risk status in children: (i) maternal self-report diagnosis of an ED and (ii) maternal ED behaviours over lifetime. Research into the neuropsychological functioning of ED subjects generally attempts to associate neuropsychological differences with particular ED diagnoses (i.e. AN/BN). For several reasons, the use of a lifetime behavioural phenotype may be more effective. Grouping subjects with an ED according to the ED behaviours/symptoms that they have exhibited over the course of their life would: (i) deal with limitations inherent in using current ED classification due to the instability of diagnoses; and (ii) circumvent limitations associated with the heterogeneity of the EDNOS category. In addition, it has been repeatedly suggested that a quantitative trait approach to psychiatric illness may be more relevant than current diagnostic categorization, particularly with respect to ED research (e.g. Treasure, 2012; Zucker, et al., 2007). The National Institute of Mental Health (NIMH) has recently adopted this view, announcing a strategic plan to re-classify pathology based on observable behaviour and neurobiological measures for the purposes of research. It has been suggested in this proposal that the limited clinical impact of recent research regarding mental health is due to new findings only moderately mapping onto current diagnostic categories; and this is because current diagnostic criteria are based on subjective clinical observation and patient symptom reports, rather than objective phenomenological and evidence based differences (Insel, et al., 2010). Following on from this theoretical perspective, it is possible that findings from research regarding the neuropsychological profile of ED individuals do not perfectly map onto diagnostic groups due to the questionable nature of diagnostic criteria; and this could also partly explain conflicting evidence in the literature. It is likely that observable phenotypic features of ED (such as ED behaviours) will be more directly associated with differences in cognitive functioning.

Chapter Two

The Neuropsychological Profile of Eating Disorders

2.1 Chapter Overview

As stated previously, this thesis investigates neuropsychological functioning and social cognition in children at high risk of developing an ED. This chapter provides contextual background and theoretical reasoning for this investigation: firstly discussing the benefits of neuropsychological research with regard to ED etiology and treatment, paying particular consideration to how the high risk research design can contribute to the field; and then exploring neuropsychological research in relation to ED and ED phenotypes to date.

2.2 Investigating Neuropsychological Functioning and the Potential of High Risk Research

Eating disorders (ED) have a complex etiology that is not yet fully understood, making intervention and treatment difficult. Despite its relatively low prevalence, EDs have one of the highest risks for premature death of all psychiatric disorders (e.g. Arcelus, Mitchell, Wales, & Nielsen, 2011; Birmingham, Su, Hlynsky, Goldner, & Gao, 2005; Harris & Barraclough, 1998), and research suggests between 5 and 12% of patients will die per decade (Agras, 2001). Considering this, it is imperative that research focuses on factors that may affect risk status for ED, with a view to developing effective prevention and intervention strategies. In recent years, research into the cognitive profile of individuals suffering from ED has increased. There has been some suggestion that the central nervous system plays a role in the development of these disorders (Lezak, Howieson, & Loring, 2004), and that neurobiological factors could lead to increased risk (Nunn, Frampton, Gordon, & Lask, 2008). It is possible that particular cognitive styles may affect risk status for disordered eating, and identification of these could lead to early and effective intervention. The overall aim of this thesis is to investigate whether the differences

in neurocognitive functioning that have been observed in eating disordered groups might be present prior to onset of the disorder, so it is important to understand why an investigation of neurocognitive functioning in ED groups is essential, and to appreciate the significance of knowing whether differences observed are present prior to onset.

Neuropsychological research has made a valuable contribution to the understanding of psychiatric disorders by providing predictors of the course of illness and indicating optimal methods of treatment (Keefe, 1995). Also, neuropsychological tests can improve understanding of the relationship between cognitive impairments and clinical symptoms (Keefe, 1995). The complexity of psychiatric illness makes it difficult to conduct research on the basis of overt symptoms. This is particularly pertinent in the field of eating disorders due to the heterogeneity in symptom presentation, instability of diagnosis, and the effects of restricted nutritional intake. Eating disorders are complex and there is still much progress to be made with regard to etiology and risk factors. Investigation into the neurocognitive profile of individuals with an ED can help provide a deeper understanding of observable symptoms, while also illuminating the pathway between these observable symptoms and genetic vulnerability. In addition, the identification of cognitive disturbance that is associated with presence of an ED has already informed treatment design, and will continue to do so in the future.

Research into the cognitive profile of subjects with ED has revealed impairments in specific executive functions, including attention (e.g. Dobson & Dozois, 2004; Faunce, 2002), cognitive flexibility (Roberts, Tchanturia, & Treasure, 2010; Tchanturia, et al., 2012), and inhibition (Galimberti, Martoni, Cavallini, Erzegovesi, & Bellodi, 2011; Rosval, et al., 2006; Southgate, 2005). There is also a great deal of evidence to support the presence of visuo-spatial impairments and weak central coherence in ED groups (Cooper, 1987; Whyte, 2006). Moreover, a recent meta-analysis found that subjects with AN score higher than the normative population on the National Adult Reading Test (NART) (Nelson, 1991), and the Wechsler Intelligence Scales (Lopez, Stahl, & Tchanturia, 2010; Wechsler, 1990). There are however conflicting findings, with some studies finding no differences or improved

executive functioning in ED samples (I. Gillberg, Rastam, Wentz, & Gillberg, 2007; Pieters, et al., 2003). Impaired social and interpersonal functioning has also been observed in ED groups(Oldershaw, et al., 2011); and there is growing evidence of an overlap in phenotypic expression between AN and Autism Spectrum Disorder (ASD) (Treasure, 2012; Zucker, 2007).

It is possible that the neurocognitive differences observed in ED subjects are present prior to onset, and may contribute towards development of an ED. The opposite; that cognitive impairment follows onset of an ED, cannot however be ruled out. Deficits observed in clinical studies might be a secondary effect of other features of the disorder, such as low nutritional intake; while continued impairments observed in subjects who have recovered from an ED could be long-term effects or scars of the disorder. Having an understanding of which cognitive deficits are present prior to onset, and which are secondary to the disorder, will further our understanding of which neuropsychological profiles are linked to susceptibility for ED; and this can inform strategies for intervention.

There are currently four methods of inquiry that have been used to investigate the neurocognitive profile of ED individuals prior to onset of the disorder. The first is the retrospective design which, though providing an important insight, is limited by recall bias. The second is to investigate neuropsychological functioning in individuals that have recovered from an ED. Again, this method is informative; however it does not rule out the possibility that differences observed were not present prior to onset, but are still present in recovery due to being scars of the disorder. The third is to investigate sub-clinical populations high in ED symptomatology or dieting behaviours, under the premise that dieters are at higher risk of developing an ED than those who do not diet (Gendall, Joyce, Sullivan, & Bulik, 1998; Jacobi, Hayward, de Zwaan, Kraemer, & Agras, 2004; Stice, Mazotti, Krebs, & Martin, 1998b). This provides some insight into cognitive functioning prior to clinical level ED symptoms; however changes in cognitive functioning could be associated with the onset of sub-clinical psychopathology. Finally, recent studies have investigated the neuropsychological functioning of first degree relatives of probands, and this is discussed in more detail below.

2.2.1 Heritability and Genetic Liability

The basis for investigating neuropsychological functioning in the first degree relatives of probands comes from evidence of a genetic liability for the development of an ED. Family studies have shown that both AN and BN are more common in relatives of probands than in the relatives of non-eating disordered individuals (Ben-Dor, Laufer, Apter, Frisch, & Weizman, 2002; Holland, Sicotte, & Treasure, 1988; Strober, Freeman, Lampert, Diamond, & Kaye, 2000); in fact, research suggests that there is a 7-12 fold increase in the prevalence of an ED in the first degree relatives of probands in comparison to controls (Lilenfeld, et al., 1998; Strober, et al., 2000). Twin studies also provide evidence for the presence of genetic liability, reporting heritability estimates of 54% to 83% for AN and BN (Lear, Orit, & Apter, 2007). In a more recent twin study of BN, Mazzeo and colleagues found that liability was significantly influenced by additive genetic factors (Mazzeo, et al., 2009). Though they found that environmental factors also had a significant influence, it was to a much lesser degree. The results of this study also showed that vomiting in particular was more heritable than other BN symptoms. Adoption studies are thought to circumvent many of the study limitations associated with family and twin studies; and an adoption study conducted by Klump and colleagues also found significant genetic influence on all ED diagnoses (59-82%) (Klump, Suisman, Burt, McGue, & Iacono, 2009). Limited research has been conducted on the children of ED probands; however female children of women with an ED have been shown to be at increased risk of ED disturbance (Byrne, 2003; Field, et al., 2008).

2.2.2 Intermediate Phenotypes

Evidence suggests that particular cognitive differences might be intermediate phenotypes of ED. Intermediate phenotypes, in the context of mental illness, are heritable traits that are on the pathway between genetic vulnerability and the development of a psychological disorder (Rasetti, 2011). For ED, where clinical presentation is complex and heterogeneous, the identification of intermediate

phenotypes is particularly useful in the search for vulnerability genes. The relationship between overt phenotype and genotype is a particularly complex one for ED, whereas the relationship between intermediate phenotypes (i.e. neuropsychological functioning) and underlying genes may be a simpler one. It is vital to know whether differences in neuropsychological functioning are independent of illness state for neuropsychological functioning to be considered a possible intermediate phenotype.

If the neuropsychological differences observed in probands are also present in unaffected first degree relatives at a higher rate than the general population, they can be considered candidate intermediate phenotypes. Investigating the neurocognitive profile of individuals at high risk of developing an ED might be a fruitful area of research; however risk factor studies ideally need to be conducted with samples that are young enough not to have developed any eating concerns (Lee, et al., 2007).

2.2.3 The Use of the High Risk Design in Research Pertaining to other Psychiatric Disorders

Like the first-degree relatives of ED probands, the first-degree relatives of individuals with schizophrenia, depression, and bipolar disorder are at higher risk of developing these disorders than the general population (Kendler, et al., 1993; Kieseppa, Partonen, Haukka, Kaprio, & Lonnqvist, 2004; Levinson, 2006; Lichtenstein, et al., 2009). As a result, research investigating children at high risk of developing these disorders is extensive. Evidence indicates that the deficits in neuropsychological functioning and emotion recognition that are observed in probands are also observed in children at high risk of developing schizophrenia (Amminger, et al., 2011; Cornblatt & Erlenmeyer-Kimling, 1985; Davalos, 2004; Eack, 2010; Erlenmeyer-Kimling & Cornblatt, 1987; 2008; Rutschmann, Cornblatt, & Erlenmeyer-Kimling, 1977); depression (Mannie, 2007; Monk, et al., 2008); and bipolar disorder (Brotman, et al., 2008; Melissa, et al., 2008); and the high risk research design has been shown to be an effective way of identifying intermediate

phenotypes for these disorders. Research pertaining to the heritability of ED (discussed above) and associated neuropsychological deficits (discussed below) is now at a point where use of the high risk research design could contribute to the search for intermediate phenotypes for these disorders.

2.3 Neuropsychological Functioning and Social Cognition in Individuals with an Eating Disorder

Following is an outline of research investigating the potential association between diagnosis of an ED and differential neuropsychological and social processing. The evidence discussed is specifically relevant to the cognitive constructs explored in high risk children for this thesis, and particular consideration is given to research that investigates whether differences are independent of illness state. Also discussed is the (often conflicting) evidence that neuropsychological differences are associated with particular ED diagnoses and subtypes; considering the possible advantages of using a lifetime ED behavioural phenotype, rather than ED diagnoses, in neuropsychological research.

2.3.1 Intelligence & Global Cognition

Clinicians have frequently suggested that individuals with AN show increased intelligence in comparison to the general population, and that this contributes to the manipulation and planning that allows the disorder to go undetected for a long period of time (Lopez, et al., 2010). The Wechsler Intelligence Scales and its subtests assess overall IQ and elements of cognitive functioning, and have frequently been used to investigate cognition in ED groups. The following section of this chapter gives a brief overview of the relevant research pertaining to intelligence and global cognition in relation to ED; mainly focusing on studies that have employed the Wechsler Intelligence Scales, as this was the measure used in the present research.

2.3.1.1 Intelligence

A recent meta-analysis found that AN groups have higher full scale IQ than the general population, scoring on average 5.9 points (95% CI: 7.9, 13.6) above the average IQ of the normative population (Lopez, et al., 2010). Unfortunately, the majority of studies that use the Wechsler Intelligence Scales only report Full Scale IQ; rather than reporting the results from individual subtests, or verbal and performance summary scores. Stedal and colleagues have found however that AN patients show superior verbal and non-verbal performance, scoring significantly higher than the normative mean on the Vocabulary and Matrix reasoning subtests of the Wechsler Adult Intelligence Scale (WAIS) (Stedal, Rose, Frampton, Landrø, & Lask, 2012).

In contrast to the increased IQ reported by Lopez and colleagues; a study comparing a community based sample of AN adolescents and a community based adolescent comparison group found no differences in Full scale IQ as assessed by the Wechsler Adult Intelligence Scale-Revised (WAIS-R). The AN group did perform significantly worse on the Object Assembly sub-test however; which is reflective of perceptual difficulties, figure-ground deficits, and poor visual memory or visual motor coordination (I. Gillberg, Gillberg, Råstam, & Johansson, 1996). When tested again at 24 years of age, it was found that the AN group still exhibited significantly poorer performance on the Object Assembly subtest, and also significantly lower full-scale IQ (I. Gillberg, et al., 2007). It is possible that the findings of Gillberg and colleagues contrast with the results of the previously mentioned meta-analysis (Lopez, et al., 2010) because they were investigating a community sample rather than clinical samples. The selective nature of clinical samples used in other studies means that findings can only be generalized to AN patients who seek and receive treatment in secondary and tertiary care.

With regard to BN patients, Galderisi and colleagues found no differences in full scale, verbal or performance IQ in comparison to healthy controls(Galderisi, 2010); however more investigation is needed regarding IQ/intellectual functioning in BN groups.

Studies comparing ED patients with psychiatric controls also find evidence of superior intellectual functioning. An early study found that AN patients scored higher than psychiatric controls on verbal and academic measures, but scored lower in measures of spatial reasoning (Maxwell, Tucker, & Townes, 1984). These findings are limited however due to the use of a very small AN sample. Blanz and colleagues compared the intellectual functioning of a large sample of ED patients, to patients with other disorders that were matched on age, sex, socio-economic status, and year of admission; and results showed that ED patients had significantly higher IQ (Blanz, Detzner, Lay, Rose, & Schmidt, 1997).

One study compared the IQ of patients meeting full DSM-IV or ICD-10 criteria for AN with patients who met criteria pertaining to the essential psychopathology and self-starvation of AN, but did not meet the criteria of amenorrhea or weight loss below 85% and were therefore defined as EDNOS or atypical (Watson, 2003). Though groups showed few significant differences in illness history, treatment response, psychopathology, or bone density, differences were observed in intellectual functioning. For those patients of the age to complete the WISC, patients fulfilling all diagnostic criteria for AN trended towards significantly higher scores than EDNOS/Atypical patients on full scale IQ (7.2 points higher); verbal IQ (6.9 points higher); and performance IQ (5.1 points higher). For those AN patients that were old enough to complete the WAIS, patients fulfilling all criteria for AN performed significantly better than EDNOS/Atypical patients on full scale IQ (4.6 points higher) and verbal IQ (6.9 points higher); and also trended towards significantly higher scores on performance IQ (2.4 points higher). This study highlights the importance of considering the phenotypic differences with ED diagnoses.

2.3.1.2 Visio-spatial Functioning

With regard to the investigation of intelligence and global cognition in this thesis, a particular interest is taken in visuo-spatial functioning. This is due to the extensive evidence of visuo-spatial impairment that has been found in ED groups using a variety of tasks (e.g. Cooper, 1987; Fowler, et al., 2006; Maxell, Tucker, & Townes, 1984; Stedal, Frampton, Landro, & Lask, 2011; Stedal, et al., 2012; Tenconi, et al., 2010; Whyte, 2006). A number of performance subtests in the Wechsler Intelligence Scales examine visuo-spatial functioning: the Coding and Picture Completion Subtests rely on visual memory; and the Block Design and Object Assembly subtests are reliant on good visual motor coordination, perceptual organization, and visual integration. As mentioned above, Gillberg and colleagues have observed significantly lower object assembly scores in a community sample of AN individuals when compared with a community sample of controls (I. Gillberg, et al., 1996). AN patients have also been found to score significantly lower than controls on the Picture Completion subtest (Kingston, Szmuckler, Andrews, Tress, & Desmond, 1996). Various versions of the Block Design task have been employed, with impaired performance being found in AN groups (Andres-Perpina, et al., 2011; Kingston, et al., 1996). However, there is also evidence of no differences in the performance of AN patients and healthy controls (Castro-Fornieles, et al., 2007; Mathias & Kent, 1998; Murphy, Nutzinger, Paul, & Leplow, 2002); and BN patients and healthy controls (Lopez, Tchanturia, Stahl, & Treasure, 2008).

One particular study of interest investigated visuo-spatial functioning in AN patients who were acute, weight restored, and recovered; unaffected sisters of AN patients; and healthy controls (Tenconi, et al., 2010). AN patients exhibited poorer performance than healthy controls on both the Block Design and Object Assembly tasks, and also the Overlapping Figures test which assesses visual interference and spatial exploration. No significant differences in task performance were observed between any of the three AN groups, which provides evidence for the relationship between AN and visuo-spatial impairment being independent of illness state. In addition, it was found that the unaffected sisters of AN patients showed poorer performance than healthy controls on all three tasks; with their performance being

at an intermediate level between AN patients and healthy controls. These findings implicate impaired visuo-spatial abilities as a putative intermediate phenotype of AN.

2.3.1.3 Interim Conclusions

The majority of research investigating intelligence and global cognition in ED groups has focused on patients with AN, however patients have not been differentiated according to their restricting/binge-purge subtypes. It is possible that the contradictory findings regarding intelligence in AN groups are due to the heterogeneity of samples with regard to diagnosis and clinical severity. As stated above, Gillberg and colleagues employed a community sample of AN adolescents, rather than a clinical sample, and found no differences in comparison to controls(I. Gillberg, et al., 1996). This may suggest that high IQ is associated with a severe form of AN; and the findings of Watson and colleagues, who observed higher IQ in AN patients with amenorrhea (indicating increased severity) in comparison to AN-type patients without (Watson, 2003), could be taken as support for this hypothesis.

2.3.2 Executive Functioning

Despite being a construct that is frequently discussed and readily researched, the concept of executive functioning, also known as executive or cognitive control (Davidson, Amso, Anderson, & Diamond, 2006; Funahashi, 2001), has no formal definition. Most agree however that executive functions are required for flexible, goal directed behaviour which is responsive to a changing environment, and therefore vital for adaptive human behaviour (e.g. Anderson, 2001; Elliott, 2003; Funahashi, 2001; Jurado & Rosselli, 2007). Executive functioning, which is thought to have an impact on all aspects of behaviour, can be distinguished from general cognitive abilities which are considered to be domain specific (Lezak, et al., 2004). It is commonly suggested that Working Memory (WM), Attention, Inhibition and Cognitive Flexibility are the principle components of executive functioning (e.g. P.

Anderson, 2002; Davidson, et al., 2006; Elliott, 2003; Funahashi, 2001; Jurado & Rosselli, 2007; Miyake, et al., 2000); and that these skills, which are mainly mediated by the prefrontal cortex (e.g. Funahashi, 2001; Jurado & Rosselli, 2007; P. Ohrmann, et al., 2004), work together to enable, guide and control thought, emotion and behaviour. The difficulty in measuring these constructs individually within the system of executive functioning is that they all overlap and work interactively. Many tasks measuring attention can also be conceptualized as measuring working memory; and are referred to in the literature as working memory tests as well as tests of executive attention. Also, inhibition can be measured using tasks which are thought to be reflective of motoric inhibition, and tasks that are thought to reflect attentional control or cognitive inhibition. Furthermore, many of the tasks measuring working memory, attention and inhibition rely on some level of cognitive flexibility. The truth is that the majority of tasks measuring executive functioning rely upon more than one aspect of the construct.

Research exploring the executive functioning of ED subjects has not always been consistent (e.g. Andres-Perpina, et al., 2011; Palazidou, Robinson, & Lishman, 1990; Zakzanis, Campbell, & Polsinelli, 2010). It is unknown however, whether this is due to a true lack of evidence for the existence of executive impairments, or whether these inconsistencies in the evidence highlight inconsistencies between research measures, and the interactive nature of the executive functioning system. Below is a discussion of the evidence regarding the constructs of working memory, attention and inhibition, which are explored in this thesis.

2.3.2.1 Working Memory

Working memory (WM) refers to a set of storage and executive control processes that enable information to be held temporarily in mind and manipulated, while suppressing irrelevant information that may cause interference (Baddeley, 2007; Cowan, 1995; Shallice, 1988). Though one early study found evidence of WM deficits in AN patients, both in the acute phase of illness and after weight

restoration (Green, Elliman, Wakeling, & Rogers, 1996a); findings from this early study cannot be generalized due to the very small, clinical sample employed. Recent research consistently provides evidence to suggest that ED patients show comparable WM capacity to healthy controls, both in the acute phase of illness and after weight restoration/recovery (Bosanac, et al., 2007; Nikendei, et al., 2011). There is also some evidence to suggest that patients with AN exhibit superior working memory performance in comparison to healthy controls. In one study superior working memory was observed in underweight adolescent females presenting with their first episode of AN (Hatch, et al., 2010); and Hatch and colleagues found that after weight restoration working memory improved in the AN group relative to their performance prior to weight gain.

More recently, researchers have investigated the influence of food, weight, and shape cognitions on working memory performance. Kemps and colleagues investigated working memory deficits using the double span memory task, and found that AN patients showed impaired performance in comparison to healthy controls. As part of the study however, participants completed a self-report measure assessing pre-occupying cognitions about food, weight and body shape. AN patients reported significantly more pre-occupying cognitions than healthy controls, and when this was controlled for differences between groups became non-significant (2006). Extending this result, two studies found that healthy controls made more errors on the N-back task (Gevins & Cutillo, 1993) than female patients with restricting AN; but this superior performance by AN groups was compromised by the subliminal presentation of food stimuli, and on these trials patient's performance was comparable to controls (Brooks, et al., 2012; Dickson, et al., 2008). The authors speculate that individuals with AN continuously use their working memory system to suppress their appetite on a daily basis. This may make their working memory system excessively proficient, to a point that it is counterproductive i.e. through excessive rumination, inflexible thought, or attention to detail. This study is limited by its very small sample size however.

A review by Van den Eynde and colleagues highlights the paucity of neuropsychological research pertaining to BN and EDNOS sub-groups. The few

studies that have investigated working memory in bulimic groups have found no impairments on a range of tasks (Bosanac, et al., 2007; Brand, Franke-Sievert, Jacoby, Markowitsch, & Tuschen-Caffier, 2007; Galderisi, 2010; Lauer, Gorzewski, Gerlinghoff, Backmund, & Zihl, 1999); more research is required however.

Interim Conclusions

It is clear from the small number of studies investigating working memory performance in ED groups that further research is required. Studies to date suffer from having very small samples. In addition, a wide range of different tasks have been used, making comparisons between studies difficult. Despite this, the evidence points towards AN groups having a working memory capacity that is either comparable, or possibly even superior to healthy controls. If it is the case that presence of an ED is associated with superior working memory it would be interesting to know whether this is present prior to onset, or whether superior performance is a result of a constant use of the system to inhibit appetitive drives as Brooks and colleagues suggest (Brooks, et al., 2012).

2.3.2.2 Attention

The act of attending to any stimulus varies as a result of that which requires attention and the surrounding environment in which an individual is required to attend: i.e. whether one is required to attend to more than one stimulus simultaneously; whether it is necessary to switch between different stimuli; or whether attending to a stimulus also necessitates the inhibition of other distracting or pre-potent stimuli. As a result, attention cannot be regarded as a single construct (Manly, et al., 2001).

In the field of ED, a wide variety of tasks have been used to measure different kinds of attention, making it difficult to compare findings. In addition, the majority of studies use small clinical samples limiting the power of the investigations; and making findings specific to treatment seeking ED populations. The following

section of this thesis outlines recent research pertaining to the attentional capacities of ED groups according to the specific attentional construct being measured.

Attentional Control

Attentional control, also referred to as cognitive inhibition, reflects an individual's ability to inhibit pre-potent, irrelevant or distracting stimuli while performing a specific task. The majority of research investigating attentional control within ED groups uses the Stroop task (Stroop, 1935), which requires the inhibition of a well-learned pre-potent response. A great deal of research has been conducted using the original word-colour version of the Stroop, and also a modified version of the Stroop which uses disease salient stimuli. The conclusions from a review of Stroop performance were that while the attentional bias seen in BN groups extends to a range of different stimuli, attentional bias within AN groups appears to be specific to body and weight stimuli (Dobson & Dozois, 2004).

The implied association between BN and impaired attentional control was further explored in a study which investigated whether the *level* of bulimic symptomatology was associated with performance on the emotional Stroop task (J. M. G. Williams, Mathews, & MacLeod, 1996). A comparison was made between healthy controls, women with sub-clinical BN type symptoms, and women diagnosed with BN (Lokken, Marx, & Ferraro, 2006). Results showed that the *level* of BN symptomatology was the best predictor of task performance, with an increase in severity being associated with poorer performance. The association between attentional control and BN type symptomatology was also investigated in a recent study which compared Stroop performance of ED patients who binged and purged with patients who restricted. Claes and colleagues found that bingeing and purging patients took longer to complete the original Stroop, and they made more errors (Claes, Mitchell, & Vandereycken, 2011). Unfortunately this study did not employ a healthy control group for comparison.

Kemps and Wilsdon recently explored the association between impaired attentional control and impulsivity in BN subjects. They assessed the performance

of female patients with BN on the Stroop task, and other attentional tasks that require the inhibition of pre-potent responses. BN patients exhibited significantly poorer performance on all measures when compared with healthy controls (Kemps & Wilsdon, 2010). As part of the study participants also completed a self-report measure of impulsivity, and BN patients were found to be more impulsive than healthy controls. Interestingly, the researchers found that controlling for impulsivity reduced group differences to non-significance for both the Stroop colour naming task, and the excluded letter fluency task. The authors propose that their findings provide support for the notion that the cognitive disinhibition/lack of attentional control that is characteristic of BN patients is reflective of an impulsive nature (Lena, et al., 2004).

Attentional control has also been investigated in sub-clinical groups high in ED cognitions and dieting behaviours. Findings indicate an association between poor performance on a modified Stroop task and ED cognitions (Pringle, Harmer, & Cooper, 2010); episodes of overeating; and shape and weight concerns (Aspen, et al., 2011); suggesting deficits in attentional control exist prior to clinical level ED and may therefore be present prior to onset.

Selective Attention

Selective attention, often referred to as information processing, refers to an individual's ability to selectively attend to relevant stimuli. Using the d2 Brickenkamp Letter Cancellation Task (LCT) (Brickenkamp & Zillmer, 1998), Brand and colleagues found no differences in selective attention between BN patients and healthy controls (Brand, et al., 2007); however findings from this study are limited by the small sample employed which may not have provided sufficient power to pick up subtle differences. A more recent study by Van den Eynde and colleagues, using the same task, found that both BN patients, and patients with the BN type EDNOS, performed more poorly than healthy controls (Van den Eynde, Samarawickrema, et al., 2011). Impaired selective attention/information processing has also been observed in AN patients (Fowler, et al., 2006). Research investigating selective attention in recovered ED patients is limited; however an early study found that though AN and BN groups showed

impaired selective attention during the acute phase of illness, both groups showed pronounced and significant improvements after seven months of therapy (Lauer, et al., 1999). This suggests that impaired selective attention may be state dependent, and therefore not present prior to onset of an ED.

Divided Attention

Divided attention refers to an individual's ability to attend to more than one task simultaneously. Poor performance on tests of divided attention have been observed in both AN (Ohrmann, et al., 2004) and BN (Lauer, et al., 1999) patients. Research investigating divided attention within recovered ED groups is sparse; however, Lauer and colleagues did find that the deficits in divided attention that were observed in AN and BN groups were much improved after seven months of therapy (Lauer, et al., 1999). This suggests deficits in divided attention may be a secondary effect of an ED, rather than being present prior to onset.

Sustained Attention

Sustained attention refers to an individual's ability to keep attention focused on stimuli for an extended period of time. In a systematic review of neurocognition in bulimic groups, the authors concluded that findings pertaining to sustained attention in BN groups were mixed (Van den Eynde, Guillaume, et al., 2011). With regard to AN, Seed and colleagues found that patients were severely impaired on a vigilance task measuring sustained attention, when compared with healthy controls (Seed, Dixon, McCluskey, & Young, 2000); however this finding is limited by the small sample sizes of both participant and healthy control groups. Research investigating sustained attention in recovered groups is limited, however Hatch and colleagues found that after weight gain, the performance of AN patients was superior to that of healthy controls (Hatch, et al., 2010) which suggests that the deficits observed are state dependent, rather than being present prior to onset.

Allocation of Attentional Processing

Bosanac and colleagues found that in comparison to healthy controls, underweight AN and BN patients exhibited low 'Power of Attention' scores on the Cognitive Drug Research Battery (CDR) (Simpson, Surmon, Wesnes, & Wilcock, 1991).

'Power of Attention' is a measure of allocation of attentional processing to a particular task (Bosanac, et al., 2007). Further investigation of this construct is required however as evidence is limited.

Switching of Attention

A meta-analysis performed by Stedal and colleagues showed that patients with AN perform significantly worse than controls on the Trail Making Test (Reitan, 1992; Stedal, et al., 2011), showing an impaired ability to switch attention. This same group also found subtle impairments in attention switching in their own sample of 155 patients with AN using the Trail Making Test (Stedal, et al., 2012); though patient data was compared to normative data for comparison, rather than employing a healthy control group. In a study comparing ED patients who restricted with patients who binged and purged, Claes and colleagues found that bingeing and purging patients took longer to complete the Trail Making Test (Claes, et al., 2011). Unfortunately this study also did not employ a healthy control group for comparison. With regard to performance in recovery, Hatch and colleagues found that AN patients performance was superior to that of healthy controls after weight gain (Hatch, et al., 2010), which suggests that the deficits observed are not independent of illness state.

Interim Conclusions

While the majority of research points towards the existence of some attentional impairment in ED individuals, it is unclear whether these impairments are traits associated with risk of developing the disorder or are caused by it. Research investigating the attentional capacities of weight restored and recovered groups suggests that performance improves (Hatch, et al., 2010; Lauer, et al., 1999); however this type of research is limited due to the small number of studies and the lack of research regarding the majority of attentional constructs. To date, no research has been conducted investigating the attentional capacities of first degree relatives of probands. In addition, a more systematic approach is required in the investigation of attentional capacity which uses a variety of measures assessing different attentional constructs.

Despite the indication of ED being associated with some level of attentional impairment, it is important to acknowledge the mixed findings in the literature. The limited research investigating the relationship between attentional capacity and the specific restricting and binge-purge subtypes of AN and BN have produced interesting results. As outlined above, research points towards an association between bingeing and purging behaviours and poorer performance in tasks assessing attentional control and switching of attention (Claes, et al., 2011). In addition, both BN patients and BN type EDNOS patients exhibit similar deficits in selective attention (Van den Eynde, Samarawickrema, et al., 2011). More research is required, but it is possible that particular impairments in attention are specifically associated with bingeing and/or purging behaviours, rather than a diagnosis of AN or BN; and this may provide a partial explanation for contradictory findings in the literature.

2.3.2.3 Behavioural Inhibition

Inhibition has long been considered critical for efficient executive functioning due to its role in suppressing and controlling actions and thoughts that are, or have become inappropriate due to changes in the environment; enabling flexible and goal directed behaviour (e.g. Funahashi, 2001; Verbruggen & Logan, 2008). It has been suggested that an inability to inhibit counterproductive thoughts, feelings or actions could be key to the development of AN (Oberndorfer, Kaye, Simmons, Strigo, & Matthews, 2011). However, a lack of inhibition is generally associated with bulimic individuals, or anorexic individuals who engage in bingeing behaviour (AN-BP), because of the "loss of control" criteria that is necessary for diagnosis of a binge (Lock, Garrett, Beenhakker, & Reiss, 2011).

Previous research investigating inhibition in restricting and eating disordered groups has produced inconsistent findings. As Waxman reports in her review, studies using behavioural measures of inhibitory control are evenly divided, making it difficult to draw any conclusions (Waxman, 2009). One possible reason for this is the use of different neuropsychological tasks to assess this construct. In

addition, the different tasks may also measure different elements of the construct of inhibition. It has been suggested, for example, that performance on two behavioural measures commonly used to assess motor inhibition in ED groups: the stop-signal task (Logan, 1994), and the Go/No-Go task (Mesulam, 1985); are not comparable as they are measuring distinct facets of inhibition (Meule, Lukito, Vögele, & Kübler, 2011). Both tasks require the inhibition of pre-potent responses; however the act of inhibiting is required at different points. In the stop-signal task, the cue to act is given in every trial, and in a minority of trials it is followed by a cue to inhibit that action. In this way, the stop-signal task is assessing an individual's ability to inhibit a behavioural response that has already been initiated. In contrast, for the Go/No-go task the decision to respond (or not) is made at the beginning of every trial, therefore inhibitory control is applied prior to the action/response being initiated. It is possible therefore that performance in one of these tasks will differ from the other due to differences in what specifically is being measured, rather than differences in methodology or sample characteristics. The following section of this thesis outlines recent research in this area, focusing on results from studies using these two behavioural measures.

Stop-signal Task

The limited research investigating performance of ED patients on the Stop-Signal task provides mixed findings. An early study using the Stop-signal task to assess inhibitory control across ED subtypes (AN-R, AN-BP, and BN) found no differences in performance in comparison to healthy controls, though it is important to note that sample sizes in this study were very small (Claes, Nederkoorn, Vandereycken, Guerrieri, & Vertommen, 2006). More recently, Boisseau and colleagues also found no differences in Stop-signal task performance between ED patients and healthy controls, though in this study ED patients were not divided into their sub-types and once again sample sizes were small (Boisseau, et al., 2012). In contrast to the findings from these two studies, Galimberti and colleagues recently found that AN patients performed more poorly than healthy controls on the Stop-signal Task, but no differences were observed between BN patients and healthy controls (Galimberti, et al., 2011). It is possible that studies finding no significant differences in Stop-signal performance between ED patients and healthy controls

do not have the required power to detect subtle differences; however more research is required to investigate this further.

Go/No-go Task

Though different variations of the Go/No-go task have been used to assess inhibitory control in ED groups, they all rely on inhibition of a pre-potent behavioural response *prior to initiation* of that response. In other words, this task does not require participants to stop an action that they have already started; rather it requires participants to not respond in the way that they are used to responding. It is important to note however that many versions of the Go/No-go task use reward/punishment in the form of monetary gains and losses; meaning performance could be associated with differential responses to reward or threat stimuli rather than being specific to response inhibition.

In a study comparing Go/No-go task performance across ED subtypes, Rosval and colleagues found that patients with AN-BP and BN performed more poorly than patients with AN-R and healthy controls; though this difference was only significant for the AN-BP group (Rosval, et al., 2006). In addition, these differences were only observed in the punishment condition of the task. Though this condition is thought to be most sensitive to problems with response inhibition, it is important to consider the possibility that this finding is also associated with response to threat cues. In contrast to these results, Van den Eynde and colleagues conducted a systematic review of neurocognition in bulimic type eating disorders and concluded that there was no evidence of BN patients exhibiting impaired performance on the Go/No-go task (Van den Eynde, Guillaume, et al., 2011). The same team of researchers found no differences in Go/No-go task performance in their own study comparing patients with BN or EDNOS-BN with healthy controls (Van den Eynde, Samarawickrema, et al., 2011). In an earlier study however, Bruce and colleagues used the Go/No-go task to investigate inhibitory control in BN patients that either did or did not misuse laxatives (Bruce, Koerner, Steiger, & Young, 2003). Results showed that under cues of punishment, BN patients who did misuse laxatives performed significantly worse than both healthy controls and BN patients who did not misuse laxatives, while these last two groups performed

comparably. As this difference in performance was only observed in response to cues of punishment, the authors suggest that BN patients who misuse laxatives may be more disinhibited when faced with the possibility of an adverse event.

Hatch and colleagues have also found impaired Go/No-go performance in adolescent AN patients and observed that this group made significantly more errors than healthy controls (Hatch, et al., 2010). In one particularly interesting study, Brooks and colleagues investigated performance on the Go/No-go task with and without the additional subliminal presentation of aversive and food stimuli (Brooks, et al., 2012). They found that patients with AN made significantly more errors than healthy controls. However, while the presentation of both aversive and food stimuli were associated with controls taking longer to correctly respond to targets, the performance of AN patients was not significantly affected by these subliminal presentations.

Recovered Groups

A study comparing neurocognition in first presentation adolescent AN patients before and after weight gain, found that while patients made significantly more errors on the Go/No-go task than healthy controls when they were underweight, their performance not only improved but was superior to that of healthy controls after weight restoration (Hatch, et al., 2010).

Sub-clinical populations

Nederkoorn, Eijs, & Jansen (2004), found decreased inhibition in restrained eaters using the stop-signal task (Nederkoorn, Van Eijs, & Jansen, 2004). Research using the Go/No-Go task however has revealed superior behavioural inhibition in restrained eaters (Meule, et al., 2011). As the authors of this study point out, this contradiction could indicate that restrained eaters show differing levels of inhibitory control depending upon the situation. Meule et al. (2011) suggest that this can be seen in the everyday behaviour of restrained eaters who generally show superior control in being able to restrict food intake (much like responses on the Go/No-go task), but once the decision to eat has been made they can find it

difficult to inhibit this already activated behaviour (like the decreased inhibition shown in performance of the stop-signal task).

Interim Conclusion

As can be seen, findings from studies investigating behavioural inhibition in ED populations have been varied and inconsistent. Though there is evidence of both impaired and enhanced inhibitory control from studies investigating sub-clinical populations, the lack of research investigating behavioural inhibition in recovered groups and the first-degree relatives of probands makes it impossible to conclude whether disinhibition is a trait associated with ED. Research in this area is vital to inform the development of interventions in the future.

Research using the stop-signal task is limited and studies do not differentiate between AN and BN sub-types. Studies using the Go/No-Go task that differentiate between AN and BN subtypes are more common, however findings are mixed. The presence of bingeing behaviours and the use of laxatives have both been associated with impaired inhibitory control, above and beyond a diagnosis of AN or BN (Bruce, et al., 2003; Claes, et al., 2011). These findings suggest that an attempt to further investigate contradictory findings regarding inhibitory control in both AN and BN groups should differentiate patients by the ED behaviours they experience.

2.3.3 Social Cognition

Social cognition refers to the set of cognitive processes that enable an individual to understand, relate to, and communicate effectively with others. These processes include skills in a range of dimensions: such as understanding the thoughts and feelings of others, (often referred to as emotional theory of mind); understanding socially accepted conventions such as conversational turn taking; and basic skills such as the ability to maintain eye contact, or the ability to recognise emotion from faces. Problems with social and interpersonal functioning have long been reported in eating disordered patients; and it has been suggested that interpersonal difficulties are at the core of eating disorder psychopathology (Fairburn, 1991).

Despite the evidence associating social and interpersonal difficulties with eating disorders, interpersonal psychotherapy (IPT) has demonstrated inferior outcomes in comparison to specialist supportive clinical management (McIntosh, et al., 2005; McIntosh, et al., 2006). An intervention or treatment in the social domain may need to address more basic social cognitive processes, prior to use of a more global intervention such as IPT (Zucker, et al., 2007). The development of such an intervention would require knowledge of the cognitive and behavioural features that characterize interpersonal processes in ED groups, for example emotion recognition.

Interpersonal difficulties have also been found to effect treatment of an ED, with evidence of difficulties in forming a therapeutic alliance in AN groups (Vitousek, Watson, & Wilson, 1998); and high levels of social anxiety being associated with disengagement from treatment (Goodwin, 2002). Overt differences in social and interpersonal functioning may be associated with underlying deficits in social communication and emotion recognition. As with differences in intellectual and executive functioning, it is possible that these differences are present prior to onset, perhaps affecting risk status for development of an ED. Research into groups with other psychiatric illnesses such as schizophrenia have found that indices of social cognition (i.e. social perception) mediate the relationship between neurocognitive impairment and overt functioning (Sergi, Rassovsky, Nuechterlein, & Green, 2006). It is possible that a similar relationship exists within ED groups. The following section of this thesis provides an overview of the relevant literature pertaining to social and interpersonal functioning, and emotion recognition, in relation to ED.

2.3.3.1 Social Functioning and Interpersonal Difficulties in Eating Disordered Groups

Women with ED have been shown to demonstrate significant impairments in a range of social domains (Zucker, 2007). A diagnosis of both AN and BN has been associated with impaired social relationships; with ED women reporting feeling more nervous, less sociable and less calm in comparison to controls (Bohle, von Wietersheim, Wilke, & Feiereis, 1991). Research also suggests that eating disordered individuals show difficulties with both social communication, and the expression of emotion (Leon, Lucas, Colligan, Ferdinande, & Kamp, 1985). A recent study showed that individuals with disorders of the binge/purge spectrum had a decreased ability to infer causality in interpersonal relationships, and were more likely to attribute negative affect within those relationships when compared to healthy individuals (Rothschild-Yakar, Eviatar, Shamia, & Gur, 2011). These differences also remained significant when controlling for depression, indicating a direct relationship between disordered eating and interpersonal difficulties.

Social and interpersonal difficulties in the family context

Studies investigating interpersonal functioning in the family context can provide evidence of social difficulties, however findings in the literature are inconsistent (e.g. Cook-Darzens, Doyen, Falissard, & Mouren, 2005; Whitney & Eisler, 2005). One consistency across studies however, is the discrepancy of reports among family members regarding interpersonal functioning; and it has been suggested that this discordance may be representative of differences in social perception and the way family members view social interactions (Zucker, 2007). Discordant reports of affective expression have been found between adolescents with AN and their mothers (Casper & Troiani, 2001). Findings from this study also showed that adolescents with AN-BP and their mothers were significantly more likely to report impaired family functioning than AN-R patients or healthy controls; highlighting the importance of comparing social functioning across ED subtypes. In another study, Cook-Darzens and colleagues interviewed all family members in 40 families that included an adolescent with AN (Cook-Darzens, et al., 2005). They found that perceptions of family functioning were significantly more discordant in families

including an adolescent with AN, than in healthy control families; and that reports of emotional closeness and conflict avoidance were inconsistent between family members of AN probands. Inconsistent reports regarding conflict avoidance were also found by Karwautz and colleagues in their investigation of sister pairs discordant for AN (Karwautz, et al., 2003). Research has additionally been conducted comparing interpersonal family functioning as perceived by family members and clinicians. Gowers and North (Gowers & North, 1999) found that both clinicians and patients were more critical of interpersonal functioning within the family context than parents; and improvements in the patients ED were not accompanied by improvements in family functioning.

Premorbid social functioning and comorbidity

Research investigating the presence of social difficulties prior to onset of an ED have either relied on retrospective accounts; or explored patterns of comorbidity with disorders that are defined by social deficits, and have onset prior to development of the ED. Evidence supports the notion that social and interpersonal difficulties exist prior to onset of an ED with studies finding high prevalence of separation anxiety disorder (Silberg & Bulik, 2005), social phobia (Melfsen, Walitza, & Warnke, 2006), and neurodevelopmental disorders of the ASD spectrum (Connan, Campbell, Katzman, Lightman, & Treasure, 2003) presenting in childhood. Furthermore, evidence suggests that individuals with an ED frequently experience social anxiety prior to onset (Kaye, 2004); and that the prevalence of premorbid social anxiety is higher in ED groups than in the general population (Godart, 2002). In addition, a retrospective study found that women with a history of AN-BP reported significantly higher levels of loneliness, shyness and feelings of inferiority in adolescence than healthy controls; and women with an history of BN reported higher levels of shyness in adolescence (Troop & Bifulco, 2002).

Eating Disorders and Autism Spectrum Disorders: and overlap of phenotypic expression

The notion that a quantitative trait approach to psychiatric illness may be more relevant than current diagnostic categorisation has growing support; particularly with respect to ED research (e.g. Treasure, 2012; Zucker, 2007). It has been

suggested that there may be an association between developmental traits that are normally associated with ASD and development of an ED (C. Gillberg, 1983, 1992). In their longitudinal study of AN in a community sample, Gillberg and colleagues found an overrepresentation of ASD in comparison to healthy controls (I. Gillberg, Råstam, & Gillberg, 1994). This AN group have also been found to have significantly more relatives presenting with social impairments that are associated with ASD (Råstam, Gillberg, & Wentz, 2003). More recently, Hambrook and colleagues found that females with an ED scored significantly higher on the Autism Spectrum Quotient than healthy controls (Garner, 1991b).

There is growing evidence of an overlap of intermediate phenotypes between AN and ASD (e.g. Faunce & Job, 2000; Odent, 2010; Treasure, 2012); and it has been suggested that the extensive research conducted investigating social cognition in ASD could be used as a 'roadmap' for future research investigating social cognition in ED (Zucker, 2007). Studies have shown that the interpersonal patterns present in ASD probands can be found at higher rates in family members, advocating social and interpersonal difficulties as possible intermediate phenotypes of the disorder (Piven, 2001). Taking a similar approach, an investigation of social and interpersonal functioning within family members of ED probands could help to identify potential intermediate phenotypes for ED in the domain of social cognition.

2.3.3.2 Emotion Recognition

The investigation of emotion recognition abilities in ED groups is a relatively new field of inquiry, however the majority of research indicates the presence of some level of disturbance (Faunce & Job, 2000). Zonnevijjlee-Bender and colleagues (Zonnevijlle-Bendek, van Goozen, Cohen-Kettenis, van Elburg, & van Engeland, 2002) were the first to empirically investigate the ability of adolescents with an ED to produce an emotional label in response to a facial expression. The faces were presented for two seconds each, and were expressing one of seven possible emotions: happiness, anger, sadness, fear, disgust, surprise, or contempt.

Participants were tested using both a free labeling paradigm, where they were expected to independently generate an emotional label; and a forced-choice paradigm with fixed possible responses. Results showed that the ED groups performed worse than healthy controls on both versions of the task. As a control measure, participants were also tested on their ability to match non-emotional faces. No differences were found between ED individuals and healthy controls, indicating that the observed deficit was specific to the identification of emotions, rather than due to deficits in the processing of facial cues. Unfortunately, the ED sample investigated in this study was too small to divide into diagnostic sub-groups (AN/BN/EDNOS). In addition, performance on each individual emotion was not investigated; which is limiting as evidence suggests there are differences in the processing of distinct emotions (Jones, Harmer, Cowen, & Cooper, 2008).

Following this initial study, the same group investigated the performance of adolescent AN patients on the same task, in comparison to both healthy controls, and a psychiatric control group made up of patients with depression or anxiety (Zonnevylle-Bender, Goozen, Cohen-Kettenis, Elburg, & Engeland, 2004). Both the AN group and the psychiatric control group showed comparative performance on the facial emotion recognition task; and both performed worse than healthy controls. Once again, this study was limited in that it did not analyse recognition of the different emotions individually. Finally, these researchers compared the performance of adolescent patients with AN to the performance of adult patients with AN, on the same facial emotion recognition task. No differences were found between adolescent and adult patients, but a healthy control group was not included for comparison (Zonnevylle-Bender, van Goozen, et al., 2004).

Another early study investigated the emotion recognition capacities of inpatients with AN, using a forced choice facial emotion recognition task with an even wider range of emotions: interest, happiness, surprise, sadness, disgust, contempt, anger, shame, and fear (Kucharska-Pietura, Nikolaou, Masiak, & Treasure, 2003). This investigation also examined performance on the Voice Emotion Recognition Test (VERT), in which neutral sentences are spoken aloud in a manner conveying one of six emotions: happiness, sadness, fear, anger, surprise, disgust, and neutral.

Individuals with AN (in comparison to healthy controls) exhibited impaired recognition of negative emotions from faces, particularly sadness and fear; and impaired recognition of emotion from voices, particularly happiness and sadness. Group differences in facial emotion recognition remained after controlling for a variety of clinical and socio-demographic factors, mainly due to inpatients with AN finding it more difficult to recognise fear; however, no group differences in vocal emotion recognition remained after adjusting for covariates. This early study highlights the importance of analyzing performance in relation to each distinct emotion, and also indicates that deficits in emotion recognition may vary across modality. As noted by Jansch and colleagues however, the fact that more negative than positive emotions were used in the task may have biased the result, revealing more difficulties in the recognition of negative emotions by AN individuals (Jänsch, Harmer, & Cooper, 2009).

Since these initial studies this particular field of inquiry has grown to include a range of emotion recognition tasks; with some studies finding deficits in emotion recognition and others not. Mendlewicz and colleagues (Mendlewicz, Linkowski, Bazelmans, & Philippot, 2005) compared the emotion recognition capacities of patients with AN, patients with depression and healthy controls. Though they did find that depressed patients were less accurate at recognising emotion from faces than healthy controls, no impairments were found in the AN groups. Kessler and colleagues (Kessler, Schwarze, Filipic, Traue, & von Wietersheim, 2006) investigated the emotion recognition capacity of both AN and BN inpatients on the Facially Expressed Emotion Labeling (FEEL) test; which also adopts a forced choice paradigm, but limits the range of emotions to anger, fear, sadness, happiness, surprise, and disgust. They reported no differences in the performance of AN and BN groups; and no differences between the ED group as a whole and healthy controls, except for a small but significant decrease in the recognition of surprise by individuals with an ED.

The majority of the following research in the field has focused on the emotion recognition capacities of AN patients. Pollatos and colleagues (Pollatos, 2008) explored the possibility that the observed impairments in emotion recognition

from facial cues might be reflected in brain activity by measuring visual-evoked potentials. Also using a forces choice paradigm, and limiting the range of emotions to the same six emotions as Kessler (Kessler, et al., 2006); the authors found that AN patients made significantly more mistakes than healthy controls. When analyzing recognition of each emotion individually, results showed significantly decreased performance in the recognition of neutral, sad and disgusted faces. With regard to brain activity, findings showed that AN patients exhibited increased N200 amplitudes in response to all face categories. The authors highlight that in the literature, enhanced N200 amplitudes are reflective of the reduced resources available for attentional control (T. Dennis & Chen, 2007); and suggest that this view is consistent with their findings, as enhanced N200 amplitudes were correlated with lower task performance. A second finding regarding brain activity was that AN patients showed decreased P300 amplitudes when responding to negative emotions, and the authors interpret this as evidence for a diminished cognitive processing ability for negative facial emotions.

An investigation into facial emotion recognition within AN individuals, which used the Facial Expression Recognition Test (FERT), revealed decreased emotion recognition; increased misclassification of emotions; and slower responses in comparison to controls (Jänsch, et al., 2009). The FERT differs from previously described tests of emotional recognition in that each facial expression morphs from neutral (0% intensity) to full emotion (100% intensity) in 10% increments; and is in this way more representative of how facial emotion recognition is perceived in everyday life. Unlike previous studies, no significant differences were found between groups on any individual emotion, only in overall performance. The results of this study also suggest that medicated individuals may respond quite differently to those not using medication. A comparison of AN patients that were and were not taking medication at the time of testing showed that the medicated group were more accurate at identifying all emotions aside from fear; but were slower than the un-medicated group at identifying all emotions aside from disgust. In addition, AN patients taking medication misclassified more faces as fearful, while those not on medication did not. Finally, un-medicated patients showed less accuracy in the recognition of disgust, than medicated patients. Results also

suggest that depressive symptoms, while making some difference when additionally controlled for, do not provide a complete explanation for the deficits in emotional processing observed (Jänsch, et al., 2009). Castro and colleagues (Castro, Davies, Hale, Surguladze, & Tchanturia, 2010) also investigated the effect of comorbid psychiatric disorders on facial emotion recognition in individuals with AN. Focusing only on the recognition of happy and sad faces, the authors found that AN patients performed more poorly than controls in the recognition of sad faces; however no differences were found between groups in the discrimination of happy faces. They also found that the presence of obsessive-compulsive symptoms was the strongest predictor of the decreased emotion recognition of sad faces observed in the AN group.

There has been one investigation into the facial emotion recognition capacities of individuals with BN. Legenbauer and colleagues (Legenbauer, Vocks, & Rüddel, 2008) used an assessment which presented static faces expressing one of the six basic emotions used in previous studies described above. No differences were found in the overall recognition of emotion between BN and healthy control groups; but the BN group was significantly less accurate in the recognition of surprise specifically. Women with BN have also shown differences in emotion processing in response to film clips, revealing an enhance ability to recognise negative emotion (Kenyon, et al., 2011).

More complex emotion recognition has been assessed in ED groups using the Reading the Mind in the Eyes (RME) task, in which participants are shown a series of photographs depicting a pair of eyes that are expressing a complex emotional state (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Participants are expected to choose the correct emotional state to match the eyes from the four options provided. There is some evidence in the literature of women with AN performing poorly on this task in comparison to controls (Harrison, Sullivan, Tchanturia, & Treasure, 2009; Russell, Schmidt, Doherty, Young, & Tchanturia, 2009), though there is also evidence to the contrary (Medina-Pradas, Navarro, Alvarez-Moya, Grau, & Obiols, 2012). There is also limited evidence of women with

BN and EDNOS performing poorly on the RME task (Melfsen, et al., 2006); but once again there is also evidence to the contrary (Kenyon, et al., 2011).

Emotion Recognition in Recovered Samples

With the aim of establishing whether deficits in emotion recognition are a trait associated with ED psychopathology; or are an effect of state and due to secondary features of the illness such as low nutritional intake; two studies have investigated the presence of impaired emotion recognition in women who have recovered from AN. Oldershaw and colleagues used the RME task; the Reading the Mind in the Voice (RMV) task, a task assessing recognition of emotion from voices; and the Reading the Mind in Films (RMF) task, a task assessing the recognition of emotion from film clips (Oldershaw, 2010). Currently ill participants and recovered participants were worse than healthy controls in recognising negative emotions in the RME task. In contrast, participants recovered from AN were better than currently ill participants at inferring positive emotions from voices; and both recovered participants and healthy controls were better than currently ill participants at inferring negative emotions from voices. Finally, currently ill AN participants were worse than both of the other groups at identifying negative emotions in the RMF task. The authors conclude from their findings that poor emotion recognition is an effect of state, rather than being a trait associated with AN. The second study also used the RME task, but the findings were quite different. Harrison and Colleagues found that both the AN group, and the recovered AN group, performed significantly worse than controls; and the authors concluded that deficits in emotion recognition appear to be a trait associated with AN, rather than an effect of state (Harrison, 2010).

Emotion Recognition in Non-clinical Samples

Under the premise that dieters are at higher risk of developing an ED than those who do not diet (Cook-Darzens, et al., 2005; Jacobi, Hayward, et al., 2004; Rothschild-Yakar, et al., 2011), there are an increasing number of investigations with dieting groups, and non-clinical samples with high eating pathology. The aim of these studies is to gain some insight into whether decreased or biased emotion recognition is present prior to onset of an ED, and could possibly contribute to the

development of the disorder. Jones and colleagues investigated facial emotion recognition in a group of female undergraduate students, comparing the performance of women with either high and low levels of ED symptoms (Jones, et al., 2008). They found that women with high levels of ED symptoms were less accurate when recognising happy and neutral faces; showed a trend towards poorer discrimination of angry faces; but were better at discriminating surprise. They also found that these differences remained when controlling for feelings of depression and anxiety. Pringle and colleagues also found an association between ED symptoms and emotion recognition capacity in a group of female dieters; with incorrect classification of both neutral and angry faces significantly predicting subclinical ED symptoms (Pringle, et al., 2010).

Two further studies by Ridout and colleagues extended this research. In the first, they found that women with high levels of subclinical ED symptoms (in comparison to those with low levels of symptoms) exhibited an overall deficit in the recognition of emotion from video-taped social interactions; with a specific association between impaired anger recognition and body dissatisfaction (Ridout, Thom, & Wallis, 2010). In the second study they investigated whether emotion recognition capacity was affected by the intensity of facial expression (Ridout, Wallis, Autwal, & Sellis, 2012). Results showed that in comparison to women with low levels of subclinical ED symptoms, women with high levels of ED symptoms were less accurate overall; and showed specific deficits in the recognition of anger and fear, making more fear-as-anger and anger-as-fear errors. This deficit in facial emotion recognition was found to be more evident when participants were responding to expressions of lower intensity. In addition, the researchers once again found that deficits in anger recognition specifically were related to body dissatisfaction; which is consistent with their finding above when using video-taped social interactions as stimuli.

Interim Conclusions

It is clear that further research is required into the social functioning/communication and emotion recognition capacities of ED groups. Current research investigating social functioning in ED groups highlights the

importance of differentiating by subtype; with the AN-BP subtype showing a particularly strong association with impairments (Casper & Troiani, 2001; Hartmann, Zeeck, & Barrett, 2010; Troop & Bifulco, 2002). As highlighted above, this subtype has also been linked with difficulties in treatment and poor treatment outcome (Steinhausen, 2002); and it is possible that impaired social functioning contributes to these difficulties. Given the heterogeneity of AN-BP samples, it would be interesting to investigate whether it is the presence of restriction, combined with bingeing and/or purging behaviours, that is particularly associated with impaired social functioning.

The majority of research investigating emotion recognition has employed AN samples, with groups rarely being divided into their restricting/binge-purge subtypes. Given the evidence regarding social functioning, it seems that differentiating ED individuals according to their restricting/binge-purge subtypes, or the presence of ED behaviours such as restricting/bingeing/purging, is vital. It is possible that the increased presence of impaired social functioning in AN-BP groups could be associated with impaired emotion recognition that is also specifically associated to this ED subtype.

2.4 Conclusions

This chapter explains how the high-risk method can contribute to neuropsychological research in the field of ED; and discusses the importance of knowing whether the neuropsychological differences observed in clinical groups are present prior to onset and are therefore independent of illness state, possibly making them putative intermediate phenotypes of the disorder. As can be seen from the review above, despite conflicting findings in the literature, the presence of an ED does appear to be associated with differences in neuropsychological functioning and social cognition. The inconsistencies present in the literature are to be expected if taking into account limitations of current research. Frequently the measures used in various studies are very different, and findings are therefore incomparable. The heterogeneity of the samples used, with regard to the severity

of illness, time of onset, and duration of illness could also have an effect, especially if executive dysfunction exists as a result of the disorder, or is made more severe by it (Kaplan, 2002). In addition, comparisons are generally made to normative groups, which cannot give evidence of individual impairment in comparison to premorbid functioning (Bayless, et al., 2002). There are also methodological limitations that could explain contradictory findings. As has been highlighted throughout this chapter, many studies have used very small samples, while others have lacked a control group for comparison (Bayless, et al., 2002).

It is possible that some of the deficits found may be the result of restricting nutritional intake and/or low weight. Experiments have shown that individuals currently dieting display poor working memory and planning abilities, and the results of this line of research generally implicate preoccupying cognitions about food as the mediating variable (e.g. Green, et al., 2003; Green & Rogers, 1998). However, impaired neuropsychological functioning could exist in sufferers prior to onset and affect risk status for the development of an ED. Brain abnormalities within ED individuals have been discovered, and though many suggest these are a result of malnutrition, there is evidence to suggest that not all of these abnormalities revert back to normality after weight restoration (Lena, et al., 2004). Investigation pertaining to cognitive flexibility (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005; Kanakam, Raoult, Collier, & Treasure, 2012; Roberts, et al., 2010; Tenconi, et al., 2010) and central coherence (Kanakam, et al., 2012; Tenconi, et al., 2010) in women with an ED and their unaffected sisters has provided some evidence of similar impairments in both groups; with performance that is significantly poorer than healthy controls with no personal or family history of an ED. These studies implicate impaired cognitive flexibility and weak central coherence as intermediate phenotypes, possibly affecting risk status for developing an ED. Studies of this nature are vital for other neuropsychological constructs within the systems of executive functioning, intelligence, global cognitive functioning, and social cognition.

Chapter 3

Aims and Methodology

3.1 General Aims

The aim of the studies in this thesis was to investigate neuropsychological functioning, social communication, and emotion recognition, in children at high risk of developing an ED, due to being born to a mother with an ED. High risk status has been defined in two ways: (i) maternal self-report of a diagnosis of an ED during pregnancy with the index child; and (ii) maternal ED behaviours over lifetime. This chapter gives an explanation of how this was done, and discusses relevant methodological considerations. The studies conducted employ sub-samples from the Avon Longitudinal Study of Parents and Children (ALSPAC): a longitudinal cohort study that is also explained in detail. The specific aims of each of the studies in this thesis are described below.

Study One: Intelligence, Global Cognition and Executive Functioning in Children at High Risk of Developing an Eating Disorder (Chapter 4)

The aim of this study was to investigate whether children at high risk of developing an ED show differences in intelligence, global cognition, attention, working memory, and inhibition, when compared to children who are not at high risk. For this study high risk status in the children was determined via self-report of an ED diagnosis by the mother, before the birth of the index child. The intelligence and executive functioning of children whose mothers reported history of an ED was compared with children whose mothers reported no history of any psychiatric illness.

Study Two: Are Maternal Lifetime ED Behavioural Phenotypes Associated with Children's Intelligence, Global Cognition and Executive Functioning? (Chapter 4)

The aim of this study was to investigate whether lifetime maternal eating disorder behaviours are an accurate predictor of executive functioning and general

intelligence in children at high risk. For this study high risk status in the children was defined as the presence of maternal eating disorder behaviours over lifetime. Data on maternal lifetime eating disorder behaviours were collected as part of a two-phase prevalence study. The children of mothers who had engaged in eating disorder behaviours over their life were compared with the children of mothers who had not.

Study Three: The Relationship between Social Communication and Emotion Recognition from Facial and Non-facial Cues, in a Community-Based Sample of Children (Chapter 5).

The aim of this study was to provide further validation for the use of the Emotional Triangles Task, a novel measure of emotion recognition from social motion cues that has previously only been used in a sample of adults with Autism Spectrum Disorder. The effectiveness of this measure was investigated in a large community sample of children with the purpose of validating its effectiveness in (i) children as well as adults, and (ii) the general population as well as an autistic sample; prior to using the task to investigate emotion recognition in children at high risk of developing an ED. This was done by determining whether the capacity to recognise emotion from social motion cues (Emotion Triangles Task) was associated with social communication difficulties, as measured by the Social Communication Disorders Checklist (SCDC); and by comparing emotion recognition from social motion cues with emotion recognition from facial expression as measured by the Diagnostic Analysis of Non-Verbal Accuracy (DANVA).

Study Four: Social Communication and Emotion Recognition in Children at High Risk of Developing an ED (Chapter 6)

The aim of this study was to investigate whether children at high risk of developing an ED show differences in social communication and emotion recognition, in comparison to children who are not at high risk. For this study high risk status in the children was determined via self-report of an ED diagnosis by the mother, before the birth of the index child. Social communication and emotion recognition of children whose mothers reported history of an ED was compared with children whose mothers reported no history of any psychiatric illness.

Study Five: Are maternal ED behavioural Phenotypes Associated with Social Communication and Emotion Recognition Difficulties in Offspring? (Chapter 6)

The aim of this study was to investigate whether maternal lifetime ED behaviours are an accurate predictor of children's social communication and emotion recognition abilities. For this study high risk status in the children was defined as the presence of maternal eating disorder behaviours over lifetime. Data on maternal lifetime eating disorder behaviours were collected as part of a two-phase prevalence study. The children of mothers who had engaged in eating disorder behaviours over their life were compared with the children of mothers who had not.

3.2 The Avon Longitudinal Study of Parents and Children (ALSPAC)

3.2.1 Study Overview

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a multi-generational, longitudinal, and prospective, population-based study of women (who were recruited during pregnancy), and the child that they were pregnant with at the time. ALSPAC was founded with the aim of increasing knowledge and understanding of the contribution of both environmental and genetic influences on health and development over time. Women were eligible if they lived in a pre-defined study area in South West England (formerly known as Avon) at the time of pregnancy; and if their expected date of delivery was between 1 April 1991 and 31 Dec 1992. Biomedical, psychological, and lifestyle information about the mothers and their children has been collected over the last 19-22 years, through questionnaires, clinics and psychological assessments.

3.2.2 Participants

Women were excluded from the initial recruitment if they experienced loss of their pregnancy prior to 23 weeks (n = 717), leaving 14,541 pregnancies in the initially recruited pregnancy cohort. A further 674 pregnancies were excluded post recruitment due to there being no live birth (n = 604), or due to the birth outcome being unknown (n = 69). One additional pregnancy was also excluded due to there being only one live birth from a twin pregnancy. The initial pregnancy cohort was inclusive of 13,761 mothers plus the 13,867 children that they gave birth to: inclusive of 195 twins, 3 triplets, and 1 quadruplet. (De Haan, Belsky, Reid, Volein, & Johnson, 2004; Izard, 2002).

Sample characteristics and representativeness

For the 13,761 women that were initially enrolled, obstetric and socio-demographic data collected 8 months after childbirth has been used to assess whether the ALSPAC cohort is representative of the area of Avon, and the whole of Great Britain. Results from the 8 month post-natal questionnaire were compared to data from the 1991 census on mothers with an infant less than a year old. The 8 month questionnaire was completed by approximately 80% of the initially enrolled cohort; therefore the comparisons made are representative of eligible pregnancies that were enrolled, and enrolled pregnancies that completed this questionnaire (Izard, 2002). Mother's enrolled in the cohort who completed the 8 month postnatal questionnaire were more likely to live in owner occupied housing; have a car in their household; and be married, than those in Avon or the whole of Great Britain. They were also less likely to be non-white. It is noteworthy that despite socio-demographic factors indicating a higher socio-economic position on the whole, a higher proportion of mothers enrolled in the cohort lived in houses with more than one person sharing a room on average (see table 1).

Table 1 Socio-demographic characteristics of mothers enrolled in the ALSPAC cohort, mothers in Avon, and mothers in the whole of Great Britain

Characteristic	ALSPAC Participants (%)	Avon (%)	Great Britain (%)
Owner Occupied Housing	79.1	68.7	63.4
1 + person per room	33.5	26.0	30.8
Car in household	90.8	83.7	75.6
Married couple	79.4	71.7	71.8
Non-white mother	2.2	4.1	7.6

1. Table adapted from an ALSPAC cohort profile (Izard, 2002)

3.2.3 Procedures

Recruitment & Maternal Questionnaires

Eligible women were recruited using posters; which were displayed in places that were likely to be frequented by pregnant mothers such as doctor's surgeries, ante-natal clinics, chemists, and playgroups. Information about the study was also passed on to newly pregnant women by the midwife that they initially met with. In addition, ALSPAC received both local and national media coverage inviting eligible mothers to participate. Women were initially given a card to complete and return; asking for their name, contact details, date of their last menstrual period and their estimated due date. By completing and returning this card women were effectively expressing an interest in participation, and they were sent a brochure with full details of the study. The brochure outlined the overall aims of ALSPAC; provided assurances that all information collected would be kept confidential and unconnected to their name/contact details; and explained that though there were no tangible benefits for the mother, there would be a great deal of benefit for future generations as a result of the data that were collected. The brochure also explained that from this point onwards ALSPAC would presume that the mother was happy to participate, but the mother could opt out by informing the study team at any point, either now or in the future. Those women who did not opt out over the next week were sent their first questionnaire, which was appropriate to their gestational time point. If the mother did not respond to any of the maternal questionnaires, or any questionnaires sent after the birth of the child, reminders were sent by post. For mothers who did not respond to a questionnaire for a month, a member of the ALSPAC study team made contact by phone and/or visited their home to help with completion.

Socio-Demographic Data

A benefit of working with the ALSPAC cohort is the wealth of socio-demographic data that are available. Following is a breakdown of the variables that have been used as confounders/mediators within this thesis, how this data was prepared, and the response rate for each variable. The majority of this information was collected via the "Your Pregnancy" questionnaire that was sent to mothers at 32 weeks gestation. Additionally, data on marital status was collected via the "Your

Environment" questionnaire which was sent to mothers at 8 weeks gestation; and parity was determined as part of the questionnaire titled "Having a Baby" which was sent to mothers as 18 weeks gestation.

Maternal Age at Delivery: Maternal age at delivery was determined by calculating the difference between the dates that the mother and study child were born. The extreme lower (under 16 years old) and upper (over 43 years old) age ranges were grouped for confidentiality. Data on maternal age at delivery were available on 100% of the initially enrolled cohort, and was used as a continuous variable as a covariate.

Maternal Education: Mothers were asked to report their acquired education using a likert scale with the following possible responses: (i) No qualifications; (ii) no qualifications higher than CSE or GCSE level; (iii) O-level or equivalent; (iv) A-level or equivalent; (v) Teaching or nursing qualification; (vi) University degree. Mothers who answered "not known" were coded in the lowest educational category, under the assumption they had not completed any of the qualifications presented in the questionnaire. These responses were used to determine the mother's highest level of education through which five possible categories were derived: (i) CSE/None; (ii) Vocational qualifications; (iii) O level; (iv) A level; (v) Degree. For ease of use in statistical analysis, this variable was dichotomized into two categories: (i) Qualifications up to, including, and equivalent to O level; and (ii) Qualifications equivalent to A level and above. The response rate for this variable was 94.2% of the initially enrolled cohort.

Marital Status: Mothers were asked whether or not they were married. This dichotomous variable was available on 90.7% of women in the initially enrolled cohort.

Ethnicity: Ethnic origin was enquired about using the same questioning format as the 1991 United Kingdom Census, which provided nine possible categories: White; Black – Caribbean; Black - African; Black – other; Indian; Pakistani; Bangladeshi; Chinese; Other – specified. Mothers were asked to report the ethnic origins of her

partner and her parents, as well as her own ethnicity. A large majority of the cohort described themselves as white (95.2%); therefore this variable was dichotomized into White or Other (inclusive of all non-white ethnicities). Data were available on 93.7% of the initially enrolled cohort.

Parity: Mothers reported on the number of previous pregnancies they'd had, both live-born and stillbirth. This variable was dichotomized into primiparae or multiparae for ease of use in statistical analyses, and was available on 100% of the initially enrolled cohort.

Child Gender: Information on the gender of the study child was obtained through birth notification, and this dichotomous variable (male or female) was available on 100% of the cohort.

Family Income: Mothers were asked to report the weekly family income (inclusive of benefits), and were given five possible categories to choose from: (i) less than £100 per week; (ii) £100 - £199 per week; (iii) £200 - £299 per week; (iv) £300 - £399 per week; (v) more than £400 per week. These data were used as a continuous variable due to statistical limitations associated with multiple imputation, and were available on 89.9% of the initially enrolled cohort.

Social Class: Social class was based on parental occupation defined by the UK Registrar General's occupational coding. Occupation of both parents was coded on a scale ranging from social class I (professional) to social class V (unskilled manual). Lowest combined social class of both parents was allocated to the family and dichotomized into Non-manual (categories I to III-manual) and Manual (categories III-manual to V).

Gestational Age: Gestational age was calculated using the mothers estimated due date, which was in turn based on the date of her last menstrual period. These data were used as a continuous variable and were available on 100% of the initially enrolled cohort.

3.3 Sample 1: Maternal Self-Reported ED diagnosis (Studies 1 and 4)

For studies one and four of this thesis, high risk status in children was defined by maternal self-report of an ED diagnosis prior to the birth of the index child. The following section of this chapter describes the sample used in these studies, and the procedures employed.

Grouping

At 12 weeks gestation all women in ALSPAC were asked the question "Have you ever had…" followed by a range of possible psychiatric and psychological problems in a questionnaire entitled "About Yourself". Among the responses were the options 'Anorexia Nervosa' and 'Bulimia Nervosa", and mothers were able to answer yes to either one of these, or both. At this time, EDNOS did not exist as a diagnostic category. Four categories were derived: (i) No history of maternal ED; (i) Maternal history of Anorexia Nervosa; (ii) Maternal history of Bulimia Nervosa; (iv) Maternal history of both Anorexia and Bulimia Nervosa. These data were available on 83.5% of the initially enrolled sample.

From the 11, 088 women eligible for inclusion in these studies: 171 women answered yes to a history of AN; 199 women answered yes to a history of BN; and 82 women answered yes to a history of both AN+BN. The nature of data collection in large cohort studies makes it difficult to validate these self-report diagnoses via clinical interview; however, a second questionnaire asking about eating disordered behaviours was completed by mothers at 18 weeks gestation. Using the data from this second questionnaire, Micali and colleagues (Hudson, 2007) explored the differences in ED cognitions, ED behaviours, and BMI between the three ED groups and the unexposed group. The results of these analyses revealed distinct profiles for each group. Women who reported lifetime AN at 12 weeks gestation, also reported significantly more lifetime self-induced vomiting (23.4%) and laxative use (25%) than women with no history of an ED (3.6% and 3.2% respectively). They also had a significantly lower BMI prior to pregnancy (m = 21.5; SD = 3.2) than women who did not report an ED at 12 weeks (m = 22.9; SD = 2.8). Women

who reported a history of BN also reported significantly more lifetime self-induced vomiting (56.3%) and laxative use (29.1%) than women who did not report an ED; but, as would be expected, reported a comparable pre-pregnancy BMI (m = 23.1; SD = 4.3). Women reporting a history of both AN+BN reported the highest level of self-induced vomiting (62.2%) and laxative use (55%); both of which were significantly higher than women who reported no history of an ED. Women in the AN+BN group, like those in the AN group, also reported a significantly lower pre-pregnancy BMI (m = 21.5; SD = 3.0). The significantly higher percentage of ED behaviours experienced by women reporting a lifetime ED, in comparison to women reporting no history of an ED, suggests that the self-report diagnosis in this cohort was relatively valid. In addition, the striking differences in the percentage of ED behaviours experienced between the three ED groups (AN, BN, and AN+BN) means that grouping them together into one ED category could conceal possible differences in the children of women from each of these groups. Therefore, all three ED categories were considered to be fairly reliable; and were kept separate for all analyses in this thesis.

Inclusion and Exclusion Criteria

The developmental trajectories for multiple births are known to be different to singleton births; therefore pregnancies with multiple births were excluded from all analyses in this thesis (n = 208). Mother-child pairs were excluded from studies one and four if mothers had not completed the 12 week questionnaire (n = 2,019), or if they had reported history of any other psychiatric illness other than an eating disorder (n = 1,166). Subsequently, a sample of 11, 088 women were eligible for studies 1 and 5.

Comparison Group

The aim of studies one and five of this thesis was to make a comparison between the children of women with a lifetime history of an ED (AN, BN, or AN+BN), and the children of women with no history of an ED. A total of 10, 636 women reported no history of any psychiatric conditions, and children of these women were used as a comparison group for all analyses in studies one and four.

3.4 Sample 2: Maternal lifetime ED behaviours (Studies 2 and 5)

For studies two and five high risk status of children was determined using data collected on lifetime history of ED behaviours. This information was collected as part of this thesis using a two-phase prevalence study. The following section of this thesis explains the procedures used in the prevalence study, and provides a description of the sample used in studies two and five.

3.4.1 Two phase prevalence study

Phase One

For phase one of this study, the Eating Disorder Diagnostic Survey (EDDS; described below) (Stice, 2000) was adapted to cover lifetime symptomatology and sent to the 9,465 women in the ALSPAC cohort who were still eligible for participation. Of the 9,465 mothers invited to participate, 1,137 (12%) completed the survey on line, and 4,594 (48%) returned questionnaires in paper format. Fifteen of the 5,731 returned questionnaires were duplicates; therefore the total number of responses was 5,716 (60.4%).

From the 5,716 women who completed and returned the screening questionnaire as part of phase one, all of those screening positive (n = 934), and a random 12.2% of the overall sample who screened negative (n = 698) were offered an in depth clinical interview. Women were included in the screen positive group if there was evidence of (i) weight and shape concerns; (ii) bingeing; and/or (iii) compensatory behaviours (see table 2) following the algorithm used by Stice and colleagues for diagnosis of an ED using the EDDS (Stice, 2000). Weight and shape concerns were considered present if the participant scored a minimum of 16 out of 24 on four items in the EDDS assessing weight and shape concerns, i.e. “Have you ever had a definite fear that you might gain weight or become fat?” Bingeing was considered present if participants reported bingeing at a minimum frequency of twice a week, reported experiencing a “loss of control” while bingeing, and also answered yes to four or more cognitive symptoms that are associated with bingeing, i.e. “Did you

eat alone because you were embarrassed by how much you were eating?" Compensatory behaviours were considered present if participants reported seven or more occasions when compensatory behaviours were used over the period of a week; and these could be any combination of restricting, purging or exercising behaviours. EDDS guidelines recommend a cut-off of at least eight occasions over a week (Stice, Telch, & Rizvi, 2000); however, as the EDDS was being used as a lifetime screening tool rather than to diagnose, a cut-off of seven or more behaviours was adopted to be over-inclusive. Self-reported ED during pregnancy was also used as an indicator of lifetime ED, therefore all women who self-reported an ED in pregnancy were also approached for interview. Of these only 114 women did not return the questionnaire but were included in the sample to interview. The final sample was made up of 1746 women.

Table 2 Cut-off criteria for a screen positive on EDDS (Stice, 2000)

	Cut-off
1. Shape and weight concern	• A score ≥ 16 on weight and shape concern items of the EDDS
2. Evidence of ever bingeing	• Bing frequency of ≥ twice a week • Bingeing as above and a sense of a loss of control • Four or more cognitive symptoms associated with bingeing
3. Evidence of ever compensatory behaviours	• Seven or more incidences a week of any combination of compensatory behaviours (though the EDDS guidelines recommend a cut off of 8, as the EDDS is being used here as a screening measure, a cut off of 7 was decided upon to be over inclusive).

Phase two

Interviews were conducted using the research version of the SCID-IV (First, et al., 2002); and a lifeline developed as part of the Longitudinal Interval Follow-up Evaluation (LIFE) (Keller, et al., 1987) onto which lifetime history of symptoms was plotted (both measures described in detail below). Initial contact with participants was attempted via telephone. Those that were contactable were given

a brief explanation of the study describing the interview and outlining our overall aims. At this point, women who expressed an interest or requested further information were emailed the description of the study (written expressly for this purpose), and a consent form. Participants were also given the option of receiving this information by post rather than email. During this initial phone conversation, an appointment was made with the participant for a convenient time that the interviewer could phone again. At second contact, if the participant was happy to participate and it was a convenient time for them, the interview was conducted over the phone. If the participant expressed a wish to participate, but did not have time to do the interview then, another appointment was made. Participants were also offered the option of a face-to-face interview, rather than a telephone interview. Three participants opted for face-to-face interviews, and for these women an appointment was made for them to come in to the ALSPAC headquarters to be interviewed. For women who were not home or unavailable when initial contact was attempted, further attempts were made at various times of the day and evening to conduct the interview at a convenient time. If these further attempts were also unsuccessful, a letter was sent to the participant explaining why they were being contacted, with full details of the study and consent forms (n = 819). Participants were asked to complete the consent form and a form asking for the best telephone number to contact them on and the most convenient times to phone, if they were interested in participating. Participants were given the option of responding via post (a pre-paid envelope was included), email, or telephone. A second letter (identical to the first) was sent to all participants who did not respond to the first letter (n = 462). A total of 279 women responded to one of the two letters sent. Interviews were conducted with all of the women who (i) were contactable; (ii) did not wish to be excluded from the study; and (iii) had time to complete the interview (n = 1143).

Women who received information about the study via post had the option of completing and returning the consent form enclosed. For those women who received information via email or did not send back the consent form, consent was taken over the telephone with a witness present at the interviewers end to verify

that consent was taken. Interviews were conducted over a period of 18 months when the index children were between 18 and 20 years of age.

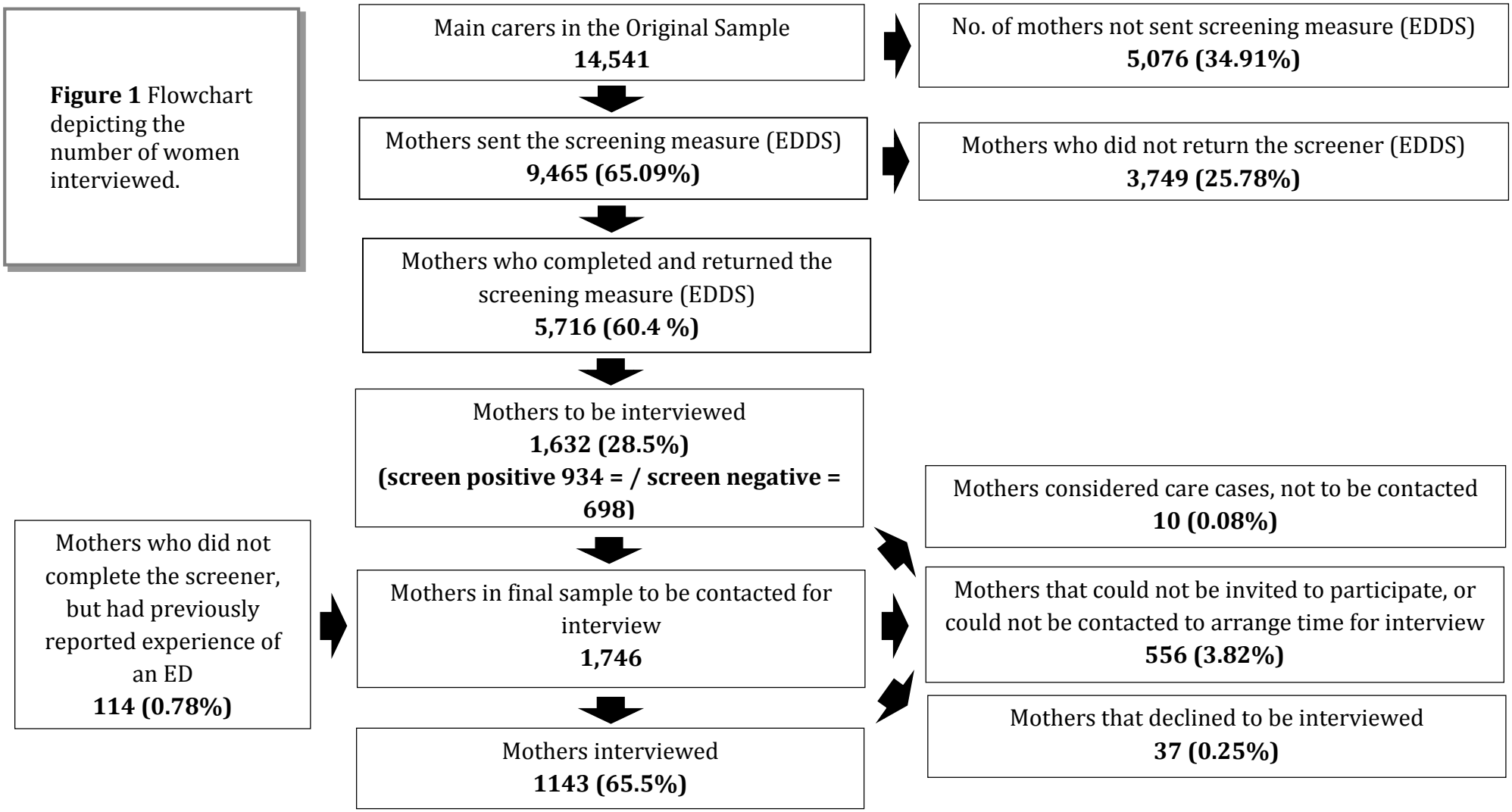
From the 1,632 women in the sample who participated in phase 1, interviews were conducted with 1,110 (68%). Interviewers were unable to interview 522 women, of whom: 10 were "care cases," which means that they had been highlighted by the ALSPAC study team as mothers that were too vulnerable to be contacted at present (0.61%); 29 participants declined participation (1.8%); and interviewers were unable to contact 483 (29.6%). It was only possible to interview 33 (28.9%) of the 114 women that had not participated in Phase 1; with 8 women declining participation (7%); and interviewers being unable to contact the rest (n = 73; 64%). A breakdown of these figures across screen positive and screen negative groups can be found in Table 3.

Table 3 Number and percentage of participants who screen positive and negative across interviewed and not interviewed groups.

	Screened Positive	Screened Negative	Total
Total Sample	934 (100)	698 (100)	1632 (100)
Interviewed	590 (63.2)	520 (74.5)	1110 (68.0)
Not Interviewed	344 (36.8)	178 (25.5)	522 (32.0)
Care Cases	5 (0.5)	5 (0.7)	10 (0.61)
Declined	5 (0.5)	24 (3.4)	29 (1.8)
Could not Contact	334 (35.8)	149 (21.3)	483 (29.6)

*Mothers in the sample to be interviewed who did not complete the screening measure are excluded (n = 114 of which 33 women were interviewed; 8 women declined participation; and interviewers being unable to contact the other 73).

Figure 1 Flowchart depicting the number of women interviewed.



3.4.2 Measures

Phase 1

The Eating Disorder Diagnostic Scale (EDDS)

The EDDS (Stice, et al., 2000) is a brief, self-report scale designed for the diagnosis of AN, BN, and BED over the previous three or six months. It has been shown to be both valid and reliable (Lee, et al., 2007; Stice, Fisher, & Martinez, 2004); has good test-retest reliability, with Kappa coefficients of between 0.71 and 0.95 (Stice, et al., 2000); and shows excellent agreement with "gold standard" measures of ED diagnosis, such as the Eating Disorder Diagnostic Interview (Ridout, et al., 2010).

The EDDS was adapted to assess lifetime history of an ED for the current study and used as the screening measure for phase one of this study. The wording of all relevant questions was changed to ask whether symptoms had *ever* been present. For example, the question "How many times per week on average over the past 3 months have you made yourself vomit to prevent weight gain or counteract the effects of eating?" was adapted into two questions: (a) "Have you ever made yourself vomit to prevent weight gain or counteract the effects of eating?"; and (b) "At its worst, how many times per week on average did you make yourself vomit to prevent weight gain or counteract the effects of eating?"(see appendix 2 for adapted scale).

Phase 2

Structured Clinical Interview for Axis I DSM-IV-TR Disorders (SCID-IV): Eating Disorders Section

The ED section of the research version of the SCID-IV (First, et al., 2002) was used to conduct diagnostic interviews with mothers in the second phase of this study. The SCID-IV is a semi-structured interview designed to diagnose Axis I DSM-IV-TR disorders (American Psychiatric Association, 2000). A series of open ended questions enquiring about the presence of ED symptoms (i.e. restricting, bingeing or purging) and cognitions (i.e. fear of fatness or denial of low weight), are

supported by a range of prompts designed to encourage elaboration from the interviewee if necessary. In this way, the interviewer can elicit enough information to determine whether the symptoms present (if any) meet the diagnostic criteria set out in the DSM-IV-TR. The SCID-IV has a high inter-rater reliability for the diagnosis of an ED, with kappa coefficients reported to be between 0.61 and 0.77 (Lobbestael, Leurgans, & Arntz, 2010). As a lifetime history of ED symptoms was being investigated, relevant questions were repeated where appropriate to gather information pertaining to each episode of an ED throughout the participant's life. For example, the question "How often were you eating that much (AND COMPENSATORY BEHAVIOUR)?" was asked for each episode of an ED where the participant was bingeing and using a compensatory behaviour such as vomiting. In this way, the interviewer was able to elicit information on the frequency of ED behaviours for each episode of an ED. The SCID-IV also uses a series of skip rules, used to avoid questions that are no longer relevant due to the answers given to previous questions. These skip rules were ignored in certain situations so that all relevant information was gathered. For example, following the skip rules in the SCID-I would mean that if an interviewee did not confirm the presence of low weight, and also did not confirm the presence of bingeing behaviours, they would then not be asked about the presence of any purging behaviours. Due to the fact that information was being gathered about all ED behaviours, not just ED diagnosis, the skip rules were ignored. This meant that interviewees who had only ever experienced purging behaviours were still asked about their presence (i.e. vomiting, purging, use of diuretics, and fasting) and frequency.

The Longitudinal Interval Follow-up Evaluation (LIFE): The Lifeline

As part of the interview, the course of each symptom was plotted on a lifeline (see appendix 3) which was developed as part of the LIFE interview (Keller, et al., 1987). This is a time-line covering the period from first presentation of an ED symptom to the time of inclusion in the study. The course of each behaviour was plotted alongside age, changes in BMI and the presence of amenorrhea. The Lifeline enabled interviewers to gather information regarding the onset and remittance of individual ED behaviours for each episode over lifetime.

3.4.3 Interviewer training and inter-rater reliability

Interviews were conducted by three interviewers, trained using an eight step program based on training recommendations set out in the SCID-IV-TR training manual. First interviewers read through appropriate sections in the SCID training manual. Second, they learned the eating disorder section of the SCID, making sure to understand all of the questions, instructions and diagnostic criteria. Third, interviewers watched the relevant parts of the SCID training video. Forth, recordings of previously conducted interviews were rated and results were checked for inter-rater reliability with a qualified assessor from the Institute of Psychiatry. Fifth, interviewers practiced reading out the questions in the SCID aloud. Sixth, practice interviews were conducted with colleagues able to assume the role of an eating disordered patient. Seventh, interviewers sat in on interviews being conducted by an experienced interviewer. Finally, interviews were conducted under supervision to check readiness. On-going supervision was available from an experienced interviewer and a trained clinician throughout. Interviewers demonstrated excellent inter-rater reliability with 100% agreement (inter-class correlation coefficient = 1.00). Regular meetings to discuss the difficult cases and obtain diagnoses and case-ness were held monthly with colleagues and Dr Micali (supervisor).

3.4.4 Scoring and data preparation

All data from the interviews were coded and entered by the interviewers according to strict guidelines; and 10% of data were cross-checked by a researcher not involved in this study prior to any analyses.

3.4.5 Grouping Criteria

Grouping criteria were determined after extensive discussion between the PhD candidate and the two supervisors; both of whom have extensive clinical and research experience, and are specialists in the field of ED. It was decided that women would be categorized into five possible groups, using a hierarchy of behaviours (Anderluh, et al., 2009).

1. Restricting and/or Excessive Exercising (no purging/no bingeing) = women who had, at any time in their life, engaged in dietary restriction at a frequency of at least once a week for a period of at least three months; and/or had engaged in excessive exercise to lose weight at a frequency of at least once a week for a period of at least three months (n = 127; 11.1%).

2. Purging (no bingeing) = women who had, at any time in their life, engaged in purging behaviours (i.e. vomiting/abuse of laxatives, diuretics or slimming pills) at a frequency of at least once a week for a period of at least three months, but had never engaged in bingeing behaviours. Women in this group could additionally have engaged in restriction and/or excessive exercise to lose weight (n = 67; 5.95%).

3. Bingeing (no purging) = women who had, at any time in their life, engaged in bingeing behaviours (with loss of control) at a frequency of at least once a week for a period of at least three months, but had never engaged in purging behaviours. Women in this group could additionally have engaged in restriction and/or excessive exercise to lose weight (n = 68; 5.95%).

4. Bingeing and Purging = women who had, at any time in their life, engaged in both bingeing and purging behaviours (not necessarily simultaneously) at a frequency of at least once a week for a period of at least three months. Women in this group could additionally have engaged in restriction and/or excessive exercise to lose weight (n = 71; 6.21%).

5. Unexposed group = women who did not meet any of the above criteria were used as a comparison group (n = 810; 70.87%).

Exclusion Criteria

The developmental trajectories for multiple births are known to be different to singleton births; therefore pregnancies with multiple births were excluded from all analyses in this thesis. Out of the 1,143 women interviewed, 14 women had multiple births and were therefore excluded from all analyses; leaving a final sample of 1,129 women.

Sample characteristics and representativeness

A series of logistic regression analyses were conducted to explore the differences between women who were interviewed and the whole ALSPAC cohort. Results showed that the women that were interviewed had higher odds of: being married during pregnancy; being more highly educated; being of a higher social class; and being older when they were pregnant with their study child. These variables were accounted for in all analyses accordingly.

3.5 Neuropsychological Assessment of Children

3.5.1 Interim Overview

For all of the studies in this thesis the outcome variable was child data on cognitive development. This was collected via behavioural assessments that were conducted during regular "Focus Clinics" held by ALSPAC at their headquarters (described below), and questionnaires completed by the mothers on their children's behaviour. A breakdown of the relevant clinics, the number of eligible families and the number that attended, and the assessments within each clinic that form a part of this thesis, can be found in table 4. The measures themselves are described in the relevant results chapters (chapters four and five).

3.5.2 Procedures

The “Focus Clinics”, to which all parents/children were invited, were held from age 8 onwards. Children were tested on a variety of measures and tests were carried out in four different orders to avoid any order effect. Testing lasted half a day, and a break was scheduled in, to prevent the children becoming tired. Decisions on the optimum measures and methods of testing were made in collaboration with experts from the relevant fields, and after workshops and pilot tests had been conducted with the relevant age groups.

The staff conducting the assessments were trained and continuously supervised to maintain standards. Families were eligible if the child was alive, if their address was known, and if they had not previously declined participation in the whole study. It is possible for participants to decline participation in parts of the ALSPAC study; for example, completion of questionnaires specifically. An initial letter describing the clinic, and asking if the parents were interested in attending with their children, was sent three months prior to the child turning the ideal age of testing. For families living over two hours away, this letter was sent out four months in advance to encourage attendance. If a response had not been received within the first three weeks after this initial invitation, a postal reminder was sent. After a further two weeks of non-response, families were referred to the ‘Family Liaison’ team, who attempted to contact families through phone calls or face to face visits. Families who were still not contactable were sent a final “Last Chance” letter. Those families who expressed an interest were sent a further letter with an appointment time, which they were asked to confirm if convenient.

Table 4 Breakdown of Relevant Clinics, Attendance Figures, and Applicable Cognitive Assessments

Clinic	**Ideal Age of Study Child**	**Eligible Population from Initial Cohort**	**Children who Attended from Initial Cohort**	**Assessments Relevant to the Thesis (Cognitive Construct being assessed)**
Focus at 8	8 ½	12,749	7,488	➢ Wechsler Intelligence Scale for Children III (intelligence and global cognition) ➢ Tests of Everyday Attention for Children (selective attention, divided attention, and attentional control) ➢ Diagnostic Analysis of Non-Verbal Communication (facial emotion recognition)
Focus 10+	10 ½	11, 868	7,563	➢ Counting Span Task (working memory) ➢ Stop-signal Task (behavioural inhibition)
Teen Focus 2	13 ½	10, 580	5,844	➢ Emotional Triangles (emotion recognition from social motion cues) ➢ Reaction Time (focused and sustained attention)
Wellbeing of My Teenage Son/Daughter (Questionnaire completed by mother)	13 ½	9, 927 (sent questionnaire)	6,811 (completed questionnaire)	➢ Social Communication Disorders Checklist (social communication)

Data Preparation

Data from questionnaire and behavioural assessments were coded and entered by undergraduate students from Bristol University who were closely supervised. All coding was cross-checked prior to being keyed in, and verified after. Any textual replies were keyed in and categorized by question. These responses were then coded by a trained specialist in the appropriate field, rather than by the student that initially keyed in the response. To maintain confidentiality, data from ALSPAC are sent to collaborating researchers with participant IDs that are specific to the primary investigator. This prevents the linking of datasets without the knowledge of ALSPAC, and means that no personal data are connected to names/contact details. Data preparation that was conducted after the data were received from ALSPAC is detailed in the relevant chapters of this thesis.

3.5.3 Participants

Inclusion of children for each analysis in this thesis was dependent on both maternal data on ED exposure, and child data on the relevant neuropsychological assessment being present. Children were excluded from the relevant analysis if the child did not attend testing sessions assessing: I.Q., Attention, and Facial Emotion Recognition at age 8 (4887); working memory and inhibition at age 10 (4896); emotion recognition from social cues and reaction time at age 13 (6067); or if parents did not complete the questionnaire on their child's social communication abilities when children were 13 (5102). Final sample sizes for each analysis (after accounting for missing data and outliers) can be found in results tables in the relevant results chapters. As explained above, two methods were used to define high risk status of children: (i) maternal self-report diagnosis of an ED (studies 1 and 4); and (ii) maternal ED behaviours over lifetime (studies 2 and 5). The socio-demographic data for each of these two samples is described below.

Sample 1: Maternal Self-Report Diagnosis of an ED (Studies 1 and 4)

Socio-demographic data for children assessed at each time point can be found in table 5. Minorities of children assessed at all ages were non-white; and were of a low socio-economic class or from low income families. Samples assessed at each time point were similar across all other socio-demographic factors. Socio-demographic data were also compared across index groups for participants in the original sample tested at 8 years of age (see table 6). Only slight differences in socio-demographic factors across index groups were observed for the samples assessed at the following time points, and relevant socio demographic factors are adjusted for in each analysis.

Sample 2: Maternal ED Behaviours over Lifetime (Studies 2 and 5)

Socio demographic data for children assessed at each time point can be found in table 7. Minorities of children assessed at all time points were non-white and were of a low socio-economic class. Samples assessed at each time point were similar across all socio-demographic factors (see table 7). Socio-demographic data were also compared across index groups for participants in the original sample tested at 8 years of age (see table 8). Once again, only slight differences were observed at following time points and relevant socio demographic factors are adjusted for in each analysis.

Table 5 Sample 1 (At risk status defined by maternal self-report diagnosis of an ED): socio-demographics for children assessed at each age.

	Age 8 ½	Age 10½	Age 13 ½	Age 13½ (questionnaire)
Child Gender (male), N (%)	3076 (49.6)	3050 (49.3)	2457 (51.0)	2989 (50.5)
Child Ethnicity (white), N (%)	5757 (92.8)	5752 (96.3)	4820 (96.4)	5735 (96.5)
Maternal Education (≥ A level), N (%)	2701 (43.6)	2643 (43.6)	2235 (44.6)	2630 (44.5)
Maternal ED, N (%)				
Lifetime AN	93 (1.5)	83 (1.3)	72 (1.4)	91 (1.5)
Lifetime BN	97 (1.6)	103 (1.7)	91 (1.8)	108 (1.8)
Lifetime AN & BN	43 (0.7)	45 (0.7)	41 (0.8)	44 (0.7)
Family Income per Week, N (%)				
< £100	210 (4.1)	225 (4.4)	-	-
£100	640 (12.5)	638 (12.5)	-	-
£200	1356 (26.6)	1357 (26.7)	-	-
£300	1235 (24.2)	1235 (24.3)	-	-
>£400	1661 (32.6)	1632 (32.1)	-	-
Lowest Combined Parental Social Class (Manual: III-manual – V) N(%)	-	-	600 (12.0)	717 (12.1)
Maternal Age at Delivery, m (SD)	29.17 (4.49)	29.10 (4.50)	29.18 (4.46)	29.18 (4.50)

1. Categorical variables (child gender, maternal education, parity, child ethnicity, family income, social class): numbers and percentages
2. Continuous variables (maternal age at delivery,): means (standard deviations).

Table 6 Sample 1: Comparison of socio demographic data between index groups, for children who were assessed at 8 years old.

	AN *n* = 93 (1.5%)	BN *n* = 97 (1.6%)	AN &BN *n* = 43 (0.7%)	Controls *n* = 5968 (96.2%)
Child Gender (male), % (OR, 95% C.I.)	55.91 (1.29, 0.86-1.95)	47.42 (0.92, 0.62-1.37)	51.16 (1.07, 0.59-1.95)	49.53
Marital Status % (OR, 95% C.I.)	69.9 (0.62, 0.31-0.76)*	73.2 (0.62, 0.39-1.00)*	65.1 (0.40, 0.21-0.76)*	82.3
Maternal Education (≥ A level), % (OR, 95% C.I.)	58.24 (1.77, 1.17-2.70)*	45.65 (1.07, 0.71-1.61)	74.42 (3.70, 1.86-7.35)**	44.04
Multi-parity, % (OR, 95% C.I.)	51.69 (0.93, 0.62-1.42)	53.13 (0.99, 0.66-1.48)	51.16 (0.92, 0.51-1.67)	53.38
Child Ethnicity (white) % (OR, 95% C.I.)	94.12 (1.68, 0.67-4.18)	94.51 (1.56, 0.63-3.88)	97.62 (0.65, 0.09-4.78)	96.40
Maternal Age at Delivery m (SD; B, 95% C.I.)	30.70 (5.21; 1.56, 0.64-2.48)**	28.95 (4.39; -0.19, -1.09-0.71)	30.37 (4.55; 1.24, -0.11-2.58)	29.14 (4.47)
Family Income per Week m (SD; B, 95% C.I.)	3.49 (1.25; -0.20, -0.46-0.07)	3.69 (1.29; 0.00, -0.26-0.26)	3.72 (1.24; 0.04, -0.33-0.40)	3.69 (1.16)

**p≤0.05, ** p≤0.001 v. Controls*

1. Categorical variables (child gender, maternal education, parity, child ethnicity): percentages (odds ratios, 95% confidence intervals).
2. Continuous variables (maternal age at delivery, family income): means (standard deviations; B, 95% C.I.).
3. Family Income per Week Coding: 1=<£100; 2=£100; 3=£200; 4=£300; 5=>£400

Table 7 Sample 2: socio-demographic characteristics for children assessed at each testing point.

	Age 8 ½	Age 10 ½	Age 13 ½	Age 13½ (questionnaire)
Child Gender (male), N (%)	489 (42.8)	457 (49.5)	407 (50.0)	515 (51.3)
Marital Status at Enrolment (married), N (%)	728 (63.7)	688 (74.5)	681 (83.7)	776 (75.8)
Child Ethnicity (white), N (%)	821 (71.8)	775 (83.9)	785 (96.4)	992 (96.9)
Maternal Education (≥ A level), N (%)	454 (39.7)	430 (46.5)	417 (51.2)	477 (46.6)
Maternal ED, N (%)				
Restricting and Excessive Exercising	127 (11.1)	96 (10.4)	82 (10.1)	113 (11.0)
Purging	67 (5.9)	54 (5.8)	42 (5.2)	52 (5.1)
Bingeing	68 (5.9)	55 (6.0)	44 (5.4)	59 (5.8)
Bingeing & Purging	71 (6.2)	62 (6.7)	50 (6.1)	60 (5.9)
Lowest Combined Parental Social Class (Manual: III-manual – V) N(%)	84 (7.3)	86 (9.3)	80 (9.8)	93 (9.1)
Maternal Age at Delivery, m (SD)	29.80 (4.45)	29.73 (4.46)	29.65 (4.42)	29.65 (4.40)

1. Categorical variables (child gender, maternal education, child ethnicity, social class): numbers and percentages
2. Continuous variables (maternal age at delivery,): means (standard deviations).

Table 8 Sample 2: Comparison of socio-demographic data between index groups, for children who were assessed at 8 years old.

	Restricting	**Purging**	**Bingeing**	**Bingeing & Purging**	**Unexposed**
	n = 127 (%)	*n* = 67 (%)	*n* = 68 (%)	*n* = 71 (%)	*n* = 764
Child Gender (male) % (OR, 95% C.I.)	44.9 (1.86, 0.78-1.79)	37.3 (0.74, 0.43-1.27)	39.7 (0.88, 0.51-1.51)	40.8 (0.89, 0.52-1.50)	42.9
Marital Status at Enrolment (married) % (OR, 95% C.I.)	55.1 (0.79, 0.44-1.45)	58.2 (0.66, 0.32-1.38)	55.9 (0.72, 0.34-1.53)	56.3 (0.49, 0.25-0.93)*	67.5
Maternal Education (≥ A level), % (OR, 95% C.I.)	31.5 (0.80, 0.51-1.26)	40.3 (1.11, 0.62-1.98)	33.8 (0.94, 0.51-1.72)	45.1 (1.37, 0.77-2.43)	41.5
Child Ethnicity (white) % (OR, 95% C.I.)	62.2 (0.87, 0.25-2.99)	67.2 (0.37, 0.12-1.13)	63.2 (0.71, 0.16-3.13)	66.2 (0.52, 0.15-1.80)	75.9
Parity (multi-parity) % (OR, 95% C.I.)	33.9 (1.01, 0.64-1.60)	34.3 (0.92, 0.50-1.67)	35.3 (0.95, 0.53-1.73)	43.7 (1.23, 0.70-2.16)	41.4
Lowest Combined Parental Social Class (Manual: III-manual – V) % (OR, 95% C.I.)	5.5 (0.81, 0.36-1.83)	9.0 (1.30, 0.53-3.18)	4.4 (0.63, 0.19-2.10)	7.0 (0.92, 0.35-2.40)	8.2
Maternal Age at Delivery m (SD; B, 95% C.I.)	29.47 (4.75; -0.45, -1.46-0.56)	29.49 (5.35; -0.43, -1.72-0.87)	29.83 (5.04; -0.09, -1.41-1.23)	29.20 (4.55; -0.71, -1.95-0.53)	29.97 (4.28)

**p≤0.05, ** p≤0.001 v. Controls*

1. Categorical variables (child gender, maternal education, parity, child ethnicity): percentages (odds ratios, 95% confidence intervals).
2. Continuous variables (maternal age at delivery, family income): means (standard deviations; B, 95% C.I.).
3. Family Income per Week Coding: 1=<£100; 2=£100; 3=£200; 4=£300; 5=>£400

3.6 Statistical Analyses

All analyses were carried out using SPSS version 18.0. Results presented are two-tailed and the standard significance level of 0.05 was used to determine differences between exposed and unexposed groups. For all analyses, exploratory statistics were conducted to investigate whether data fulfilled the assumptions for parametric testing (i.e. normal distribution). For data that did not fulfill parametric assumptions, normalization of data was attempted. Where data could not be normalized variables were dichotomized to allow for parametric testing, so that in further analyses it was possible to adjust for the relevant confounders and mediators.

3.6.1 Power Calculations

Due to the fact that an existing longitudinal cohort was employed for the studies in this thesis, preliminary power calculations were not relevant as group sizes could not be increased. However, using the smallest and largest group sizes, power was calculated for small (0.2), medium (0.5) and large (0.8) effect sizes according to Cohen's recommendations; when using the standard two-tailed significance level of $p = 0.05$. This study was found to have >70% power to detect differences with a large effect size between the smallest and largest exposed and unexposed groups; and 10 – 30% power for detecting differences with small to medium effect sizes. The nature of high risk research means it is possible that only small sized effects will be observed. Due to the low power of the studies in this thesis to detect small effect sizes, it was decided that trends towards significance (≤ 0.1) would also be taken into consideration when interpreting results.

3.6.2 Attrition

Selective attrition was assessed for each study and is reported in relevant chapters. Missing socio-demographic data (potential confounders and mediators) were determined to be missing at random: meaning that systematic differences between missing and observed values are likely to be explained by differences in the observed data. As a result, multiple random imputation was used to impute missing socio-demographic data. For all analyses, ten imputed data-sets were created and combined to obtain valid overall estimates, according to the rules set out by Rubin (Rubin, 2008).

3.6.3 Ethical Approval

Ethical approval for the studies in this thesis was obtained by the ALSPAC Law and Ethics committee, and local research ethics committees.

3.7 Methodological Considerations

3.7.1 Suitability of the Sample: the strengths and limitations of investigating the effects of a disorder in a general population sample

Sample Size

A key strength of the studies in this thesis is the use of a large general population cohort: ALSPAC. As described in chapter 2, the majority of studies investigating cognitive functioning in eating disordered groups (or first degree relatives) use small samples, increasing the risk of making a type II error. Previous experiments have shown that the effects of an ED (the independent variable) on cognitive functioning (the dependent variable) are large enough to be detected in clinical groups using small or medium samples. Due to the lack of research investigating the cognitive development of children at high risk (i.e. children born to women with an ED), it is difficult to predict the necessary sample size to detect differences between children at risk and children who are not. It is possible that lack of nutrition associated with having an ED might exaggerate any pre-existing cognitive impairments in clinical groups, increasing the size of the effect. This is unlikely to be the case with our sample of children at risk, who were assessed at a young enough age that they are unlikely to have developed any severe ED cognitions or behaviours. Using a large sample increased the power of our studies; making it less likely that small effects would be missed, and that the null hypothesis would be incorrectly rejected. It is worth noting however that due to the prevalence of ED being low, and the general attrition over time in ALSPAC, exposed groups (i.e. maternal ED) are still relatively small. This may mean that subtle differences are not detected due to a loss of power.

Representativeness: Clinical versus Population Samples

The majority of studies investigating cognitive functioning in ED groups use clinical samples, with participants being selected due to their association to some form of inpatient or outpatient treatment. This is limiting for a number of reasons. Firstly, there is an inherent selection bias in using clinical groups to recruit participants. Cases who attend clinics for treatment of an ED are different from

cases that do not, therefore findings might only be generalizable to cases with severe disorder. Secondly, research suggests that 26-60% of individuals with an ED are unlikely to receive treatment or be identified by the health care system (Fairburn & Harrison, 2003; Keski-Rahkonen, et al., 2007; Mond, Hay, Rodgers, & Owen, 2007). Though this is partly due to severity, it is possible that this is also due to other factors such as the availability of treatment options in the area, or the willingness of an individual to seek help. Thirdly, many studies use participants that have been selected from both inpatient and outpatient treatment groups. This means that samples are heterogeneous with regard to their level of severity and BMI, and also their exposure to treatment. Lastly, research suggests that individuals who receive specialist treatment for their ED are also likely to suffer from comorbid disorders such as anxiety and depression; and additional features such as self-injurious behaviours (Paul, Schroeter, Dahme, & Nutzinger, 2002). Considering these limitations, it is fair to conclude that studies using clinical samples are not representative of the whole ED population, and findings from these studies cannot be generalized to less severe cases. It is therefore important that findings from studies using clinical samples are replicated in community samples to determine their relevance and impact on different ED groups.

In addition to the limitations of clinical research with regard to ED groups, there are also limitations with regard to control groups. In chapter one, the lack of a control group for comparison in many studies investigating cognitive impairments has been discussed. Furthermore, when a control group is employed for comparison, it is common for this control group to be recruited from samples of undergraduate students or hospital staff. This method of recruitment is likely to lead to bias.

Confounders and Mediators

Much of the research investigating cognitive functioning in ED groups is limited by the lack of data on variables that could potentially confound or mediate effects. In addition to the main exposure variable, in our case high-risk for ED, there are other variables that could affect outcome (children's cognitive development). Confounders are associated to both the exposure and the outcome variable, but

affect the outcome through a different causal pathway. They therefore represent alternative explanations for some or all of the effect observed. In contrast, a mediator (i.e. maternal education) lies on the causal pathway between the exposure of interest and the outcome. This means that though a mediator has an effect on the outcome it does not represent an alternative explanation of the effect observed, but rather it mediates the effect of the exposure variable on the outcome variable. Studies in the literature that do not consider additional variables that could potentially confound or mediate effects are limited. Accounting for these additional factors could diminish the association between ED and cognitive functioning; therefore it is possible that in these studies the true effect is smaller than has been supposed. Adequate consideration of additional risk factors is vital to prevent type I errors.

Investigating a General Population Sample

The studies in this thesis use a general population cohort (ALSPAC), which can help minimize many of the limitations outlined above. ALSPAC is a large population study with high response rates; providing a much larger sample for analysis. The use of this large sample increases the power of our investigations. As highlighted above, this is particularly pertinent to the studies in this thesis, as the effects observed were predicted to be comparatively small. Due to the low prevalence of ED in the general population, a population cohort that was not as large as ALSPAC may not provide enough ED cases to make reliable inferences. ALSPAC provides an opportunity to investigate effects of interest in a population sample, reducing the selection bias that is inherent in investigations of clinical samples; as well as making it more possible to generalize results to the whole ED population. Due to being a population based study, ALSPAC also provides a control population for comparison that is more representative of the general population than those recruited for most clinical studies. Finally, ALSPAC has collected a large quantity of additional data pertaining to socio-demographic and environmental factors. This additional information makes it possible to adjust for factors that may confound or mediate associations. Though many studies may have enough data to adjust for one or two potentially confounding factors, the effect of confounding can be cumulative. The wealth of additional data collected as part of the ALSPAC study,

combined with the power of a large sample, means that several confounders can be taken into account; making inferences more reliable. For all of the studies in this thesis potentially confounding factors have been adjusted for statistically, making it possible to discover what the association between risk factor and outcome would be if groups were identical on the confounding variables.

3.7.2 Eating Disorder Classification

Investigations conducted with large population cohorts have clear advantages; however, diagnostic classification of a sample the size of ALSPAC can be difficult. For two of the studies in this thesis: study one (chapter four) and study four (chapter six) high risk status of the children was determined by maternal self-reported ED in pregnancy. Though clinical interviews are considered to be the "gold standard" in psychiatric research, there are practical limitations to conducting clinical interviews with a large population cohort. The time and cost of conducting a large number of interviews cannot be ignored, and the many interviewers necessary would raise concerns about consistency and reliability. In addition, participants may find it more difficult to report history of an ED in a face to face interview, while questionnaires maintain the feeling of anonymity. This reluctance to discuss ED history is likely to be exaggerated in a population sample of women as they are less likely to have received treatment or previously discussed their disorder, in comparison to a clinical sample of women who will have experienced diagnostic interviews before and may be more comfortable talking about their ED.

An alternative to self-report and clinical interview is to assess history of an ED using a diagnostic screening tool. However, evidence suggests that many screening instruments yield higher sensitivities and specificities when used with clinical case-control samples, than when used with population samples (e.g. Jacobi, Abascal, & Taylor, 2004; Luck, et al., 2002; Mond, Hay, Rodgers, Owen, & Beumont, 2004). It must also be taken into consideration that a short screening scale (i.e. "Have you ever had anorexia? / Have you ever had bulimia?") is more likely to be included in a bigger survey (like those used in ALSPAC), and can be expected to

have a higher completion rate (Streiner, 1995). Despite this, research suggests that more complex behaviours such as binge eating, or ED cognitions such as weight and shape concerns, are better assessed via interview methods (Fairburn, 1994; Peterson, et al., 2007). With regard to diagnosis however, there is evidence that self-report of AN or BN is predictive of a broad diagnosis (0.80 and 0.75 respectively), and out-performs longer screening measures such as the Eating Disorder Inventory (Garner, 1991a; Keski-Rahkonen, et al., 2006).

Despite the evidence supporting the use of self-report in population samples, it is important to consider the limitations. The difference between a diagnosis of AN and BN is complex and self-report may have been incorrect for women who never sought help or received a diagnosis from a clinician. It is also possible that some women answered no to history of an ED because they were unaware that they had previously been diagnosable, or they did not want to reveal their illness. However, the questions used have been found to be highly sensitive in a general population sample indicating the likelihood of false positives rather than false negatives (Micali, et al., 2012). The relationship between the self-reported diagnoses used in this thesis cannot be mapped onto DSM criteria, particularly as the ED category EDNOS also did not exist at the time maternal ED was assessed. However as discussed above, behavioural data provide support for the validity of the self-report diagnosis used in this thesis (Micali, Simonoff, & Treasure, 2007a). In addition, the prevalence of ED in this sample was 3.7% overall: 1.4% for AN; and 1.6% for BN. Although this is high in comparison to other prevalence estimates for women of childbearing age: 0.2 – 1.5% for AN and 0.4 – 0.8% for BN; when taking partial ED diagnosis into account, prevalence increases to approximately 5% (Striegel-Moore, et al., 2006). This suggests that a sub-set of the women reporting a history of AN, BN or AN+BN would have been classified as EDNOS if clinical interviews were used to determine maternal diagnosis, and if EDNOS has existed as a ED category at the time.

The optimal method of conducting epidemiological surveys of eating disorders is a two-stage screening procedure which consists of a self-report screening questionnaire, followed by a semi-structured diagnostic interview (Hoek & van

Hoeken, 2003; Jacobi, Abascal, et al., 2004). This method has been adopted for studies two (chapter four) and five (chapter six), where high risk status in the children is determined by lifetime history of ED behaviours in mothers. For these two studies a screening measure was sent to the eligible cohort; then a semi-structured interview was conducted with a sub-sample of the mothers that completed the screening measure (detailed above).

It is worth noting here that in this thesis findings from studies using maternal self-report of an ED diagnosis as the exposure variable (studies one and four) cannot be directly compared with findings using maternal lifetime ED behaviours as the exposure variable (studies two and five). Data on maternal self-report ED diagnoses were collected by ALSPAC at 12 weeks gestation, whereas data on maternal lifetime ED behaviours were collected when the study children were between 18 and 20 years of age. This means that the data on maternal ED behaviours are inclusive of any ED symptoms with an onset after the pregnancy with the study child, while data on self-report diagnosis are not.

Chapter 4

The Neuropsychological Profile of Children at High Risk of Developing an Eating Disorder

4.1 Intelligence, Global Cognition, and Executive Functioning in Children at High Risk of Developing an Eating Disorder

Study one from this chapter has been published as an original article: Kothari, R., Solmi, F., Treasure, J. & Micali, N. (2012) The Neuropsychological Profile of Children at High Risk of Developing an Eating Disorder. *Psychological Medicine,* Available on CJO 2012 doi:10.1017/S0033291712002188

4.1.1 Introduction

As discussed in chapter one, a great deal of research has been conducted into the neuropsychological profile of individuals with an ED. There are contradictions in the literature, with some studies finding differences between ED groups and healthy controls, and others not. This has been discussed extensively in chapter two, but a brief summary is provided below.

Anorexia Nervosa

Overall, evidence suggests that women with AN exhibit comparatively high IQ (Lopez, et al., 2010) and comparable or better working memory capacity (e.g. Bosanac, et al., 2007; Hatch, et al., 2010; Nikendei, et al., 2011), in comparison to healthy controls. There is also evidence of AN groups having deficits in a range of attentional processes including selective attention (e.g. Fowler, et al., 2006), divided attention (e.g. Ohrmann, et al., 2004), sustained attention (e.g. Seed, et al., 2000), allocation of attentional processing (e.g. Bosanac, et al., 2007), and switching of attention (e.g. Stedal, et al., 2011). Studies investigating behavioural inhibition, especially those that use the stop-signal task, are scarce and provide

mixed findings (e.g. Claes, et al., 2006; Galimberti, et al., 2011). With regard to visuo-spatial functioning, there is overwhelming evidence for the presence of impairments using a range of tasks (e.g. Fowler, et al., 2006; Lopez, Tchanturia, Donaldson, Sepulveda, & Treasure, 2006; Stedal, et al., 2011; Tenconi, et al., 2010). Investigations using the tasks employed in the present study have revealed lower scores on the object assembly task (I. Gillberg, et al., 2007; Green, Rogers, Elliman, & Gatenby, 1994), the picture completion subtest (Kingston, et al., 1996), and the block-design task (Andres-Perpina, et al., 2011), in comparison to healthy controls.

Studies investigating working memory capacity in weight restored or recovered AN groups also indicate comparable or superior levels of working memory performance (Bosanac, et al., 2007; Hatch, et al., 2010; Nikendei, et al., 2011). With regard to attentional functioning, there is evidence indicating that impairments in selective attention, divided attention, sustained attention, and switching of attention improve with recovery (Hatch, et al., 2010; Lauer, et al., 1999); suggesting deficits are state dependent and unlikely to be present prior to onset. This evidence is limited by the small number of studies conducted however; and performance on tasks measuring other attentional constructs has not yet been investigated in recovered groups. To date there are no studies investigating behavioural inhibition (as measured by the stop-signal task), in recovered AN groups; however a study investigating a sub-clinical population has found evidence of deficits in restrained eaters (Nederkoorn, et al., 2004), suggesting impaired behavioural inhibition may be present prior to onset of clinical level AN. With regard to visuo-spatial functioning, the results of one study: assessing the performance of recovered AN patients and first degree relatives of probands, on both the block-design and object assembly tasks; has provided evidence for impairments in visuo-spatial functioning being independent of illness state and a putative intermediate phenotype of AN (Tenconi, et al., 2010).

Bulimia Nervosa

Less research has been conducted investigating neuropsychological functioning in individuals with BN. The few studies investigating intelligence and working memory capacity have found no differences in comparison to controls (Bosanac, et

al., 2007; Brand, et al., 2007; Galderisi, 2010; Lauer, et al., 1999); and no studies have been conducted with recovered groups or first-degree relatives. With regard to attentional functioning, BN patients have been found to show impairments in attentional control (Dobson & Dozois, 2004), selective attention (Van den Eynde, Guillaume, et al., 2011), divided attention (Lauer, et al., 1999), and allocation of attentional processing (Bosanac, et al., 2007); while findings regarding sustained attention are mixed (Van den Eynde, Guillaume, et al., 2011). Similar to findings from studies investigating weight restored or recovered AN patients; recovered BN patients show pronounced and significant improvements in selective and divided attention (Lauer, et al., 1999), suggesting the deficits observed are a consequence of the illness, rather than a possible causal factor that is present prior to onset. Studies investigating behavioural inhibition have provided some evidence for impaired functioning (Claes, et al., 2011; Rosval, et al., 2006); however studies using the stop-signal task are limited and findings are mixed (Boisseau, et al., 2012; Claes, et al., 2006). With regard to visuo-spatial functioning, studies using the tasks employed in the current study are too few to draw any conclusions.

As discussed previously, it is possible that the differences observed are present prior to onset, and may contribute towards the development of an ED. The opposite: that cognitive impairment follows onset of an ED, is also possible. Deficits observed in clinical studies might be a secondary effect of other features of the disorder, such as low nutritional intake. Also, continued impairments observed in subjects who have recovered from an ED could be long-term effects or scars of the disorder. One method of investigating cognition prior to onset of a disorder is to investigate the cognitive profile of individuals that are at a higher risk of developing that disorder. Evidence indicates that the deficits in neuropsychological functioning and emotion recognition that are observed in probands are also observed in children at high risk of developing schizophrenia (e.g. Amminger, et al., 2011; Cornblatt & Erlenmeyer-Kimling, 1985; Davalos, 2004; Eack, 2010; Erlenmeyer-Kimling & Cornblatt, 1987; 2008; Rutschmann, et al., 1977); depression (e.g. Mannie, 2007; Monk, et al., 2008); and bipolar disorder (e.g. Brotman, et al., 2008; Melissa, et al., 2008); and the high risk research design has

been shown to be an effective way of identifying intermediate phenotypes for these disorders.

The first-degree relatives of ED probands can be considered high risk (discussed extensively in chapter 2). If they also show impaired/superior functioning, these cognitive differences can be considered state independent and putative intermediate phenotypes of ED. Though such studies have been conducted they are few and far between, investigating limited neuropsychological constructs and using relatively small samples (Holliday, et al., 2005; Roberts, et al., 2010; Tenconi, et al., 2010).

To summarise, neuropsychological differences observed in patients and recovered subjects may not be present prior to onset of an ED. One method of exploring this is to investigate samples that are considered to be at high risk of developing and ED. The present research is the first study to investigate the neuropsychological profile of children at high risk of developing an ED, who are young enough not to have developed any ED cognitions or symptoms. This is also the first high risk study in the field of ED that employs a large community sample; making it possible to generalize findings to the general population, not just clinical groups.

4.1.2 Aims & Hypothesis

The aim of this study was to investigate the neuropsychological profile of children at high risk for an ED, in comparison to children who are not. In particular the aim was to determine whether cognitive development: specifically intelligence and global cognition; working memory; attention; and inhibition; was impaired in children at high risk of developing an ED. Based on previous literature the hypotheses were that in comparison to the children of healthy control mothers, children at risk of AN (due to being born to a mother with AN) would show comparatively higher intelligence (Lopez, et al., 2010); comparable or superior working memory capacity; worse performance on the TEA-Ch as a measure of attention (e.g. Dobson & Dozois, 2004; Faunce, 2002); and poorer visuo-spatial

functioning (e.g. Tenconi, et al., 2010). It was also hypothesized that children at risk of AN were more likely to score in the poorest 10% on outcomes of the Reaction Time task as a measure of attention. Due to the paucity of evidence pertaining to neuropsychological functioning in BN groups, clear hypotheses could not be made.

4.1.3 Methods

4.1.3.1 Design

Longitudinal prospective.

4.1.3.2 Participants

Sample size for each analysis was dependent on both maternal data on ED exposure, and child data on neuropsychological functioning being present. Inclusion and exclusion criteria for this study are detailed in the chapter 3 (Aims and Methodology). Final sample sizes for each analysis can be found in the relevant results tables. Assessments were conducted when children were approximately 8 (intelligence and attention), 10 (working memory and inhibition), and 13 (attention) years of age, with mean ages being: 103.8 months, 127.8 months, and 150 months; respectively.

4.1.3.3 Measures

Exposure

At 12 weeks gestation, the mothers completed a questionnaire about their health. All women were asked whether they had a history of Anorexia Nervosa (AN) and/or Bulimia Nervosa (BN). Of the women that responded, 446 reported a history of lifetime ED: AN (171), BN (194), or both (81).

Outcomes: Cognitive assessment of Children

General Intelligence & Domain Specific Cognitive Functioning: The Wechsler Intelligence Scale for Children, 3rd edition (WISC)

Intelligence and cognitive function was assessed at age 8 using the Wechsler Intelligence Scale for Children, 3rd UK edition (Wechsler, Golombok, & Rust, 1992), the most current version of the WISC at the time. This measure of intelligence is based on Wechsler's theory that intelligence is not a solitary ability, but is instead a global capacity made up of a variety of factors including memory, reasoning and cognitive ability. Wechsler believed that different skills were used in different ways, depending upon the demands of the task at hand; therefore a variety of tasks was required to capture the global concept of intelligence (Wechsler, 1981). At this time the WISC-III was one of the most frequently used assessments of cognitive ability for both clinical and general populations of children; and it has excellent internal consistency, construct validity, criterion validity and test-retest reliability (Sattler, 2001).

A short form of the measure was used, where alternate items of each subtest were administered, except for the coding subtest which was administered in full. All of the ten sub-tests were considered individually, as well as the summary scores; Performance IQ (PIQ), Verbal IQ (VIQ), and Full-scale IQ (FIQ). In addition, three out of the four available factor based index scores for the WISC-III were also considered; the verbal comprehension index, the perceptual organisation index, and the freedom from distractibility index. The forth factor based index score was unavailable as it requires the result of an optional sub-test, the symbol search, which was not administered. As part of the assessment the children were also assessed using a forwards and backwards digit span task. Though this measure is often described as an assessment of working memory, it is questionable whether it really fulfils the requirement of information processing that is necessary for this classification. Below are descriptions of each sub-test and the skills they aim to assess; and also an explanation of summary and index scores.

Verbal Subtests

Information

The information subtest is made up of oral, general knowledge questions. It is a measure of general cultural knowledge, acquired facts, long-term memory and recall (Blatt & Allison, 1968; Sattler, 1974). High scores on this subtest could be a result of good verbal skills or long-term memory; a good education or increased cultural exposure; or a strong ability to learn and recall specific or factual information. Low scores may be indicative of limited educational or cultural background; low socio-economic condition; poor memory or verbal abilities (Nicholson & Alcorn, 1993).

Similarities

In the similarities subtest, the child must explain how two different things (e.g., horse and cow), or two different concepts (e.g., hope and fear) are similar. It measures abstract reasoning and logical thinking (Sattler, 1974). High scores on this subtest could be due to good logical thinking or verbal capacities, but could also indicate some removal from reality. Low scores could be caused by poor abstract reasoning, logical thinking, or verbal capabilities (Nicholson & Alcorn, 1993).

Arithmetic

The arithmetic subtest consists of a series of mental arithmetic problems that are described verbally and presented orally. The child is required to solve the problems without paper. This test is a measure of mental arithmetic, numerical reasoning and accuracy, attention and concentration (Sattler, 1974). A high score is indicative of good focused attention and short-term memory; good educational background and ability to do simple calculations; freedom from distractibility; or possibly obsessive-compulsive personality. Low scores on this sub-test could be due to poor attentional or short-term memory capacities; inattention, distractibility or a lack of concentration; poor numerical skills; an inability to deal with concrete concepts; or anxiety (Nicholson & Alcorn, 1993).

Vocabulary

In this subtest, the child is required to give oral definitions of various words to demonstrate understanding of their meaning. It is a measure of verbal fluency and language development (Sattler, 1974). A high score demonstrates a good command of language, good communication skills and a well-developed ability to express oneself. High scores could also be due to good educational and cultural background, or possibly obsessive-compulsive personality. Low scores in this sub-test are indicative of poor verbal fluency and language development. This could be due to poor educational or cultural background; social withdrawal or a speech defect (Nicholson & Alcorn, 1993).

Comprehension

In the comprehension sub-test, children are asked questions on different topics assessing their social knowledge and practical understanding, e.g., why are the names in the telephone book in alphabetical order? The questions are designed to measure common sense, moral conscience, and social development (Sattler, 1974). High comprehension scores are indicative of good social and verbal development, an ability to get along with others, and a good understanding of the rules of society. A low score could be a sign of low social intelligence or understanding; social isolation or a speech defect, poor common sense or possibly problems with planning (Nicholson & Alcorn, 1993).

<u>Performance Subtests</u>

Picture Completion

This task requires the child to identify the missing parts of familiar pictures, and measures attention to detail and visual discrimination. There is also a requirement for the child to be able to separate the essential and non-essential parts of the picture from the whole (Sattler, 1974). High scores could be revealing good attention to detail, visual memory, or concentration capacities. Low scores may

indicate a lack of attention to detail or poor concentration, poor visual memory, or possibly anxiety (Nicholson & Alcorn, 1993).

Coding

In this sub-test the child has to copy shapes which correspond to particular numbers as quickly as possible. The task assesses visual-motor coordination, associative visual learning, and visual short-term memory; as well as speed, concentration, and fine-motor dexterity (Sattler, 1974). High scores imply good visual memory and learning, good hand-eye coordination, and possibly a perfectionist personality. Low scores could be due to poor visual memory or associative learning, distraction, or an inability to sequence (Nicholson & Alcorn, 1993).

Picture Arrangement

The child is required to order groups of cartoon pictures so that they make a sensible and meaningful story. This subtest assesses planning and logical thinking, social knowledge, and the ability to interpret the actions depicted in the pictures(Sattler, 1974). High scores show an ability to understand the consequences of actions, good sequencing abilities, and a good knowledge and understanding of the social environment. Low scores could be a symptom of withdrawal or poor empathy, as well as poor sequencing skills and social knowledge (Nicholson & Alcorn, 1993).

Block Design

In the block design task, the child is required to recreate pictures showing geometric designs with real coloured blocks. It assesses the child's ability to analyse and synthesize an abstract design; so assesses spatial analysis skills and abstract visual problem solving abilities (Sattler, 1974). High scores reveal good visual motor coordination and perceptual organisation ability; and possible a perfectionist personality. Low scores signal poor perceptual skills and visual motor coordination, difficulties dealing with the abstract, and possible figure-ground deficits(Nicholson & Alcorn, 1993).

Object Assembly

The child is required to put together puzzles of cut-apart silhouette object. This subtest measures the ability to visualize component parts of a whole concrete object, and reassemble them (Sattler, 1974). High scores suggest a good visual integrative reasoning style, good visual motor coordination and visual memory. Low scores could be a sign of perceptual difficulties, figure-ground deficits, poor visual memory or visual motor coordination (Nicholson & Alcorn, 1993).

Summary Scores

Full-scale IQ (FIQ)

A summary score of all scaled verbal and performance subtest scores, this summary score is representative of the child's overall level of intelligence and global cognition.

Verbal IQ (VIQ)

A summary score of all scaled verbal subtest scores, the VIQ is an expression of the child's verbal ability; language development; and social and cultural understanding. It is a good predictor of school achievement, but is language specific.

Performance IQ (PIQ)

A summary score of all scaled performance subtest scores, the PIQ is a reflection of non-verbal skills and problem solving abilities. It is also less reliant on cultural knowledge and could be considered similar to Catell's construct of fluid ability(Nicholson & Alcorn, 1993).

Factor/Index Scores

Verbal Comprehension Index

This factor or index score is indicative of the child's verbal knowledge and understanding, particularly knowledge obtained through formal education. High scores could be a reflection of extensive exposure to culture, education, or the environment generally; as well as good verbal skills. Low scores indicate poor education or exposure to the environment, and could be a sign of verbal skills or a speech problem (Nicholson & Alcorn, 1993).

Perceptual Organisation Index

This factor or index score is representative of the child's ability to interpret and organise visually perceived materials. Low scores could be a sign of possible perceptual problems, or an inability to organise visually (Nicholson & Alcorn, 1993).

Freedom from Distractibility Index

This factor or index score is reflective of the child's ability to focus their attention and concentration. Low scores indicate distractibility or an inability to concentrate on a particular stimuli/problem (Nicholson & Alcorn, 1993).

Working Memory: The Counting Span Task

Working memory capacity was assessed at 10 years of age using the counting span task (Case, Kurland, & Goldberg, 1982), a computer based task which has both a processing component and a storage component. In this computer based task the child was presented with a set of screens showing red and blue dots on a white background. For each screen, the child was required to count the number of red dots aloud (processing component). At the end of each set, the child was asked to recall how many red dots were on each screen in order (storage component). Initially two practice sets of two screens were completed. Following this the child completed three sets of two screens, three sets of three screens, three sets of four screens and finally three sets of five screens. All of the sets were worked through regardless of performance. The computer program automatically calculated two final scores: the *global score* which indicates the number of trials that the child

responded to correctly; and the *span score* which is based on the number of sets that were correctly recalled, weighted by the number of screens within each set. The span score, representative of working memory span, is the main outcome measure for this assessment; possible scores range between 0 and 5.

Attention: The Test of Everyday Attention for Children (TEA-Ch)

Selective attention, divided attention and attentional control were assessed at age 8 using three subtests from the Tests for Everyday Attention for Children (Manly, et al., 2001). This battery of tests is based upon an assessment of differential attention for adults, the Test of Everyday Attention (TEA)(Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996), and has been validated for use in both clinical and general population samples (Manly, et al., 2001).

Selective Attention: Sky Search

This task assessed the child's ability to selectively attend while filtering out irrelevant and distracting information. The child was presented with a sheet showing rows of paired spacecrafts. In most of the pairs the spacecrafts were different to each other, but in a few they were identical. The child was instructed to circle the identical pairs of spacecrafts as quickly as possible without missing any out, and then tick a box to signal that he/she has circled all of the identical pairs they could find. Initially the child completed a practice sheet, and the tester went through any errors. Following this, a larger sheet was presented to the child containing a greater number of space craft pairs, twenty of which were identical. The final score for this task is the average time taken to find and circle each pair of identical spacecrafts (controlled for motor performance); therefore a lower score is representative of better performance.

Divided Attention: Sky Search (Dual Task Measure)

To assess the child's ability to effectively divide attention across two tasks, the child repeated the above sky search task, while simultaneously being played several series' of spacecraft noises. As well as circling all of the identical spacecrafts as quickly as possible, the child was also required to silently count the number of spacecraft noises they heard and give a total at the end of each series

throughout the counting task. A practice trial was administered prior to the experimental trial, and the child was given the opportunity to discuss any problems with the task. The final score is the average time taken to find and circle each pair of identical spacecrafts (controlled for motor performance), weighted by performance on the counting part of the task. Scores were calculated so that poor counting performance inflated the average time taken to circle each space craft, (as detailed by the manual); therefore a lower score is representative of better performance.

Attentional Control: Opposite Worlds

This task was used to assess the child's ability to inhibit pre-potent verbal responses. The child was shown a trail of 24 numbers, made up only of 1's and 2's. In the control condition (same world trial) the child was required to read out each number in turn as quickly as possible. In the experimental condition (opposite world trial), the child had to give a verbal response that contradicted the visual information they were given, calling out "1" for each 2 in the trail, and "2" for each 1 in the trail. In both conditions the tester kept their finger next to the number in the trail that the child was required to respond to, only moving his/her finger to the next number in the trail when the child answered correctly. In this way, any errors showed up as a time penalty. The child was given a demonstration and a practice trial of each condition, followed by four test trials; a same world trial, two opposite world trials, and finally another same world trial. The purpose of the same world trial was to reinforce the pre-potent response of reading the numbers out correctly, and identify any difficulties the child may experience. The final score for this task is the average time taken across the two opposite world trials; therefore a lower score is representative of better performance.

<u>Attention: The Reaction Time Task</u>

The Reaction Time Task, administered when the children were 13 years of age, is made up of three computer based assessments (described below) designed to measure attention and information processing. This measure is part of the Cognitive Drug Research battery, and has been shown to be reliable and valid for

use with both clinical populations and young, middle-aged and older non-clinical populations (Wesnes, Ward, Ayre, & Pincock, 1999).

Simple Reaction Time

This task is a pure measure of reaction time to an expected event; assessing alertness, concentration and speed. The child is required to await the presence of the word "yes" on the screen, and respond as quickly as possible by pressing the corresponding key. One score is derived, Simple Reaction Time, (measured in milliseconds). A lower score is therefore indicative of better performance.

Choice Reaction

This task is a measure of reaction time and identification of the correct stimulus; assessing alertness, concentration, speed and information processing. The child is required to await the presence of the word "yes" or "no" on the screen, and respond as quickly as possible by pressing the corresponding key. Two scores are derived. The first is Accuracy, which reflects accuracy of responses (measured in units), and a higher score is indicative of better performance. The second is Speed, which reflects the average time taken to respond (measured in milliseconds), and a lower score represents better performance.

Digit Vigilance

This task is a measure of sustained vigilance where a lack of continued attention or distraction can lead to targets being missed and lower scores. The child is presented with one number on the right hand side of the screen, and a series of changing numbers in the middle of the screen. Whenever one of the numbers in the middle of the screen matches the number on the right, the child has to press the corresponding key as quickly as possible. Three scores are derived. The first is Targets Detected, which reflects the number of digits correctly identified, and a higher score represents better performance. The second is Speed, which reflects the average response time of target detection, and a lower score is indicative of better performance. The third is False Alarms, which reflects the number of incorrect key presses, and a lower score represents better performance.

The administrator read out the instructions prior to the start of each task and made sure to check that the child understood. If the child was unsure the administrator demonstrated and then restarted the task for the child to complete. Two main summary scores are derived from the different scores highlighted above. The first, Continuity of Attention, is a combination of accuracy scores from the Choice Reaction and Digit Vigilance tasks, minus the Digit Vigilance false alarms. This score represents the ability to sustain attention, and is measured in units. A higher Continuity of Attention Score is indicative of better performance. The second, Power of Attention, is a combination of speed scores from the three tasks. It reflects the level of effortful concentration and the ability to focus attention, and is measured in milliseconds. A lower Power of Attention score represents better performance.

Inhibition: The Stop-Signal Task

Inhibition was assessed at 10 years old using the stop-signal paradigm (Logan, 1994), which specifically assesses an individual's ability to stop a planned or pre-potent behavioural response(Williams, Ponesse, Schachar, Logan, & Tannock, 1999). This measure has been shown to be both valid and reliable for use with children from the general population, and disordered children (Kindlon, Mezzacappa, & Earls, 1995). Another computer based task, the child placed their two index fingers in two stimulus boxes labeled X and O and had to fixate on a smiley face that was presented on the computer screen. There were two types of trials in this behavioural measure. In the primary trial, either an X or an O was presented on the screen (the go-signal) and the child was required to press the corresponding button as quickly as possible. In the stop-signal trials, the go-signal (X or O) is presented on the screen as above, but is then followed by a bleep (the stop-signal). The outcome of this is that on all trials, the child is expected to respond to the go-signal by trying to press either the X or the O button as quickly as possible, however on the stop-trials the child is expected to inhibit this response. Initially the children completed a block of 30 primary trials (15 Xs and 15 Os), and these trials were used to calculate an individual mean reaction time for each child. The children then completed a block of 24 practice trials (8 primary and 16 stop-signal trials). Two experimental blocks of 48 trials (32 primary and 16

stop-signal trials) were then completed. On the stop-signal trials, the bleep (stop-signal) was played either 150ms or 250ms before the child's mean reaction time, as calculated by the primary task trials. Using this design and scoring procedure of the stop-signal paradigm means that a child's stopping efficiency was not associated with the speed of their response to the go-signal, and the children's performance could be assessed by the number of stop-signal trials that they correctly responded on (Handley, Capon, Beveriddge, Dennis, & Evans, 2004); therefore a higher score was indicative of better performance.

4.1.3.4 Procedure

The study was approved by the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees.

4.1.3.5 Analyses

All variables were checked for inconsistencies/outliers using tabulations, graphs and plots. Values that were inconsistent with the relevant assessment were treated as missing values. The distribution of variables was inspected for normality. Three outcome variables from the stop-signal task were not normally distributed (and could not be transformed); they were therefore transformed into binary variables using the bottom 10% as a cut-off.

The association between mother's eating disorder status and children's' neuropsychological profile was explored using linear and logistic regression. Confounders that could potentially influence outcomes, as indicated by evidence in the literature, were initially tested in univariate models, and included in the multivariate analysis if they were associated with both exposure and outcome, and if they were likely to affect the outcome through an alternative causal pathway (see section 3.7: "Methodological Considerations"). Additional analyses were carried out by including maternal education as a covariate in a third model, due to this variable potentially being a mediator of effects. All results from measures of executive functioning (attention, working memory and inhibition), were

additionally co-varied for child Full-scale IQ in a fourth model. SPSS 18 was used for all analyses. A two-tailed significance level of $p \leq 0.05$ was used, but results significant to the $p \leq 0.1$ level were also highlighted as only small effect sizes were expected.

Missing covariate data

Multiple random imputation was used to deal with missing covariate data. All predictor and outcome variables were used as predictors in the imputation model. Missing data were imputed for maternal education, marital status, child ethnicity, family income at age eight, age of child at time of testing, and parity. All analyses were run on both complete case and imputed datasets for comparison and differences were negligible. Due to the fact that complete case analysis is thought to suffer from more chance variation, and multiple imputation is assumed to correct any bias, only results based on multiple imputation are presented.

4.1.4 Results

4.1.4.1 Attrition & Missingness

Attrition

Overall attrition, i.e. children not attending face-to-face assessments, was predicted by a range of socio-demographic factors. A significantly greater proportion of children who attended the relevant assessments at age 8, 10 and 13 were female; white; did not have siblings; came from families with a higher income and/or social class; and had parents who were married. Children who attended assessments also had mothers who were more highly educated and older at the time of delivery. These variables were included as confounders accordingly.

Additional missingness of specific outcomes was dealt with by testing the role of relevant socio-demographic variables as predictors of missing outcome data, by estimating the odds of having missing data across each cognitive assessment. Missingness was predicted in at least one assessment by parity, gestational age,

child ethnicity, and marital status. These variables were also included as confounders accordingly.

Missingness

Maternal AN was predictive of missing data on particular WISC subtests at age 8. A sensitivity analysis was done using multiple random imputation to impute the missing outcome variables at age 8, and the data were re-analysed to check for any differences. Differences were small and it was concluded that results would not be biased.

Selective Attrition

Selective attrition across index groups was tested for using logistic regression, by estimating the odds of each group having missing data at age 8, 10 and 13. Children of women with BN were less likely to have attended assessment sessions at age 8 (OR: 0.74, 95% CI: 0.56, 0.98; p = 0.04). No other differences were found.

4.1.4.2 Socio-demographic Data

Socio-demographic data for the sample used in this study are described in chapter 3 (Aims and Methodology).

4.1.4.3 General Intelligence & Domain Specific Cognition in Children at High Risk

The children of AN mothers showed higher full-scale IQ (B: 3.58, 95% CI: 0.15, 7.00, p = 0.04), and performance IQ (B: 3.93, 95% CI: 0.37, 7.5, p = 0.03) scores, in comparison to the children of unexposed mothers. Maternal education was found to explain the relationship between maternal AN and full-scale IQ (B: 2.18, 95% CI: -1.03, 5.39, p = 0.18), and to a lesser extent performance IQ (B: 3.10, 95% CI: -0.37, 6.58, p = 0.08). With regard to WISC subtest scores, the children of AN mothers showed comparatively high Picture Arrangement scores (B: 1.34, 95% CI: 0.33, 2.35, p = 0.01), while the children of BN mothers showed comparatively low Object Assembly scores (B: -0.9, 95% CI: -1.66, -0.13, p = 0.02). The children of AN

mothers also showed significantly higher scores in the Perceptual Organisation Index (B: 2.4, 95% CI: 0.14, 4.66, p = 0.04). No other differences were found between the children of ED mothers and the children of unexposed mothers (see tables 9 - 12).

Table 9 Linear Regression Analysis of Children's Verbal IQ Subtest Scores: comparisons of exposed and unexposed groups (B coefficients and 95% confidence intervals)

		n (%)	**Model 1** B (95% C.I.)	**Model 2** B (95% C.I.)	**Model 3** B (95% C.I.)
Information	Unexposed	5917 (92.3)	Ref.	Ref.	Ref.
	AN	90 (1.5)	-0.16 (-0.8, 0.48)	-0.31 (-0.92, 0.30)	-0.42 (-1.03, 0.18)
	BN	96 (1.6)	0.01 (-0.60, 0.63)	0.05 (-0.54, 0.64)	0.01 (-0.57, 0.6)
	AN+BN	43 (0.7)	0.34 (-0.58, 1.26)	0.17 (-0.71, 1.05)	-0.11 (-0.98, 0.76)
Similarities	Unexposed	5920 (95.7)	Ref.	Ref.	Ref.
	AN	89 (1.4)	0.43 (-0.4, 1.26)	0.30 (-0.51, 1.11)	0.15 (-0.65, 0.95)
	BN	96 (1.6)	-0.10 (-0.90, 0.7)	-0.06 (-0.84, 0.72)	-0.11 (-0.88, 0.66)
	AN+BN	43 (0.7)	0.89 (-0.3, 2.08)	0.73 (-0.43, 1.89)	0.38 (-0.77, 1.52)
Arithmetic	Unexposed	5903 (96.3)	Ref.	Ref.	Ref.
	AN	89 (1.5)	-0.02 (-0.88, 0.83)	-0.09 (-0.93, 0.76)	-0.22 (-1.06, 0.62)
	BN	96 (1.6)	-0.15 (-0.98, 0.67)	-0.12 (-0.93, 0.7)	-0.16 (-0.97, 0.65)
	AN+BN	43 (0.7)	0.02 (-1.21, 1.25)	-0.09 (-1.30, 1.12)	-0.39 (-1.59, 0.81)
Vocabulary	Unexposed	5893 (96.3)	Ref.	Ref.	Ref.
	AN	89 (1.5)	0.48 (-0.43, 1.4)	0.25 (-0.63, 1.13)	0.04 (-0.82, 0.90)
	BN	95 (1.6)	-0.04 (-0.93, 0.84)	0.001 (-0.85, 0.85)	-0.05 (-0.88, 0.79)
	AN+BN	43 (0.7)	0.6 (-0.71, 1.91)	0.35 (-0.91, 1.61)	-0.13 (-1.36, 1.11)
Comprehension	Unexposed	5859 (96.3)	Ref.	Ref.	Ref.
	AN	88 (1.4)	0.48 (0.3, 1.26)	0.44 (-0.33, 1.21)	0.35 (-0.42, 1.13)
	BN	96 (1.6)	0.09 (-0.66, 0.83)	0.10 (-0.61, 0.84)	0.08 (-0.66, 0.81)
	AN+BN	43 (0.7)	-0.14 (-1.25, 0.97)	-0.20 (-1.30, 0.90)	-0.39 (1.49, 0.70)

§p≤0.1, *p≤0.05, **p≤0.01

(1) Higher scores indicate better performance. (2) Model 1: Adjusted for child age and gender, and tester. Model 2: (Fully adjusted model) adjusted for child age and gender, tester, family income and maternal age at delivery. Model 3: Adjusted for child age and gender, tester, family income, maternal age and delivery and maternal education.

Table 10 Linear Regression Analysis of Children's Performance IQ Subtest Scores: comparisons of exposed and unexposed groups (B coefficients and 95% confidence intervals)

		n (%)	**Model 1** B (95% C.I.)	**Model 2** B (95% C.I.)	**Model 3** B (95% C.I.)
Picture Completion	Unexposed	5892 (96.3)	Ref.	Ref.	Ref.
	AN	90 (1.5)	0.56 (-0.21, 1.33)	0.52 (-0.24, 1.28)	0.44 (-0.32, 1.2)
	BN	96 (1.6)	0.26 (-0.48, 1.01)	0.28 (-0.45, 1.0.2)	0.26 (0.48, 0.99)
	AN+BN	43 (0.7)	0.63 (-0.47, 1.74)	0.56 (-0.54, 1.65)	0.37 (-0.72, 1.46)
Coding	Unexposed	5912 (93.3)	Ref.	Ref.	Ref.
	AN	87 (1.4)	-0.05 (-0.68, 0.57)	-0.03 (-0.65, 0.59)	-0.08 (-0.70, 0.54)
	BN	96 (1.6)	-0.10 (-0.69, 0.49)	-0.09 (-0.68, 0.50)	-0.10 (-0.69, 0.49)
	AN+BN	43 (0.7)	0.54 (-0.35, 1.42)	0.52 (-0.36, 0.57)	0.40 (-0.47, 1.28)
Picture Arrangement	Unexposed	5830 (96.3)	Ref.	Ref.	Ref.
	AN	85 (1.4)	**1.18 (0.46, 2.49)***	**1.41 (0.39, 2.42)***	**1.34 (0.33, 2.35)***
	BN	94 (1.6)	-0.43 (-1.4, 0.54)	-0.4 (-1.36, 0.57)	-0.43 (-1.39, 0.54)
	AN+BN	43 (0.7)	-0.13 (-1.56, 1.3)	-0.22 (-1.64, 1.20)	-0.38 (-1.8, 1.04)
Block Design	Unexposed	5878 (96.3)	Ref.	Ref.	Ref.
	AN	88 (1.4)	0.46 (-0.33, 1.26)	0.43 (-0.35, 1.21)	0.29 (-0.48, 1.07)
	BN	94 (1.5)	0.37 (-0.40, 1.13)	0.38 (-0.38, 1.13)	0.34 (-0.41, 1.09)
	AN+BN	43 (0.7)	0.22 (-0.91, 1.35)	0.13 (-0.98, 1.25)	-0.19 (-1.29, 0.92)
Object Assembly	Unexposed	5579 (96.3)	Ref.	Ref.	Ref.
	AN	83 (1.4)	-0.11 (-0.92, 0.7)	-0.14 (-0.95, 0.67)	-0.22 (-1.02, 0.59)
	BN	92 (1.6)	**-0.89 (-1.66, -0.12)§**	**-0.88 (-1.64, -0.12)***	**-0.9 (-1.66, -0.13)***
	AN+BN	40 (0.7)	0.32 (-0.85, 1.48)	0.27 (-0.89, 1.43)	0.07 (-1.09, 1.22)

§p≤0.1, *p≤0.05, **p≤0.01

(1) Higher scores indicate better performance. (2) Model 1: Adjusted for child age and gender, and tester. Model 2: (Fully adjusted model) adjusted for child age and gender, tester, family income and maternal age at delivery. Model 3: Adjusted for child age and gender, tester, family income, maternal age at delivery and maternal education.

Table 11 Linear Regression of Children's Summary IQ Scores: comparisons of exposed and unexposed groups (B coefficients and 95% confidence intervals)

		n (%)	**Model 1** B (95% C.I.)	**Model 2** B (95% C.I.)	**Model 3** B (95% C.I.)
Full Scale IQ	Unexposed	5869 (96.3)	Ref.	Ref.	Ref.
	AN	87 (1.4)	**3.58 (0.15, 7.00)***	**3.05 (-0.23, 6.33)§**	2.18 (-1.03, 5.39)
	BN	96 (1.6)	-1.03 (-4.29, 2.23)	-0.80 (-3.94, 2.33)	-1.06 (-4.11, 1.99)
	AN+BN	43 (0.7)	2.64 (-2.21, 7.49)	1.85 (-2.8, 6.49)	-0.07 (-4.61, 4.47)
Verbal IQ	Unexposed	5895 (96.3)	Ref.	Ref.	Ref.
	AN	89 (1.5)	1.38 (-2.08, 4.83)	0.63 (-2.67, 3.93)	-0.21 (-0.34, 3.02)
	BN	96 (1.6)	-0.30 (-3.63, 3.03)	-0.06 (-3.25, 3.12)	-0.33 (-3.43, 2.78)
	AN+BN	43 (0.7)	2.08 (-2.87, 7.02)	1.16 (-3.56, 5.89)	-0.77 (-5.39, 3.85)
Performance IQ	Unexposed	5886 (96.3)	Ref.	Ref.	Ref.
	AN	87 (1.4)	**3.93 (0.37, 7.50)***	**3.75 (0.24, 7.26)***	**3.10 (0.37, 6.58)§**
	BN	96 (1.6)	-1.29 (-4.69, 2.11)	-1.14 (-4.48, 2.20)	-1.34 (-4.64, 1.96)
	AN+BN	43 (0.7)	2.40 (-2.66, 7.46)	1.95 (-3.02, 6.91)	0.52 (-4.39, 5.44)

§p≤0.1, *p≤0.05, **p≤0.01

(1) Higher scores indicate better performance. (2) Model 1: Adjusted for child age and gender, and tester. Model 2: (Fully adjusted model) adjusted for child age and gender, tester, family income and maternal age at delivery. Model 3: Adjusted for child age and gender, tester, family income, maternal age at delivery and maternal education.

Table 12 Linear Regression of Children's Index and Digit Span Scores: comparisons of exposed and unexposed groups (B coefficients and 95% confidence intervals)

		n (%)	**Model 1** B (95% C.I.)	**Model 2** B (95% C.I.)	**Model 3** B (95% C.I.)
Verbal Comprehension Index	Unexposed	5850 (96.3)	Ref.	Ref.	Ref.
	AN	89 (1.5)	1.18 (-1.14, 3.5)	0.63 (-1.58, 2.85)	0.07 (-2.1, 2.24)
	BN	95 (1.6)	-0.25 (-2.5, 2.00)	-0.01 (-2.17, 2.14)	-0.17 (-2.27, 1.93)
	AN+BN	43 (0.7)	1.62 (-1.71, 4.95)	0.99 (-2.18, 4.17)	-0.29 (-3.4, 2.82)
Perceptual Organisation Index	Unexposed	5550 (93.4)	Ref.	Ref.	Ref.
	AN	82 (1.4)	**2.86 (0.54, 5.19)***	**2.69 (0.41, 4.98)***	2.4 (0.14, 4.66)
	BN	87 (1.5)	-0.45 (-2.71, 1.81)	-0.37 (-2.59, 1.85)	-0.47 (-2.66, 1.73)
	AN+BN	41 (0.7)	1.08 (-2.2, 4.36)	0.77 (-2.44, 3.99)	-0.14 (-3.33, 3.05)
Freedom from Distractibility Index	Unexposed	5740 (96.3)	Ref.	Ref.	Ref.
	AN	86 (1.4)	0.12 (-1.15, 1.39)	-0.03 (-1.28, 1.22)	-0.23 (-1.47, 1.00)
	BN	92 (1.5)	-0.11 (-1.34, 1.12)	-0.08 (-1.29, 1.13)	-0.10 (-1.3, 1.09)
	AN+BN	42 (0.7)	0.29 (-1.52, 2.11)	0.04 (1.82, 0.003)	-0.43 (-2.19, 1.33)
Digit Span	Unexposed	5759 (94.2)	Ref.	Ref.	Ref.
	AN	86 (1.4)	-0.08 (-0.73, 0.58)	-0.14 (-0.79, 0.51)	-0.23 (-0.87, 0.41)
	BN	93 (1.5)	0.17 (-0.46, 0.8)	0.17 (-0.45, 0.8)	0.16 (-0.46, 0.78)
	AN+BN	42 (0.7)	0.27 (-0.67, 1.2)	0.17 (-0.76, 1.09)	-0.04 (-0.95, 0.88)

§p≤0.1, *p≤0.05, **p≤0.01; (1) Higher scores indicate better performance. (2) Model 1: Adjusted for child age and gender, and tester. Model 2: (Fully adjusted model) adjusted for child age and gender, tester, family income and maternal age at delivery. Model 3: Adjusted for child age and gender, tester, family income, maternal age at delivery and maternal education.

4.1.4.4 Working Memory in Children at High Risk

The children of AN mothers showed slightly better WM span scores in the fully adjusted model (B: 0.19, 95% CI: 0.01, 0.38, p = 0.08), and when co-varying for child IQ (B:0.18 , 95% CI: -0.005, 0.37 , p = 0.06). The children of AN+BN mothers also showed better global working memory scores when co-varying for child IQ (B: 2.26, 95% CI: -0.02, 4.54, p = 0.05). No other differences in WM performance were found between the children of exposed and unexposed mothers (see table 13).

Table 13 Linear Regression Analysis of Children's Working Memory Scores: comparisons of exposed and unexposed groups (B coefficients and 95% confidence intervals)

		n (%)	**Model 1** B (95% C.I.)	**Model 2** B (95% C.I.)	**Model 3** B (95% C.I.)	**Model 4** B (95% C.I.)
WM Span Score	Unexposed	5553 (96.2)	Ref.	Ref.	Ref.	Ref.
	AN	77 (1.3)	**0.2 (0.01, 0.38)***	**0.19 (0.01, 0.38)***	**0.17 (-0.02, 0.36)§**	**0.18 (-0.01, 0.37)§**
	BN	98 (1.7)	-0.07 (-0.24, 0.1)	-0.06 (-0.23, 0.11)	-0.07 (-0.23, 0.10)	0.71 (-0.86, 2.28)
	AN+BN	43 (0.7)	0.14 (-0.12, 0.39)	0.14 (-0.11, 0.39)	0.11 (-0.14, 0.36)	**2.26 (-0.02, 4.54)****
WM Global Score	Unexposed	5553 (96.2)	Ref.	Ref.	Ref.	Ref.
	AN	77 (1.3)	1.03 (-0.68, 2.75)	0.95 (-0.75, 2.65)	0.75 (-0.94, 2.44)	**0.18 (-0.01, 0.37)§**
	BN	98 (1.7)	-0.39 (-1.92, 0.13)	-0.27 (-1.77, 1.24)	-0.30 (-1.80, 1.2)	-0.004 (-0.18, 0.17)
	AN+BN	43 (0.7)	1.43 (-0.86, 3.72)	1.41 (-0.85, 3.67)	1.07 (-1.18, 3.32)	0.19 (-0.07, 0.44)

§p≤0.1, *p≤0.05, **p≤0.01

(1) Higher scores indicate better performance. (2) Model 1: Adjusted for child age and gender, and tester. Model 2: (Fully adjusted model) adjusted for child age and gender, tester, family income and maternal age at delivery. Model 3: Adjusted for child age and gender, tester, family income, maternal age at delivery and maternal education. Model 4: Adjusted for child age and gender, tester, family income, maternal age at delivery, maternal education, and child IQ.

4.1.4.5 Attention in Children at High Risk (TEA-Ch)

There was weak evidence that the children of AN mothers took longer to complete the attentional control task than the children of unexposed mothers in the fully adjusted model (B: 0.77, 95% CI: -0.09-1.63, p = 0.08), and this became stronger when co-varying for child IQ (B: 0.99, 95% CI: 0.18, 1.79, p = 0.02). No group differences were found in performance on the selective or divided attention tasks (see table 14).

Table 14 Linear Regression Analysis of Children's Attention Scores as Measured by The TEA-Ch at age 8: comparisons of exposed and unexposed groups (B coefficients and 95% confidence intervals)

		n (%)	**Model 1** B (95% C.I.)	**Model 2** B (95% C.I.)	**Model 3** B (95% C.I.)	**Model 4** B (95% C.I.)
Sky Search	Unexposed	5732 (96.3)	Ref.	Ref.	Ref.	Ref.
(Selective Attention)	AN	85 (1.4)	-0.1 (-0.5, 0.30)	-0.1 (-0.5, 0.31)	-0.06 (-0.46, 0.34)	-0.07 (-0.46, 0.33)
	BN	93 (1.6)	0.23 (-0.16, 0.61)	0.23 (-0.16, 0.61)	0.24 (-0.45, 0.62)	0.22 (-0.15, 0.59)
	AN+BN	43 (0.7)	0.13 (-0.43, 0.69)	0.14 (-0.42, 0.7)	0.21 (-0.35, 0.77)	0.22 (-0.32, 0.76)
Dual Task	Unexposed	5672 (96.3)	Ref.	Ref.	Ref.	Ref.
(Divided Attention;)	AN	84 (1.4)	1.87 (-1.81, 5.55)	-1.87 (-1.81, 5.54)	2.00 (-1.68, 5.68)	0.96 (-2.62, 4.55)
	BN	89 (1.5)	-1.69 (-5.26, 1.89)	-1.68 (-5.25, 1.89)	-1.64 (-5.021, 1.93)	-1.71 (-5.11, 1.7)
	AN+BN	42 (0.7)	-0.48 (-5.67, 4.70)	-0.39 (-5.56, 4.78)	-0.04 (-5.22, 5.14)	-0.07 (-5.01, 4.88)
Opposite Worlds	Unexposed	5752 (1.7)	Ref.	Ref.	Ref.	Ref.
(Attentional Control)	**AN**	86 (1.4)	**0.72 (-0.14, 1.59)§**	**0.69 (-0.18, 1.55) §**	**0.77 (-0.09, 1.63)§**	**0.99 (0.18, 1.79)***
	BN	93 (1.6)	0.31 (-0.53, 1.14)	0.28 (-0.55, 1.11)	0.29 (-0.54, 1.12)	0.22 (-0.55, 0.99)
	AN+BN	43 (0.7)	-0.83 (-2.05, 0.39)	-0.82 (-2.04, 0.39)	-0.66 (-1.87, 0.55)	-0.65 (-1.77, 0.47)

§p≤0.1, *p≤0.05, **p≤0.01,

(1)Scores measuring attention account for time taken to complete the task, therefore a higher score indicates poorer performance.

(2) Model 1: Adjusted for child age and gender, and tester. Model 2: (Fully adjusted model) adjusted for child age and gender, tester, family income and maternal age at delivery. Model 3: Adjusted for child age and gender, tester, family income, maternal age at delivery and maternal education. Model 4: Adjusted for child age and gender, tester, family income, maternal age at delivery, maternal education, and child IQ.

4.1.4.6 Attention in children at high risk (Reaction Time Task)

Maternal exposure to AN was predictive of children scoring in the bottom 10% on accuracy in the choice reaction time task; in the fully adjusted model (OR: 1.82, 95% CI: 1.03, 3.22, p = 0.04), and when co-varying for maternal education and child IQ (OR: 1.83, 95% CI: 1.03, 3.23, p = 0.04, 95% CI: 1.01, 3.41, p = 0.05 respectively). Maternal exposure to AN also trended towards being predictive of children not scoring in the top 10% for simple reaction time in the fully adjusted model (OR: 0.30, 95% CI: 0.07, 1.24, p = 0.1), and when adjusting for both maternal education and child IQ (OR: 0.19, 95% CI: 0.03, 1.32, p = 0.1). Finally, maternal exposure to both AN+BN trended towards being predictive of children scoring in the top 10% on false alarms in the digit vigilance task when adjusting for both maternal education and child IQ (OR: 2.59, 95% CI: 0.83, 8.08, p = 0.1; see table 15 and 16).

Table 15 Logistic Regression Analysis of Children's Reaction Time Scores: comparison of exposed and unexposed groups (odds ratios and 95% confidence intervals).

		Model 1 OR (95% C.I.)	**Model 2** OR (95% C.I.)	**Model 3** OR (95% C.I.)	**Model 3** OR (95% C.I.)
Simple	Unexposed	Ref.	Ref.	Ref.	Ref.
Reaction	**AN**	**0.28 (0.07, 1.15)§**	0.30 (0.07, 1.24)	**0.31 (0.08, 1.28)**§	**0.19 (0.03, 1.32)§**
Time	BN	0.99 (0.45, 2.18)	0.96 (0.43, 2.14)	0.95 (0.42, 2.11)	1.12 (0.46, 2.71)
	AN+BN	0.74 (0.22, 2.46)	0.75 (0.23, 2.50)	0.81 (0.24, 2.71)	1.21 (0.34, 4.28)
Digit	Unexposed	Ref.	Ref.	Ref.	Ref.
Vigilance	AN	0.55 (0.20, 1.52)	0.63 (0.22, 1.77)	0.65 (0.23, 1.84)	0.84 (0.29, 2.44)
(Targets	BN	1.29 (0.63, 2.62)	1.26 (0.61, 2.59)	1.24 (0.60, 2.56)	1.52 (0.69, 3.37)
detected)	AN+BN	0.55 (0.63, 2.62)	0.55 (0.13, 2.33)	0.59 (0.14, 2.52)	0.88 (0.19, 4.02)
Digit	Unexposed	Ref.	Ref.	Ref.	Ref.
Vigilance	AN	0.94 (0.40, 2.21)	0.88 (0.37, 2.05)	0.87 (0.37, 2.04)	0.97 (0.41, 2.30)
(Speed)	BN	1.34 (0.66, 2.73)	1.32 (0.66, 2.63)	1.32 (0.66, 2.63)	1.14 (0.48, 2.70)
	AN+BN	0.78 (0.24, 2.57)	0.77 (0.26, 2.33)	0.76 (0.23, 2.44)	0.90 (0.04, 2.22)
Digit	Unexposed	Ref.	Ref.	Ref.	Ref.
Vigilance	AN	1.05 (0.45, 2.45)	1.13 (0.48, 2.68)	1.18 (0.50, 2.80)	1.49 (0.61, 3.62)
(False	BN	0.80 (0.32, 2.00)	0.78 (0.31, 1.96)	0.77 (0.30, 1.94)	0.78 (0.27, 2.23)
Alarms)	**AN+BN**	1.85 (0.70, 4.88)	1.87 (0.70, 4.96)	2.02 (0.76, 5.37)	**2.59 (0.83, 8.08)***

§p≤0.1, *p≤0.05, **p≤0.01,

(1) Model 1: Minimally adjusted model: adjusted for child age and gender, and tester. Model 2: Fully adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, and marital stability. Model 3: IQ adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, marital stability, and child IQ.

(2) Simple Reaction Time scores indicate the likelihood of each group being in the highest 10% for time taken (worst performance) in comparison to controls. Digit Vigilance Targets Detected and Digit Vigilance Speed scores indicate the likelihood of each group scoring in the bottom 10% (worst performance) in comparison to controls. Digit Vigilance False Alarms scores indicate the likelihood of each group being in the highest 10% for false alarms (worst performance) in comparison to controls.

(3) N (%) of groups: Unexposed = 5441 (96.2%); AN = 83 (1.5%); BN = 88 (1.6%); AN+BN = 41 (0.7%).

Table 16 Logistic Regression Analysis of Children's Reaction Time Scores (continued): comparison of exposed and unexposed groups (odds ratios and 95% confidence intervals).

		Model 1 OR (95% C.I.)	**Model 2** OR (95% C.I.)	**Model 3** OR (95% C.I.)	**Model 3** OR (95% C.I.)
Choice Reaction (Accuracy)	Unexposed	Ref.	Ref.	Ref.	Ref.
	AN	**1.74 (0.99, 3.06)§**	**1.82 (1.03, 3.22)***	**1.83 (1.03, 3.23)***	**1.85 (1.01, 3.41)***
	BN	1.28 (0.70, 2.33)	1.25 (0.69, 2.26)	1.24 (0.69, 2.58)	1.37 (0.70, 2.65)
	AN+BN	1.68 (0.75, 3.78)	1.72 (0.76, 3.86)	1.72 (0.77, 3.87)	1.68 (0.66, 4.29)
Choice Reaction (Time)	Unexposed	Ref.	Ref.	Ref.	Ref.
	AN	0.96 (0.41, 2.24)	0.94 (0.40, 2.23)	0.97 (0.41, 2.30)	1.22 (0.50, 2.98)
	BN	0.97 (0.44, 2.14)	0.94 (0.43, 2.10)	0.94 (0.42, 2.09)	0.73 (0.29, 1.86)
	AN+BN	0.75 (0.23, 2.51)	0.74 (0.22, 2.45)	0.77 (0.23, 2.57)	0.36 (0.05, 2.93)
Continuity of Attention	Unexposed	Ref.	Ref.	Ref.	Ref.
	AN	0.81 (0.35, 1.90)	0.91 (0.38, 2.15)	0.94 (0.38, 2.24)	1.25 (0.51, 3.06)
	BN	1.38 (0.70, 2.72)	1.34 (0.67, 2.67)	1.32 (0.66, 2.63)	1.14 (0.49, 2.64)
	AN+BN	1.15 (0.40, 3.31)	1.16 (0.40, 3.39)	1.24 (0.43, 3.64)	1.39 (0.38, 5.02)
Power of Attention	Unexposed	Ref.	Ref.	Ref.	Ref.
	AN	0.59 (0.21, 1.64)	0.59 (0.21, 1.65)	0.60 (0.22, 1.68)	0.75 (0.26, 2.16)
	BN	1.13 (0.53, 2.38)	1.08 (0.51, 2.29)	1.07 (0.50, 2.28)	0.91 (0.40, 2.07)
	AN+BN	1.00 (0.35, 2.88)	0.98 (0.34, 2.85)	1.04 (0.36, 3.01)	0.77 (0.17, 3.37)

§p≤0.1, *p≤0.05, **p≤0.01,

(1) Model 1: Minimally adjusted model: adjusted for child age and gender, and tester. Model 2: Fully adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, and marital stability. Model 3: IQ adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, marital stability, and child IQ.

(2) Choice Reaction Time, and Power of Attention scores indicate the likelihood of each group being in the highest 10% (worst performance) for time taken in comparison to controls. Choice Reaction Accuracy, and Continuity of Attention scores indicated the likelihood of each group scoring in the bottom 10% (worst performance) in comparison to controls.

(3) N (%) of groups: Unexposed = 5441 (96.2%); AN = 83 (1.5%); BN = 88 (1.6%); AN+BN = 41 (0.7%).

4.1.4.7 Inhibition in children at high risk

Maternal exposure to BN trended towards being predictive of children scoring in the bottom 10%, in the difficult condition of the stop-signal task; both in the fully adjusted model (OR: 1.67, 95% CI: 0.93-3.02, p = 0.1), and when co-varying for both maternal education and child IQ (OR: 1.62, 95% CI: 1.21-2.17, p = 0.1). In the easy condition of the stop-signal task, there was weak evidence that maternal AN was predictive of children scoring in the bottom 10%, when co-varying for child IQ (OR: 1.8, 95% CI: 0.93-3.48, p = 0.08; see table 17).

Table 17 Linear and Logistic Regression Analysis of Children's Behavioural Inhibition Scores: comparison of exposed and unexposed groups.

		n (%)	Model 1	Model 2	Model 3	Model 4
Easy Condition	Unexposed	5530 (96.3)	Ref.	Ref.	Ref.	Ref.
(likelihood of scoring in	**AN**	77 (1.3)	1.56 (0.84, 2.92)	1.56 (0.84, 2.91)	1.56 (0.84, 2.92)	**1.80 (0.93, 3.48)§**
the bottom 10%)	BN	96 (1.7)	1.01 (0.52, 1.96)	1.00 (0.52, 1.94)	1.00 (0.52, 1.94)	0.79 (0.37, 1.69)
OR (95% C.I.)	AN & BN	42 (0.7)	0.45 (0.11, 1.85)	0.45 (0.11, 1.82)	0.45 (0.11, 1.84)	0.27 (0.04, 1.97)
Difficult Condition	Unexposed	5530 (96.3)	Ref.	Ref.	Ref.	Ref.
(likelihood of scoring in	AN	77 (1.3)	1.48 (0.77, 2.87)	1.11 (0.59, 2.12)	1.48 (0.77, 2.87)	1.11 (0.55, 2.26)
the bottom 10%)	**BN**	96 (1.7)	**1.58 (0.94, 2.65)§**	**1.57 (0.95, 2.62)§**	**1.67 (0.93, 3.02)§**	1.62 (1.21, 2.17)
OR (95% C.I.)	AN & BN	42 (0.7)	1.17 (0.49, 2.79)	1.15 (0.49, 2.71)	1.34 (0.56, 3.23)	0.90 (032, 2.51)
Primary Trials	Unexposed	5530 (96.3)	Ref.	Ref.	Ref.	Ref.
(likelihood of scoring in	AN	77 (1.3)	0.63 (0.25, 1.59)	0.53 (0.21, 1.31)	0.63 (0.25, 1.59)	0.51 (0.18, 1.40)
the bottom 10%)	BN	96 (1.7)	0.92 (0.47, 1.79)	0.92 (0.47, 1.79)	1.13 (0.55, 2.31)	0.88 (0.60, 1.30)
OR (95% C.I.)	AN & BN	42 (0.7)	1.56 (0.68, 3.57)	1.57 (0.69, 3.60)	1.66 (0.71, 3.89)	0.98 (0.34, 2.84)
Mean Reaction Time in	Unexposed	5530 (96.3)	Ref.	Ref.	Ref.	Ref.
Primary Trials	AN	77 (1.3)	-6.69 (-21.83, 8.45)	-7.45 (-22.58, 7.69)	-7.11 (-22.25, 8.03)	-2.65 (-18.34, 13.04)
B (95% C.I.)	BN	96 (1.7)	0.87 (-12.71, 14.44)	0.7 (-12.86, 14.26)	0.78 (-12.77, 14.34)	-1.99 (-16.62, 12.64)
	AN & BN	42 (0.7)	0.87 (-12.71, 14.44)	2.32 (-14.05, 22.69)	2.90 (-12.77, 14.34)	2.68 (-18.5, 23.85)

§p≤0.1, *p≤0.05, **p≤0.01

(1) Model 1: Adjusted for child age and gender, and tester. Model 2: (Fully adjusted model) adjusted for child age and gender, tester, family income and maternal age at delivery. Model 3: Adjusted for child age and gender, tester, family income, maternal age at delivery and maternal education. Model 4: Adjusted for child age and gender, tester, family income, maternal age at delivery, maternal education, and child IQ.

(2) Inhibition scores indicating the likely-hood of scoring in the bottom 10% are the results of logistic, rather than linear, regression. The results therefore indicate the likelihood of each group scoring in the bottom 10% in comparison to controls.

4.1.5 Interim Discussion

The aim of this study was to investigate intelligence, global cognition, and executive functioning in children who are at high risk of developing an eating disorder, in comparison to children who are not. Results of statistical analysis showed that in comparison to the children of unexposed women, the children of women reporting AN demonstrated higher Full-scale and Performance IQ; superior working memory capacity; and poorer attentional control. In addition, the children of women who reported AN exhibited decreased accuracy in a measure of attentional alertness, concentration and information processing. The children of women reporting BN demonstrated poorer performance on the Object Assembly subtest of the WISC-III; and there was also a weak association between maternal AN, and BN and comparatively low behavioural inhibition. These findings are discussed in greater detail below.

4.1.5.1 Intelligence and Global Cognition

As predicted, the children of AN mothers demonstrated comparatively high Full-scale IQ; with high Performance IQ appearing to make the main contribution to this. Interestingly, Performance IQ is considered to be the most heritable in childhood, in comparison to Verbal IQ and Full scale IQ, and is representative of problem solving ability (van Soelen, 2011). On the whole, research investigating intelligence in AN patients has revealed high IQ in comparison to healthy controls (Lopez, et al., 2010); and a psychiatric control group (Blanz, et al., 1997). Our findings indicate that children at high risk of developing an ED, due to being born to mothers reporting AN, also show comparatively high IQ.

The children of AN mothers showed comparatively high scores in the perceptual organisation index. This is a particularly interesting result as this index reflects one's ability to interpret and organise visually perceived materials. Existing research suggests that individuals with AN, and their first degree relatives, have impaired visuo-spatial abilities and weak central coherence (Tenconi, et al., 2010; Whyte, 2006). Our findings suggest that the opposite is true in the children of women with AN, and this could be for a number of possible reasons. Research in

this area has concentrated on clinical groups while a general population cohort has been investigated here; it is possible that impairments in visuo-spatial processing are only associated with an extreme AN phenotype. It is also possible that the impairments observed in clinical groups are not present prior to onset of the disorder, and are a consequence of the illness rather than a predisposing factor.

The children of AN women also showed particularly high Picture Arrangement subtest scores, indicating good planning and logical thinking, and good social knowledge and interpretation of actions. This is also particularly interesting due to the wealth of evidence pertaining to social difficulties in AN patients (Zucker, 2007). Once again, the good social knowledge observed in the children of women with AN could be for a number of possible reasons. The majority of research in this area has used social interpretation tasks that consist of human cues (i.e. faces or eyes) rather than cartoon pictures; and tasks require participants to interpret emotion rather than the order of social interactions (Faunce & Job, 2000). It is also possible that the social difficulties observed in ED groups are a secondary effect of the illness, for example due to restricted nutritional intake, and are therefore not present prior to onset.

No significant differences were observed between the children of healthy control women and the children of women reporting BN: in Full-scale IQ; Performance IQ; or Verbal IQ. Evidence indicates that there are also no differences in IQ between BN patients and healthy controls (Galderisi, 2010). Though investigations of intelligence in BN populations are rare, our finding of normal IQ in the children of BN women is consistent with findings of normal IQ in BN patients. The children of BN women did show comparatively poor performance on the Object Assembly subtest, which reflects comparatively poor visual organizational ability and visual motor co-ordination. Current research in the field pertaining to visuo-spatial functioning in BN patients is conflicting: with some evidence of similar difficulties in ED groups (I. Gillberg, et al., 2007; Jones, Duncan, Brouwers, & Mirsky, 1991; Sellbom & Gunstad, 2012), and non-clinical samples with bulimic disturbance (Bosanac, et al., 2007); and also negative findings revealing no impairments (Eysenck, 1992; Faunce, 2002). Our findings indicate that subtle impairments in

visuo-spatial functioning are present in children at high risk of developing an ED, due to being born to a mother reporting BN.

4.1.5.2 Working Memory

As hypothesized, the children of women reporting AN displayed comparatively superior working memory capacity in comparison to the children of healthy control women; a difference that was only partly mediated by maternal education and child IQ. The children of women reporting AN+BN also showed better working memory, demonstrated by their comparatively higher global working memory scores; though this difference only reached statistical significance when adjusting for child IQ. Superior working memory has also been observed in AN patients when compared to healthy controls, both in the acute phase of illness and when participants were weight restored (Hatch, et al., 2010).

There is evidence in the literature of decreased working memory capacity in AN patients (Green, Elliman, Wakeling, & Rogers, 1996b), however findings from this study are limited due to the small size of the sample employed. Kemps and colleagues also observed impaired working memory in a sample of AN patients when compared to controls; however when statistically controlling for pre-occupying cognitions about food, weight and body shape, differences between groups became non-significant (Kemps, et al., 2006). A similar association is observed in dieting groups (Green & Rogers, 1998). Though Green and colleagues found that in comparison to non-dieting healthy controls, dieting women showed poor working memory; statistically controlling for food, weight and body shape cognitions once again led to differences between groups becoming non-significant. These studies suggest that when impaired working memory is observed in AN or dieting individuals it is likely to be due to the intrusive thoughts that accompany restriction, rather than deficits in working memory being present prior to onset. Our findings lend support to this notion by finding superior working memory in children at high risk of developing an ED, due to being born to mothers with AN. It is possible however that increased working memory is a predisposing factor for onset of an ED; working counterproductively through excessive rumination,

inflexible thought, or attention to detail as Brooks and colleagues have suggested (Brooks, et al., 2012).

4.1.5.3 Attention

The children of women reporting AN took longer to complete the attentional control subtest of the TEA-Ch, than the children of healthy control women; reflecting a decreased ability to inhibit well learned pre-potent thoughts. No other differences were observed between exposed and unexposed groups on any TEA-Ch subtest. Interestingly, the children of women reporting AN+BN also showed comparatively poor performance on the Digit Vigilance subtest of the Reaction Time Task. The results of a logistic regression analysis showed that this group of children had over twice the odds of being in the highest 10% for errors made, in comparison to the children of unexposed women; though this difference only trended towards statistical significance. Like the attentional control subtest of the TEA-Ch, low accuracy on the Digit Vigilance subtest of the Reaction Time Task may be a reflection of decreased attentional control, or increased attentional impulsivity.

The children of women reporting AN also demonstrated poorer performance on the Choice Reaction subtest of the Reaction Time Task; with approximately twice the odds of scoring in the bottom 10% for accuracy in comparison to the children of healthy controls. Poor performance on this task could indicate problems with concentration, alertness, speed, or information processing. Similarly in the Simple Reaction Time subtest (which assesses alertness, concentration, and speed but not information processing) children of AN women had lower odds than unexposed children of being in the slowest 10%. The combination of these two findings suggests that the poor performance of children whose mothers reported AN, on the Choice Reaction subtest, is likely to be due to problems with information processing; otherwise referred to as selective attention.

It is intriguing that the children of women who reported AN displayed comparable performance to the children of unexposed women on the selective attention

subtest of the TEA-Ch; while performance in the Reaction Time Task indicates comparatively poor selective attention. This could be for a number of reasons. These contradictory findings could be reflective of the difficulties one encounters when attempting to compare performance on different cognitive tasks that are thought to be measuring the same cognitive construct. This is a common problem in the literature. One which has led researchers to develop a standardized battery of tasks for assessment that they hope will be used by others, making comparison between different samples more simple (Stedal, et al., 2011). This is not always possible however. In the case of this study for example, which employs a longitudinal population cohort, the cognitive assessments are chosen by researchers involved with the cohort itself not by collaborators like ourselves. Another potential reason for the contradictory results regarding selective attention is that children completed the TEA-Ch when they were 8 years of age, and completed the reaction time task when they were 13 years of age. It might be that deficits in selective attention only develop at a later age, perhaps in adolescence when executive functions go through a developmental change (Blakemore & Choudhury, 2006). It is also possible that by the age of 13 the children of women reporting AN have developed their own ED related cognitions and/or behaviours. This is currently being investigated by our team, and a future study testing this hypothesis would be informative. Finally, it is feasible that the measure of Selective Attention in the TEA-Ch was not sensitive enough to pick up on subtle impairments, while the Choice Reaction subtest of the Reaction Time Task was, though this hypothesis would also require further investigation.

In summary, our findings regarding attentional capacity suggest that the children of women reporting AN display decreased attentional control, and a high proportion of them show decreased selective attention. There was also a trend towards decreased attentional control (or increased attentional impulsivity), in a high proportion of the children whose mothers reported AN+BN. There is evidence in the literature indicating decreased attentional control in ED patients as measured by the Stroop Task (Dobson & Dozois, 2004). Interestingly, the attentional control task that is part of the TEA-Ch has been described as a children's version of the Stroop Task, and both tasks are thought to be comparable

in the cognitive structures they rely on (Manly, et al., 2001). The review by Dobson and Dozois however, found that while the attentional bias found in BN patients on the Stroop extended to a range of different stimuli, the attentional bias found in AN patients was specific to body and weight stimuli (Dobson & Dozois, 2004). Claes and colleagues also found that in a comparison of women who either restricted or binged and purged, the bingeing and purging women took longer to complete the original Stroop task and made more errors (Claes, et al., 2011). This means that while evidence in the literature suggests that decreased attentional control is characteristic of the BN phenotype; our findings suggest that decreased attentional control might be associated with an AN phenotype.

There is also evidence in the literature for impaired selective attention/information processing in AN patients (Fowler, et al., 2006). Findings from the present investigation suggest that comparatively poor selective attention is also present in children at high risk of developing an ED due to being born to a mother with AN. This supports the hypothesis that poor selective attention is present prior to onset of an ED, and might be a characteristic of AN that is independent of illness state. Problems with selective attention may be a predisposing factor for development of an ED, and may be an intermediate phenotype for AN.

4.1.5.4 Behavioural Inhibition

The children of women reporting BN showed a trend towards decreased behavioural inhibition. This group was between 57-67% more likely than controls to score in the bottom 10% in the difficult condition of the stop-signal task; though this difference only trended towards statistical significance. Interestingly, in the easier condition of the stop-signal task there was a trend towards the children of women with AN showing decreased behavioural inhibition in comparison to the children of unexposed women, but only when IQ was additionally co-varied for. Children of women with AN were 80% more likely than controls to score in the bottom 10%, although 95% confidence intervals crossed 1. There is some debate over whether it is statistically correct to adjust for IQ when analyzing performance on cognitive assessments (Dennis, et al., 2009). Dennis and colleagues suggest that

IQ does not meet the requirements for a covariate, and that adjusting for IQ can lead to overcorrected, anomalous, and counterintuitive findings. Taking into account that (i) differences between the children of women reporting AN and the children of healthy control women were observed in the easy condition of the stop-signal task, but not in the difficult condition; and (ii) differences only trended towards significance when additionally adjusting for child IQ; it is possible that this finding is overcorrected and anomalous as Dennis and colleagues suggest.

There is conflicting evidence in the literature regarding behavioural inhibition in ED. Studies have found evidence both for and against the presence of decreased inhibition in AN and BN groups (Galimberti, et al., 2011; Kemps & Wilsdon, 2009; Rosval, et al., 2006). Interestingly, this specific type of behavioural/motoric inhibition has been associated with binge eating behaviours particularly, suggesting that using the AN/BN diagnosis may be a limitation when conducting research on this construct (Rosval, et al., 2006). Our findings, by not reaching statistical significance, are also inconclusive with regard to the presence of decreased behavioural inhibition in children at high risk of developing an ED.

4.1.6 Study Summary

The findings from study one (investigating being at risk for an ED and neuropsychological functioning) revealed particular differences in the cognitive functioning of children at high risk in comparison to unexposed children. Specifically the children of women reporting AN showed comparatively high IQ, superior working memory capacity, and good visuo-spatial functioning; but comparatively poor attentional control and selective attention. The children of women reporting BN showed comparatively poor visuo-spatial functioning. Findings regarding behavioural inhibition did not reach statistical significance, but there was weak evidence for the children of women reporting AN or BN having decreased inhibitory control. Our findings lend support to the notion that these neuropsychological differences are present prior to onset and are therefore independent of illness state; making them putative intermediate phenotypes for ED.

4.2 Are Maternal Lifetime ED Behavioural Phenotypes Associated with Children's Intelligence, Global Cognition, and Executive Functioning?

4.2.1 Introduction

As discussed in chapter one there is evidence in the literature of specific ED behaviours being associated with specific differences in neuropsychological functioning, which suggests that lifetime ED behaviours may provide more distinct phenotypes in comparison to ED diagnoses. Watson and Anderson (2003) found that women meeting all criteria for AN had higher IQ than women who met all criteria for AN except amenorrhea (Watson, 2003), suggesting high IQ may be associated with behaviours that lead to very low weight such as extreme restriction and purging. Claes and colleagues found that patients who binged and purged exhibited decreased attentional control and impaired switching of attention in comparison to patients who restricted (Claes, et al., 2011), indicating an association between decreased attentional capacity and a bingeing/purging phenotype. BN patients who use laxatives have been shown to have poorer inhibitory control than healthy controls, and BN patients who do not use laxatives (Bruce, et al., 2003); which suggests that there may be an association between inhibitory control and a purging phenotype.

4.2.2 Aims & Hypotheses

As with study one, the primary aim of this study was to investigate the neuropsychological profile of children at high risk of developing an ED, by using maternal ED behaviours as a risk marker. Based on previous literature, it was predicted that: (i) children at risk due to being born to women who presented exclusively with lifetime restrictive behaviours would show comparatively high IQ and superior working memory; (ii) children at risk due to being born to women who presented with lifetime bingeing and purging behaviours would show

decreased attentional capacity as measured by the TEA-Ch, and would be more likely to perform in the poorest 10% on outcomes of the Reaction Time task; and (iii) children at risk due to being born to women who presented with lifetime purging would be more likely to score in the poorest 10% on Stop-signal outcomes as a measure of inhibitory control.

4.2.3 Methods

4.2.3.1 Design

Longitudinal

4.2.3.2 Participants

For inclusion in this study, data on maternal lifetime ED behaviours and children's neuropsychological functioning were both necessary, therefore sample size varied for the analysis of each neuropsychological measure. Full details of the interview protocol, and inclusion and exclusion criteria can be found in chapter 3 (Aims and Methodology). Final sample sizes for each analysis can be found in the relevant results tables. Assessments were conducted when children were approximately 8 (intelligence and attention), 10 (working memory and inhibition), and 13 (attention) years of age, with mean ages being: 103.8 months, 127.8 months, and 150 months; respectively.

4.2.3.3 Measures

Exposure

Data on maternal exposure to eating disorder behaviours were gathered via in depth interviews using the Structured Clinical Interview for DSM-IV-TR (Research version) with the additional use of the Lifeline section of the LIFE interview (Keller, et al., 1987). A full explanation of these measures and the interview protocol can be found in chapter 3 (Aims and Methodology), along with a detailed description of how exposed groups were categorized.

Outcomes: Cognitive assessment of Children

General Intelligence & Domain Specific Cognitive Functioning was assessed at age 8 using the Wechsler Intelligence Scale for Children, 3rd edition (WISC) (Wechsler, et al., 1992). Selective attention, divided attention, and attentional control were assessed using subtests from the Tests of Everyday Attention for Children (TEA-Ch) (Manly, et al., 2001). Working memory capacity and inhibition were measured at age 10 using the Counting Span Task (Case, et al., 1982), and the Stop-Signal Task respectively. Focused attention and continuity of attention were assessed at age 13 using the Reaction Time Task. A detailed description of these tasks can be found earlier in this chapter (Study 1. Measures).

4.2.3.4 Procedure

The study was approved by the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees. A full account of the procedures and protocol for administering interviews and deriving exposure variables can be found in chapter 3 (Aims and Methodology).

4.2.3.5 Analysis

All analytical procedures were identical to those used in study one: including the transformation of outcomes that were not normally distributed into binary variables for logistic regression analysis; use of confounders; and statistical models (see Study One: Measures, for a full description). In addition, the divided attention outcome variable of the TEA-Ch was also not normally distributed and was therefore transformed into a binary variable using the top centile (indicating worst performance) as a cut-off.

Like study one, association between mother's ED status and children's neuropsychological functioning was explored in four models. In the minimally adjusted model child age, child gender and tester were confounded for due to these variables being determined a-priori confounders. Additional confounders that could potentially influence outcomes were adjusted for in a second model (fully adjusted model) after testing whether these variables met criteria for confounding. Additional analyses were carried out by including maternal education as a covariate in a third model, due to this variable potentially being a mediator of

effects. All results from measures of executive functioning (attention, working memory and inhibition), were additionally co-varied for child Full-scale IQ in a fourth model. Due to the paucity of evidence in the literature a two-tailed significance level of $p \leq 0.05$ was used. Results significant to the $p \leq 0.1$ level were also highlighted for discussion as only small effect sizes were expected.

Missing covariate data

Multiple random imputation was used to deal with missing covariate data. All predictor and outcome variables were used as predictors in the imputation model. Missing data were imputed for maternal education, marital status, child ethnicity, social class, maternal age at delivery, and parity for at least one of the analyses. All analyses were run on both complete case and imputed datasets for comparison and differences were negligible. Due to the fact that complete case analysis is thought to suffer from more chance variation, and multiple imputation is assumed to correct any bias, only results based on multiple imputation are presented.

4.2.4 Results

4.2.4.1 Attrition & Missingness

Attrition

Overall attrition for the assessment of maternal lifetime ED behaviours: i.e. women who were not interviewed; was predicted by a range of socio-demographic factors. Full interview protocol can be found in chapter three (Aims and Methodology). A significantly greater proportion of the mothers interviewed were of a higher social class; were more highly educated; were married during pregnancy; and older at the time of delivery. These variables were included as confounders accordingly.

Overall attrition for the assessment of children's cognition, i.e. children not attending face-to-face assessments, was predicted by a range of socio-demographic factors. A significantly greater proportion of children who attended the relevant assessments at age 8, 10 and 13 were female, white, did not have siblings, came

from families with a higher income or of a higher social class, and had parents who were married at the time of delivery. Children who attended assessments also had mothers who were older and more highly educated. These variables were included as confounders accordingly.

Missingness

Additional missingness of specific outcomes was dealt with by testing the role of relevant socio-demographic variables as predictors of missing outcome data, by estimating the odds of having missing data across each cognitive assessment. Missingness was predicted in at least one assessment by social class, maternal education, and maternal age at delivery. These variables were included as confounders accordingly.

Maternal restricting and excessive exercising alone was also predictive of missing data in the assessment of children's working memory capacity. A sensitivity analysis was conducted using multiple random imputation to impute missing outcome variables, and the data were re-analysed to check for any differences. Differences were small and it was concluded that the results would not be biased.

4.2.4.2 Socio-demographics

Socio-demographic data for the sample used in this study can be found in chapter 3 (Aims and Methodology).

4.2.4.3 General Intelligence & Domain Specific Cognition in children at high risk

Restricting/Excessive Exercising Group

Maternal restricting/excessive exercising was weakly associated with children exhibiting comparatively high Full-scale IQ scores; but only in the model additionally adjusting for maternal education (B: 3.21, 95% CI: -0.09, 6.51, p = 0.06). There was also a trend in the association of maternal restricting/excessive exercising and high Verbal IQ scores in the children, in the minimally (B: 3.08, 95% CI: -0.40, 6.56, p = 0.08), and fully (B: 3.11, 95% CI: -0.28, 6.51, p = 0.07) adjusted

models. This association became significant to the 0.05 level when additionally adjusting for maternal education (B: 3.59, 95% CI: 0.26, 6.91, p = 0.03). In addition, a weak association was observed between maternal restricting/excessive exercising and children exhibiting comparatively high scores in the Verbal Comprehension Index in the minimally adjusted model (B: 2.26, 95% CI: -0.06, 4.57, p = 0.06); and this association became statistically significant in both the fully adjusted model (B: 2.29, 95% CI: 0.02, 4.55, p = 0.05), and when additionally covarying for maternal education (B: 2.59, 95% CI: 0.37, 4.81, p = 0.02). With regard to the individual subtests of the WISC-III, maternal restricting/excessive exercising was significantly associated with children exhibiting high scores in the Vocabulary subtest. This was the case in the minimally adjusted model (B: 0.96, 95% CI: 0.02, 1.89, p = 0.05); the fully adjusted model (B: 1.00, 95% CI: 0.08, 1.91, p = 0.03); and when additionally covarying for maternal education (B: 1.10, 95% CI: 0.19, 2.00, p = 0.02; see tables 18, 20 and 21).

Purging Group

The children of women in the Purging group exhibited comparatively high scores on the Similarities subtest of the WISC-III, in the fully adjusted model (B: 1.16, 95% CI: 0.08, 2.25, p = 0.04); and when additionally covarying for maternal education (B: 1.09, 95% CI: 0.03, 2.16, p = 0.05; see table 18).

Bingeing and Purging Group

Children in this group trended towards having comparatively lower scores in the Block Design sub-test in the model additionally adjusting for maternal education (B: -0.97, 95% CI: -1.95, 0.01, p = 0.053; see table 19).

Table 18 Linear Regression Analysis of Children's Verbal IQ Subtest Scores: comparison of exposed and unexposed groups.

		n (%)	**Model 1** B (95% C.I.)	**Model 2** B (95% C.I.)	**Model 3** B (95% C.I.)
Information	Unexposed	681(71.5)	Ref.	Ref.	Ref.
	R & EE	102 (10.7)	0.47 (-0.18, 1.11)	0.48 (-0.15, 1.12)	**0.57 (-0.05. 1.19)§**
	Purging	54 (5.7)	0.15 (-0.72, 1.01)	0.23 (-0.62, 1.08)	0.18 (-0.65, 1.10)
	Bingeing	56 (5.9)	**-0.79 (-1.63, 0.06)§**	**-0.83 (-1.67, 0.00)***	**-0.79 (1.61, 0.02)§**
	Bingeing & Purging	60 (6.3)	-0.64 (-1.46, 0.18)	-0.60 (-1.40, 0.21)	**-0.75 (-1.54, 0.05)§**
Similarities	Unexposed	680 (71.6)	Ref.	Ref.	Ref.
	R & EE	102 (10.7)	0.62 (-0.19, 1.44)	0.63 (-0.18, 1.43)	**0.72 (-0.07, 1.52)***
	Purging	53 (5.6)	**1.06 (-0.04, 2.17)§**	**1.16 (0.08, 2.25)***	**1.09 (0.03, 2.16)***
	Bingeing	55 (5.8)	0.20 (-0.88, 1.28)	0.16 (-0.91, 1.22)	0.18 (-0.87, 1.23)
	Bingeing & Purging	60 (6.3)	-0.82 (-1.86, 0.21)	-0.77 (-1.80, 0.25)	**-0.94 (-1.95, 0.08)§**
Arithmetic	Unexposed	678 (71.5)	Ref.	Ref.	Ref.
	R & EE	102 (10.8)	0.38 (-0.50, 1.25)	0.36 (-0.50, 1.22)	0.45 (-0.41, 1.30)
	Purging	53 (5.6)	0.48 (-0.70, 1.66)	0.54 (-0.62, 1.17)	0.48 (-0.67, 1.63)
	Bingeing	55 (5.8)	0.10 (-1.06, 1.25)	0.01 (-1.13, 1.15)	0.03 (-1.09, 1.16)
	Bingeing & Purging	60 (6.3)	-0.02 (-1.13, 1.09)	-0.03 (-1.13, 1.07)	-0.18 (-1.27, 0.91)
Vocabulary	Unexposed	675 (71.5)	Ref.	Ref.	Ref.
	R & EE	102 (10.8)	**0.96 (0.02, 1.89) ***	**1.00 (0.08, 1.91)***	**1.10 (0.19, 2.00)***
	Purging	53 (5.6)	0.28 (-0.99, 1.54)	0.39 (-0.84, 1.63)	0.32 (-0.90, 1.54)
	Bingeing	54 (5.7)	0.32 (-0.93, 1.57)	0.29 (-0.93, 1.52)	0.33 (-0.88, 1.54)
	Bingeing & Purging	60 (6.4)	**1.01 (-0.17, 2.20)§**	**1.10 (-0.06, 2.27)§**	0.94 (0.22, 2.09)
Comprehension	Unexposed	668 (69.8)	Ref.	Ref.	Ref.
	R & EE	102 (10.7)	0.27 (-0.50, 1.05)	0.24 (-0.54, 1.01)	0.26 (-0.51, 1.03)
	Purging	53 (5.5)	0.82 (-0.22, 1.86)	0.82 (-0.22, 1.86)	0.81 (-0.23, 1.84)
	Bingeing	54 (5.6)	0.21 (-0.82, 1.23)	0.15 (-0.88, 1.17)	0.16 (-0.87, 1.18)
	Bingeing & Purging	60 (6.3)	**0.85 (-0.13, 1.83)§**	0.80 (-0.18, 1.78)	0.76 (-0.22, 1.74)

§p≤0.1, *p≤0.05, **p≤0.01,

(1) Higher scores indicate better performance.

(2) Model 1: Minimally adjusted model, adjusted for child age and gender, and tester. Model 2: Fully adjusted model, adjusted for child age and gender, tester, social class, maternal age at delivery, and marital stability. Model 3: Maternal Education Model, adjusted for child age and gender, tester, social class, maternal age at delivery, marital stability, and maternal education.

Table 19 Linear Regression Analysis of Children's Performance IQ Subtest Scores: comparison of exposed and unexposed groups

		n (%)	**Model 1** B (95% C.I.)	**Model 2** B (95% C.I.)	**Model 3** B (95% C.I.)
Picture Completion	Unexposed	675 (71.3)	Ref.	Ref.	Ref.
	R & EE	102(10.8)	0.55 (-0.20, 1.31)	0.57 (-0.19, 1.33)	**0.64 (-0.12, 1.39)§**
	Purging	54 (5.7)	0.08 (-0.93, 1.09)	0.11 (-0.90, 1.12)	0.07 (-0.93, 1.07)
	Bingeing	56 (5.9)	-0.08 (-1.07, 0.91)	-0.09 (-1.07, 0.90)	-0.06 (-1.04, 0.92)
	Bingeing & Purging	60 (6.3)	0.22 (-0.74, 1.18)	0.25 (-0.71, 1.21)	0.13 (-0.83, 1.09)
Coding	Unexposed	678 (71.5)	Ref.	Ref.	Ref.
	R & EE	101(10.7)	-0.15 (-0.76, 0.46)	-0.14 (-0.75, 0.47)	-0.13 (-0.74, 0.48)
	Purging	54 (5.7)	-0.20 (-1.01, 0.62)	-0.14 (-0.95, 0.67)	-0.15 (-0.96, 0.66)
	Bingeing	55 (5.8)	-0.41 (-1.21, 0.40)	-0.38 (-1.19, 0.42)	-0.38 (-0.19, 0.42)
	Bingeing & Purging	60 (6.3)	-0.27 (-1.05, 0.50)	-0.21 (0.99, 0.56)	-0.24 (-1.01, 0.54)
Picture Arrangement	Unexposed	664 (71.4)	Ref.	Ref.	Ref.
	R & EE	100 (10.8)	0.30 (-0.72, 1.32)	0.26 (-0.75, 1.28)	0.29 (-0.72, 1.31)
	Purging	53 (5.7)	0.34 (-1.03, 1.70)	0.38 (-0.98, 1.73)	0.35 (-1.00, 1.70)
	Bingeing	54 (5.8)	0.52 (-0.83, 1.86)	0.44 (-0.90, 1.78)	-0.27 (1.56, 1.02)
	Bingeing & Purging	59 (6.3)	-0.19 (-1.49, 1.10)	-0.21 (-1.50, 1.08)	0.48 (-0.14, 1.10)
Block Design	Unexposed	676 (71.5)	Ref.	Ref.	Ref.
	R & EE	102 (10.8)	0.41 (-0.37, 1.20)	0.41 (-0.37, 1.19)	0.49 (-0.28, 1.26)
	Purging	53 (5.6)	-0.40 (-1.46, 0.66)	-0.33 (-1.38, 0.72)	-0.39 (-1.43, 0.65)
	Bingeing	55 (5.8)	0.05 (-0.99, 1.09)	0.01 (-1.02, 1.04)	0.03 (-0.99, 1.05)
	Bingeing & Purging	60 (6.3)	**-0.86 (-1.86, 0.14)§**	**-0.84 (-1.83, 0.16)§**	**-0.97 (-1.95, 0.01)§**
Object Assembly	Unexposed	631 (71.1)	Ref.	Ref.	Ref.
	R & EE	96 (10.8)	-0.56 (-1.39, 0.23)	-0.57 (-1.37, 0.24)	-0.54 (-1.35, 0.27)
	Purging	51 (5.7)	0.85 (-0.22, 1.93)	0.91 (-0.16, 1.99)	**0.90 (-0.17, 1.98)§**
	Bingeing	52 (5.9)	-0.23 (-1.29, 0.84)	-0.22 (-1.28, 0.85)	-0.20 (-1.27, 0.86)
	Bingeing & Purging	57 (6.4)	-0.60 (-1.62, 0.43)	-0.53 (-1.55, 0.49)	-0.57 (-1.59, 0.45)

§p≤0.1, *p≤0.05, **p≤0.01, (1) Higher scores indicate better performance. (2) Model 1: Minimally adjusted model, adjusted for child age and gender, and tester. Model 2: Fully adjusted model, adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, and marital stability. Model 3: Maternal Education Model, adjusted for child age and gender, tester, social class, maternal age at delivery, marital stability, and maternal education.

Table 20 Linear Regression Analysis of Children's Summary IQ Scores: comparison of exposed and unexposed groups

		n (%)	**Model 1** B (95% C.I.)	**Model 2** B (95% C.I.)	**Model 3** B (95% C.I.)
Full Scale IQ	Unexposed	670 (71.4)	Ref.	Ref.	Ref.
	R & EE	101 (10.8)	2.78 (-0.66, 6.22)	2.77 (-0.59, 6.14)	**3.21 (-0.09, 6.51)§**
	Purging	53 (5.7)	2.33 (-2.29, 6.94)	2.80 (-1.72, 7.32)	2.46 (-1.95, 6.88)
	Bingeing	54 (5.8)	0.40 (-4.16, 4.96)	0.21 (-4.27, 4.70)	0.39 (-3.98, 4.77)
	B & P	60 (6.4)	-1.15 (-5.50, 3.20)	-0.90 (-5.17, 3.38)	-1.69 (-5.88, 2.50)
Verbal IQ	Unexposed	675 (71.5)	Ref.	Ref.	Ref.
	R & EE	102 (10.8)	**3.08 (-0.40, 6.56)§**	**3.11 (-0.28, 6.51)§**	**3.59 (0.26, 6.91)***
	Purging	53 (5.6)	3.47 (-1.22, 8.16)	**3.92 (-0.66, 8.51)§**	3.58 (-0.89, 8.06)
	Bingeing	54 (5.7)	0.54 (-4.10, 5.18)	0.28 (-4.26, 4.82)	0.48 (-3.95, 4.90)
	B & P	60 (6.4)	0.33 (-4.09, 4.75)	0.51 (-3.83, 4.84)	-0.31 (-4.55, 3.94)
Performance IQ	Unexposed	673 (71.4)	Ref.	Ref.	Ref.
	R & EE	101 (10.7)	1.12 (-2.41, 4.65)	1.13 (-2.36, 4.63)	1.44 (-2.03, 4.91)
	Purging	53 (5.6)	1.00 (-3.74, 5.74)	1.36 (-3.34, 6.06)	1.13 (-3.52, 5.78)
	Bingeing	55 (5.8)	-0.54 (-5.18, 4.11)	-0.64 (-5.25, 3.98)	-0.56 (-5.12, 4.01)
	B & P	60 (6.4)	-2.70 (-7.16, 1.77)	-2.46 (-6.89, 1.98)	-3.01 (-7.42, 1.30)

§p≤0.1, *p≤0.05, **p≤0.01,

(1) Higher scores indicate better performance. (2) Model 1: Minimally adjusted model, adjusted for child age and gender, and tester. Model 2: Fully adjusted model, adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, and marital stability. Model 3: Maternal Education Model, adjusted for child age and gender, tester, social class, maternal age at delivery, marital stability, and maternal education. Model 4: IQ adjusted model, adjusted for child age and gender, tester, social class, maternal age at delivery, marital stability, maternal education, and child IQ.

Table 21 Linear Regression Analysis of Children's IQ Index and Digit Span Scores: comparison of exposed and unexposed groups

		n (%)	**Model 1** B (95% C.I.)	**Model 2** B (95% C.I.)	**Model 3** B (95% C.I.)
Verbal	Unexposed	669 (71.5)	Ref.	Ref.	Ref.
Comprehension	**R & EE**	102 (10.9)	2.26 (-0.06, 4.57)	**2.29 (0.02, 4.45)***	**2.59 (0.37, 4.81)***
Index	**Purging**	53 (5.7)	2.36 (-0.76, 5.48)	**2.66 (-0.39, 5.72)§**	2.45 (-0.54, 5.44)
	Bingeing	53 (5.7)	0.22 (-2.89, 3.32)	0.09 (-2.94, 3.13)	0.20 (-2.77, 3.17)
	B & P	59 (6.3)	0.28 (-2.68, 3.24)	0.46 (-2.25, 3.36)	-0.02 (-2.87, 2.83)
Perceptual	Unexposed	627 (70.8)	Ref.	Ref.	Ref.
Organisation	R & EE	99 (11.2)	0.75 (-1.48, 2.99)	0.81 (-1.41, 3.03)	0.99 (-1.20, 3.20)
Index	Purging	52 (5.9)	0.63 (-2.37, 3.63)	0.87 (-2.11, 3.84)	0.73 (-2.21, 3.67)
	Bingeing	51 (5.8)	0.86 (-2.15, 3.88)	0.83 (-2.16, 3.82)	0.95 (-2.00, 3.91)
	B & P	57 (6.4)	-1.38 (-4.25, 1.48)	-1.20 (-4.05, 1.65)	-1.56 (-4.38, 1.27)
Freedom from	Unexposed	655 (71.6)	Ref.	Ref.	Ref.
Distraction	R & EE	99 (10.8)	0.46 (-0.83, 1.75)	0.44 (-0.84, 1.71)	0.59 (-0.67, 1.85)
	Purging	52 (5.7)	0.60 (-1.13, 2.34)	0.73 (-0.98, 2.44)	0.63 (-1.05, 2.31)
	Bingeing	52 (5.7)	0.77 (-0.96, 2.50)	0.70 (-1.00, 2.40)	0.78 (-0.90, 2.45)
	B & P	57 (6.2)	-0.14 (-1.79, 1.52)	-0.05 (-1.69, 1.59)	-0.27 (-1.88, 1.35)
Digit Span	Unexposed	657 (71.5)	Ref.	Ref.	Ref.
	R & EE	99 (10.8)	-0.003 (-0.67, 0.66)	-0.001 (-0.66, 0.65)	0.07 (-0.59, 0.72)
	Purging	52 (5.7)	0.05 (-0.84, 0.94)	0.11 (-0.77, 0.99)	0.06 (-0.81, 0.93)
	Bingeing	53 (5.8)	0.72 (-0.15, 1.60)	0.70 (-0.17, 1.57)	**0.74 (-0.12, 1.60)§**
	B & P	58 (6.3)	0.03 (-0.81, 0.87)	0.07 (-0.76, 0.91)	-0.02 (-0.85, 0.80)

§p≤0.1, *p≤0.05, **p≤0.01,

(1) Higher scores indicate better performance. (2) Model 1: Minimally adjusted model, adjusted for child age and gender, and tester. Model 2: Fully adjusted model, adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, and marital stability. Model 3: Maternal Education Model, adjusted for child age and gender, tester, social class, maternal age at delivery, marital stability, and maternal education.

4.2.4.4 Working memory in children at high risk

Maternal Bingeing and Purging was associated with children exhibiting higher Global Working Memory scores, than the children of healthy controls in the fully adjusted model (B: 2.08, 95% CI: 0.03, 4.14, p = 0.05). Additionally covarying for maternal education slightly weakened the significance of this association (B: 1.95, 95% CI: -0.09, 4.00, p = 0.06); however, when child IQ was added to the model the relationship became highly significant (B: 2.69, 95% CI: 0.64, 4.74, p = 0.01). No other differences in WM performance were found between the children of exposed and unexposed mothers (see table 22).

Table 22 Linear Regression Analysis of Children's Working Memory Scores: comparisons of exposed and unexposed groups (B coefficients and 95% confidence intervals)

		n (%)	Model 1 B (95% C.I.)	Model 2 B (95% C.I.)	Model 3 B (95% C.I.)	Model 4 B (95% C.I.)
Span Score	Unexposed	643 (71.4)	Ref.	Ref.	Ref.	Ref.
	Restriction & EE	91 (10.1)	0.07 (-0.12, 0.27)	0.06 (-0.13, 0.25)	0.07 (-0.12, 0.26)	0.03 (-0.17, 0.21)
	Purging	50 (5.5)	0.04 (-0.21, 0.30)	0.05 (-0.20, 0.31)	0.04 (-0.21, 0.29)	0.004 (-0.24, 0.25)
	Bingeing	55 (6.1)	0.03 (0.22, 0.27)	0.03 (-0.21, 0.27)	0.02 (-0.22, 0.26)	0.02 (-0.22, 0.26)
	Bingeing & Purging	62 (6.9)	0.16 (-0.07, 0.38)	0.16 (-0.07, 0.39)	0.14 (-0.08, 0.37)	0.19 (-0.04, 0.41)
Global Score	Unexposed	643 (71.4)	Ref.	Ref.	Ref.	Ref.
	Restriction & EE	91 (10.1)	0.17 (-1.58, 1.91)	-0.03 (-1.77, 0.03)	0.10 (-1.63, 1.83)	-0.22 (-1.94, 1.51)
	Purging	50 (5.5)	0.60 (-1.58, 1.91)	0.74 (-1.55, 3.03)	0.60 (-1.68, 2.87)	-0.03 (-2.28, 2.23)
	Bingeing	55 (6.1)	0.54 (-1.66, 2.73)	0.58 (-1.60, 2.75)	0.51 (-1.65, 2.67)	0.74 (-1.43, 2.92)
	Bingeing & Purging	62 (6.9)	**2.03 (-0.06, 4.11)§**	**2.08 (0.03, 4.14)***	**1.95 (-0.09, 4.00)§**	**2.69 (0.64, 4.74)****

§p≤0.1, *p≤0.05, **p≤0.01,

(1) Higher scores indicate better performance.

(2) Model 1: Minimally adjusted model, adjusted for child age and gender, and tester. Model 2: Fully adjusted model, adjusted for child age and gender, tester, social class, maternal age at delivery, and marital stability. Model 3: Maternal Education model, adjusted for child age and gender, tester, social class, maternal age at delivery, marital stability, and maternal education. Model 4: IQ adjusted model, adjusted for child age and gender, tester, social class, maternal age at delivery, marital stability, maternal education, and child IQ.

4.2.4.5 Attention in children at high risk (TEA-Ch)

No statistically significant differences were found between the exposed and unexposed groups in selective attention, divided attention, or attentional control, as assessed by the TEA-Ch at age 8 (see table 23).

Table 23 Linear and Logistic Regression Analysis of Children's Attention Scores as Measured by The TEA-Ch: comparisons of exposed and unexposed groups (B coefficients/Odds Ratios and 95% confidence intervals)

		n (%)	Model 1	Model 2	Model 3	Model 4
Selective Attention	Unexposed	651 (71.1)	Ref.	Ref.	Ref.	Ref.
B (95% C.I.)	Restriction	102 (11.1)	0.16 (-0.18, 0.51)	0.17 (-0.17, 0.52)	0.16 (-0.19, 0.50)	0.24 (-0.10, 0.58)
	Purging	50 (5.5)	0.13 (-0.35, 0.61)	0.14 (-0.34, 0.62)	0.16 (-0.32, 0.64)	0.18 (-0.30, 0.65)
	Bingeing	53 (5.8)	0.15 (-0.32, 0.61)	0.16 (-0.31, 0.62)	0.15 (-0.31, 0.62)	0.14 (-0.32, 0.60)
	Bingeing & Purging	60 (6.6)	0.30 (-0.15, 0.74)	0.31 (-0.13, 0.75)	0.34 (-0.1, 0.78)	0.32 (-0.11, 0.75)
Divided Attention	Unexposed	662 (71.3)	Ref.	Ref.	Ref.	Ref.
OR (95% C.I.)	Restriction	102 (11.0)	1.01 (0.53, 1.94)	1.01 (0.52, 1.96)	1.01 (0.52, 1.96)	1.17 (0.58, 2.38)
	Purging	51 (5.5)	0.93 (0.37, 2.32)	0.85 (0.33, 2.18)	0.85 (0.33, 2.19)	0.87 (0.31, 2.41)
	Bingeing	53 (5.7)	0.82 (0.33, 2.05)	0.89 (0.35, 2.23)	0.89 (0.35, 2.23)	0.78 (0.28, 2.16)
	Bingeing & Purging	60 (6.5)	1.27 (0.57, 2.79)	1.22 (0.55, 2.73)	1.23 (0.55, 2.74)	1.23 (0.54, 2.79)
Attentional Control	Unexposed	658 (71.6)	Ref.	Ref.	Ref.	Ref.
B (95% C.I.)	Restriction	101 (11.0)	-0.11 (-0.95, 0.74)	-0.06 (-0.91, 0.78)	-0.09 (-0.93, 0.75)	0.29 (-0.50, 1.08)
	Purging	50 (5.4)	-0.12 (-1.28, 1.05)	-0.13 (-1.29, 1.03)	-0.10 (-1.26, 1.06)	-0.06 (-1.15, 1.03)
	Bingeing	50 (5.4)	0.02 (-1.15, 1.18)	0.12 (-0.25, 1.28)	0.11 (-1.05, 1.27)	0.25 (0.84, 1.34)
	Bingeing & Purging	60 (6.5)	-0.23 (-1.30, 0.84)	-0.25 (-1.32, 0.81)	-0.20 (-1.26, 0.87)	-0.30 (-1.30, 0.69)

§p≤0.1, *p≤0.05, **p≤0.01,

(1) Model 1. Minimally adjusted model: adjusted for child age and gender, and tester. Model 2. Fully adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, and marital stability. Model 3. Maternal education model: adjusted for child age and gender, tester, social class, maternal age at delivery, marital stability, and maternal education. Model 4. IQ adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, marital stability, maternal education, and child IQ.

(2) Scores measuring Selective Attention and Attentional Control account for time taken to complete the task, therefore a higher score indicates poorer performance and analysis was done using linear regression. Divided attention scores indicating the likelihood of scoring in the bottom 10% are the results of logistic, rather than linear, regression. These results indicate the likelihood of each group scoring in the bottom 10% (worst performance)in comparison to controls.

4.2.4.6 Attention in children at high risk (Reaction Time Task)

Maternal purging was predictive of children scoring in the bottom 10% for the number of targets detected in the Digit Vigilance subtest of the Reaction Time Task: in the fully adjusted model (OR: 2.81, 95% CI: 1.10, 7.18, p = 0.03); and when additionally adjusting for maternal education and child IQ (OR: 3.42, 95% CI: 1.27, 9.20, p = 0.02). The children of mothers in this group also had higher odds of scoring in the bottom 10% for Continuity of Attention. Again, this was the case in the fully adjusted model (OR: 2.62, 95% CI: 1.03, 6.71, p = 0.05); and when adjusting for maternal education and child IQ (OR: 3.76, 95% CI: 1.38, 10.27, p = 0.01). No other differences in attentional capacity, as assessed by the reaction time task, were found between exposed and unexposed groups (see tables 24 and 25).

Table 24 Logistic Regression Analysis of Children's Reaction Time Scores: comparisons of exposed and unexposed groups (Odds Ratios and 95% confidence intervals)

		Model 1 OR (95% C.I.)	**Model 2** OR (95% C.I.)	**Model 3** OR (95% C.I.)	**Model 3** OR (95% C.I.)
Simple Reaction Time	Unexposed	Ref.	Ref.	Ref.	Ref.
	R & EE	1.14 (0.53, 2.44)	1.23 (0.52, 2.89)	1.18 (0.50, 2.80)	1.28 (0.49, 3.36)
	Purging	1.41 (0.55, 3.63)	1.04 (0.34, 3.22)	1.08 (0.35, 3.33)	0.99 (0.26, 3.74)
	Bingeing	1.59 (0.63, 4.03)	1.59 (0.46, 4.57)	1.64 (0.57, 4.72)	1.10 (0.29, 4.09)
	B & P	1.21 (0.44, 3.31)	1.17 (0.38, 3.60)	1.18 (0.38, 3.64)	1.24 (0.38, 4.04)
Digit Vigilance (Targets detected)	Unexposed	Ref.	Ref.	Ref.	Ref.
	R & EE	1.04 (0.52, 2.09)	0.71 (0.29, 1.73)	0.71 (0.29, 1.72)	0.94 (0.36, 2.43)
	Purging	1.93 (0.83, 0.13)	**2.81 (1.10, 7.18)***	**2.94 (1.45, 7.52)***	**3.42 (1.27, 9.20)***
	Bingeing	1.45 (0.58, 3.65)	1.38 (0.45, 4.26)	1.48 (0.48, 4.56)	0.91 (0.22, 3.77)
	B & P	0.94 (0.35, 2.53)	0.88 (0.28, 2.76)	0.93 (0.30, 2.88)	0.53 (0.14, 2.01)
Digit Vigilance (Speed)	Unexposed	Ref.	Ref.	Ref.	Ref.
	R & EE	0.79 (0.36, 1.72)	1.03 (0.46, 2.28)	1.04 (0.47, 2.31)	0.98 (0.39, 2.44)
	Purging	1.74 (0.72, 4.20)	2.03 (1.28, 3.22)	2.01 (0.82, 4.93)	2.19 (0.83, 5.80)
	Bingeing	0.19 (0.03, 1.44)	0.23 (0.03, 1.73)	2.30 (0.03, 1.73)	0.27 (0.04, 2.03)
	B & P	0.39 (0.09, 1.66)	0.42 (0.20, 0.90)	0.42 (0.41, 1.69)	0.46 (0.10, 2.04)
Digit Vigilance (False Alarms)	Unexposed	Ref.	Ref.	Ref.	Ref.
	R & EE	0.84 (0.36, 1.94)	0.69 (0.26, 1.88)	0.68 (0.25, 1.85)	0.85 (0.30, 2.41)
	Purging	1.41 (0.46, 4.30)	1.86 (0.59, 5.87)	2.11 (0.66, 6.72)	2.36 (0.71, 7.80)
	Bingeing	1.33 (0.44, 3.98)	1.81 (0.56, 5.84)	2.06 (0.63, 6.74)	1.05 (0.22, 4.95)
	B & P	1.57 (0.57, 4.33)	2.13 (0.75, 6.06)	2.25 (0.78, 6.45)	1.67 (0.52, 5.37)

§p≤0.1, *p≤0.05, **p≤0.01, (1) Model 1: Minimally adjusted model: adjusted for child age and gender, and tester. Model 2: Fully adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, and marital stability. Model 3: IQ adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, marital stability, and child IQ. (2) Simple Reaction Time scores indicate the likelihood of each group being in the highest 10% for time taken (worst performance) in comparison to controls. Digit Vigilance Targets Detected and Digit Vigilance Speed scores indicate the likelihood of each group scoring in the bottom 10% (worst performance) in comparison to controls. Digit Vigilance False Alarms scores indicate the likelihood of each group being in the highest 10% for false alarms (worst performance) in comparison to controls. (3) N (%) of samples: Unexposed = (%); R & EE = 76 (9.7%); Purging = 44 (5.6%); Bingeing = 44 (5.6%); Bingeing & Purging = 49 (6.3%).

Table 25 Logistic Regression Analysis of Children's Reaction Time Scores: comparisons of exposed and unexposed groups continued (Odds Ratios and 95% confidence intervals)

		Model 1 OR (95% C.I.)	**Model 2** OR (95% C.I.)	**Model 3** OR (95% C.I.)	**Model 3** OR (95% C.I.)
Choice Reaction (Accuracy)	Unexposed	Ref.	Ref.	Ref.	Ref.
	R & EE	0.45 (0.16, 1.29)	**0.27 (0.06, 1.16)§**	0.26 (0.06, 1.13)	0.31 (0.07, 1.36)
	Purging	0.49 (0.11, 2.11)	0.61 (0.14, 2.71)	0.63 (0.14, 2.84)	0.71 (0.15, 3.33)
	Bingeing	0.84 (0.24, 2.86)	1.26 (0.35, 4.51)	1.31 (0.36, 4.69)	1.45 (0.40, 5.33)
	B & P	1.44 (0.56, 3.71)	1.83 (0.68, 4.91)	1.86 (0.69, 5.00)	1.53 (0.51, 4.58)
Choice Reaction (Time)	Unexposed	Ref.	Ref.	Ref.	Ref.
	R & EE	0.81 (0.37, 1.78)	1.04 (0.46, 2.33)	1.01 (0.45, 2.27)	1.01 (0.40, 2.57)
	Purging	1.59 (0.62, 4.08)	1.28 (0.42, 3.90)	1.35 (0.41, 4.39)	1.19 (0.34, 4.21)
	Bingeing	1.29 (0.51, 3.24)	1.56 (0.60, 4.04)	1.62 (0.62, 4.25)	1.89 (0.68, 4.95)
	B & P	0.46 (0.11, 1.99)	0.53 (0.12, 2.29)	0.54 (0.26, 1.11)	0.56 (0.26, 1.20)
Continuity Of Attention	Unexposed	Ref.	Ref.	Ref.	Ref.
	R & EE	0.90 (0.41, 1.98)	0.65 (0.24, 1.76)	0.64 (0.24, 1.72)	0.88 (0.31, 2.54)
	Purging	1.89 (0.77, 4.60)	**2.62 (1.03, 6.71)***	**2.79 (1.09, 7.17)***	**3.76 (1.38, 10.27)****
	Bingeing	0.54 (0.13, 2.34)	0.70 (0.15, 3.19)	0.75 (0.17, 3.44)	0.43 (0.05, 3.43)
	B & P	1.69 (0.70, 4.09)	1.82 (0.69, 4.80)	0.91 (0.72, 5.03)	1.46 (0.49, 4.35)
Power of Attention	Unexposed	Ref.	Ref.	Ref.	Ref.
	R & EE	1.05 (0.51, 2.16)	1.27 (0.61, 2.66)	1.25 (0.60, 2.63)	1.26 (0.55, 2.92)
	Purging	1.56 (0.61, 3.97)	1.12 (0.42, 2.98)	1.14 (0.38, 3.42)	1.05 (0.29, 3.76)
	Bingeing	1.04 (0.39, 2.77)	1.20 (0.44, 3.30)	1.22 (0.44, 3.36)	1.01 (0.33, 3.12)
	B & P	0.22 (0.03, 1.61)	0.23 (0.08, 0.63)	0.23 (0.08, 0.64)	0.24 (0.09, 0.68)

§p≤0.1, *p≤0.05, **p≤0.01, (1) Model 1: Minimally adjusted model: adjusted for child age and gender, and tester. Model 2: Fully adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, and marital stability. Model 3: IQ adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, marital stability, and child IQ. (2) Choice Reaction Time, and Power of Attention scores indicate the likelihood of each group being in the highest 10% (worst performance) for time taken in comparison to controls. Choice Reaction Accuracy, and Continuity of Attention scores indicated the likelihood of each group scoring in the bottom 10% (worst performance) in comparison to controls. (3) N (%) of samples: Unexposed = (%); R & EE = 76 (9.7%); Purging = 44 (5.6%); Bingeing = 44 (5.6%); Bingeing & Purging = 49 (6.3%).

4.2.4.7 Inhibition in children at high risk

No statistically significant differences were found between exposed and unexposed groups on measures of behavioural inhibition, as assessed by the stop-signal task at age 10 (see table 26).

Table 26 Linear and Logistic Regression Analysis of Children's Behavioural Inhibition Scores: Comparison of exposed and unexposed groups.

		n (%)	Model 1	Model 2	Model 3	Model 4
Mean Reaction Time in Primary Trials B (95% C.I.)	Unexposed	631 (71.0)	Ref.	Ref.	Ref.	Ref.
	Restriction & EE	95 (10.7)	**-12.25 (-26.42, 1.93)§**	**-12.43 (-26.64, 1.77)§**	**-12.90 (-27.11, 1.31)§**	-5.62 (-20.30, 9.07)
	Purging	49 (5.5)	-12.20 (-31.43, 7.03)	-13.34 (-32.60, 5.91)	-12.84 (-32.09, 6.40)	-11.38 (-30.82, 8.06)
	Bingeing	54 (6.1)	6.09 (-12.21, 24.38)	5.45 (-12.84, 23.75)	5.49 (-12.80, 23.78)	4.71 (-14.04, 23.46)
	Bingeing & Purging	60 (6.7)	0.69 (-16.77, 18.15)	-0.03 (-17.50, 17.45)	0.57 (-13.92, 18.06)	3.70 (-14.01, 21.41)
Number of Primary Trials Correct OR (95% C.I.)	Unexposed	631 (71.0)	Ref.	Ref.	Ref.	Ref.
	Restriction & EE	95 (10.7)	0.90 (0.43, 1.89)	0.85 (0.40, 1.81)	0.86 (0.40, 1.82)	0.85 (0.38, 1.90)
	Purging	49 (5.5)	1.19 (0.47, 3.04)	1.13 (0.44, 2.92)	1.13 (0.44, 2.91)	1.18 (0.45, 3.13)
	Bingeing	54 (6.1)	0.79 (0.27, 2.34)	0.76 (0.26, 2.25)	0.76 (0.26, 2.25)	0.87 (0.29, 2.63)
	Bingeing & Purging	60 (6.7)	0.83 (0.33, 2.06)	0.77 (0.31, 1.94)	0.77 (0.30, 1.93)	0.76 (0.29, 1.95)
Number of SS Trials Correct At 250ms Delay OR (95% C.I.)	Unexposed	631 (71.0)	Ref.	Ref.	Ref.	Ref.
	Restriction & EE	95 (10.7)	1.10 (0.53, 2.29)	1.19 (0.56, 2.51)	1.20 (0.57, 2.54)	1.13 (0.49, 2.59)
	Purging	49(5.5)	1.21 (0.48, 3.05)	1.26 (0.49, 3.20)	1.13 (0.44, 2.91)	1.50 (0.57, 3.90)
	Bingeing	54 (6.1)	1.25 (0.50, 3.13)	1.34 (0.53, 3.40)	0.76 (0.26, 2.25)	1.49 (0.57, 3.90)
	Bingeing & Purging	60(6.7)	0.72 (0.24, 2.10)	0.76 (0.26, 2.27)	0.77 (0.30, 1.93)	0.65 (0.19, 2.25)
Number of SS Trials Correct at 150ms Delay OR (95% C.I.)	Unexposed	631 (71.0)	Ref.	Ref.	Ref.	Ref.
	Restriction & EE	95 (10.7)	0.70 (0.33, 1.46)	0.74 (0.35, 1.56)	0.74 (0.35, 1.58)	0.61 (0.26, 1.41)
	Purging	49 (5.5)	0.80 (0.30, 2.12)	0.79 (0.30, 2.13)	0.79 (0.29, 2.11)	0.80 (0.29, 2.16)
	Bingeing	54(6.1)	1.18 (0.52, 2.68)	1.20 (0.52, 2.75)	1.20 (0.52, 2.75)	1.12 (0.46, 2.70)
	Bingeing & Purging	60 (6.7)	0.79 (0.32, 1.95)	0.81 (0.32, 2.02)	0.81 (0.32, 2.02)	0.68 (0.25, 1.84)

§p≤0.1, *p≤0.05, **p≤0.01

(1) Model 1: Adjusted for child age and gender, and tester. Model 2: (Fully adjusted model) adjusted for child age and gender, tester, social class and maternal age at delivery. Model 3: Adjusted for child age and gender, tester, family income, maternal age at delivery and maternal education. Model 4: Adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, and child IQ.

(2) Inhibition scores indicating the likely-hood of scoring in the bottom 10% are the results of logistic, rather than linear, regression. The results therefore indicate the likelihood of each group scoring in the bottom 10% in comparison to controls.

4.2.5 Interim Discussion

The aim of this study was to investigate intelligence, global cognition, and executive functioning in children who are at high risk of developing an eating disorder, in comparison to children who are not. In contrast to study one of this chapter, data on maternal lifetime ED behaviours were used to determine high risk status of the children, as opposed to maternal self-reported diagnosis. Overall, the results showed that the children of women in the restricting/excessive exercising group had higher Verbal IQ; higher scores in the Verbal Comprehension Index; and higher scores in the Vocabulary subtest of the WISC-III, in comparison to controls. This group also showed a trend towards having comparatively high Full-scale IQ. The children of women in the Purging group showed comparatively high scores in the Similarities subtest of the WISC-III, when compared to the children of healthy control women. The children of women in the Purging group also had comparatively higher odds of scoring in the bottom 10% for number of targets detected in the Digit Vigilance subtest, and higher odds of scoring in the bottom 10% on Continuity of Attention, in the Reaction Time Task. Finally, the children of women in the Bingeing and Purging group showed a trend towards having lower scores on the Block-design subtest of the WISC-III than unexposed children; but exhibited significantly higher Global Working Memory scores.

4.2.5.1 Intelligence and Global Cognition

As can be seen from the summary above, the children of women with a restricting/excessive exercising phenotype showed higher scores than unexposed children in a range of WISC-III scores associated with verbal intelligence. High Verbal IQ scores appeared to make the main contribution to the comparatively high Full-scale IQ that was observed in this group; and comparatively high scores were also observed in the Verbal Comprehension Index, and the Vocabulary subtest. This profile of intelligence/cognition is thought to reflect good verbal knowledge and understanding, particularly the kind of knowledge that is obtained through formal education. High scores in the in the Vocabulary sub-test demonstrates a good command of language, good communication skills, and a well-developed ability to express oneself; which could be a result of the child being

exposed to a good educational and cultural background. The Verbal IQ score is a summary score of all scaled verbal subtest scores. Our findings indicate that in comparison to unexposed women, the children of women with a restricting/excessive exercising phenotype have better verbal ability and language development; and superior social and cultural understanding. In addition, Verbal IQ is a good predictor of school achievement, which suggests that this group of children will achieve comparatively higher school grades.

High scores in the Verbal Comprehension Index are also thought to reflect extensive exposure to culture and education; as well as good verbal skills, but it is only in the fully adjusted models that the differences observed between the children of women with a restricting/excessive exercising phenotype and the children of unexposed women become statistically significant. Under the assumption that a child's exposure to cultural influences, and the quality of formal education they will experience, might be associated with variables that are adjusted for in the fully adjusted models (i.e. social class); our findings suggest that the children of women with a restricting/excessive exercising phenotype may have a natural aptitude for this type of learning, and their high scores are not due to better education or more cultural exposure. This is only speculation however, and requires further investigation.

The children of women with a Purging phenotype exhibited higher scores in the Similarities subtest when compared to unexposed women. High scores on this subtest are thought to be reflective of good logical thinking and verbal capacities. Interestingly, the children in this group showed a trend ($p \leq 0.01$) towards comparatively higher scores in other Verbal subtests, Verbal IQ, and the Verbal Comprehension Index; however these differences did not reach statistical significance (see tables 18, 19 and 21). If considering these trends however, it appears that the children of women with a Purging phenotype have a similar profile to the children of women with a Restricting/Excessive Exercising phenotype, also exhibiting good verbal knowledge and understanding. It is possible that a larger sample would have provided enough power for the differences observed to reach statistical significance.

The comparatively high IQ scores observed in the children of women with Restricting/Excessive Exercising and Purging phenotypes confirms our hypotheses that the children in these groups would exhibit comparatively high intelligence. In a study comparing the intelligence of AN women who do and do not meet criteria for amenorrhea (Watson, 2003), it was found that the group of patients who did have amenorrhea had higher IQ scores than those who did not; suggesting high IQ is associated with ED behaviours that lead to extremely low weight (restricting and purging), rather than bingeing behaviours. The results of this study suggest that this is also true for the children of women who exhibit a Restricting/Excessive Exercising/Purging phenotype, but not for the children of women who exhibit bingeing behaviours.

There are studies that have found no differences in IQ between AN patients and healthy controls. Gillberg and colleagues found no differences between groups, and suggested that this was due to their investigation employing a community sample rather than a clinical sample (I. Gillberg, et al., 1996). Like Gillberg's study, this investigation employs a large community sample, but differences in IQ were still observed between children at high and low risk, and this could be for a number of reasons: (i) the larger sample employed in this study may have had the necessary power to detect subtle differences between groups; (ii) the AN group in Gillberg's study were not divided according to the AN-R/AN-BP subtypes meaning their ED sample was more heterogeneous with regard to symptomatology; or (iii) a considerable proportion of the AN group in Gillberg's study experienced cross-over to another diagnosis, but these changes in diagnoses were not taken into consideration. In this study participants were grouped according to maternal lifetime ED, rather than presentation at initial diagnosis. In addition, participants were grouped according to maternal behavioural phenotype, which may have a more direct relationship with cognitive functioning than diagnosis.

Galderisi and colleagues found no differences in Full-scale, Verbal or Performance IQ, between BN patients and healthy controls (Galderisi, 2010). The results of this study show that the same is true for children at high risk, who are born to mothers

with a BN like phenotype. This suggests that overall IQ of BN patients is comparable to healthy controls prior to onset, rather than BN patients having a comparatively high IQ (like AN patients) which is compromised as a result of the disorder.

Children of women with a Bingeing and Purging phenotype displayed worse performance on the Block-design subtest than unexposed children: indicating comparatively poor perceptual skills and visuo-motor coordination; poor spatial analysis and visual problem solving; and possible figure-ground deficits. As outlined in the interim discussion for study one, evidence pertaining to visuo-spatial functioning in AN and BN patients is conflicting: with some evidence of similar difficulties in ED groups (e.g. I. Gillberg, et al., 2007; Jones, et al., 1991; Sellbom & Gunstad, 2012), and non-clinical samples with bulimic disturbance (e.g. Bosanac, et al., 2007); and also negative findings revealing no impairments (e.g. Eysenck, 1992; Faunce, 2002). The results of this investigation suggest that subtle impairments in visuo-spatial functioning are present in children at high risk of developing an ED, due to being born to a mother with a Bingeing and Purging phenotype. It is worth noting that the mothers in this group may also have experienced restricting and/or excessive exercising; it is possible that the poor visuo-spatial functioning observed in their children is associated with a phenotype that makes individuals vulnerable to developing all possible ED symptoms.

Overall, our investigation into the development of intelligence and global cognition in children at high risk appears to make a distinction between children whose mothers have and have not experienced bingeing behaviours. The children of women who have not experienced bingeing behaviours show comparatively high scores in the verbal sub-tests of the WISC, Verbal IQ, and the Verbal Comprehension Index; which can be thought of as high crystallized intelligence. In contrast, the children whose mothers have experienced bingeing behaviours show comparatively lower scores on the Block Design subtest. These finding are consistent with the results of study one, in that the children of women with AN exhibited comparatively high IQ. There is also some contrast in the findings from both studies: while in study one maternal AN was associated with comparatively

high Performance IQ in children at risk; in study two, a maternal restricting/excessive exercising/purging phenotype was associated with comparatively high Verbal IQ in children at risk. It is difficult to explain why this is the case, except to say that the results of study two are more in line with previous research indicating higher verbal IQ in subjects with AN (Lopez, et al., 2010; Maxell, et al., 1984). It may be that behavioural phenotype has a more direct relationship with cognitive functioning than diagnosis.

4.2.5.2 Working Memory

Based on evidence in the literature, pertaining to clinical groups and using ED diagnoses, it was predicted that superior Working Memory would be observed in children at high risk who were born to mothers with a Restricting/Excessive Exercising/Purging phenotype. In contrast to my hypothesis, results of statistical analysis showed that the children of women with a Bingeing and Purging phenotype exhibited higher Global Working Memory scores. Of note, the children of women exhibiting a Bingeing phenotype also trended towards having comparatively high digit span scores on the WISC, also a measure of working memory. Though there is evidence in the literature suggesting that ED groups, and sub-clinical groups with ED symptomatology, have impaired working memory performance; deficits appear to be a result of cognitions about food, weight and body shape (e.g. Kemps, et al., 2006; Ohrmann, et al., 2004). These studies indicate that impairments in Working Memory are a secondary effect of the disorder, mediated by the intrusive thoughts that are associated with an ED; and our finding of superior Working Memory performance in children at high risk supports this. In addition, the findings from both the Counting Span Task and the WISC in this study suggest that superior working memory may be a putative intermediate phenotype that is specifically associated with a Bingeing phenotype.

While the results of study one found that the children of women reporting AN and AN+BN showed comparatively better working memory capacity, the findings from this study showed superior working memory performance in children born to mothers with a Bingeing and Purging phenotype. The differences observed in this

study are also much larger than those observed in study one. It is possible that the differences observed in study one were due to a subset of AN and AN+BN mothers that exhibited both bingeing and purging behaviours, or had the potential for exhibiting these behaviours in the future.

4.2.5.3 Attention – TEA-Ch

Based on evidence in the literature and the results of study one, it was predicted that children at high risk due to being born to mothers with a Bingeing and/or Purging phenotype would exhibit decreased attentional capacity. In contrast to my hypothesis, no statistically significant differences were observed between exposed and unexposed groups on any subtest of the TEA-Ch. In study one, performance on this task revealed significantly poorer attentional control in the children of women reporting AN; however, despite being statistically significant the differences observed were very small. It is possible that differences were too small to be detected by the smaller sample employed in this study.

4.2.5.4 Attention – Reaction Time Task

Analysis of performance on the Reaction Time Task did provide support for my hypothesis regarding attention. Children at high risk, due to being born to a mother with a Purging phenotype, had higher odds than unexposed children of scoring in the bottom 10% for targets detected in the Digit Vigilance subtest, and on the Continuity of Attention summary score. The Continuity of Attention summary score is representative of sustained attention and is made up of the accuracy of responses across sub-tests; including both targets detected and false alarms in the Digit Vigilance sub-test, and accuracy in the Choice Reaction subtest. There is evidence in the literature that indicates impairments in sustained attention within AN patients (e.g. Seed, et al., 2000), and mixed findings regarding BN patients (Van den Eynde, Guillaume, et al., 2011). Our finding suggests that poor sustained attention may be present prior to onset and therefore independent of illness state; however this putative intermediate phenotype may have a specific association with a Purging ED phenotype. In study one, the children of women

reporting AN, BN, and AN+BN had higher odds than unexposed children of performing poorly on the three subtests that contribute to the Continuity of Attention summary score. The results of this study suggest that these differences may have been observed due to the subset of mothers within each of these groups that exhibited purging behaviours, or had the potential for exhibiting these behaviours in the future.

A previous study assessing the performance of ED participants on the Reaction Time Task found that underweight AN and BN patients scored lower than healthy controls on the Power of Attention summary score, which is reflective of allocation of attentional processing (Bosanac, et al., 2007). However, these differences were not observed between weight restored patients and healthy controls, suggesting the deficits observed were due to low nutritional intake. In this study, no differences were observed between exposed and unexposed groups on the Power of Attention summary score; supporting the notion that impairments in the allocation of attentional processing are state dependent, and unlikely to be present prior to onset.

4.2.5.5 Behavioural Inhibition

Contrary to my hypothesis, no statistically significant differences were observed between exposed and unexposed groups in behavioural inhibition. As outlined previously (chapter two) studies investigating behavioural inhibition in ED groups, that use the stop-signal task, reveal mixed findings (Boisseau, et al., 2012; Claes, et al., 2011; Galimberti, et al., 2011). The results of study one revealed an association between maternal report of AN or BN and decreased behavioural inhibition; however, differences did not reach significance. Though it is possible that differences in behavioural inhibition were too subtle to detect with the smaller sample employed in this study; it is also possible that the results of this study disconfirm the tentative differences observed in study one. Our findings suggest that if behavioural inhibition is a trait associated with ED, then it is state dependent and not present prior to onset.

4.2.6 Study Summary

The findings from study two: investigating the association between maternal lifetime ED behaviours and children's neuropsychological functioning; revealed differences in cognitive functioning in children at high risk. The children of women with a Restricting/Excessive Exercising phenotype, and to some level women with a Purging phenotype, exhibited higher IQ scores related to verbal intelligence; while a maternal Bingeing and Purging phenotype was associated with comparatively lower scores in WISC-III subtests. In addition, the children of women with a Bingeing and Purging phenotype showed comparatively poor visuo-spatial functioning; but also revealed a comparatively better working memory capacity. The children of women with a Purging phenotype showed comparatively poorer sustained attention. No differences were observed between exposed and unexposed groups on a measure of behavioural inhibition. Our findings lend support to the notion that these neuropsychological differences are present prior to onset and are therefore independent of illness state; making them putative intermediate phenotypes for ED.

4.3 Overall Conclusions

Our findings suggest that the superior intellectual functioning, decreased attentional capacity, and decreased behavioural inhibition found in clinical ED samples may be present in high-risk subjects, while impairments in working memory do not appear to be. Although differences between groups were small from a clinical perspective, this is to be expected in a high-risk study. Further research is required to confirm and further explore these findings, but a clarification of the neuropsychological profile of those at high risk of developing an ED is extremely important both in relation to the identification of vulnerable individuals (and therefore preventative efforts), and in furthering our understanding of which neuropsychological profiles are linked to susceptibility for ED and which ones might be a scar of these disorders.

Strengths and Limitations

Strengths and limitations of the studies in this chapter are detailed in the strengths and limitations section of the thesis (Chapter 7: Strengths and Limitations).

Chapter 5

Social Cognition in a Community-Based Sample of Children: an Investigation of Social Communication and Emotion Recognition

5.1 Introduction

As discussed in chapter three it has been suggested that a quantitative trait approach to psychiatric illness may be more relevant than the current diagnostic categorisation, particularly with regard to research in the field of eating disorders (e.g. Treasure, 2012; Zucker, 2007). There is growing evidence to suggest that the developmental traits that are generally associated with ASD, may also be involved in the development of ED; and disorders of the autism spectrum have been found to be overrepresented in AN samples (e.g.C. Gillberg, 1983, 1992). Research also indicates an overlap of intermediate phenotypes between AN and ASD (e.g. Faunce & Job, 2000; Odent, 2010; Treasure, 2012). In an excellent review of the literature, Zucker and colleagues suggest that the extensive research investigating social cognition in ASD could be used as a "roadmap" for future research investigating social cognition in ED (Zucker, 2007). Studies have shown that the interpersonal patterns present in ASD probands are also present at elevated rates in family members, denoting interpersonal deficits as putative intermediate phenotypes of the disorder (e.g. Piven, Palmer, Jacobi, Childress, & Arndt, 1997). With this in mind, the studies in chapter six investigate the presence of social communication and emotion recognition deficits in the children of women with an ED. Social communication is assessed using the Social Communication Disorders Checklist (SCDC) (Skuse, Mandy, & Scourfield, 2005), a well-established measure that has previously been used to investigate social communication in a large general population sample (Skuse, et al., 2009). Non-verbal social communication has been assessed using a subtest of the Diagnostic Analysis of Non-verbal Accuracy (DANVA)(Nowicki & Duke, 1994), which measures one's capacity to perceive

another's emotional state from their facial expression. The DANVA is also a well-established measure that has been used to investigate non-verbal communication in the general population(Ingersoll, 2010), with results showing an association between subclinical autistic type traits and facial emotion recognition. Finally, emotion recognition from action perception, and understanding of another's mental state, has been measured using the Emotional Triangles Task (Boraston, Blakemore, Chilvers, & Skuse, 2007). This is a fairly novel measure, previously only used with a sample of autistic adults.

In this study the use of this measure is tested in a large community sample of children with the purpose of validating its effectiveness in: (i) children as well as adults, and (ii) the general population as well as an autistic sample; prior to using the task to investigate emotion recognition in children at high risk of developing an ED (chapter 6). Further to this, performance on the two emotion recognition tasks was compared.

5.2 Aims and Hypotheses

The aim of this study was to provide further validation for the use of the Emotional Triangles Task, prior to using it to investigate emotion recognition capacity in children at high risk of developing an ED. This was done by determining whether the capacity to recognise emotion from social motion cues (Emotion Triangles Task) was associated with social communication difficulties, as measured by the SCDC; and by comparing emotion recognition from social motion cues with emotion recognition from facial expression as measured by the DANVA. Based on the previous literature, it was predicted that children scoring high in social communication difficulties would exhibit poorer emotion recognition when being assessed on the recognition of emotion from social motion cues (Emotional Triangles Task), and would be more likely to make a high number of errors/misattributions when being assessed on facial emotion recognition (DANVA), than children with low scores. Due to the paucity of evidence in the literature, it was not possible to make predictions regarding the recognition of

individual emotions. However, due to the accepted gender differences associated with social emotion recognition (McClure, 2000), it was predicted that boys with social communication difficulties would show a greater degree of deficit in emotion recognition than girls.

5.3 Methods

5.3.1 Design

Longitudinal

5.3.2 Participants

A total of 3666 participants were included in this study. Children were excluded if they did not have complete data on all three measures employed: The DANVA at age 8; the Emotional Triangles Task at age 13; and the SCDC at age 13.

5.3.3 Measures

Social Communication: The Social Communication Disorders Checklist (SCDC)

The SCDC (Skuse, et al., 2005) is a 12 item questionnaire, designed to be completed by parents, measuring social reciprocity and other verbal/non-verbal social traits that are characteristic of ASD (see appendix 4). The 12 items describe a range of behaviours such as "not aware of other people's feelings" and "does not pick up on body language", and parents are asked to rate whether each behaviour has been observed in the child over the previous 6 months. A higher SCDC score is indicative of more deficits in social communication. Research has shown the measure to have good internal consistency (0.93), high test-retest reliability (0.81), and high heritability in children of both genders (0.74)(Skuse, et al., 2005). In addition, this same study found the measure to be predictive of autism in a clinical sample with a sensitivity of 0.9 and a specificity of 0.69, when using a threshold score of 9 out of 24. For a full description of the measure see previous publications (Skuse, et al., 2005; Skuse, et al., 2009).

Facial Emotion Recognition: The Diagnostic Analysis of Non-Verbal Accuracy (DANVA)

Facial emotion recognition was assessed using the faces sub-test of the DANVA(Nowicki & Duke, 1994), which has been shown to be both reliable and valid for use with children of 6 years old and above in the general population (McIntire, Danforth, & Schneider, 1999; Nowicki & Duke, 1994). This computerized task measures a child's ability to recognise emotion from facial cues. Participants are shown 24 photos depicting children's faces, and are told that the children in these photos will be expressing one of four emotions; happiness, sadness, anger or fear. Each photo is displayed for two seconds, and children are expected to respond with which emotion is being expressed. The photos displayed faces that were of either high or low intensity, making it easier or harder to recognise the emotion being expressed. Higher scores on this task represent more errors or misattributions. A total of 11 binary scores indicating whether children made more (above cut-off) or less (below cut-off) errors/misattributions are considered; which were derived by ALSPAC in collaboration with the creator of the task, Stephen Nowicki. Cut-offs for each of the variables was based upon the distribution of scores in the whole sample (see table 27).

Table 27 DANVA outcome variables with binary cut-offs used

Outcome Measures	**Binary Cut-off**
Happy Faces (errors)	At least one error
Sad Faces (errors)	At least two errors
Angry Faces (errors)	At least four errors
Fearful Faces (errors)	At least three errors
All Faces (errors)	At least seven errors
All Low Intensity Faces (errors)	At least five errors
All High Intensity Faces (errors)	At least three errors
Faces Misattributed as Happy	At least four misattributions
Faces Misattributed as Sad	At least three misattributions
Faces Misattributed as Angry	At least two misattributions
Faces Misattributed as Fearful	At least three misattributions

Emotion Recognition from Social Cues: The Emotional Triangles Task

This computerized task measures the participant's ability to attribute an emotional mental state to non-human animate entities. Participants are shown 24, 5-second animations consisting of a triangle and a circle moving around the screen. In 20 of the animations the triangle moves around in a self-propelled and purposeful manner which is designed to evoke a mental state attribution of a particular emotion; happy, sad, angry or scared. In the other four animations the triangle moves in a manner that is designed to look inanimate or 'not living'. After each animation the participant is asked one of two questions: (i) whether the triangle is living and if so how living (0 = definitely not living to 5=definitely living), or (ii) whether the triangle has a particular emotion out of the possible four, and how sure the participant is that the triangle is displaying this particular emotion (0 = not at all to 5 = extremely). In some cases this emotion correctly corresponds to the animation, while in others it does not. Prior to the 28 test trials, participants had to complete four practice trials to ensure they have understood the task. A total of 4 outcome variables, representative of emotion recognition ability for each of the four emotions assessed, will be considered here; with a higher score representing better emotion recognition ability. For further details of the task, scoring, or animations see Boraston et al., 2007 (Boraston, et al., 2007).

5.3.4 Procedure

This study was approved by the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees.

5.3.5 Analyses

All variables were checked for inconsistencies/outliers using tabulations, graphs and plots. For participants with less than 25% missing data on the SCDC, total scores were calculated using prorating. Data were analysed using the SCDC score (the predictor) as a binary variable according to the recommended cut-off of ≥ 9 which is predictive of a diagnosis of autism in clinical samples.

The distribution of variables was inspected for normality. Scores from the DANVA were not normally distributed, (and could not be transformed); therefore the binary variables that had been created (described above) were used and a logistic regression was conducted to analyse this data. Scores from the Emotional Triangles task were normally distributed, therefore linear regression was used to analyse this data.

Gender of child, age of child at time of each assessment, and the tester conducting the emotion recognition task were included as a priori covariates in a minimally adjusted model. Additional confounders that could potentially influence outcomes were adjusted for in a second model (fully adjusted model) after testing whether these variables met criteria for confounding. All analyses were conducted on boys and girls separately and together, using SPSS 18. The standard two-tailed significance level of $p \leq 0.05$ was used.

Missing covariate data

Multiple random imputation was used to deal with missing covariate data. All predictor and outcome variables were used as predictors in the imputation model. Missing data were imputed for marital status, child ethnicity, social class, age of child at time of testing, and parity for at least one of the time points. All analyses were run on both complete case and imputed datasets for comparison and differences were negligible. Due to the fact that complete case analysis is thought to suffer from more chance variation, and multiple imputation is assumed to correct any bias, only results based on multiple imputation are presented.

5.4 Results

5.4.1 Attrition

Attrition, i.e. children who did not have complete data on all three measures (after prorating of SCDC scores), was predicted by child gender, ethnicity, parity and gestational age, marital status of mother during pregnancy, and social class (see table 28). These variables were included as confounders in the fully adjusted model accordingly.

5.4.2 Socio-demographic data

The socio-demographic data of children included in this study, in comparison to the socio-demographic data of the whole ALSPAC sample, can be found in table 28. A relatively small percentage of children were non-white, of lowest parental social-class (manual), and had mothers that were unmarried during pregnancy. On all other factors, the children were split approximately equally among groups.

Table 28 Comparison of socio-demographic data of whole ALSPAC sample and sample included in study; and results of logistic regression analysis of whether socio-demographic factors are predictive of attrition

	Whole ALSPAC Sample	Sample Included in Analysis	p-value
Child Gender (male)	7579 (51.5%)	1796 (49%)	0.0001
Child Ethnicity (white)	10715 (92.5%)	3465 (94.4%)	0.0001
Parity (multiparous)	6473 (55.2%)	1814 (50.3%)	0.0001
Marital Status of Mother at Enrolment (married)	9085 (76.6%)	3056 (84.0%)	0.0001
Lowest Combined Parental Social Class (Manual: III-manual – V)	2247 (19.4%)	384 (10.5%)	0.0001
Gestational Age	39.41 (2.27)	39.49 (1.73)	0.01

N.B. p-values are the outcome of logistic regression analysis of whether socio-demographic factors are predictive of attrition

5.4.3 Emotion Recognition from Facial Cues (DANVA)

All Children

Children scoring above the cut-off on the SCDC (9/24) had higher odds than children scoring below the cut-off of making more errors in the recognition of all faces (OR: 1.56, 95% CI: 1.15, 2.12; p = 0.004); all high intensity faces (OR: 1.68, 95% CI: 1.24, 2.29; p = 0.001); and all low intensity faces (OR: 1.61, 95% CI: 1.18,2.20; p = 0.004; See methodology for description of more/less errors).

With regard to the association between SCDC score and recognition of each individual emotion, children scoring above the cut-off on the SCDC had comparatively higher odds of making more errors in the recognition of sad faces (OR: 1.62, 95% CI: 1.18, 2.24; p = 0.004; angry faces (OR: 1.49, 95% CI: 1.07, 2.09; p = 0.02); and fearful faces (OR: 1.60, 95% CI: 1.16, 2.21; p = 0.004); and higher odds of misattributing more faces as happy (OR: 2.10, 95% CI: 1.50, 2.93; p = 0.0001); and angry (OR: 1.57, 95% CI: 1.08, 2.29; p = 0.02; see table 29).

Female Children

Girls scoring above the cut-off on the SCDC had comparatively higher odds of misattributing more faces as happy (OR: 1.90, 95% CI: 1.08, 3.35; p = 0.03; see table 30).

Male Children

Boys scoring above the cut-off on the SCDC had comparatively higher odds of making more errors in the recognition of all faces (OR: 1.92, 95% CI: 1.40, 2.63; p = 0.0001); all high intensity faces (OR: 2.09, 95% CI: 1.52, 2.88; p = 0.0001); and all low intensity faces (OR: 1.82, 95% CI: 1.31, 2.51; p = 0.0001). With regard to the association between SCDC scores and recognition of each emotion individually, boys scoring above the SCDC cut-off had higher odds of making more errors in the recognition of sad faces (OR: 1.82, 95% CI: 1.20, 2.74; p = 0.004); angry faces (OR: 2.05, 95% CI: 1.37, 3.08; p = 0.0001); and fearful faces (OR: 1.69, 95% CI: 1.11, 2.58; p = 0.02); and also trended towards having higher odds of making errors in the recognition of happy faces (OR: 1.45, 95% CI: 0.98, 2.13; p = 0.06). Boys with high SCDC scores also had higher odds of misattributing more faces as happy (OR:

2.17, 95% CI: 1.42, 3.32; p = 0.001); sad (OR: 1.54, 95% CI: 1.01, 2.35; p = 0.05); and angry (OR: 1.73, 95% CI: 1.05, 2.87; p = 0.03; see table 31).

Table 29 Logistic Regression Analysis of Children's Facial Emotion Recognition (DANVA) Scores: comparison of children scoring above and below the established threshold on the SCDC (odds ratios and 95% confidence intervals).

	n	**Minimally Adjusted Model** OR (95% C.I.)	**Fully Adjusted Model** OR (95% C.I.)
Happy Faces (at least one error)	4969	1.11 (0.86, 1.43)	1.36 (1.00, 1.84)*
Sad Faces (at least two errors)	4969	**1.45 (1.11, 1.90)****	**1.62 (1.18, 2.24)****
Angry Faces (at least four errors)	4969	**1.50 (1.14, 1.97)****	**1.49 (1.07, 2.09)***
Fearful Faces (at least three errors)	4969	**1.55 (1.20, 2.02)****	**1.60 (1.16, 2.21)****
All Faces (at least seven errors)	4969	**1.62 (1.27, 2.07)****	**1.56 (1.15, 2.12)****
All Low Intensity Faces (at least five errors)	4969	**1.61 (1.25, 2.07)****	**1.61 (1.18, 2.20)****
All High Intensity Faces (at least three errors)	4969	**1.71 (1.33, 2.19)****	**1.68 (1.24, 2.29)****
Misattributed as Happy (at least four)	4872	**1.90 (1.44, 2.50)****	**2.10 (1.50, 2.93)****
Misattributed as Sad (at least three)	4872	1.23 (0.92, 1.64)	1.24 (0.87, 1.77)
Misattributed as Angry (at least two)	4872	**1.44 (1.05, 1.98)***	**1.57 (1.08, 2.29)***
Misattributed as Fearful (at least two)	4872	1.24 (0.95, 1.61)	1.19 (0.86, 1.65)

§ $p \leq 0.1$, *$p \leq 0.05$, **$p \leq 0.01$

(1) Minimally adjusted model: Adjusted for child age, child gender, and tester. Fully adjusted model: Adjusted for child age, child gender, tester, gestational age, marital status, parity, social class, and child ethnicity (descriptions of these variables can be found in chapter 2, methodology).

(2) Table shows odds of children scoring above established thresholds on the DANVA (stated in table) when scoring above the established threshold on the SCDC of ≥ 9 out of 24 vs. scoring < 9 out of 24.

Table 30 Logistic regression analysis of female children's facial emotion recognition (DANVA): comparison of children scoring above and below the established threshold on the SCDC (odds ratios and 95% confidence intervals).

N = 2499	**Minimally Adjusted Model** OR (95% C.I.)	**Fully Adjusted Model** OR (95% C.I.)
Happy Faces (at least one error)	0.96 (0.62, 1.49)	1.17 (0.69, 1.99)
Sad Faces (at least two errors)	1.15 (0.73, 1.80)	1.30 (0.75, 2.27)
Angry Faces (at least four errors)	0.98 (0.59, 1.62)	0.64 (0.31, 1.34)
Fearful Faces (at least three errors)	**1.47 (0.98, 2.20)§**	1.47 (0.87, 2.49)
All Faces (at least seven errors)	1.23 (0.82, 1.84)	0.97 (0.56, 1.66)
All Low Intensity Faces (at least five errors)	1.33 (0.88, 2.01)	1.25 (0.73, 2.13)
All High Intensity Faces (at least three errors)	1.22 (0.80, 1.86)	1.05 (0.60, 1.82)
Misattributed as Happy (at least four)	**1.88 (1.22, 2.90)****	**1.90 (1.08, 3.35)***
Misattributed as Sad (at least three)	0.76 (0.44, 1.34)	0.70 (0.33, 1.48)
Misattributed as Angry (at least two)	1.44 (0.89, 2.32)	1.41 (0.77, 2.57)
Misattributed as Fearful (at least two)	1.08 (0.71, 1.65)	0.92 (0.53, 1.60)

§ $p \leq 0.1$, *$p \leq 0.05$, $p \leq 0.01$

(1) Minimally adjusted model: Adjusted for child age and tester. Fully adjusted model: Adjusted for child age, tester, gestational age, marital status, parity, social class, and child ethnicity.

(2) Table shows odds of female children scoring above established thresholds on the DANVA (stated in table) when scoring above the established threshold on the SCDC of ≥ 9 out of 24 vs. scoring < 9 out of 24.

Table 31 Logistic regression analysis of male children's facial emotion recognition (DANVA): comparison of children scoring above and below the established threshold on the SCDC (odds ratios and 95% confidence intervals).

	n	**Minimally Adjusted Model** OR (95% C.I.)	**Fully Adjusted Model** OR (95% C.I.)
Happy Faces (at least one error)	2470	1.19 (0.86, 1.65)	1.45 (0.98, 2.13)§
Sad Faces (at least two errors)	2470	**1.66 (1.18, 2.34)****	**1.82 (1.20, 2.74)****
Angry Faces (at least four errors)	2470	**1.80 (1.29, 2.52)****	**2.05 (1.37, 3.08)****
Fearful Faces (at least three errors)	2470	**1.57 (1.11, 2.22)****	**1.69 (1.11, 2.58)***
All Faces (at least seven errors)	2470	**1. 92 (1.40, 2.62)****	**2.00 (1.36, 2.94)****
All Low Intensity Faces (at least five errors)	2470	**1.80 (1.30, 2.48)****	**1.89 (1.27, 2.80)****
All High Intensity Faces (at least three errors)	2470	**2.10 (1.53, 2.88)****	**2.16 (1.44, 3.25)****
Misattributed as Happy (at least four)	2423	**1.87 (1.31, 2.69)****	**2.17 (1.42, 3.32)****
Misattributed as Sad (at least three)	2423	**1.49 (1.06, 2.10)***	**1.54 (1.01, 2.35)***
Misattributed as Angry (at least two)	2423	1.45 (0.94, 2.23)§	1.73 (1.05, 2.87)*
Misattributed as Fearful (at least two)	2423	1.37 (0.97, 1.93)§	1.42 (0.93, 2.16)

§ $p \leq 0.1$, *$p \leq 0.05$, $p \leq 0.01$

(1) Minimally adjusted model: Adjusted for child age and tester. Fully adjusted model: Adjusted for child age, tester, gestational age, marital status, parity, social class, and child ethnicity.

(2)Table shows odds of male children scoring above established thresholds on the DANVA (stated in table) when scoring above the established threshold on the SCDC of ≥ 9 out of 24 vs. scoring < 9 out of 24.

5.4.4 Emotion Recognition from Social Motion Cues (Emotional Triangles)

All Children

Children scoring above the cut-off on the SCDC demonstrated worse performance on the Emotional Triangles task, than children scoring below the cut-off; with significantly lower scores in the happy (B: -0.51, 95% CI: -0.73, -0.29, p = 0.0001), and sad (B: -0.28, 95% CI: -0.45, -0.11, p = 0.001) conditions. High scores on the SCDC also trended towards being predictive of low scores in the scared condition (B: -0.17, 95% CI: -0.37, 0.03, p = 0.09). No association was found between scoring above the threshold on the SCDC and emotion recognition in the angry condition (see table 32).

Female Children

Girls scoring above the cut-off on the SCDC demonstrated worse performance on the Emotional Triangles task than girls scoring below the cut-off; with significantly lower scores in the happy (B: -0.47, 95% CI: -0.80, -0.14, p = 0.005), and sad (B: -0.35, 95% CI: -0.61, -0.08, p = 0.01) conditions. No significant differences were revealed in the angry or scared conditions (see table 33).

Male Children

Similarly to girls, boys scoring above the cut-off on the SCDC demonstrated comparatively lower scores in the happy condition (B: -0.55, 95% CI: -0.85, -0.24, p = 0.0001); and the sad condition of the Emotional Triangles task (B: -0.23, 95% CI: -0.45, -0.01; p = 0.04). No significant differences were found in the angry or scared conditions (see table 34).

Table 32 Linear regression analysis of children's emotion recognition (Emotional Triangles) scores: comparison of children scoring above and below the established threshold on the SCDC (B coefficients and 95% confidence intervals).

N = 4388	Minimally Adjusted Model B (95% CI)	Fully Adjusted Model B (95% CI)
Angry	0.01 (-0.15, 0.17)	-0.05 (-0.24, 0.15)
Happy	**-0.42 (-0.59, -0.24)****	**-0.51 (-0.73, -0.29)****
Sad	**-0.15 (-0.29, -0.01)***	**-0.28 (-0.45, -0.11)****
Scared	-0.15 (-0.31, 0.01)§	-0.17 (-0.37, 0.03)§

§ p ≤ 0.1, *p ≤ 0.05, p ≤ 0.01
(1) Minimally adjusted model: Adjusted for child age, child gender, and tester. Fully adjusted model: Adjusted for child age, child gender, tester, gestational age, marital status, parity, social class, and child ethnicity.
(2) Table shows Emotional Triangles scores of children scoring above the established threshold on the SCDC of ≥ 9 out of 24 vs. children scoring < 9 out of 24.

Table 33 Linear regression analysis of female children's emotion recognition scores (Emotional Triangles): comparison of children scoring above and below the established threshold on the SCDC (B coefficients and 95% confidence intervals).

N = 2237	Minimally Adjusted Model B (95% CI)	Fully Adjusted Model B (95% CI)
Angry	-0.09 (-0.37, 0.19)	-0.001 (-0.31, 0.31)
Happy	**-0.48 (-0.78, -0.17)****	**-0.47 (-0.80, -0.14)****
Sad	**-0.35 (-0.59, -0.11)****	**-0.35 (-0.61, -0.08)****
Scared	-0.19 (-0.48, 0.10)	-0.15 (-0.46, 0.17)

§ p ≤ 0.1, *p ≤ 0.05, p ≤ 0.01
(1) Minimally adjusted model: Adjusted for child age and tester. Fully adjusted model: Adjusted for child age, tester, gestational age, marital status, parity, social class, and child ethnicity.
(2) Table shows Emotional Triangles scores of children scoring above the established threshold on the SCDC of ≥ 9 out of 24 vs. children scoring < 9 out of 24.

Table 34 Linear regression analysis of male children's emotion recognition scores (Emotional Triangles): comparison of children scoring above and below the established threshold on the SCDC (B coefficients and 95% confidence intervals).

N = 2151	Minimally Adjusted Model B (95% C.I.)	Fully Adjusted Model B (95% C.I.)
Angry	-0.05 (-0.27, 0.18)	-0.06 (-0.31, 0.19)
Happy	**-0.44 (-0.72, -0.17)****	**-0.55 (-0.85, -0.24)****
Sad	-0.17 (-0.37, 0.03)§	-0.23 (-0.45, -0.01)*
Scared	-0.17 (-0.41, 0.06)	-0.17 (-0.43, 0.09)

§ $p \leq 0.1$, *$p \leq 0.05$, $p \leq 0.01$
(1) Minimally adjusted model: Adjusted for child age and tester. Fully adjusted model: Adjusted for child age, tester, gestational age, marital status, parity, social class, and child ethnicity.
(2) Table shows Emotional Triangle scores of children scoring above the established threshold on the SCDC of ≥ 9 out of 24 vs. children scoring < 9 out of 24.

5.5 Discussion

The aim of this study was to investigate whether emotion recognition capacity was associated with social communication deficits in a community sample of children using two measures: one assessing the recognition of emotion from facial cues (DANVA); and the other assessing the recognition of emotion from social motion cues (Emotional Triangles Task). This was done to validate the use of the Emotional Triangles task in a general population sample of children, prior to using it to assess emotion recognition in children at high risk of developing an ED (chapter 6). In summary, the results of statistical analysis revealed an association between social communication deficits (as measured by the SCDC), and impaired emotion recognition from facial cues (DANVA) and social motion cues (Emotional Triangles Task). These findings are discussed in more detail below.

5.5.1 Facial Emotion Recognition

Children scoring above the cut-off on the SCDC had significantly higher odds of making more errors in the recognition of all faces, all high intensity faces, and all low intensity faces. With regard to each individual emotion, children scoring above the SCDC threshold had higher odds of making more errors in the recognition of sad, angry and fearful faces; and higher odds of misattributing faces as happy and angry. When analyzing the performance of girls and boys separately, results were found to be quite different for each gender. Boys scoring above the cut-off on the SCDC had significantly higher odds of making more errors in the recognition of all faces, all high intensity faces, and all low intensity faces. With regard to each individual emotion, boys scoring above the SCDC threshold had higher odds of making errors in the recognition of sad, angry and fearful faces; trended towards having higher odds of making errors in the recognition of happy faces; and also had significantly higher odds of misattributing faces as happy and sad. The profile of girls was very different however, with the only significant association being between high SCDC scores and comparatively high odds of misattributing faces as happy. As can be seen, while boys

scoring above the SCDC threshold demonstrate comparatively poor performance across the majority of outcome variables, girls scoring above the SCDC threshold appear to be relatively unimpaired.

Ingersoll and colleagues have previously investigated the association between autistic traits and facial emotion recognition in a non-clinical sample(Ingersoll, 2010). Assessing the performance of a large sample of undergraduate students, they found that high scores on the Autism Spectrum Quotient were also associated with a high number of errors in the overall recognition of emotion from facial cues on the DANVA. Our results were not entirely consistent with this study when breaking down emotion recognition according to each emotion however. In contrast to this study, which found that a high score on the Autism Spectrum Quotient was associated with impaired recognition of anger and sadness, but not happiness or fear, our findings suggest that impaired social communication is associated with more frequent errors in the recognition of anger, sadness and fear when analyzing the performance of boys and girls together. Differences in results could be due to a number of reasons. Firstly, the study by Ingersoll investigated the association between emotion recognition, and characteristics of ASD from all three domains: restrictive and repetitive behaviours; communication; and social interaction. In contrast, the present study investigated the association between emotion recognition, and characteristics of ASD from the social and communication domains only. Secondly, the community sample investigated in this study is much larger than the sample of undergraduate students investigated by Ingersoll. It is possible that in breaking down performance according to each emotion, this previous study did not have the power to pick up differences in the recognition of fearful faces. Thirdly, in the present study emotion recognition was assessed when participants were approximately 8 years of age; while the study by Ingersoll investigated emotion recognition in a sample of undergraduate students. It is possible that the difference in findings relating to the recognition of fear is associated to the different developmental stages of the participant groups in each study. It is worth noting however that like this previous investigation, only significantly increased errors in the recognition of negative emotions from facial cues were found when

analyzing the whole sample. This is also consistent with findings from studies investigating the parents of children with autism (Palermo, Pasqualetti, Barbati, Intelligente, & Rossini, 2006), and high functioning individuals with autism (Ashwin, Chapman, Colle, & Baron-Cohen, 2006).

When analyzing the facial recognition capacity of boys and girls separately results showed that in addition to impaired recognition of sadness, anger, and fear, boys with social communication deficits also exhibited impaired recognition of happiness from facial expressions; though this association did not quite reach statistical significance. It is possible that this finding reflects impairment in the recognition of all emotions for boys who scored above the threshold on the SCDC. On the other hand, as the level of significance was not adjusted for multiple comparisons, it is possible that this finding was due to chance. Previous research investigating facial emotion recognition in a sample of male adults with Autism Spectrum Disorders has found that deficits are only observed in the recognition of anger, sadness and fear (Philip, Whalley, Stanfield, Sprengelmeyer, Santos, Young, Atkinson, Calder, Johnston, et al., 2010); therefore further investigation is required to determine whether the impaired recognition of happiness in this sample of boys is a true finding. In contrast to the performance of boys, high SCDC scores were not associated with deficits in the recognition of any emotions for girls. This finding supports the hypothesis that boys with social communication deficits would exhibit a greater degree of impairment than girls. It cannot be determined however whether the superior performance of girls scoring high on the SCDC is due to a lack of impairment in facial emotion recognition, or whether girls are better able to learn the relationship between particular facial cues and what they represent with regard to the emotions of others. It is possible that a superior ability to learn and make associations masks a true deficit in emotion recognition in girls.

When analyzing the performance of the whole sample, children high in social communication difficulties had higher odds of misattributing faces as happy and angry. When analyzing the performance of boys alone, results showed that social and

communication deficits were associated with higher odds of misattributing faces as happy and sad. Girls scoring above the threshold on the SCDC also had higher odds of misattributing faces as happy, but this association was not observed with any other emotion. Interestingly, social and communication deficits were not associated with the misattribution of faces as fearful in the whole sample, or when the performance of boys and girls was analysed separately.

Adjusting for Multiple Comparisons

As the aim of this study is to validate a novel emotion recognition task for use with children, significance levels have not been adjusted for multiple comparisons. It is worth noting however that if significance levels were adjusted using the Bonferroni-Holm method, high SCDC scores would no longer significantly predict errors in the recognition of happy or angry faces, or misattributions of faces as angry, when analysing the performance of the sample as a whole, In addition, high SCDC scores would no longer predict errors in the recognition of fearful faces, or misattributions of faces as sad or angry, when analysing the performance of boys alone. Finally, adjusting for multiple comparisons would result in there being no significant associations between SCDC scores and facial emotion recognition in girls.

5.5.2 Emotion Recognition from Social Motion Cues

Children scoring above the cut-off on the SCDC showed significantly poorer recognition of happiness and sadness than children scoring below the cut-off; and also trended towards comparatively poor recognition of fear. When analyzing the performance of girls and boys separately it was found that both groups demonstrated a similar profile to each other; and to the sample as a whole. Both girls and boys scoring above the SCDC threshold showed poorer recognition of happiness and sadness in comparison to those scoring below the threshold.

Our findings are partially consistent with the results of a previous investigation using this novel measure (Boraston, et al., 2007). Boraston and colleagues found that adults

with Autism also showed decreased performance in the recognition of sadness, but did not find impairments in the happy, angry or scared conditions. However, results of statistical analysis in this study suggest that there was a great degree of variation in the scores of these three conditions. The authors speculated that in a larger sample, deficits in the recognition of the other emotions might become apparent. Our finding that the recognition of fear and happiness are impaired in children with social communication difficulties support the prediction of Boraston and colleagues.

Adjusting for Multiple Comparisons

As mentioned above the aim of this study is to validate a novel emotion recognition task for use with children; therefore significance levels have not been adjusted for multiple comparisons. It is worth noting however that if significance levels were adjusted using the Bonferroni-Holm method, high SCDC scores would no longer significantly predict errors in the recognition of sadness from social motion cues when analysing the performance of boys alone.

5.5.3 Differences in the Recognition of Emotion from Facial Expression and Social Motion Cues

The performance of children exhibiting social communication deficits was not consistent between the two tasks. When analyzing the performance of girls and boys together, impaired recognition of emotion from sad, angry, and fearful faces was observed on the DANVA; however impaired recognition of happiness and sadness from social motion cues was observed on the Emotional Triangles Task. Despite the lack of consistency between the two tasks, the findings of this study are consistent with previous research investigating emotion recognition in individuals with Autism Spectrum Disorders. Extensive research into the facial emotion recognition capacity of samples with ASD provides evidence for the presence of impairment in the recognition of all emotions: sadness, anger, fear, surprise and disgust; but not for happiness (Ashwin, et al., 2006; Boraston, et al., 2007; Corden, Chilvers, & Skuse, 2008; Humphreys, Minshew, Leonard, & Behrmann, 2007; Pelphrey, et al., 2002;

Wallace, Coleman, & Bailey, 2008). However there is evidence in the literature pertaining to groups with ASD of impaired happiness recognition from body movement and vocal cues (Philip, Whalley, Stanfield, Sprengelmeyer, Santos, Young, Atkinson, Calder, Johnstone, et al., 2010).

The evidence to date suggests that impaired emotion recognition in ASD groups exist across a range of stimulus domains, and the specific emotions that are impaired may vary across these modalities (Philip, Whalley, Stanfield, Sprengelmeyer, Santos, Young, Atkinson, Calder, Johnstone, et al., 2010). Our findings suggest that this is not only the case in ASD populations, but also in a community sample of children high in social communication difficulties. The implications of this finding are that: (i) the association between deficits in social communication and emotion recognition may be one that exists on a spectrum throughout the whole population, rather than only being present in clinical groups; and (ii) emotion recognition capacity may vary according to the stimuli that an individual is responding too.

A secondary hypothesis of this study was that boys with social communication deficits would show a greater degree of deficit in emotion recognition than girls. Results from the DANVA confirm this hypothesis. When analyzing facial emotion recognition separately for males and females, it was found that boys with high scores on the SCDC, indicative of social communication deficits, made a high number of errors in the recognition of angry, sad and fearful faces. In contrast, girls high in social communication difficulties did not make a higher number of errors in the overall recognition of emotion from faces or in the recognition any emotion individually. In fact, the only indication that social communication difficulties were associated to facial emotion recognition in girls was that they had higher odds of frequently misattributing faces as happy. These findings indicate the presence of a general deficit in facial emotion recognition in boys, but a bias in emotion recognition in girls.

Results from the Emotional Triangles task, when analyzing the performance of boys and girls separately, were very different to results from performance on the DANVA.

In girls, high scores on the SCDC were associated with poorer emotion recognition in the happy and sad conditions; while in boys high SCDC scores were only associated with poorer emotion recognition in the happy condition. This is in contrast to our prediction that boys would show a greater degree of impairment than girls. It is possible that the female advantage in facial emotion processing (McClure, 2000), does not extend to the recognition of emotion from other domains or modalities. An alternative explanation is that females are able to learn the meaning of facial cues with regard to emotion better than males, masking an existing deficit, and that this learning is not effective at masking the deficit present when using other cues to communicate emotion (such as social motion cues).

5.6 Conclusions

The results of this study provide further validation for the Emotional Triangles Task, and its use in (i) a general population sample; and (ii) children as well as adults. Results also suggest that the Emotional Triangles task may be a better test of emotion recognition within females, who show less impairment in a test of facial emotion recognition. This finding suggests that the task would be a useful measure to assess emotion recognition in children at high risk of developing an ED.

Chapter 6

Social Cognition in Children at High Risk of Developing an Eating Disorder

6.1 Social Communication and Emotion Recognition in Children at High Risk of Developing and Eating Disorder

6.1.1 Introduction

As discussed in chapter one, research investigating the social communication and emotion recognition abilities of individuals with ED is increasing. Similar lines of research into groups with other psychiatric illnesses such as schizophrenia have found that such indices of social cognition mediate the relationship between neurocognitive impairment and overt functioning (e.g. Sergi, et al., 2006). In addition, there is growing evidence of an overlap of intermediate phenotypes between AN and ASD (e.g. Faunce & Job, 2000; Odent, 2010; Treasure, 2012), a disorder characterised by deficits in social communication. Research investigating social communication and emotion recognition in ED groups has been discussed extensively in chapter two, but a brief summary is provided below.

Social Communication and Interpersonal Functioning

Both AN and BN have been associated with impaired social relationships(e.g. Bohle, et al., 1991), and difficulties with social communication (e.g. Leon, et al., 1985). Interpersonal difficulties have been found to effect treatment, through problems forming therapeutic alliances (Vitousek, et al., 1998), and problems with social anxiety (Goodwin, 2002). Literature regarding interpersonal functioning in the family context is inconsistent, but studies do consistently show that probands, family members, and clinicians give conflicting reports regarding family interactions (Cook-Darzens, et al., 2005; Gowers & North, 1999; Whitney & Eisler, 2005); suggesting differences in the way that social relationships are perceived. Evidence suggests that this disturbance in

social communication is present prior to onset, with studies finding a high prevalence of separation anxiety disorder (Silberg & Bulik, 2005); social phobia (Melfsen, et al., 2006); social anxiety (Godart, 2002); and neurodevelopmental disorders of the ASD spectrum (Connan, et al., 2003); presenting in childhood.

Emotion Recognition ED Patients

There is growing evidence to suggest that individuals with an ED show difficulties with the recognition of emotion from faces, voices, film, and on the Reading the Mind in the Eyes (RME) task (Oldershaw, et al., 2011); though there are also studies that have found no differences between ED patients and healthy controls (e.g. Kenyon, et al., 2011; Kessler, et al., 2006; Medina-Pradas, et al., 2012; Mendlewicz, et al., 2005). There is disagreement between the studies that do find deficits, over which emotions prove problematic; however the majority of studies find that problems occur mainly with the recognition of negative emotions (e.g. Jänsch, et al., 2009; Machado, et al., 2007). As outlined in chapter two, there are a variety of possible reasons for the conflict in the literature: including the use of different facial emotion recognition tasks; variations in the time that stimuli are presented; the intensity of expression; whether the tasks use a free- or force-choice paradigm; whether the task is computerized; and the balance of negative and positive emotions displayed. It is also worth noting that the majority of research investigating emotion recognition (particularly from facial expression) has been conducted with AN patients, making it difficult to draw any conclusions regarding the abilities of patients with BN.

Emotion Recognition in Recovered ED Patients and Subclinical Samples

Two studies have investigated emotion recognition in recovered samples to determine whether deficits observed are state independent and associated with the illness itself, rather than a result of secondary features such as low nutritional intake; however findings have been mixed (Harrison, 2010; Oldershaw, 2010). Only one of these studies investigated facial emotion recognition, and no differences were found between recovered groups and healthy controls (Oldershaw, 2010). There has been limited research investigating facial emotion recognition in sub-clinical populations,

to determine whether deficits may be present prior to onset, and impaired recognition of neutral, happy and angry faces has been observed (Jones, et al., 2008; Pringle, et al., 2010). To date, there have been no published studies investigating emotion recognition in the first-degree relatives of ED probands. Such research would be useful as it is possible that an underlying deficit in the recognition of others' emotions may contribute to the difficulties in social communication that have been observed in ED groups (Oldershaw, et al., 2011; Zucker, 2007).

High Risk Research

As discussed previously, the differences in social cognition that have been observed in probands may be present prior to onset, possibly contributing towards the development of an ED. It is also possible however that observed differences in social cognition are a consequence of an ED. One method of testing this is to investigate social cognition in groups at familial high risk of developing an ED. The high risk design has been used to investigate premorbid cognition in schizophrenia (e.g. Amminger, et al., 2011; Cornblatt & Erlenmeyer-Kimling, 1985; Davalos, 2004; Eack, 2010; Erlenmeyer-Kimling & Cornblatt, 1987; 2008; Rutschmann, et al., 1977); depression (e.g. Mannie, 2007; Monk, et al., 2008); and bipolar disorder (e.g. Brotman, et al., 2008; Melissa, et al., 2008); and the high risk research design has been shown to be an effective way of identifying intermediate phenotypes for these disorders.

Summary

To summarise, differences in social cognition observed in patients and recovered subjects may not be present prior to onset. One method of investigating premorbid difficulties is to investigate children at high risk of developing and ED. This is the first study to investigate social communication and emotion recognition in children at high risk of developing an ED.

6.1.2 Aims and Hypothesis

The aim of this study was to investigate social communication and emotion recognition in children at high risk of developing an ED, in comparison to children who are not. Based on previous literature, it was hypothesized that the children at high risk, due to being born to a mother with an ED: (i) would show comparatively poorer recognition of emotion from social motion cues, (ii) would be more likely to make a high number of errors/misattributions on the facial emotion recognition task, and (iii) would be more likely to score above the accepted threshold of ≤ 9 out of 24 on the measure of social communication (SCDC). Due to the paucity of evidence, and contradictory findings, it was not possible to predict where these differences would rely with regard to specific ED diagnosis and valence of emotion; except to predict that problems with the recognition of emotion were more likely to be found amongst negative, rather than positive, emotions.

6.1.3 Methods

6.1.3.1 Design

Longitudinal prospective.

6.1.3.2 Participants

Sample size for each analysis was dependent on both maternal data on ED exposure, and child data on social cognition being present. Inclusion and exclusion criteria for this study are detailed in the chapter 3 (Aims and Methodology). Final sample sizes varied for each analysis and can be found in results tables. Assessments were conducted when children were approximately 8 (DANVA) and 13 (Emotional Triangles) years of age, with mean ages being: 103.8 months, and 150 months; respectively. The SCDC was completed by mothers when children were approximately 13 ½ years of age (mean = 157 months).

6.1.3.3 Measures

Exposure

At 12 weeks gestation, the mothers completed a questionnaire about their health. All women were asked whether they had a history of Anorexia Nervosa (AN) and/or Bulimia Nervosa (BN). Of the women that responded, 446 reported a history of lifetime ED: AN (171), BN (194), or both (81).

Outcomes: Assessments of Social Cognition in Children

Children's facial emotion recognition was assessed at age 8 using the Diagnostic Analysis of Non-Verbal Accuracy (DANVA)(Nowicki & Duke, 1994); emotion recognition from social cues was measured using the Emotional Triangles task at age 13 (Boraston, et al., 2007); and social communication deficits were measured using the Social Communication Disorders Checklist (SCDC) (Skuse, et al., 2005), which was completed by mothers when the children were 13 years of age. A detailed description of these tasks can be found in chapter 5 (Measures).

6.1.3.4 Procedure

The study was approved by the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees.

6.1.3.5 Analyses

All variables were checked for inconsistencies/outliers using tabulations, graphs and plots. Values that were inconsistent with the relevant assessment were treated as missing values. SCDC scores were prorated for participants with less than 25% missing responses, and those missing more than 25% were considered missing. The distribution of variables was inspected for normality. The SCDC score was not normally distributed, (and could not be transformed); this score was used as a binary variable with a threshold of at least 9 out of 24, as recommended in previous

literature (Skuse, et al., 2005; Skuse, et al., 2009). Scores from the DANVA were also not normally distributed, (and could not be transformed); binary variables that were created by ALSPAC in collaboration with the creator of the measure, Stephen Nowicki, were used (see chapter four, table 27).

The association between mother's eating disorder status and children's' social cognition was explored using linear (Emotional Triangles) and logistic (SCDC and DANVA) regression. Child gender, child age at time of testing, and task administrator (tester) were included in the minimally adjusted model due to being determined a-priori confounders. Confounders that could potentially influence outcomes, as indicated by evidence in the literature, were initially tested in univariate models, and included in the multivariate analysis if meeting criteria for confounding (fully adjusted model). SPSS 18 was used for all analyses and a two-tailed significance level of $p \leq 0.05$ was used. Due to the small numbers in exposed groups, individual analyses were not conducted for each gender. However, a sensitivity analysis was conducted to provide a description of performance for girls and boys separately.

Missing covariate data

Multiple random imputation was used to deal with missing covariate data. All predictor and outcome variables were used as predictors in the imputation model. Missing data were imputed for marital status, child ethnicity, social class, age of child at time of testing, and parity for at least one of the time points. All analyses were run on both complete case and imputed datasets for comparison and differences were negligible. Due to the fact that complete case analysis is thought to suffer from more chance variation, and multiple imputation is assumed to correct any bias, only results based on multiple imputation are presented.

6.1.4 Results

6.1.4.1 Attrition & Missingness

Attrition

Overall attrition, i.e. children not attending the testing sessions, or children for whom parents had not returned the SCDC, was predicted by a range of socio-demographic factors. A significantly greater proportion of children who attended the DANVA testing session at age 8, the Emotional Triangles testing session at age 13, and had the SCDC completed and returned by their parents at age 13: were female; of a higher social-class; were white; and did not have siblings. In addition, these children also had parents that were married, and mothers that were older, at the time of delivery. These variables were included as confounders accordingly.

Missingness of Specific Outcomes

Additional missingness of specific outcomes was dealt with by testing the role of relevant socio-demographic variables as predictors of missing outcome data, by estimating the odds of having missing data across each measure of social cognition. For Emotional Triangles outcomes, there was a very small amount of missing data, considered negligible; and no socio-demographic variables were predictive of missingness in DANVA scores. With regard to the SCDC, children with more than 25% of responses being unanswered (therefore making prorating inappropriate), had significantly higher odds of belonging to a lower social class, and trended towards being predictive of mothers being educated to below A level standard. These variables were also included as confounders accordingly.

Selective Attrition

Selective attrition across index groups was tested for using logistic regression, by estimating the odds of each group having missing data for each assessment. No differences were found between exposed and unexposed groups in the percentage of missing data for each measure.

6.1.4.2 Socio-demographics

Socio-demographic data for the sample used in this study are described in chapter 3 (Aims and Methodology).

6.1.4.3 Social Communication and Emotion Recognition in Children at High Risk

No statistically significant differences were observed between exposed and unexposed groups on any outcome measures (see tables 35, 37 and 39), but there was a trend for maternal report of AN+BN to be associated with children misattributing faces as fearful in the fully adjusted model (OR: 1.78, 95% CI: 0.90, 3.54, p = 0.09; see table 35). As stated above, exposed group
s were too small to run separate analysis by gender; however the sensitivity analysis revealed no differences in performance between gender that could be considered reliable when taking into consideration sample size (see tables 36, 38 and 40).

6.1.4.4 Task Performance across Gender Groups

As stated above, exposed groups were too small to run separate analysis by gender; however the sensitivity analysis revealed no differences in performance between genders that could be considered reliable when taking into consideration sample size (see tables 46, 38 and 40).

Table 35 Logistic Regression Analysis of Children's DANVA Scores: comparison of exposed and unexposed groups (odds ratios and 95% confidence intervals).

	n (%)	**Model 1** OR (95% C.I.)	**Model 2** OR (95% C.I.)
Happy Faces: at least one error			
Unexposed	5441 (96.2)	Ref.	Ref.
AN	83 (1.5)	1.09 (0.67, 1.80)	1.10 (0.67, 1.81)
BN	88 (1.6)	0.95 (0.57, 1.59)	0.96 (0.58, 1.58)
AN + BN	41 (0.7)	1.52 (0.78, 2.96)	1.53 (0.79, 2.95)
Sad Faces: at least two errors			
Unexposed	5441 (96.2)	Ref.	Ref.
AN	83 (1.5)	1.34 (0.79, 2.29)	1.37 (0.81, 2.33)
BN	88 (1.6)	1.15 (0.67, 1.97)	1.16 (0.66, 2.02)
AN + BN	41 (0.7)	0.53 (0.19, 1.50)	0.55 (0.20, 1.51)
Angry Faces: at least four errors			
Unexposed	5441 (96.2)	Ref.	Ref.
AN	83 (1.5)	1.06 (0.59, 1.91)	1.08 (0.60, 1.95)
BN	88 (1.6)	1.24 (0.71, 2.16)	1.23 (0.70, 2.13)
AN + BN	41 (0.7)	1.06 (0.47, 2.43)	1.05 (0.46, 2.37)
Fearful Faces: at least three errors			
Unexposed	5441 (96.2)	Ref.	Ref.
AN	83 (1.5)	1.22 (0.72, 2.07)	1.25 (0.73, 2.13)
BN	88 (1.6)	0.59 (0.30, 1.15)	0.59 (0.30, 1.19)
AN + BN	41 (0.7)	0.62 (0.24, 1.58)	0.62 (0.24, 1.62)
Misattributed as Happy: at least four misattributions			
Unexposed	5441 (96.2)	Ref.	Ref.
AN	83 (1.5)	0.79 (0.37, 1.60)	0.82 (0.40, 1.65)
BN	88 (1.6)	0.77 (0.38, 1.56)	0.79 (0.39, 1.58)
AN + BN	41 (0.7)	0.48 (0.15, 1.57)	0.48 (0.15, 1.56)
Misattributed as Sad: at least three misattributions			
Unexposed	5441 (96.2)	Ref.	Ref.
AN	83 (1.5)	0.99 (0.54, 1.82)	1.00 (0.55, 1.80)
BN	88 (1.6)	0.57 (0.27, 1.20)	0.57 (0.39, 0.82)
AN + BN	41 (0.7)	0.58 (0.20, 1.64)	0.57 (0.33, 0.97)
Misattributed as Angry: at least two misattributions			
Unexposed	5441 (96.2)	Ref.	Ref.
AN	83 (1.5)	1.00 (0.51, 1.96)	1.00 (0.51, 1.95)
BN	88 (1.6)	1.08 (0.57, 2.05)	1.06 (0.56, 2.02)
AN + BN	41 (0.7)	0.42 (0.10, 1.74)	0.42 (0.12, 1.46)
Misattributed as Fearful: at least two misattributions			
Unexposed	5441 (96.2)	Ref.	Ref.
AN	83 (1.5)	0.90 (0.51, 0.71)	0.93 (0.53, 1.64)
BN	88 (1.6)	0.18 (0.71, 1.96)	1.20 (0.72, 1.99)
AN + BN	41 (0.7)	1.72 (0.87, 3.40)	**1.78 (0.90, 3.54)§**
All Faces: at least seven errors			
Unexposed	5441 (96.2)	Ref.	Ref.
AN	83 (1.5)	0.93 (0.55, 1.59)	0.95 (0.56, 1.63)
BN	88 (1.6)	1.11 (0.67, 1.83)	1.10 (0.67, 1.81)
AN + BN	41 (0.7)	**0.45 (0.18, 1.16)§**	**0.45 (0.17, 1.20)§**

§ p≤0.1, * p≤0.05, ** p≤0.01

(1) Model 1. Minimally adjusted model: adjusted for child age and gender, and tester. Model 2. Fully adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, and marital stability.

(2) Table shows odds of children scoring above the established thresholds stated.

Table 36 Number and percentage of children scoring above the established thresholds for DANVA outcomes across ED groups (split by gender).

	Girls N (%)	Boys N (%)
Happy Faces: at least one error		
Unexposed	536 (19.5)	749 (27.8)
AN	6 (16.7)	16 (34.0)
BN	7 (14.6)	13 (32.5)
AN + BN	7 (35.0)	6 (28.6)
Sad Faces: at least two errors		
Unexposed	426 (15.5)	497 (18.5)
AN	6 (16.7)	12 (25.5)
BN	9 (18.8)	8 (20.0)
AN + BN	8 (10.0)	2 (9.5)
Angry Faces: at least four errors		
Unexposed	366 (13.3)	496 (18.4)
AN	6 (16.7)	8 (17.0)
BN	6 (12.5)	10 (25.0)
AN + BN	3 (15.0)	4 (19.0)
Fearful Faces: at least three errors		
Unexposed	474 (17.2)	503 (18.7)
AN	9 (25.0)	9 (19.1)
BN	6 (12.5)	4 (10.0)
AN + BN	4 (20.0)	1 (4.8)
Misattributed as Happy: at least four misattributions		
Unexposed	325 (12.0)	395 (14.9)
AN	6 (16.7)	3 (6.5)
BN	5 (10.4)	4 (10.3)
AN + BN	2 (10.5)	1 (4.8)
Misattributed as Sad: at least three misattributions		
Unexposed	328 (12.2)	509 (19.2)
AN	6 (16.7)	7 (15.2)
BN	4 (8.3)	4 (10.3)
AN + BN	2 (10.5)	2 (9.5)
Misattributed as Angry: at least two misattributions		
Unexposed	322 (11.9)	291 (11.0)
AN	4 (11.1)	6 (13.0)
BN	7 (14.6)	4 (10.3)
AN + BN	0 (0.0)	2 (9.5)
Misattributed as Fearful: at least two misattributed at fearful		
Unexposed	524 (19.4)	548 (20.7)
AN	6 (16.7)	9 (19.6)
BN	9 (18.8)	11 (28.2)
AN + BN	6 (31.6)	6 (28.6)
All Faces: at least seven errors		
Unexposed	558 (20.3)	671 (24.9)
AN	7 (19.4)	11 (23.4)
BN	10 (20.8)	11 (27.5)
AN + BN	2 (10.0)	3 (14.3)

(1) Table shows number and percentage of children scoring above cut-offs stated.

Table 37 Linear Regression Analysis of Children's Emotion Triangle Scores: Comparison of exposed and unexposed groups (B coefficients and 95% confidence intervals)

		n (%)	**Model 1** B (95% C.I.)	**Model 2** B (95% C.I.)
Angry	Unexposed	4811 (95.9)	Ref.	Ref.
	AN	72 (1.4)	0.12 (-0.22, 0.45)	0.09 (-0.24, 0.43)
	BN	91 (1.8)	-0.15 (-0.45, 0.15)	-0.14 (-0.44, 0.15)
	AN + BN	41 (0.8)	0.12 (-0.33, 0.55)	0.10 (-0.34, 0.54)
Happy	Unexposed	4811 (95.9)	Ref.	Ref.
	AN	72 (1.4)	-0.24 (-0.62, 0.15)	-0.24 (-0.43, -0.04)
	BN	91 (1.8)	-0.23 (-0.57, 0.11)	-0.23 (-0.57, 0.11)
	AN + BN	41 (0.8)	-0.16 (-0.66, 0.35)	-0.16 (-0.66, 0.34)
Sad	Unexposed	4811 (95.9)	Ref.	Ref.
	AN	72 (1.4)	0.01 (-0.27, 0.30)	0.004 (-0.28, 0.29)
	BN	91 (1.8)	0.16 (-0.1, 0.42)	0.16 (-0.10, 0.43)
	AN + BN	41 (0.8)	0.20 (-0.18, 0.58)	0.20 (-0.17, 0.56)
Scared	Unexposed	4811 (95.9)	Ref.	Ref.
	AN	72 (1.4)	0.15 (-0.2, 0.49)	0.16 (-0.19, 0.50)
	BN	91 (1.8)	-0.15 (-0.45, 0.16)	-0.14 (-0.45, 0.17)
	AN + BN	41 (0.8)	0.22 (-0.24, 0.67)	0.22 (-0.20, 0.65)

§ p≤0.1, * p≤0.05, ** p≤0.01

(1) Model 1. Minimally adjusted model: adjusted for child age and gender, and tester. Model 2. Fully adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, and marital stability.

(2) Higher scores represent better performance.

Table 38 Mean (SD) scores of children on the Emotional Triangles Task across groups (split by gender)

		Girls		Boys	
		n (%)	M (SD)	n (%)	M (SD)
Angry	Unexposed	2454 (96.0)	2.48 (1.44)	2357 (95.9)	2.72 (1.42)
	AN	35 (1.4)	2.40 (1.56)	37 (1.5)	3.03 (1.35)
	BN	46 (1.8)	2.30 (1.39	45 (1.8)	2.60 (1.49)
	AN + BN	22 (0.9)	2.52 (1.56)	19 (0.8)	2.92 (1.43)
Happy	Unexposed	2454 (96.0)	2.10 (1.55)	2357 (95.9)	2.09 (1.73)
	AN	35 (1.4)	1.80 (1.52)	37 (1.5)	1.92 (1.53)
	BN	46 (1.8)	1.82 (1.42)	45 (1.8)	1.92 (1.39)
	AN + BN	22 (0.9)	2.00 (1.45)	19 (0.8)	1.87 (1.82)
Sad	Unexposed	2454 (96.0)	1.60 (1.23)	2357 (95.9)	1.49 (1.25)
	AN	35 (1.4)	1.39 (0.92)	37 (1.5)	1.73 (1.13)
	BN	46 (1.8)	1.65 (1.24)	45 (1.8)	1.78 (1.18)
	AN + BN	22 (0.9)	1.95 (1.41)	19 (0.8)	1.53 (1.17)
Scared	Unexposed	2454 (96.0)	1.89 (1.49)	2357 (95.9)	2.39 (1.47)
	AN	35 (1.4)	2.07 (1.36)	37 (1.5)	2.51 (1.18)
	BN	46 (1.8)	1.53 (1.50)	45 (1.8)	2.47 (1.48)
	AN + BN	22 (0.9)	2.14 (1.45)	19 (0.8)	2.58 (0.92)

(1) Higher scores represent better performance.

Table 39 Logistic Regression Analysis of Children's SCDC Scores: comparison of exposed and unexposed groups (odds ratios and 95% confidence intervals)

	n (%)	**Model 1** OR (95% C.I.)	**Model 2** OR (95% C.I.)
Unexposed	5673 (95.9)	Ref.	Ref.
AN	91 (1.5)	1.28 (0.61, 2.69)	1.37 (0.65, 2.89)
BN	108 (1.8)	1.01 (0.46, 2.18)	1.01 (0.47, 2.21)
AN + BN	44 (0.7)	1.79 (0.69, 4.61)	1.90 (0.73, 4.95)

§ p≤0.1, * p≤0.05, ** p≤0.01

(1) Model 1. Minimally adjusted model: adjusted for child age and gender, and tester. Model 2. Fully adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, and marital stability.

(2) Table shows odds of children scoring above the established SCDC threshold of ≥ 9 out of 24.

Table 40 Number and percentage of children scoring above the established threshold on the SCDC across groups (split by gender).

	Girls n (%)	**Boys** n (%)
Unexposed	153 (5.4)	220 (7.7)
AN	3 (7.7)	5 (9.6)
BN	2 (3.5)	5 (9.8)
AN + BN	1 (4.3)	4 (19.0)

N.B. Table shows number and percentage of children scoring above the established SCDC threshold of ≥ 9 out of 24.

6.1.5 Interim Discussion

The aim of this study was to investigate social communication and emotion recognition in children at high risk of developing an eating disorder, in comparison to children who are not. Results of statistical analysis showed a weak association between maternal report of AN+BN, and children having higher odds than healthy control children of misattributing faces as fearful. No other statistically significant differences were observed between exposed and unexposed groups.

6.1.5.1 Social Communication

Contrary to my hypothesis, the children of mothers reporting an ED did not exhibit deficits in social communication in comparison to the children of healthy controls, as measured by the SCDC. In a recent pilot study, Hambrook and colleagues found that AN patients were significantly more impaired with regard to their social skills (Hambrook, Tchanturia, Schmidt, Russell, & Treasure, 2008). Our findings suggest that this is not the case in children at high risk, and this could be for a number of possible reasons. This study used the SCDC to measure social communication, while Hambrook and colleagues used another established measure of autistic traits, the Autism-spectrum Quotient (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001), therefore the difference in findings could be due to differences in the measures used. In addition, the Autism-spectrum Quotient is a self-report measure, while the SCDC was completed by parents; it is possible that the study by Hambrook and colleagues was actually observing differences in perceived social skills. Hambrook and colleagues employed a clinical sample while here a general population cohort was investigated, and it is possible that impairments in social communication are only associated with an extreme ED phenotype. It is also possible that the impairment observed in the clinical group is not present prior to onset of the disorder, and is a consequence of the illness rather than a predisposing factor.

There is evidence in the literature suggesting that there is a high prevalence of neurodevelopmental disorders of the ASD spectrum presenting in childhood within AN groups (e.g. Connan, et al., 2003), as well as high levels of social anxiety (e.g. Godart, Flament, Lecrubier, & Jeammet, 2000), and social phobia (e.g. Melfsen, et al., 2006), Once again, these studies employ clinical samples, while here a general population cohort has been investigated. Our finding that children at risk do not show deficits in social communication, may indicate that these premorbid traits and disorders are only associated with the extreme AN phenotype; or that deficits in this sample are too subtle to be detected with the SCDC. It is also possible that such premorbid/comorbid social disorders are only present in a subgroup of patients with AN, who have a different illness trajectory; something that has previously been suggested by Tchanturia and colleagues (Tchanturia, et al., 2004).

6.1.5.2 Emotion Recognition

A weak association was observed between maternal report of AN+BN and the misattribution of faces as fearful in the DANVA; however this is likely to be a chance finding. Research investigating facial emotion recognition in AN groups has also found evidence of a disturbance in the recognition of fear (Jänsch, et al., 2009; Machado, et al., 2007). Research investigating recovered participants tells a different story however, with one study finding no differences in facial emotion recognition between recovered AN patients and healthy controls (Oldershaw, 2010). No other studies have investigated facial emotion recognition in recovered groups, and there are no studies investigating emotion recognition in first-degree relatives. Due to this paucity of evidence, it is difficult to draw any conclusions regarding the weak association observed in this study. It is worth noting however that, due to the exploratory nature of this study, the significance level was not adjusted to account for multiple comparisons; therefore the difference observed may be due to chance. Assuming this, our finding indicates that impaired emotion recognition from faces or social motion cues is not a trait associated with high risk status for an ED. There is evidence to suggest that AN patients do not suffer from impaired emotion recognition (Fairburn,

Cooper, Cooper, McKenna, & Anastasiades, 1991; Phillips, 2008), and our findings could be taken as evidence that this is also the case for children at high risk, due to being born to mothers reporting AN. There is however a great deal of evidence supporting the presence of impaired emotion recognition in ED groups (Faunce & Job, 2000). If impairments are indeed associated with the acute phase of an ED as suggested, our findings suggest that observed deficits in clinical groups may be a result of secondary features of the disorder itself, such as low nutritional intake or social isolation. Alternatively, impairments in emotion recognition may be associated with comorbid disorders such as social anxiety or depression.

6.1.6 Study Summary

In contrast to my hypothesis, no statistically significant differences were found between children at high risk of developing an ED and children who are not, on measures of social communication and emotion recognition. A number of possible reasons for this are discussed above, including the suggestion that the deficits observed in clinical groups are not present prior to onset. It is also possible that differences are not observed due to the limitations associated with diagnostic criteria. This is explored further in the next study.

6.2 Are Maternal Lifetime ED Behavioural Phenotypes Associated with Social Communication and Emotion Recognition Difficulties in Offspring?

6.2.1 Introduction

As previously discussed in chapter one of this thesis, it is possible that specific ED behaviours will have a more direct association with specific differences in neuropsychological functioning; which suggests that specific ED behaviours might be more distinct phenotypes compared to ED diagnoses.

6.2.2 Aims and Hypothesis

The aim of this study was to investigate social communication and emotion recognition in children at high risk of developing an ED, using maternal lifetime ED behaviours as risk markers. Due to the paucity of research investigating the relationship between behavioural phenotypes of ED and social cognition, and the inconclusive findings from study four, an exploratory approach was taken with this particular study.

6.2.3 Methods

6.2.3.1 Design

Longitudinal

6.2.3.2 Participants

For inclusion in this study, data on maternal lifetime ED behaviours and children's social communication and emotion recognition were both necessary, therefore sample size varied for the analysis of each measure. Full details of the interview protocol, and inclusion and exclusion criteria can be found in chapter 3 (Aims and Methodology). Final sample sizes for each analysis can be found in the relevant results tables. Assessments were conducted when children were approximately 8 (DANVA) and 13 (Emotional Triangles) years of age, with mean ages being: 103.8 months, and 150 months; respectively. The SCDC was completed by mothers when children were approximately 13 ½ years of age (mean = 157 months).

6.2.3.3 Measures

Exposure

Data on maternal exposure to eating disorder behaviours were gathered via in depth interviews using the Structured Clinical Interview for DSM-IV-TR (Research version) with the additional use of the Lifeline section of the LIFE interview (Keller, et al., 1987). A full explanation of these measures and the interview protocol can be found in chapter 3 (Aims and Methodology), along with a detailed description of how exposed groups were categorized.

Outcomes: Measures of Social Cognition in Children

Children's facial emotion recognition was assessed at age 8 using the Diagnostic Analysis of Non-Verbal Accuracy (DANVA)(Nowicki & Duke, 1994); emotion recognition from social cues was measured using the Emotional Triangles task at age 13 (Boraston, et al., 2007); and social communication deficits were measured using the Social Communication Disorders Checklist (SCDC) (Skuse, et al., 2005), which was completed by mothers when the children were 13 years of age. A detailed description of these tasks can be found in chapter 5(Measures).

6.2.3.4 Procedure

This study was approved by the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees. A full account of the procedures and protocol for administering interviews and deriving exposure variables can be found in chapter 3 (Aims and Methodology).

6.2.3.5 Analyses

Preparation of the data for analyses, with regard to outliers; prorating of the SCDC to deal with missingness; and the distribution of variables was the same as in study one of this chapter. Once again, the SCDC and DANVA scores were transformed into binary variables, while the Emotional Triangles scores were used as continuous outcomes.

The association between mother's eating disorder status and children's' social cognition was explored using linear (Emotional Triangles) and logistic (SCDC and DANVA) regression. Child age at time of testing, child gender, and test administrator (tester) were included in the minimally adjusted model due to being determined a-priori confounders. Additional confounders that could potentially influence outcomes, as indicated by evidence in the literature, were initially tested in univariate models, and included in the multivariate analysis if meeting criteria for confounding (fully adjusted model). SPSS 18 was used for all analyses and a significance level of $p \leq 0.05$

was used. Due to the small numbers in exposed groups, individual analyses were not conducted for each gender. However, a sensitivity analysis was conducted to provide a description of performance for girls and boys separately.

Missing covariate data

Multiple random imputation was used to deal with missing covariate data. All predictor and outcome variables were used as predictors in the imputation model. Missing data were imputed for marital status, and child ethnicity, social class, maternal age at delivery, and parity for at least one of the analyses. All analyses were run on both complete case and imputed datasets for comparison and differences were negligible. Due to the fact that complete case analysis is thought to suffer from more chance variation, and multiple imputation is assumed to correct any bias, only results based on multiple imputation are presented.

6.2.4 Results

6.2.4.1 Attrition & Missingness

Attrition

Overall attrition for the assessment of maternal lifetime ED behaviours: i.e. women who were not interviewed; was predicted by a range of socio-demographic factors. A significantly greater proportion of mothers that were interviewed was of a higher social class; were married, and were older at the time of delivery. These variables were included as confounders accordingly.

Overall attrition for the assessment of children's social cognition, i.e. children not attending the testing sessions, or children for whom parents had not returned the SCDC, was predicted by a range of socio-demographic factors. A significantly greater proportion of children who attended the DANVA testing session at age 8 were of a higher social class; had mothers educated to at least A level standard; and had

mothers who were older at time of delivery. A significantly greater proportion of children who attended the Emotional Triangles testing session at age 13 were of a higher social class, and did not have siblings. Finally, a significantly great proportion of children whose parents returned the SCDC was of a higher social class, and was white. These variables were included as confounders accordingly.

6.2.4.2 Socio-demographics

Socio-demographic data for the sample used in this study are described in chapter 3 (Aims and Methodology).

6.2.4.3 Emotion Recognition from Facial Cues in Children at High Risk

The children of women in the Purging group were found to have lower odds than unexposed children of misattributing faces as sad: this was the case in the minimally adjusted model (OR: 0.10, 95% CI: 0.01, 0.76, p = 0.03); and the fully adjusted model (OR: 0.10, 95% CI: 0.03, 0.27, p = 0.02). The children of women in the Restricting/Excessive-exercising group were found to have lower odds than unexposed children of making errors in the recognition of fearful faces, though this difference only trended towards significance in the minimally adjusted model (OR: 0.47, 95% CI: 0.22, 1.03, p = 0.06); and the fully adjusted model (OR: 0.48, 95% CI: 0.22, 1.06, p = 0.07). The children of women in the Bingeing group trended towards having almost twice the odds than unexposed children of misattributing faces as fearful in the minimally adjusted model (OR: 1.90, 95% CI: 0.92, 3.93, p = 0.08); and the fully adjusted model (OR: 0.94, 95% CI: 0.94, 4.06, p = 0.07). No other statistically significant differences were found between exposed and unexposed groups (see table 41).

Table 41 Logistic Regression Analysis of Children's DANVA Scores: comparison between exposed and unexposed groups (odds ratios and 95% confidence intervals).

		n(%)	**Model 1** OR (95% C.I.)	**Model 2** OR (95% C.I.)
Happy Faces	Unexposed	571 (72.8)	Ref.	Ref.
(≥ 1 error)	R & EE	76 (9.7)	0.83 (0.45, 1.54)	0.82 (0.44, 1.53)
	Purging	44 (5.6)	0.99 (0.46, 2.15)	0.97 (0.47, 1.99)
	Bingeing	44 (5.6)	1.77 (0.88, 3.55)	1.78 (0.88, 3.58)
	B+P	49 (6.3)	0.91 (0.44, 1.91)	0.87 (0.41, 1.84)
Sad Faces	Unexposed	571 (72.8)	Ref.	Ref.
(≥ 2 errors)	R & EE	76 (9.7)	0.60 (0.29, 1.23)	0.59 (0.29, 1.18)
	Purging	44 (5.6)	0.87 (0.38, 2.00)	0.87 (0.38, 1.97)
	Bingeing	44 (5.6)	1.68 (0.79, 3.59)	1.71 (0.80, 3.66)
	B+P	49 (6.3)	0.64 (0.27, 1.52)	0.62 (0.57, 0.67)
Angry Faces	Unexposed	571 (72.8)	Ref.	Ref.
(≥ 4 errors)	R & EE	76 (9.7)	0.84 (0.41, 1.71)	0.84 (0.41, 1.72)
	Purging	44 (5.6)	0.99 (0.42, 2.33)	0.99 (0.42, 2.32)
	Bingeing	44 (5.6)	0.79 (0.31, 2.01)	0.81 (0.32, 2.06)
	B+P	49 (6.3)	1.08 (0.48, 2.42)	1.07 (0.47, 2.40)
Fearful Faces	Unexposed	571 (72.8)	Ref.	Ref.
(≥ 3 errors)	**R & EE**	**76** (9.7)	**0.47 (0.22, 1.03)§**	**0.48 (0.22, 1.06)§**
	Purging	44 (5.6)	0.61 (0.26, 1.46)	0.61 (0.27, 1.35)
	Bingeing	44 (5.6)	1.21 (0.57, 2.57)	1.25 (0.58, 2.67)
	B+P	49 (6.3)	0.66 (0.28, 1.57)	0.64 (0.27, 1.52)
Misattributed	Unexposed	571 (73.2)	Ref.	Ref.
as Happy	R & EE	74 (9.5)	0.51 (0.21, 1.25)	0.51 (0.21, 1.26)
(≥ 4)	Purging	43 (5.5)	0.61 (0.22, 1.68)	0.61 (0.36, 1.02)
	Bingeing	44 (5.6)	1.90 (0.84, 4.27)	1.94 (0.86, 4.38)
	B+P	48 (6.2)	0.70 (0.28, 1.78)	0.70 (0.28, 1.76)
Misattributed	Unexposed	571 (73.2)	Ref.	Ref.
as Sad	R & EE	74 (9.5)	0.93 (0.46, 1.85)	0.93 (0.47, 1.87)
(≥ 3)	**Purging**	**43** (5.5)	**0.10 (0.01, 0.73)***	**0.10 (0.03, 0.27)***
	Bingeing	44 (5.6)	0.87 (0.36, 2.08)	0.88 (0.36, 2.11)
	B+P	48 (6.3)	0.51 (0.19, 1.39)	0.51 (0.19, 1.37)
Misattributed	Unexposed	571 (73.2)	Ref.	Ref.
as Angry	R & EE	74 (9.5)	0.50 (0.19, 1.34)	0.52 (0.19, 1.38)
(≥ 2)	Purging	43 (5.5)	0.82 (0.29, 2.30)	0.83 (0.30, 2.33)
	Bingeing	44 (5.6)	1.14 (0.44, 2.96)	1.16 (0.45, 3.02)
	B+P	48 (6.3)	0.86 (0.31, 2.39)	0.88 (0.32, 2.41)
Misattributed	Unexposed	571 (73.2)	Ref.	Ref.
as Fearful	R & EE	74 (9.5)	0.93 (0.48, 1.81)	0.94 (0.48, 1.83)
(≥ 2)	Purging	43 (5.5)	1.28 (0.59, 2.79)	1.29 (0.87, 1.92)
	Bingeing	**44** (5.6)	**1.90 (0.92, 3.93)§**	**1.95 (0.94, 4.06)§**
	B+P	48 (6.3)	1.44 (0.69, 2.97)	1.40 (0.67, 2.92)
All Faces	Unexposed	571 (72.8)	Ref.	Ref.
(≥ 7 errors)	R & EE	76 (9.7)	0.63 (0.33, 1.21)	0.63 (0.33, 1.23)
	Purging	44 (5.6)	0.66 (0.30, 1.48)	0.65 (0.29, 1.44)
	Bingeing	44 (5.6)	1.09 (0.53, 2.25)	1.15 (0.55, 2.40)
	B+P	49 (6.2)	0.57 (0.26, 1.24)	0.53 (0.24, 1.18)

§ p≤0.1, * p≤0.05, ** p≤0.01

(1) Model 1. Minimally adjusted model: adjusted for child age and gender, and tester. Model 2. Fully adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, and marital stability. Model 3. Fully adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, maternal education, and marital stability.

(2) Table shows odds of children scoring above the established thresholds stated.

Table 42 Number and Percentage of Children Scoring Above the established thresholds on DANVA outcomes across ED groups (split by gender).

		Girls N(%)	Boys N(%)
Happy Faces	Unexposed	51 (17.8)	80 (28.2)
(≥ 1 error)	R & EE	5 (13.9)	11 (27.5)
	Purging	2 (8.3)	8 (40.0)
	Bingeing	7 (29.2)	8 (40.0)
	B+P	3 (12.5)	8 (32.0)
Sad Faces	Unexposed	56 (19.5)	55 (19.4)
(≥ 2 errors)	R & EE	3 (8.3)	7 (17.5)
	Purging	4 (16.7)	4 (20.0)
	Bingeing	5 (20.8)	6 (30.0)
	B+P	2 (8.3)	5 (20.0)
Angry Faces	Unexposed	39 (13.6)	53 (18.7)
(≥ 4 errors)	R & EE	6 (16.7)	5 (12.5)
	Purging	3 (12.5)	5 (25.0)
	Bingeing	3 (12.5)	3 (15.0)
	B+P	5 (20.8)	4 (16.0)
Fearful Faces	Unexposed	66 (23.0)	51 (18.0)
(≥ 3 errors)	R & EE	2 (5.6)	6 (15.0)
	Purging	3 (12.5)	4 (20.0)
	Bingeing	7 (29.2)	4 (20.0)
	B+P	4 (16.7)	3 (12.0)
Misattributed	Unexposed	45 (15.8)	43 (15.6)
as Happy	R & EE	0 (0.0)	6 (15.4)
(≥ 4)	Purging	2 (8.7)	3 (15.0)
	Bingeing	5 (20.8)	5 (25.0)
	B+P	3 (12.5)	3 (12.5)
Misattributed	Unexposed	43 (15.1)	49 (17.8)
as Sad	R & EE	7 (20.0)	5 (12.8)
(≥ 3)	Purging	0 (0.0)	1 (5.0)
	Bingeing	4 (16.7)	3 (15.0)
	B+P	3 (12.5)	2 (8.3)
Misattributed	Unexposed	36 (12.7)	27 (9.8)
as Angry	R & EE	2 (5.7)	3 (7.7)
(≥ 2)	Purging	3 (13.0)	2 (10.0)
	Bingeing	4 (16.7)	2 (10.0)
	B+P	2 (8.3)	3 (12.5)
Misattributed	Unexposed	59 (20.8)	51 (18.5)
as Fearful	R & EE	5 (14.3)	8 (20.5)
(≥ 2)	Purging	4 (17.4)	6 (30.0)
	Bingeing	7 (29.2)	6 (30.0)
	B+P	4 (16.7)	8 (33.3)
All Faces	Unexposed	78 (27.2)	68 (23.9)
(≥ 7 errors)	R & EE	5 (13.9)	8 (20.0)
	Purging	4 (16.7)	5 (25.0)
	Bingeing	7 (29.2)	5 (25.0)
	B+P	3 (12.5)	6 (24.0)

1. Table shows number and percentage of children scoring above the established cut-offs stated.

6.2.4.4 Emotion Recognition from Social Motion Cues in Children at High Risk

The children of mothers in the Bingeing and Purging group exhibited lower accuracy in the scared condition in comparison to unexposed children: this was the case in the minimally adjusted model (B: -0.58, 95% CI: -1.01, -0.15, p = 0.01); and the fully adjusted model (B: -0.60, 95% CI: -1.04, -0.17, p = 0.01). No other statistically significant differences were found between exposed and unexposed groups (see table 43).

Table 43 Linear Regression Analysis of Children's Motion Emotion Recognition Scores: Comparison of exposed and unexposed groups

		n (%)	**Model 1** B (95% C.I.)	**Model 2** B (95% C.I.)
Angry	Unexposed	596 (73.2)	Ref.	Ref.
	R & EE	82 (10.1)	-0.07 (-0.41, 0.27)	-0.05 (-0.39, 0.28)
	Purging	42 (5.2)	0.03 (-0.43, 0.48)	0.02 (-0.44, 0.48)
	Bingeing	44 (5.4)	0.13 (-0.32, 0.57)	0.13 (-0.32, 0.57)
	B & P	50 (6.1)	-0.18 (-0.59, 0.24)	-0.15 (-0.57, 0.27)
Happy	Unexposed	596 (73.2)	Ref.	Ref.
	R & EE	**82** (10.1)	**-0.31 (-0.68, 0.06)§**	**-0.33 (-0.70, 0.05)§**
	Purging	42 (5.2)	-0.16 (-0.67, 0.35)	-0.15 (-0.66, 0.36)
	Bingeing	44 (5.4)	-0.15, -0.65, 0.35)	-0.15 (-0.64, 0.35)
	B & P	50 (6.1)	-0.03 (-0.49, 0.44)	-0.05 (-0.51, 0.42)
Sad	Unexposed	596 (73.2)	Ref.	Ref.
	R & EE	82 (10.1)	-0.13 (-0.42, 0.17)	0.88 (-0.12, 1.88)
	Purging	42 (5.2)	-0.23 (-0.63, 0.17)	-0.24 (-0.64, 0.16)
	Bingeing	44 (5.4)	-0.10 (-0.49, 0.29)	-0.10 (-0.49, 0.29)
	B & P	50 (6.1)	-0.15 (-0.51, 0.22)	-0.12 (-0.49, 0.25)
Scared	Unexposed	596 (73.2)	Ref.	Ref.
	R & EE	82 (10.1)	-0.02 (-0.36, 0.33)	-0.02 (-0.36, 0.33)
	Purging	42 (5.2)	0.03 (-0.44, 0.50)	0.02 (-0.45, 0.49)
	Bingeing	44 (5.4)	0.12 (-0.34, 0.57)	0.12 (-0.34, 0.57)
	B & P	50 (6.1)	**-0.58 (-1.01, -0.15)****	**-0.59 (-1.02, -0.16)****

§ p≤0.1, * p≤0.05, ** p≤0.01

(1) Model 1. Minimally adjusted model: adjusted for child age and gender, and tester. Model 2. Fully adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, and marital stability.

(2) Higher scores represent better performance.

Table 44 Mean (SD) scores for girls and boys on the Emotional Triangles Task Outcomes across ED groups

		Girls		Boys	
		N	M (SD)	N	M (SD)
Angry	Unexposed	288 (70.8)	2.47 (1.37)	308 (75.7)	2.61 (1.41)
	R & EE	41 (10.1)	2.35 (1.69)	41 (10.1)	2.54 (1.66)
	Purging	24 (5.9)	2.40 (1.47)	18 (4.4)	2.63 (1.38)
	Bingeing	29 (7.1)	2.66 (1.25)	15 (3.7)	2.69 (1.35)
	B & P	25 (6.1)	2.50 (1.94)	25 (6.1)	2.43 (1.69)
Happy	Unexposed	288 (70.8)	2.12 (1.50)	308 (75.7)	2.54 (1.66)
	R & EE	41 (10.1)	2.09 (1.59)	41 (10.1)	1.87 (1.61)
	Purging	24 (5.9)	1.91 (1.74)	18 (4.4)	1.96 (1.60)
	Bingeing	29 (7.1)	2.00 (1.59)	15 (3.7)	2.01 (1.65)
	B & P	25 (6.1)	2.48 (1.50)	25 (6.1)	2.10 (1.68)
Sad	Unexposed	288 (70.8)	1.72 (1.26)	308 (75.7)	1.63 (1.27)
	R & EE	41 (10.1)	1.65 (1.25)	41 (10.1)	1.52 (1.30)
	Purging	24 (5.9)	1.46 (1.35)	18 (4.4)	1.45 (1.19)
	Bingeing	29 (7.1)	1.66 (1.48)	15 (3.7)	1.57 (1.33)
	B & P	25 (6.1)	1.54 (1.53)	25 (6.1)	1.50 (1.27)
Scared	Unexposed	288 (70.8)	1.94 (1.50)	308 (75.7)	2.16 (1.50)
	R & EE	41 (10.1)	2.01 (1.61)	41 (10.1)	2.15 (1.52)
	Purging	24 (5.9)	1.83 (1.48)	18 (4.4)	2.18 (1.45)
	Bingeing	29 (7.1)	2.19 (1.17)	15 (3.7)	2.20 (1.22)
	B & P	25 (6.1)	1.52 (1.56)	25 (6.1)	1.57 (1.68)

(1) Higher scores represent better performance.

6.2.4.5 Social Communication in Children at High Risk

Maternal Bingeing + Purging was predictive of children scoring above the threshold of at least 9 out of 24 on the SCDC in the minimally adjusted model (OR: 2.40, 95% CI: 1.07, 5.39, p = 0.03); and the fully adjusted model (OR: 2.59, 95% CI: 1.13, 5.93, p = 0.02). No other statistically significant differences were observed between exposed and unexposed groups (see table 45).

Table 45 Logistic Regression Analysis of Children's SCDC Scores: Comparison of exposed and unexposed groups (odds ratios and 95% confidence intervals)

	n (%)	**Model 1** OR (95% C.I.)	**Model 2** OR (95% C.I.)
Unexposed	751 (73.2)	Ref.	Ref.
R & EE	104 (10.1)	1.29 (0.61, 2.73)	1.35 (0.63, 2.90)
Purging	52 (5.1)	1.36 (0.47, 4.00)	1.31 (0.44, 3.91)
Bingeing	59 (5.8)	1.77 (0.72, 4.38)	1.86 (0.75, 4.65)
B & P	60 (5.8)	**2.40 (1.07, 5.39)***	**2.59 (1.13, 5.93)***

§ p≤0.1, * p≤0.05, ** p≤0.01
(1) Model 1. Minimally adjusted model: adjusted for child age and gender, and tester. Model 2. Fully adjusted model: adjusted for child age and gender, tester, social class, maternal age at delivery, and marital stability.
(2) Table shows odds of children scoring above the established SCDC threshold of ≥ 9 out of 24.

Table 46 Number and percentage of girls and boys scoring above the threshold on the Emotional Triangles Task Outcomes across ED groups

	Girls n %	Boys n %
Unexposed	1 (0.3)	1 (0.3)
R & EE	1 (2.0)	8 (12.7)
Purging	1 (3.3)	3 (13.6)
Bingeing	1 (2.9)	5 (20.8)
Bingeing & Purging	4 (13.8)	4 (12.9)

(1) Table shows number and percentage of children scoring above the established SCDC threshold of ≥ 9 out of 24.

6.2.4.6 Task Performance across Gender Groups

As stated above, exposed groups were too small to run separate analysis by gender; however the sensitivity analysis revealed no differences in performance between genders that could be considered reliable when taking into consideration sample size (see tables 42, 44 and 46).

6.2.5 Interim Discussion

The aim of this study was to investigate social communication and emotion recognition abilities in children at high risk of developing an ED, using maternal lifetime ED behaviours as a risk marker. Overall the results of statistical analyses suggest that there may be a systematic disturbance in the recognition of fear in children at high risk when compared to unexposed children: with a trend towards children of women with a Restricting/Excessive Exercising phenotype having comparatively lower odds of making errors in the recognition of fear from faces; a trend towards women with a Bingeing phenotype having comparatively higher odds of misattributing facial expressions as fearful; and maternal Bingeing and Purging being significantly associated with children exhibiting comparatively poorer performance in the recognition of fear from social motion cues. In addition, maternal Purging was associated with children having comparatively lower odds of misattributing faces as sad. With regard to social communication, maternal Bingeing and Purging was associated with children having comparatively higher odds of scoring above the threshold of at least 9 out of 24 on the SCDC, indicating social communication deficits. Due to this study being exploratory in nature, significance levels have not been adjusted for multiple testing. As a result, it is possible that some findings are a result of chance. These findings are discussed in more detail below.

6.2.5.1 Social Communication

In contrast to the findings from study one (where children's high risk status was determined via maternal self-report of an ED diagnosis) the findings from this study found that children at high risk of developing an ED, due to being born to mothers exhibiting a Bingeing and Purging phenotype, had more than twice the odds as unexposed children of scoring above the threshold of at least 9 out of 24 on the SCDC; indicating substantial social communication deficits. As can be seen from the summary above, the children of mothers exhibiting a Bingeing and Purging phenotype also exhibited significantly poorer performance in the recognition of fear from social motion cues, as measured by the Emotional Triangles Task. In addition, this group of children showed comparatively poorer performance in the recognition of happiness, sadness and anger on this task, but differences did not reach significance. This could be an indication that deficits in emotion recognition may be associated with, or perhaps even contribute to, impaired social communication in this group. The literature pertaining to clinical groups indicates an association between ED diagnosis and impaired social communication in the acute phase of illness (e.g. Hartmann, et al., 2010; Hudson, Hiripi, Pope, et al., 2007; V. V. McIntosh, Bulik, McKenzie, Luty, & Jordan, 2000). Also, research investigating the presence of comorbid disorders associated with impaired social functioning suggest that problems in the social domain may be present prior to onset of an ED (Zucker, 2007). Our findings may lend support to this theory by finding impaired social communication in children at high risk of developing an ED. However, it is important to note that the SCDC was completed by mothers and difficulties in social communication reported for children at risk may actually reflect social communication problems in the mothers.

6.2.5.2 Fear Recognition

Performance of children at high risk, on both emotion recognition tasks, indicates some level of disturbance in fear processing. The difference in performance on the Emotional Triangles task reached statistical significance, with the children of women exhibiting a Bingeing and Purging phenotype showing decreased recognition of fear

from social motion cues in comparison to unexposed children. Differences observed between exposed and unexposed children on the DANVA only trended towards significance: with the children of women with a Restricting/Excessive Exercising phenotype having lower odds of making errors when recognising fear from faces; and the children of women with a Bingeing phenotype having higher odds of misattributing faces as fearful. As mentioned above, it is possible that these findings are due to chance as significance levels were not adjusted for multiple testing; however there is evidence in the literature of ED patients also showing a disturbance in the processing of fear. Kucharska-Pietra and colleagues found that AN patients were impaired in their recognition of fear, and this association remained significant after adjusting for a variety of clinical and socio-demographic factors (Kucharska-Pietura, et al., 2003). Interestingly, Jansch and colleagues found that AN patients taking medication misclassified more faces as fearful, while un-medicated patients did not (Jänsch, et al., 2009). Problematic fear recognition has also been observed in a sub-clinical population. Ridout and colleagues found that in comparison to women with low levels of ED symptoms, women with high levels of ED symptoms showed specific deficits in the recognition of fear and anger, making more fear-as-anger and anger-as-fear misclassifications (Ridout, et al., 2012). The results of study four in this thesis also showed a trend towards high risk children having disturbed fear processing, with children of women reporting AN+BN having higher odds than unexposed children of misattributing faces as fearful. The various findings in this chapter regarding differential fear processing are difficult to compare, and it is hard to draw any clear conclusions; it does seem however that children at high risk of developing an ED show a systematic disturbance in the recognition of fear, and this requires further investigation. It is possible that the recognition of fear is associated with some other factor of the ED phenotype, rather than ED diagnosis or behaviours.

6.2.5.3 Sadness Recognition

As stated in the summary of findings above, the children of women exhibiting a Purging phenotype had lower odds than unexposed children of misattributing faces as

sad, and this is a particularly difficult finding to interpret. Evidence in the literature investigating clinical groups suggests that AN patients are impaired in their recognition of sadness from faces (Castro, et al., 2010; Pollatos, 2008). It is possible that children at risk attend to facial cues of sadness less than unexposed children, making them less likely to misattribute faces as sad when making errors; a trait that may be exaggerated in clinical groups leading to a deficit in recognising sadness from facial expression. This however is speculation, and further investigation is required before conclusions can be drawn.

6.2.5.4 Happiness Recognition

Studies investigating the recognition of individual emotions from faces by clinical AN groups consistently shows impaired recognition of negative emotions, but no deficits with regard to the recognition of happiness (Oldershaw, et al., 2011). In addition, one study investigating the recognition of happiness and sadness only found that AN patients were impaired in their recognition of sad faces, but no differences were observed between AN patients and controls in the recognition of happy faces (Castro, et al., 2010). Consistent with this evidence, which suggests that deficits in the recognition of happiness are not associated to the ED phenotype, the findings from this study also found no differences in happiness recognition between children at high risk and children who are not, on either emotion recognition task.

Interestingly, there is some evidence of impaired happiness recognition in a subclinical population thought to be at comparatively high risk of developing an ED. Jones and colleagues compared the facial emotion recognition capacities of women exhibiting high and low levels of ED related symptoms, and found that women exhibiting high levels of ED related symptoms were less accurate when recognising happy faces (Jones, et al., 2008). It is possible that happiness recognition may be impaired in a subgroup of high risk individuals that do not go on to develop a clinical ED, but it is difficult to draw any conclusions regarding this due to the paucity of evidence in the field.

6.2.5.5 Anger Recognition

Though there is a great deal of evidence suggesting that patients with AN exhibit deficits in the recognition of negative emotions from faces, studies that have investigated the recognition of individual emotions have not found impairments in the recognition of anger specifically (Oldershaw, et al., 2011). Consistent with this evidence, which suggests that deficits in the recognition of anger are not associated to the ED phenotype, the findings from this study also found no differences in anger recognition between children at high risk and children who are not, on either emotion recognition task.

6.3 Chapter Conclusions

As discussed in chapter 3 (Aims and Methodology) findings from studies using maternal self-report diagnosis of an ED as an indicator of risk in children cannot be directly compared with findings from studies using maternal ED behaviours over lifetime as an indicator of risk. This is due to the fact that data on maternal ED diagnosis were collected by ALSPAC at 12 weeks gestation, whereas data on maternal ED behaviours were collected when index children were between 18 and 20 years of age. This means that data on maternal ED behaviours are inclusive of any ED symptoms with an onset after the pregnancy of the study child, while data on self-report diagnosis are not. Findings regarding social communication and emotion recognition from the two studies in this chapter are very different: with differences being observed between exposed and unexposed groups in the sample of children for whom high risk is defined by maternal ED behaviours; but little difference found between exposed and unexposed groups in the sample of children for whom high risk is defined by maternal self-report of ED diagnosis. It is possible that this difference is associated with maternal lifetime ED behaviours being closer to a core phenotype and therefore a better predictor of children's social communication and emotion recognition capacities. It is also possible that the presence of an ED after birth of the index child is in some way more detrimental to children's capacity to communicate and recognise emotions. As outlined above, and in chapter 2, there is a great deal of evidence to suggest that women with an ED exhibit interpersonal deficits and deficits in emotion recognition. Perhaps maternal deficits in social cognition have some effect on the development of these constructs in children, rather than impairments being traits that are intermediate phenotypes of the eating disorder itself. This is not something that can be determined from the findings in this thesis, but should be investigated in future research. If the social cognition of children whose mothers have an eating disorder has the potential of developing abnormally due to maternal deficits, it is vitally important that interventions are developed to reduce the impact of this differential development in adolescence and adulthood.

Strengths and Limitations

Strengths and limitations of the studies in this chapter are detailed in the strengths and limitations section of the thesis (Chapter 7: Strengths and Limitations).

Chapter 7

General Discussion & Conclusions

Evidence suggests that diagnosis of an ED is associated with differential neuropsychological and social functioning. This has been observed both during the acute phase of illness and in recovery. Current research makes it difficult to be definitive about whether the differential processing observed is present prior to onset of an ED. It is possible that the deficits observed in patient groups are due to secondary features of the disorder, while continuing differences observed in recovered groups may be a result of scarring. Differences in neuropsychological functioning and social cognition that are present prior to onset may affect risk status for the development of an ED. One method of exploring differences in cognitive functioning prior to onset of a psychological disorder is to investigate populations that are at higher risk of developing that disorder. Family, twin and adoption studies have shown that the first degree relatives of probands are at higher risk of developing an ED themselves than the general population. The studies in this thesis attempt to explore the presence of pre-morbid differences in neuropsychological and social functioning by investigating a group at high risk: the children of mothers with a lifetime ED.

There are a small number of studies in the literature that have investigated executive functioning in the first degree relatives of probands. Findings from these studies suggest that deficits in cognitive flexibility and central coherence are not only present in ED patients, but also in their unaffected sisters. Unfortunately these studies are limited by the small samples employed. In addition, high risk studies in the field of ED ideally need to be conducted with samples young enough not to have developed severe ED related cognitions or behaviours. The studies in this thesis are the first to investigate neuropsychological functioning and social cognition in a community sample of children that are at high risk, i.e. a *large* sample at a *young* age (8 to 13 years old).

As described in chapter two, there are limitations associated with the diagnostic criteria for ED that have an effect on research findings; and observable behavioural phenotypes are likely to have a more direct relationship with cognitive functioning than ED diagnoses. In this thesis, high risk status in the children was defined in two ways: (i) maternal self-report of an ED diagnosis prior to birth of the index child; and (ii) maternal ED behaviours experienced over lifetime. The studies in this thesis are the first to use behavioural ED phenotypes in combination with the high risk research design.

This chapter provides a summary of the findings from the studies in this thesis. In depth discussion that places these findings in context, providing comparison with current evidence can be found in the relevant discussion sections of each study (chapters 4 and 6). This chapter is a discussion of the most interesting findings from these studies with possible interpretations; also making reference to clinical implications and avenues for future research.

7.1 Neuropsychological Functioning in Children at High Risk of Developing an ED.

7.1.1 Study 1. Intelligence, Global Cognition and Executive Functioning in Children at High Risk of Developing an ED: Summary of Results

In study one, high risk status in the children was defined by maternal self-report of an ED prior to birth of the index child. Results showed that in comparison to unexposed children, children at high risk of developing an ED due to being born to a mother with AN, showed higher IQ, superior working memory, decreased attentional control and selective attention, and possibly a subtle decrease in behavioural inhibition. None of these constructs have previously been investigated in the first degree relatives of probands, however all of these differences have previously been observed in AN patients during the acute phase of illness, and in some cases during recovery (e.g. Dobson & Dozois, 2004; Galimberti, et al., 2011; Hatch, et al., 2010; Lopez, et al., 2010).

Children at high risk of developing an ED, due to being born to a mother with BN, showed comparatively poor visual organizational ability and visual motor coordination; and possibly a subtle decrease in behavioural inhibition. Research pertaining to the cognitive functioning of BN patients is limited and conflicting (Van den Eynde, Guillaume, et al., 2011), but there is some evidence of similar deficits being present in clinical groups (e.g. I. Gillberg, et al., 2007; Kemps & Wilsdon, 2009). The findings from this study implicate high IQ, superior working memory, decreased attentional capacity, poor visuo-spatial functioning, and possibly poor behavioural inhibition, as putative intermediate phenotypes of ED.

7.1.2 Study Two. Do Maternal Lifetime ED Behavioural Phenotypes Predict Children's Neuropsychological Functioning?: Summary of Results

In study two, high risk status of the children was defined by maternal ED behaviours experienced over lifetime. Results showed that children at high risk due to being born to women with a restricting/excessive exercising phenotype showed comparatively high IQ. Children at high risk due to being born to women with a Purging phenotype showed good logical thinking and verbal capacities; but comparatively poor selective attention/information processing and sustained attention. Children at high risk due to being born to women with a Bingeing phenotype showed comparatively poor verbal abilities; and children at high risk due to being born to women with a Bingeing and Purging phenotype showed comparatively poor visuo-spatial ability. Though there is evidence to suggest that all of these differences are present in ED patients (see above), research has not specifically explored the association between these cognitive structures and behavioural phenotypes in clinical groups. Like the findings of study one, the results of this study also implicate high IQ, superior working memory, decreased attentional capacity, and poor visuo-spatial functioning, as putative intermediate phenotypes of ED. Unlike the findings from study one, exposed and unexposed groups showed no differences in behavioural inhibition; though in study one the differences observed only trended towards statistical significance.

7.1.3 Possible Interpretations and Clinical Implications

Common findings from the two studies in this chapter are that children at high risk show comparatively better intellectual functioning (maternal AN/Restricting and Excessive Exercising), and superior working memory (maternal AN/AN+BN/Bingeing and Purging); however they also show poor visuo-spatial processing (maternal BN/Bingeing and Purging). Additional findings from study one (that were not observed in study two) were that children at high risk showed superior visuo-spatial functioning (maternal AN), comparatively poor attentional control (maternal AN), and

decreased selective attention (maternal AN). There was also some evidence to suggest that children at risk showed decreased behavioural inhibition (maternal AN/BN). An additional finding in study two, that was not present in study one, was that children at high risk showed poor sustained attention (maternal Purging) in comparison to unexposed children.

As discussed in chapter three, the superior intellectual functioning found in children at high risk (AN/Restricting and Excessive Exercising) is consistent with evidence in the literature of a diagnosis of AN being associated with high IQ (Lopez, et al., 2010). Taken together, these findings suggest that superior intellectual functioning may be an underlying trait associated with the AN/Restricting ED phenotype which is: (i) independent of illness state; (ii) present prior to onset of an ED; and (iii) a putative intermediate phenotype.

In both physical and psychological fields, premorbid intellectual functioning has been associated with cognitive reserve: defined as the level of cognitive capacity an individual has prior to onset of disease or injury. Evidence suggests that high cognitive reserve predicts one's ability to sustain greater brain injury before exhibiting functional deficits (Stern, 2003). High premorbid IQ/cognitive reserve has been shown to be a predictor of better treatment outcome for disorders such as schizophrenia (Barnett, Salmond, Jones, & Sahakian, 2006), and autism (Howlin, Magiati, Charman, & MacLean, 2009). The findings of one recent study suggest that there may be a similar association in ED, with high premorbid IQ being predictive of better neuropsychological improvement in AN patients during recovery (Keifer, et al., 2010). This is certainly something that requires further investigation.

Of interest is that in study one of this chapter (risk status defined by maternal diagnoses), maternal AN was predictive of both superior (intellectual ability, visuo-spatial processing and working memory) and inferior (attentional control) cognitive functioning. However, in study two (risk status defined by maternal lifetime behavioural phenotype), maternal Restricting/Excessive Exercising was only

predictive of superior functioning (intellectual ability). It may be that generally good neuropsychological functioning/cognitive reserve is part of the core pathology of restricting only ED, and may be associated with decreased risk for the development of other ED behaviours (i.e. bingeing/purging) over the course of illness. In other words, it is possible that high cognitive reserve, in a sub-group of patients with restricting AN, is in some way associated with lower risk of cross-over to an AN-BP, BN, or EDNOS diagnosis. An alternative explanation is that high intellectual functioning/cognitive reserve and a lifetime Restricting/Excessive Exercising phenotype are both the consequence of a third factor. For example, traits characteristic of individuals with AN-R: such as perfectionism, perseverance, and persistence (the desire to do well and to keep trying in the face of adversity); could contribute to success in intellectual learning and cognitive development, while also preventing the use of bingeing or purging behaviours which could be thought of as a consequence of "failure" in the quest for low weight.

The findings from these studies provide grounding for further investigation regarding the association between intelligence and ED. For example, do patients with high IQ have better prognosis, or respond better to treatment; are they less likely to cross-over into a different ED diagnosis; how could the high IQ observed be incorporated into treatment; and does IQ decline for patients with a particularly long duration of illness? Future research may make it possible to predict which patients are at high risk of developing bingeing/purging behaviours based on intellectual functioning or level of perfectionist traits at first presentation. Evidence of superior intellectual functioning should be taken into account in clinical practice, and doing so may have a positive effect on the therapeutic relationship. Due to the individual variation in intellectual functioning however, it may be worth testing ED patients individually rather than assuming this to be the case. This could be important to prevent the overestimation of intellectual functioning for some, which may in turn have a detrimental effect on therapy.

The findings from this chapter suggest that maternal BN/Bingeing and Purging phenotype specifically is associated with poor visuo-spatial functioning and motor coordination in children. Despite evidence of impaired visuo-spatial functioning being associated with a diagnosis of AN in the literature (e.g. Favaro, et al., 2012; Tenconi, et al., 2010), maternal AN was associated with comparatively better visuo-spatial functioning in children (study one). Potential reasons for this have been discussed extensively in the discussion for study one. It is worth noting however that the potential association between poor visuo-spatial functioning and AN is based on research using current ED diagnosis to categorize patients. It is possible that poor visuo-spatial processing may in some way be associated with high risk of developing bingeing/purging behaviours, leading to diagnostic cross-over.

Deficits in visuo-spatial processing may directly or indirectly contribute to the disturbance in body image exhibited by ED patients (Frampton, 2012), possibly causing a bias in visual processing that is associated with the distortion of body image associated with diagnosis of an ED. Our findings suggest that the poor visuo-spatial functioning that has been observed in ED groups may also be present prior to onset. The deficits observed in these children at risk are subtle but significant. It is possible that the subtle deficits observed here at age 8 become more severe during adolescence, or are accentuated by the development of an ED. The findings from this chapter indicate a need for further research investigating premorbid visuo-spatial functioning. Longitudinal studies investigating the development of such deficits would be helpful in understanding how these subtle impairments may eventually affect the development of a distorted body image; and in turn help to create interventions focusing on improving this ability, with the aim of preventing such a deficit from contributing to the development of an ED.

The results from both of the studies in this chapter provide evidence for subtle impairments in attentional processing in children at high risk. In study one maternal AN was associated with poor attentional control/attentional inhibition and poor selective attention/information processing in children. Findings differed slightly in

study two, with a maternal Purging phenotype being associated with poor selective attention/information processing and decreased sustained attention. Considering the findings from both studies, it appears that attentional impairments are associated with an ED phenotype that is characterized by purging but not bingeing. It has been suggested that attentional deficits in ED groups may be associated with the attentional bias that is observed towards weight, shape and food; and the inability to divert/inhibit attention from these stimuli (Zucker, Moskvich, & Soo, 2011). The construct of information processing/selective attention particularly is thought to be associated with individuals being more attentive to these ED relevant stimuli than healthy controls (Dobson & Dozois, 2004).

Research investigating attentional capacity in ED patients has provided mixed findings on a range of attentional constructs, and it has been suggested that deficits in working memory may underlie observed deficits in attention (Green, et al., 1996b). The findings of this chapter found no deficits in working memory within children at high risk, suggesting that the observed deficits in attention are unrelated to impairments in working memory. It is also conceptually possible that problems with selective attention underlie the visuo-spatial deficits associated with ED; however the findings from these studies suggest that visuo-spatial impairments are more likely to be associated with a bingeing and purging phenotype while attentional impairments seem more likely to be associated with a restricting/purging phenotype.

The act of attending to any stimuli varies as a result of (i) that which requires attention, and (ii) the surrounding environment in which an individual is required to attend: i.e. whether one is required to attend to two or more stimuli simultaneously; whether it is necessary to switch between different stimuli; or whether attending to a stimulus also necessitates the inhibition of other distracting stimuli. As a result, attention cannot be regarded as a single construct (Manly, et al., 2001). Poor performance on the attentional control task used in this thesis is thought to indicate a decreased ability to inhibit a well learned pre-potent response. This deficit in attentional control could translate into an inability to inhibit the pathological (food,

shape and weight related) thoughts and behaviours common to AN, and a perseveration of these thoughts and behaviours in the face of both physical and social impairment. In addition, the lack of ability to inhibit a pre-potent response could contribute to the deficit in cognitive flexibility, for which there is a great deal of evidence in the literature (e.g. Tchanturia, et al., 2012; Tchanturia, et al., 2011).

The results from these studies implicate poor attentional functioning as a putative intermediate phenotype for ED of a restricting/purging phenotype. This basic impairment may make individuals more vulnerable to developing a selective attentional bias towards their own body during adolescence, a period of substantial change; in turn increasing vulnerability for the development of disordered eating. An intervention aimed at improving attentional capacity within vulnerable groups may prevent such impairment from contributing to the development of an ED in later life. It is also possible that lack of success in treatment may be associated with attentional deficits and problems with information processing, as well as or instead of resistance to therapy. Targeting attentional deficits during therapy may improve treatment outcome.

Recent research increasingly implicates superior working memory as a core symptom of AN (e.g. Brooks, et al., 2012; Dickson, et al., 2008; Fowler, et al., 2006). Interestingly, findings from chapter four found superior working memory in the children of women with AN and AN+BN (study one); and in the children of women exhibiting a Bingeing and Purging phenotype (study two). It is worth noting that in study one, high risk status due to maternal AN+BN was more strongly associated with superior working memory than maternal AN. This could indicate a relationship between superior working memory and ED with a bingeing and purging phenotype.

The mixed findings in this chapter regarding behavioural inhibition in children at risk are consistent with the mixed findings from studies investigating behavioural inhibition in clinical ED groups. Though some patients with AN-R consistently maintain their level of control, successfully restricting their eating over long periods;

many experience a breakdown of this control, leading to symptom fluctuation and diagnostic cross-over to AN-BP and then to BN (Tozzi, et al., 2005). This could either mean that inhibitory control changes over time or that the vulnerability for this to occur was present prior to onset and prevented by some other factor, cognitive or otherwise. Mixed findings in the literature and in study one of this thesis may reflect an association between behavioural inhibition and diagnostic cross-over that is not yet understood.

Steiger and colleagues have proposed an association between binge eating and poor inhibitory control in BN (Steiger, Lehoux, & Gauvin, 1999). It is possible that tasks assessing the inhibition of behaviours that are in response to external cues are not ideal for assessing behavioural inhibition in ED groups. The inability to inhibit behaviours such as bingeing may well be due to basic cognitive processes associated with behavioural inhibition. However, tasks assessing the inhibition of behaviours in response to internal, rather than external, stimuli may be more efficient at detecting such a disturbance. In addition, behavioural tasks assessing inhibitory control are generally administered in a neutral environment, and this was also the case for the studies in this thesis. This means that factors which may influence the ability to inhibit behavioural responses in everyday life such as environmental triggers or autonomic arousal are not accounted for, limiting the generalisability of findings. Though only subtle to no observable differences were found between exposed and unexposed groups, it is possible that under different conditions there would be observable differences in inhibitory control.

The decreased performance on measures of attentional and (possibly) behavioural inhibition exhibited by children at risk could represent decreased executive control (top down) processes. This could lead to a decreased ability to inhibit negative reactions (bottom up) (Claes, et al., 2011), and make children at risk more vulnerable to the use of negative coping mechanisms. Inhibitory dysfunction could also be a barrier to treatment (Lauer, et al., 1999). A cognitive remediation therapy (CRT) that focuses on inhibitory control may be a good addition to treatment, perhaps in

combination with existing CRT for ED which focuses on cognitive inflexibility and weak central coherence (Tchanturia, Davies, & Campbell, 2007).

Evidence suggests that a high number of cognitive deficits is associated to poorer post-treatment prognosis for ED (Hamsher, Halmi, & Benton, 1981; Szmukler, et al., 1992); and that ED symptoms decrease upon treatment of cognitive problems (Lena, et al., 2004). These findings make treatment focused on basic cognitive functions an attractive and viable addition to other therapies. Clinicians should be cautious however when applying findings based on mean group scores for neuropsychological tests to individual patients, as evidence suggests that individual patients with AN exhibit varying neuropsychological profiles (Rose, Frampton, & Lask, 2012). Individual assessments of patients may be useful prior to the utilization of specific cognitive based treatments such as cognitive remediation therapy (Tchanturia, et al., 2007).

The neuropsychological profile of our high risk groups contrast with the profile of individuals at high risk for developing schizophrenia. This suggests that our findings are likely to be specific to the development of an ED, rather than the development of psychological disorders in general. Research into the neuropsychological profile of individuals at high risk for schizophrenia has revealed low IQ scores (TIQ = 98.48) in comparison to controls (TIQ = 105.15), and comparatively poor performance on all measures of memory (e.g Byrne, Hodges, Grant, Owens, & Johnstone, 1999); while this sample of children at high risk for ED exhibit high IQ and superior working memory. Similarly to the children in this sample however, individuals at high risk for schizophrenia also exhibit decreased attentional control/attentional inhibition. It may also be the case that our high risk group shows similarities with individuals at high risk for Obsessive Compulsive Disorder (OCD). Impaired behavioural inhibition has also been observed in OCD patients and their unaffected first-degree relatives (e.g. Chamberlain, et al., 2007). This suggests that impaired behavioural inhibition could be an underlying trait in both AN and OCD, two disorders that are often speculated to be part of the same spectrum (e.g. Altman & Shankman, 2009; Bellodi, et al., 2001), and

which present clinically through an inability to inhibit particular pathological behaviours.

7.2 Social Cognition in Children at High Risk of Developing an Eating Disorder

7.2.1 Study Four. Social Communication and Emotion Recognition in Children at High Risk of Developing an Eating Disorder: Summary of Results

In study four, high risk status in the children was defined by maternal self-report of an ED prior to birth of the index child. Results showed little difference in social communication and emotion recognition capacity between the children at high risk, and the children who were not.

Children at high risk of developing an ED, due to being born to mothers with AN+BN, showed higher odds than unexposed children of misattributing faces as fearful; though this difference only trended towards significance.

7.2.2 Study Five. Are Maternal Lifetime ED Behavioural Phenotypes a Better Predictor of Children's Social Communication and Emotion Recognition: Summary of Results

In study five, high risk status in the children was defined by maternal ED behaviours experienced over lifetime. Results showed that in comparison to unexposed children, children at high risk of developing an ED due to being born to women with a Restricting/Excessive Exercising phenotype had lower odds of making errors in the recognition of fear from faces and exhibited poorer recognition of happiness from social motion cues. Children at high risk due to being born to women with a Purging phenotype had comparatively lower odds of misattributing faces as sad; and children at high risk due to being born to women with a Bingeing phenotype had comparatively higher odds of misattributing faces as fearful. Children at high risk due to being born to women with a Bingeing and Purging phenotype showed

comparatively poor performance in the recognition of fear from social motion cues, and also had higher odds of exhibiting deficits in social communication.

7.2.3 Possible Interpretations and Clinical Implications

The common finding from the two studies in this chapter was that children at high risk of developing an ED, due to being born to a mother with AN+BN (study one) or a mother exhibiting a Bingeing phenotype (study two), had higher odds of misattributing faces as fearful. It is interesting to note however that the majority of the additional differences observed between exposed and unexposed children in study two were also related to fear processing. Maternal Restricting/Excessive Exercising was found to be associated with children having lower odds of making errors in the recognition of fear from faces, and maternal Bingeing and Purging was found to be associated with children having comparatively poor recognition of fear from social motion cues.

These findings are particularly interesting in light of Strober's theory that an underlying causal factor for development of AN may be a susceptibility to extreme fear conditioning accompanied by an increased resistance to fear extinction (Strober, 2004). Strober notes parallels between phobic anxiety and the morbid fear of weight gain that is observed in patients with ED, suggesting etiological links between AN and anxiety. This possible association has been posited by many due to the increased rates of both premorbid and comorbid anxiety disorders within ED patients (e.g. Bulik, Sullivan, Fear, & Joyce, 1997; Herman & Polivy, 1980); and the prevalence of anxious personality traits in women with ED such as harm avoidance, restraint, and perfectionism. It is possible that one genetically inherited trait affecting risk status for the development of an ED, is a disturbance in the way that fear is attended to, perceived and learned; and this may be a trait shared with anxiety disorders. Interestingly, a study using positron emission tomography found some evidence for an over-expression of the neuronal circuitry that is involved with the regulation of fear conditioning, within weight recovered AN women (Holender, 1986).

Strober suggests that based on his hypothesis, the first-degree relatives of AN probands should show differences in fear processing/learning in comparison to the relatives of healthy controls. This is in line with the results of these studies; not only in the children of mothers with AN+BN, but also in the children of women exhibiting Restricting/Excessive Exercising, Bingeing, and Bingeing and Purging phenotypes. It is possible that Strober's theory may extend across all EDs rather than being specific to AN. In addition to differential fear processing, children at high risk also exhibited differences in the recognition of sadness and happiness. Social perception is fundamental to effective social interaction, and requires one to infer the motivations and emotions of others from a variety of cues. The results of this study suggest that impairments in emotion recognition from both facial cues and social motion cues are present in children at high risk. This kind of impairment can make complex social inferences challenging and may contribute to impaired development of social communication.

In comparison to the children of unexposed mothers, children at high risk due to being born to women with a Bingeing and Purging phenotype had over twice the odds of having high scores on the Social and Communication Disorders Checklist (SCDC); designed to measure social reciprocity and other verbal/non-verbal social traits that are characteristic of ASD. A high score is indicative of deficits in social communication typical of the ASD spectrum. This finding is consistent with a previous study which also found that the first degree relatives of ED probands (initially presenting with a diagnosis of AN) exhibit ASD like symptoms of social impairment (Råstam, et al., 2003). Deficits in social communication and ASD type traits have also been observed in AN patients (e.g. Oldershaw, 2010; Oldershaw, et al., 2011; Zucker, 2007). It has been suggested that there is considerable overlap between ASD and AN, and approaching research from a perspective less focused on diagnostic labels may enhance research exploring the relationship between neurocognitive profiles and genetic vulnerability. The contrast between the findings from this thesis and the existing research is that ASD type traits have thus far been associated with AN in the

literature, while deficits in social communication are observed here in children at high risk due to being born to women with a Bingeing and Purging phenotype. It is worth noting though that the lack of evidence for an association between the ASD and BN/EDNOS phenotypes may be due to the paucity of research investigating this association.

Research investigating social and interpersonal functioning in autism spectrum disorders has found that family members exhibit similar deficits at a more subtle level (Piven, 2001). The findings from this thesis suggest the same may be true for individuals with ED. Individuals with high functioning ASD are often not detected until adolescence when peer relations and interpersonal functioning become more complex and challenging (Wing, 1997). A similar effect may occur in the development of ED, where onset is typically in adolescence. Subtle deficits may not impair day to day life until adolescence, when social communication begins to rely more heavily on *non-verbal* perception of others' intentions and emotions. It is possible that impaired social communication and emotion recognition are putative intermediate phenotypes of ED. Results from this chapter support the notion that there are benefits in exploring social cognition and emotion recognition in family members of probands, especially when investigating neurocognitive and genetic contributions to the development of an ED.

It is curious that more significant differences in social communication and emotion recognition were observed between exposed and unexposed groups when high risk status was defined by maternal ED behaviours over lifetime, rather than maternal self-report ED diagnosis. As study two was accounting for ED status over the lifetime, this sample may have had a greater proportion of children for whom the maternal ED was present within their lifetime and not just prior to their birth. Social and emotional deficits in the mothers may have contributed to insecure attachment relationships being formed, or development of emotion perception being biased or disturbed. If impaired socio-emotional functioning is also an intermediate phenotype of ED, children at risk may have had the genetic vulnerability and been exposed to an

environment conducive to the expression of that genetic vulnerability. It is worth noting that the SCDC was completed by the mothers, and results may be a reflection of maternal deficits in social communication, interpersonal difficulties between the mother and child, or maternal reports being biased. Alternatively, it is possible that, as predicted, lifetime ED behaviours provide a better phenotype than ED diagnosis for association with social and emotional constructs.

Socio-emotional deficits have been associated with slow treatment progress and poor illness prognosis (e.g. Goodwin, 2002; Porcelli, et al., 2003; Speranza, Loas, Wallier, & Corcos, 2007; Zipfel, Löwe, Reas, Deter, & Herzog, 2000), but AN patients have been found to be motivated to improve in the domains of social acceptance and interpersonal functioning (e.g. Serpell, Teasdale, Troop, & Treasure, 2004; Serpell, Treasure, Teasdale, & Sullivan, 1999). Treatment programs that engage patients in social and interpersonal improvement may lead to less treatment drop-out and improved treatment outcome. This is particularly important in light of evidence indicating difficulty in forming therapeutic alliances in with AN patients (Vitousek, et al., 1998). Support for interventions focusing on social and interpersonal elements of ED also comes from evidence that a disturbance in attachment development is predictive of premature treatment termination (Tasca, Taylor, Ritchie, & Balfour, 2004). Research investigating social and emotional functioning in disorders such as schizophrenia and autism have led to the development of effective interventions (e.g. Bellini & Peters, 2008; Horan, et al., 2009); and an intervention focused on social cognition has recently been developed for AN, receiving a positive response from patients (Money, Genders, Treasure, Schmidt, & Tchanturia, 2011). The association between basic cognitive processes in the social domain (i.e. emotion perception) and the impact of therapy/ability for therapists to form therapeutic alliances has not yet been explored. This would be an interesting line of research which may lead to the development of interventions that target basic cognitive processes in the social domain, which in turn may lead to better treatment outcome and illness prognosis.

7.3 Theoretical Implications

The differences in processing across different cognitive structures observed in this sample of children at high risk may work in combination to increase risk for development of an ED. Attentional and visuo-spatial impairments could increase the attentional bias towards body related stimuli that is already present during adolescence. This attentional bias could interact with a hypersensitivity to fear cues, emphasizing the importance of maintaining a low weight or increasing the fear of bodily changes during puberty. It has been suggested that the conscious aspects of working memory are guided by stimuli that is perceived non-consciously (Baars & Franklin, 2003). The superior working memory observed in children at risk may work counter-productively in this situation; leading individuals to ruminate on negative ED related thoughts that are already emphasized by attentional bias and a hypersensitivity to fear cues. In addition, impaired attentional control may also prevent individuals from inhibiting these negative ED related thoughts.

Deficits in neuropsychological functioning and social cognition may also be detrimental to one's problem solving ability, making it difficult for individuals to navigate a social life which becomes increasingly complex during adolescence. Deficits in social communication and emotion perception may only become apparent and detrimental to functioning at this time, adding an additional obstacle to a period of intense internal and external change. Maladaptive eating may be a coping mechanism used to deal with the conflict that is experienced at this time (Ruiz, Leon, Diaz, Paredes, & Resendiz, 2012).

Research into schizophrenia has found that in some cases social cognition mediates the relationship between neurocognitive impairments and overt functioning (Sergi, et al., 2006; Sergi, et al., 2007). It appears that this may also be the case with ED; and the cognitive profile of the children at risk in this sample may represent a cognitive based vulnerability, predisposing children exhibiting this cognitive style to higher risk of developing an ED.

7.4 Strengths and Limitations

The studies in this thesis are the first to investigate cognitive function in children at high risk of developing an ED, and the first to investigate intellectual functioning, working memory, attention, and emotion recognition in the first degree relatives of probands. The research conducted does have strengths, but also limitations. Working with the Avon Longitudinal Study of Parents and Children (ASLPAC) has allowed the use of a large cohort of children. This is particularly beneficial with research investigating ED due to its low prevalence in the population. Because ALSPAC is a longitudinal study, data on the cognitive function of children were collected prospectively which allows causal inferences to be made. A limitation of this however is that the measures used to assess cognition could not be chosen based on evidence of their previous use in relation to ED. As a result, the measures used to assess cognitive function of the children in this sample have had little or no use with ED populations, making comparison of the findings with existing literature more difficult. In addition, neuropsychological measures never measure one cognitive functioning in isolation; though this is a limitation with all research using neuropsychological tests. The strength of this type of behavioural testing however is that outcomes are objective and based on performance; as opposed to the results from self-report measures which tend to be more biased.

A strength of investigating cognition in a non-clinical sample (particularly with regard to ED research), is that that findings are not attributable to the potential effects of limited nutritional intake. This is important as dietary restraint has been shown to have a negative effect on cognitive performance in children (e.g. Brunstrom, Davison, & Mitchell, 2005), and adults (e.g. Green, et al., 1994; Keys, et al., 1950). The use of a non-clinical sample also means that it is possible to generalize the findings from this thesis to subjects at risk for ED in the general population; however it is important to consider sample bias in relation to attrition. Analysis showed that women who attended clinics with their children were more likely to be older, more highly

educated, and of a higher social class, which means that our findings are representative of a well educated population of a high socio-economic status.

The findings from the two samples employed in this thesis are not directly comparable due to differences in the methods used to define high risk status in the children. Firstly, the methods of collecting data regarding maternal ED status differed. Maternal ED diagnosis was determined via self-report (studies one and four) and maternal behaviours over lifetime were determined via clinical interview (studies two and five). Secondly, data regarding maternal ED status were collected at two different time points. Maternal ED diagnosis was reported prior to the birth of the index child, and therefore reflected maternal ED history up to birth of the child. In contrast, data regarding maternal ED behaviours over lifetime were collected when children were between 18 and 20 years of age, and were therefore representative of maternal ED experience over the majority of lifetime. Thirdly self-reported ED might have included women who had mild or sub-threshold disorders, whilst lifetime ED behaviour grouping was made to reflect clinical severity.

Limitations also arise in relation to the collection of data regarding exposure. The pros and cons of both exposure measures have been discussed at length in chapter 3 (Aims and Methodology). In relation to self-reported ED there is evidence that self-report measures such as the ones used in this study might be as sensitive and specific as more commonly used measures (Keski-Rahkonen, et al., 2006); moreover the prevalence of ED in this sample is comparable to that found in epidemiological studies of women (Micali, Simonoff, & Treasure, 2007b). It is also worth noting that though ED diagnosis (studies one and four) was obtained via self-report, lifetime history of ED behaviours (studies two and five) was obtained through in-depth interviews using a well validated clinical measure (SCID-IV). When using maternal ED behaviours over lifetime as an indicator of risk in children, weight/BMI was not taken into account. This would have been difficult, unless only lowest weight over lifetime was recorded.

It is possible that a proportion of women in the unexposed group for studies two and five had been diagnosed with a psychiatric illness (other than ED), or that women in exposed groups for all studies had a comorbid diagnosis. It is unlikely that this would lead to bias however, due to the small percentage of women that are likely to be affected. In addition, mental health of the children was not taken into account. Research has consistently shown no association between depressed mood and cognitive functioning in AN (e.g. Bayless, et al., 2002; Fassino, et al., 2001; Green, et al., 1996a; Kingston, et al., 1996; Lauer, et al., 1999; Mathias & Kent, 1998; Szmukler, et al., 1992). However this cannot be assumed for children at risk, or for other psychiatric disorders.

7.5 Future implications for research

In addition to the possibilities for future research that have been discussed above, the next step from this study would be to investigate whether the cognitive differences observed in these children at high risk contribute to the development of ED behaviours and ED diagnosis in adolescence. It would be particularly interesting to compare children at high risk who do show differences in cognitive functioning with children at high risk who do not. This could be a first step towards quantifying the effect of differential cognitive functioning on risk status within a larger risk model. It would also be important to look at how differential cognitive functioning affects development of an ED in children that are not at high risk, by: (i) investigating which of the unexposed children go on to develop an ED; and (ii) whether this is affected by differences in cognitive development. Findings from such a study could be vital for knowing which cognitive differences are associated with development of an ED, and which are unrelated.

Further clarification of the findings from this study is required. Due to a variety of limitations (i.e. sample size) it was not possible to compare cognitive functioning across children whose mothers experienced an ED prior to pregnancy, those whose onset was after pregnancy, and those who met criteria for diagnosis during pregnancy. This is important due to the possibility that maternal low weight during pregnancy may affect the cognitive development of children. In addition, due to the fact that ALSPAC is a child based study, data on the cognitive development of siblings and data on paternal ED were not available. Future research investigating children at high risk would benefit from assessing all the children of women with an ED and running statistical analysis that accounts for this. Finally, maternal data on neuropsychological functioning were not available. Future studies should assess the neuropsychological functioning of both parents and children to investigate whether cognitive differences are similar between family members.

In addition to investigating the development of ED in the sample of children employed for this thesis, it would be useful to initiate a similar but new study in which the development of relevant cognitive structures are assessed consistently throughout the child's development through both neuropsychological tasks and brain imaging. Longitudinal studies of this nature could provide an understanding of how cognition develops prior to onset of an ED, and at which time points development differs. There are several implications for this type of research: (i) an improvement in the understanding of how neuropsychological development is associated to the development of brain structure and function within those who go on to develop an ED; (ii) the identification of early risk markers could give an indication of which children are likely to develop an ED and therefore which children would benefit from intervention; (iii) knowing when the relevant differences in cognitive development occur would indicate when intervention strategies would be most effective; (iv) having an understanding of how and when cognitive development varies from the norm may contribute to the search for genetic markers of risk. Such a study would also provide an opportunity to use neuropsychological tasks that have previously been validated for use within the ED population, making direct comparisons with research investigating clinical groups possible. Furthermore, this type of study could also research the development of other psychiatric disorders that are frequently associated with ED, such as anxiety, OCD, and ASD; with the aim of identifying cognitive differences that are associated with traits that are similar and different across these disorders.

7.6 Conclusions

The findings from this thesis suggest that children at high risk for ED (due to having a mother with an ED) show differences in: intellectual functioning, visuo-spatial processing, attentional capacity, working memory, behavioural inhibition, social communication, and emotion recognition; when compared to children not at high risk. This suggests that these specific cognitive differences that have been observed in ED groups may be present prior to onset and are putative intermediate phenotypes for ED.

Differential patterns of cognition were observed for children born to women with differing ED diagnoses/behavioural phenotypes over lifetime. This highlights the importance of differentiating between ED diagnoses for the purposes of research, and also implies that a lifetime diagnosis/phenotype may provide the homogeneity required for investigation into neuropsychological profiles, intermediate phenotypes and possible genetic correlates.

Although differences between groups were small from a clinical perspective, this is to be expected in a high-risk study. Further research is required to confirm and further explore our findings, but a clarification of the neuropsychological profile of those at high risk of developing an ED is extremely important: both in relation to the identification of vulnerable individuals (and therefore preventative efforts); and in furthering our understanding of which neuropsychological profiles are linked to susceptibility for ED, and which ones might be a scar of these disorders.

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