Autobiographical memory and early-onset depression: Insights from the environment, genetics and brain structure

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Declaration and statements

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This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

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This thesis is being submitted in partial fulfillment of the requirements for the degree of PhD.

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Thesis summary

Difficulty remembering specific events from the personal past, known as overgeneral autobiographical memory (AM), has been associated with adult depression. However, evidence for overgeneral memory as a risk factor for early-onset depression is less consistent, and the aetiology of overgeneral memory is not well understood. The aim of this thesis was to examine whether overgeneral memory could be a risk factor or risk mechanism for early-onset depression.

I first examined the cross-sectional and longitudinal relationships between overgeneral memory and depression. Overgeneral AM to negative cues was associated with cross-sectional depressive symptoms and depressive symptoms three years later, thereby indicating temporal precedence. I also assessed whether overgeneral memory was a risk mechanism through which known risk factors for depression (stressful life events (SLEs) and genetic risk) exert their effects. Although overgeneral memory was associated with SLEs, it did not mediate the relationship with depression. Instead, results suggested overgeneral memory and SLEs exert independent effects on subsequent depression. In contrast, overgeneral memory was not associated with common genetic risk for depression. Finally I investigated whether white matter connections in the brain could help explain the link between overgeneral memory and depression. White matter tracts previously associated with depression were linked to specific AMs that were positive in content but not to other measures of AM.

In combination, these finding suggest that overgeneral memory is a risk factor for early-onset depression although observed effect sizes were small. Thus, targeting overgeneral memory could be useful for treatment and prevention of early-onset depression. Overgeneral memory was not a mechanism for known risk factors of depression (SLEs and genetic risk). The association with white matter tracts involved in depression provides preliminary evidence that overgeneral memory could be a risk mechanism for depression. Nevertheless, preliminary evidence from this small cross-sectional study requires replication in larger, longitudinal studies.

Publications resulting from work in this thesis

Warne, N., Collishaw, S., & Rice, F. (2019). Examining the relationship between stressful life events and overgeneral autobiographical memory in adolescents at high familial risk of depression. *Memory, 27*(3), 314-327.

Related publications to which I have contributed

Rice, F., & Warne N. (2019) Pediatric depression. In J. Quevedo, A. F. Carvalho, & C. A. Zarate, *Neurobiology of depression: Road to novel therapeutics* (pp. 415-424). Oxford, UK: Academic Press.

Hodgetts, C. J., Postans, M., Warne, N., Varnava, A., Lawrence, A. D., & Graham, K. S. (2017). Distinct contributions of the fornix and inferior longitudinal fasciculus to episodic and semantic autobiographical memory, *Cortex, 94,* 1-14. https://doi.org/10.1016/j.cortex.2017.05.010

Statement of contribution

The data used in this thesis is from two samples: The Avon Longitudinal Sample of Parents and Children (ALSPAC) and the Early Prediction of Adolescent Depression (EPAD) study.

ALSPAC

The ALSPAC cohort is an ongoing longitudinal sample with all data collected and cleaned by the ALSPAC research team at University of Bristol. I was not involved with data collection or cleaning but I conducted all activities relating to this thesis. I was involved in drafting the project proposal, requesting ALSPAC data and was responsible for selecting required variables and the practicalities of acquiring the data. I created all summary variables used in the thesis with the exception of the genetic analysis where Dr Richard Anney performed the quality control procedures and created polygenic risk scores. I was responsible for statistical analysis, interpretation and write-up of results.

EPAD

Original data from the EPAD study was collected and cleaned by researchers at Cardiff University from 2007 to 2011. I used summary clinical variables from a psychiatric interview created by the original team but was responsible for creating other summary variables and performing analyses for this thesis. I also performed interpretation and write-up of the findings.

In Chapter 4 I performed additional analyses with memory content valence variables. I transcribed all memories from audio recordings and coded each of the transcripts. Second coding was performed for inter-rater reliability by Dr Frances Rice on a proportion of the transcripts.

EPAD genetic samples had not been processed prior to my joining the group; I was responsible for overseeing all aspects of processing the EPAD genetic data (Chapter 5). I liaised with the MRC Centre for Neuropsychiatric Genetics and Genomics core lab team (Dr Alex Evans, Bozo Lugonja) to get the EPAD samples genotyped and data transferred. Quality control, imputation and creation of polygenic risk scores was conducted by Dr Richard Anney. I was responsible for all subsequent analysis of the genetic data seen in Chapter 5.

I conducted the neuroimaging study (Chapter 6) with a subsample of the original EPAD participants. I was responsible for all aspects: conception, design, ethics, recruitment, data collection, data cleaning, and data analysis. The MRI scanning sequence was set up by Peter Hobden according to my specifications and MRI scanning of participants was undertaken by trained MRI operators (Allison Cooper, Peter Hobden, Sonya Foley). An undergraduate Psychology student (Kirsten Mann) helped with some of the data collection (clinical interviews), data input and data cleaning. Kirsten also second-coded the clinical interviews and memories according to specificity. Dr Robert Potter, a senior psychiatrist, reviewed sub-threshold and clinical cases of depression. I was responsible for all data processing, analysis, interpretation and write-up of findings.

Abbreviations

ALSPAC – Avon Longitudinal Study of Parents and Children

AM – Autobiographical memory

AMSneg – Specific autobiographical memory to negative cues

AMSneut – Specific autobiographical memory to neutral cues

AMSpos – Specific autobiographical memory to positive cues

AMT – Autobiographical Memory Test

BodyCC – Body of the corpus callosum

DSM-IV - Diagnostic Statistical Manual of Mental Disorders, 4th edition

EPAD – Early Prediction of Adolescent Depression

FA – Fractional anisotropy

GenuCC – Genu of the corpus callosum

MDD – Major Depressive Disorder

OGMneg – Overgeneral autobiographical memory to negative cues

OGMneut – Overgeneral autobiographical memory to neutral cues

OGMpos – Overgeneral autobiographical memory to positive cues

PGC – Psychiatric Genomics Consortium

PLIKS – Psychotic-like symptoms

PRS – Polygenic risk scores

SLEs – Stressful life events

SLF III – Third branch of the superior longitudinal fasciculus

TBSS – Tract-based Spatial Statistics

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1. Introduction

1.1. Depression

Depression or Major Depressive Disorder (MDD) is a common and frequently recurrent psychiatric condition that causes significant impairment (Kessler, 2012). Depression is characterised by symptoms of low mood, loss of interest or pleasure, and decreased energy or fatigue (APA, 2013; World Health Organisation, 1994). Other symptoms include physical changes such as changes in appetite, weight and sleep; worthlessness and inappropriate guilt; and cognitive difficulties such as difficulty concentrating and indecisiveness. Diagnostic criteria (Diagnostic Statistical Manual of Mental Disorders, 5th edition (DSM-5; APA, 2013) and International Classification of Diseases, 10th edition (ICD-10; World Health Organisation, 1994)) require symptoms to be present for at least two consecutive weeks and cause significant distress and/or functional impairment. Criteria for adults and under 18s are the same with the exception that irritability may be present instead of low mood in children and adolescents under DSM-5 criteria.

Depression can be viewed categorically as a disorder or dimensionally as a continuum of symptoms normally distributed across the general population. Evidence supports a dimensional view as higher levels of symptoms are associated with increased likelihood of developing MDD (Fergusson, Horwood, Ridder, & Beautrais, 2005; Klein, Shankman, Lewinsohn, & Seeley, 2009), significant impairment (Angold, Costello, Farmer, Burns, & Erkanli, 1999; Gotlib, Lewinsohn, & Seeley, 1995), and negative outcomes (Wesselhoeft, Sorensen, Heiervang, & Bilenberg, 2013). There are different ways of measuring depressive symptoms including via questionnaires, semi-structured interviews and structured interviews, each with different thresholds for endorsing symptoms and scoring methods.

Typically the most conservative estimates of depressive symptoms are from semi-structured interviews (Rice, Davidovich, & Dunsmuir, 2017a) as these require impairment in line with diagnostic criteria. Thus, the number of depressive symptoms endorsed is partly dependent upon the measure used and high levels of depressive symptoms cannot necessarily be equated with a clinical diagnosis of MDD.

Depression is the leading cause of disability worldwide affecting over 300 million people (Friedrich, 2017; World Health Organization, 2017). Epidemiological studies suggest a lifetime prevalence of MDD between 6% and 25% (Kessler et al., 2014) and those with depression also have a high chance of relapse or recurrence (Klein & Allman, 2014). Depression comes with high costs for individuals and society as a whole. For instance, depression is closely associated with risk of suicide, with 23-52% of individuals dying by suicide having a history of MDD (Nock, Millner, Deming, & Glenn, 2014). Depression is also associated with reduced educational attainment, unemployment and job loss, poorer physical health and health-related behaviours, and reduced social functioning (Davis, Uezato, Newell, & Frazier, 2008; Kawakami et al., 2012; Kessler, 2012; Kupferberg, Bicks, & Hasler, 2016; Lee et al., 2009).

Depression in under 18s is a particularly important issue as up to 75% of depressed adults report having their first episode of MDD during childhood or adolescence (Kim-Cohen et al., 2003). In childhood the risk of developing depression is relatively low (1-2%) (Egger & Angold, 2006) but the incidence dramatically increases during adolescence (4-5%) and young adulthood (10-17%) (Moffitt et al., 2010; Thapar, Collishaw, Pine, & Thapar, 2012) – particularly in females (Maughan, Collishaw, & Stringaris, 2013). Young adulthood is the peak period for new onsets of MDD (Rohde, Lewinsohn, Klein, Seeley, & Gau, 2013;

Weissman et al., 2006). Consequently, adolescence and young adulthood constitute risk periods for the first onset of MDD. Depression that begins early is associated with particularly poor outcomes and a chronic, long-term course of symptoms (Dunn & Goodyer, 2006; Patton et al., 2014; Rutter, Kim-Cohen, & Maughan, 2006). Over half of adolescents completing suicide meet the criteria for current MDD (Hawton & Van Heeringen, 2009) and suicide is a leading cause of death in this age group (Windfuhr et al., 2008). Episodes of adolescent depression are frequently recurrent, with 50-70% of remitted cases experiencing another depressive episode within 5 years (Dunn & Goodyer, 2006; Kovacs et al., 1984; Kovacs, Obrosky, & George, 2016; Lewinsohn, Rohde, Seeley, Klein, & Gotlib, 2000), but relatively few young people with clinically impairing symptoms access health services or receive treatment (Neufeld, Dunn, Jones, Croudace, & Goodyer, 2017; Potter et al., 2012). Therefore, it is necessary to improve understanding of the aetiology of early-onset MDD so that individuals at high risk can be identified and effective treatments and prophylactic measures can be developed.

MDD has a complex, multifactorial aetiology with multiple risk factors contributing to a depressive episode. Genetic, environmental, biological, cognitive, and neural factors are all involved in the aetiology of depression (Rice & Rawal, 2011; Sullivan, Neale, & Kendler, 2000; Thapar et al., 2012). Distal risk factors for depression can have direct effects on the disorder, as well as indirect effects via more proximal cognitive, biological and neural processes or mechanisms (Rutter, Pickles, Murray, & Eaves, 2001; Thapar et al., 2012). Interventions that target causal risk and protective factors as well as the mechanisms through which depression develops are likely to be effective. Another important consideration for prevention and intervention is the degree to which a factor or mechanism is modifiable (Garber,

2006). Mechanisms such as cognitive biases and biological/neural pathways can be targeted and potentially altered with cognitive therapies or medication.

It is particularly important to differentiate between correlates of depression, risks that precede the disorder, and risks that are mechanistically involved in how depression develops. Risk factors are more than just correlated with depression, they are associated with higher rates of the disorder than the general population and have temporal precedence to the negative outcome (Garber, 2006; Kazdin, Kraemer, Kessler, Kupfer, & Offord, 1997; Kraemer et al., 1997; Rutter et al., 2001). Temporal precedence is an important distinction as factors that present before the onset of depression indicate either an underlying predisposition or a 'prodromal state' and could be potential clinical targets for interventions before the first episode of MDD (Rohde, Lewinsohn, & Seeley, 1990). Temporal precedence also reduces the likelihood that the observed effect is due to symptoms themselves influencing risk factor, i.e. reverse causation (Gage, Munafò, & Davey Smith, 2016). Although risk factors predate depression, they may not be causal, or involved mechanistically, in the aetiology of the disorder. Risk mechanisms, however, are causative as they explain the risk process through which other distal or known risk factors exert their pathological effect (Garber, 2006; Rutter et al., 2001; Thapar et al., 2012). Consequently, risk mechanisms are likely to be consistent across different samples, be biologically plausible (or explained by a mechanism), be acceptable based on current knowledge, and affect the disorder when experimentally manipulated (Academy of Medical Sciences, 2007; Hill, 1965; Rutter, 2007). Effectively targeting risk mechanisms will therefore affect the likelihood of developing a disorder (Hollon et al., 2002). The following section description provides a brief overview of the known risk factors for depression that are the background to this thesis.

1.2. Risk factors

As MDD is a complex disorder encompassing both environmental and genetic risk factors (Sullivan et al., 2000; Thapar et al., 2012) it is important not to consider risks for depression in isolation. Heritability estimates for MDD are modest (around 40%) with environmental factors (e.g. poverty, interpersonal stresses, victimisation, abuse, etc) playing an important role in the development of the disorder (Lau, Lester, Hodgson, & Eley, 2014; Sullivan et al., 2000). Cognitive factors are also important, with some of the earliest theories of depression based on descriptions of the negative thinking patterns seen in individuals affected by depression (Beck, 2008). It is important to consider the neural underpinnings that contribute to depression. For instance, brain structure and function likely underlie cognitive biases and depressive symptomatology. Cognitive and neural factors may also be risk mechanisms through which other known risk factors exert their effects (Rutter et al., 2001; Thapar et al., 2012). Typically, theories focus on one particular element but it is widely accepted that the aetiology of MDD is complex. This section begins with the more distal risk factors such as environment and genetics followed by the more proximal, malleable, factors such as cognition and neural correlates through which distal risk factors may exert their effects (Thapar et al., 2012).

1.2.1. Environmental factors

1.2.1.1 Stressful life events

Stressful life events (SLEs) are one of the most robust risk factors for depression (Maughan et al., 2013; Thapar et al., 2012) and are thought to play a direct causal role in the development of depressive episodes (Kendler & Gardner, 2010; Kendler, Karkowski, & Prescott, 1999; Rice et al., 2017b). Evidence has implicated stressful events such as interpersonal loss (e.g. death of a loved one), disappointment (e.g.

doing badly on an exam), and changes in circumstance (e.g. parental divorce, moving house), as well as more traumatic events that are severely threatening or dangerous (e.g. assault, motor vehicle accident, abuse or neglect, war), in predicting childhood and adolescent depression (Friis, Wittchen, Pfister, & Lieb, 2002; Nolen-Hoeksema, Girgus, & Seligman, 1992; Penza, Heim, & Nemeroff, 2006; Rice et al., 2017b; Thapar et al., 2012). Research shows that adolescent girls experience a greater number of SLEs than adolescent boys (Ge, Conger, & Elder, 2001; Hamilton, Stange, Abramson, & Alloy, 2015; Shih, Eberhart, Hammen, & Brennan, 2006), which may be one explanation for the emergence of gender differences in depression that is typically seen in mid adolescence (Rice, Harold, & Thapar, 2003; Thapar et al., 2012). SLEs occurring in early development can have potentially long-lasting effects with adverse childhood experiences predicting lifetime and recent incidence of depression in adults (mean age 56.6 years) (Chapman et al., 2004); although this could also be due to continuing adversity, and retrospective reporting is a methodological issue in most studies. Despite SLEs having long-lasting and contemporaneous effects, evidence suggests that SLEs have stronger effects on MDD when they both occur within the same developmental period (Shanahan, Copeland, Costello, & Angold, 2011). The relationship between SLEs and MDD is also stronger for 'behaviour-dependent' events that the individual has contributed to or evoked (such as losing a friend through arguments, or doing badly in school or work), than for 'behaviour-independent' events that the individual cannot control (such as death of a loved one) (Hammen, 2005; Kendler et al., 1999). Behaviour-dependent SLEs are more heritable than behaviour-independent SLEs, and effects on environmental risk exposure is one way in which genetic factors can affect depression (i.e. genetic environment correlation, or rGE) (Kendler & Baker, 2007).

It is not clear how SLEs affect MDD. It is not a deterministic relationship as not everyone who experiences a SLE becomes depressed (Brown & Harris, 1978; Monroe, Slavich, & Georgiades, 2014). A number of biological, developmental, psychological and sociodemographic factors may act as mechanisms through which SLEs influence depression (Hammen, 2005). One possibility is that SLEs affect depression through cognitive factors. For instance, some studies report that cognitive emotion regulatory strategies mediate the association between SLEs and depression such that only individuals with maladaptive strategies develop MDD when exposed to a SLE (Stikkelbroek, Bodden, Kleinjan, Reijnders, & van Baar, 2016). Indeed, the stress diathesis model for depression has indicated stress may trigger an episode of depression in the presence of an underlying vulnerability (e.g. genetic predisposition or cognitive vulnerability) (Monroe & Simons, 1991) and Beck's expanded cognitive model of depression suggests that previous and recent stress is likely to contribute to depression by interacting with cognitive vulnerability (Beck, 2008). There has been some evidence to support the cognitive diathesis-stress vulnerability in adults but less evidence in children (Cole et al., 2008; Scher, Ingram, & Segal, 2005). Previous associations between cognitive biases, SLEs and depression could be attributable to shared method variance when informants report on both the risk factors and the outcome (Jacobs, Reinecke, Gollan, & Kane, 2008; Rice et al., 2015; Rutter et al., 2001). Consequently, more objective measures of cognition are needed; for instance performance-based measures that tap into unconscious cognitive biases rather than biases reported based on self-reflection (Jacobs et al., 2008; LeMoult & Gotlib, 2018; Rice et al., 2015). Further work investigating how performance-based cognitive biases interact with SLEs and contribute to depression is therefore warranted.

1.2.1.2 Economic disadvantage/low socioeconomic status

MDD is associated with economic disadvantage or low socioeconomic status (SES) (Dohrenwend et al., 1992; Joinson, Kounali, & Lewis, 2017; Lima et al., 2013; Ostler et al., 2001; Patel, Araya, De Lima, Ludermir, & Todd, 1999; Reading & Reynolds, 2001). Research suggests that low income affects risk for mental health regardless of how developed a country is (Patel et al., 1999; Yatham, Sivathasan, Yoon, da Silva, & Ravindran, 2018). Economic disadvantage has a direct effect on developing early-onset MDD (Rice et al., 2017b), and poverty is also related to elevated depressive symptoms across development (McLeod & Shanahan, 1996). Parent and offspring depression has also been found to mediate the relationship between low SES and a wide range of undesirable adolescent social outcomes (Devenish, Hooley, & Mellor, 2017).

1.2.2. Genetics

1.2.2.1 Heritability of MDD

Early research using family and twin designs highlighted that genetic factors play a role in depression as relatives of depressed individuals show higher rates of MDD than individuals who do not have any depressed relatives. For instance, there is a higher rate of depression in first-degree relatives of depressed individuals (sharing on average 50% of their genes) than there is in first-degree relatives of healthy controls (odds ratios 1.7 to 4.0) (Rice, Harold, & Thapar, 2002b; Shih, Belmonte, & Zandi, 2004). Furthermore, the most common and potent risk factor for early-onset depression is having a parent with the disorder, which increases the risk of offspring depression 3 to 4 fold (Rice et al., 2002b; Weissman et al., 2006). This risk is greater than for other first-degree relatives of MDD probands (Rice et al., 2002b), so is likely to be attributable to both genetic and environmental factors associated with

having a parent with MDD. Classic twin studies compare identical (monozygotic) twins who share 100% of their genes and non-identical (dizygotic) twins who only share on average 50% of their genes to quantify the heritable and environmental contributions to MDD. These heritability estimates cover the direct effect of all genes as well as some of the genetic-environmental interplay (correlations with the environment). Evidence from twin studies suggests that 30-40% of variance in MDD in adults is due to genetics (Lau et al., 2014; Sullivan et al., 2000) and heritability of MDD may be higher in females (42%) compared to males (29%) (Kendler, Gatz, Gardner, & Pedersen, 2006). Twin studies in children and adolescents are less clear. Genetic contributions to depressive symptoms are small in childhood but increase in adolescence (Rice, Harold, & Thapar, 2002a; Silberg et al., 1999; Thapar & McGuffin, 1994). This could be caused by increases in gene-environment correlation around adolescence as adolescents are more able to shape their own environments than in childhood (Rice, 2010; Rice et al., 2003).

Studies using adoption designs have not implicated a strong genetic component to MDD. Adoption studies partition out the variance for genetics and environment by looking at different relationships between biological relatives and environmental relatives. Adoption studies investigating MDD and depressive/internalising symptoms (i.e. inner-directed symptoms such as somatic complaints, withdrawal and anxiety/depression (Achenbach, 1966)) have found a strong environmental component and minimal genetic contribution (Cadoret, 1978; Cadoret, O'Gorman, Heywood, & Troughton, 1985; Eley, Deater-Deckard, Fombonne, Fulker, & Plomin, 1998; Tully, Iacono, & McGue, 2008; van den Oord, Boomsma, & Verhulst, 1994; von Knorring, Cloninger, Bohman, & Sigvardsson, 1983; Wender et al., 1986). However, a recent large register-based study analysing a number of different family types (including adoptive relationships) found genetic and

rearing environmental effects to have approximately equal contributions to MDD diagnosis (Kendler, Ohlsson, Sundquist, & Sundquist, 2018).

The inconsistency in findings between twin and adoption studies may be due to inflated heritability from twin studies as variance from passive gene-environment correlation is also included in the estimate (e.g. parental genetics affecting the environment that parents provide for their children) (Rice et al., 2002b). Genetic influences may also be reduced in family studies as different genes could be involved in depression in adults and children (Rice, 2014), whereas in twin studies individuals of exactly the same age are compared. It may also be the case that genetic liabilities are only expressed in certain environments (e.g. Natsuaki et al. 2010), however further research is required before any strong conclusions can be made.

In summary, family, twin and adoption studies have indicated that both genetic and environmental factors are likely to play a role in the onset of MDD. Studies that have investigated the specific regions and genes that have been implicated in MDD are outlined below.

1.2.2.2 Molecular genetic findings

Progress has been made on identifying specific genetic variants associated with MDD through various techniques. Early techniques investigated coinheritance of risk in families through linkage studies and in the general population with pre-selected candidate genes. More recent studies, known as Genome Wide Association Studies (GWAS), compare large numbers of cases and controls to ascertain which common genetic loci (Single Nucleotide Polymorphisms, or SNPs) across the genome are associated with a disorder. This is consistent with the view of a multifactorial aetiology for MDD where there are multiple risk factors with small to moderate effect sizes. Early attempts at GWAS from the Psychiatric Genomics Consortium

(PGC) MDD working group were not able to discover MDD-associated SNPs that surpassed the genome-wide significance level ($p < 5 \times 10^{-8}$) after correcting for multiple testing despite having a large sample size of 9,240 cases and 9,519 controls (Ripke et al., 2013). This is likely due to reduced power stemming from the clinical heterogeneity of the disorder, high prevalence of MDD in the population, and the relatively modest heritability estimates (Flint & Kendler, 2014; Levinson et al., 2014; Sullivan, Daly, & O'Donovan, 2012). Recent increases in sample size have enabled the identification of SNPs associated with MDD that pass the level for genome-wide significance. For example, 15 loci associated with self-reported depressive symptoms have been identified using 45,773 cases and 106,354 controls (Hyde et al., 2016) and 2 loci for depressive symptoms have been identified in 180,866 individuals (Okbay et al., 2016). Recently the PGC MDD working group's second analysis found 44 genome-wide significant loci for MDD using 135,458 cases and 344,901 controls (Wray et al., 2018). These loci are associated with BMI (body mass index), neuroinflammatory responses, and the HPA-axis (hypothalamic-pituitary-adrenal axis). The genes implicated in depression were preferentially expressed in neurons in the prefrontal cortex and anterior cingulate cortex, indicating MDD as a brain disorder.

1.2.3. Cognitive factors

Individuals with MDD show a number of cognitive deficits and cognitive biases, as well as maladaptive emotion regulation. Deficits are characterised by impairments or below normal-level cognitive functioning. For instance, adults with MDD have displayed reductions in tests of attention, processing speed, learning and memory, inhibitory control and executive functioning in comparison to healthy controls (Gohier et al., 2009; LeMoult & Gotlib, 2018; Rock, Roiser, Riedel, & Blackwell, 2014; Snyder, 2013). In contrast, a cognitive bias indicates a particular style of

processing information as opposed to an overall reduction in functioning. Individuals with depression have been reported to have negative biases, and lack the positivity bias seen in non-depressed individuals (LeMoult & Gotlib, 2018). There is also considerable evidence that depression is associated with ineffective emotion regulatory strategies (Gotlib & Joormann, 2010; LeMoult & Gotlib, 2018). Although an exhaustive review is beyond the scope of this chapter, the following sub-sections provide a broad overview of the most prominent cognitive factors that are associated with depression and may constitute risk factors for the disorder.

1.2.3.1 Cognitive deficits

Approximately 40% of currently or formerly depressed patients exhibit impairments in at least one cognitive domain (Gualtieri & Morgan, 2008), and difficulties in concentrating and decision-making are diagnostic symptoms of depression (APA, 2013; World Health Organisation, 1994). Impairments in a number of cognitive domains have been reported in depression compared to healthy controls, including deficits in attention, processing speed, learning and memory, inhibitory control and executive functioning (Gohier et al., 2009; LeMoult & Gotlib, 2018; Rock et al., 2014; Snyder, 2013). Cognitive impairments have a major impact on psychosocial functioning and can limit functional recovery from MDD (Rock et al., 2014; Trivedi & Greer, 2014). Although cognitive deficits may contribute to the maintenance of MDD, it is not clear whether they temporally precede the first onset of the disorder. A number of cognitive deficits have been seen in first-episode MDD, namely: attention, working memory, episodic memory, IQ, processing speed, inhibition, set-shifting and verbal fluency (Ahern & Semkovska, 2017). As these cognitive deficits are seen in the first-episode of the disorder it suggests they are not caused by repeated depressive episodes or long-term medication use. However, there is limited

longitudinal research investigating cognition before the onset of depressive symptoms so it is unclear whether they would constitute risk factors for MDD.

Several reviews and meta-analyses report memory deficits in depression. Meta-analyses have found that working memory, the ability to maintain and manipulate information over a short delay (Baddeley, 1999), is impaired in individuals with depression in comparison to controls (Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Rock et al., 2014; Snyder, 2013). However, in structured, task-focused situations, depressed participants' working memory is at similar levels to non-depressed participants (Hertel, 1998, 2004), indicating that it may be task irrelevant thoughts or ruminations that are affecting working memory rather than a deficit in working memory itself. The evidence is mixed on whether individuals with depression have deficits in long-term memory such as episodic verbal and visual memory (i.e. delayed recall of word lists and complex pictures). Some meta-analyses suggest depressed individuals do display deficits in episodic verbal and visual memory (Ahern & Semkovska, 2017; Lee et al., 2012; Rock et al., 2014), but a meta-analysis of first-onset depression found no impairments in episodic visual memory (Ahern & Semkovska, 2017). Impairments in episodic verbal and visual memory do not persist following remission in first-episode depression (Maeshima et al., 2012), suggesting these impairments may be associated with mood state. Nevertheless, longitudinal studies that assess memory before the onset of depression are required to unpick whether memory deficits could be risk factors for depression.

One of the most researched cognitive deficits in depression is the impairment in executive functioning. Executive functioning is characterised as effortful higher-level cognitive processes that guide goal-directed behaviours such as decision making, planning, selective attention, inhibition, shifting between task goals (set-shifting), updating, working memory, verbal fluency, and processing speed (Alvarez

& Emory, 2006; Banich, 2009; Miyake et al., 2000). A meta-analysis of 113 studies found that individuals with depression displayed consistent deficits in the executive functioning domains of inhibition, set-shifting, updating, working memory (verbal and visuospatial), planning and verbal fluency in comparison to healthy controls (Snyder, 2013). This meta-analysis also found evidence that some of these deficits (inhibition, set-shifting, verbal working memory and verbal fluency) are moderated by current depression severity in that deficits were larger in individuals with more severe depressive symptoms. This indicates that mood state may have an effect on executive functioning. Furthermore, a recent meta-analysis suggested that some deficits in executive functioning (e.g. set-shifting) return to normal levels with remission of depression (Ahern & Semkovska, 2017). Therefore, some elements of executive functioning may be concomitants or consequences of depressed mood and some may be risk factors that precede the onset of depression.

There is very little research on whether deficits in executive functioning precede depression (Snyder, Miyake, & Hankin, 2015). Preliminary research has found either no prospective effects of executive functioning (Friedman, du Pont, Corley, & Hewitt, 2018; Giollabhui, Olino, Nielsen, Abramson, & Alloy, 2019; Schaefer et al., 2017) or a reciprocal relationship between depression and executive functioning (Giollabhui et al., 2019). Thus, if a relationship is present between executive functioning and depression it is likely to be complex. This potential relationship is also confounded by the fact that cognitive deficits, or reduced performance on cognitive tasks, are likely to be affected by motivational issues in individuals with depression (Scheurich et al., 2008). Furthermore, systematic reviews have found impairments in executive functioning are common across psychiatric disorders (Snyder et al., 2015) and it is not clear if any aspect of executive functioning is specific to MDD (Snyder, 2013).

1.2.3.2 Cognitive biases

Early theories of depression stressed the importance of negative thoughts and cognitions in preceding and underlying mood symptoms (Abramson et al., 1999; Abramson, Metalsky, & Alloy, 1989; Abramson, Seligman, & Teasdale, 1978; Beck, 1967, 1976, 2008). These cognitive biases are distinct from cognitive deficits as they indicate a preponderance or preference for a particular way of functioning rather than a reduction in functioning. Cognitive biases in depression include a preference for attending to and recalling negative material (Gotlib & Joormann, 2010; Lloyd & Lishman, 1975; Matt, Vázquez, & Campbell, 1992); interpreting ambiguous events or scenarios as negative (Lawson, MacLeod, & Hammond, 2002; Rude, Wenzlaff, Gibbs, Vane, & Whitney, 2002); implicit and automatic negative self-beliefs (Abela et al., 2011; Sheppard & Teasdale, 2004); and overgeneralisations (drawing incorrect conclusions about something as a whole from one specific instance, e.g. failing to get a job and thinking that you are unemployable) (Beck, 1967, 1976, 2008; Thew, Gregory, Roberts, & Rimes, 2017).

The most robust evidence for a cognitive bias in MDD has been found for memory (Hertel & Brozovich, 2010; Kircanski, Joormann, & Gotlib, 2012; LeMoult & Gotlib, 2018). For instance, individuals with MDD display four distinct but inter-related biases in autobiographical memory – someone's memory for their past, personal experiences (Dalgleish & Werner-Seidler, 2014). These include a bias for negative memories, diminished positive memories, overgeneral memory, and an altered relationship with emotional memories. These four autobiographical memory biases are typical examples of the negative biases and overgeneralisations that are common in depression (Beck, 1967, 1976, 2008; Gotlib & Joormann, 2010). A bias for negative memories is common in depression. Not only are negative memories recalled more often in those who are depressed compared to those who are not

depressed (Matt et al., 1992), but they are recalled more quickly than positive memories (Lloyd & Lishman, 1975). A negative bias in encoding memories is also likely as selective attention to negative experiences (Gotlib & Joormann, 2010) and interpretation of ambiguous situations as negative (Dearing & Gotlib, 2009) are likely to result in more negative experiences being encoded. Similarly, positive memories are diminished in depression in that there is reduced recall of positive memories (Gotlib & Joormann, 2010; Matt et al., 1992) and there is reduced positive affect derived from recalling positive memories in comparison to individuals without depression (Joormann & Siemer, 2004; Joormann, Siemer, & Gotlib, 2007). This may be because the positive memories that depressed participants recall lack concrete details (Werner-Seidler & Moulds, 2012) to enable effective emotional regulation. Alternatively, recall of positive memories may be so discrepant to the negative sense of self that it may promote rumination and worsening of mood (Joormann et al., 2007; Werner-Seidler, Tan, & Dalgleish, 2017).

In addition to valenced memory biases, when asked to recall a specific incident from their personal past depressed individuals recall fewer specific past events and more events that span longer than 24 hours or repeated instances in time, known as overgeneral memory (Williams et al., 2007). Not being able to recall specific memories, particularly of positive events, can be detrimental for mood repair (Joormann & Siemer, 2004; Ramirez et al., 2015), problem-solving (Goddard, Dritschel, & Burton, 1996, 1997), social functioning (Harris, Paterson, & Kemp, 2008), and sense of self (Askelund, Schweizer, Goodyer, & van Harmelen, 2019), and may contribute to onset of depressive symptoms (Rawal & Rice, 2012b; Williams et al., 2007). An altered relationship with emotional memories is also evident in depression, with conscious and unconscious avoidance or suppression more prevalent in depression (Beblo et al., 2012). These techniques appear unhelpful

as depressed individuals report more intrusive, unwanted memories (Dalgleish & Yiend, 2006). Individuals with depression are also more likely to report that they view their memories from an observer perspective (as if looking down on themselves) rather than from a first person perspective (Bergouignan et al., 2008; Lemogne et al., 2006). This can reduce distress in the short-term (McIsaac & Eich, 2002; Nigro & Neisser, 1983), but may not be as effective over the long-term as it prevents effective processing of affect from distressing memories (Holmes & Mathews, 2010; Kuyken & Moulds, 2009) and mood repair from positive memories (McIsaac & Eich, 2002; Nigro & Neisser, 1983). In combination, these four autobiographical memory biases may affect the onset and maintenance of depression (Dalgleish & Werner-Seidler, 2014).

Overgeneral memory, in particular, may be a potential risk factor for depression. As well as being more common in individuals with current depression (Liu, Li, Xiao, Yang, & Jiang, 2013; Williams et al., 2007), overgeneral memory has also been seen in remitted depression (Mackinger, Pachinger, Leibetseder, & Fartacek, 2000b; Spinhoven et al., 2006a), and it is prospectively associated with subsequent depressive symptoms and MDD (Rawal & Rice, 2012b; Sumner, Griffith, & Mineka, 2010). Temporal precedence to the disorder suggests that the association is not just a correlate of current mood state, but that overgeneral memory could be a risk factor for MDD (Garber, 2006; Kazdin et al., 1997; Kraemer et al., 1997; Rutter et al., 2001). However, it is unclear as yet whether overgeneral memory could be a mechanism through which depression develops, and there is limited overgeneral memory research in adolescence (Hitchcock, Nixon, & Weber, 2014), which is a key risk period for depression (Maughan et al., 2013). Preliminary studies using adolescent samples have found that overgeneral memory is associated with subsequent MDD and depressive symptoms (Hipwell, Sapotichne, Klostermann,

Battista, & Keenan, 2011; Rawal & Rice, 2012b; Sumner et al., 2011), but inconsistency remains as other studies have found not found this prospective relationship (Crane et al., 2016; Gutenbrunner, Salmon, & Jose, 2017). Overgeneral memory may therefore be a risk factor for early-onset depression but this requires further investigation. Overgeneral memory is modifiable (Williams, Teasdale, Segal, & Soulsby, 2000) so could be a useful target for interventions if it were a risk mechanism for depression. Given overgeneral memory is associated with a number of potential risk factors for depression (namely rumination (Williams et al., 2007), executive functioning impairments (Williams et al., 2007), ineffective emotion regulation (Joormann & Siemer, 2004; Joormann et al., 2007), negative sense of self (Askelund et al., 2019; Conway & Pleydell-Pearce, 2000), impaired social functioning (Harris et al., 2008) and impaired social problem solving (Goddard et al., 1996, 1997)), interventions targeting overgeneral memory have the potential to reduce onset of depression and associated functional impairment via a range of different pathways.

1.2.3.3 Emotion regulation strategies

Emotion regulation refers to the automatic and controlled processes through which individuals modify the onset, magnitude, length and expression of an emotional response (Joormann & Stanton, 2016). Individuals with depression display a number of maladaptive emotional regulation strategies that are open to conscious introspection including increased rumination, suppression and avoidance, and reduced cognitive reappraisal, problem solving and acceptance (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Schäfer, Naumann, Holmes, Tuschen-Caffier, & Samson, 2017). Three cognitive emotion regulation strategies that have received the most consideration in the literature are rumination, distraction and cognitive reappraisal (LeMoult & Gotlib, 2018). Nevertheless, it should also be acknowledged

that much research on rumination, distraction and cognitive reappraisal relies on people being able to report their emotion regulation strategies, which may not always be possible for younger populations, and some emotion regulation may not be open to conscious introspection (Jacobs et al., 2008; Rice et al., 2015; Rutter et al., 2001). Moreover, it is increasingly acknowledged that higher order emotion regulation comes about via lower level cognitive processes (Jacobs et al., 2008; Roiser, Elliott, & Sahakian, 2012), for instance, through the cognitive biases in attention and memory described in section 1.2.3.2. These cognitive processes are thought to be mechanisms through which pharmacological and psychological treatments exert their effect on depression (Harmer, Duman, & Cowen, 2017; Harmer, Goodwin, & Cowen, 2009; Roiser et al., 2012). Research in emotion regulation using self-report methods to assess emotion regulation is also limited by shared method variance (Rutter et al., 2001; Williams & Brown, 1994). The following section provides an overview of the three most researched emotion regulation strategies that rely on conscious introspection: rumination, distraction and cognitive reappraisal.

Rumination is the tendency to repeatedly and passively think about feelings and problems (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Evidence has suggested that rumination is present during depressive state (Aldao et al., 2010; Schäfer et al., 2017), and those with higher rumination are more likely to develop subsequent MDD (Nolen-Hoeksema et al., 2008). Rumination has also been associated with overgeneral memory (Williams et al., 2007) and impaired problem-solving (Donaldson & Lam, 2004; Nolen-Hoeksema et al., 2008), which are linked to depression (Gotlib & Asarnow, 1979; Marx, Williams, & Claridge, 1992; Nezu, 1986; Williams et al., 2007). However, it has been suggested that items used to measure rumination and depression may overlap (Joormann & Stanton, 2016; Treynor, Gonzalez, & Nolen-Hoeksema, 2003). Therefore, rumination may be

tapping into a prodromal-like depression state in prospective studies, or be a shared negative rater bias, rather than acting as a distinct risk factor.

One potential intervention for rumination, and an emotion regulation strategy in its own right, is distraction (Joormann & Stanton, 2016; Nolen-Hoeksema et al., 2008). Distraction can occur by thinking about something other than the negative thoughts or engaging in activities to distract from negative thoughts. Distraction is an adaptive strategy which is employed less frequently by depressed participants than by healthy controls (Lyubomirsky & Nolen-Hoeksema, 1993). There is mixed evidence on whether distraction is beneficial for individuals with depression. When depressed and dysphoric individuals are instructed to use thought distraction it is effective in reducing negative mood (Joormann et al., 2007; LeMoult, Yoon, & Joormann, 2016). However, the improvement in mood can be temporary and distraction has been criticised as it fails to address any of the underlying problems in depression (Kross & Ayduk, 2008). Distraction may also be maladaptive in some cases, especially when it leads to avoidance (Aldao et al., 2010; Schäfer et al., 2017). Nevertheless, engaging in activities as a way of distracting from negative thoughts may be potentially helpful and is one factor targeted in behavioural activation treatment for depression (Ekers et al., 2014; Veale, 2008).

Cognitive reappraisal is the process of re-interpreting an emotive stimuli or situation in order to change the emotional response (Gross, 1998; Gross & John, 2003). A reduction in cognitive reappraisal has been reported in depressed participants in comparison to previously depressed participants and healthy controls (D'Avanzato, Joormann, Siemer, & Gotlib, 2013). Cognitive reappraisal is effective in improving negative mood in depressed participants when it is used as a strategy (Ellis, Vanderlind, & Beevers, 2013; Millgram, Joormann, Huppert, & Tamir, 2015; Smoski, LaBar, & Steffens, 2014), but it does not predict improvement of depressive

symptoms (Chambers et al., 2015) or recovery from depressive episode (Arditte & Joormann, 2011). Nevertheless, cognitive reappraisal is one approach used to treat depression in Cognitive Behavioural Therapy (Samoilov & Goldfried, 2006). Further research isolating the effectiveness of targeting cognitive appraisal for treatment is required in light of the inconsistencies in the literature.

1.2.3.4 Conclusions

To summarise, a number of cognitive deficits, cognitive biases and maladaptive emotion regulation strategies are evident in depression. There is likely a complex relationship between cognitive deficits and depression – for instance some domains of executive functioning appear to be associated with mood state, whereas others display a bidirectional relationship with depression. Further longitudinal work is required to identify whether cognitive deficits can be considered risk factors for depression. Extensive work has been conducted into cognitive biases in depression, particularly the memory biases that are evident in depression. There is strong evidence for a number of autobiographical memory biases in depression. Evidence suggests that one particular autobiographical memory bias, overgeneral memory, may be a risk factor for depression as it predicts subsequent depression in adults (Sumner et al., 2010; Williams et al., 2007). There is also emerging evidence that overgeneral memory may predict subsequent depressive symptoms and early-onset MDD in adolescence (Hipwell et al., 2011; Rawal & Rice, 2012b; Sumner et al., 2011), a key risk period for the onset of MDD. Additional longitudinal studies with larger samples are required to explore whether overgeneral memory is a risk factor or risk mechanism for early-onset depression. The fact that overgeneral memory is malleable (Williams et al., 2000), suggests that it may be a good target for therapeutic interventions if it is found to be a risk mechanism for depression. Overgeneral memory is also associated with a number of other potential risk factors

for depression, so interventions targeting overgeneral memory have the potential to affect depression through a number of different pathways. A number of potentially maladaptive emotion regulation strategies are also present in depression, including rumination as well as reductions in distraction and cognitive reappraisal. Evidence on the efficacy of targeting these strategies to improve depressive symptoms is mixed and there may be inflation in observed associations with depression due to shared method variance when participants report on their emotional regulation and their depressive symptoms. Emotion regulation is also likely influenced by lower level cognitive biases such as attention and memory that are potentially better targets for interventions given they are thought to be mechanisms for current treatments of depression (Harmer et al., 2017, 2009; Roiser et al., 2012). Given this and the wide range of evidence for autobiographical memory biases in depression, autobiographical memory was chosen for the focus of this thesis. Overgeneral memory, in particular, was selected as there is robust evidence that overgeneral memory is associated with adult depression as well as preliminary evidence for overgeneral memory as a risk factor for early-onset depression in adolescents. Further discussion of the relationship between overgeneral memory and depression is presented in section 1.3.

1.2.4. Neural correlates

Cognitive biases seen in MDD, like overgeneral memory, are likely associated with input from multiple brain regions involved in memory, emotion, visual imagery and sense of self. MDD is a disorder characterised by altered neural connections between brain areas or 'dysconnectivity' (Hulvershorn, Cullen, & Anand, 2011; Keedwell & Linden, 2013). A wealth of literature exists on alterations in brain functions and regions associated with MDD. Functional and structural neuroimaging studies have found depressed individuals show alterations in the hippocampus, amygdala, medial

prefrontal cortex (mPFC), anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (dlPFC) and the striatum in comparison to healthy controls (Diener et al., 2012; Drevets, Price, & Furey, 2008; Graham et al., 2013; Hamilton et al., 2012; Miller, Hamilton, Sacchet, & Gotlib, 2015; Pizzagalli & Treadway, 2014; Sexton, Mackay, & Ebmeier, 2013; Wang et al., 2017). Although these studies typically have small sample sizes (and are therefore susceptible to false positives), studies with larger sample sizes have found converging evidence. For instance, the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) MDD consortium combined neuroimaging data from research groups around the world and found cortical alterations in the OFC and ACC (2,148 MDD patients; 7,957 controls) (Schmaal et al., 2017), along with subcortical alterations in the hippocampus (1,728 MDD patients, 7,199 controls) (Schmaal et al., 2016), in MDD patients when compared to healthy controls. Nevertheless, evident decreases in cortical thickness and grey matter volume were greatest in individuals with recurrent MDD (Schmaal et al., 2017, 2016) and no differences were apparent between first-episode cases and controls (Schmaal et al., 2016), indicating these changes may be negative sequelae of MDD rather than an underlying predisposition. While probably not reflecting an underlying predisposition for MDD, changes associated with MDD provide insight into the pathogenesis of depression and potential maintenance factors. Although biases in how emotional material is processed are common in depression, the hippocampus is largely involved in learning and memory and is important for integrating emotional and cognitive processes through its connections (Doré et al., 2018; Femenía, Gómez-Galán, Lindskog, & Magara, 2012; Millan et al., 2012; Small, Schobel, Buxton, Witter, & Barnes, 2011). These findings therefore imply that cognitive biases and disturbances may play a role in MDD. Alternatively, cognition may develop or worsen as a consequence of recurrence.

As MDD is considered to be due to disconnections between brain areas (Hulvershorn et al., 2011; Keedwell & Linden, 2013) white matter tracts that connect regions of the grey matter together in the brain are pertinent as they provide a potential anatomical marker of neuronal communication. White matter in the brain has primarily been assessed using diffusion weighted Magnetic Resonance Imaging (dwMRI). Through dwMRI, researchers try to map the diffusion of water molecules in the brain, thereby providing an indirect measure of tissue microstructure (Jones, 2008). Diffusion can be mapped with a series of radiofrequency (RF) pulses at different time points in an MRI scanner to produce information on how much movement there is for each small segment, or voxel, in the brain. Models can be applied to the raw data to calculate the principal direction of diffusion within each voxel and display it as an ellipsoid that elongates on whichever perpendicular axis has the most diffusion. Algorithms then connect adjacent ellipsoids travelling in the same direction to produce 'streamlines' that represent white matter trajectories. Whole brain analyses (for instance, tract-based spatial statistics (TBSS; Smith et al., 2006, 2004)) or tract-specific analyses can be performed and metrics of the microstructural properties of white matter extracted.

The white matter metric most frequently used is fractional anisotropy (FA), representing a measure (between 0 and 1) of the amount of free movement of water molecules. Water movement in a hindered space, for example, within tightly packed axons in white matter tracts, would show 'anisotropic' movement or increased movement in a certain direction as structures would hinder movement in other directions. Voxels within white matter tracts will therefore have FA metrics closer to 1. Unhindered water movement, such as cerebrospinal fluid inside the ventricles, will present with FA close to 0, indicating free movement in any given direction, or 'isotropic' movement. It is important to note that FA is dependent on many different

factors within white matter that force water molecules to travel in any specific direction, and as such it is related to, but does not exclusively measure myelin content or axonal density (Beaulieu, 2002). However, FA does provide a general proxy measure of (orientation-dependent) tissue microstructure (Jones, Knösche, & Turner, 2013).

Individual studies using tract-specific and whole brain analyses have implicated a wide number of white matter tract differences between individuals with depression and healthy controls. These include white matter tracts involved in: reward processing such as the medial forebrain bundle (Bracht, Doidge, Keedwell, & Jones, 2015a; Bracht et al., 2014); emotion processing such as the cingulum (Bessette, Nave, Caprihan, & Stevens, 2014; Cullen et al., 2010) and the uncinate fasciculus (LeWinn et al., 2014; Zhang et al., 2012); and cognition such as the corpus callosum (Aghajani et al., 2014; De Diego-Adeliño et al., 2014; Guo et al., 2012a; b) and the superior longitudinal fasciculus (Cullen et al., 2010; Lai & Wu, 2014; Murphy et al., 2012).

Meta-analyses that have focused on whole brain white matter have highlighted FA reductions in tracts such as the superior and inferior longitudinal fasciculi (SLF and ILF, respectively), the corpus callosum, the arcuate fasciculus, and the anterior and posterior thalamic radiations in MDD (Chen et al., 2016; Jenkins et al., 2016; Jiang et al., 2017; Kelly et al., 2016; Liao et al., 2013; Murphy & Frodl, 2011; Wise et al., 2016). Jiang et al. (2017) found FA reductions in the genu of the corpus callosum, the third branch of the right SLF (right SLF III) and anterior thalamic projections in first-onset, medication naïve MDD patients compared with healthy controls. As individuals were experiencing their first episode of depression, the white matter differences in this study are less likely to be due to the disorder itself as repeated episodes have not occurred. Similarly, the differences are unlikely

to be due to medication as the sample is medication-naïve. Converging findings for these tracts have been seen in individual studies based on adolescents with MDD (Aghajani et al., 2014; Bessette et al., 2014; Cullen et al., 2010; Henderson et al., 2013; LeWinn et al., 2014) and for the corpus callosum and SLF in a study comparing adolescents at high familial risk of developing MDD and controls not at familial risk of MDD (Huang, Fan, Williamson, & Rao, 2011). Furthermore, FA in the anterior corpus callosum mediated the transition from subthreshold depression at age 13 to depressive disorder at age 16 (Vulser et al., 2018). Therefore the corpus callosum and SLF may be white matter tracts that are affected before the onset of the disorder, indicating potential precursors to MDD. There is a paucity of longitudinal studies tracking white matter before the onset of MDD (Dohm, Redlich, Zwitserlood, & Dannlowski, 2017), and such studies are required before any strong conclusions can be made. However, current findings show early promise for underlying neural connections that contribute to the aetiology of MDD.

In conclusion, preliminary evidence from studies of white matter tracts in MDD highlights the corpus callosum and right SLF III. These are more likely to represent brain alterations that precede the disorder because they have been identified in a meta-analysis of first-onset medication naïve participants, studies of adolescent depression and a study of adolescents at high familial risk of depression.

1.2.5. Summary of risk factors

As seen in the previous sections, MDD is a multifactorial disorder involving environmental, genetic, cognitive and neural risk correlates and risk factors. Although some of these risk factors are likely to precede the disorder (for instance, SLEs, genetics, overgeneral memory), further longitudinal studies are required to determine whether these risks do occur before the onset of a major depressive

episode. As MDD is a complex disorder it is likely that there is a complex relationship between all of these risk factors. This thesis focuses on overgeneral memory as there is emerging evidence that it may be a risk factor for adult depression (Sumner et al., 2010; Williams et al., 2007) and would be a potentially useful target for interventions as it is modifiable (Williams et al., 2000). I also sought to examine how overgeneral memory is related to other known risk factors involved in depression and whether it might be a mechanism that helps to explain how depression develops. The following sections review the evidence to date on overgeneral memory and evaluate its potential role as a risk factor for depression.

1.3. Overgeneral memory and depression

When asked to recall a specific event or autobiographical memory (AM), individuals with MDD tend to retrieve overgeneral memories (Liu et al., 2013; Williams et al., 2007). Overgeneral memory encompasses reduced AM specificity (recalling fewer 'specific events' defined as lasting less than a day) and more overgeneral memories defined as memories covering extended time periods or repeated events. The following section details how AM is assessed, the link with depression and development of overgeneral memory.

1.3.1. Assessment of autobiographical memory

Overgeneral memory is typically assessed using the Autobiographical Memory Test (Williams & Broadbent, 1986). In this paradigm, participants are given a series of emotional cue words (positive, negative or neutral) and are asked to recall a memory lasting less than a day and occurring at a specific time and place for each cue word. Participants are given a number of practice trials with the interviewer giving prompts to ensure they have understood the task properly before moving on to the main trials. Participants are given a time limit in which to recall a memory – usually 30 or 60

seconds. The responses are then transcribed and coded by researchers according to how specific they are (Williams et al., 2007; Williams & Broadbent, 1986). For instance, a participant recalling a memory for the word 'happy' would provide a *specific memory* (i.e. an event lasting less than a day) with the response 'when I went to Barry Island for the afternoon'; an *extended memory* (an event lasting more than 24 hours) with the response 'when I went on holiday to Spain for a long weekend'; a *categoric memory* (multiple events of the same theme) with the response 'every time I go to the beach'; a *semantic associate* (related to the word but not a memory) with the response 'beach', or not be able to recall an event at all (*omission*). Overgeneral memory is typically defined as an increase in memories that are not specific (i.e. categoric and extended memories) known as 'overgeneral AM' (Williams et al., 2007). However, there are differences between studies with some using a reduction in specific AMs and increases in any non-specific responses (i.e. extended, categoric, semantic associates and omissions) as measures of overgeneral memory (Sumner, 2012; Williams et al., 2007).

Although the cue word oral version of the AMT is most commonly used, there are also alternative ways of measuring AM. For instance, other cueing paradigms using scenarios, activities and free recall have been found to elicit overgeneral autobiographical memories (Williams et al., 2007). Instead of spoken instructions and responses, written versions involving minimal instructions have also been used as greater numbers of participants can be assessed using this method (Crane et al., 2014, 2016; Heron et al., 2012) and it may be more sensitive to detecting overgeneral memory in non-clinical samples (Debeer, Hermans, & Raes, 2009; Griffith et al., 2009). The association between overgeneral memory on a written AMT and depression is thus far inconsistent, with some studies finding an association (Debeer et al., 2009; Raes, Hermans, Williams, & Eelen, 2007; Raes,

Verstraeten, Bijttebier, Vasey, & Dalgleish, 2010) and others not (Crane et al., 2016; Gutenbrunner et al., 2017; Sumner, Mineka, & McAdams, 2013). Nevertheless, research conducted using think-aloud tasks, semi-structured interviews and sentence completion tasks supports the conclusion that depression can be associated with overgeneral memory using different methodologies (Anderson, Boland, & Garner, 2016; Barnhofer, de Jong-Meyer, Kleinpass, & Nikesch, 2002; Bergouignan et al., 2008).

1.3.2. Is overgeneral memory a risk factor for depression?

For overgeneral memory to be a risk factor for depression it must be associated with increases in depression in comparison to the general population and show temporal precedence to the disorder (Garber, 2006; Kazdin et al., 1997; Kraemer et al., 1997). Despite inconsistencies in methodology and AM definition, a plethora of evidence has found that depressed individuals recall more overgeneral AMs, fewer specific AMs and more non-specific responses than non-depressed controls. For instance, in the seminal review by Williams et al. (2007), there was widespread support for a link between increased overgeneral AM and reduced AM specificity being associated with MDD diagnosis and high levels of depressive symptoms. More recently, meta-analyses by Liu et al. (2013) and Ono, Devilly, & Shum (2015) found that individuals with MDD report fewer specific AMs (effect sizes g = 1.051 and 0.95 respectively) and more overgeneral AMs (effect sizes g = 1.115 and 0.56 respectively) than controls when assessed on the AMT. When specific AM and overgeneral AM were broken down by valence of emotional cue word, response to negative cues generally had lower effect sizes (Liu et al.: specific positive g = .969, specific negative g = .665; overgeneral positive g =.570, overgeneral negative g = .467; Ono et al.: specific positive g = 1.04, specific negative g = .84; overgeneral

positive g = .68, overgeneral negative g = .45). These findings suggest cue valence is important to consider.

Examination of this association in younger samples is important as a large proportion of adult cases begin in adolescence (Kessler et al., 2005; Kim-Cohen et al., 2003; Maughan et al., 2013; Thapar et al., 2012) and adolescence is a critical developmental period for sense of self (Rathbone, Moulin, & Conway, 2008) so is likely to be important for AM as people tend to recall events consistent with their sense of self (Conway & Pleydell-Pearce, 2000). Indeed, adolescence constitutes the beginning of the 'reminiscence bump', the life period from which individuals tend to recall more AMs, and find AMs easier to retrieve, than any other life period (Jansari & Parkin, 1996). Exploration of the overgeneral memory-depression relationship in adolescence may therefore help understand the development of both AM and depression. Thus far, cross-sectional studies have found higher rates of overgeneral AM and reduced AM specificity in depressed children and adolescents (Champagne et al., 2016; Kuyken, Howell, & Dalgleish, 2006; Park, Goodyer, & Teasdale, 2002; Rawal & Rice, 2012b; Valentino, Toth, & Cicchetti, 2009; Vrielynck, Deplus, & Philippot, 2007). Overgeneral memory is also associated with increases in depressive symptoms in the general population (Kuyken & Dalgleish, 2011; Raes et al., 2010). Moreover, a systematic review reported consistent moderate to large effect sizes for the association between overgeneral memory and depression (Cohen's d = 0.45 to 1.10) in child and adolescent samples irrespective of whether AM specificity or overgeneral AM was the focus of the study (Hitchcock et al., 2014).

Research has also been conducted on whether overgeneral memory is associated with subsequent depression, thereby indicating temporal precedence. The majority of studies in adults (17/22, 77.3%) are consistent with a prospective link between overgeneral memory and depression (Table 1.1. Adult samples). Of these

studies, 10 find support for a prospective relationship with specific AMs, 6 with overgeneral AMs and 2 with non-specific AMs. There were 6 studies that assessed the prospective relationship for both overgeneral AM and reduced AM specificity, with an equal number of studies supporting a link with overgeneral AM (Anderson, Goddard, & Powell, 2010; Hermans et al., 2008b; Mackinger, Loschin, & Leibetseder, 2000a), and reduced AM specificity (Boelen, Huntjens, & van den Hout, 2014; Bryant, Sutherland, & Guthrie, 2007; Hermans et al., 2008b). Cue valence was examined in 12 (54.5%) studies but little difference was seen in the number of studies finding associations with negative valence (4/11, 36.4%) and positive valence (5/12, 41.7%). Interestingly, there were differences in study results based on depression outcome measure used. Only half (8/15, 53.3%) of studies that used self-reported questionnaire measures of depressive symptoms (e.g. Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996)) found an association between baseline overgeneral memory and subsequent depression. In contrast, all studies using observer-rated (e.g. clinician or researcher rated) depressive symptoms (8/8, 100%) or MDD diagnosis (2/2, 100%) of depression found a prospective association. In the studies using examining both self-reported and observer-rated depression outcomes, prospective associations were reported only for observer-rated outcomes in two studies (Dalgleish, Spinks, Yiend, & Kuyken, 2001; Hermans et al., 2008a), while one study found prospective associations for both self- and observer-rated symptoms (Peeters, Wessel, Merckelbach, & Boon-Vermeeren, 2002). Self-reported depressive symptoms on questionnaires are typically comprised of a wide range of possible symptoms associated with depression, whereas observer-rated scales and interviews are consistent with diagnostic criteria (DSM or ICD) and are more stringent. Thus, inconsistencies in the literature may be attributable to differences in depression assessment methodology.

Table 1.1. Studies assessing the prospective relationship between overgeneral memory and depression

Study	Sample	Mean age (SD) in years at baseline [range]	% female	AM assess-ment	Memory analysed	Depression measure at follow-up	Covariates	Interaction tested	Length of follow-up	Evidence of prospective association (effect size)	Evidence of interaction (effect size)
Adult samples (over 18)											
Anderson et al. (2010)	Non-clinical - students (n=135)	22.2 (6.8) [18-48]	82.2%	Oral AMT	specific categoric	BDI	T1 BDI, daily hassles	AM x daily hassles	96.5 days	x (β = 0.09) ✓ (β = 0.17)	✓(β = -1.76) x (β = 0.47)
Boelen et al. (2014)	Non-clinical - students (n=142)	21.5 (2.3)	90.1%	SCEPT	specific overgeneral	Residualised change in BDI	Gender, T1 anxiety	AM x SLEs	1 year	✓ (β = -0.24) x (not reported)	x (largest β = 0.06)
Brewin, Reynolds, & Tata (1999)	Clinical - MDD patients (n=52)	42.2 (13.9) [20-73][a]	62.9%[a]	Oral AMT	overgeneral (total, +, -)	BDI	T1 BDI		6 months	x (largest β = 0.11)	
Brewin, Watson, McCarthy, Hyman, & Dayson (1998)	High-risk - cancer patients with high (n=43) and low (n=57) depressive symptoms	54 (13.3) [24-81][a]	73.8%[a]	Oral AMT	overgeneral (total, +, -)	HADS	T1 HADS, cancer stage		6 months	x (not reported)	
Brittlebank, Scott, Williams, & Ferrier (1993)	Clinical - patients taking anti-depressants (n=19)	42.7 (14)[a]	72.7%[a]	Oral AMT	non-specific (neutral, -) non-specific (+)	HRSD	T1 HRSD, T1 DAS		7 months (n=13)	x (not reported) ✓ (not reported)	

Study	Sample	Mean age (SD) in years at baseline [range]	% female	AM assess-ment	Memory analysed	Depression measure at follow-up	Covariates	Interaction tested	Length of follow-up	Evidence of prospective association (effect size)	Evidence of interaction (effect size)
Bryant et al. (2007)	High-risk - fire fighter recruits (n=46)	29.6 (5)[a]	0%	Oral AMT	specific (+) specific (-) categoric (+, -) extended (+, -) omission (+, -)	BDI-II	T1 BDI-II, TEQ, CAPS		4 years	✓ (β = -0.32) x (not reported)	
Dalgleish et al. (2001)	Clinical - SAD patients (n=21)	42.1 (12.2) [16-60]	81%	Oral AMT	non-specific (+)	HRSD BDI	T1 HRSD T1 BDI		6-8 months	✓ (β = 0.41) x (β = 0.39)	
Gibbs & Rude (2004)	Non-clinical - students (n=81)	21.2 (2.6)	60.5%	Oral AMT	categoric	BDI	T1 BDI, NLEQ	AM x SLEs	4-6 weeks	x (β = 0.10)	✓ (β = 0.22)
Hermans et al. (2008b)	Clinical - MDD inpatients (n=26)	39.9 (10.8) [24-59]	53.8%	Oral AMT	categoric specific categoric specific	SCID MDD diagnosis BDI-II	T1 BDI-II, CBT (yes/no), DAS, SLCS-R		3-4 weeks,	✓(OR = 2.05) ✓(not reported) x (β = 0.16) x (β = 0.13)	
Hipwell, Reynolds, & Crick (2004)	High-risk - pregnant women (n=94)	30.3 (4.4) [17-39]	100%	Oral AMT	specific (+) specific (-) specific (+) specific (-)	EPDS	T1 BDI, T1 neuroticism, education, PBI, emotional difficulties (yes/no), DSC		2 weeks after birth 8 weeks after birth	x (β = -0.20) x (β = 0.15) ✓ (β = -0.25) x (β = 0.09)	
Kleim & Ehlers (2008)	High-risk - assault survivors (n=190)	34.4 (11.2)[a]	32.5%[a]	Oral AMT	specific	SCID MDD diagnosis SCID MDD symptoms	T1 SCID MDD symptoms, ASD diagnosis	AM x sex/ childhood abuse/ ethnicity/ MDD history	6 months post-assault	✓ (not reported) ✓ (β = -0.14)	✓ MDD (β = -0.19)

Study	Sample	Mean age (SD) in years at baseline [range]	% female	AM assess-ment	Memory analysed	Depression measure at follow-up	Covariates	Interaction tested	Length of follow-up	Evidence of prospective association (effect size)	Evidence of interaction (effect size)
Liu et al. (2016)	Clinical - first-episode MDD (n=125; at follow up remitted n=94; non-remitted n=34)	Remitted 39.2 (12.1); Non-remitted 37.7 (12.8)	66.4%	Oral AMT	overgeneral	HRSD	Illness duration, T1 HRSD, T1 rumination		12 months	✓ (β = 0.43)	
Mackinger et al. (2000a)	High-risk - pregnant women (n=50)	29.3 (4.4) [20-40]	100%	Oral AMT	categoric (-) categoric (+) specific (+, -) extended (+, -)	Change in 10 item EPDS	Mental speed, all AM indices		5 months (3 months after birth)	✓ (β = 0.36) x (not reported)	
Mackinger et al. (2004)	Clinical - alcohol dependency and MDD (n=65)	43.2 (8.3)	0%	Oral AMT	specific (total) specific (+) specific (aggressive) specific (-)	MADRS	T1 MADRS, MMSE, mental speed, severity of alcohol dependence		21-35 days	✓ (β = -0.38) ✓ (β = -0.31) ✓ (β = -0.40) x (not reported)	
Peeters et al. (2002)	Clinical - MDD patients (n=25)	41.5 [27-58]	60%	Written AMT	specific (-) specific (+) specific (-) specific (+)	Average T2+T3 MADRS Average T2+T3 SDS	T1 MADRS, duration of episode		3 and 7 months	✓ (β = -0.66) x (β = 0.40) ✓ (b = -4.2) x (not reported)	
Raes et al. (2008)	Clinical - MDD patients undergoing ECT (n=25)	52.6 (11.9) [33-81]	52%	Written AMT	categoric	HRSD change from end of ECT to follow up	T1 HRSD, HRSD post-treatment		1 week after end of ECT (T1 to end of ECT not reported)	✓ (β = 0.57)	

Study	Sample	Mean age (SD) in years at baseline [range]	% female	AM assess-ment	Memory analysed	Depression measure at follow-up	Covariates	Interaction tested	Length of follow-up	Evidence of prospective association (effect size)	Evidence of interaction (effect size)
Raes et al. (2006a)	Clinical - MDD patients (n=24)	40.2 (11.6) [21-65][a]	67.9%[a]	Oral AMT	specific (-) specific (+) non-specific (-) non-specific (+) specific (-)	HRSD	T1 HRSD, all AM indices Above plus rumination		7 months	✓ (β = -0.91) x (β = 0.15) x (β = -0.52) x (β = 0.33) x (β = -0.22)	
Spinhoven, Van der Does, Van Dyck, & Kremers (2006b)	Clinical - BPD outpatients (n=55; 37 with comorbid T1 MDD)	BPD+ MDD 29.8 (8.6); BPD- MDD 31.7 (7.9)	90.9%	Modified trait oral AMT	specific (+, -) categoric (+, -)	BDI	T1 BDI		15 months	x (not reported)	
Sumner et al. (2013)	High-risk - students high and low MDD symptoms (n=30)	19.2 (0.9) [17-21][a]	56.3%[a]	SDMT Oral AMT miAMT	specific	DID	T1 DID		10 weeks	✓ (β = -0.40) x (β = -0.18) x (β = -0.11)	
Van Daele, Griffith, Van den Bergh, & Hermans (2014)	Non-clinical - community sample (n=156)	38.8 (14.1) [18.9-68.8]	66%	Written AMT	categoric	DASS-21 trajectory	Gender, education, age		5, 6, 12 and 18 months	✓ (slope = 0.08)	
van Minnen, Wessel, Verhaak, & Smeenk (2005)	High-risk - women with failed IVF treatment (n=74)	33.3 (3.9) [24-43]	100%	Oral AMT	Specific (total, -) NSR specific (total, -) Specific (+) SR specific (total, +, -) NSR specific (+)	BDI residual gain scores			4 weeks	✓ (rs=-0.21 to 0.30) x (rs -0.21 to 0.19)	

Study	Sample	Mean age (SD) in years at baseline [range]	% female	AM assess-ment	Memory analysed	Depression measure at follow-up	Covariates	Interaction tested	Length of follow-up	Evidence of prospective association (effect size)	Evidence of interaction (effect size)
Yanes, Morse, Hsiao, Simms, & Roberts (2012)	Clinical – HIV+ patients with mild depression (n=46)	45 (9.9)	34.8%	Oral AMT	specific	Change in DASS-21	T1 DASS-21, perceived stress	AM x perceived stress	4 months	x (b = 0.06)	✓ (b = 0.09)
Youth samples (under 18)											
Crane et al. (2016)	Unselected population cohort (n=2620)	[95% 13 years 1-3 months]	61.6%[a]	Written AMT	specific	Above/ below short MFQ clinical cut point	T1 MFQ symptoms, gender, SES factors	AM x SLEs	3 years	x (OR = 0.97)	x (OR = 0.99)
Gutenbrunner et al. (2017)	Community sample (n=269)	Boys 13.1 (1.2) Girls 12.5 (1) [10-15]	46.5%	Written miAMT	specific (+, -, total) overgeneral (+, -, total)	Change in CDI-2	Gender, age	AM x rumination trajectory	T1-T2 12 months; T2-T3 11 months	x (not reported)	x (not reported)
Hamlat et al. (2015)	Community sample (n=160)	12.44 (0.63) [12-13]	43.8%	Oral AMT	overgeneral specific	CDI	T1 CDI, age, SES, T1-T2, SLEs, race, rumination	Gender x AM x SLEs x rumination	9 months	x (β = 0.62) x (β = -0.18)	✓ 4-way (β = -.05) ✓ SLEs (β = -.08)
Hipwell, Sapotichne, Klostermann, Battista, & Keenan (2011)	High risk - enriched for depressive symptoms (n=195)	11.5 (0.4)	100%	Oral AMT	overgeneral overgeneral (+) overgeneral (-)	K-SADS-PL MDD symptoms	T1 K-SADS-PL MDD symptoms, race, SES, verbal IQ	AM x race	1 year	✓ (b = 0.02) ✓ (b = 0.02) x (b = 0.01)	✓ (b = -0.02) ✓ (b = -0.02) x (b = -0.01)
Park, Goodyear, & Teasdale (2005)	Clinical - first episode MDD (n=94)	Boys 14.6 (1.5) Girls 14.9 (1.3) [12-17]	70.2%	Oral AMT	categoric	K-SADS-PL MDD diagnosis	T1 MFQ, T1 HRSD, IQ, DSC		12-15 months	x (not reported)	

Study	Sample	Mean age (SD) in years at baseline [range]	% female	AM assess-ment	Memory analysed	Depression measure at follow-up	Covariates	Interaction tested	Length of follow-up	Evidence of prospective association (effect size)	Evidence of interaction (effect size)
Rawal & Rice (2012b)	High risk - children of parents with recurrent MDD (n=242)	13.7 (2) [10-18][a]	59.6%[a]	Oral AMT	overgeneral (-) overgeneral (+) overgeneral (total) overgeneral (-)	CAPA MDD symptoms CAPA new-onset MDD	T1 CAPA symptoms, age, IQ, gender	AM x gender	12.5 months	✓ (β = 0.12) x βs < .08 ✓ (B = 0.50)	✓ (β = 0.18)
Stange, Hamlat, Hamilton, Abramson, & Alloy (2013)	Community sample (n=174)	12.3 (0.6) [12-13][a]	57.9%[a]	Oral AMT	overgeneral	CDI	T1 CDI, T1 K-SADS-E MDD, SES, gender, age	AM x emotional abuse x race	8 months	x (β = 0.18)	✓ (β = -0.25)
Sumner et al. (2011)	High risk - previous major/minor depression (n=55)	17.1 (0.4) [16-18]	75%	Oral AMT	specific	SCID MDD episode	T1 SCID, T1 IDD, chronic interpersonal stress	AM x chronic interpersonal stress	16.1 months	✓(OR = 0.45)	✓(OR = 0.22)

N.B. n quoted is for analysis with all covariates mentioned; [a] = information only present for baseline n.

Abbreviations: *Sample:* BPD - Borderline Personality Disorder; ECT - electroconvulsive therapy; IVF - in vitro fertilisation; MDD - Major Depressive Disorder; SAD - Seasonal Affective Disorder. *AM assessment:* AMT- Autobiographical Memory Test; miAMT - minimal instruction Autobiographical Memory Test; SCEPT - Sentence Completion for Events in the Past Test; SDMT - Self-Defining Memory Task.

Memory analysed: (-) - response to negative cue; (+) - response to positive cue; NSR - non-stress related; SR - stress related.

Depression measure at follow up: BDI - Beck Depression Inventory; CAPA - Child and Adolescent Psychiatric Assessment; CDI - Children's Depression Inventory; DASS-21 - Depression Anxiety Stress Scale-21; DID - Diagnostic Inventory for Depression; DSM-IV - Diagnostic Statistical Manual for Mental Disorders, 4th edition; HADS - Hospital Anxiety and Depression Scale; HRSD - Hamilton Rating Scale for Depression; K-SADS-PL - Kiddie Schedule for Affective Disorder and Schizophrenia-Present and Lifetime; MADRS - Montgomery-Asberg Depression Rating Scale; MFQ - Mood and Feelings Questionnaire; SCID - Structured Clinical Interview for DSM-IV; SDS - Self-rating Depression Scale; T2 - Time 2; T3 - Time 3.

Covariates: AM - autobiographical memory; ASD - Acute Stress Disorder; CAPS - Clinician Administered PTSD Scale; CBT - Cognitive Behavioural Therapy; DAS - Dysfunctional Attitudes Scale; DSC - Depressed States Checklist; IDD - Inventory to Diagnose Depression; K-SADS-E - Kiddie Schedule for Affective Disorder and Schizophrenia-Epidemiological; MMSE - Mini-Mental State Examination; NLEQ - Negative Life Events Questionnaire; PBI - Parental Bonding Inventory; SES - socioeconomic status; SLCS-R - Self-liking/Self-Competence Scale Revised; SLEs - stressful life events; TEQ - Traumatic Events Questionnaire; T1 - Time 1.

Prospective studies in childhood and adolescence are particularly important as they offer the opportunity to examine the relationship between overgeneral memory and depression before the potential scarring effects of depressive episodes have occurred. Fewer prospective studies have been conducted with youth samples (participants under 18) as can be seen in Table 1.1. (Youth samples). The findings from these studies are inconsistent, with only 3 of the 8 studies (37.5%) suggesting a prospective link between overgeneral memory and depression. Of these studies, 2 find a prospective relationship for overgeneral AM (Hipwell et al., 2011; Rawal & Rice, 2012b) and 1 for specific AM at baseline (Sumner et al., 2011). Three studies examined cue valence, with one study supporting an association with negative valence (Rawal & Rice, 2012b) and one study supporting an association with positive valence (Hipwell et al., 2011). Youth studies that support a prospective link between overgeneral memory and depression differ from studies that do not find an association in two ways. Firstly, supporting studies use depression outcomes rated by observers on interviews, whereas none of the four studies using self-reported depression outcomes find a prospective association. Secondly, supporting studies use samples at high risk of developing depression, in comparison to non-supporting studies that have used community or population samples. Two additional studies found an interaction whereby a prospective relationship was present, but only in specific subgroups of the sample that were at high-risk of developing depression (Hamlat et al., 2015; Stange et al., 2013). This has led some to argue that the prospective association between overgeneral memory and depression may only be present in samples already at risk for MDD (Crane et al., 2016; Gutenbrunner et al., 2017). Further research is required to determine why this difference occurs and whether overgeneral memory can predict subsequent depression in population-based samples.

In summary, there is robust evidence for a link between overgeneral memory and concurrent depression but a prospective link is less clear. In adults and children/adolescents with MDD there are higher rates of overgeneral memory than in the general population. In longitudinal studies with adult participants a prospective association between overgeneral memory and depression is observed in the majority (17/22) of studies. However, there are fewer studies in younger age groups looking at a prospective association and results from these studies are inconsistent (3/8 studies supporting a prospective association). Inconsistencies in both the adult and youth literature stem from differences in AM measure used (definition and valence) as well as differences in depression outcomes. Studies investigating the prospective association in adolescent depression also vary according to sample (high-risk versus typical risk of developing depression). Consequently, the evidence base for an association with adolescent depression is less strong and more studies in youth samples are required. Replications of methodology used in studies of high-risk samples in population-based samples are warranted as they can highlight whether inconsistencies in the literature are due to methodological differences or differences in participant risk for depression.

1.3.3. Why might overgeneral memory be important in depression?

Despite the wealth of research investigating the presence of overgeneral memory in depression (section 1.3.2; Liu et al., 2013; Ono, Devilly, & Shum, 2015; Williams et al., 2007), the processes through which overgeneral memory may influence mood and contribute to depression are less clear. A number of potential mechanisms have been suggested, but these disparate theories have yet to be unified in a comprehensive model. One area of research has focused on AM as a strategy for emotion regulation which, when disrupted, can lead to periods of low mood and depression. For instance, recalling positive AMs can improve mood in non-depressed

adults (Joormann & Siemer, 2004; Joormann et al., 2007; Seebauer et al., 2016) and in depressed adults when concrete details are focused on (Werner-Seidler & Moulds, 2012) or self-relevant positive memories are recalled (Werner-Seidler et al., 2017). Activating neural substrates for positive experiences has also been seen to reduce depressive-like symptoms in mice (Ramirez et al., 2015). Therefore, if an individual is unable to retrieve specific positive AMs, they may have difficulties in regulating low mood which over time may lead to depression.

AM is also important for sense of self. AMs are closely associated with aspects of the self and self-schemas, validating and supporting how we perceive ourselves (Conway & Pleydell-Pearce, 2000). Difficulties in retrieving specific AMs, particularly positive memories, may therefore promote negative self-thoughts and low self-esteem, which are common features in depression (Beck, 1967, 2008; Gotlib & Joormann, 2010; World Health Organisation, 1994). Indeed, early depression research by Beck suggested that dysfunctional attitudes or negative thoughts about the self are associated with cognitive errors such as negative overgeneralisations (Beck, 1967, 2008). A recent longitudinal study found that in adolescents experiencing stressful life events, positive AM specificity reduced subsequent depressive symptoms via a reduction in negative self-cognitions (Askelund et al., 2019). Therefore, promoting negative thoughts and self-schema may be one way through which overgeneral memory can influence depressive symptomatology.

Collective reminiscence of AMs serves an important social function (Harris et al., 2008). Not only does reminiscing about events in groups reduce the negative emotions and increase the positive tone associated with memories in comparison to reminiscing by oneself (Maswood, Rasmussen, & Rajaram, 2018), telling personal stories and recalling shared memories help with establishing and maintaining relationships (Harris et al., 2008). Depression is associated with interpersonal

difficulties and poor social functioning (Kupferberg et al., 2016), and there is some evidence to suggest these difficulties can precede the onset of MDD (Eberhart & Hammen, 2006; Segrin & Rynes, 2009). Indeed, one common psychological treatment for depression, interpersonal therapy (IPT), targets interpersonal relationships and social functioning to improve mood (Hollon et al., 2002; Markowitz & Weissman, 2012). Overgeneral memory may contribute to poor or less effective social functioning, or social functioning may affect overgeneral memory, thereby increasing susceptibility to depression. Nevertheless, longitudinal studies are required to test this.

Similarly, overgeneral memory may influence liability to depression through social problem-solving. Overgeneral memory is associated with reduced efficacy of social problem-solving (Goddard et al., 1996, 1997; Leahy, Ridout, Mushtaq, & Holland, 2018; Raes et al., 2005). It has been proposed that this is because recalling specific information from previous experiences may be useful in guiding approaches for social problems that have no obvious solution (Pillemer, 2003). Difficulties in social problem-solving are common in depression (Gotlib & Asarnow, 1979; Marx et al., 1992; Nezu, 1986) so this may be one way that overgeneral memory affects depression.

In conclusion, the mechanisms through which overgeneral memory can lead to depression are likely complex. Overgeneral memory may affect depression through a number of processes but evidence for these links is preliminary. Thus far, research has looked at the cross-sectional associations but longitudinal examinations are required to explore which factors are mediators or mechanisms for how overgeneral memory affects depression. Deficits in accessing specific AMs and increases in overgeneral AMs may affect depression via a number of factors; namely inability to repair negative mood, negative self-schema, poorer social functioning

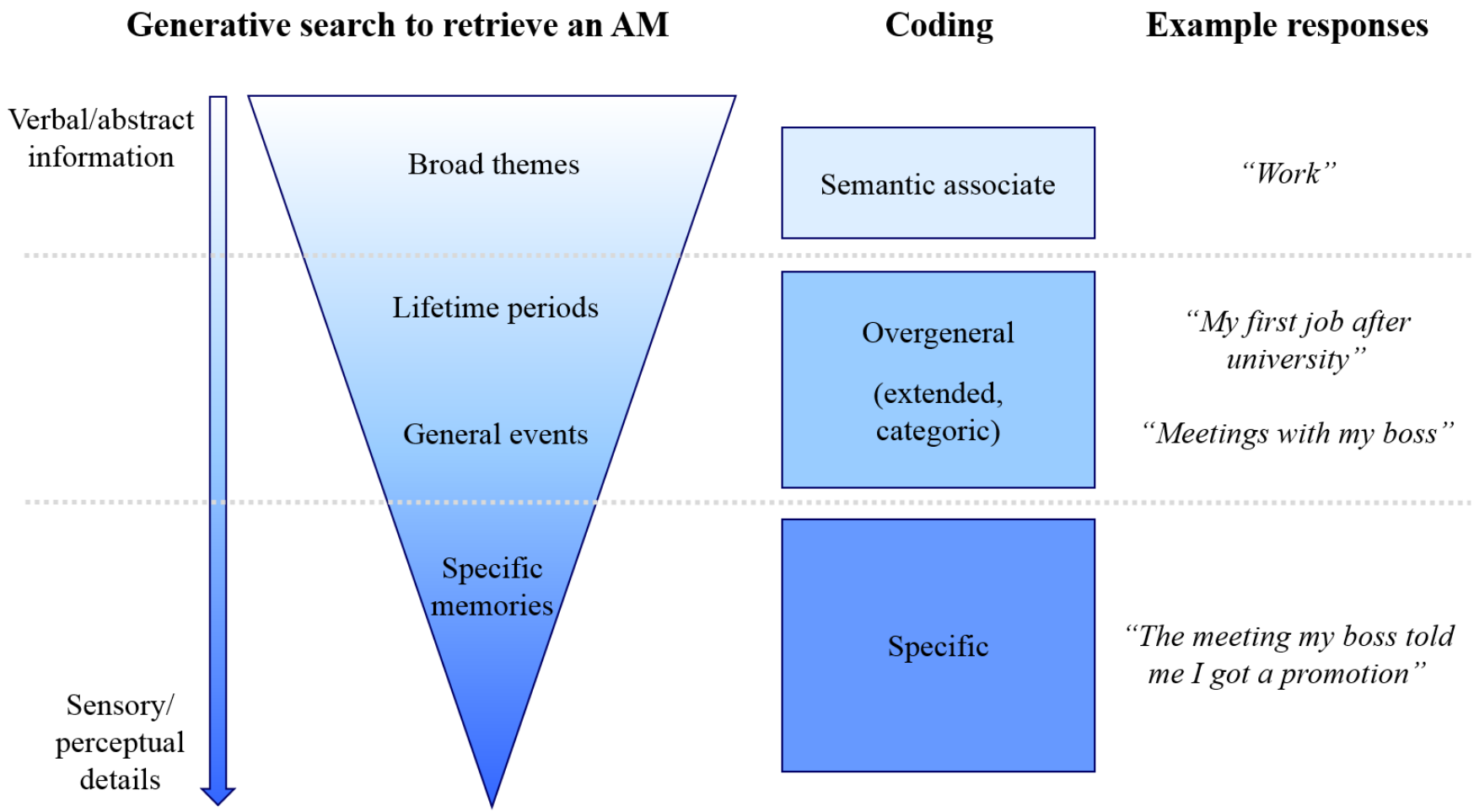
and poorer social problem-solving. There is building evidence that inability to access positive specific memories may promote low mood but it not clear how this develops into MDD. Thus far, the strongest evidence is for negative self-schema as there is longitudinal evidence that positive AM specificity reduces subsequent depression symptoms through a reduction in negative self-cognitions (Askelund et al., 2019). The ability to recall specific AMs is also clearly important for social functioning and social problem-solving. However, further longitudinal research is required to explore these sorts of associations and how they link to depression. As with most risk factors for psychiatric conditions, overgeneral memory is likely to contribute to depression through a combination of these processes, in addition to other processes and factors yet to be identified.

1.3.4. Aetiology of overgeneral memory

Despite the involvement of overgeneral memory in depression, little is understood about how the phenomenon develops. The most prominent theory on how overgeneral memory develops is known as the CaR-FA-X model (Williams et al., 2007). This theory proposes that for generative retrieval (i.e. intentionally searching for a memory that does not spring to mind automatically), individuals undertake a hierarchical search starting at a more abstract level with conceptual information before working down the levels to more specific sensory and perceptual details (Conway & Pleydell-Pearce, 2000; Williams et al., 2007). For instance, as presented in Figure 1.1., searching for a specific memory for the word 'achieve' could begin at a broad, conceptual level (e.g. 'work') and progress through lifetime periods (e.g. 'my first job after university') to general events (e.g. 'meetings with my boss'), and then to a specific memory containing event-specific knowledge (e.g. 'the meeting my boss told me I got a promotion'). Retrieval of an overgeneral memory occurs when this hierarchical search is truncated early so that a more general memory is recalled

rather than moving down the levels to retrieve a specific memory. Several processes are thought to prevent the progression of this hierarchical search for which the CaR-FA-X model is named: **c**apture **a**nd **r**umination, **f**unctional **a**voidance and reduced e**x**ecutive resources.

Figure 1.1. Generative retrieval of an autobiographical memory (AM) according to the CaR-FA-X model (Williams et al., 2007)



Capture and rumination occurs when an emotional cue word activates self-relevant information and causes an individual to ruminate on self-concepts related to the cue. As the participant is ruminating at this general level, they are unable to continue the search to find a specific memory and retrieve an overgeneral memory instead. *Functional avoidance* is thought to develop over time as an emotion regulatory strategy in response to stressors. Functional avoidance involves passively avoiding remembering the specific details of negative events (such as perceptual details like smells, sounds, sights that can be highly emotionally arousing) because these may evoke distressing feelings. The individual remains at the general level of AM search in order to avoid these painful feelings. It is proposed that this may be adaptive in the short term (Hermans et al., 2008a; Raes, Hermans, Williams, & Eelen, 2006b) but maladaptive if it becomes generalised to other (non-distressing) memories. *Reduced executive resources* refers to the inability to actively search down the hierarchy from general knowledge to event-specific knowledge due to reduced executive functioning or resources; for instance, reductions in inhibition, working memory capacity, updating and maintaining information in working memory, and verbal fluency (Sumner, 2012). The CaR-FA-X model has received considerable support in the literature (see Sumner (2012) for a review) but several aspects require further investigation, including how stressors and trauma contribute to functional avoidance and longitudinal studies examining how functional avoidance develops over time (Sumner, 2012; Williams et al., 2007).

Other theories of the development of autobiographical memory have also implicated childhood and adolescence as important periods of development. For instance, Fivush (2011) proposes that AM recall is a socio-cultural skill that is learnt via maternal-reminiscing style in childhood and develops through adolescence as an individual's sense of self becomes more defined. Research has found mothers who

exhibit elaboration and open-questioning when reminiscing with their child were more likely to have children who recalled more information about past events in mother-child interactions than mothers with a low elaborative reminiscing style (Fivush, Haden, & Reese, 2006; Valentino, 2011). The theory put forth by Bauer (2015) proposes that forgetting is important for the development of AM (particularly in youth), and that in addition to AM recall increasing over childhood, there is a decrease in forgetting over time. Such theories highlight the importance of exploring the relationship between overgeneral memory and depression in younger age ranges such as adolescence.

1.3.5. Overgeneral memory and other psychiatric symptoms and disorders

Whether overgeneral memory could be a risk factor for disorders other than MDD is also an important question. Given the strong phenotypic and genetic associations between depression and other psychiatric disorders (Kessler et al., 2003; Lee et al., 2013; Thapar et al., 2012; Wray et al., 2018), common risk factors are likely. The majority of overgeneral memory research has examined the relationship with a single disorder rather than assessing whether overgeneral memory could be a risk factor for multiple disorders. There is evidence to suggest an overgeneral memory bias exists in post-traumatic stress disorder (PTSD) (Moore & Zoellner, 2007; Ono et al., 2015; Williams et al., 2007) but prospective studies controlling for depression are needed to determine if overgeneral memory could be a risk factor for PTSD. Other disorders linked to MDD (such as anxiety disorders, Obsessive Compulsive Disorder and Borderline Personality Disorders) are typically not associated with overgeneral memory once depression is taken into account (Spinhoven et al., 2006b; Wenzel, Jackson, & Holt, 2002; Wenzel & Jordan, 2005; Wessel, Meeren, Peeters, Arntz, & Merckelbach, 2001; Wilhelm, McNally, Baer, & Florin, 1997). More recent research has indicated that overgeneral memory is not associated with anxiety and

externalising disorders in adolescents at high familial risk of MDD (Rawal & Rice, 2012b). Nevertheless, given anxiety is a clinical antecedent for early-onset MDD (Rice et al., 2017b; Rutter et al., 2006; Wittchen, Kessler, Pfister, & Lieb, 2000) and the paucity of research on AM and anxiety, future research examining AM and depression should also ensure the link with anxiety is assessed.

Emerging evidence has suggested individuals with schizophrenia may have an overgeneral memory bias. In a meta-analysis of 14 studies of AM in schizophrenia, AM specificity was significantly reduced in patients with schizophrenia spectrum disorders compared with healthy controls (effect size g = 0.97; Berna et al., 2016). This effect size is similar in size to those seen in depression meta-analyses (Liu et al. g = 1.05; Ono et al. g = .95); however there was considerable variation in the methods employed to assess AM in studies examining the relationship between schizophrenia and AM specificity. There is less research investigating overgeneral AM, but early studies show that individuals with schizophrenia recall more overgeneral AMs than controls (Kaney, Bowen-Jones, & Bentall, 1999; Warren & Haslam, 2007; Wood, Brewin, & McLeod, 2006) and recall similar levels of overgeneral AM to individuals with depression (Warren & Haslam, 2007). Nevertheless, further research is required to investigate the link between overgeneral AM and schizophrenia, particularly prospective longitudinal studies that can determine whether overgeneral memory can be a risk factor for schizophrenia. Such studies would be beneficial in determining whether overgeneral memory is related to depression specifically or extends to other psychiatric conditions that involve emotional distress.

1.3.6. Rationale for thesis

In summary, overgeneral memory has been associated with contemporaneous depression, and prospective associations with subsequent depression suggest that overgeneral memory may be a risk factor for depression. However, there are several areas that still warrant investigation due to inconsistencies and gaps in the literature. Firstly, there are generally fewer studies in adolescence and the evidence for a prospective association between overgeneral memory and depression is less consistent in adolescents. Consequently, more studies in youth samples are needed. In particular, whether overgeneral memory displays temporal precedence to depression in adolescents at typical-risk of developing MDD requires investigation as no prospective association has been found in community and population samples. Secondly, whether overgeneral memory is a risk process through which other known risk factors (e.g. environmental and genetic influences) exert their influence on depression has not yet been explored. Given that overgeneral memory has been shown to be modifiable through intervention (Hitchcock, Werner-Seidler, Blackwell, & Dalgleish, 2017; Williams et al., 2000), it is important to determine whether overgeneral memory could be a risk mechanism which could reduce depression when manipulated. Finally, there is a need to consider plausible mechanisms that might underlie the link between overgeneral memory and depression as this can provide support for overgeneral memory as a risk mechanism (Academy of Medical Sciences, 2007; Hill, 1965; Rutter, 2007). Autobiographical memory is likely to be related to cognitive and neural circuitry. Given the literature on altered brain connectivity in depression, examining white matter tracts that transfer information across the brain is one way of investigating this question.

1.4. Aims of the thesis

The primary aim of the thesis is to examine whether overgeneral memory could be a risk factor or risk mechanism for early-onset depression. In order to do this, a number of studies are included, several of which use a longitudinal design, to examine the association of overgeneral memory with depression, and the development and aetiology of AM. Specifically, the thesis aims to:

1) Test the longitudinal relationship between overgeneral memory and depression (and investigate the discrepancy in findings according to sample type);
2) Examine the longitudinal development of AM. Specifically, whether (a) stressful life events and (b) genetic risk for MDD influence AM as a way of investigating whether overgeneral memory is a mechanism through which known risk factors for depression exert their effects on depression liability; and
3) Examine whether white matter tracts known to show reduced FA in MDD are also associated with AM.

This thesis focuses on adolescents and young adults, as this is an important period of risk for the onset of depression (Maughan et al., 2013), and further research is required in younger samples due to the aforementioned smaller and more inconsistent evidence base (section 1.3.2). Two adolescent samples are used in this thesis – a general population cohort (The Avon Longitudinal Study of Parents and Children, ALSPAC), and a cohort at high familial risk of developing MDD due to having a parent with recurrent depression (The Early Prediction of Adolescent Depression (EPAD) study).

Although selecting a single measure of overgeneral memory that is likely to be associated with depression based on the previous literature is not straight forward, I did this to minimise issues of multiple testing and potential data mining. Different studies have focused on different indices of overgeneral memory but in this thesis I focus on overgeneral AM to negative cues as my primary variable. This is because overgeneral AM to negative cues was associated with subsequent depression in the largest study of individuals at high-risk of developing MDD to date (Rawal & Rice, 2012b). Overgeneral AM to negative cues is also theoretically important because overgeneral memory is hypothesised to develop through functional avoidance of negative events, and therefore may develop for negative memories before becoming generalised to all memories (section 1.3.4; Williams et al., 2007)

The rest of the thesis is set out as follows: Chapter 2 presents details on each of the samples (ALSPAC and EPAD), measures and procedures. Chapter 3 explores the prospective relationship between overgeneral AM and depression in a large, population-based UK sample (ALSPAC) and aims to replicate previous findings in high risk samples (Rawal & Rice, 2012b). Chapter 4 examines the relationship between SLEs and overgeneral memory in the high-risk sample (EPAD). Due to the timing of life event assessments in ALSPAC it was not possible to replicate these analyses in the general population sample. Chapter 5 examines whether polygenic risk scores for MDD are associated with overgeneral AM to negative cues. Analyses are performed in both cohorts. Chapter 6 assesses whether white matter tracts linked to depression are associated with overgeneral memory over and above depressive symptoms. This was performed in a subsample of EPAD cohort that participated in a neuroimaging study as young adults. Chapter 7 considers findings from the empirical chapters as well as limitations, clinical implications and future directions of the research.

1.5. Research questions

In conclusion, in this thesis I hope to address the following questions:

1. Is overgeneral memory longitudinally associated with depression in a population-based sample?
2. Could overgeneral memory be a risk mechanism through which other known risk factors for depression (i.e. stressful life events, genetic variants associated with depression) exert their effect?
3. Is white matter microstructure previously associated with MDD related to overgeneral memory?

2. Methods

This chapter summarises the samples and general methods that will be used throughout the thesis. Two samples were used: the Avon Longitudinal Study of Parents and Children (ALSPAC), which includes typically developing offspring that are broadly representative of the UK general population (Golding, Pembrey, Jones, & The ALSPAC Study Team, 2001); and the Early Prediction of Adolescent Depression (EPAD) study, which is a UK high-risk cohort that focuses on offspring of depressed parents (Mars et al., 2012). These cohorts were chosen as they 1) both measure autobiographical memory and depression in adolescence; 2) have molecular genetic data available; and 3) are longitudinal, allowing investigation of the relationship between memory and depression over time. Using both high-risk and population-based samples enables investigation of the overgeneral AM-depression relationship across the genetic and environmental risk spectrum. ALSPAC represents the general population better but will have a lower incidence of depression, whereas the EPAD study has a higher incidence of depression due to parental depression conferring environmental and genetic risk. As previous research has mainly focused on normative and high-risk adolescent samples separately, this thesis aims to build on previous work by considering the overgeneral AM-depression relationship with both types of sample.

The primary variables of interest in this thesis were autobiographical memory and depression. Overgeneral AM to negative cues was the primary AM indicator throughout the thesis because it has been prospectively associated with subsequent depression in the high-risk sample (Rawal & Rice, 2012b) and negative valence is theoretically important for the development of overgeneral memory (Chapter 1, section 1.3.4; Williams et al., 2007). Where associations were present for

overgeneral AM to negative cues, further tests assessed alternative AM indices – overgeneral AM to positive cues, specific AM to negative cues, specific AM to positive cues. Memory content valence was also considered where possible as overgeneral memory is thought to develop first for negative *memories* (Williams et al., 2007) and cue valence and memory content valence may not necessarily be the same (Lemogne, Limosin, & Fossati, 2013; Young, Erickson, & Drevets, 2012b). There may therefore be differences in results for cue valence and memory content valence. Depression measures used in the thesis were MDD diagnosis and symptom count according to DSM-IV criteria (American Psychiatric Association, 1994) and self-reported depressive symptomatology broadly defined (on questionnaires). When included as a covariate, broadly defined depressive symptoms were used as this provides a dimensional measure of current mood. Where possible, DSM-IV depressive symptom count was used as an outcome as this is more closely aligned to diagnostic criteria for MDD.

Risk factors of interest were: SLEs and genetic liability to MDD given their involvement in the aetiology of depression (see Chapter 1, sections 1.2.1.1 and 1.2.2).

Potential covariates or confounding factors that were considered were: age, gender and IQ. These factors were chosen as covariates as they are associated with both depression (Maughan et al., 2013; Twenge & Nolen-Hoeksema, 2002; Zammit et al., 2004) and overgeneral memory (Andreano & Cahill, 2009; Heron et al., 2012; Park et al., 2002; Reese, Haden, & Fivush, 1996; Williams et al., 2007). Not all previous studies have accounted for IQ when looking at the association between autobiographical memory (Williams et al., 2007). This is a limitation as reductions in AM specificity and increases in overgeneral AM may be due to differences in IQ since lower IQ is associated with depression (Zammit et al., 2004), as well as with

reduced AM specificity and increased overgeneral memory (Heron et al., 2012; Park et al., 2002). If IQ is not adjusted for, then observed associations between overgeneral memory and depression may in fact be driven by a common association with lower IQ. Adjusting for IQ may also take into account the cognitive deficits that have been associated with depression as IQ encompasses factors such as processing speed, working memory, perceptual reasoning, verbal comprehension (Wechsler, 1991, 2003). Inconsistencies in the prospective association between overgeneral memory and adolescent depression (Table 1.1) are likely due to differences in methodology – one of these differences being the control, or lack of control, for IQ. Given prospective relationships are evident when controlling for measures of IQ (Hipwell et al., 2011; Rawal & Rice, 2012b), and control for IQ has been identified as a limitation of the field (Williams et al., 2007), this thesis builds on previous work by adjusting for IQ in all analyses. Adjusting for IQ, in addition to age and gender, helps ensure results are attributable to the tested associations in each chapter rather than associations with age, gender and IQ/general cognitive ability.

AM assessment was considered baseline for both samples: age 13 in ALSPAC and Wave 2 (age 10-18 years, mean 13.74 years) in EPAD. Where multiple assessments of depression outcomes/covariates, risk factors and covariates were available, those nearest to baseline assessments were chosen for inclusion in analyses. Measures were not identical across cohorts but where possible similar measures at similar time points have been used throughout.

2.1. ALSPAC cohort

2.1.1. Sample

Pregnant mothers who were expecting to deliver between 1st April 1991 and 31st December 1992 in the Avon area of Bristol, UK, were invited to participate in the

study. A total of 14,541 pregnant women enrolled in the ALSPAC study and had completed at least one questionnaire or clinic by 19th July 1999. Of these pregnancies there were 14,676 foetuses (due to multiple foetuses per pregnancy) with 14,062 live births, and 13,988 children were alive at 1 year of age.

The sample was subsequently supplemented when the oldest children were 7 years old with participants who failed to join the study at the initial recruitment stage. A further 713 children were enrolled. As AM was measured at age 13 this thesis makes use of the total bolstered sample (15,247 pregnancies and 15,458 foetuses). 14,775 of these were live births and 14,701 were alive at 1 year. Further details on sample recruitment can be found in Boyd et al. (2013) and Golding et al. (2001). The study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). Sample sizes for those completing the measures used in the thesis are outlined in the Measures section below.

2.1.2. Procedure

Ethical approval was obtained from the ALSPAC Ethics and Law Committee and Local Research Committees. Data for the ALSPAC cohort was collected at various time points throughout pregnancy and after birth via questionnaires and focus clinics at University of Bristol. Data collection for this sample is ongoing. Project approval for the analyses in this thesis was gained from the ALSPAC Executive Committee (project number b2647). Information about how the data was collected for each measure used in the thesis is presented below.

2.1.3. Measures

2.1.3.1 Autobiographical Memory Test

Adolescents completed a written, minimal instruction version of the Autobiographical Memory Test adapted from Williams and Broadbent (1986) as part of the questionnaire mail-out 'Food and Things' at age 13 (Crane et al., 2014, 2016; Heron et al., 2012). Of the 5,785 participants, 2,491 (43.2%) were male and 3,294 (56.9%) were female. Participants were instructed to write a real memory for each of 10 words (5 positive: excited, happy, lucky, relaxed, relieved; 5 negative: bored, failure, hopeless, lonely, sad) that were presented in a pseudo-random order. Participants were instructed to leave the space blank if they could not think of a memory. Due to the nature of written AMTs without supervision, no practice trials were administered. Full instructions are presented in Appendix 2.1.

Responses were coded by ALSPAC researchers as either: specific (a single event that occurred on one day and at a particular time and place), extended (an event lasting two or more days), categoric (repeated events within the same theme), or semantic associates (information pertaining to the cue word but not a memory). Errors (for instance, statements that were about the future, statements about a lack of memory; or statements that were incomprehensible) and no responses were combined to form omissions. Inter-rater reliability was good to excellent between two initial raters (weighted $\kappa = .82$; unweighted $\kappa = .78$) and a third rater (weighted $\kappa = .79$; unweighted $\kappa = .74$) (see Heron et al., 2012).

I created total overgeneral AM variables by summing categoric and extended responses. The primary variable of interest in this thesis was number of overgeneral responses to negative cues (OGMneg; possible range 0 to 5). Secondary variables, namely overgeneral responses to positive cues (OGMpos), specific responses to

negative cues (AMSneg) and specific responses to positive cues (AMSpos) were also created (possible ranges 0 to 5). As memory transcripts were not available to me, I was unable to provide objective ratings for the valence of each memory.

2.1.3.2 Depression

2.1.3.2.1 Development and Wellbeing Assessment

Clinical symptoms of depression were measured on the depression subsection of the Development and Wellbeing Assessment (DAWBA; Goodman, Ford, Richards, Gatward, & Meltzer, 2000). The DAWBA is an interview with items that map onto DSM-IV and DSM-V depression symptoms (American Psychiatric Association, 1994; APA, 2013). Parents reported on their offspring's depression at multiple time points on a questionnaire version of the DAWBA. Parent report via questionnaire at 13 years 10 months was used as this was the closest time point to offspring AMT completion (13 years, 1 month; n = 7,050). Total DSM-IV depressive symptom count (possible range 0 to 9) and DSM-IV MDD diagnosis (yes/no) were calculated according to DSM-IV criteria (American Psychiatric Association, 1994). DSM-IV MDD diagnosis required at least 5 symptoms of depression to be present, one of which being low mood or loss of interest, with combined clinical impairment or distress.

2.1.3.2.2 Mood and Feelings Questionnaire

Depression was also reported on the short version of the Mood and Feelings Questionnaire (sMFQ; Angold et al., 1995). The sMFQ measures the core symptoms of DSM-III-R depression and respondents reported whether these symptom statements are 'not true' (0), 'sometimes' (1), and 'true' (2) for the previous 2 weeks. Totals were created by summing the scores and allowing for 20% missingness. This approach is recommended to account for small amounts of missingness in mental

health measures (Goodman, 2001). Both parents and offspring reported on the sMFQ separately at multiple time points over the course of the study. For time nearest to the AMT, offspring completed a computerised version of the sMFQ during a focus clinic (Teen Focus 1, TF1) at 12.5 years (n = 6,757). An additional child reported sMFQ was available at age 13.5 years; however, the earlier sMFQ was used as a measure of contemporaneous depressive symptoms as the mean age at completion was closer (153.54 months) to the mean age of individuals completing the AMT (157.41 months) than the later sMFQ (165.86 months). Parents reported on offspring depressive symptoms via postal questionnaire at 13 years 1 month (n = 7,076). Additional offspring and parent reports on the sMFQ were obtained at age 16.5 via questionnaire mail out (ns = 5,084 and 5,636 respectively).

2.1.3.3 Covariates and descriptive factors

A number of factors were used as covariates and descriptive factors in the thesis. This varies by chapter but in general most of the chapters consider IQ as a covariate as it is associated with depression and AM (Heron et al., 2012; Zammit et al., 2004). Most chapters also provide descriptive information about economic disadvantage.

Child IQ was assessed in clinic sessions using the Wechsler Intelligence Scale for Children-III (WISC-III; Wechsler, 1991) at age 8 years (n = 7,341) and the Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999) at age 15.5 years (n = 4,951). The age 8 measure was used as it had the largest available sample size and the WASI may underestimate IQ in this sample (ALSPAC Teen Focus 3 documentation, Data Dictionary available at: www.bristol.ac.uk/alspac/researchers/).

Economic disadvantage was assessed by maternal questionnaire completed at child age 11 years, 2 months (n = 6,549). This time point was chosen as it was

closest to the AMT. The questionnaire asked about the average weekly household income including benefits each week. Economic disadvantage was coded in line with the international definition of poverty: ≤60% of the median income of the sample (Gordon, 2006; Rice et al., 2017b), i.e. under and above £289 a week (approximately £15,028 a year).

2.1.4. Genetic data

ALSPAC children (n = 9,912) were genotyped using the Illumina HumanHap550 quad chip by 23andme subcontracting the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory Corporation of America, Burlington, North Carolina, USA. Data underwent the standard ALSPAC quality control (QC) procedures by ALSPAC researchers (exclusions for: sex mismatches, minimal or excessive heterozygosity, individual missingness >3%, call rate <95%, identity by descent (IBD) <0.8, non-European ancestry and violations of Hardy Weinberg Equilibrium (HWE) (p<5e-7). A total of 9,115 children passed these QC procedures. Child and mother genetic data were combined, subject to further QC (SNP missingness >1% and ID mismatches), and imputed using the 1000 genomes phase 1 version 3 reference panel. Mother genetic data was not used in this thesis. The ALSPAC data was also subject to the same QC procedures post-imputation (performed by Dr Richard Anney) as the EPAD sample (see section 2.2.4). Individuals were excluded on the basis of sex mismatches, individual and SNP call rate <98%, MAF <1%, HWE p>10e-10, and minimal or excessive heterozygosity (outside 4 standard deviations).

Following QC and imputation procedures, genetic information was available for 8,782 children in ALSPAC.

2.2. EPAD study

2.2.1. Recruitment and sample

Parents with MDD were recruited from GP surgeries in South Wales (n = 263), a research database of individuals with MDD (n = 64) and via posters in local health centres/hospitals and Depression Alliance Newsletter (n = 10). More detailed information on recruitment can be seen in Figure 2.1, taken from Mars et al. (2012). All participants underwent telephone screening. Participants were recruited to the study if they had a history of recurrent depression (i.e. had at least 2 episodes; this was confirmed at interview); if they had no history of psychotic or bipolar disorder diagnosis; and if they were living with their biological child aged 9-17 years at baseline. Families were excluded if their child had an IQ of less than 50 due to potential difficulties with the assessment battery. If the family had more than one child within the 9-17 years age range then the youngest child was selected. This resulted in a total sample of 337 families (315 mothers, 22 fathers and their offspring: 197 females, 140 males aged 9-17 years, mean age 12 years).

Figure 2.1. Recruitment for EPAD study; taken from Mars et al. (2013)

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Two families were later excluded due to change in parental diagnosis to bipolar disorder at Wave 2 so analyses in this thesis focus on 335 offspring of parents with depression.

The EPAD sample was assessed at three time points. Wave 2 occurred on average 16 months (SD 2.63) after Wave 1 and Wave 3 occurred 13 months (SD 1.57) on average after Wave 2. Retention rates were high on both follow-up sessions. At Wave 2, 95.8% (321/335) performed the interview or questionnaire (31 families completed questionnaire only). At Wave 3, 92.5% (310/355) completed some form of assessment (26 families completed questionnaires only).

2.2.2. Procedure

Data were collected from 2007 to 2011 via interviews, cognitive assessments and questionnaires. Interviews and cognitive assessments were conducted in the participants' homes (99.6%) to make them feel more at ease with the assessments, or at Cardiff University (0.4%). Parents and children were interviewed in different rooms of the house where possible. The interviews were performed by trained Psychology graduates who had weekly supervision with two child psychiatrists (Professor Anita Thapar and Dr Rob Potter). Consent to participate was gained from parents and assent or consent from the young person as appropriate depending on their age. Questionnaires were sent 2 weeks before each interview and contained an assessment battery of questionnaires on mental health issues and sociodemographic factors. Questionnaires were filled out by parents and children. Ethical approval for the study was gained by the Multi-regional Ethics Committee (MREC number 06/MRE09/48). I focus on measures obtained on the offspring throughout the thesis.

2.2.3. Measures

2.2.3.1 Autobiographical Memory Test

Offspring completed the Autobiographical Memory Test (AMT; Williams et al., 2007; Williams & Broadbent, 1986) as previously reported (Rawal & Rice, 2012b; a) at Waves 2 and 3 of the study. Participants were asked to recall a specific autobiographical memory for a total of 12 emotional cue words: 6 positive and 6 negative from one of two word sets (Word set 1: loyal, mistake, joy, rejected, weakness, smile, needy, achieve, angry, loved, tired, ambitious; Word set 2: friendly, happy, failure, disliked, respect, ugly, caring, useless, sunny, worse, lonely, perfect). These words were matched on familiarity, emotionality, imageability and frequency (Rawal & Rice, 2012b; a). Participants initially completed three practice trials and received feedback with further prompting to be specific for any nonspecific responses. During the main trials each of the 12 cue words was read aloud and participants were given 30 seconds in which to respond. If a specific memory was not retrieved participants were verbally prompted (e.g. 'Can you think of a specific time?') and if no memory was retrieved an omission was recorded.

Responses were coded according to standard coding systems (Williams & Broadbent, 1986) by the original EPAD researchers. Responses were coded as either: specific (memories specific to time and place e.g. 'the day we got our dog from the rescue shelter'), extended (spanning longer than one day e.g. 'when we went on holiday with our dog'), categoric (repeated events of a similar nature e.g. 'when walking my dog') or semantic associates (related to cue word but not a memory e.g. 'my dog'). There was high inter-rater reliability from two independent raters who coded the responses of 45 participants (17.51% of the full sample; average agreement $\kappa = 0.93$) (Rawal & Rice, 2012b; a). The primary outcomes were number

of overgeneral AMs (total categoric plus extended memories; possible range 0 to 12) and overgeneral AM to negative cues (possible range 0 to 6) in line with previous research in this sample (Rawal & Rice, 2012b). Secondary outcomes included number of specific memories (possible range 0 to 12), and number of overgeneral AMs to positive cues, number of specific AMs to negative cues, number of specific AMs to positive cues (possible ranges 0 to 6).

In the EPAD sample where the original recordings and memory transcripts were available, content of the memories was also coded for valence. I transcribed the recordings and coded all memories as negative, neutral or positive according to the memory content. Responses from 45 participants were also coded by an independent rater (F.R.). Inter-rater reliability was good: average weighted κ across all cues was 0.65 (SD 0.26) and average percentage agreement was 86.15% (SD 8.80). This is similar to previously reported rates of agreement for researcher-rated memory valence (Schulkind, Rahhal, Klein, & Lacher, 2012). Disagreements were discussed and coded according to consensus between raters. The following variables were calculated based on the valence of the memories themselves: overgeneral AMs that were positive in content, overgeneral AMs that were negative in content, specific AMs that were positive in content, and specific AMs that were negative in content (possible ranges 0 to 12). Overgeneral and specific AMs neutral in content were not used in analyses due to low endorsement by raters (8.7% neutral compared with 45.3% negative and 46% positive).

2.2.3.2 Depression

2.2.3.2.1 Child and Adolescent Psychiatric Assessment

Both parents and offspring reported separately on the offspring's symptoms over the previous 3 months on the Child and Adolescent Psychiatric Assessment (CAPA;

Angold & Costello, 2000). The CAPA is a semi-structured clinical interview assessing psychiatric symptoms according to DSM-IV criteria. A number of disorders were assessed – anxiety disorders, oppositional defiant disorder, ADHD (parent only), eating disorders, bipolar disorder, psychosis, as well as depressive disorders. Two interviewers cross-rated interviews and depressive symptom agreement was high for child and parent-reports (mean $\kappa = 0.90$ and 0.96 respectively; Mars et al., 2012; Sellers et al., 2013). Cases reaching DSM-IV or ICD-10 diagnostic threshold or with subthreshold symptoms were reviewed in weekly clinical consensus meetings by two psychiatrists (A.T., R.P.). DSM-IV MDD symptom count (possible range 0 to 9) was calculated. If either the parent or the young person endorsed the symptom it was counted as present (i.e. reports were combined using an OR rule). This approach was used as it is recommended in clinical practice and it is less susceptible to reporting bias than using a single informant (Kessler, 1997; NICE, 2005; Rutter & Sroufe, 2000). This was not possible in the ALSPAC cohort as parent and study child did not complete measures covering the same reporting period. MDD diagnosis was defined according to DSM-IV criteria, i.e. at least 5 symptoms including one core symptom (low mood/irritability or loss of interest) plus impairment.

2.2.3.2.2 Mood and Feelings Questionnaire

Depressive symptoms were also reported over the last 3 months via the long version of the Mood and Feelings Questionnaire (MFQ; Angold & Costello, 1987). This comprised 34 items covering the core symptoms of DSM-III-R depression. Parents and offspring completed the MFQ about the offspring at each wave of the study. This thesis used MFQ scores from Waves 2 and 3. Parent and offspring reports were combined using an OR rule to create a total depressive symptom score allowing for 15% missingness by mean imputation (Goodman, 2001).

2.2.3.3 Stressful life events

SLEs were reported by parents and offspring on a modified version of the life events checklist (Johnson & McCutcheon, 1980) at each wave of the study. The list contained positive and negative events but only those that were unambiguously negative were considered stressful. At Wave 1 respondents reported on the lifetime occurrence of 13 SLEs considered possible for participants to reliably report over the lifetime (see Table 2.1). At Wave 2 participants reported on a mixture of more and less severe SLEs (n = 21) that occurred over the past 12 months (Table 2.1). Parents and children also rated the impact of each life event on a 5 point scale (1 Very pleasant, 2 A bit pleasant, 3 No effect/neutral, 4 A bit unpleasant, 5 Very unpleasant). Parent and child reports were combined for each item so that if one respondent reported a life event then it was considered present (OR rule for each item) as multiple informants are considered to provide valid information with discrepancies reflecting omissions and differential knowledge of the event (Gest, Reed, & Masten, 1999). Items were summed to generate total number of lifetime SLEs and total number of recent SLEs allowing for 20% missingness using mean imputation.

2.2.3.4 Covariates and descriptive factors

IQ and economic disadvantage were used as a covariate and a descriptive factor respectively. *Child IQ* was assessed at interview (Wave 1) using 10 subscales on the Wechsler Intelligence Scale for Children IV (WISC-IV; Wechsler, 2003). *Economic disadvantage* was a dichotomous variable defined as whether participants met the international definition for poverty, i.e. ≤60% of the median income (Gordon, 2006), in this sample: Wave 1 parent-reported household income of ≤£20,000 (Rice et al., 2017b).

Table 2.1. Stressful life events reported in the EPAD study

Lifetime SLEs	***Recent SLEs (in the past 12 months)***
Death of parent, brother or sister*	Death of parent, brother or sister
Death of a close friend*	Parent getting into trouble with the police
Serious illness or injury to child*	Parent going to prison
Bullying by another young person	Death of a close friend
Serious injury or illness to parent, brother or sister*	Parents divorced or separated
Serious illness or injury to a close friend	Serious illness or injury to a close friend
Death of grandparent	Bullying by another young person
Death of pet	Death of grandparent
Parent going to prison*	Death of pet
Parents divorced or separated*	Losing a close friend through arguments or being dropped
Parent getting into trouble with the police	Serious injury or illness to parent, brother or sister
Father losing job	Increased quarrelling between parents
Mother losing job	Doing badly in an exam
	Close friend moves a long way away
	Doing badly in school work
	Breaking up with a boyfriend/girlfriend
	Parent nagging or picking on this child more
	Serious illness or injury to child
	Parent less interested or loving towards child
	Father losing job
	Mother losing job

SLEs – Stressful life events. * denotes more severe life event used in sensitivity analyses for Chapter 4.

2.2.4. Genetic data

Participants were given the option of providing a saliva sample for genetic research and specific consent was obtained. Saliva samples were collected at every wave where consent was given. Where multiple saliva samples were available, the earliest wave was selected for genotyping. If there were issues with the first sample, the second sample was used. DNA was extracted from 303 offspring samples and genotyped in-house at the MRC Centre for Neuropsychiatric Genetics and Genomics by the core team using Illumina 'Infinium Psych Array' custom chips and the

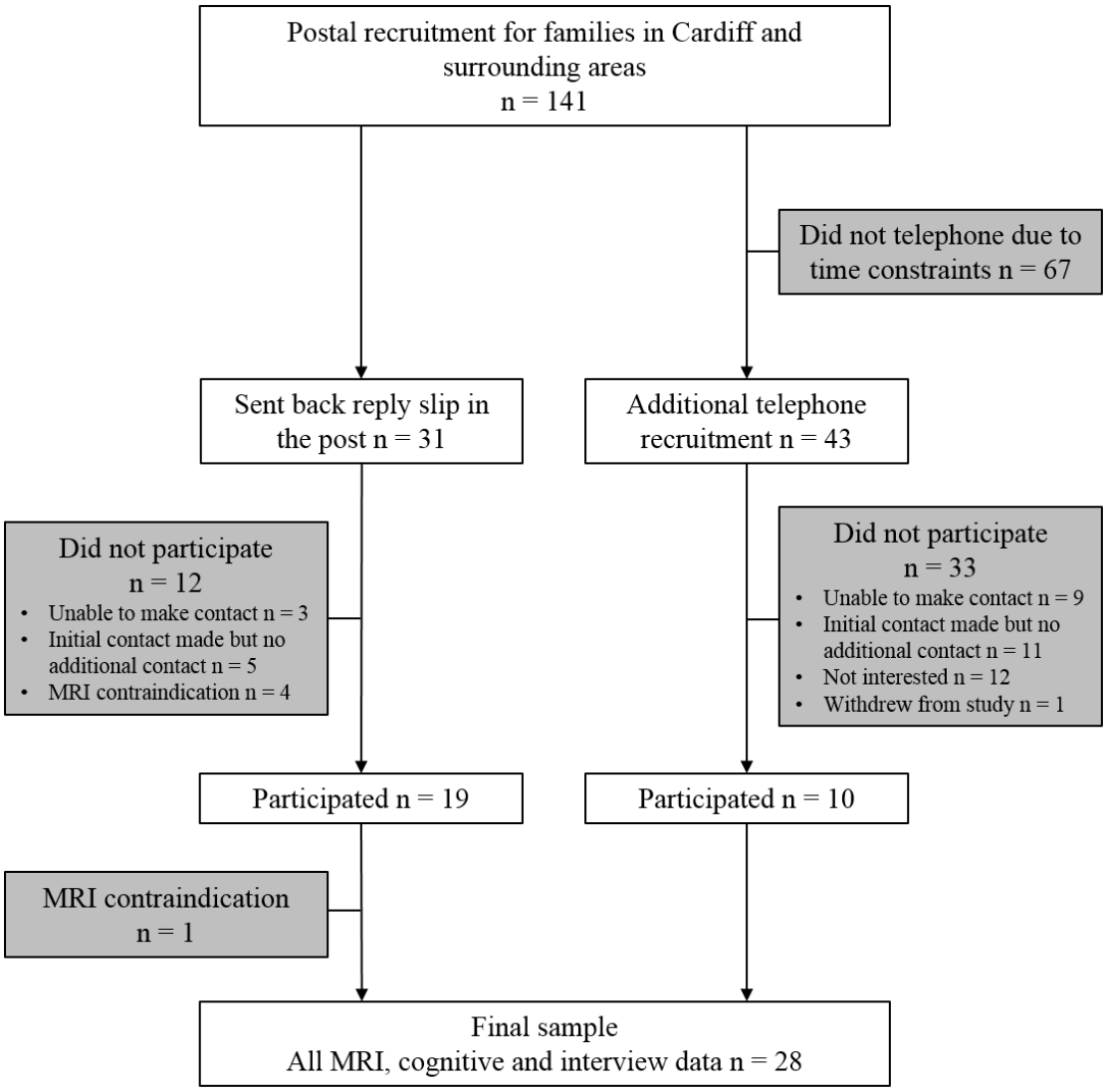
hg19+1 genome build. QC procedures were applied to individual and autosomal SNP data by Dr Richard Anney. Individuals were excluded on the basis of sex mismatches, individual and SNP call rate <98%, MAF <1%, HWE p>10e-10, and minimal or excessive heterozygosity (outside 4 standard deviations). Genetic data was imputed on the Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html) using the 1000 genomes phase 1 version 3 reference panel. Following QC and imputation procedures, genetic information was available for 274 offspring in EPAD.

2.3. EPAD neuroimaging subsample

2.3.1. Recruitment and sample

A subsample of offspring who participated in the original EPAD study were also invited to take part in a neuroimaging study (August 2017 – January 2018). Letters were sent to 141 families informing parents and offspring of the study if they lived in Cardiff or the surrounding areas. Postal packs included a brief letter about the study, the information sheet, and a reply card the parents/participants could return via Freepost if they were interested in hearing more or taking part in the study. Telephone recruitment followed up everyone who replied (n = 31) and a sample of those who had not replied to gauge interest where possible (n = 43). Potential participants were screened over the telephone for inclusion/exclusion criteria and underwent an additional screening check two days before the testing session confirming these details. Of those phoned, 29 participants attended Cardiff University for a testing session. A full break down of recruitment and sample can be seen in Figure 2.2. One participant was later excluded from analysis as she did not complete the MRI component due to a contraindication disclosed on the day of testing.

Figure 2.2. Recruitment for the neuroimaging subsample of the EPAD study



2.3.2. Inclusion and exclusion criteria

To be eligible to participate in the neuroimaging study, individuals had to be the original offspring assessed in the EPAD study, be over 18 years old, have previously consented to be contacted for future studies, and pass all health and MRI safety checks. Due to the nature of using an MRI machine it was necessary to screen all participants for MRI contraindications or factors that could pose a safety issue in the MR environment. Standard Cardiff University Brain Research Imaging Centre (CUBRIC) safety screening and protocols were used for this (Appendix 2.2). In general, participants who had any electrically-operated devices or metal in or on their

body could not take part. An experienced MRI operator was consulted for any cases of potential concern. Participants who had received inpatient hospital treatment or intensive home treatment in the last month, were currently feeling unwell or had experienced recent changes in psychoactive medication were excluded from participating. This was to ensure that participants were well enough to attend a session at CUBRIC and would be able to cope with the confines of the MR environment

2.3.3. Procedure

Participants were invited to a testing session at CUBRIC at a time convenient to them. Participants were posted or emailed a questionnaire pack upon booking. Participants attended CUBRIC for approximately 3 hours for cognitive tests, an MRI scan and a clinical interview. Cognitive tests included the Autobiographical Memory Task (AMT; Rawal & Rice, 2012b; a; Williams & Broadbent, 1986), an adapted AMT for future thinking, and the Auditory Verbal Learning Task (AVLT; Schmidt, 1996). The MRI included a T1-weighted structural scan, diffusion weighted scan and resting-state fMRI with physiological monitoring (this was not used in the thesis). The clinical interview involved questions on current and lifetime diagnoses, medication and service use and the depression section of the Young Adult Psychiatric Assessment. Participants were remunerated £30 in High Street Vouchers and had all travel expenses paid. Ethical approval was gained from Cardiff University School of Medicine Research Ethics Committee (SMREC reference number: 16/17) and School of Psychology Research Ethics Committee (Reference number: EC.17.07.11.4919).

2.3.4. Measures

2.3.4.1 Cognitive Measures

2.3.4.1.1 Autobiographical Memory Test

Participants performed the AMT with the same instructions as in previous waves for continuity. Participants were told the memory needed to last less than a day, be specific to time and place, were given three practice items and 30 seconds to recall each item (see section 2.2.3.1 for further information on the EPAD AMT protocol). The word lists included the same positive and negative cue words from previous waves but also included 6 neutral words in each word list (see Table 2.2.). As overgeneral memory is thought to develop first for negative events and then generalise to all memories (Williams et al., 2007), neutral cue words were included as an alternative valence to positive and negative cue words. Neutral cue words were chosen in line with the procedure used to select negative and positive cue words in Wave 2 of EPAD (Rawal & Rice, 2012b; a). I initially identified neutral words from previous publications using the AMT in young adult populations, and also words of neutral valence (4.9-6.1) (Young, Erickson, & Drevets, 2012a) from 'Affective norms for English words' (Bradley & Lang, 1999). From this list, 2 sets of 6 neutral cue words were selected that were matched for how familiar, emotional and imageable they were to 21 raters (1-10 scale); and on frequency based on Thorndike & Lorge (1944) (see Table 2.2. for word lists). The order of word lists was sorted randomly and participants were assigned the same word list as they had completed in previous waves.

Following each memory, participants were also asked the valence or emotion of the memory (on a scale of -3 'very negative' to +3 'very positive'; Table 2.2.). Responses were recoded as negative (-3 to -1), neutral (0), and positive (+1 to +3).

Table 2.2. Autobiographical Memory Test word lists and memory characteristic questions

Word list 1	**Word list 2**
Mistake	Sunny
Weakness	Huge*
Nature*	Evening*
Conversation*	Perfect
Tired	Disliked
Joy	Happy
Rejected	Lonely
Poetry*	Search*
Advice*	Fabric*
Walking*	Worse
Fashion*	Gigantic*
Ambitious	Listening*
Loved	Useless
Achieve	Respect
Needy	Ugly
Angry	Failure
Loyal	Friendly
Smile	Caring

Memory characteristics						
What emotion is associated with the memory?						
Very negative (-3)	*Moderately negative (-2)*	*Mildly negative (-1)*	*Neutral (0)*	*Mildly positive (+1)*	*Moderately positive (+2)*	*Very positive (+3)*

* denotes a new neutral cue word.

Memories were transcribed and coded in the same way as previous waves (specific, extended, categoric, semantic associate, omission; see section 2.2.3.1) by two independent raters (NW and KM). Inter-rater reliability was excellent (average κ = .89; percentage agreement = 96.42%). Any discrepancies were resolved through discussion.

Overgeneral AM to negative cues (possible range 0 to 6) was the primary outcome. Additional variables were created to examine relationships with depression

and other indices of autobiographical memory based on specificity and cue; namely, number of specific and number of overgeneral AMs (possible ranges 0 to 18), number of overgeneral AMs to positive cues and neutral cues (possible ranges 0 to 6), and number of specific AMs to positive, negative and neutral cues (possible ranges 0 to 6). Additional variables were created according to participant-rated memory content valence: positive, negative and neutral specific memories, and positive, negative and neutral overgeneral memories (possible ranges 0 to 18).

2.3.4.1.2 Auditory Verbal Learning Test

The Auditory Verbal Learning Test (Schmidt, 1996) was used as a measure of general long-term memory ability. The AVLT required the participants to immediately recall an initial list of 15 words, 5 times in a row, followed by an interference list (also 15 words), then recall the initial list. After a delay (average time 32:36, SD 4:02 minutes) participants were then asked to recall the initial list that they repeated multiple times. The delayed recall score (possible range 0 to 15) was the outcome variable as it was considered the outcome from the AVLT most similar to the long term nature of autobiographical memory but without the involving the self as seen in AM.

2.3.4.2 Clinical interview

Participants were first asked general questions about any psychiatric diagnosis, medication and services they may currently be using or have ever used. Participants were asked: 'Have you received a diagnosis or has a medical professional ever told you that you have…' for a series of psychiatric conditions. If they had ever received a diagnosis, follow up questions were asked about who had diagnosed them and when they were diagnosed. Participants were also asked about any current and

previous psychiatric medication they may have taken and what services they may have accessed for help with mental health issues.

Participants also reported symptoms on the depression section of the Young Adult Psychiatric Interview (YAPA; Angold & Costello, 2000). This is the young adult version of the CAPA that was administered in previous waves. Total depressive symptoms and diagnosis were scored according to DSM-IV criteria. Inter-rater reliability for symptoms between myself and KM on all 28 interviews was excellent ($\kappa = .92$). Cases reaching criteria for DSM-V criteria or with subthreshold symptoms were taken to clinical meetings and reviewed by one of the child psychiatrists involved in the original EPAD study (R.P.).

2.3.4.3 Questionnaires

Participants were asked to fill out a battery of questionnaires on their mental health symptoms and cognitive style. Questionnaires used in the thesis are listed below. Participants were given the option of completing questionnaires online or on paper – questionnaires were worded exactly the same on both but there were some slight variations in colour and formatting. 13 individuals chose to complete the paper version, 15 chose the online version.

2.3.4.3.1 Mood and Feelings Questionnaire

In line with previous waves of the study, the 34-item MFQ (Angold & Costello, 1987) was used to assess symptoms of depression. This was identical to what was included in EPAD Waves 1-3 and assessed symptoms over the previous 3 months. Participants reported on statements of depression on a scale of 'not true' (0), 'sometimes' (1), and 'true' (2). Responses were summed for a total score (possible range 0-68) and allowed for 15% missingness using mean imputation. This measure

has been used successfully in young adult samples (Khandaker, Pearson, Zammit, Lewis, & Jones, 2014).

2.3.4.3.2 Beck Depression Inventory-II

Participants also reported depressive symptoms on the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) as this is a measure more commonly used in adult populations (Wang & Gorenstein, 2013). The BDI-II was developed based on DSM-IV depressive symptoms and includes 21 items covering symptoms ranging from sadness and pessimism, to concentration difficulty, indecisiveness, changes in sleeping and eating, and suicidal thoughts or wishes. Participants reported on each symptom over the past 2 weeks and each item had different responses ranging in severity from 0 (not present) to 3 (present and substantial/impairing). Total score was created (possible range 0-63) allowing for 15% missingness using mean imputation.

2.3.4.4 MRI

Each participant underwent screening and experienced the MR environment in the 'mock'/practice scanner if they chose to. MRI scanning was undertaken at CUBRIC on a Siemens Magnetom Prisma 3T MRI with software level VE11b and a 32 channel head coil. Participants were scanned by trained MRI operators. Each participant had the same series of scans: a standard T1-weighted structural scan, a diffusion scan with multi-shell acquisition, and a resting-state fMRI scan with physiological monitoring. Each scan was conducted according to standard CUBRIC parameters which are outlined for scans used in the thesis below.

A sagittal T1-weighted scan ('MP-RAGE') provided information on general brain structure. The T1-weighted scan was performed with GRAPPA2, a technique that reduces scanning time by acquiring information on multiple brain slices/sections at the same time. As with all types of MRI scan, the T1-weighted scan was aligned to

the AC/PC (anterior commissure/posterior commissure) line (parameters: repetition time (TR) 2300ms; echo time (TE) 3.06ms; inversion time (TI) 850ms; flip angle 9°). The voxel resolution was 1mm x 1mm x 1mm.

The diffusion scan provided information on white matter microstructure. This scan used (non-gated) multi-shell acquisition, i.e. acquired 30 direction (b value: 1200) and 60 direction (b value: 2400) data. 80 axial brain slices were taken parallel to AC/PC line with a TR of 9400ms and TE of 67ms. The scans were 2mm x 2mm x 2mm resolution. The scanning process included changes in phase encoding direction (from anterior-posterior to posterior-anterior) to account for potential distortions in image acquisition.

2.3.4.4.1 Diffusion MRI Processing

The diffusion MRI data underwent the standard CUBRIC processing pipeline. In general, this included correcting for sources of distortion and artefacts in the data and linking the diffusion data to the standard structural scan for each participant. Standard algorithms were used to connect adjacent voxels with the same principle direction of diffusion throughout the brain, thereby creating 'streamlines' of fibre trajectories.

Specifically, the data were corrected for subject motion and Eddy Current (EC) distortions in ExploreDTI version 4.8.3 (Leemans, Jeurissen, Sijbers, & Jones, 2009) and co-registered to the T1-weighted image using affine registration and appropriate re-orienting of encoding vectors (Leemans & Jones, 2009). A correction for Echo Planar Imaging (EPI) distortions was employed, effectively warping the diffusion data to the T1-weighted image to create a 1.5 x 1.5 x 1.5mm^3 resolution image. A diffusion tensor model was fitted to the data to compute FA (Basser, Mattiello, & LeBihan, 1994), and whole brain tractography was performed using a

modified damped Richardson Lucy pipeline (Dell'Acqua et al., 2010). This protocol terminates streamlines if the angle threshold is greater than 45° or if the fibre orientation density function dips below 0.05. Data were corrected for partial volume artefacts caused by cerebrospinal fluid using a free water elimination method (Pasternak, Sochen, Gur, Intrator, & Assaf, 2009) for tract-specific analyses.

3. The cross-sectional and longitudinal relationship between overgeneral memory and adolescent depression in a UK population cohort

Overgeneral AM for negative cues has been associated with subsequent adolescent depressive symptoms and disorder in high-risk samples but not in population-based samples. This chapter examines the relationship between overgeneral memory and depressive symptoms in a large sample of 13-year-olds from the Avon Longitudinal Study of Parents and Children. Gender and maternal depression status were examined as potential moderators of these relationships given previous findings of stronger effects in females and in samples at elevated risk of depression due to having a parent with MDD. Regression models investigated the relationship of overgeneral AM for negative cues with contemporaneous (age 12.5, n = 3,154), and prospective (age 16.5, n = 2,345) depressive symptoms. Overgeneral AM for negative cues was significantly associated with both contemporaneous and prospective depressive symptoms. AM specificity for negative cues was associated with contemporaneous but not prospective depressive symptoms, highlighting a mood congruent effect. Other indices of AM were not associated with prospective depressive symptoms. There was no evidence that the relationship between overgeneral AM and depression was moderated by gender or maternal depression status. Findings illustrate a prospective link between overgeneral AM for negative cues and depression in a population cohort. This study provides evidence that overgeneral memory is a risk factor for adolescent depression and this association is not restricted to high-risk samples.

3.1. Introduction

Previous work has highlighted that increased overgeneral AM and reduced AM specificity are associated with MDD in adults (see Chapter 1, section 1.3.2) and in younger samples of children and adolescents. For instance, depressed children and adolescents recall more overgeneral AMs and fewer specific AMs in comparison to controls (Champagne et al., 2016; Park et al., 2002; Rawal & Rice, 2012b). Furthermore, overgeneral AM and reduced AM specificity are correlated with contemporaneous adolescent depressive symptoms in clinical (Park et al., 2005, 2002), high-risk (Hipwell et al., 2011) and non-clinical community samples (Kuyken & Dalgleish, 2011; O'Carroll, Dalgleish, Drummond, Dritschel, & Astell, 2006; Raes et al., 2010).

The association between overgeneral memory and adult depression extends beyond current low mood (see Chapter 1, section 1.3.2). A meta-analysis of 15 studies found that both reduced AM specificity ($r = -.10$, $\beta = -.17$) and overgeneral AM ($r = .13$, $\beta = .11$) significantly predicted higher depressive symptoms at follow up when adjusting for baseline depressive symptoms (Sumner, Griffith, & Mineka, 2010). However, this meta-analysis was restricted to adult samples. There are fewer studies on this prospective relationship in younger age groups and the results are less consistent (see Chapter 1, Table 1.1 and section 1.3.2). As the incidence of MDD increases in adolescence (Maughan et al., 2013; Thapar et al., 2012), and theory considers the development of AM and overgeneral AM to occur through childhood and adolescence (Bauer, 2015; Fivush, 2011; Williams et al., 2007), it is important to consider the prospective relationship between overgeneral memory and depression in adolescence. Using younger age groups who have not developed MDD also allows the examination of overgeneral memory-depression relationships before any potential 'scarring' effects of previous depressive episodes on cognition have

occurred (Kessing, 1998; Lewinsohn, Steinmetz, Larson, & Franklin, 1981; Schaefer et al., 2017), which may be in an issue in studies of adults with recurrent depression (Ahern & Semkovska, 2017).

Previous research exploring the prospective relationship between overgeneral memory and depression in youth samples is discussed below. Research can be broadly broken down into examinations of groups at high-risk of developing MDD and samples at typical risk of developing MDD (i.e. population and community samples).

3.1.1. High-risk samples

High-risk samples have been investigated as they provide the opportunity for examination of greater numbers of new onset cases over a short follow up and are important for identifying individuals at particularly high risk who would benefit from preventative interventions (Garber, 2006; Rose, 1985). Three studies have investigated the relationship between AM and depression specifically in samples at high-risk of developing MDD. Findings have highlighted a prospective link between overgeneral memory and depression, but that this relationship may differ by type of AM (valence and definition) and by gender. For instance, in a sample of 11-year-old girls (n = 195) enriched for depression (by oversampling those with high depressive symptoms at age 8) overgeneral AM for positive cues was associated with DSM-IV depressive symptom count one year later when adjusting for baseline depressive symptoms, race, poverty and verbal IQ (Hipwell et al., 2011). This relationship was not evident for overgeneral AM to negative cues. Research in adolescents with a history of major or minor depressive disorder (n = 55, aged 16-18 years, 75% female) found the proportion of specific AMs predicted an episode of MDD 16 months later when adjusting for baseline depression (Sumner et al., 2011). There was

also an interaction with chronic interpersonal stress such that fewer specific AMs predicted MDD in those with high but not low stress. The largest high-risk examination of the prospective relationship to date investigated offspring of depressed parents aged 10-18 (n = 277) from the Early Prediction of Adolescent Depression (EPAD) study (Rawal & Rice, 2012b). Increased overgeneral AM to negative cues predicted DSM-IV depressive symptom count at one year follow up when adjusting for baseline symptoms, gender, age and IQ. There was a significant gender interaction such that overgeneral AM to negative cues predicted depressive symptoms in females but not males. Overgeneral AM to negative cues also predicted new onset of MDD (n = 14) but not new onset of anxiety or externalising disorders when excluding those with depressive disorder at baseline. Overgeneral AM to positive cues was not associated with depressive symptoms or new-onset MDD at follow-up.

Evidence from high-risk samples therefore highlights the importance of AM valence, AM definition (overgeneral versus specific) and gender. Differences in valence may affect the prospective association as one study found an association with positively-cued memories (Hipwell et al., 2011) and one study found an association with negatively-cued memories (Rawal & Rice, 2012b). As valence is theoretically important, (i.e. overgeneral memory develops as a functional avoidance strategy first for negative memories before becoming generalised to other memories (Williams et al., 2007)), and negative biases are common across cognitive domains in depression (Gotlib & Joormann, 2010; Matt et al., 1992; Roiser et al., 2012), valence is likely an important factor in prospective AM-depression relationships. In combination with previous research highlighting overgeneral AM and specific AM are not different ends of the same spectrum (Sumner, 2012), the fact that one study found evidence for an association with specific AM (Sumner et al., 2011) and two

studies with overgeneral AM (Hipwell et al., 2011; Rawal & Rice, 2012b) suggests there may also be differences in the prospective relationship according to AM definition. Furthermore, the association between overgeneral memory and subsequent depression was found in predominantly female samples (Hipwell et al., 2011; Sumner et al., 2011) and only in females when gender was directly compared (Rawal & Rice, 2012b). Thus, cue valence, AM definition and gender may act as moderators for the association between overgeneral memory and depression, as has previously been suggested (Hitchcock et al., 2014).

Although high-risk samples are beneficial for exploring the development of overgeneral memory as a cognitive risk factor, it is difficult to determine whether associations with depression are due to overgeneral memory or the presence of additional risk factors associated with higher depression risk status such as SLEs or differences in parenting (Bouma, Ormel, Verhulst, & Oldehinkel, 2008; Goodman & Gotlib, 1999). Therefore, utilising population and community samples with typical risk of developing MDD allows for further interrogation of the AM-depression prospective relationship; in particular whether this generalises to non-selected populations.

3.1.2. Typical (non-high) risk samples

Of the four studies that have investigated overgeneral memory and subsequent depression in population and community samples, evidence for a prospective link was only found in individuals with additional risk factors. In one community sample of 174 12- to 13-year-olds there was no main effect of overgeneral AM on depressive symptoms 8-9 months later but there was a three-way interaction where overgeneral AM was positively associated with depressive symptoms in Caucasians with higher levels of emotional abuse (Stange et al., 2013). Further research from the same

sample (n = 160) found a four-way interaction, whereby there was an association between overgeneral AM and subsequent depressive symptoms in girls with high levels of rumination following a SLE (Hamlat et al., 2015). Taking into account valence and AM definition, a recent study of community youth (n = 269) failed to find an association between any of the six indices of autobiographical memory assessed (total, positively-cued and negatively-cued overgeneral and specific AMs) and *changes* in depressive symptoms across time points (Gutenbrunner et al., 2017). Collectively, results from these modestly-sized normative groups therefore suggest a relationship between overgeneral memory and subsequent depression only occurs in the presence of other vulnerability factors. Additional research in the largest population study of AM and depression to date has also failed to find a longitudinal relationship. In Crane et al. (2016), proportion of specific AMs at age 13 was not associated with subsequent depression at age 16 categorised by a clinical cut-point on a short self-report questionnaire in the ALSPAC cohort (n = 3,708). There was also no evidence of an interaction with SLEs. These results have led researchers to question whether a relationship between overgeneral memory and depression exists in the absence of other vulnerability factors (Crane et al., 2016; Gutenbrunner et al., 2017).

3.1.3. Inconsistencies and gaps in the literature

Collectively, results of studies examining the association between autobiographical memory and adolescent depression are inconsistent. Three studies find an association. Two studies find an association only in particular sub groups and two studies find no association. There is therefore a need for further investigation in order to clarify this relationship.

In particular, issues highlighted as requiring examination are: valence of overgeneral memory, adjustment for potential confounders, additional risk factors and gender. Findings from studies with participants at high-risk of developing depression indicate differences in the prospective relationship according to valence, but with the exception of Guttenbrunner et al. (2016) this has not been investigated in community or population samples. As theory highlights overgeneral memory develops first for negative memories (Williams et al., 2007), examining valence is particularly important in younger age groups. While many studies do adjust for confounders, there are differences in what confounders are adjusted for. Adjusting for baseline depression is necessary to ensure results are not due to an association with earlier depressive symptoms. It is also important to adjust for other factors associated with overgeneral memory and depression (for instance, gender, age, and IQ; Andreano & Cahill, 2009; Heron et al., 2012; Maughan et al., 2013; O'Carroll et al., 2006; Park et al., 2002; Williams et al., 2007), but this has not been done consistently in the previous research. Whether additional risk factors are required for an association between overgeneral memory and subsequent depression is a question that requires further investigation. Inconsistencies between high-risk and typical risk samples may mean that overgeneral memory is only associated with depression in sub-groups at high-risk of developing depression (Crane et al., 2016; Gutenbrunner et al., 2017). Although there has been consideration of risk factors such as SLEs and rumination (Crane et al., 2016; Hamlat et al., 2015; Stange et al., 2013), no research has examined the effect of having a parent with depression on the longitudinal relationship between overgeneral memory and depression in adolescents. Finally, differences in gender are also an important consideration given the aforementioned findings with females in high-risk samples and the gender differences in depression

(Maughan et al., 2013; Thapar et al., 2012) and AM (Heron et al., 2012) in adolescence.

Differences in findings for the AM-depression prospective relationship between high-risk and population samples may therefore be due to methodological differences between studies. Once differences in methodology are resolved, a prospective relationship between overgeneral memory and depression may also be evident in samples at typical risk of developing depression. Consequently, I set out to replicate the prospective relationship seen in high-risk studies, examining memory valence, adjusting for important covariates, and examining potential moderators in a large population-based sample.

Whether overgeneral memory could be a risk factor for other psychiatric disorders in adolescence is another question that has received little attention in the literature. The previous EPAD study found that overgeneral AM to negative cues did not predict anxiety or externalising disorders once depression was taken into account (Rawal & Rice, 2012b); however, very few studies have looked at multiple outcomes, instead tending to focus on one disorder. One question not yet addressed is whether overgeneral memory is associated with subsequent schizophrenia-related traits or dimensional traits related to schizophrenia such as psychotic-like symptoms (Ronald & Pain, 2018; Zammit et al., 2013) in adolescence. These traits are conceptually related to schizophrenia but have also been associated with depression (McGrath et al., 2016) so merit consideration. As depression and anxiety symptoms are highly correlated (Huppert, 2008; Maughan et al., 2013) and anxiety is an antecedent for early-onset MDD (Rice et al., 2017b; Rutter et al., 2006; Wittchen et al., 2000), the relationship between overgeneral memory and anxiety also requires more investigation. Consequently, I also examined the extent to which overgeneral memory was associated with anxiety and psychotic-like symptoms.

3.1.4. The current study

The aim of the current study was to replicate findings seen in the high-risk sample by Rawal and Rice (2012) in a UK population sample, the Avon Longitudinal Study of Parents and Children (ALSPAC). Previous work in the ALSPAC cohort has failed to find a prospective relationship between proportion of specific AMs at age 13 and depressive symptoms at age 16 (Crane et al., 2016). The current examination used theory and knowledge from high-risk samples to examine the relationship between overgeneral AM for negative cues and depression, adjusting for age, IQ and gender. Given that previous work has focused on the relationship of AM with current depression (Hitchcock et al., 2014), I first sought to replicate this in ALSPAC by determining 1) if there was a cross-sectional relationship between overgeneral AM for negative cues and contemporaneous depressive symptoms. I then assessed 2) whether there was a longitudinal relationship between overgeneral AM for negative cues and subsequent depressive symptoms (assessed 3 years later at age 16). As gender is important in overgeneral memory and depression I tested 3) whether the relationships between overgeneral AM and depression were moderated by gender. I also tested 4) whether these relationships were specific to overgeneral AM to negative cues by investigating associations with different valences and definitions of AM (overgeneral AM for positive cues, AM specificity for negative cues, AM specificity for positive cues). To test whether additional risk factors influence the relationship between AM and depression I examined 5) whether associations between overgeneral AM and depressive symptoms were present only in those with high familial risk for depression by using maternal depression status as a moderator. I also assessed 6) whether overgeneral memory could be also be a risk factor for other disorders by testing the contemporaneous and prospective relationships with anxiety and psychotic-like symptoms. Finally, I performed sensitivity checks on the

association between AM and depression by testing: whether results remained for parent-reported adolescent depressive symptoms and whether results remained when adjusting for SES covariates.

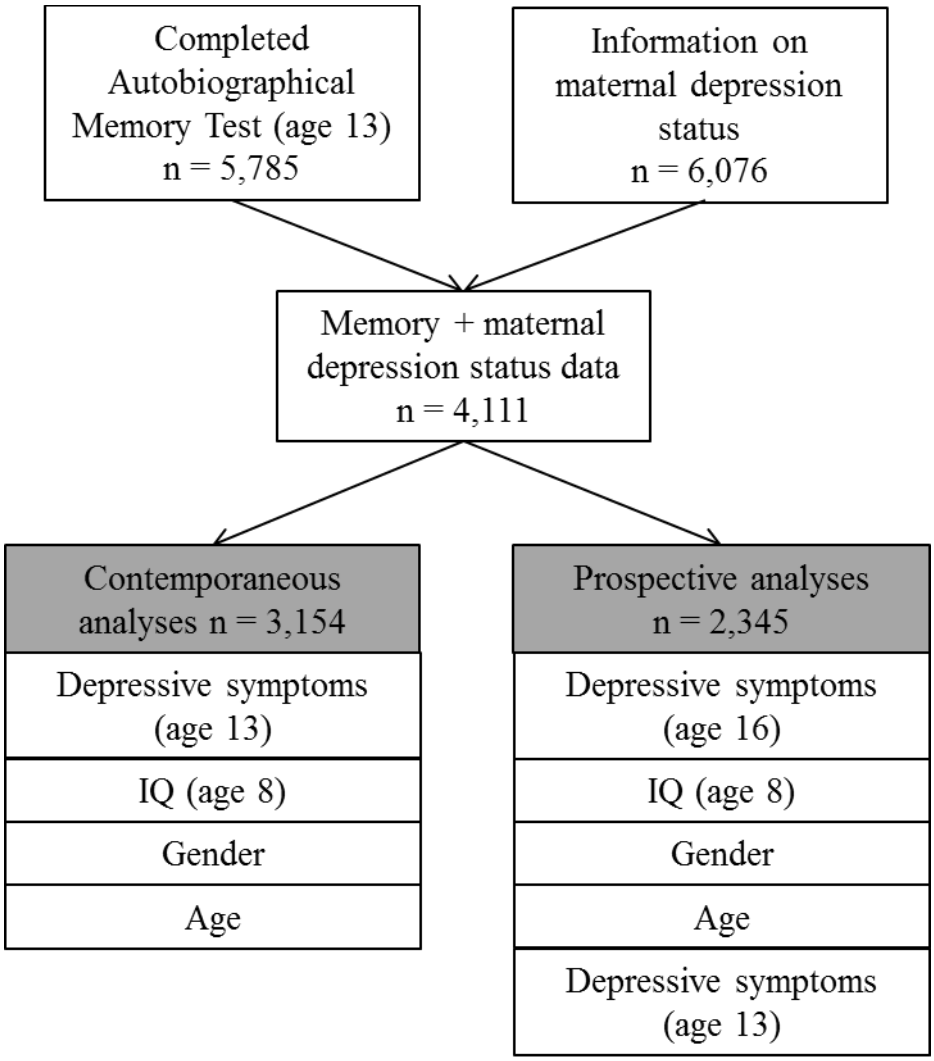
It was anticipated that overgeneral AM for negative cues (but no other AM measure) would be associated with depression (both contemporaneous and prospective), and that the relationships would be stronger in females than males. It was also hypothesised that maternal depression status would not moderate the relationships as inconsistencies in the previous literature are likely to be due to methodological differences rather than sample differences (i.e. high-risk versus typical risk). Given that anxiety has not previously been associated with overgeneral AM (Rawal & Rice, 2012b; Williams et al., 2007) it was anticipated that overgeneral AM for negative cues would not be associated with anxiety symptoms. It was hypothesised that psychotic-like symptoms would be associated with a general AM deficit (increase in overgeneral AM and decrease in AM specificity regardless of cue), given both reduced AM specificity and overgeneral AM are associated with schizophrenia in adults (Berna et al., 2016; Warren & Haslam, 2007; Wood et al., 2006). Sensitivity checks for parent-reported adolescent depressive symptoms and adjusting for SES factors were expected to provide similar results to the main analysis.

3.2. Methods

3.2.1. Sample

The current study used the ALSPAC cohort (Boyd et al., 2013). A full description of the cohort can be found in Chapter 2, Methods. Analyses were performed on individuals (n = 4,111) with data on autobiographical memory (assessed at age 13) and maternal depression (see section 3.2.2.2 Maternal depression status; Figure 3.1).

Figure 3.1. Numbers for ALSPAC phenotypic analysis



Of these, 3,154 individuals (1,410 males, 1,744 females) also had data on depression at age 13 (for contemporaneous depression analyses) and 2,345 individuals (952 males, 1,393 females) had data on depression at age 16 (for prospective depression analyses).

3.2.2. Measures

3.2.2.1 Autobiographical Memory Test

Adolescents completed a written, minimal instruction version of the AMT as part of a questionnaire mail-out at age 13 (Crane et al., 2014, 2016; Heron et al., 2012).

Further details are provided in Chapter 2, section 2.1.3.1. Responses were coded by ALSPAC researchers as either: specific, extended, categoric, or semantic associate. Errors and no responses were combined to form omissions. Inter-rater reliability was excellent (see Heron et al., 2012).

I created all AM summary variables. Categoric and extended responses were summed to create total overgeneral responses. The primary predictor variable was number of overgeneral responses to negative cues (OGMneg). Secondary predictor variables were the numbers of overgeneral responses to positive cues (OGMpos), specific responses to negative cues (AMSneg) and specific responses to positive cues (AMSpos).

3.2.2.2 Maternal depression status

To ensure comparability with previous findings in the high-risk EPAD sample (Rawal & Rice, 2012b) and with chapters in this thesis using the EPAD sample (Chapters 4-6), a maternal depression variable identified whether each child's mother had experienced severe, recurrent depression from when mothers were pregnant with the study child to when the study child was 12 years of age (yes/no). This was derived from maternal reports on regular questionnaires over this period asking 'Have you had depression in the last year/last two years/since your child was born/ever?' and three instances of the question 'Have you ever had severe depression?'. Mothers were coded as having severe, recurrent depression if they reported at least two separate instances of depression with one of these being reported as severe. This method is based on the approach used previously to identify mothers with severe, recurrent depression (Hammerton, Harold, Thapar, & Thapar, 2013).

3.2.2.3 Mood and Feelings Questionnaire

Adolescent depressive symptoms were primarily measured via self-report on the short version of the Mood and Feelings Questionnaire (sMFQ; Angold et al., 1995). Current depressive symptoms (possible range 0-26) were measured at 12.5 years (α = .834) by a computerised questionnaire during a focus clinic session. Prospective depressive symptoms were assessed on a paper sMFQ mailed out at 16.5 years (α = .907).

Parents also reported on their child's depressive symptoms on the sMFQ via questionnaire mail-outs. Total scores were created in the same way as for self-reported sMFQs. Parent-reported adolescent depressive symptoms were assessed at age 13 (α = .871) and at age 16.5 (α = .883).

3.2.2.4 Covariates and descriptive variables

Analyses adjusted for a number of factors known to be associated with overgeneral memory and MDD, namely, IQ, age and gender (Andreano & Cahill, 2009; Heron et al., 2012; Maughan et al., 2013; Park et al., 2002; Williams et al., 2007; Zammit et al., 2004). IQ was assessed in clinic sessions using the WISC-III (Wechsler, 1991) at age 8 (see Chapter 2, section 2.1.3.3 for more information). Age at completion of the AMT questionnaire was recorded in months.

A number of SES indicators were adjusted for in sensitivity analyses: parity, economic disadvantage, and maternal education. *Parity* was included as a covariate as number of other siblings may affect the mother-child relationship; specifically the amount of time mothers spend reminiscing and elaborating with their children which is a theoretically important factor in the development of overgeneral AM (Fivush et al., 2006; Valentino, 2011). Mothers reported on the number of previous children on a questionnaire at 18 weeks gestation. Parity was coded as first born, second born, or

third or more born. *Economic disadvantage* was assessed on a maternal questionnaire at age 11 years, 2 months of the study child. The questionnaire asked the average weekly household income including benefits each week. Economic disadvantage was coded in line with the international definition of poverty ≤60% of the median income of the sample (Gordon, 2006; Rice et al., 2017b). *Maternal education* was reported by mothers at 32 weeks gestation. Mother's highest educational qualification was coded as either A levels or degree (1) or lower than A levels (0; O level/GCSE, vocational, none/CSE).

3.2.2.5 Anxiety and psychotic-like symptoms

Analyses were repeated with measures for anxiety (Generalised Anxiety Disorder, GAD) and psychotic-like symptoms in sensitivity analyses. Measures selected were closest to the time points used in main analyses (ages 13 and 16). GAD symptoms were derived from number of worries and number of physical symptoms on the Development and Wellbeing Assessment (DAWBA; Goodman et al., 2000). Parents completed a questionnaire version of the DAWBA about their child at 13 years, 10 months. Offspring completed a self-report computer version at the clinic (Teen Focus 3, TF3) aged approximately 15.5 years. Symptom counts were created such that presence was only endorsed if it occurred 'more days than not' for the previous 6 months consistent with DSM-V criteria for GAD (APA, 2013). Informants reported on 7 worries (past behaviour, school, disasters, own health, bad things happening to others, the future, other specific worries) at age 13, and 11 worries at 15.5 years (those assessed at age 13 plus worries for: friends, death and dying, bullying, appearance). Both time points reported on the same physical symptoms (restlessness, fatigue, concentration difficulties, irritability, muscle tension, sleep disturbance). Items were summed to produce total anxiety symptom count at each age (age 13 possible range 0-13; age 15.5 possible range 0-17).

Psychotic-like symptoms were measured via the self-report psychotic-like symptoms questionnaire (PLIKS-Q). The PLIKS-Q was completed at the same time as the AMT (13 years) and subsequent depressive symptoms (16.5 years). Individuals reported on whether they had experienced ('yes, definitely'; 'yes, maybe'; 'no, not at all') 10 positive symptoms associated with schizophrenia, namely: delusions (being spied on, thought reading, reference, control, grandiose abilities) hallucinations (auditory and visual) and thought interference (thought insertion, withdrawal and broadcasting). At age 13 informants reported on symptoms since their 12th birthday and at age 16.5 they reported on symptoms since their 15th birthday. Binary variables were created at each age to indicate whether any PLIKS had been endorsed as 'yes, definitely' (coded 0 no, 1 yes) in line with previous research using the PLIKS-Q and interview (Sieradzka et al., 2014; Zammit et al., 2008; Zammit, Owen, Evans, Heron, & Lewis, 2011).

3.2.3. Statistical analysis

All analyses were performed in SPSS version 23.0. Descriptive statistics and Pearson's correlations were initially performed. Associations between overgeneral AM and depressive symptoms were examined with multiple regression models using standardised predictor variables (Cohen, Cohen, West, & Aiken, 2003). Overgeneral AM to negative cues (OGMneg) was used as a predictor for contemporaneous and prospective depressive symptoms. The effect of covariates was assessed in Step 1 (IQ, age, gender), followed by the main effect of OGMneg in Step 2. Baseline depressive symptoms (age 13) were included as an additional covariate for all prospective analyses. An OGMneg by gender interaction term was included in Step 3 to determine whether the relationships between OGMneg and depressive symptoms were moderated by gender (coded 0 males, 1 females). Any significant gender interactions were followed up with simple slopes analyses (Dawson, 2014).

Where OGMneg was significantly associated with depression outcomes, analyses were repeated using secondary AM indices (OGMpos, AMSneg, AMSpos) as predictors. This was done to establish whether the AM-depression relationship was present for a particular valence (positive, negative) or AM definition (overgeneral AM, reduced AM specificity).

A second series of regression models were used to assess whether maternal depression status moderated the relationship between overgeneral memory and depressive symptoms using an OGMneg by maternal depression interaction. A three-way interaction term (OGMneg by maternal depression by gender) also examined whether both gender and maternal depression status moderated the overgeneral memory-depression relationships.

To test whether OGMneg could be a risk factor for other disorders, analyses were performed repeating the original depression analyses with other psychopathology outcomes (anxiety and psychotic-like symptoms). Linear regression models were performed to assess the relationship of OGMneg with contemporaneous and prospective anxiety, namely GAD. Logistic regression models were used to assess the relationships between OGMneg and contemporaneous and prospective presence of psychotic-like symptoms. Contemporaneous analyses with alternative psychopathology outcomes adjusted for baseline depressive symptoms (self-reported sMFQ at age 12.5) and prospective analyses adjusted for baseline psychopathology (anxiety or psychotic-like symptoms), as well as baseline and prospective depressive symptoms (self-reported sMFQ at ages 12.5 and 16.5) to ensure any results were attributable solely to change in anxiety and psychotic-like symptoms rather than the overlapping symptoms of MDD. As with the depression analyses, if an association was found with OGMneg, analyses were repeated with secondary AM indices (OGMpos, AMSneg, AMSpos).

Sensitivity analyses were performed repeating main analyses with parent-reported adolescent sMFQ symptoms to test whether results replicated for parent-reported depressive symptoms. Checks were also performed adjusting for indicators of SES (economic disadvantage, parity, maternal education) to explore whether lack of adjust for important SES factors contributed to any differences in results between the current analysis and Crane et al. (2016).

3.3. Results

3.3.1. Descriptive analyses

Descriptive information on the sample and univariate correlations between study variables are presented in Table 3.1. OGMneg was correlated with all measures of psychopathology but the largest correlations were seen for depressive symptoms at age 12.5 years ($r = .112$, $p < .001$) and 16 years ($r = .116$, $p < .001$). Age in months was correlated with OGMneg ($r = -.033$, $p = .036$) and IQ was correlated with all AM indices ($rs = -.072$ to $.149$, $ps < .001$), highlighting the need to control for these variables in AM analyses using this cohort. As would be expected, all measures of psychopathology were significantly correlated ($rs = .062$ to $.337$, $ps < .004$).

3.3.2. Relationship between OGMneg and depressive symptoms

Results of regression analyses examining the association between OGMneg and depressive symptoms (contemporaneous and prospective) are presented in Table 3.2. OGMneg was associated with greater contemporaneous ($\beta = .107$, $p < .001$) and prospective ($\beta = .073$, $p < .001$) depressive symptoms after adjusting for IQ, age and gender.

Table 3.1. Descriptive information and associations between autobiographical memory, psychopathology and covariates

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Gender (female)															
2. Age at AMT (months)	**-.099**														
3. IQ	-.020	**-.048**													
4. Economic disadvantage	.014	.009	**-.143**												
5. Maternal depression	**.046**	.022	**-.052**	**.215**											
6. Depressive symptoms 12.5 years	**.121**	.004	-.010	.020	**.081**										
7. Depressive symptoms 16.5 years	**.225**	-.007	**-.043**	**.068**	**.129**	**.337**									
8. Anxiety symptoms 13 years	.007	.010	**-.059**	**.101**	**.132**	**.130**	**.097**								
9. Anxiety symptoms 15.5 years	**.097**	**.044**	**-.072**	.013	**.062**	**.169**	**.194**	**.096**							
10. PLIKS 13 years	**.083**	-.015	**-.037**	**.061**	**.103**	**.201**	**.131**	**.062**	**.123**						
11. PLIKS 16.5 years	**.076**	-.003	**-.042**	**.061**	**.052**	**.127**	**.235**	**.104**	**.117**	**.266**					
12. OGMneg	**.046**	**-.033**	**-.072**	.011	<.001	**.112**	**.116**	**.049**	**.059**	**.097**	**.091**				
13. OGMpos	**-.071**	.002	**-.110**	-.019	-.021	-.002	.019	.019	-.004	-.010	.012	**.483**			
14. AMSneg	**.118**	-.011	**.149**	**-.045**	-.010	**.105**	**.060**	-.018	.032	**.084**	.036	**-.248**	**-.210**		
15. AMSpos	**.145**	-.027	**.146**	-.030	<.001	.015	.032	-.018	**.038**	**.056**	.030	**-.087**	**-.501**	**.572**	
Mean or %	54.9%	157.337	107.235	14.2%	18.4%	3.965	5.789	0.154	0.190	0.157	0.126	1.319	1.244	1.359	2.427
SD or n	2257/ 4111	1.193	15.820	582/ 3505	758/ 4111	3.791	5.547	0.807	0.997	0.364	0.332	1.244	1.220	1.340	1.478

AMT – Autobiographical Memory Test; AMSneg – autobiographical memory specificity to negative cues; AMSpos - autobiographical memory specificity to positive cues; OGMneg – overgeneral autobiographical memory to negative cues; OGMpos – overgeneral autobiographical memory to positive cues; PLIKS – psychotic-like symptoms. Correlations significant at $p < .05$ indicated in bold.

3.3.3. Moderation by gender

The OGMneg by gender interaction term did not significantly predict depressive symptoms in contemporaneous or prospective analyses (Table 3.2).

3.3.4. Testing the specificity of the OGMneg-depression relationships

Analyses were repeated with alternative AM indices (OGMpos, AMSneg, AMSpos) to determine whether results were specific to OGMneg. In contemporaneous analyses, OGMpos (β = .006, B (95% CI) = .023 (-.122, .158), p = .735), AMSpos (β = -.007, B (95% CI) = -.025 (-.160, .110), p = .719) and their respective gender interaction terms (OGMpos x gender β = .005, B (95% CI) = .027 (-.241, .296), p = .843; AMSpos x gender β = .001, B (95% CI) = .004 (-.264, .272), p = .979) were not associated with contemporaneous depressive symptoms. However, there was a main effect of AMSneg such that *more* AMSneg responses were associated with *more* contemporaneous depressive symptoms (β = .094, B (95% CI) = .354 (.221, .486), p < .001). The AMSneg by gender interaction was also found to predict contemporaneous depressive symptoms (β = .054, B (95% CI) = .265 (.001, .530), p = .05). When this interaction was followed up with simple slopes analysis by gender, the AMSneg-depression relationship was significant in females (t = 5.534, p < .001) but not in males (t = 1.888, p = .059).

None of the alternative AM indices were associated with prospective depressive symptoms (β_{OGMpos} = .027, B (95% CI) = .151 (-.061, .364), p = .163; β_{AMSneg} = .015, B (95% CI) = .080 (-.125, .285), p =.444; β_{AMSpos} = .005, B (95% CI) = .026 (-.187, .239), p = .810). Gender interaction terms were also non-significant (βs -.006 to .026, ps > .406).

Table 3.2. Regression models with main effect of OGMneg predicting current and subsequent depressive symptoms and gender interactions

	Contemporaneous depressive symptoms (n = 3,154)						**Prospective depressive symptoms (n = 2,345)**					
	Model change			**Coefficients**			**Model change**			**Coefficients**		
	R^2	**p**	**f^2**	**β**	**B (95% CI)**	**p**	**R^2**	**p**	**f^2**	**β**	**B (95% CI)**	**p**
Step 1: Covariates	**.014**	**<.001**	**.014**				**.153**	**<.001**	**.181**			
Full scale IQ				-.008	-.033 (-.170, .105)	.642				-.028	-.128 (-.345, .088)	.246
Age				.015	.078 (-.101, .256)	.393				-.008	-.045 (-.415, .326)	.814
Gender				.118	.893 (.630, 1.156)	**<.001**				.195	2.159 (1.743, 2.576)	**<.001**
Age 12.5 depressive symptoms										.315	1.818 (1.601, 2.034)	**<.001**
Step 2: Main effect	**Δ.011**	**<.001**	**.012**				**Δ.005**	**<.001**	**.006**			
OGMneg				.107	.405 (.273, .536)	**<.001**				.073	.406 (.198, .615)	**<.001**
Step 3: Moderation by gender	Δ<.001	.528	<.001				Δ<.001	.337	<.001			
OGMneg x Gender				.016	.084 (-.178, .347)	.528				-.028	-.204 (-.619, .212)	.337

OGMneg – overgeneral autobiographical memory to negative cues. Results significant at $p < .05$ are indicated in bold.

3.3.5. Moderation by maternal depression status

Mean OGMneg, depressive symptoms and covariates stratified by maternal depression status are presented in Table 3.3. Offspring of mothers with depression had significantly higher depressive symptoms (at 12.5 and 16.5 years) and decreased IQ in comparison to offspring with non-depressed mothers; however, adolescent OGMneg did not differ according to maternal depression status.

Regression analyses examining maternal depression status as a moderator were not significant for contemporaneous depression (β = .017, B (95% CI) = .159 (-.202, .519), p = .388) or prospective depression (β = -.005, B (95% CI) = -.080 (-.675, .514), p = .719). Similarly, the three-way interaction of OGMneg by maternal depression status by gender was not associated with contemporaneous depression (β = .018, B (95% CI) = .238 (-.486, .963), p = .519) or prospective depression (β = -.045, B (95% CI) = -.929 (-2.120, .262), p = .126).

3.3.6. Relationship between OGMneg and anxiety symptoms

OGMneg regression analyses were repeated using contemporaneous and prospective anxiety outcome measures to determine whether OGMneg could be a risk factor for other disorders. Adjusting for covariates used in the previous analyses in addition to depressive symptoms, OGMneg was not associated with contemporaneous anxiety symptoms (β = .018, B (95% CI) = .014 (-.022, .049), p = .443; n = 1741) or prospective anxiety symptoms (β = .022, B (95% CI) = .023 (-.036, .082), p = .442; n = 1214). Two-way and three-way interactions with gender and maternal depression status were also not significant for contemporaneous and prospective anxiety symptoms (βs -.016 to .024, ps > .570).

Table 3.3. Mean OGMneg, depressive symptoms and covariates by maternal depression status

		Mean (SD)				
		OGMneg	**Depressive symptoms at age 12.5**	**Depressive symptoms at age 16.5**	**IQ**	**Age (months)**
Maternal depression status	*Not depressed*	1.319 (1.233)	3.825 (3.708)	5.475 (5.321)	107.598 (15.739)	157.325 (1.121)
	Depressed	1.321 (1.293)	4.637 (4.103)	7.421 (6.359)	105.392 (16.114)	157.392 (1.470)
Test statistic		t(4109) = .029, p = .977	**t(800.367) = 4.446, p < .001**	**t(601.485) = 6.229, p < .001**	**t(3432) = 3.035, p = .002**	t(4109) = 1.391, p = .164

OGMneg – overgeneral autobiographical memory to negative cues. Significant group differences as indicated by t-test results at $p < .05$ are indicated in bold.

3.3.7. Relationship between OGMneg and psychotic-like symptoms

Results for regression analyses with psychotic-like symptoms were more complex. In contemporaneous analyses adjusting for previous covariates and depressive symptoms (n = 3,116) more OGMneg was associated with psychotic-like symptoms (OR (95% CI) = 1.219 (1.105, 1.345), p < .001) but no interaction of gender was evident (OR (95% CI) = 1.007 (.824, 1.230), p = .947). Associations were also evident for AMSneg (OR (95% CI) = 1.189 (1.075, 1.315), p = .001) and AMSpos (OR (95% CI) = 1.200 (1.077, 1.336), p = .001) with contemporaneous psychotic-like symptoms such that more specific memories were associated with increased risk of having at least one psychotic-like symptom. However, there was no association with OGMpos (OR (95% CI) = .943 (.847, 1.052), p = .291) and all gender interaction terms were non-significant (ORs = .856 to 1.055, ps > .168).

In prospective analyses (n = 2,322), OGMneg was associated with subsequent psychotic-like symptoms (OR (95% CI) = 1.138 (1.001, 1.294), p = .049) but there was no interaction with gender (OR (95% CI) = 1.261 (.964, 1.649), p = .090). No other measure of AM was associated with subsequent psychotic-like symptoms at 16.5 years (ORs = 1.016 to 1.057, ps > .430) and there were no gender interactions (ORs = .978 to 1.264, ps > .128).

The relationships between OGMneg and contemporaneous/prospective psychotic-like symptoms were not moderated by maternal depression status or maternal depression status by gender (ORs .916 to 1.156, ps > .519).

3.3.8. Sensitivity analyses

3.3.8.1 Parent-reported depressive symptoms

Analyses were repeated using parent-reported depressive symptoms (contemporaneous and prospective) as outcomes. Patterns of results remained the

same. OGMneg was significantly associated with contemporaneous depressive symptoms (β = .080, B (95% CI) = .264 (.152, .376), p < .001) and prospective depressive symptoms (β = .064, B (95% CI) = .212 (.100, .325), p < .001). Gender, maternal depression status, and gender by maternal depression status did not moderate these relationships (βs -.037 to .020, ps > .167). No other measure of AM was associated with contemporaneous (βs -.015 to .032, ps > .070) or prospective depressive symptoms (βs .020 to .022, ps > .214). There was no evidence of gender interactions for additional AM measures with contemporaneous (βs -.023 to .030, ps > .274) and prospective depressive symptoms (βs -.020 to .005, ps > .448).

3.3.8.2 Adjusting for socioeconomic factors

Adding SES factors (parity, economic disadvantage and maternal education) as covariates did not alter results. OGMneg was associated with contemporaneous (β = .106, B (95% CI) = .396 (.255, .536), p < .001) and prospective depressive symptoms (β = .077, B (95% CI) = .428 (.202, .655), p < .001). Gender, maternal depression status, and gender by maternal depression status did not moderate the relationships between OGMneg and depressive symptoms (βs -.034 to .027, ps > .285).

3.4. Discussion

The current study examined the relationship between overgeneral memory and depression in ALSPAC, a large UK population cohort. Based on previous research in high-risk samples and theoretical work, OGMneg was explored in relation to contemporaneous and prospective depressive symptoms. Moderation of these relationships by gender and maternal depression status was also investigated. More OGMneg was associated with more depressive symptoms in both the cross-sectional and longitudinal analyses. More AMSneg was associated with contemporaneous depressive symptoms only. No other measure of AM was associated with depressive

symptoms prospectively – that association was observed only for OGMneg. Analyses with interaction terms revealed that the overgeneral memory-depression relationships were not altered by gender, maternal depression status or both gender and maternal depression status. Consequently, differences observed in the literature for high-risk and population-based samples are likely due to methodological differences.

This is the first study to find that overgeneral memory is associated with both contemporaneous and prospective depressive symptoms in a large adolescent population-based cohort. The association between OGMneg and contemporaneous depression has been found previously in cross-sectional studies of adolescents from community samples (Kuyken & Dalgleish, 2011; O'Carroll et al., 2006) but not in such a large sample. When investigating alternative AM indices, AMSneg was associated with depression cross-sectionally such that *more* negative specific AMs were associated with *more* depressive symptoms. The effect size was only marginally smaller for AMSneg ($\beta = .094$) than OGMneg ($\beta = .107$), but they were both smaller than previous cross-sectional relationships seen with depressive symptoms in community adolescents (OGMneg $\beta = .14$, OGMpos $\beta = .28$; Kuyken & Dalgleish, 2011). The direction of the AMSneg result is unexpected given that depression has been previously associated with reductions in AM specificity (Hitchcock et al., 2014; Liu et al., 2013; Williams et al., 2007), but could be explained by mood congruence. As depression is commonly associated with a bias for producing fewer positive and more negative memories (Dalgleish & Werner-Seidler, 2014; Matt et al., 1992), adolescents with more depressive symptoms may be more likely to recall more negative memories regardless of whether they are specific or overgeneral. This is further supported by the stronger association of AMSneg and cross-sectional depressive symptoms in females given that females experience an

increase in depressive symptoms relative to males in adolescence (Maughan et al., 2013).

The relationship between OGMneg and prospective depressive symptoms has not previously been seen in community samples (Crane et al., 2016; Gutenbrunner et al., 2017), but is in line with findings from the EPAD high-risk sample of adolescents (Rawal & Rice, 2012b). Effect sizes for the prospective association were smaller in the ALSPAC cohort ($\beta = .073$) compared to previous analyses in the EPAD sample (whole sample $\beta = .12$; females only $\beta = .19$; Rawal & Rice, 2012b). This is unsurprising given the EPAD sample is enriched for depressive symptoms and its risk factors, but the smaller effect for ALSPAC could explain why previous non-high risk studies with modest sample sizes have failed to find a significant prospective association. Mood congruent effects did not extend across time as only OGMneg was associated with prospective depressive symptoms. These results suggest a genuine prospective overgeneral memory-depression relationship independent of current mood/baseline depression. Current findings are in line with theory that overgeneral AM develops as an emotion regulatory strategy in adolescence in response to stressful life events and this happens first for negative memories (Kuyken & Dalgleish, 2011; Williams et al., 2007). This research suggests OGMneg may be a risk factor for increased depressive symptoms in population-based samples (Garber, 2006; Kazdin et al., 1997; Kraemer et al., 1997; Rutter et al., 2001), and that inconsistencies in the previous literature are likely to be due to methodological differences. The prospective association is consistent across two different samples (ALSPAC and EPAD (Rawal & Rice, 2012b)) with different environmental circumstances and using different ways of measuring AM, thereby giving greater confidence in results.

Current results contrast with a previous analysis of the same sample by Crane et al. (2016). In the present analysis I adjusted for factors similar to those included in the Crane et al. (2016) study (e.g. gender, depression at baseline) as well as a number of additional factors (e.g. age and IQ). Sensitivity analyses adjusting for SES factors for AM and MDD (parity, economic disadvantage and maternal education) showed that the prospective association between OGMneg and depression was retained. The lack of previous association in ALSPAC may result from Crane and colleagues investigating specific AM rather than overgeneral AM or from not exploring the effect of valence. Although previous work on the ALSPAC AMT has suggested positive and negative responses may lie on the same continuum (Heron et al., 2012), there is good theoretical grounding and empirical evidence to suggest that depression may be associated with negative cues and memories in adolescence (Rawal & Rice, 2012b; Williams et al., 2007). Current analyses found that the prospective relationship with depressive symptoms was observed only for OGMneg and that it held for both self-reported and parent-reported adolescent depressive symptoms, so it is unlikely to be spurious. Thus AM definition and valence are important to consider when examining the relationship between overgeneral memory and depression in adolescent samples

Findings based on individuals at increased risk of depression have indicated the prospective relationship is present in adolescent females (Hipwell et al., 2011; Rawal & Rice, 2012b; Sumner et al., 2011) and some work in community samples has also highlighted gender is important (Hamlat et al., 2015). However, gender was found not to moderate the relationship between overgeneral memory and depressive symptoms. The only gender difference found in the current study was between AMSneg and contemporaneous depressive symptoms. This relationship was stronger for females than males and may reflect mood congruence.

Despite previous claims that overgeneral memory is only associated with depression in high-risk samples (Crane et al., 2016; Gutenbrunner et al., 2017), there was no evidence for maternal depression status moderating the relationships with contemporaneous or prospective depressive symptoms in ALSPAC. Evidence is mixed as to whether the relationship between maternal depression and offspring depression can differ by offspring gender (Bureau, Easterbrooks, & Lyons-Ruth, 2009; Fergusson, Horwood, & Lynskey, 1995; Lewis, Rice, Harold, Collishaw, & Thapar, 2011; Quarini et al., 2016; Sheeber, Davis, & Hops, 2002), but maternal depression status and gender together did not moderate the AM-MDD relationship in this study. Therefore, although having a mother with depression has been associated with a higher risk of depression and increased risk factors like stressful life events (Goodman & Gotlib, 1999; Rice et al., 2002b; Weissman et al., 2006), familial risk for depression did not affect the relationship between OGMneg and depressive symptoms in this population-based sample. Risk for offspring depression was indeed increased by having a mother with depression in the sense that mean depression scores were higher for adolescents with a depressed mother, but maternal depression did not affect OGMneg (Table 3.3). Conversely, previous cross-sectional work by Woody, Burkhouse and Gibb (2015) has found children of depressed mothers (n = 103) recall less AMSneg than children of non-depressed mothers (n = 120). It is unclear why the differences in results have occurred, but they may be due to methodological differences between studies. For instance, fairly rigorous exclusion criteria were used in the paper by Woody and colleagues, and they used an oral AMT with practice trials whereas the ALSPAC cohort has no exclusion criteria and uses a written, minimal-instruction AMT. However, results from the current analysis suggest that OGMneg is associated with depression and is a risk factor present in the general population, rather than just in high-risk samples.

Findings from analyses addressing whether OGMneg could be a risk factor for other disorders were mixed. Despite the strong association between depression and anxiety (Rice et al., 2017b; Rutter et al., 2006; Wittchen et al., 2000), no associations were seen with OGMneg and anxiety symptoms, thereby suggesting OGMneg is not a risk factor for anxiety. This is consistent with previous evidence (Rawal & Rice, 2012b; Wenzel & Jordan, 2005; Wessel et al., 2001). However, almost all AM measures were associated with psychotic-like symptoms cross-sectionally. Contrary to hypotheses, more AMSneg and more AMSpos were associated with an increased likelihood of experiencing at least one psychotic-like experience when adjusting for contemporaneous depressive symptoms. Findings therefore do not indicate a decrease in AM specificity being associated with concurrent psychotic-like symptoms, but are in line with the current finding of increased AMSneg seen in contemporaneous depression. Associations of AM and psychotic-like symptoms are unlikely to be a mood bias as increases in AM specificity for both positive and negative cues were seen. A general increase in memory or cognitive ability is also unlikely as IQ is negatively correlated with psychotic-like symptoms at ages 13 age 16.5 (Table 3.1). Thus, the present results suggest that reductions in AM specificity are not associated with current psychotic symptoms in youth unlike what has been seen in the adult schizophrenia literature (Berna et al., 2016; Ricarte et al., 2014; Wood et al., 2006). Further investigation of the relationship between AM and psychotic-like symptoms and schizophrenia-traits in adolescence is therefore required.

The longitudinal relationship between AM and psychotic-like symptoms was specific to OGMneg. Similar to the results with depressive symptoms, the temporal precedence suggests OGMneg could be a risk factor for psychotic-like symptoms (Garber, 2006; Kazdin et al., 1997; Kraemer et al., 1997; Rutter et al., 2001). There

is much genetic and phenotypic overlap between schizophrenia and depression which suggests common risk factors are likely for depressive and psychotic-like symptoms. For instance, the common genetic variants that contribute to the genetic risk for schizophrenia and depression overlap (Lee et al., 2013; Wray et al., 2018). Furthermore, genetic risk for schizophrenia manifests as depression (Nivard et al., 2017) and negative symptoms of schizophrenia (Jones et al., 2016) in adolescence, and these negative symptoms have strong commonalities with depressive symptoms (Kulhara et al., 1989; Siris, 2000; Stefanis et al., 2002). Nevertheless, although psychotic-like symptoms are an important phenomenon, it is not clear they are specifically measuring psychosis or schizophrenia. Psychotic-like symptoms are associated with subsequent psychotic disorders in adolescence (Zammit et al., 2013) but not with established risk factors for schizophrenia such as family history of schizophrenia or older paternal age (Zammit et al., 2008). There is also conflicting evidence on whether there is a genetic association between schizophrenia and psychotic-like symptoms in adolescence (Jones et al., 2016; Pain et al., 2018; Zammit et al., 2014). Psychotic-like symptoms are however associated with family history of MDD (Zammit et al., 2008) and show genetic associations with depression (Pain et al., 2018; Ronald & Pain, 2018). It has also been suggested that psychotic-like symptoms may be a measure of general distress rather than being specific to schizophrenia (Kelleher et al., 2012; McGrath et al., 2016). As the current study adjusted for depressive symptoms, the association between OGMneg and psychotic-like symptoms is unlikely to be attributable to depression. Therefore OGMneg could be a risk factor for general distress rather than psychosis in particular. Further longitudinal research using measures more specific to psychosis and schizophrenia are necessary to unpick whether OGMneg could be a risk factor for psychotic disorders rather than general distress.

3.4.1. Strengths and limitations

This analysis benefits from a large sample which is broadly representative of the general population (Boyd et al., 2013; Golding et al., 2001) and has prospective information over time for a wide range of factors associated with AM and depression. The relationship between overgeneral memory and depression was assessed over 3 years – a longer time lag than any other existing adolescent prospective study in the literature (see Introduction, Table 1.1.).

Nevertheless, the study should be viewed in light of its limitations. Firstly, as with all longitudinal datasets, ALSPAC suffers from attrition (Martin et al., 2016; Taylor et al., 2018; Wadsworth et al., 2003; Appendix 3.1). It is therefore not clear whether results would be the same if everyone who started in the cohort was retained, and results may be more conservative than if the whole population were still included. Secondly, the use of the same informant (adolescent) reporting on depressive symptoms and autobiographical memory may introduce bias for negative material. However, the results replicated when parent-reported depressive symptoms were used and the AMT is performance based rather than self-reported so is less affected by shared method variance than some other cognitive measures (Jacobs et al., 2008; Rice et al., 2015; Rutter et al., 2001). Consequently, using the offspring as the main informant is unlikely to have introduced negative bias in results but it cannot be ruled out entirely. Thirdly, the study used self-report questionnaires to assess depression so it is not clear to what extent results would replicated for MDD. Nevertheless, depression can be viewed dimensionally on a continuum of severity, with higher sub-threshold depressive symptoms being associated with an increased likelihood of developing MDD and significant impairment (Angold et al., 1999; Fergusson et al., 2005; Gotlib et al., 1995; Klein et al., 2009; Rice et al., 2017a). Therefore associations with depressive symptoms are likely to be similar to

associations with clinical MDD. Fourthly, due to the nature of the data collection, measures were not always available at the same time point or child age. For instance, there was no self-reported measure of depressive symptoms at exactly the time as the written AMT. In these cases, the measure assessed closest in time was selected. The closest measure of anxiety symptoms was the GAD section of the DAWBA which is more stringent than many questionnaires as it requires symptoms to be present 'more days than not' in the previous 6 months for symptoms to be endorsed. There were also fewer participants completing the DAWA, Therefore, the more stringent threshold for symptoms and smaller sample could have affected results for anxiety symptoms. Finally, valence is measured by cue under the assumption that memories cued by negative words are more likely to be negative themselves but it may be that is not the case (cue-memory valence convergence is considered for EPAD samples in sections 4.2.2.2 and 6.2.3.1). Previous work has highlighted that cue-memory valence similarity can be altered by MDD status, in that those with MDD produced fewer positive memories than healthy controls to positive and neutral cue words (Young et al., 2012b). Assessment of both cue and memory content valence has been advised (Lemogne et al., 2013), however, use of secondary ALSPAC data precluded this.

3.4.2. Conclusion

In sum, the current study has found OGMneg shows a cross-sectional and longitudinal relationship with adolescent depressive symptoms in a large population-based sample. The prospective relationship was specific to OGMneg. Gender and maternal depression status were not found to moderate the AM-depression relationship. Results highlight OGMneg as a potential risk factor for depression in an adolescent sample at typical risk of developing depression which has not been found previously. OGMneg is unlikely to be a general risk factor for all psychopathology as

there was no association with anxiety symptoms, but it may also be a risk factor for psychotic-like symptoms or general distress.

Although the present study indicates that overgeneral memory is associated with increased risk for depressive symptomatology, it not clear whether overgeneral memory acts as a mediator (or a risk mechanism) through which other known risk factors exert their effects on liability to depression. The following two chapters therefore focus on the relationships between overgeneral memory and other risk factors for depression; namely SLEs (Chapter 4) and genetics (Chapter 5).

4. Examining the relationship between stressful life events and overgeneral autobiographical memory in adolescents at high familial risk of depression

Overgeneral memory may be a risk factor for adolescent depression but little is known about how overgeneral memory arises in this age group. Stressful life events (SLEs) are strongly implicated in the onset of depression and are considered important in theoretical work on AM. I investigated whether exposure to lifetime and recent SLEs contributed to the development of overgeneral memory in a sample of adolescents at high familial risk of depression (n = 257) and examined the effects of gender and memory valence. Whether AM mediated the relationship between SLEs and MDD was also assessed. Exposure to a higher number of lifetime SLEs was associated with an *increase* in specific AMs. Associations of recent SLEs with AM differed by gender. For girls, more recent SLEs were associated with more overgeneral AMs. For boys, more recent SLEs were associated with fewer overgeneral AMs and more specific AMs. No measure of AM mediated the relationship between SLEs and subsequent DSM-IV depressive symptom count. Results suggest a complex relationship between AM and SLEs and that overgeneral AM and SLEs may exert independent effects on subsequent depression.

4.1. Introduction

Despite the involvement of overgeneral memory in depression, little is understood about how the phenomenon develops. The CaR-FA-X model (see Chapter 1, section 1.3.4 for an overview) is a prominent theory that suggests overgeneral AM arises through capture and rumination, functional avoidance and impaired executive control (Williams et al., 2007). This theory proposes that individuals retrieving a specific memory will use a generative retrieval process which starts at a broad, generic level before moving down towards event-specific knowledge. If this hierarchical search is interrupted then an overgeneral AM may be retrieved instead of a more specific AM. Support has been found for rumination and impaired executive control contributing to overgeneral memory (Dalgleish et al., 2007; Rawal & Rice, 2012a; Sumner, 2012), but the role of functional avoidance is less clear (Sumner, 2012). The functional avoidance mechanism is posited to occur when individuals passively avoid recalling specific details of AMs as a way of reducing emotional distress. Overgeneral memory is hypothesised to develop early in life initially as an emotion regulatory strategy to deal with memories of traumatic or stressful life events (SLEs) but then becomes generalised to other memories through reinforcement (Hermans et al., 2008a; Williams et al., 2007). Thus, overgeneral memory may mediate the relationship between SLEs and MDD.

A considerable amount of research has explored functional avoidance indirectly by assessing overgeneral memory in individuals who have experienced traumatic events (such as abuse, sudden serious illness/injury, combat, motor vehicle accidents, assault and rape; Moore & Zoellner, 2007; Ono et al., 2015). Evidence has suggested that trauma alone is not sufficient for overgeneral memory to develop (Moore & Zoellner, 2007; Williams et al., 2007) and research on whether the relationship between trauma and AM could be moderated by factors such as age (e.g.

childhood) and type of trauma (e.g. sexual abuse) is inconsistent (Crane & Duggan, 2009; Johnson, Greenhoot, Glisky, & McCloskey, 2005; Moore & Zoellner, 2007; Sumner, 2012; Valentino et al., 2009). Although the majority of these studies have only indirectly assessed functional avoidance, more direct evidence in non-clinical samples has suggested that avoiding specific details of negative memories can act as an effective emotion regulation strategy to specific stressors (Anderson et al., 2010; Hermans et al., 2008a). Overgeneral AM and reduced AM specificity are also associated with cognitive strategies such as thought suppression and dissociation (Schonfeld & Ehlers, 2006; Williams et al., 2007), thereby highlighting the role of overgeneral AM as a cognitive avoidance strategy. Thought suppression and dissociation are also implicated in disorders linked with increased overgeneral AM such as depression and PTSD (Lyssenko et al., 2018; Wenzlaff & Wegner, 2000).

Despite the evidence for an association between trauma and overgeneral memory (Moore & Zoellner, 2007; Ono et al., 2015), there has been less consideration of the association between overgeneral memory and SLEs that are not overtly traumatic, such as disappointment and loss events, despite their importance in the aetiology of depression (Goodyer, Cooper, Vize, & Ashby, 1993; NICE, 2005). Studies that have explored SLEs and overgeneral memory tend to focus on recent specific stressors in adult samples (e.g. failing first university exam (Hermans et al., 2008a) and daily hassles (Anderson et al., 2010)). Given that the functional avoidance mechanism likely develops early in life in response to a wide range of stressors, more work is necessary in younger samples looking at a range of lifetime and recent SLEs. Lifetime exposures to trauma and SLEs are important as rather than being time-limited, they can act as risk factors that have long-lasting effects and can accumulate over time (Chapman et al., 2004; Repetti, Taylor, & Seeman, 2002; Rutter & Sroufe, 2000). However, research into recent SLEs is also warranted as

they are common and are thought to play a causal role in MDD (Kendler & Gardner, 2010; Kendler et al., 1999), including in samples at high familial risk of depression (Goodyer et al., 1993; Rice et al., 2017b). Although both recent and lifetime SLEs play a role in depression, stronger effects are seen between SLEs and MDD when they occur in the same developmental period (Shanahan et al., 2011); thus different effects may be seen between SLEs and overgeneral memory depending on recency of the events.

Adolescence is likely to be an important period for the development of overgeneral memory as it is a key period for increases in SLEs, biological sensitivity to stress, and rates of MDD (Ge et al., 2001; Lupien, McEwen, Gunnar, & Heim, 2009; Maughan et al., 2013). Gender differences in SLEs and depression also begin to emerge in adolescence. Adolescent girls display an increase in social stress in comparison to adolescent boys and this heightened sensitivity to stress is thought to contribute to the increase in depressive symptomatology (Rice et al., 2003; Shih et al., 2006; Thapar et al., 2012). There may therefore be gender differences in the effect of SLEs on overgeneral AM in adolescence but this has not been previously investigated. As around 40% of depressed parents' offspring develop MDD by young adulthood (Weissman et al., 2016, 2006), studying the relationship between SLEs and overgeneral memory in adolescent samples at high familial risk of depression can potentially help elucidate whether targeting AM is a useful prevention strategy for those at risk.

Although SLEs have classically been seen as risk factors for psychopathology, moderate amounts or particular types of stress may be adaptive and promote development of coping mechanisms. It has been highlighted that children in supportive, enriching environments and children experiencing high levels of adversity or chronic stress both exhibit heightened sensitivity to stress, whereas

those experiencing moderate stressors do not display this heightened sensitivity (Boyce & Ellis, 2005; Ellis & Boyce, 2008). Several instances of such curvilinear relationships between SLEs and mental health have been reported (Höltge, Mc Gee, & Thoma, 2018; McLafferty et al., 2018; Shapero et al., 2015); however the nature of the stressor (e.g. exam stress versus death of mother) is also likely to be important. Given the previous literature on curvilinear relationships between SLEs and mental health, it is also important to assess non-linear relationships between SLEs and AM.

Valence of memory may also play a role in the relationship between SLEs and overgeneral memory. Functional avoidance is thought to develop initially for negative memories and then generalise to more positive memories (Williams et al., 2007). Previous research has also found associations between adolescent depression and overgeneral AMs for negative cues but not positive cues (Rawal & Rice, 2012b; Woody et al., 2015). Consequently, SLEs may be more strongly associated with negative overgeneral AMs than positive overgeneral AMs in adolescence. Previous studies have primarily focused on valence of cue words under the assumption that cue valence and memory content valence are the same. However, this is not always the case (see Chapter 4, section 4.2.2.2, and Chapter 6, section 6.2.3.1) and cue-memory valence similarity can vary depending on MDD status (Young et al., 2012b). Consequently, separate analyses for cue valence and memory valence have been advised (Lemogne et al., 2013). It is therefore important to consider both cue and memory valence when investigating the relationship between SLEs and overgeneral memory. Although self-ratings would presumably be the gold standard, researcher-rated valence has been used in cases where self-ratings are not available (Chen et al., 2015; Meyer, Karl, & Flor, 2015; Sansom-Daly, Bryant, Cohn, & Wakefield, 2014; Schulkind et al., 2012).

4.1.1. The current study

The aim of the current study was to explore the relationship between SLEs and AM in a prospective longitudinal sample of adolescents with depressed parents (EPAD; Mars et al., 2012, 2013). Previous work with this sample found that overgeneral AM for negative cue words predicts subsequent DSM-IV MDD and depressive symptom count (Rawal & Rice, 2012b). In order to better understand the developmental pathways underlying overgeneral AM as a risk mechanism for depression, the current study examined: 1) the relationship between SLEs and AM. I particularly focused on examining the relationship between SLEs and overgeneral AM given that overgeneral AM is the aspect of autobiographical memory most strongly associated with vulnerability for subsequent depression in this sample. I examined AM specificity as a secondary outcome as this is consistent with previous literature (Liu et al., 2013; Moore & Zoellner, 2007; Williams et al., 2007), and improving AM specificity has been implicated as a potential treatment strategy for depression (Hitchcock et al., 2017; Kohler et al., 2015). Both linear and non-linear relationships were assessed. I additionally examined the role of a) recency of exposure to SLEs (whether the association differed for lifetime versus recent exposure to SLEs); b) gender; and c) emotional valence (cue word and memory content valence). It was hypothesised that SLEs (lifetime and recent) would be associated with more overgeneral AMs and fewer specific AMs, given that increased SLEs, more overgeneral AMs and reduced AM specificity are associated with depression (Kendler et al., 1999; Liu et al., 2013; Williams et al., 2007). Stronger relationships for females were anticipated given that the predictive relationship between overgeneral AM and depression is stronger in girls (Rawal & Rice, 2012b) and girls experience a greater number of social stressors in adolescence (Hamilton et al., 2015; Shih et al., 2006). Based on the functional avoidance theory (Williams et al., 2007),

it was anticipated that SLEs would have a stronger relationship with negative overgeneral AMs and overgeneral AMs generated from negative cue words given that negative cue words are more likely to result in negative memories. 2) I also set out to test if overgeneral memory mediated the relationship between SLEs and subsequent DSM-IV depressive symptom count. I was particularly interested in testing the hypothesis that overgeneral AM for negative cues mediated the relationship between SLEs and depression given the previously reported association between overgeneral AM for negative material and depressive disorder in this sample (Rawal & Rice, 2012b). Sensitivity analyses checked the role of event severity and previous episodes of MDD.

4.2. Methods

4.2.1. Sample and design

Data were collected during three waves of the EPAD study (Mars et al., 2012, 2013) via interviews at the participants' homes and questionnaires (see Chapter 2 for further information on the sample). Parents and children reported on SLEs at baseline (Wave 1, n = 279) and a second time point (Wave 2, n = 261). AM was assessed at the second time point (Wave 2, n = 257, 155 female, 102 male) which occurred on average 16 months after baseline. See Table 4.1 for descriptive information on this sample.

4.2.2. Measures

4.2.2.1 Stressful life events

Life events were assessed using a modified version of the Life Events Checklist (Johnson & McCutcheon, 1980) as described in Chapter 2, section 2.2.3.3. Negative events were reported by parents and children as ever occurring in the lifetime at Wave 1 (13 items) and over the past 12 months at Wave 2 (21 items). It was judged

that these SLEs could be recalled retrospectively with accuracy (Brewin, Andrews, & Gotlib, 1993). Items were summed to generate total number of lifetime SLEs and total number of recent SLEs. The reporting time frames for lifetime SLEs (Wave 1) and recent SLEs (Wave 2) did not overlap as the second assessment occurred on average 16 months later. Parents and children also rated the impact of each life event on a 5 point scale (1 Very pleasant, 2 A bit pleasant, 3 No effect/neutral, 4 A bit unpleasant, 5 Very unpleasant).

4.2.2.2 Autobiographical Memory Test

Participants completed the Autobiographical Memory Test (AMT; Williams & Broadbent, 1986) as previously reported (Chapter 2, section 2.2.3.1; Rawal & Rice, 2012b, 2012a). Participants were asked to recall a specific personal memory for 12 emotional cue words (6 positive, 6 negative). Each of the 12 cue words was read aloud and participants were given 30 seconds in which to respond, with prompting for non-specific memories.

Rating AMs as specific or overgeneral: Responses were coded as either: specific, extended, categoric, semantic associates or omissions by the original EPAD research team. Raters were blind to history of SLEs. There was high inter-rater reliability from two independent raters who coded the responses of 45 participants (average agreement $\kappa = 0.93$; Rawal & Rice, 2012b; a). Number of overgeneral AMs (categoric plus extended responses) was the primary outcome. Number of specific AMs was a secondary outcome. Additional outcomes related to valence of the cue word, namely overgeneral AMs to positive cues such as ‘happy’ and ‘sunny’ (OGMpos), overgeneral AMs to negative cues such as ‘angry’ and ‘mistake’ (OGMneg), specific AMs to positive cues (AMSpos), and specific AMs to negative cues (AMSneg). The possible range for each of these variables was 0 to 6.

Rating AM content valence: I transcribed and rated each memory for valence (negative, neutral or positive). Inter-rater reliability was good (see Chapter 2, section 2.2.3.1). Outcome variables were calculated based on overgeneral and specific AMs that were positive or negative in content, namely: positive overgeneral AMs, negative overgeneral AMs, positive specific AMs and negative specific AMs. Although closely aligned, valence of memory content did not always match the cue valence. For instance, 9.12% of memories in response to positive cue words were coded as neutral or negative and 8.66% of memories recalled for negative cues were rated as neutral or positive (Appendix 4.1).

4.2.2.3 Covariates, psychopathology at follow-up, and descriptive variables

Analyses adjusted for a number of factors known to be associated with overgeneral memory: IQ, age, gender and depressive symptoms (Andreano & Cahill, 2009; Park et al., 2002; Williams et al., 2007). *Child IQ* was assessed at interview (Wave 1) using 10 subscales on the WISC-IV (Wechsler, 2003). WISC-IV scores were standardised so the mean in the total sample was 100, in line with population norm scoring. *Child current depressive symptoms* contemporaneous with performance of the AMT (Wave 2) were assessed using the Mood and Feelings Questionnaire (MFQ; Angold & Costello, 1987), which comprised 34 items and covered the previous 3 months. The MFQ was chosen as a covariate as it allowed control for a full range of depressive symptoms. The MFQ has good reliability and validity, and is considered a valid screening tool for depression (Angold, 1989; Daviss et al., 2006; Kent, Vostanis, & Feehan, 1997). Index parent and child rated depressive symptoms were combined using an OR rule for each item (see Chapter 2, section 2.2.3.2) to provide a reliable estimate of children's current depression (Cronbach's $\alpha = 0.954$).

Child DSM-IV depressive symptom count at follow-up was measured at Wave 3 using combined parent and child reports on the Child and Adolescent Psychiatric Assessment (CAPA; Angold & Costello, 2000). This is a semi-structured diagnostic interview assessing psychiatric symptoms and impairment over the previous 3 months. MDD symptoms were summed to form total current DSM-IV depressive symptom count (possible range 0-9). DSM-IV depressive symptom count was used as the depression outcome.

Child working memory was assessed using the working memory subscale on the WISC-IV (Wechsler, 2003). *Economic disadvantage* was a dichotomous variable defined as whether participants met the international definition for poverty, i.e. ≤60% of the median income (Gordon, 2006), in this sample: Wave 1 parent-reported household income of ≤£20,000 (Rice et al., 2017b).

4.2.3. Procedure

SLEs were assessed via questionnaires at Waves 1 and 2; AMT data was collected at interview at Wave 2; questionnaire depressive symptoms and DSM-IV depressive symptoms counts were assessed at Waves 2 and 3 via questionnaires and interviews respectively.

4.2.4. Statistical analysis

SPSS version 23.0 was used for analyses. Descriptive analyses included Pearson's correlation coefficients and t-tests. To examine the first research question, associations between SLEs and AM were examined using hierarchical multiple regression models with standardised predictor variables (Cohen et al., 2003). Total number of lifetime and recent SLEs were examined as predictors in separate models. The primary outcome variable was number of overgeneral AMs. The secondary outcome variable was number of specific AMs. In regression models, the effect of

covariates (gender, IQ, age, contemporaneous depressive symptoms (MFQ) at Wave 2) on AM was assessed in Step 1 and Step 2 examined the main effect of SLEs. A SLE by gender interaction term was introduced in Step 3 to determine whether the relationship between SLEs and overgeneral AM was moderated by gender (coded males 0, females 1). Where significant gender interactions were observed, they were followed up by simple slopes analysis for males and females (Dawson, 2014). Non-linear main effects of SLEs on AM were tested by including a quadratic term.

Where a main effect of SLEs on AM was observed, follow-up regression analyses examined the influences of cue word valence and memory content valence (positive, negative) separately. To investigate the difference in the relative magnitude of associations by valence, 95% confidence intervals (CIs) of β were estimated using bias corrected bootstrapping (1,000 re-samples) and compared (Cumming, 2009). Valence differences were considered non-significant when the upper CI of the smaller β coefficient exceeded the lower CI of the larger β coefficient by more than 50%; however, CIs overlapping less than 50% indicated a significant difference between positive and negative valence at $p < .05$ (Cumming, 2009). Where moderation of gender was evident, separate regression models for males and females were performed for each cue valence and memory valence. Overlapping CIs were compared (as above) to assess differences in relative magnitude of valence associations (positive versus negative) for boys and girls separately.

To test if AM mediated the relationship between SLEs and subsequent DSM-IV depressive symptom count, mediation analyses were performed using the PROCESS version 3.0 SPSS macro (Hayes, 2017). Variables were mean centred and 95% confidence intervals (CIs) were generated using 5,000 bootstrap samples. Initial mediation models investigated whether overgeneral AM to negative cues (M) mediated the relationships between SLEs (X) and prospective DSM-IV depressive

symptom count at Wave 3 (Y) when adjusting for current depressive symptoms on the MFQ (Wave 2). OGMneg was considered to mediate the relationship between SLEs and MDD when CIs for the indirect effect did not cross zero. Although OGMneg was the hypothesised mediator, for completeness, mediation models also examined the mediation effects of the additional AM measures (OGMpos, AMSneg, AMSpos). Finally, moderated mediation was performed using PROCESS, model 8, in SPSS (Hayes, 2015) to assess whether mediation differed by gender.

A sensitivity check examined the effect of severity of SLEs whereby separate analyses were run for more and less severe lifetime SLEs (see Table 4.1). More severe SLEs were identified as rarer events that encompassed death or serious illness of a first-degree relative, self or close friend as well as events that were Adverse Childhood Experiences, for example, parental divorce (Chapman et al., 2004). Additional sensitivity checks were performed to ensure results were attributable to SLEs rather than a previous depressive episode. Regression models examining effects of SLEs on AM were repeated excluding individuals with a previous episode of MDD at Wave 1; n = 6).

Table 4.1. Frequency and average impact of lifetime and recent stressful life events

Stressful life event	N	Frequency (%)	Mean impact	SD impact
Lifetime				
Death of parent, brother or sister*	11	4.280	4.682	0.560
Death of a close friend*	19	7.393	4.632	0.523
Serious illness or injury to child*	69	26.848	4.543	0.741
Bullying by another young person	130	50.584	4.538	0.566
Serious injury or illness to parent, brother or sister*	122	47.471	4.475	0.589
Serious illness or injury to a close friend	33	12.840	4.439	0.659
Death of grandparent	137	53.307	4.372	0.683
Death of pet	164	63.813	4.372	0.640
Parent going to prison*	3	1.167	4.333	0.577
Parents divorced or separated*	91	35.409	4.220	0.810
Parent getting into trouble with the police	20	7.782	3.875	0.759
Father losing job	42	16.342	3.750	0.828
Mother losing job	24	9.339	3.708	0.859
Recent (in the past 12 months)				
Death of parent, brother or sister	1	0.389	5.000	0.000
Parent getting into trouble with the police	2	0.778	5.000	0.000
Parent going to prison	1	0.389	5.000	0.000
Death of a close friend	15	5.837	4.733	0.458
Parents divorced or separated	8	3.113	4.625	0.518
Serious illness or injury to a close friend	15	5.837	4.567	0.495
Bullying by another young person	39	15.175	4.526	0.769
Death of grandparent	35	13.619	4.486	0.562
Death of pet	59	22.957	4.441	0.595
Losing a close friend through arguments or being dropped	49	19.066	4.429	0.645
Serious injury or illness to parent, brother or sister	37	14.397	4.419	0.618
Increased quarrelling between parents	53	20.623	4.311	0.630
Doing badly in an exam	65	25.292	4.238	0.607
Close friend moves a long way away	28	10.895	4.214	0.947
Doing badly in school work	46	17.899	4.152	0.613
Breaking up with a boyfriend/girlfriend	63	24.514	4.119	0.776
Parent nagging or picking on this child more	63	24.514	4.095	0.812
Serious illness or injury to child	9	3.502	4.056	1.286
Parent less interested or loving towards child	21	8.171	4.024	0.782
Father losing job	27	10.506	3.685	1.011
Mother losing job	10	3.891	3.600	0.937

Impact severity on a scale of 1 to 5 (1 Very pleasant, 2 A bit pleasant, 3 No effect/neutral, 4 A bit unpleasant, 5 Very unpleasant). * indicates more severe stressful life event in sensitivity analyses.

4.3. Results

4.3.1. Descriptive analyses

The impact severity ratings of SLEs are presented in Table 4.1. As can be seen, all mean impact ratings were towards the negative end of the rating scale (4 and 5), providing evidence that these events are likely to be stressful. Descriptive information on the sample including gender differences and associations between study variables is illustrated in Table 4.2. As expected, girls experienced a greater number of recent SLEs ($t(217) = 2.225$, $p = .027$) and more depressive symptoms than boys (Wave 2 questionnaire depressive symptoms $t(240) = 2.622$, $p = .009$; Wave 3 DSM-IV depressive symptom count $t(241) = 3.119$, $p = .002$). Participants typically produced more specific AMs than overgeneral AMs. Overgeneral AM and specific AM were associated with different covariates. Thus, participants with a higher IQ ($r = .192$, $p = .002$) retrieved more specific AMs. In contrast, overgeneral AM was correlated with depressive symptoms: questionnaire depressive symptoms at Wave 2 ($r = .173$, $p = .007$) and DSM-IV depressive symptom count at Wave 3 ($r = .144$, $p = .024$). Lifetime SLEs were associated with lower IQ ($r = -.172$, $p = .01$), lower working memory ($r = -.211$, $p = .001$), economic disadvantage ($r = .230$, $p < .001$) and (older) child age ($r = .280$, $p < .001$). Lifetime SLEs and recent SLEs were associated with all depression indices (lifetime: $rs > .174$, $ps < .011$; recent: $rs > .360$, $ps < .001$).

Table 4.2. Descriptive information, gender differences and associations between SLEs, AM, depressive symptoms, covariates and descriptive variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Age														
2. IQ	**-.126**													
3. Working memory	-.014	**.667**												
4. Economic disadvantage	.067	**-.232**	-.094											
5. W2 depressive symptoms (MFQ)	.092	-.075	-.071	**.177**										
6. W3 DSM-IV depressive symptom count (CAPA)	**.188**	-.099	-.047	**.165**	**.509**									
7. SLEs (lifetime)	**.280**	**-.172**	**-.211**	**.230**	**.215**	**.174**								
8. SLEs (recent)	.092	-.046	-.025	-.015	**.538**	**.360**	**.148**							
9. Overgeneral AM (total)	-.092	.055	-.002	.022	**.173**	**.144**	-.060	.098						
10. Specific AM (total)	.108	**.192**	.107	-.063	-.100	-.094	.126	-.069	**-.503**					
11. OGMpos	-.086	.033	-.021	-.051	.067	.041	-.100	.049	**.818**	**-.438**				
12. OGMneg	-.065	.057	.018	.088	**.220**	**.192**	.003	.114	**.811**	**-.382**	**.327**			
13. AMSpos	.110	**.209**	**.147**	-.011	-.106	-.070	**.166**	-.111	**-.461**	**.875**	**-.529**	**-.219**		
14. AMSneg	.082	**.131**	.043	-.098	-.070	-.093	.058	-.011	**-.426**	**.885**	**-.247**	**-.448**	**.550**	
Mean or %	13.735	96.534	97.516	30.3%	**16.814**	**1.798**	3.771	**2.822**	2.039	6.817	1.109	0.930	3.518	3.300
SD or n	2.019	11.728	13.762	77/254	13.639	1.919	1.937	2.099	1.849	2.917	1.144	1.126	1.623	1.691
Range	10-18	69-131	56-135		0-57	0-9	0-9	0-9	0-9	0-12	0-5	0-6	0-6	0-6

AM = autobiographical memory; AMSneg – specific autobiographical memories to negative cues; AMSpos – specific autobiographical memories to positive cues; CAPA = Child and Adolescent Psychiatric Assessment; IQ = Intelligence Quotient; MFQ = Mood and Feelings Questionnaire; OGMneg – overgeneral autobiographical memories to negative cues; OGMpos – overgeneral autobiographical memories to positive cues; SLEs = stressful life events; W2 = Wave 2; W3 = Wave 3. Correlations and significant gender differences in means from t-tests significant at $p < .05$ indicated in bold.

4.3.2. Relationship between lifetime stressful life events and autobiographical memory

4.3.2.1 Overgeneral autobiographical memory

Results of hierarchical multiple regression analyses examining the association between lifetime SLEs and overgeneral AM are shown in Table 4.3. There was no main effect of lifetime SLEs on overgeneral AMs (β = -.061, p = .396) and no lifetime SLEs by gender interaction (β = -.013, p = .902). There was no evidence of non-linear effects of SLEs on overgeneral AM as the quadratic term was non-significant (Table 4.3).

4.3.2.2 Specific autobiographical memory

Unexpectedly, more lifetime SLEs were associated with a *greater* number of specific AMs (β = .178, p = .012). There was no moderation by gender or association between the quadratic term and specific AMs (Table 4.3).

Cue word valence and memory content valence. Follow-up analyses of the main effect of lifetime SLEs on AM specificity by cue word showed a significant relationship for AMSpos (β = .220, p = .002) but not AMSneg (β = .093, p = .203). The difference in βs for positive and negative cues did not differ significantly as the upper bound CI of AMSneg exceeded 50% of the CI for AMSpos (p > .05; Table 4.3).

Similarly, lifetime SLEs were significantly associated with specific AMs that were positive in content (β = .241, p = .001) but not specific AMs that were negative in content (β = .125, p = .085). The effect of lifetime SLEs on specific AM did not differ significantly by memory content valence (Table 4.3).

Table 4.3. Regression models investigating the effect of lifetime SLEs on number of overgeneral AMs and specific AMs.

	Overgeneral AM (n=213)						**Specific AM (n=213)**					
	Model change			**Coefficients**			**Model change**			**Coefficients**		
	R^2	***p***	***f^2***	**β**	**B (95% CI)**	***p***	**R^2**	***p***	***f^2***	**β**	**B (95% CI)**	***p***
Step 1: Covariates	**.057**	**.015**	**.061**				**.087**	**.001**	**.095**			
Full scale IQ				0.019	0.037 (-0.229, 0.304)	.782				0.245	0.761 (0.341, 1.180)	**<.001**
Age				-0.167	-0.303 (-0.549, -0.058)	**.016**				0.174	0.508 (0.122, 0.893)	**.010**
MFQ depressive symptoms				0.186	0.355 (0.093, 0.616)	**.008**				-0.083	-0.252 (-0.663, 0.159)	.228
Gender				-0.011	-0.040 (-0.543, 0.463)	.876				-0.002	-0.012 (-0.803, 0.779)	.976
Step 2: Main effect SLEs	Δ.003	.396	.003				**Δ.028**	**.012**	**.031**			
Lifetime SLEs				-0.061	-0.111 (-0.367, 0.146)	.396				0.178	0.512 (0.114, 0.910)	**.012**
Step 3: Moderation by gender	Δ<.001	.902	<.001				Δ.002	.554	.002			
Lifetime SLEs x Gender				-0.013	-0.030 (-0.517, 0.456)	.902				0.059	0.227 (-0.527, 0.981)	.554

AM = Autobiographical Memory; CI = Confidence Interval; IQ = Intelligence Quotient; MFQ = Mood and Feelings Questionnaire (Wave 2); SLEs = stressful life events. Results significant at $p < .05$ are indicated in bold.

The quadratic term (lifetime SLEs x lifetime SLEs) was not significantly associated with overgeneral AM (β = -0.447, B (95% CI) = -0.826 (-1.694, 0.042), ΔR^2 = 0.016, f^2 = 0.017, p = .062) or specific AM (β = 0.280, B (95% CI) = 0.825 (-0.528, 2.178), ΔR^2 = 0.006, f^2 = 0.007, p = .230).

Lifetime SLEs were significantly associated with AMSpos (β = 0.220, bootstrapped 95% CI = 0.089, 0.359, p = .002), but not AMSneg (β = 0.093, bootstrapped 95% CI = -0.047, 0.234, p = .203). Similarly, lifetime SLEs were significantly associated with specific positive AMs (β = 0.241, bootstrapped 95% CI = 0.103, 0.381, p = .001) but not specific negative AMs (β = 0.125, bootstrapped 95% CI = -0.009, 0.266, p = .085).

4.3.3. Relationship between recent stressful life events and autobiographical memory

4.3.3.1 Overgeneral autobiographical memory

When the relationship between recent SLEs and overgeneral AM was examined (Table 4.4), there were no main or quadratic effects of recent SLEs. A significant SLE by gender interaction was evident ($\beta = .349$, $p = .002$). Simple slopes analysis showed effects in opposing directions for males ($t = -2.233$, $p = .027$) and females ($t = 1.996$, $p = .047$).

Analyses for recent SLEs and positive/negative overgeneral AM examined separately for males and females are presented in Table 4.5. In both boys and girls, SLEs were generally more strongly associated with OGMneg and overgeneral AMs negative in content, than OGMpos and overgeneral AMs positive in content. However, 95% CIs for positive and negative associations overlapped more than 50%, indicating no substantial valence differences (Cumming, 2009).

4.3.3.2 Specific autobiographical memory

There was no significant main effect of recent SLEs on specific AMs and there was no evidence for a non-linear relationship (Table 4.4). However, a significant SLE by gender interaction was also present for specific AMs ($\beta = -.349$, $p = .001$). Simple slopes analyses by gender found boys experiencing more recent SLEs recalled *more* specific AMs ($t = 2.346$, $p = .020$), but the association with *fewer* specific AMs in girls was not significant ($t = -1.862$, $p = .064$).

Analyses for recent SLEs and positive/negative specific AM in males and females are presented in Table 4.5. For boys the association with specific AMs was more strongly associated for AMSneg and specific AMs negative in content, but in girls the association was marginally stronger for AMSpos and specific AMs positive

in content. Again, the overlapping 95% CIs suggest there were no substantive differences in valence.

Table 4.4. Regression models investigating the effect of recent SLEs on number of overgeneral AMs and specific AMs.

	Overgeneral AM (n=214)						**Specific AM (n=214)**					
	Model change			**Coefficients**			**Model change**			**Coefficients**		
	R^2	***p***	***f^2***	**β**	**B (95% CI)**	***p***	**R^2**	***p***	***f^2***	**β**	**B (95% CI)**	***p***
Step 1: Covariates	**.071**	**.004**	**.077**				**.080**	**.002**	**.087**			
Full scale IQ				0.090	0.181 (-0.091, 0.453)	.190				0.177	0.563 (0.137, 0.989)	**.010**
Age				-0.172	-0.316 (-0.562, -0.070)	**.012**				0.195	0.566 (0.181, 0.951)	**.004**
MFQ depressive symptoms				0.198	0.390 (0.123, 0.656)	**.004**				-0.141	-0.438 (-0.856, -0.020)	**.040**
Gender				0.014	0.051 (-0.459, 0.561)	.844				0.005	0.029 (-0.770, 0.828)	.943
Step 2: Main effect SLEs	Δ<.001	.836	<.001				Δ<.001	.953	<.001			
Recent SLEs				0.016	0.033 (-0.278, 0.344)	.836				-0.005	-0.015 (-0.502, 0.473)	.953
Step 3: Moderation by gender	**Δ.044**	**.002**	**.050**				**Δ.044**	**.001**	**.050**			
Recent SLEs x Gender				0.349	0.882 (0.340, 1.423)	**.002**				-0.349	-1.389 (-2.237, -0.540)	**.001**

AM = Autobiographical Memory; CI = Confidence Interval; IQ = Intelligence Quotient; MFQ = Mood and Feelings Questionnaire (Wave 2); SLEs = stressful life events. Results significant at $p < .05$ are indicated in bold.

The quadratic term (recent SLEs x recent SLEs) was not significantly associated with overgeneral AM (β = 0.245, B (95% CI) = 0.585 (-0.352, 1.522), ΔR^2 = 0.007, f^2 = 0.007, p = .220) or specific AM (β = -0.367, B (95% CI) = -1.380 (-2.842, 0.082), ΔR^2 = 0.015, f^2 = 0.017, p = .064).

Table 4.5. Association between recent SLEs and cue/memory valenced AMs in boys and girls

	Overgeneral AM						Specific AM					
	Boys			Girls			Boys			Girls		
	β	**bootstrapped 95% CI**	**p**	**β**	**bootstrapped 95% CI**	**p**	**β**	**bootstrapped 95% CI**	**p**	**β**	**bootstrapped 95% CI**	**p**
Cue valence												
Positive	-0.057	-0.312, -0.223	.644	0.007	-0.218, 0.205	.945	0.151	-0.104, 0.405	.212	-0.206	-0.413, 0.038	**.043**
Negative	-0.295	-0.571, -0.005	**.015**	0.230	0.068, 0.454	**.024**	0.268	0.078, 0.497	**.025**	-0.084	-0.300, 0.144	.424
Memory content valence												
Positive	-0.108	-0.366, 0.158	.374	0.022	-0.196, 0.201	.838	0.176	-0.070, 0.409	.146	-0.181	-0.395, 0.019	.078
Negative	-0.215	-0.464, 0.080	.081	0.224	0.041, 0.444	**.023**	0.212	-0.017, 0.466	.084	-0.156	-0.366, 0.047	.138

AM = Autobiographical Memory; CI = Confidence Interval. Results significant at $p < .05$ are indicated in bold. 95% confidence intervals were compared for valence (positive versus negative) separately for boys and girls.

4.3.4. Mediation

I next tested whether OGMneg mediated the association between SLEs and subsequent depression. There was no evidence of an indirect effect of OGMneg on subsequent DSM-IV depressive symptom count when lifetime SLEs (B = .001, SE = .005, 95% CI = -.007, .012) or recent SLEs (B < .001, SE = .004, 95% CI = -.009, .010) were predictor variables. There was also no evidence of moderated mediation by gender (lifetime SLEs: B = .003, SE = .009, 95% CI = -.013, .026; recent SLEs: B = -.011, SE = .016, 95% CI = -.047, .018).

Additional mediation models which were run for completeness also found no evidence for mediation or mediated moderation of the other AM indices (Table 4.6).

4.3.5. Sensitivity analyses

Sensitivity analyses assessed the role of event severity in the unexpected observation that *greater* lifetime SLEs were associated with a *greater* number of specific AMs, which was the opposite direction to that hypothesised (see section 4.1.1). Regression analyses were performed separately for more severe lifetime SLEs (e.g. death of parent, brother or sister) and less severe lifetime SLEs (e.g. mother/father losing job) (see Table 4.1). More severe lifetime SLEs significantly predicted total specific AMs (β = .144, B (95% CI) = .410 (.025, .794), p = .037), AMSpos (β = .197, B (95% CI) = .314 (.102, .527), p = .004) and specific AMs positive in content (β = .239, B (95% CI) = .384 (.170, .597), p < .001). Less severe lifetime SLEs were not associated with specific AMs (β = .131, B (95% CI) = .381 (-.016, .777), p = .060), but were significantly associated with AMSpos (β = .150, B (95% CI) = .245 (.024, .466), p = .030) and specific AMs positive in content (β = .141, B (95% CI) = .232 (.008, .455), p = .042).

To determine whether results were attributable to a prior depressive episode, analyses assessing the relationship between SLEs and AM were repeated excluding individuals with a prior depressive episode. All results remained the same with one exception - simple slopes analysis revealed males with more SLEs reported fewer overgeneral AMs and more specific AMs but the positive association between recent SLEs and overgeneral AM in girls was no longer significant ($t = 1.860$, $p = .064$). Consequently, presence of a prior depressive episode is unlikely to have affected the results.

Table 4.6. Summary of mediation models testing for indirect effect of SLEs on DSM-IV depressive symptoms count through autobiographical memory indices.

		Mediation											Moderated mediation	
Predictor	**Mediator**	**Effect of X on M**			**Effect of M on Y**			**Direct Effect**			**Indirect Effect**		**Index of Moderated Mediation**	
(X)	**(M)**	**B (SE)**	**95% CI**	**p**	**B (SE)**	**95% CI**	**p**	**B (SE)**	**95% CI**	**p**	**B (SE)**	**95% CI**	**B (SE)**	**95% CI**
Lifetime SLEs (n=205)	OGMneg	-0.034 (0.038)	-0.110, 0.042	.377	-0.038 (0.075)	-0.185, 0.109	.611	0.042 (0.041)	-0.039, 0.122	.307	0.001 (0.005)	-0.007, 0.012	0.003 (0.009)	-0.013, 0.026
	OGMpos	-0.063 (0.040)	-0.141, 0.016	.119	-0.019 (0.072)	-0.160, 0.123	.794	0.042 (0.041)	-0.039, 0.122	.308	0.001 (0.005)	-0.011, 0.012	-0.001 (0.006)	-0.013, 0.013
	AMSneg	0.078 (0.061)	-0.042, 0.199	.200	-0.043 (0.047)	-0.136, 0.049	.357	0.046 (0.041)	-0.034, 0.127	.257	-0.003 (0.005)	-0.017, 0.004	-0.003 (0.008)	-0.024, 0.009
	AMSpos	**0.176 (0.058)**	**0.062, 0.289**	**.003**	-0.096 (0.049)	-0.194, 0.001	.052	0.060 (0.041)	-0.021, 0.141	.148	-0.017 (0.010)	-0.039, 0.001	-0.007 (0.012)	-0.032, 0.018
Recent SLEs (n=207)	OGMneg	0.007 (0.042)	-0.075, 0.090	.860	-0.570 (0.077)	-0.209, 0.096	.462	0.040 (0.046)	-0.052, 0.131	.391	<0.001 (0.004)	-0.009, 0.010	-0.011 (0.016)	-0.047, 0.018
	OGMpos	0.029 (0.044)	-0.058, 0.117	.508	-0.063 (0.073)	-0.207, 0.081	.392	0.041 (0.046)	-0.050, 0.133	.374	-0.002 (0.005)	-0.015, 0.007	-0.010 (0.013)	-0.041, 0.011
	AMSneg	0.051 (0.065)	-0.077, 0.178	.433	-0.034 (0.050)	-0.134, 0.065	.496	0.041 (0.046)	-0.050, 0.133	.376	-0.002 (0.004)	-0.013, 0.005	0.011 (0.014)	-0.017, 0.040
	AMSpos	-0.059 (0.062)	-0.182, 0.064	.343	-0.039 (0.052)	-0.142, 0.064	.459	0.037 (0.047)	-0.054, 0.129	.425	0.002 (0.005)	-0.007, 0.013	0.011 (0.015)	-0.018, 0.044

Mediation models adjusting for current depressive symptoms on the Mood and Feelings Questionnaire (Wave 2). AMSneg – specific autobiographical memories to negative cues; AMSpos – specific autobiographical memories to positive cues; OGMneg – overgeneral autobiographical memories to negative cues; OGMpos – overgeneral autobiographical memories to positive cues; SLEs – stressful life events. Results significant at $p < .05$ are indicated in bold.

4.4. Discussion

The current study investigated the relationship between lifetime and recent SLEs and overgeneral memory in an adolescent sample at high familial risk for MDD. No main effect of lifetime SLEs on overgeneral AM was observed. Unexpectedly, a greater number of lifetime SLEs was associated with recall of more specific AMs. For recent SLEs, results differed: there were no main effects on AM but there were significant interactions with gender. For boys, a greater number of recent SLEs was associated with *fewer* overgeneral AMs and *more* specific AMs. For girls, the effect was in the opposite but expected direction such that more recent SLEs were associated with more overgeneral AMs. However, there was no evidence that overgeneral memory mediated the relationship between SLEs and subsequent DSM-IV depressive symptoms count or for moderated mediation by gender. These results suggest that the relationship between SLEs and AM is complex, differing based on event recency, gender, and overgenerality/specificity. Results also suggest that SLEs and AM may exert independent effects on subsequent depression.

The present study found no association between lifetime SLEs and overgeneral AM but a greater number of lifetime SLEs were associated with more specific AMs. This pattern of results was unexpected given that previous literature has demonstrated that both SLEs and overgeneral memory have positive associations with depression (Kendler et al., 1999; Liu et al., 2013; Rawal & Rice, 2012b; Williams et al., 2007) and that more traumatic events have been implicated in overgeneral memory (Williams et al., 2007). One possible explanation for the unexpected finding is that participants who recall more lifetime SLEs may simply have better memory in general. Previous research in adults has highlighted that difficulty maintaining task goals or instructions in working memory is associated with greater overgeneral AM (Yanes, Roberts, & Carlos, 2008), so better recall of

task instructions could underlie the increased specificity for lifetime SLEs finding. However, this seems unlikely to be the case as more lifetime SLEs were associated with lower IQ and poorer working memory (Table 4.2). Sensitivity analyses also suggest this result is unlikely to be due to a previous episode of MDD.

Research has highlighted the mood enhancing benefits of recalling positive AMs (Joormann et al., 2007; Ramirez et al., 2015). It is therefore possible that recalling specific positive AMs may act as a coping strategy in the presence of previous SLEs. Indeed, moderate levels of stress may be beneficial and buffer against depressive episodes (Boyce & Ellis, 2005; Ellis & Boyce, 2008; Shapero et al., 2015). Although the association for lifetime SLEs and specific AMs was stronger for positive cues and memories, overlapping CIs suggest relationships with valence did not vary substantially. Furthermore, AM specificity to positive cues did not mediate the relationship between lifetime SLEs and subsequent DSM-IV depressive symptom count (Table 4.6) so recalling positive AMs in response to SLEs is unlikely to act as a coping strategy that protects against subsequent depressive symptomatology.

By definition, the measure of SLEs examined in this study was broad and included severe but less common events (e.g. death of a parent) as well as less severe more common events (e.g. mother or father losing job, death of a pet). All SLEs were rated as having a negative impact by combined parent and child reports (Table 4.1) and associations with AM specificity indices remained when more severe and less severe SLEs were examined separately. Correlations of lifetime SLEs with demographic and psychopathology variables were consistent with what would be predicted and existing literature (i.e. more SLEs were associated with lower IQ, economic disadvantage, older age and greater current and subsequent depressive symptomatology) (Franz et al., 2011; Goodyer et al., 1993; Hartlage, Alloy,

Vázquez, & Dykman, 1993; McLeod & Kessler, 1990; Repetti et al., 2002), but there may be inherent differences between traumatic events and SLEs. Trauma involves witnessing or experiencing an incident that may be life-threatening (e.g. road traffic accident, sexual assault) whereas SLEs (e.g. parental divorce, relative dying from natural causes) are less likely to involve threat to life. Consequently, the unexpected results for lifetime SLEs and AM specificity compared to the trauma and AM literature (Moore & Zoellner, 2007; Ono et al., 2015) may be a result of differences between SLEs and trauma.

Gender differences were observed for associations between recent SLEs on overgeneral and specific AM: more SLEs were associated with more overgeneral AMs in girls (the hypothesised direction) and boys displayed increased SLEs with decreased overgeneral AM and more specific AMs (the opposite direction). Such results could indicate that boys and girls react differently to recent SLEs and there is some evidence to support this view. First, girls are more sensitive to social stressors compared to boys and are more likely to develop depressive symptoms following social stress (Calvete, Camara, Estevez, & Villardon, 2011; Oldehinkel & Bouma, 2011; Shih et al., 2006). Second, a previous analysis of this sample illustrated that the association between overgeneral AM and subsequent depressive symptoms and disorder differed significantly by gender such that this relationship was substantially stronger for girls than boys (Rawal & Rice, 2012b). The moderated mediation analysis suggests that OGMneg is not a mechanism by which the stronger relationship between recent SLEs and MDD in adolescent girls compared to boys can be explained. One possibility is that boys and girls differ in how and what they recall; for example, research has shown that females' AMs contain more emotional and relational content (Fivush, 2011) and that there are gender differences in brain activity for the emotional aspects of AM (Compère et al., 2016). Nevertheless, no

mean-level differences in AM were observed between genders (Table 4.2). Alternatively, as girls experienced more recent SLEs, this could have affected the results if a certain number of SLEs was required to produce the anticipated overgeneral AM response (i.e. a threshold effect). Nevertheless, results of analyses using quadratic terms for recent and lifetime SLEs suggest that there is unlikely to be non-linear relationships between SLEs and AM.

In boys and girls, associations between recent SLEs and AM valence were sometimes observed more strongly for one valence than the other (Table 4.5). As overgeneral AM is thought to develop in response to functional avoidance of negative stimuli (Williams et al., 2007) and previous analyses of this sample found OGMneg to predict MDD (Rawal & Rice, 2012b), it was anticipated that more SLEs would be associated with increases in OGMneg and overgeneral AMs negative in content. However, in current analyses with recent SLEs, observed stronger associations for negative cues compared to positive cues did not translate to significant differences in valence associations as CIs overlapped substantially. Nevertheless, assessment of SLEs and AM valence in younger samples is warranted to determine if significant valence differences are apparent earlier in development.

If overgeneral AM develops via a functional avoidance mechanism it may mediate the relationship between SLEs and subsequent depression. However, OGMneg did not mediate the relationship between lifetime or recent SLEs and subsequent depression, and there was no evidence of moderated mediation by gender. Given that recent SLEs were associated with increased overgeneral AM in girls and previous analysis of this sample has found OGMneg is associated with prospective increases in depressive symptoms and new onset MDD (Rawal & Rice, 2012b), this pattern of results suggests that SLEs and OGMneg exert independent effects on prospective depression. Previous work has mainly focused on overgeneral

AM as a moderator of the SLE-MDD relationship with mixed findings (Anderson et al., 2010; Crane et al., 2016; Gibbs & Rude, 2004; Sumner et al., 2011). The current work extends developmental findings and highlights that the relationship between OGMneg and subsequent MDD is unlikely to develop as a result of recent or lifetime SLEs. Nevertheless, more complex relationships between overgeneral memory and subsequent depression may also exist; for instance, moderation by socioeconomic deprivation and other cognitive liability factors such as rumination (Hamlat et al., 2015; Stange et al., 2013).

It should be noted that the sample was at high risk of MDD from having at least one parent with recurrent depression which may have affected results. Having a parent with a mental health condition may in itself be considered a SLE (Chapman et al., 2004; Cheong, Sinnott, Dahly, & Kearney, 2017; Hammen, 2002; Hammen, Shih, & Brennan, 2004). Furthermore, offspring of depressed parents tend to report more SLEs than the general population (Bouma et al., 2008; Goodman & Gotlib, 1999). Consequently the EPAD sample is likely to be enriched for SLEs but this estimate does not include parent mental health as a SLE. In addition, as parents themselves are likely have increased levels of overgeneral memory (Williams et al., 2007), their less elaborative reminiscing may contribute to their offspring developing less elaborated (or less specific) AMs (Fivush et al., 2006). Thus, the EPAD sample may be enriched for overgeneral AM and reduced AM specificity[1]. Although having such a high-risk group is informative, replication in a community-based/population sample is required to determine whether current results are specific to this high-risk sample. Due to differences in that nature of SLEs obtained and when they were

[1] In practice, mean overgeneral AM was lower, and mean specific AM was higher in the EPAD sample compared with ALSPAC (see Appendix 4.2). This is likely to be due to differences in administration of the AMT. With the oral AMT in EPAD, participants had practice trials and prompting which would have increased AM specificity in comparison to ALSPAC participants who had a written AMT with no supervision or help.

measured, it was not possible to accurately replicate this analysis in the ALSPAC cohort.

Current findings also highlight the difference between overgeneral AM and AM specificity in that different patterns of association with SLEs, depressive symptomatology and demographic correlates were observed for overgeneral and specific AM. For instance, number of lifetime SLEs was associated with AM specificity but not overgeneral AM. Moreover, specific and overgeneral AM also appeared to have different prospective relationships with DSM-IV depressive symptom count and MDD (based on the current study and previous work with this sample (Rawal & Rice, 2012b)). In combination, these findings suggest that AM specificity and overgeneral AM are not different ends of the same spectrum in this sample.

4.4.1. Strengths and limitations

This study benefits from longitudinal data from an informative sample. Exploration in high-risk individuals is merited due to the importance of this group for targeted intervention and prevention approaches (Garber, 2006; Stice, Shaw, Bohon, & Marti, 2009). The use of longitudinal data allows exploration of SLEs and MDD across development. Measures of SLEs and depressive symptoms incorporated reports from multiple informants. This approach is recommended in routine clinical practice for depression in young people and is also less susceptible to reporting bias than information from single informants (Kessler, 1997; Rutter & Sroufe, 2000). This study also examined SLEs experienced both previously in the lifetime and recently, a practice rarely used in the literature, but clearly important given the different relationships seen with overgeneral memory.

Nevertheless, this study should be viewed in light of a number of limitations. First, SLEs were reported retrospectively. This may have been particularly problematic for lifetime SLEs which required retrospective recall across the lifetime as opposed to during the previous 12 months for recent SLEs. To some degree, collating reports across multiple informants assuages this limitation (Gest et al., 1999). Second, life events were assessed by questionnaire checklist rather than interview. Third, the analysis was conducted in a high-risk group and may not generalise to low-risk individuals. Fourth, the sample size was modest, especially for exploring gender differences. Finally, memory content valence was rated by researchers as no participant ratings were available. Consequently, participants may have experienced emotion of the memory differently to researcher rating.

4.4.2. Conclusion

This research has begun to untangle the complex relationship between SLEs and AM in a sample at high risk of MDD. Research into overgeneral memory is important as it may act as a risk mechanism for MDD. The present study found a main effect of lifetime SLEs on AM specificity. Gender differences were also found which suggests that following exposure to recent SLEs, boys and girls react differently as far as overgeneral memory is concerned. AM did not mediate the relationship between SLEs and subsequent DSM-IV depressive symptom count. In sum, although SLEs and overgeneral AM are well-established risk factors for MDD, they may exert independent effects in adolescents at high familial risk of depression. The following chapter explores the relationship between the distal risk factor of genetics and overgeneral memory.

5. Overgeneral autobiographical memory and polygenic risk for Major Depressive Disorder

It is not known whether overgeneral memory could be a risk mechanism through which known risk factors exert their effect on depression. The present chapter examines whether genetic risk for depression is associated with overgeneral memory in a high-risk sample (EPAD) and a population-based sample (ALSPAC). Genetic risk was defined as MDD polygenic risk scores - aggregated risk from multiple common genetic variants associated with MDD at a set significance threshold, based on the most recent MDD genome-wide association study from the Psychiatric Genomics Consortium. Regression models assessed whether MDD polygenic risk was associated with overgeneral AM to negative cues and specific AM to negative cues given their previous associations with depression. Analyses also investigated relationships with overgeneral AMs and specific AMs that were negative in content in the EPAD sample. Polygenic risk for MDD was not associated with any measure of overgeneral memory in either sample. This suggests that overgeneral memory is unlikely to be a mechanism through which common genetic risk for depression exerts its effect during adolescence.

5.1. Introduction

Risk factors increase the probability of a disorder above the rate in the general population and temporally precede the outcome (Garber, 2006; Kazdin et al., 1997; Kraemer et al., 1997; Rutter et al., 2001). Overgeneral memory is likely to be a risk factor for depression as greater levels of overgeneral AM and reduced AM specificity are seen in MDD (Hitchcock et al., 2014; Williams et al., 2007). Moreover, OGMneg is associated with subsequent development of depressive symptoms in at risk participants (Rawal & Rice, 2012b) and in the general population (Chapter 3), thereby showing temporal precedence. It is assumed that known risk factors (such as environmental or genetic factors) can exert their effects through proximal risk mechanisms and these are likely to be cognitive or neural (Rutter et al., 2001; Thapar et al., 2012). Understanding the mechanisms through which these known risk factors exert their effect is informative for improving understanding of the pathogenesis of depression. It is not yet clear whether overgeneral memory would constitute one of these more proximal risk mechanisms. Therefore it is informative to investigate the aetiology of overgeneral memory. Given that depression is moderately heritable (see Chapter 1, section 1.2.2.1), one possibility is that genes associated with depression exert their effects on depression by contributing to overgeneral memory. As the previous chapter (Chapter 4) focused on the association between an environmental risk factor for depression (SLEs) and overgeneral memory, the current chapter examines whether there is an association between common genetic risk for MDD and overgeneral memory.

There are no genetic studies of AM and depression, with the exception of small candidate gene studies based on the serotonin transporter promoter polymorphism (5-HTTLPR). These studies have found that 5-HTTLPR risk variants are associated with reduced AM specificity when interacting with recent life events

(Lemogne et al., 2009) and previous history of MDD (Sumner et al., 2014). Early evidence from candidate gene studies has implicated 5-HTTLPR in depression but more recent MDD genome-wide association studies (GWAS) examining risk across the whole genome have not found 5-HTTLPR to be associated with depression when controlling for multiple comparisons (Ripke et al., 2013; Wray et al., 2018). Candidate gene approaches are susceptible to false positives which may partly explain why 5-HTTLPR has not been consistently associated with MDD (Culverhouse et al., 2018; Sharpley, Palanisamy, Glyde, Dillingham, & Agnew, 2014). Consequently, examining the relationship between common genetic variation identified by MDD GWAS and overgeneral memory is a less biased approach, and also encompasses substantially more genetic variation than is seen from just one genetic risk variant.

GWAS have enabled the discovery of common variants (or Single Nucleotide Polymorphisms, SNPs) of small effect that in combination produce additive risk for psychiatric disorders (Plomin, Haworth, & Davis, 2009). Although there was limited success in identifying SNPs in early MDD GWAS, more recent GWAS have discovered a number of common variants associated with depression (see Chapter 1, section 1.2.2.2 for an overview). A recent MDD GWAS from the Psychiatric Genomics Consortium (PGC) has identified 44 loci reaching genome-wide significance ($p = 5 \times 10^{-8}$; Wray et al., 2018). Polygenic risk scores (PRS) are aggregate measures of genetic risk, which as well as including variants associated with a disorder that surpass the test of genome wide significance, also include variants that fall below this threshold. PRS are calculated for individuals from an independent sample by summing the total number of alleles showing association with a trait or disorder under a certain p threshold weighted by effect size from a

discovery sample (Wray et al., 2014). PRS are therefore useful biological indicators of genetic risk to psychiatric disorders (Kendler, 2016).

As yet, no study has examined the relationship between common genetic variation (PRS) for depression and overgeneral memory. Consequently, examination of the relationship between MDD PRS and overgeneral memory is warranted. Association with MDD PRS would indicate that overgeneral memory may be a risk mechanism through which risk genes contribute to the onset of depression.

5.1.1. The current study

The aim of the current study was to explore the relationship between MDD PRS and overgeneral memory in two samples: a sample at high risk for developing MDD by having a parent with the disorder (EPAD) and a cohort of adolescents from the general population at typical risk of developing MDD (ALSPAC). PRS were created for each individual based on results from the GWAS conducted by the MDD working group of the Psychiatric Genomics Consortium (Wray et al., 2018). These MDD PRS index the cumulative genetic burden of common risk alleles associated with MDD in the PGC GWAS discovery sample primarily based on adult-onset MDD patients. Given that OGMneg was the AM measure more strongly associated with prospective depression in ALSPAC and EPAD (Chapter 3; Rawal & Rice, 2012), analyses focused on the association between MDD PRS and OGMneg. The association between MDD PRS and specific AM to negative cues (AMSneg) was also examined as AMSneg is associated with contemporaneous depression (Chapter 3) and increasing AM specificity may be an effective treatment for adolescent depression (Neshat-Doost et al., 2013). Where valence of memory content itself was available (i.e. in the EPAD sample), analyses were performed for overgeneral AMs and specific AMs that were negative in content as examining both cue and memory

content valence has previously been advised (Lemogne et al., 2013). Covariates known to be associated with MDD PRS and AM - namely ancestry-based principal components to account for population stratification, gender, age, IQ and depressive symptoms (Andreano & Cahill, 2009; Park et al., 2002; Reich, Price, & Patterson, 2008; Williams et al., 2007) - were included in analyses.

Given that increased MDD PRS, increased overgeneral AM, and reduced AM specificity are associated with depression (Hitchcock et al., 2014; Williams et al., 2007; Wray et al., 2018), it was hypothesised that there would be positive relationships between MDD PRS and OGMneg and negative relationships between MDD PRS and AMSneg. Analyses with AM indices based on memory content valence were predicted to mirror the cue valence results. It was anticipated these associations would be specific to these AM indices, that is, MDD PRS would not show associations with other overgeneral memory indices (OGMpos and reduced AMSpos).

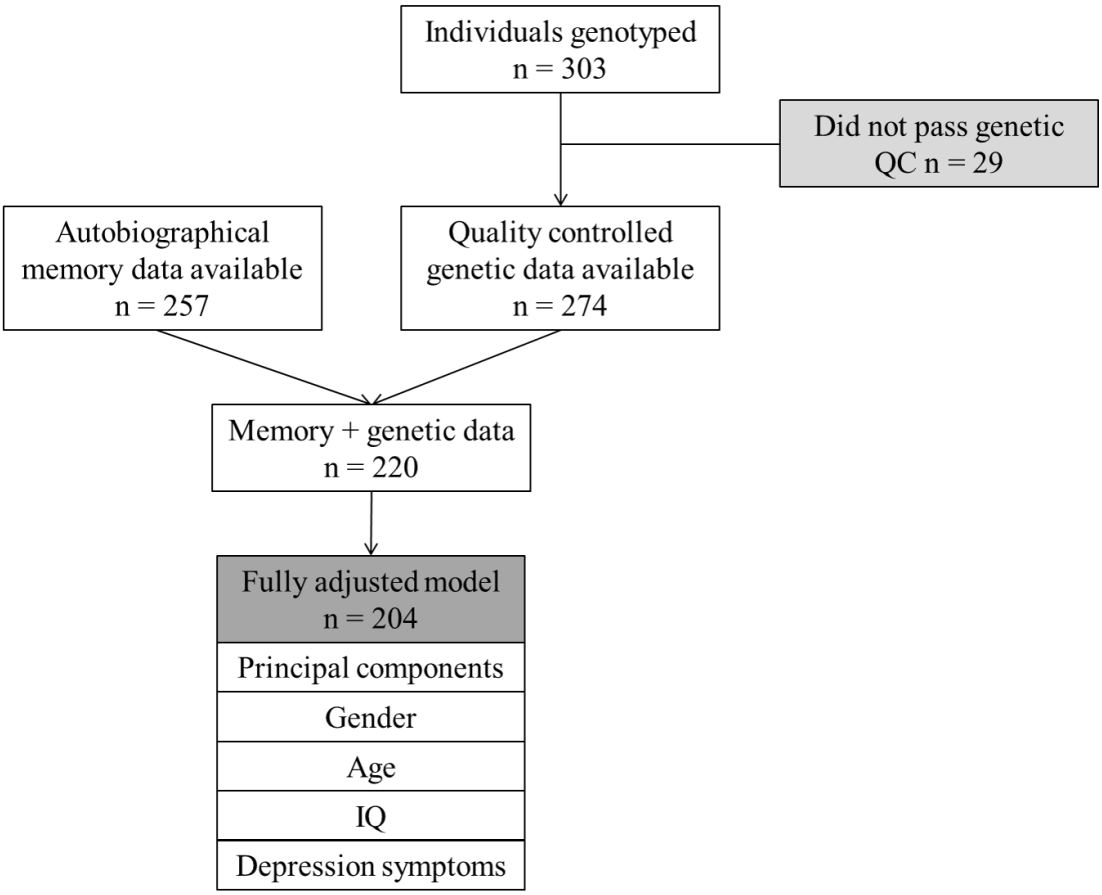
5.2. Methods

5.2.1. Participants

5.2.1.1 EPAD sample

Offspring from the EPAD sample (see Chapter 2, Methods) with phenotypic data on AM at Wave 2 and quality controlled genetic data available were included in the analyses (n = 220, 93 male, 127 female). Individuals were aged 10-18 years old (mean 13.81 years, SD 1.96). A flow chart of participant selection is presented in Figure 5.1.

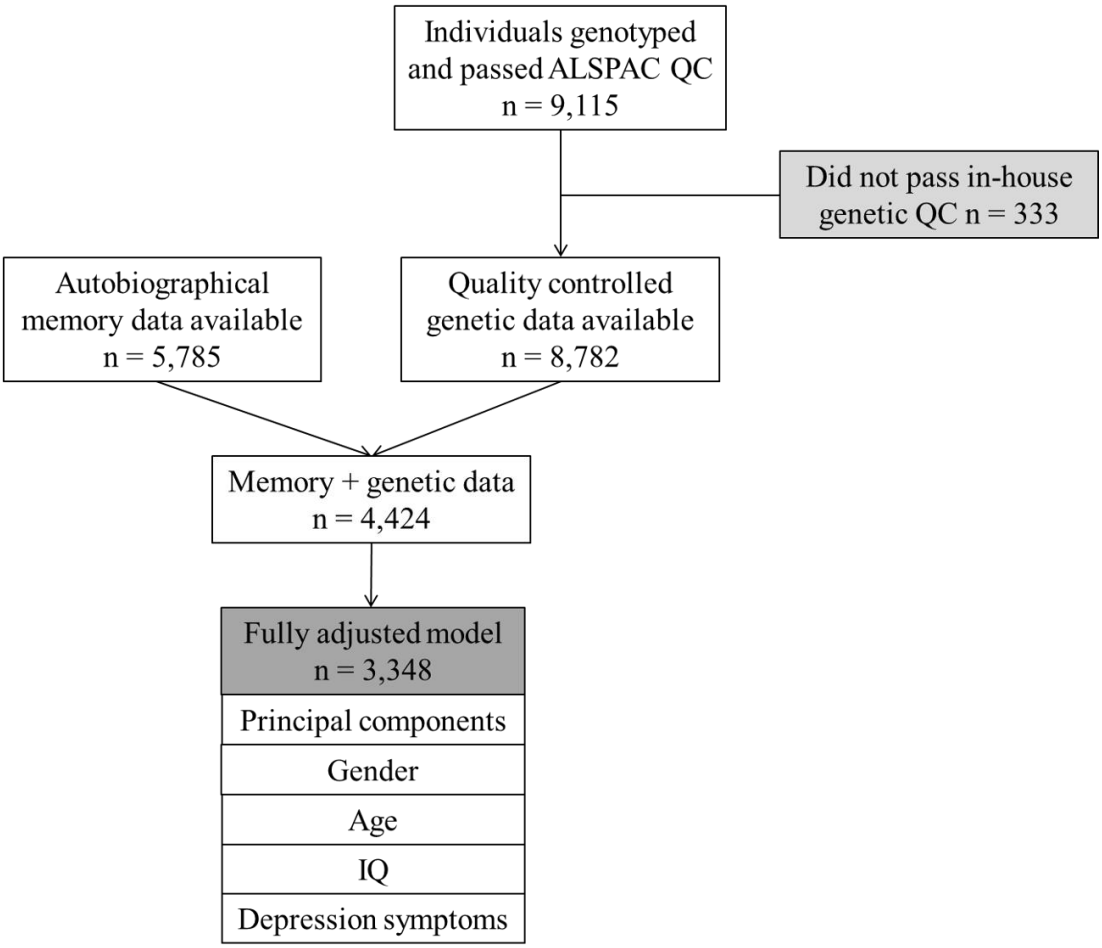
Figure 5.1. Numbers in the EPAD sample



5.2.1.2 ALSPAC cohort

ALSPAC offspring who had data on AM at age 13 and quality controlled genetic data were included in analyses (n = 4,424; 1930 male; 2494 female). Participants were aged between 157 and 179 months (13 years 1 month to 14 years 11 months), with a mean age of 157.41 (SD 1.41) months (or 13.12 years). A flow chart of participant selection is presented in Figure 5.2.

Figure 5.2. Numbers in the ALSPAC sample



5.2.2. Genetic data

5.2.2.1 EPAD sample

Saliva samples were obtained at each wave of the EPAD study where consent was given. Details on genotyping, quality control (QC) and imputation are detailed in Chapter 2, section 2.2.4. Following QC procedures, genetic data was available for 274 offspring in EPAD.

5.2.2.2 ALSPAC cohort

The ALSPAC offspring samples were genotyped, underwent QC and imputation by ALSPAC researchers (detailed information available in Chapter 2, section 2.1.4). Genetic data also underwent subsequent post-imputation QC in line with the EPAD

sample, performed by Dr Richard Anney. Following QC procedures, genetic information was available for 8,782 adolescents in ALSPAC.

5.2.2.3 Polygenic risk scores

Polygenic risk scores (PRS) were generated by Dr Richard Anney using the available summary statistics of the second analyses from the PGC MDD working group as a training set (59,851 cases and 113,154 controls; Wray et al., 2018). Summary statistics for this training set are publicly available at https://www.med.unc.edu/pgc/results-and-downloads. PRS were calculated for each individual using the --score command in PLINK (version 1.09; Purcell et al., 2007). This sums the number of risk alleles weighted by their log odds ratio for depression from the training dataset. Analysis focused on MDD risk alleles identified at the $p < 0.5$ threshold as this threshold captures maximal phenotypic variance (Ripke et al., 2013) resulting in PRS based on 143,262 linkage disequilibrium (LD)-independent SNPs ($R^2 < 0.2$) in EPAD and 167,535 SNPs in ALSPAC. PRS for additional p-value thresholds (0.1, 0.05, 0.01, 0.001, 0.0001, 0.00001, 0.000001, and 0.0000001) were created for sensitivity analyses (see Appendix 5.2).

5.2.3. Phenotypic outcomes

Overgeneral memory was measured with the AMT for the EPAD and ALSPAC cohorts (more information in Chapter 2, sections 2.2.3.1 and 2.1.3.1). The primary outcome variable was total number of overgeneral AMs (categorical + extended responses) to negative cues (OGMneg). The secondary outcome measure was number of specific AMs to negative cues (AMSneg). In the EPAD sample, where it was possible to rate the valence of the memories themselves (see Chapter 2, section 2.2.3.1), number of overgeneral AMs that were negative in content (negative

overgeneral AMs) and number of specific AMs that were negative in content (negative specific AMs) were also examined.

Additional AM measures created for sensitivity analyses included overgeneral AM to positive cues (OGMpos), and AM specificity to positive cues (AMSpos).

5.2.4. Covariates and descriptive variables

Analyses adjusted for a number of covariates in including principal components to control for population stratification in the genetics, and other factors linked to AM: gender, age, IQ and depressive symptoms. Current depressive symptoms were included as covariates to ensure associations were not confounded by both PRS and overgeneral memory being associated with depression.

Principal components (PCs) were created by Dr Richard Anney using scripts available at: https://github.com/ricanney/stata/blob/master/documents/bim2eigenvec.md. PCs were included to adjust for population stratification – where differences in allele frequencies between cases and controls are attributable to ancestry rather than disease (Reich et al., 2008). Evidence has found that PRS are highly associated with different ancestries (Curtis, 2018; International Schizophrenia Consortium, 2009), thereby highlighting the importance of adjusting for PCs to prevent spurious associations caused by ancestry differences.

Age was measured at completion of the AMT in both samples. IQ was measured on the WISC-IV (Wechsler, 2003) at Wave 1 in the EPAD sample and using WISC-III (Wechsler, 1991) at age 8 in the ALSPAC cohort (further information available in the Chapter 2, sections 2.2.3.4 and 2.1.3.3).

The presence of depressive symptoms was assessed using combined parent and child reports on the 34-item Mood and Feelings Questionnaire (MFQ; Angold & Costello, 1987) at Wave 2 in the EPAD sample. In ALSPAC, the self-rated short MFQ (sMFQ; Angold et al., 1995) at 12.5 years was used. The MFQ was chosen as the depression covariate as it provided a fuller range of symptoms than the more stringent measures available. However, sensitivity analyses were performed using more stringent DSM-IV depressive symptom count measurements to ensure results were not attributable to how depression was covaried for. In the EPAD study DSM-IV depressive symptom count was ascertained from parent and child reported on the Child and Adolescent Psychiatric Assessment (CAPA; Angold & Costello, 2000) concurrent with AM assessment (Wave 2). DSM-IV depressive symptom counts in ALSPAC were measured using parent-reported questionnaire version of the Depression and Wellbeing Assessment (DAWBA; Goodman et al., 2000) at age 13. Additional information on all depression measures is available in Chapter 2.

A number of descriptive variables were included for both samples. *Economic disadvantage* was coded in line with the international definition of poverty ≤60% of the median income of each sample (Gordon, 2006; Rice et al., 2017b). Additional depression measures previously described (Chapter 2, Methods) were used for descriptive analysis; namely, current DSM-IV MDD diagnosis (Wave 2 CAPA in EPAD; age 13 DAWBA in ALSPAC), Wave 1 and 3 DSM-IV depressive symptom counts (CAPA) in EPAD, and self- and parent-reported questionnaire depressive symptoms (sMFQ) at ages 12.5/13 and 16 in ALSPAC.

5.2.5. Statistical analysis

Initial analyses were conducted in Stata version 13 to assess the amount of phenotypic variance in depression explained by MDD PRS. Separate regression

models examined the effect of MDD PRS (adjusting for number of SNPs, sex and principal components 1 to 10) on depression outcomes. This is commonly used as a way of assessing how much variance in the phenotype that PRS can account for (e.g. Wray et al., 2018). In EPAD, depression outcomes were questionnaire depressive symptoms (MFQ), DSM-IV depressive symptom count (CAPA) and DSM-IV MDD diagnosis (CAPA) at Wave 2. In ALSPAC, depression outcomes were self-reported questionnaire depressive symptoms (sMFQ) at 12.5 years, and parent-reported DSM-IV depressive symptom count (DAWBA) and DSM-IV MDD diagnosis (DAWBA) at 13 years. This was consistent with depression measures used in previous chapters.

SPSS version 23.0 was used for all subsequent analyses. Analyses were performed first for the EPAD sample and then using the ALSPAC cohort. Descriptive information (mean, standard deviation) was calculated for all variables in each sample. Pearson correlation coefficients were performed to assess initial relationships between variables.

A series of linear regression models with standardised predictor variables (Cohen et al., 2003) were used to examine the relationship between MDD PRS and overgeneral memory in each sample. The predictor in each model was standardised MDD PRS derived from PGC MDD summary scores (Wray et al., 2018). The primary outcome variable was OGMneg given the prospective association with depression (Chapter 3; Rawal & Rice, 2012b). The secondary outcome was AMSneg given the contemporaneous association with depression (Chapter 3). Where possible, valence of the memories themselves were used as additional outcomes, i.e. overgeneral AMs negative in content and specific AMs negative in content for the EPAD sample. Each regression model included covariates in Step 1, followed by main effect in Step 2 for MDD PRS. Regression models adjusted for principal components, gender, age, IQ, and depressive symptoms. If associations reached

significance additional regression models were performed assessing other AM measures as dependent variables (OGMpos, AMSpos) to assess whether associations were only evident for OGMneg/AMSneg. Sensitivity analyses were performed using a more stringent measure of depressive symptoms (CAPA/DAWBA) as a covariate. Sensitivity analyses also examined associations between MDD PRS and AM indices using PRS derived from the different p-value thresholds from the discovery sample (Wray et al., 2018).

5.3. Results

5.3.1. Phenotypic variance explained by polygenic risk

The proportion of variance in depression explained by MDD PRS was very low. In EPAD, MDD PRS at a p-value threshold of 0.5 accounted for 0.019% of the variance in questionnaire depressive symptoms, 0.121% of the variance in DSM-IV depressive symptom count and 0.071% of the variance in DSM-IV MDD diagnosis. None of these associations was significant at $p < .05$. In ALSPAC, MDD PRS accounted for 0.130% ($p = .007$) of the variance in questionnaire depressive symptoms, 0.135% ($p = .007$) of the variance in DSM-IV depressive symptom count and 0.002% ($p > .05$) of the variance in MDD diagnosis. Variance explained by MDD PRS derived from alternative p-value thresholds are presented in Appendix 5.1.

5.3.2. EPAD study

5.3.2.1 Descriptive analysis

Descriptive information on the sample and univariate correlations are presented in Table 5.1. Measures of depression were correlated with OGMneg and overgeneral AMs negative in content but not AMSneg or specific AMs negative in content (rs <

.083, ps > .219). MDD PRS were correlated only with DSM-IV depressive symptom count at Wave 1 (r = .158, p = .019) and female gender (r = .135, p = .045).

5.3.2.2 Relationship between genetic risk for depression and overgeneral memory

Regression models assessing the relationships between PRS and overgeneral memory are displayed in Table 5.2. Positive relationships were observed between MDD PRS and each measure of AM but none of the associations were significant at $p < .05$.

5.3.2.3 Sensitivity analyses

Results did not differ when using DSM-IV depressive symptoms count as a covariate instead of questionnaire depressive symptoms ($\beta s < .072$, ps > .314). Associations between MDD PRS at a range of p-value thresholds and AM were non-significant but effect sizes were larger for the p-value threshold of 0.05 (Appendix 5.2).

Table 5.1. Descriptive information and correlations between autobiographical memory, depression measures, polygenic risk scores and covariates in the EPAD sample

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Gender (female)														
2. Age (years)	.119													
3. IQ	.075	-.055												
4. Economic disadvantage	.012	.091	**-.258**											
5. W1 DSM-IV depressive symptom count (CAPA)	.131	**.206**	**-.151**	**.226**										
6. W2 DSM-IV depressive symptom count (CAPA)	**.155**	**.221**	**-.165**	**.160**	**.492**									
7. W3 DSM-IV depressive symptom count (CAPA)	**.181**	**.199**	-.101	**.180**	**.393**	**.608**								
8. W2 DSM-IV MDD (CAPA)	.084	-.007	-.050	.107	**.261**	**.586**	**.292**							
9. W2 depressive symptoms (MFQ)	**.165**	.104	-.096	**.180**	**.422**	**.666**	**.533**	**.344**						
10. OGMneg	.013	-.004	-.014	.061	**.139**	.089	**.232**	.112	**.219**					
11. Overgeneral AMs negative in content	.070	-.029	.077	.024	.125	.059	**.218**	.057	**.209**	**.902**				
12. AMSneg	.005	.024	**.174**	-.079	-.008	-.010	-.081	-.043	-.005	**-.420**	**-.377**			
13. Specific AMs negative in content	.027	.066	.115	-.020	.033	.083	-.025	.035	.056	**-.390**	**-.340**	**.870**		
14. MDD PRS	**.135**	.007	-.002	-.021	**.158**	.074	-.049	.001	.048	.044	.035	.020	.015	
Mean or %	57.7%	13.809	96.101	29.5%	1.582	1.845	1.783	5.5%	16.578	0.909	0.891	3.300	3.009	0.01107
SD or n	127/220	1.963	11.362	65/219	1.845	1.878	1.925	12/220	13.334	1.094	1.165	1.691	1.647	0.00002

AMs – autobiographical memories; AMSneg – specific autobiographical memories to negative cues; CAPA - Child and Adolescent Psychiatric Assessment; DSM-IV – Diagnostic and Statistical Manual of Mental Disorders – 4th edition; MDD – Major Depressive Disorder; MFQ – Mood and Feelings Questionnaire; OGMneg – overgeneral autobiographical memories to negative cues; PRS – polygenic risk scores; W1 – wave 1; W2 – wave 2; W3 – wave 3. Significant correlations at $p < .05$ indicated in bold.

Table 5.2. Regression models examining the association of depression polygenic risk scores on autobiographical memory indices in the EPAD and ALSPAC cohorts

		EPAD (n = 204)				ALSPAC (n = 3348)			
	Outcome	**ΔR^2**	**β**	**B (95% CI)**	**p**	**ΔR^2**	**β**	**B (95% CI)**	**p**
Cue valence	OGMneg	.001	.033	.034 (-.114, .182)	.649	<.001	.009	.011 (-.031, .053)	.603
	AMSneg	.010	.102	.168 (-.064, .400)	.155	<.001	-.016	-.022 (-.068, .024)	.354
Memory content valence	Overgeneral AMs negative in content	<.001	.018	.019 (-.133, .172)	.802				
	Specific AMs negative in content	.004	.066	.107 (-.120, .333)	.355				

ALSPAC – Avon Longitudinal Study of Parents and Children; AMs – autobiographical memories; AMSneg –specific autobiographical memories to negative cues; EPAD - Early Prediction of Adolescent Depression; OGMneg –overgeneral autobiographical memories to negative cues. Results significant at $p < .05$ indicated in bold.

5.3.3. ALSPAC cohort

5.3.3.1 Descriptive analysis

Descriptive analyses for the ALSPAC cohort are presented in Table 5.3. There were similar gender proportions to the EPAD sample and the mean MDD PRS was similar between samples. In ALSPAC, OGMneg was correlated with all measures of depression (rs .036 to .109, ps < .027) but not with MDD PRS. AMSneg was correlated with questionnaire depressive symptoms (rs .035 to .111, ps < .045) but not with DSM-IV depressive symptom count (r = .016, p = .325) or diagnosis (r = -.003, p = .876). MDD PRS were positively correlated with all measures of depressive symptoms (rs .039 to .078, ps < .017) but not DSM-IV MDD diagnosis (r = .007, p = .675). MDD PRS were also correlated with IQ (r = .072, p <.001) and economic disadvantage (r = .057, p = .001).

5.3.3.2 Relationship between genetic risk for depression and overgeneral memory

Regression models examining the associations between MDD PRS and overgeneral memory were non-significant in the ALSPAC sample (Table 5.2). Effect sizes were smaller for the ALSPAC regression models than the EPAD regression models. Observed cue valence results were in the same direction for OGMneg in both samples, but direction of results differed for AMSneg: MDD PRS had a non-significant negative relationship with AMSneg in ALSPAC but a non-significant positive relationship in the EPAD sample.

5.3.3.3 Sensitivity analyses

Results did not differ when using DSM-IV depressive symptom count as a covariate (OGMneg β = .004, p = .826; AMSneg β = -.004, p = .822). Results remained non-

significant when assessing MDD PRS derived from a range of different p-value thresholds (Appendix 5.2).

Table 5.3. Descriptive information and correlations between autobiographical memory, depression measures, polygenic risk scores and covariates in the ALSPAC sample

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Gender (female)													
2. Age (months)	**-.104**												
3. IQ	-.027	**-.043**											
4. Economic disadvantage	.019	.003	**-.144**										
5. SR depressive symptoms (sMFQ) 12.5 years	**.121**	.007	<.001	.030									
6. PR depressive symptoms (sMFQ) 13 years	**.053**	-.006	**-.112**	**.075**	**.244**								
7. SR depressive symptoms (sMFQ) 16 years	**.225**	<.001	-.038	**.050**	**.343**	**.224**							
8. PR depressive symptoms (sMFQ) 16 years	**.135**	.022	**-.058**	**.040**	**.185**	**.397**	**.367**						
9. DSM-IV depressive symptom count (DAWBA) 13 years	**.060**	**.045**	**-.038**	**.070**	**.140**	**.343**	**.167**	**.266**					
10. DSM-IV MDD (DAWBA) 13 years	.001	<.001	-.024	**.044**	**.070**	**.130**	**.041**	**.121**	**.415**				
11. OGMneg	**.051**	.006	**-.079**	-.004	**.109**	**.083**	**.108**	**.080**	**.042**	**.036**			
12. AMSneg	**.109**	-.004	**.145**	**-.052**	**.111**	.008	**.060**	**.035**	.016	-.003	**-.243**		
13. MDD PRS	.007	.013	**-.072**	**.057**	**.039**	**.047**	**.078**	**.048**	**.059**	.007	.013	-.015	
Mean or %	56.4%	157.406	106.811	15.8%	3.962	2.286	5.783	2.064	0.364	0.5%	1.316	1.376	0.01494
SD or n	2494/4424	1.405	15.892	532/3357	3.846	3.214	5.506	3.295	1.120	18/3820	1.223	1.355	0.00002

AMSneg –specific autobiographical memories to negative cues; DAWBA – Depression and Wellbeing Assessment; DSM-IV – Diagnostic and Statistical Manual of Mental Disorders – 4th edition; MDD –Major Depressive Disorder; OGMneg – overgeneral autobiographical memories to negative cues; PR - parent-reported; PRS – Polygenic Risk Scores; sMFQ –Mood and Feelings Questionnaire short version; SR = self-reported. Significant correlations at $p < .05$ indicated in bold.

5.4. Discussion

The current study investigated the relationship between common genetic risk for MDD and overgeneral memory in an adolescent sample at high familial risk of developing depression (EPAD) and a sample of adolescents from the general population (ALSPAC). MDD PRS were not associated with OGMneg or AMSneg in either sample. Similarly, where valence of memory content was available (in the EPAD sample), there were no associations between MDD PRS and overgeneral AMs or specific AMs that were negative in content. These findings indicate that overgeneral memory is unlikely to be a mechanism through which common gentic variants exert their effects on depression, or that the association is very small and the current study lacked the statistical power to detect such a small effect size.

Contrary to hypotheses, there were no significant associations between MDD PRS and OGMneg or AMSneg in either sample. As higher MDD PRS are associated with depression (Wray et al., 2018) and depression is associated with more overgeneral AM and reduced AM specificity (Williams et al., 2007), positive relationships between genetic risk for MDD and OGMneg and negative relationships for AMSneg were anticipated. Nevertheless, current findings show that common genetic risk for depression was not associated with OGMneg or AMSneg. Results were in the anticipated positive direction for OGMneg, but in the EPAD sample there was a positive relationship between MDD PRS and AMSneg. This direction was consistent with the positive relationship evident in ALSPAC for AMSneg and contemporaneous depressive symptoms (Chapter 3) but fell short of significance. Additional analysis with memory content valence and sensitivity analyses with MDD PRS at different p-value thresholds (Appendix 5.2) also found no association between genetic risk for MDD and overgeneral memory. As previous studies have indicated, family members of individuals with depression also display overgeneral

memory (Young, Bellgowan, Bodurka, & Drevets, 2013), shared environmental factors (such as low maternal elaborative reminiscing (Fivush et al., 2006; Valentino, 2011)), are likely to be associated with the development of overgeneral memory.

There are a number of reasons for a lack of association between MDD PRS and overgeneral memory. Firstly, the modest association between overgeneral memory and depression, the relatively small proportion of variance in depression explained by MDD PRS, and the modest sample sizes are all likely to have affected power to detect a significant association. For instance, only a proportion of the association between overgeneral memory and depression is likely to be attributable to the link between MDD PRS and overgeneral memory. As the phenotypic association between overgeneral memory and depression is only modest (Chapter 3; Liu et al., 2013; Ono et al., 2015; Rawal & Rice, 2012b; Sumner et al., 2010), the effect size between MDD PRS and overgeneral memory will therefore be limited. The association between MDD PRS and overgeneral memory is further affected by the association between MDD PRS and depression, which in these samples is small (MDD PRS only explained up to 0.135% of the variance in depression phenotypes (Appendix 5.1)). To be able to detect such small effects would require large sample sizes. Although the effect size may be increased in high-risk samples enriched for depression and its risk factors (like EPAD), sample sizes for the current analysis were modest in comparison to other genetic studies (for instance, in comparison to the PGC MDD sample of 135,458 cases and 344,901 controls (Wray et al., 2018)). Thus, the study may not be adequately powered to find a statistically significant effect for a realistically small effect size.

Secondly, the SNPs captured by the GWAS are based on predominantly adult-onset MDD so it is possible that the MDD PRS in these analyses may not adequately explain genetic liability for adolescent-onset depression. Results from

studies with genetically informative designs (e.g. family, twin and adoption studies) suggest that there is genetic heterogeneity between childhood, adolescent and adult depression (Rice, 2014), and MDD PRS have previously been associated with adult emotional problems (depression and anxiety) but not with childhood and adolescent emotional problems (Riglin et al., 2017). Therefore, SNPs associated with increased risk for adult-onset MDD may differ to SNPs associated with increased risk for earlier-onset MDD. Although there was substantial heterogeneity in age of onset in the PGC MDD GWAS (Wray et al., 2018), it was predominantly based on adult-onset samples. Thus, developmental differences in the onset of MDD between discovery and target samples may have also affected the results.

5.4.1. Strengths and limitations

This is the first study to examine the link between polygenic risk for MDD and overgeneral memory. It builds on previous work (Lemogne et al., 2009; Sumner et al., 2014) by using multiple genetic risk loci rather than a candidate gene approach. This study also benefits from examining genetic risk for MDD and overgeneral memory in two, well-characterised cohorts. The use of a high-risk cohort and a typical-risk cohort has enabled investigation of the relationship between MDD PRS and overgeneral memory across the risk spectrum.

However, this study should also be viewed in light of its limitations. Firstly, PRS are useful biological indicators of genetic liability (Kendler, 2016) but, as previously mentioned, the MDD PRS only explained a very small proportion of the variance in depression phenotypes (EPAD maximum 0.121%; ALSPAC maximum 0.135%). In comparison, MDD PRS have accounted for up to 2.1% of the variance in depression phenotype in a very large sample of adults (Wray et al., 2018). The association between MDD PRS and overgeneral memory is further limited by the

modest phenotypic association between overgeneral memory and depression. It is therefore likely that the analyses were underpowered. In comparison with other psychiatric PRS, MDD PRS predict a smaller proportion of variance in the disorder phenotype (for instance, ~2% in comparison to ~7% in schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014)). This is likely to be due to depression having greater phenotypic heterogeneity, being more common and less heritable than other psychiatric disorders (Levinson et al., 2014; Sullivan et al., 2012), but future MDD GWAS with increased samples sizes are likely to detect more SNPs of small effect that, in combination, account for more of the variance in depression. Consequently, using MDD PRS from subsequent, larger, MDD GWAS that account for more phenotypic variance in depression may highlight a relationship between depression genetics and OGMneg or AMSneg that could not be detected in the current study. Secondly, differences between samples (e.g. genotyping platforms, written versus oral AMT, differences in depression measures and reporters) make direct comparison of the results in the two samples difficult. Thirdly, as both samples were longitudinal, they both suffer from attrition. Previous analysis in ALSPAC has found that higher psychiatric PRS are associated with attrition (Martin et al., 2016; Taylor et al., 2018) and therefore associations with phenotypes may be underestimated as those with higher genetic risk and related phenotypes are less likely to have participated. Finally, although it was possible to rate memory content valence in the EPAD sample, data restrictions prevented the rating and subsequent analysis of memory content valence in the ALSPAC cohort.

5.4.2. Conclusion

In conclusion, there was no significant association between MDD PRS and overgeneral memory indices in the EPAD and ALSPAC samples. Further research in larger sample sizes using PRS derived from larger discovery samples which can

account for more variance in depression may be better able to detect an association between genetic risk for depression and overgeneral memory.

The following chapter considers whether brain white matter previously associated with MDD is related to overgeneral memory as a way of identifying if white matter could be a biological mechanism that partly explains the link between overgeneral memory and depression.

6. Examining the link between structural brain connectivity associated with depression and overgeneral memory

The current chapter examines whether structural brain connectivity in regions previously associated with depression are related to overgeneral memory. A subsample of offspring of depressed parents from the EPAD study (n = 28) participated in a neuroimaging study in young adulthood (aged 18-25 years). I assessed the relationships between white matter microstructure indexed by fractional anisotropy (FA) in tracts previously related to depression (genu and body of the corpus callosum, right superior longitudinal fasciculus (SLF) III) and overgeneral memory. I also performed an exploratory whole brain white matter analysis to ascertain what areas of white matter were associated with overgeneral memory. There were no associations between FA in the tracts of interest and OGMneg. However, increased white matter FA in the body of the corpus callosum and right SLF III was associated with recall of more specific AMs that were positive in content. In whole brain analyses, there were no significant white matter regions associated with overgeneral memory after controlling for multiple comparisons. Recall of specific AMs positive in content can improve mood, therefore the relationship between FA in white matter linked to depression and specific positive memories may index emotion regulation. This study provides preliminary evidence that white matter could be a potential neurobiological mechanism for the relationship between overgeneral memory and depression but further research in larger samples is required before any strong conclusions can be drawn.

6.1. Introduction

A risk factor is more likely to be causal if the association between the risk and the outcome can be explained by an underlying mechanism (Academy of Medical Sciences, 2007; Hill, 1965; Rutter, 2007). Here I examine structural brain connectivity as a potential explanatory mechanism linking overgeneral memory and depression. As depression can be considered a disorder of connections in the brain (Hulvershorn et al., 2011; Keedwell & Linden, 2013), and retrieving autobiographical memories involves multiple brain regions (e.g. memory, emotional regulation, executive functioning and visual imagery; Cabeza & St Jacques, 2007; Svoboda, McKinnon, & Levine, 2006), an exploration of brain connectivity as a variable that may link these two factors is relevant. Structural connectivity refers to the white matter tracts (bundles of axons projecting across the brain) that connect different areas of the brain. White matter can be assessed in-vivo in the human brain through diffusion-weighted MRI (dwMRI), which indirectly measures tissue microstructure by mapping the diffusion of water molecules in the brain (Jones, 2008). The most commonly used metric of white matter, fractional anisotropy (FA), measures the degree to which water diffusion is constrained along one direction in a voxel (Jones, 2008). FA provides an orientation-dependent measure of tissue microstructure (Jones et al., 2013) with lower FA being associated with poorer cognitive task performance and higher levels of psychopathology (Fields, 2008, 2010; Jenkins et al., 2016; Johansen-Berg, 2010; Kanai & Rees, 2011). Additional information on dwMRI and FA can be found in Chapter 1, section 1.2.4. Finding an association between overgeneral memory and white matter microstructure (FA) in tracts previously related to depression would provide support for overgeneral memory being a potentially causal risk factor for MDD because a mechanism linking the two can be defined.

Despite the wealth of literature implicating overgeneral memory in depression (Chapter 1, section 1.3), the limited neuroimaging research on the topic has focus on grey matter rather than on white matter. Functional MRI (fMRI) studies during recall of specific AMs have reported differential Blood Oxygen Level Dependent (BOLD) activity in MDD compared to controls in grey matter regions such as the medial frontal gyrus, anterior cingulate cortex (ACC), ventrolateral prefrontal cortex (vlPFC), medial PFC and amygdala (Young et al., 2013; Young, Bodurka, & Drevets, 2017; Young, Siegle, Bodurka, & Drevets, 2016). Studies have also explored differential functional connectivity in individuals with MDD compared to healthy controls as indexed by task-independent (or 'resting-state') BOLD activity in grey matter regions that are temporally correlated but spatially distinct. These studies have found that individuals with MDD have reduced functional connectivity in the orbitofrontal cortex, precuneus, angular gyrus and amygdala, and this dysconnectivity is correlated with overgeneral memory (Liu et al., 2017; Young et al., 2016; Zhu et al., 2012). Although functional connectivity assesses grey matter activity across the brain which is temporally coherent or connected, it does not assess the structures that physically connect the areas of this functional circuit, such as white matter. Only one structural study on AM in MDD has been performed to date (Young, Bellgowan, Bodurka, & Drevets, 2015), but this study focused on grey matter. No studies have examined the relationship between structural connectivity or white matter pathways, overgeneral memory and depression. One way this relationship could be investigated is by assessing whether overgeneral memory is associated with white matter previously linked to MDD in the literature.

Studies of the relationship between white matter microstructure and depression have identified a number of white matter tracts associated with depression status. Reduced FA has been reported in MDD patients compared to healthy controls

in tracts such as the medial forebrain bundle (Bracht et al., 2015a, 2014), the cingulum (Bessette et al., 2014; Cullen et al., 2010), the uncinate fasciculus (LeWinn et al., 2014; Zhang et al., 2012), the corpus callosum (Aghajani et al., 2014; De Diego-Adeliño et al., 2014; Guo et al., 2012a; b) and the superior longitudinal fasciculus (Cullen et al., 2010; Lai & Wu, 2014; Murphy et al., 2012). However, many of the studies investigating the relationships between MDD and white matter have used tract-specific approaches with small sample sizes (less than 20 participants per group), without using a clinical interview to ascertain MDD diagnosis, and without adequately controlling for multiple comparisons. Consequently, meta-analyses on whole brain approaches that have larger sample sizes, interview for MDD diagnosis, and control for multiple comparisons likely provide more reliable information on white matter differences in MDD.

Meta-analyses based on whole brain white matter approaches report individuals with MDD have reduced FA in the body and genu of the corpus callosum, the anterior and posterior thalamic radiations, the arcuate fasciculus and the inferior and superior longitudinal fasciculi (Chen et al., 2016; Jenkins et al., 2016; Jiang et al., 2017; Kelly et al., 2016; Liao et al., 2013; Murphy & Frodl, 2011; Wise et al., 2016). Importantly, an international consortium that has combined dwMRI data across multiple research groups, the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) MDD working group, compared white matter of MDD patients (n = 348) and controls (n = 602) using the same processing and analysis pipeline for all participants, making it the largest meta-analysis to date with harmonised protocols (Kelly et al., 2016). Individuals with MDD displayed a reduction in FA in the body of the corpus callosum (Cohen's d = -0.34) and genu of the corpus callosum (Cohen's d = -0.27) compared to healthy controls. Reduced FA in the genu of the corpus callosum has also been implicated in a meta-analysis of

medication-naïve individuals with first-onset MDD along with the third branch of the right superior longitudinal fasciculus (SLF III) and anterior thalamic projections (Jiang et al., 2017). The results from this latter study would suggest that white matter microstructural differences are not a result of previous MDD episodes (reverse causation) or antidepressant medication, and therefore are likely indicative of the individuals' predisposition to depression. These tracts have also been implicated in adolescent MDD (Aghajani et al., 2014; Bessette et al., 2014; Cullen et al., 2010; Henderson et al., 2013; LeWinn et al., 2014), and the corpus callosum and SLF differ between adolescents at high familial risk of MDD and controls at low risk (Huang, Fan, Williamson, & Rao, 2011). Furthermore, FA in the anterior corpus callosum mediates the relationship between subthreshold depression at age 14 and depressive disorder at age 16 (Vulser et al., 2018), therefore may contribute to the development of MDD. In combination, the previous evidence suggests that structural alterations in the corpus callosum (genu and body) and right SLF III are associated with MDD and may in fact act as precursors to the disorder as they have been shown in samples of first-onset MDD, unaffected individuals at high-risk of MDD, and early-onset MDD.

The corpus callosum is the largest white matter tract in the brain and its function is to connect the left and right hemispheres. The genu of the corpus callosum is the anterior portion which connects prefrontal and orbitofrontal regions (Catani & Thiebaut de Schotten, 2008). The central part of the corpus callosum is known as the body and this connects precentral frontal regions and parietal lobes (Catani & Thiebaut de Schotten, 2008; Hofer & Frahm, 2006). The genu is thought to transfer motor information across the frontal lobes and be involved in taste, whereas the body is thought to integrate somatosensory, motor and some auditory information (Fabri & Polonara, 2013). Integration of information across hemispheres

via the corpus callosum is also necessary for a wide range of cognitive processes (Gazzaniga, 2000; Hinkley et al., 2012; Huang et al., 2015).

The SLF has been implicated in cognitive control (Chaddock-Heyman et al., 2013). Five distinct functional branches of the SLF have been suggested in humans – the first, second and third branches (SLF I, II and III), the tempoparietal component (SLF TP), as well as the arcuate fasciculus (Kamali, Flanders, Brody, Hunter, & Hasan, 2014). The SLF III is the most lateral branch and runs from the supramarginal gyrus/inferior parietal lobule to the ventral premotor cortex and prefrontal cortex (Dick & Tremblay, 2012; Kamali et al., 2014; Makris et al., 2005). The right SLF III connects areas involved in visuospatial attention (Corbetta & Shulman, 2002), prosody (Ross, 1981) and music processing (Loui, Alsop, & Schlaug, 2009), and is largely thought to be involved in language processes (Dick & Tremblay, 2012). The left SLF III connects brain regions thought to be involved in praxis (Heilman & Watson, 2008) and verbal fluency (Schiff, Alexander, Naeser, & Galaburda, 1983). Analyses in this chapter focus on the right SLF III as this has been associated with first-episode MDD (Jiang et al., 2017).

6.1.1. The current study

The aim of the current study was to explore the association between white matter tracts associated with depression and overgeneral memory in a sample of young adults at high familial risk for depression. This sample previously participated in the original EPAD study as children and adolescents (Rawal & Rice, 2012a; b). Two complementary neuroimaging approaches were taken to address whether white matter tracts associated with depression were related to overgeneral memory. An *a priori* tract of interest approach ('tractography') was used to determine whether white matter FA robustly associated with depression in previous research was

associated with measures of overgeneral memory. An advantage of this approach is that FA is extracted for the entire white matter connection which is conceptually more meaningful than a cluster of voxels in a small section of white matter as seen in whole brain analyses. Furthermore, as crossing fibres are present in 90% of voxels (Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2013), whole brain voxel-based analyses that attribute individual voxels to a specific white matter tract can be speculative (Bracht, Linden, & Keedwell, 2015b). Anatomical localisation of tractography conducted on each individual participant's dwMRI scan is more accurate than whole brain analyses that warp and thin white matter in dwMRI scans so it can be combined across subjects (Cercignani, 2010). However, as a tract of interest approach only allows examination of associations with pre-selected tracts, an exploratory whole brain approach was also used to assess the relationship between overgeneral memory and white matter across the brain.

For the tract of interest approach, I sought to examine 1) whether there was a relationship between FA in each white matter tract associated with depression (genu of the corpus callosum, body of the corpus callosum, and right SLF III) and OGMneg given the prospective association seen with depression in Chapter 3 and the previous literature (Rawal & Rice, 2012b). Nevertheless, overgeneral memory is first thought to develop in response to negative events before becoming generalised to other events irrespective of valence (Williams et al., 2007), and fMRI studies have focused on reduced AM specificity (Liu et al., 2017; Young et al., 2013, 2017, 2016). Therefore I also assessed 2) whether FA in the aforementioned white matter tracts was associated with AM measures that were related to depression in the current sample (AMSpos, specific AMs positive in content; Table 6.2). As the white matter tracts of interest are associated with cognition, sensitivity analyses were performed using a long-term memory measure as an alternative outcome. This was

done to ensure observed results were not due to a reduction in a general cognition (i.e. reduced long-term memory) rather than an overgeneral memory bias.

The whole brain voxel-based exploratory approach was done using a method called tract-based spatial statistics (TBSS; Smith et al., 2004, 2006). With this method, a group 'tract skeleton' is created which represents the central portion of each white matter tract common to all participants. Analyses were performed that assessed the relationship between each voxel of this tract skeleton and overgeneral memory. Similar to the tract-specific analysis, I examined 1) the whole brain white matter association with OGMneg. I also assessed 2) whether other AM indices associated with depression in the current sample (AMSpos, specific AMs positive in content) were associated with white matter across the brain. Due to the large number of tests run, correction for multiple comparisons was performed (Smith & Nichols, 2009).

I hypothesised that lower FA in white matter previously linked to depression would be associated with measures of overgeneral memory (more OGMneg, less AMSpos, and less specific AMs positive in content), thereby highlighting overgeneral memory as a potential risk mechanism for depression. I also anticipated that any associations would be specific to the AM bias and not extend to a general reduction in long-term memory.

6.2. Methods

6.2.1. Sample

The sample included 28 individuals (6 male, 22 female; aged 18 to 25 years; see Table 6.1.) who participated in the original EPAD study in childhood and adolescence. Full information on recruitment is available in Chapter 2, section 2.3.1. Individuals were sent information by post and this was followed up with phone calls,

texts and emails. Individuals indicating interest in participating underwent telephone screening to determine if they were safe to be scanned and a testing session at Cardiff University was arranged.

6.2.2. MRI

Scan acquisition and processing of the data is outlined in Chapter 2, section 2.3.4.4. In brief, standard T1-weighted structural and dwMRI scans were performed on a 3T scanner at CUBRIC (Cardiff University Brain Research Imaging Centre). Data were processed using the standard pipeline which included correcting for distortions, linking the two scans, and creating fibre trajectories or 'streamlines' by tracking principle directions of diffusion across voxels throughout the brain.

6.2.2.1 Tractography

Manual tractography was performed to reconstruct individual tracts of interest from the whole brain tractography data using ExploreDTI version 4.8.3 (Leemans et al., 2009). Tracts of interest were the genu of the corpus callosum (genuCC), the body of the corpus callosum (bodyCC) and right SLF III. To isolate these tracts of interest from all white matter streamlines in the brain, a series of regions of interest or 'gates' were manually drawn on different slices of the brain. These gates work by either including streamlines that cross them (e.g. the green and blue gates on Figures 6.1 and 6.2) or excluding streamlines that cross them (e.g. the red gates on Figures 6.1 and 6.2). Inclusion and exclusion gates were drawn around visible anatomical landmarks or areas of the brain to demarcate streamlines belonging to the tracts of interest according to the standard published protocols outlined below. Algorithms in ExploreDTI reconstructed the tracts by selecting all streamlines passing through inclusion gates and excluding all streamlines passing through exclusion gates. These

tracts can be visualised (e.g. Figures 6.1 and 6.2) and average FA across the tract can be extracted.

The genuCC was reconstructed as the anterior sixth of the corpus callosum (Hofer & Frahm, 2006) using standardised protocol from Misaghi, Zhang, Gracco, De Nil and Beal (2018). Inclusion gates were placed on and around the midline encompassing the corpus callosum genu. Exclusion gates were placed lateral to corticospinal tracts in each hemisphere and midway on the corpus callosum to prevent sideways and backward projections. Once the tract was reconstructed, erroneous streamlines that were anatomically implausible were also removed with exclusion gates. Example gate placement and tract can be seen in Figure 6.1 (a-c & g).

The bodyCC was reconstructed as the middle portion of the corpus callosum (Hofer & Frahm, 2006) using the protocol outlined in Misaghi et al. (2018). Inclusion gates were placed on and around the midline encompassing the corpus callosum body. As with the genu, exclusion gates were placed lateral to the corticospinal tract in each hemisphere. An additional exclusion gate was placed below the base of the corpus callosum to remove streamlines projecting from the brainstem. Once the tract was reconstructed, any streamlines that were anatomically implausible (for instance, crossing cingulum streamlines) were also removed with exclusion gates. Example gate placements and tract reconstruction are displayed in Figure 6.1 (d-f & g).

The right SLF III was reconstructed according to CUBRIC tractography protocol developed from Thiebaut De Schotten et al. (2011) in the right hemisphere of the brain. Inclusion gates were placed around the inferior frontal gyrus on a coronal slice at the level of the anterior commissure (Figure 6.2 a) and on a coronal

slice at the level of the posterior commissure encompassing the parietal lobe (Figure 6.2 b). An exclusion gate was drawn on an axial slice at the level of the posterior commissure encompassing the temporal lobes to remove fibres from the arcuate fasciculus (Figure 6.2 c). Once the tract was reconstructed, anatomically implausible streamlines were removed with exclusion gates. Example gates and tract are presented in Figure 6.2.

Figure 6.1. Examples of inclusion (green and blue) and exclusion gates (red) for genu of the corpus callosum (a-c) and body of the corpus callosum (d-f) on coronal, sagittal and axial slices, with reconstructed tracts (g: genu in red, body in yellow).

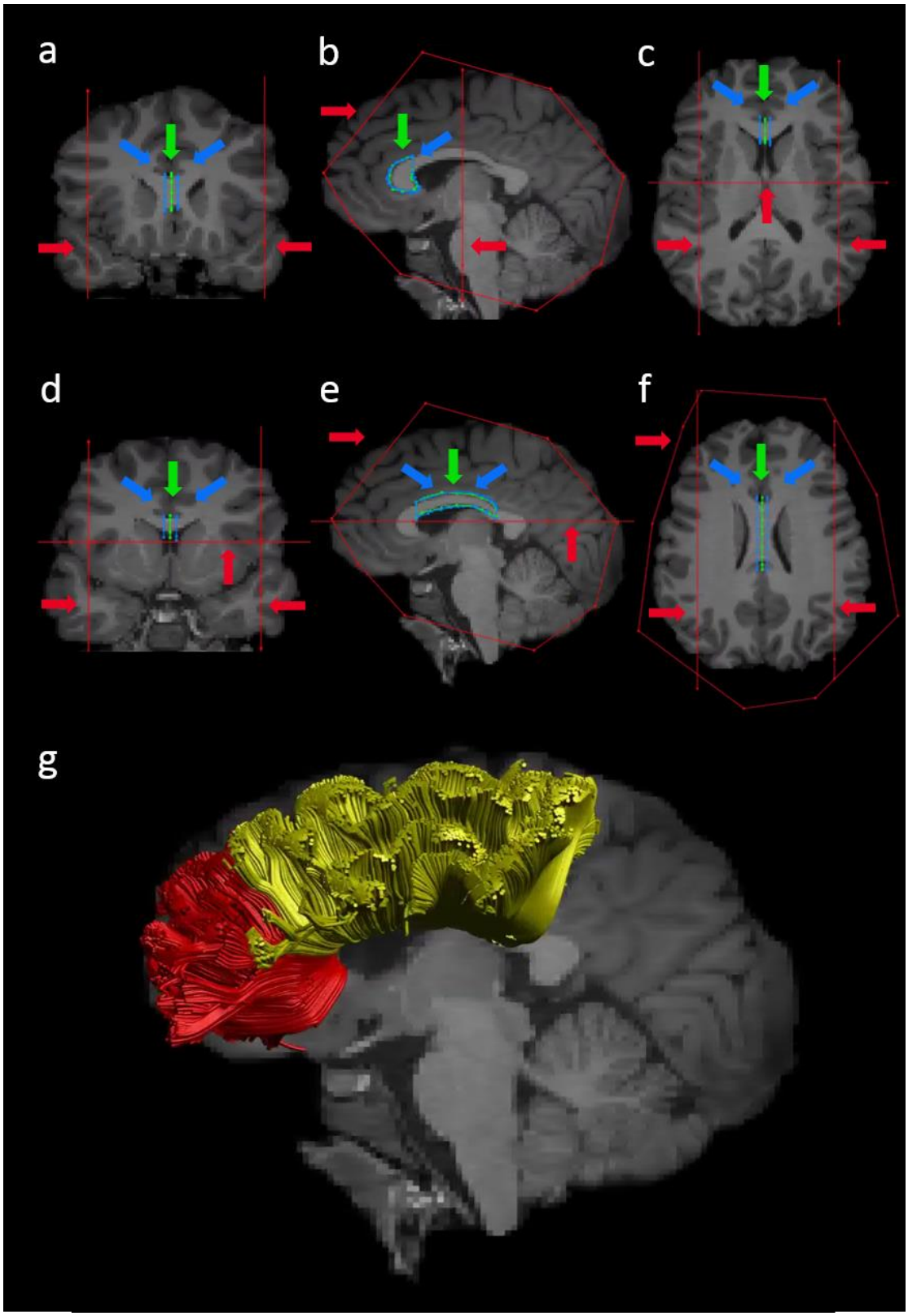
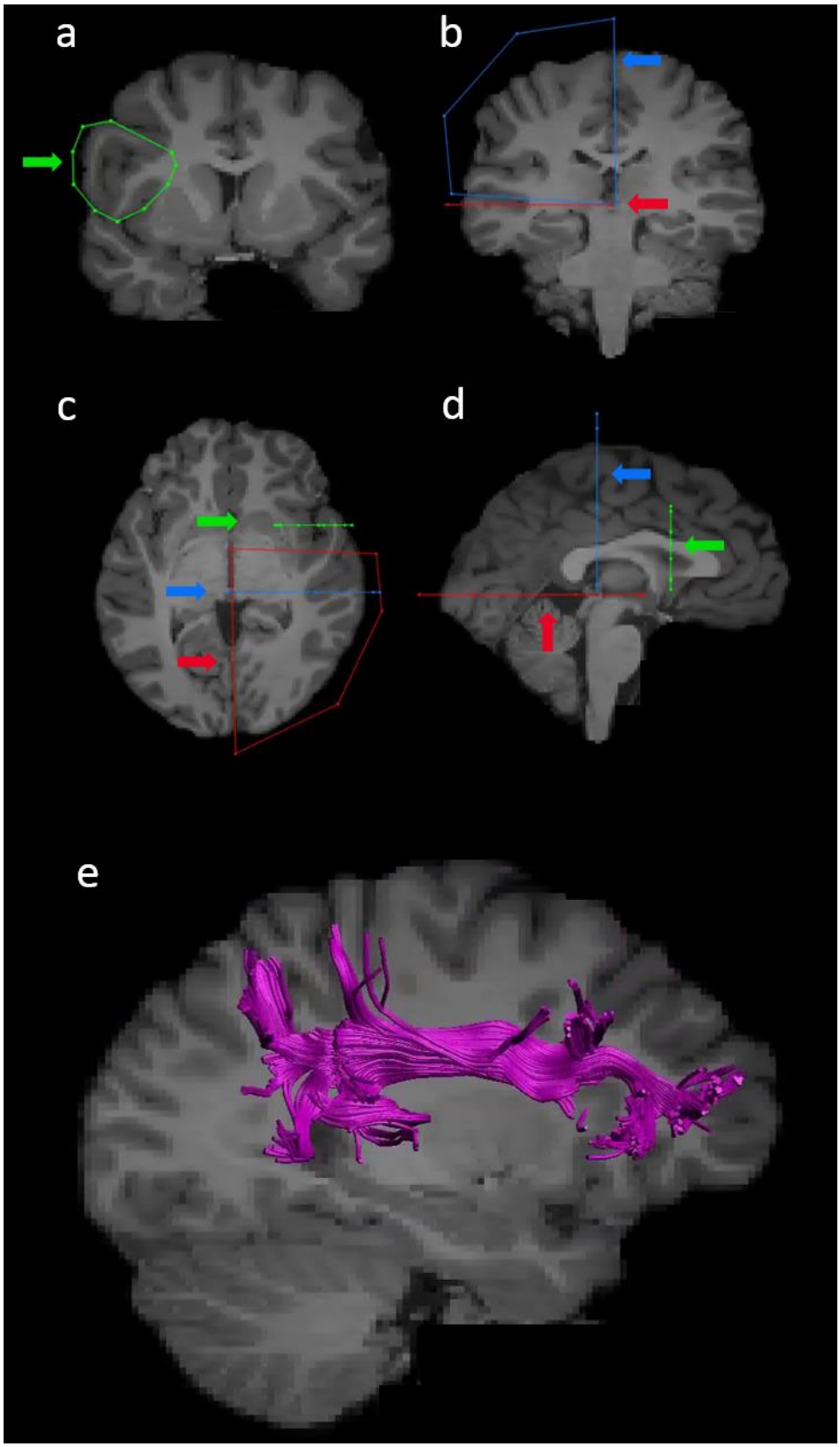
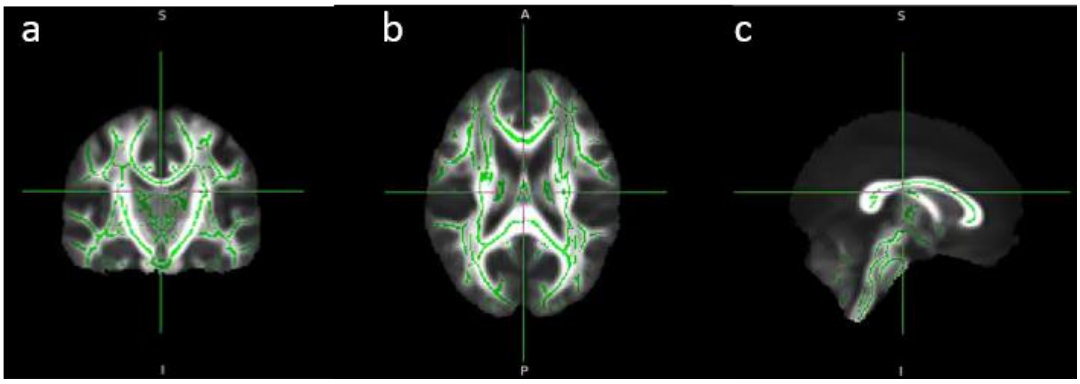


Figure 6.2. Examples of gate placement (a-d) for right superior longitudinal fasciculus III and reconstructed tract (e).



Inclusion gates in green and blue, exclusion gates in red. a) Inclusion gate around the inferior frontal gyrus level with the anterior commissure; b) Inclusion gate around the parietal lobe level with the posterior commissure (blue) and exclusion gate around the temporal lobe level with the posterior commissure (red); c) axial view of all gates; d) sagittal view of all gates; e) example right SLF III.

Figure 6.3. Mean FA skeleton (green) used for tract-based spatial statistics on coronal (a), axial (b), and sagittal (c) slices



6.2.2.2 TBSS

Whole brain voxel-wise statistical analysis of the FA data was conducted using TBSS (Smith et al., 2006, 2004) following the standard protocol available online (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide). Participants' data was aligned to a standard space using non-linear registration and the mean FA image was thinned to create a white matter tract skeleton representing the central part of each tract common to all participants. The standard threshold of FA $\geq$ 0.2 was applied to the tract skeleton. The aligned FA data from each participant was projected onto this skeleton for subsequent voxel-wise statistics (see Figure 6.3.).

6.2.3. Cognitive measures

As described in Chapter 2, participants completed the AMT (Rawal & Rice, 2012b; a; Williams & Broadbent, 1986). Participants also completed the Auditory Verbal Learning Test (AVLT; Schmidt, 1996) to test their general long-term memory. This measure was used in sensitivity analyses to ensure results were not attributable to long-term memory rather than an AM bias.

6.2.3.1 Autobiographical memory indices

A number of indices were generated to explore the link between white matter tracts and AM. This included total specific AMs and total overgeneral AMs (possible range

0-18); number of specific AMs for each cue valence (positive, negative and neutral; possible ranges 0-6); and number of overgeneral AMs for each cue valence (positive, negative and neutral; possible ranges 0-6).

As cue valence and memory content valence can differ (Lemogne et al., 2013; Young et al., 2012b), number of specific AMs and overgeneral AMs for each memory content valence were also calculated (positive, negative and neutral as rated by participant; possible ranges 0-18). Correspondence between cue and self-reported memory content valence is presented in Appendix 6.1. Correspondence was lower than that seen in the adolescent EPAD sample (Appendix 4.1) with 15.23% of memories for positive cues reported as neutral or negative, and 20.42% of memories for negative cues being reported as positive or neutral. Neutral cue words rarely resulted in neutral memories (59.33% positive, 24.67% negative).

6.2.3.2 Long-term memory

The delayed recall score from the AVLT was used as a general measure of long-term memory in sensitivity analyses. This was number of words recalled from a list previously repeated 5 times after a 30 minute delay (possible range 0-15). Higher scores reflect better recall, or better long-term memory. Delayed recall was used as it was most similar to the long-term nature of autobiographical memory but did not include elements of the self that are seen in AM.

6.2.4. Depressive symptoms and MDD diagnosis

Detailed information on the measures used is presented in Chapter 2, section 2.3.4. In brief, participants reported on DSM-IV symptoms of depression (American Psychiatric Association, 1994) over the past 3 months via a semi-structured psychiatric interview, the Young Adult Psychiatric Assessment (YAPA; Angold & Costello, 2000). Sub-threshold and clinical cases were reviewed by a senior

psychiatrist (R.P.). DSM-IV depressive symptom count (possible range 0-9) and DSM-IV MDD diagnosis were used in correlational analyses. Diagnosis of lifetime depression (yes/no) was self-reported at interview in response to the question 'Have you received a diagnosis or has a medical professional ever told you that you have depression?'. Total questionnaire depressive symptoms were measured on the MFQ (Angold & Costello, 1987) and the BDI-II (Beck et al., 1996).

6.2.5. Statistical analysis

6.2.5.1 Tractography

SPSS version 23.0 was used for analyses. Descriptive analyses included Pearson's correlation coefficients. Initial analyses included white matter tracts (genuCC, bodyCC, right SLF III) as predictor variables and overgeneral memory as the outcome variable in a series of hierarchical multiple regression models with standardised predictor variables. The primary outcome was OGMneg. AM indices that were related to depression measures in descriptive correlations were included as additional outcomes (AMSpos, specific AMs positive in content). Consistent with previous chapters, regression models adjusted for gender, age and IQ (Andreano & Cahill, 2009; Park et al., 2002; Williams et al., 2007). A dimensional measure of depressive symptoms (MFQ) was also included as a covariate in line with previous chapters to ensure associations between white matter and AM were not attributable to shared association with current depressive symptoms. Covariates were entered in Step 1, followed by the main effect of tract FA in Step 2.

A sensitivity check was performed to test whether white matter-overgeneral memory relationships could be attributable to reduced long-term memory rather than an AM bias. Significant tract-AM relationships were followed up with regression models using general long-term memory as an outcome.

6.2.5.2 TBSS

Standard TBSS analysis was used to assess the relationships between whole brain FA and overgeneral memory indices (Smith et al., 2006, 2004). This approach uses general linear models to test for correlations between FA in each voxel of the core white matter tract skeleton and the variable of interest. Consistent with tractography analysis I first looked at associations with OGMneg, followed by AMSpos and specific AMs that were positive in content. Analyses adjusted for covariates used in tractography analyses (age, gender, IQ, depressive symptoms on the MFQ). Sensitivity analyses also examined each memory variable without covariates as addition of each explanatory variable decreased power by one degree of freedom, and loss of power is an issue when correcting for multiple comparisons in whole brain analyses. All variables included in the models were demeaned/mean centred (i.e. the mean was subtracted from each value) as is standard practice with TBSS analyses (Smith et al., 2006, 2004). Threshold-Free Cluster Enhancement (Smith & Nichols, 2009) was used to correct for multiple comparisons across the brain using a statistical significance rate of $p < .05$.

6.3. Results

6.3.1. Descriptive analysis

Descriptive information (demographic, clinical and cognitive) on the sample is presented in Table 6.1. Univariate correlations for cognitive and clinical variables are displayed in Tables 6.2. As can be seen, OGMneg was not correlated with any measure of depression, which was unexpected. However, AMSpos and specific AMs positive in content were correlated with measures of depression. Thus individuals recalling more AMSpos were less likely to have a current DSM-IV MDD diagnosis ($r = -.450$, $p = .016$), had fewer depressive symptoms on the BDI-II ($r = -.394$, $p =$

.038), and were more likely to be female (r = .519, p = .005). Similarly, individuals recalling more specific AMs that were rated as positive in content were less likely to have a current DSM-IV diagnosis of depression (r = -.448, p = .017) and had fewer depressive symptoms on the BDI-II (r = -.380, p = .046).

Table 6.1. Descriptive information (demographic, clinical and cognitive) on the young adult neuroimaging sample

	Mean or %	SD or n	Range
Demographic variables			
Gender (female)	78.57%	22/28	
Age	21.21	1.81	18-25
IQ	97.89	10.57	77-118
Clinical variables			
Current DSM-IV MDD diagnosis	10.71%	3/28	
Current DSM-IV depressive symptom count	1.75	1.76	0-6
Self-reported lifetime MDD diagnosis	32.14%	9/28	
Depressive symptoms (MFQ)	16.21	11.61	3-44
Depressive symptoms (BDI-II)	10.46	10.15	0-46
Cognitive variables			
General long-term memory (AVLT)	10.18	3.30	3-15
Specific AM (total)	13.39	2.56	8-18
Overgeneral AM (total)	1.29	1.67	0-7
AMSpos	4.75	1.11	2-6
AMSneg	4.07	1.36	1-6
AMSneut	4.57	1.07	2-6
OGMpos	0.29	0.46	0-1
OGMneg	0.54	0.96	0-4
OGMneut	0.46	0.79	0-3
Specific AMs positive in content	7.36	1.59	3-10
Specific AMs negative in content	4.75	2.35	2-12
Specific AMs neutral in content	1.29	1.21	0-5
Overgeneral AMs positive in content	0.46	0.64	0-2
Overgeneral AMs negative in content	0.64	1.16	0-5
Overgeneral AMs neutral in content	0.18	0.39	0-1

AM – autobiographical memory; AMSneg – specific autobiographical memories to negative cues; AMSneut – specific autobiographical memories to neutral cues; AMSpos – specific autobiographical memories to positive cues; AVLT – Auditory Verbal Learning Test; BDI-II – Beck Depression Inventory-II; DSM-IV – Diagnostic Statistical Manual of Mental Disorders, 4th edition; MDD – Major Depressive Disorder; MFQ – Mood and Feelings Questionnaire; OGMneg – overgeneral autobiographical memory to negative cues; OGMneut – overgeneral autobiographical memory to neutral cues; OGMpos – overgeneral autobiographical memory to positive cues.

Table 6.2. Correlations of autobiographical memory indices with demographic and clinical information

	Gender	Age	IQ	DSM-IV depressive symptom count	DSM-IV MDD diagnosis	Self-reported lifetime MDD diagnosis	Depressive symptoms (MFQ)	Depressive symptoms (BDI-II)
Specific AM (total)	.359	.165	-.026	.080	-.192	.258	.041	-.136
Overgeneral AM (total)	.091	-.082	-.157	-.265	-.271	-.120	-.219	-.178
AMSpos	**.519**	.322	-.053	-.299	**-.450**	.158	-.217	**-.394**
AMSneg	.158	.129	-.051	.303	.068	.307	.138	.134
AMSneut	.118	-.104	.058	.118	-.079	.062	.148	-.087
OGMpos	.138	-.121	.144	-.321	-.219	-.097	-.303	-.307
OGMneg	.020	-.026	-.195	-.181	-.197	-.148	-.167	-.125
OGMneut	.088	-.072	-.180	-.153	-.207	-.018	-.084	-.046
Specific AMs positive in content	.231	-.169	.117	-.232	**-.448**	-.206	-.333	**-.380**
Specific AMs negative in content	.358	.204	.039	.164	.188	.306	.185	.058
Specific AMs neutral in content	-.240	.173	-.284	.157	-.180	.220	.164	.100
Overgeneral AMs positive in content	.109	.103	-.020	-.157	-.257	-.144	-.189	-.149
Overgeneral AMs negative in content	.065	-.050	-.121	-.227	-.195	-.120	-.164	-.152
Overgeneral AMs neutral in content	.016	-.370	-.283	-.203	-.162	.078	-.140	-.068

AM – autobiographical memory; AMSneg – specific autobiographical memories to negative cues; AMSneut – specific autobiographical memories to neutral cues; AMSpos – specific autobiographical memories to positive cues; BDI-II – Beck Depression Inventory II; DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MDD – Major Depressive Disorder; MFQ – Mood and Feelings Questionnaire; OGMneg – overgeneral autobiographical memory to negative cues; OGMneut – overgeneral autobiographical memory to neutral cues; OGMpos – overgeneral autobiographical memory to positive cues. Correlations significant at $p < .05$ indicated in bold.

6.3.2. Tractography

6.3.2.1 Are white matter tracts previously associated with depression related to indices of overgeneral memory?

Regression models examining whether tract FA (genuCC, bodyCC and right SLF III) was associated with overgeneral memory outcomes are presented in Table 6.3. No measure of tract FA was associated with OGMneg or AMSpos. FA in the body of the corpus callosum ($\beta = .456$, $p = .018$) and right SLF III ($\beta = .431$, $p = .028$) was associated with specific AMs that were positive in content.

6.3.2.2 Are white matter tracts previously associated with depression related to long-term memory?

Regression analyses found FA in the bodyCC ($\beta = -.306$, B (95% CI) = -1.009 (-2.374, .357), $p = .140$) and right SLF III ($\beta = -.209$, B (95% CI) = -.689 (-2.108, .729), $p = .324$) were not significantly associated with long-term memory. The direction of associations was such that in cases of more FA there was reduced long-term memory but these did not reach significance at $p < .05$. These findings are consistent with a link between white matter previously associated with depression and an AM bias, rather than a general reduction in long-term memory.

6.3.3. TBSS

Exploratory whole brain voxel-based analyses assessed whether white matter was associated with OGMneg, AMSpos and specific AMs that were positive in content. Analyses adjusting for covariates found that no areas of white matter were significantly associated with any of the AM indices at $p < .05$ when correcting for multiple comparisons (Smith & Nichols, 2009). Sensitivity analyses that did not include covariates also found no significant associations between white matter FA and memory indices ($p < .05$, whole-brain corrected).

Table 6.3. Regression analyses for white matter tract fractional anisotropy predicting overgeneral memory outcomes

	Genu corpus callosum				Body corpus callosum				Right SLF III			
	ΔR^2	**β**	**B (95% CI)**	**p**	**ΔR^2**	**β**	**B (95% CI)**	**p**	**ΔR^2**	**β**	**B (95% CI)**	**p**
OGMneg	<.001	0.001	0.001 (-0.452, 0.454)	.996	.003	0.057	0.055 (-0.367, 0.477)	.790	.002	0.045	0.043 (-0.384, 0.469)	.837
AMSpos	.004	0.067	0.074 (-0.352, 0.500)	.722	.049	0.229	0.254 (-0.128, 0.636)	.182	.051	0.237	0.263 (-0.122, 0.648)	.171
Specific AMs positive in content	.129	0.399	0.636 (-0.24, 1.296)	.058	.193	**0.456**	**0.726 (0.139, 1.313)**	**.018**	.169	**0.431**	**0.686 (0.082, 1.290)**	**.028**

AMs = autobiographical memories; AMSpos – specific autobiographical memory to positive cues; OGMneg – overgeneral autobiographical memory to negative cues; SLF – superior longitudinal fasciculus. Results significant at $p < .05$ indicated in bold.

6.4. Discussion

The current study explored white matter connectivity as a potential biological mechanism underlying the relationship between overgeneral memory and depression. I assessed whether white matter microstructure previously associated with depression was associated with indices of autobiographical memory. In tract-specific analyses, FA in tracts previously associated with depression in the literature (genuCC, bodyCC and right SLF III) were not associated with OGMneg or AMSpos. However, FA in the bodyCC and the right SLF III was positively associated with specific AMs that were positive in content. Sensitivity analyses showed that these results were not attributable to reduced long-term memory. Whole brain exploratory voxel-based analyses failed to find any association between white matter FA and overgeneral memory indices when controlling for multiple comparisons. This study provides preliminary evidence that white matter associated with MDD may be linked to overgeneral memory. Nevertheless additional research in larger samples is required to confirm this.

Contrary to hypotheses, there was no association between white matter previously linked to depression and OGMneg in the current study. This may be attributable to the lack of association between OGMneg and measures of depression used in the sample (Table 6.2). This was surprising given that OGMneg has been implicated in the development of adolescent depression in the ALSPAC cohort (Chapter 3) and the EPAD study (Rawal & Rice, 2012b), and that the young adults in the current sample previously participated as adolescents in the EPAD study. Nevertheless, meta-analyses of adult samples report the largest effect sizes for the cross-sectional relationship between AMSpos and depression and smallest effect sizes for OGMneg and depression (Liu et al., 2013; Ono et al., 2015). Indeed, current analyses highlighted that AMSpos and specific memories that were positive in

content were associated with current DSM-IV MDD diagnosis and depressive symptoms (Table 6.2.). Therefore, it is possible that the overgeneral memory bias for negative cues or memories may be related to age. This is supported by theory as the functional avoidance mechanism is thought to arise in response to negative events and memories before becoming generalised to all memories (Williams et al., 2007). Nevertheless, longitudinal studies are required to assess the relationship between different AM indices and depression over adolescence and into adulthood to determine whether there is a change in the relationship over time.

FA in the bodyCC and right SLF III was associated with specific AMs that were positive in content. These positive associations were consistent with previous work that has indicated both reduced FA in these tracts and reduced AM specificity are associated with MDD (Jiang et al., 2017; Kelly et al., 2016; Williams et al., 2007). The indicators of AM associated with depression in correlational analyses were both related to positive valence (cue word and self-rated content). However, the only AM indicator significantly associated with white matter tracts was specific AM that was positive in content. Previous evidence has highlighted that cue and memory valence are not necessarily the same (Young et al., 2012b) and memory valence did not always match cue valence in the current sample (see Appendix 6.1) . Participants in the current study rated on average 7.36 specific memories as positive (range 3 – 10) despite only 6 positive cues being presented indicating that positive memories were recalled in response to all cue word types. Recall of positive specific AMs has previously been shown to improve mood (Joormann & Siemer, 2004; Joormann et al., 2007; Ramirez et al., 2015). Therefore, recalling specific positive memories may be indexing current emotional regulation ability. Thus, white matter microstructure in the bodyCC and right SLF III indexed by FA may be associated with the emotional regulation aspect of recalling positive memories. This is supported by

previous research that the corpus callosum likely supports the interhemispheric communication of emotional information (Shobe, 2014) but there is less evidence for an association between emotional regulation and the SLF. The current work, therefore, highlights the importance of investigating both memory and cue valence. Nonetheless, as only one AM measure was associated with white matter and the sample is small, results should be considered as preliminary as they require replication.

Whole brain voxel-based analysis with TBSS failed to find an association between white matter FA and overgeneral memory indices. This is somewhat surprising given that the hypotheses were derived from meta-analyses of whole brain approaches and, intuitively, associations with TBSS measures of FA would have been anticipated over tractography. However, there are inherent differences in tractography and TBSS methods that may explain why an association was found in tractography but not TBSS. Tractography is performed on each individual's dwMRI scan separately whereas TBSS involves warping each of the scans to an average scan. Anatomical localisation of white matter is therefore likely to be more accurate for tractography as the scan has not been manipulated (Cercignani, 2010). Furthermore, tractography involves reconstructing the entirety of a white matter tract, whereas TBSS focuses on the central portion of the tract or the 'tract skeleton' (Cercignani, 2010; Smith et al., 2006, 2004). Although both methods have some overlap of the white matter they assess, tractography is measuring more of the white matter tract (the additional outer portion) and this may be where the association between overgeneral memory and FA presents. Alternatively, TBSS requires correction for multiple comparison due to the large number of tests conducted across the brain, and with the small sample size, there may not have been adequate power to detect an association in TBSS analyses.

6.4.1. Strengths and limitations

This study benefits from careful examination of neuroimaging, clinical and cognitive data to determine whether white matter tracts previously related to depression were associated with overgeneral memory. As has been advised previously (Lemogne et al., 2013), I assessed both cue and memory valence in overgeneral memory, a practice rarely conducted in previous research. The use of a sample at elevated risk for depression is a strength for an initial, more exploratory, study like this as such samples are enriched for depression and its risk factors as shown in Chapter 3, Table 3.3 and previous research (Bouma et al., 2008; Garber, 2006; Goodman & Gotlib, 1999; Rice et al., 2002b; Weissman et al., 2006).

The study should also be viewed in light of its limitations. Firstly, the sample size was relatively small (n = 28) and therefore findings should be treated with caution. Replication in a larger sample is required before any strong conclusions can be drawn. Secondly, there may be developmental differences in AMT task performance. The AMT cue words and paradigm were originally adapted for use with adolescents (Rawal & Rice, 2012a; b), but were also used with the young adult sample for continuity. There was a higher proportion of specific memories in this young adult sample (mean specific AMs 13.39 out of a possible 18; Table 6.1) than in the previous adolescent sample (mean specific AMs 6.82 out of a possible 12; Table 4.2) which could mean the AMT paradigm used was too easy for the young adult sample. Developmental differences in AMT performance could therefore have contributed to the different pattern of results with AM and depression. Thirdly, differences in FA can be attributed to a variety of factors including myelination, axon density, membrane permeability, and partial volume effect (Beaulieu, 2002; Jones et al., 2013). As FA is not measuring a precise aspect of white matter inferring 'structural integrity' would be inappropriate (Jones et al., 2013). Other more complex

models that index more specific biological factors, such as CHARMED (Composite Hindered and Restricted Model of Diffusion) which measures axonal density (Assaf et al., 2013; Assaf & Basser, 2005) and qMT (quantitative Magnetization Transfer) which likely measures myelination (Levesque et al., 2010), may be able to provide better insight into what aspect of white matter is associated with depression and overgeneral memory. Fourthly, reconstructing the right SLF III was more difficult than the genuCC and bodyCC due to its close proximity to the right SLF II. Thus, results for the right SLF III should be interpreted more cautiously than tracts that were more reliably reconstructed (genuCC and bodyCC). Finally, although a relationship is evident between AM and white matter linked to depression, as this is a cross-sectional study no strong inferences can be made about whether white matter could be a causal risk mechanism underlying the link between overgeneral memory and depression. Longitudinal studies are required to test this.

6.4.2. Conclusion

The current study examined the association between white matter previously linked to depression and overgeneral memory. In tract-specific analyses, FA in the body of the corpus callosum and right SLF III was associated with specific AMs that were positive in content. This may in part reflect an emotion regulation strategy. The association between white matter FA and positive AM specificity suggests that white matter could be a potential neurobiological mechanism of overgeneral memory than can predispose an individual to MDD. Nevertheless, further longitudinal work in larger samples is required to explore this before any strong conclusions can be drawn.

7. General Discussion

7.1. Overview

In this thesis I investigated the link between overgeneral autobiographical memory and early-onset depression using a number of different approaches (longitudinal analysis, genetic epidemiology, white matter microstructure neuroimaging). Overgeneral autobiographical memory is an example of the overgeneralisations and memory biases that are common in depression (Beck, 2008; Gotlib & Joormann, 2010; LeMoult & Gotlib, 2018; Thew et al., 2017). Overgeneral autobiographical memory was the focus of this thesis as evidence in adults suggested that it could be a risk factor for depression (Chapter 1, section 1.3.2; Sumner et al., 2010; Williams et al., 2007), but, in younger samples, there are fewer studies with more inconsistent findings (Chapter 1, section 1.3.2). Overgeneral autobiographical memory is thought to occur when processes (capture and rumination, functional avoidance, impaired executive control) truncate the hierarchical search for a memory at a general level resulting in the recall of memories of extended time periods or repeated instances rather than specific memories (Williams et al., 2007). It is hypothesised that this memory bias can lead to the development of depression through a number of psychological/cognitive mechanisms. For instance, an individual experiencing a negative or painful event may passively avoid recalling the specific details of that negative memory as a means of emotional regulation (Williams et al., 2007). As this is adaptive in the short-term (Anderson et al., 2010; Hermans et al., 2008a), avoiding recall of specific details may become generalised to other memories, including positive memories. With this bias to remain at an overgeneral level, an individual would be unable to use recall of positive specific AMs to improve their mood (Joormann & Siemer, 2004; Joormann et al., 2007; Ramirez et al., 2015), which may

in turn promote low mood. Collective remembering of specific AMs also serves an important function in social interactions (Harris et al., 2008) and collaborative reminiscence of an event can act as an emotion regulatory strategy (Maswood et al., 2018). Lack of specific AMs may also interfere with social problem solving (Goddard et al., 1996, 1997; Leahy et al., 2018), which is an important issue in depression (Rudolph, Hammen, & Burge, 1994). Therefore, being unable to recall specific AMs in social situations could also increase the chance of developing mood disturbances.

The primary aim of this thesis was to explore whether overgeneral autobiographical memory could be a risk factor for early-onset depression. The primary research questions were:

1. Is overgeneral memory longitudinally associated with depression in a population-based sample?
2. Could overgeneral memory be a risk mechanism through which other known risk factors for depression (i.e. stressful life events, genetic variants associated with depression) exert their effect?
3. Is white matter microstructure previously associated with MDD related to overgeneral memory?

Each of these research questions is discussed below with reference to the findings from the thesis and the previous literature. I then go on to discuss the potential clinical implications, the strengths and limitations of this work, and future directions.

7.2. Is overgeneral memory longitudinally associated with depression in a population-based sample?

Chapter 3 focused on the prospective relationship between overgeneral memory and depressive symptoms in a population-based sample given that previous research had reported a prospective association only in samples at high-risk of developing depression (Hipwell et al., 2011; Rawal & Rice, 2012b; Sumner et al., 2011). I focused on OGMneg in analyses given that a prospective association between OGMneg and adolescent depression was evident in the largest high-risk study to date (Rawal & Rice, 2012b) and theory has indicated overgeneral AM may develop first for negative memories (Williams et al., 2007). I found that OGMneg was associated with depressive symptoms cross-sectionally and longitudinally. The prospective relationship with subsequent depression was observed only for OGMneg and no other measure of AM. Maternal depression status did not affect the prospective relationship, highlighting that the prospective association was not restricted to high-risk samples as has previously been suggested (Crane et al., 2016; Gutenbrunner et al., 2017). This prospective relationship has not been reported previously in community samples, including those based on the same cohort (ALSPAC; Crane et al., 2016). Crane and colleagues focused on AM specificity and did not consider valence of AM cues which may explain the differences in findings. Given the temporal precedence, current findings suggest that OGMneg could be a risk factor for subsequent depression in adolescents in the general population (Garber, 2006; Kazdin et al., 1997; Kraemer et al., 1997; Rutter et al., 2001). Results also highlighted the importance of considering the definition and valence of AM when investigating the relationship between overgeneral memory and depression in adolescents (Lemogne et al., 2013; Sumner, 2012).

Effect sizes for the prospective association between OGMneg and depressive symptoms differed by cohort. Previous findings in the EPAD sample (Rawal & Rice, 2012b) suggested the effect for the prospective relationship was larger (EPAD whole sample $\beta = .12$; EPAD females only $\beta = .19$) than in those with typical risk for depression (ALSPAC $\beta = .073$). This may in part explain why associations were previously seen in high-risk samples but not in population samples. Although weak associations do not preclude causation, there is greater evidence for causation when the association is stronger (Academy of Medical Sciences, 2007; Hill, 1965; Rutter, 2007). With an effect this small it is not clear whether OGMneg would be an effective target for adolescent depression in the general population. Interventions of preventative measures have a stronger chance of success if there is a strong predictive association between the targeted mechanisms and the disorder (Wight, Wimbush, Jepson, & Doi, 2015). I discuss the clinical utility of targeting overgeneral memory for depression interventions and preventative measures further below (section 7.6).

I also investigated whether OGMneg could be a risk factor for symptoms of other psychiatric problems and related traits (anxiety and psychotic-like symptoms) given the paucity of research looking at the relationship between overgeneral memory and symptoms of more than one disorder. Contemporaneous and prospective relationships with OGMneg did not extend to anxiety symptoms but OGMneg was also associated prospectively with psychotic-like symptoms. This suggests that OGMneg could also be a risk factor for subsequent psychotic-like symptoms as it shows temporal precedence (Garber, 2006; Kazdin et al., 1997; Kraemer et al., 1997; Rutter et al., 2001). Psychotic-like symptoms are conceptually related to schizophrenia (Ronald & Pain, 2018; Zammit et al., 2013) but also show associations with a range of other psychiatric disorders, including depression

(Kelleher et al., 2012; McGrath et al., 2016). Depressive symptoms were adjusted for in analyses with psychotic-like symptoms, so it seems unlikely the association between OGMneg and psychotic-like symptoms is entirely due to the fact that psychotic-like symptoms and depression are correlated; however, residual confounding cannot be ruled out. Nonetheless, psychotic-like symptoms show association with a range of psychiatric disorders (McGrath et al., 2016), meaning that caution is needed in the interpretation of the finding of association between OGMneg and psychotic-like symptoms. Additional research investigating this prospective association is therefore warranted.

7.3. Could overgeneral memory be a risk mechanism through which other known risk factors for depression (i.e. stressful life events, genetic variants associated with depression) exert their effect?

Chapter 4 examined the relationship between SLEs and overgeneral memory and whether overgeneral memory was a risk mechanism through which SLEs affected subsequent depression. There was a main effect of lifetime SLEs on AM specificity in that more *lifetime* SLEs were associated with recall of more specific AMs. Moderation of gender was evident for recent SLEs such that boys experiencing more *recent* SLEs recalled more specific AMs and fewer overgeneral AMs, whereas girls experiencing more recent SLEs recalled more overgeneral AMs. Nevertheless, no measure of AM mediated the relationship between either lifetime or recent SLEs and subsequent depressive symptoms and there was no evidence of moderated mediation by gender. Combined with the previous literature (Rawal & Rice, 2012b), these results suggest that overgeneral memory is not a proximal risk mechanism for SLEs to exert their effect on depression; instead, SLEs and overgeneral memory may have independent effects on subsequent depressive symptoms.

Results from Chapter 4 do, however, suggest that SLEs may be involved in the development of overgeneral memory, particularly with recent SLEs in girls. There has been considerable evidence to suggest that more severe traumatic events can be involved in the development of overgeneral memory (Moore & Zoellner, 2007; Ono et al., 2015; Williams et al., 2007), but there is limited evidence for less severe SLEs or gender differences in the aetiology of overgeneral memory. Theory suggests that overgeneral memory develops in response to functional avoidance to SLEs (Williams et al., 2007), which may be more common in girls than boys as girls experience more SLEs and are more sensitive to social or interpersonal stressors (Calvete et al., 2011; Oldehinkel & Bouma, 2011; Shih et al., 2006). Girls did experience an overall greater number of recent SLEs than boys in the current study but an SLE threshold at which the relationship with overgeneral memory changes is unlikely as there was no evidence for an association between quadratic SLEs term and overgeneral memory. Nevertheless, this study did not assess whether particular types of SLEs (e.g. loss, interpersonal, disappointment) affected the development of overgeneral memory differently. Gender differences in whether recent SLEs contribute to the development of overgeneral memory may therefore be affected by the type of SLE experienced.

The relationship between common genetic risk for depression and OGMneg was examined in Chapter 5. Analyses were performed in the high-risk EPAD sample and in the ALSPAC population-based cohort. Polygenic risk for MDD at the recommended p-value threshold of 0.5 (Ripke et al., 2013) was not associated with OGMneg or AMSneg in either sample. Sensitivity analyses with other MDD PRS p-value thresholds also found no evidence of an association with OGMneg. However, MDD PRS only accounted for a very small proportion of variance (maximum of 0.135% for p-value threshold 0.5) in depression in these samples. The phenotypic

association between OGMneg and depression in these samples was also modest (Chapter 3; Rawal & Rice, 2012b), and the relationship between common genetic risk for depression and OGMneg is likely to make up only a small proportion of this phenotypic association. In combination, these factors suggest the study was underpowered. Samples using MDD PRS derived from the second PGC MDD GWAS (Wray et al., 2018) have found evidence of an association between MDD PRS and a depression-related phenotypes in sample sizes between 78 and 2,640 (Foo et al., 2018; Trautmann et al., 2018). Therefore the lack of power in the current sample is likely to be due to small effect size between OGMneg and MDD PRS, and not just the modest sample size. It is also possible that MDD PRS may influence depression via alternative mechanisms such as inflammation, body mass index and education (Hepgul, Cattaneo, Zunszain, & Pariante, 2013; Wray et al., 2018).

In combination, findings from Chapters 4 and 5 suggest that overgeneral memory does not mediate the relationship between known risk factors (SLEs and MDD PRS) and depression. SLEs were chosen as known risk factor as they have been robustly associated MDD and are likely to play a causal role in the onset of depression (Kendler & Gardner, 2010; Kendler et al., 1999; Rice et al., 2017b). Although PRS only predict a small amount of variance in depression (Chapter 5; Wray et al., 2018), they are useful biological indicators of genetic liability (Kendler, 2016). Current findings suggest that SLEs and MDD PRS act on MDD via other mechanisms. Although overgeneral memory was not associated with the two known depression risk factors examined in this thesis, it is possible that overgeneral memory acts as a more proximal risk mechanism for other risk factors for depression, or has a causal association independent of other preceding risk factors. It is also possible that overgeneral memory is only a minor cause of depression in that it is causal but does not have a substantive effect in comparison to other risk factors. Further research

looking at how overgeneral memory is related to other distal risk factors is therefore warranted.

While cognitive biases are common in MDD (Gotlib & Joormann, 2010; LeMoult & Gotlib, 2018), and overgeneral memory is one of these biases, there are other theories about how depression develops in response to SLEs and genes. The diathesis-stress model posits that stress triggers a depressive episode in the presence of an underlying vulnerability such as genetic predisposition or cognitive bias (Monroe & Simons, 1991). Therefore, genetic liability for depression and SLEs may interact to contribute to depression. SLEs may also affect depression through other cognitive vulnerabilities, such as negative schemas and biases (Beck, 2008), as well as biological factors like the HPA axis (Dean & Keshavan, 2017; Hammen, 2005) and inflammation (Dean & Keshavan, 2017; Pariante, 2017). Genetic risk for depression may exert its effects through pathways involved in BMI and educational attainment (Wray et al., 2018). Genes are also likely to act through neurotransmitters and inflammation to promote low mood (Delgado, 2000; Hepgul et al., 2013). It is likely that SLEs and genetic liability for depression have a complex relationship with other risk factors to contribute towards the aetiology of depression. However, in this instance, an overgeneral memory bias does not mediate the relationship between SLEs or common genetic variation, and depression.

7.4. Is white matter microstructure previously associated with MDD related to overgeneral memory?

White matter microstructure was examined as a potential biological mechanism for the relationship between overgeneral memory and depression in Chapter 6. White matter microstructural properties were measured by FA which reflects the amount of water movement in a single direction in a voxel. Although many researchers have

equated FA with white matter 'structural integrity', there are many factors that can affect FA within a voxel, including axon alignment and number of axons in a voxel, therefore it is inappropriate to assume FA reflects changes in microstructural integrity (Jones et al., 2013). Instead FA is a useful measure of orientation-dependent tissue microstructure (Jones et al., 2013) with lower white matter FA associated with poorer performance in cognitive tasks and higher levels of psychopathology (Fields, 2008, 2010; Jenkins et al., 2016; Johansen-Berg, 2010; Kanai & Rees, 2011).

In this thesis I investigated whether FA in white matter previously linked to MDD and whole brain white matter FA was associated with OGMneg and measures of AM associated with current depression (AMSpos and specific AMs that were positive in content). Tract-specific analyses revealed FA in the body of the corpus callosum and right SLF III were associated with specific AMs that were positive in content, but no associations were evident in whole brain analyses. This study provides preliminary evidence that FA in white matter linked to MDD is associated with overgeneral memory. As this relationship was only present for self-rated positive specific AMs rather than positively-cued specific AMs, it suggests FA in these white matter tracts might be associated with emotional regulation.

Differences in findings for tract-specific and TBSS approaches may be due to inherent advantages and limitations of each approach. Advantages of tract-specific analyses like tractography are that FA is extracted for the entirety of the tract rather than just the central part of the tract (the tract skeleton) as in TBSS (Smith et al., 2006, 2004), and anatomical localisation is more accurate than in whole-brain voxel based approaches (Bracht et al., 2015b; Cercignani, 2010). Thus, the association of positive specific AMs with tract-specific FA may reflect FA in the outer portion of the white matter tracts or better anatomical localisation. Alternatively, as TBSS

analyses controlled for multiple comparisons across the brain (Smith & Nichols, 2009), there may not have been adequate power to detect an association.

Unexpectedly, current depressive symptoms and diagnosis were not associated with OGMneg but instead with positive AM specificity measures. This is contrary to what has been found in adolescent samples (Chapter 3; Rawal & Rice, 2012b) but is consistent with meta-analyses of adult samples suggest that AM specificity for positive cues has the strongest relationship with current depression (Liu et al., 2013; Ono et al., 2015). It is not yet clear whether the difference in AM measure associated with depression is due to methodological differences between studies or represents a developmental change in the overgeneral memory-depression relationship. Further research would benefit from larger sample sizes and longitudinal assessment to understand the long-term relationship between overgeneral memory and depression, and how white matter may help explain this relationship.

7.5. Overgeneral memory as a risk factor and causal risk mechanism for depression

Taking all chapters and the previous literature into consideration, OGMneg is likely to be a risk factor for subsequent adolescent depression as there are greater rates in depressed populations (Rawal & Rice, 2012b) and OGMneg shows temporal precedence to depressive symptoms in high-risk (Rawal & Rice, 2012b) and population-based samples (Chapter 3). However, evidence thus far is inconsistent on whether OGMneg constitutes a causal risk mechanism for depression (Academy of Medical Sciences, 2007; Hill, 1965; Rutter, 2007). The observed association between OGMneg and depression is consistent with substantial knowledge on negativity bias and overgeneralisation seen in depression (Beck, 2008; Roiser et al., 2012; Thew et

al., 2017). OGMneg was examined as a mediator given current understanding that risk factors act on more proximal cognitive and neural processes (Thapar et al., 2012). OGMneg was not a mediator for environmental (SLEs, Chapter 4) or genetic (MDD PRS, Chapter 5) known risk factors. Although this does not preclude a causal association between OGMneg and depression, further research is required to assess how OGMneg is associated with other risk factors in the multifactorial aetiology of MDD. I also examined the neural basis of OGMneg as risk factors can act on depression via more proximal neural factors (Thapar et al., 2012) and depression is thought to be a disorder characterised by altered connections in the brain (Hulvershorn et al., 2011; Keedwell & Linden, 2013). There was no evidence for OGMneg being associated with white matter microstructure in tracts previously linked to MDD (Chapter 6) which could have supported OGMneg as a causal risk mechanism (Academy of Medical Sciences, 2007; Hill, 1965; Rutter, 2007). Instead there was a relationship between white matter FA and specific AMs that were positive in content. Lack of power for genetic and neuroimaging analyses (Chapters 5 and 6) could have contributed to the lack of associations and investigation in larger sample sizes is encouraged.

When considering overgeneral memory as a whole (i.e. including any type of AM definition and valence), there would be some support for overgeneral memory being a causal mechanism using established criteria (Academy of Medical Sciences, 2007; Hill, 1965; Rutter, 2007) as: 1) overgeneral AM and reduced AM specificity are associated with depression in a range of samples (Hitchcock et al., 2014; Liu et al., 2013; Ono et al., 2015; Williams et al., 2007), 2) the association is in line with current knowledge of overgeneralisations in depression (Beck, 2008; Thew et al., 2017) and 3) increasing AM specificity reduces depressive symptoms (Hitchcock et al., 2017; Neshat-Doost et al., 2013). However, there are inconsistencies in the

literature and a particular issue is that different studies find different indices of AM to be associated with depression. AM specificity and overgeneral AM are not necessarily different ends of the same spectrum (Sumner, 2012), and they have different correlates (Chapters 3-6). Nonetheless, as seen from work in this thesis and related literature, OGMneg is likely a risk factor for depression (Chapter 3; Rawal & Rice, 2012b). Additional research may find further support for OGMneg as a causal risk mechanism for depression but it seems likely that it will be a minor cause.

In sum, findings from this thesis and the previous literature suggest that OGMneg is likely to be a risk factor for early-onset depression. The evidence for OGMneg being a risk mechanism through which depression develops is less clear as OGMneg does not mediate the effects of known risk factors and was not associated with a potential biological mechanism (white matter FA). The relationships between AM indices, depression and other risk factor is complex and requires further exploration.

7.6. Clinical implications

If overgeneral memory is a causal risk mechanism for depression then targeting it will affect the likelihood of the disorder (Garber, 2006; Hollon et al., 2002). Overgeneral memory is modifiable in adults (Williams et al., 2000) so may prove beneficial for interventions and preventative measures in adolescents. A number of early trials have investigated whether improving AM specificity can improve the clinical symptoms of MDD. A meta-analysis of 15 randomised control trials (RCTs) found different memory training protocols were able to improve depression (d = 0.32; Hitchcock et al., 2017). Of the RCTs included, only one was based on a youth sample (Neshat-Doost et al., 2013), the rest were based on adult samples. In this study, adolescents receiving memory specificity training (MEST) for five weeks (n =

12) had fewer depressive symptoms than controls (n = 11) two months post-training (d = 0.97). However, this study had a very small sample size. Further studies investigating whether targeting overgeneral memory in adolescence are therefore warranted. One such study is being currently being conducted. This is an early intervention in 16-18 year olds with high depressive symptoms that incorporates methods to improve AM specificity, reduce distress for past negative events, and increase positive thinking about the future (Pile et al., 2018). The intervention will be compared with the recommended therapy for this age group (non-directive supportive therapy), which is an important consideration given that previous research has found no superiority of cognitive therapy over other types of psychological therapy for depression in adolescents (Goodyer et al., 2017). Should this intervention be more effective in reducing depressive symptoms than the control intervention it suggests overgeneral memory would be a useful target for adolescent depression.

Therapies acting on overgeneral memory are likely to affect similar mechanisms targeted in effective conventional therapies such as cognitive behavioural therapy (CBT) and interpersonal therapy (IPT; Hollon et al., 2002). CBT helps individuals become aware of negative or unhelpful thoughts, feelings and behaviour and how they can be modified (Beck, Rush, Shaw, & Emery, 1979). This can include reducing overgeneralisations, increasing positive attributions and reducing negative attributions (Beck et al., 1979), therefore likely acts on similar mechanisms to those underlying overgeneral memory in depression. IPT focuses on helping individuals improve interpersonal relationships and social functioning to improve mood (Markowitz & Weissman, 2012). As recalling specific AMs plays an important social role (Harris et al., 2008) and is important for social problem solving (Goddard et al., 1996, 1997; Leahy et al., 2018), it is likely that improving AM specificity will indirectly affect relationships. Overgeneral memory is therefore a

promising target for therapy as it can affect multiple processes affected in depression.

Less work has been conducted using overgeneral memory in prevention for depression. Established preventative interventions aimed at a general population level (universal prevention) have the potential to reach large numbers of adolescents (including the most vulnerable) and require no initial screening (Greenberg & Riggs, 2015; Rose, 1985). However, assessing the efficacy of such preventative measures is difficult as long follow-up periods are necessary to determine whether acting on presumably causal mechanisms have indeed reduce likelihood of the disorder. As current results show the effect size for the prospective relationship between overgeneral memory and depression was smaller in a population sample than a high risk group (Chapter 3; Rawal & Rice, 2012b), it is also not clear whether a prevention measure aimed at the entire population would be effective in preventing depression. Only one study to date has explored overgeneral memory as a preventative target in adolescents in the general population. In a non-randomised trial, overgeneral memory was targeted through Mindfulness-Based Cognitive Therapy (MBCT) and compared to two other active therapy groups and a control (Rice et al., 2015). Following the intervention individuals experiencing MBCT did not experience a significant reduction in overgeneral memory and actually displayed an increase in depressive symptoms. As the prevention was ineffective at reducing overgeneral memory it is unclear whether overgeneral memory could be a mechanism to prevent subsequent depression in unselected adolescents. Consequently, further research establishing an intervention that can reduce overgeneral memory in adolescents and exploring whether it can prevent subsequent depression is required. Other preventative measures for adolescent depression have proved more successful in selective populations at high-risk for depression (Brent et

al., 2015; Stice et al., 2009). Given the effect size for the prospective link between overgeneral memory and depression is larger in the offspring of depressed parents, this may be a good group to target for preventative measures.

7.7. Strengths and limitations

This thesis focuses on overgeneral memory, which if it is a risk mechanism for depression, is malleable (Williams et al., 2000), and therefore provides opportunities for development of more effective interventions for depression. This thesis benefits from using two well-characterised samples enabling assessment of the relationship between overgeneral memory and depression in conjunction with numerous covariates and risk factors. Both samples are longitudinal, allowing temporal precedence to be examined. Combining results from high-risk and population samples has also enabled interpretation across the genetic and environmental risk spectrum. This thesis has used a number of different approaches (psychology, genetics, neuroimaging) to assess whether overgeneral memory could be a risk factor or risk mechanism for depression. The use of different techniques to address the same aim has the potential to increase scientific certainty if findings point to the same result (Munafo & Davey Smith, 2018).

Limitations of each study are mentioned in the respective chapters and are discussed briefly below. More generally, the interdisciplinary nature of this thesis has resulted in a broad exploration of the relationship between overgeneral memory and depression using several different techniques, many of which required specialist training. This meant that in some instances time limitations did not allow detailed follow up on some unexpected results with unanswered questions that arose from results in the Chapters. For instance, I was unable to explore the mechanisms underlying the prospective associations between overgeneral memory and

depression/psychotic-like symptoms in ALSPAC in Chapter 3 or examine the association between overgeneral memory and rare genetic variants (e.g. Copy Number Variations) linked to depression in Chapter 5.

Although this thesis uses the largest available population-based and high-risk samples with overgeneral memory and depression measures, there was low power to detect an effect in genetic analyses, particularly in the EPAD sample. This is in part due to PRS explaining a small proportion of variance in depression, which is an inherent issue in this field. Newer GWAS with larger sample sizes (for instance, (Howard et al., 2019)) may aid in detection of common genetic variants that describe more phenotypic variation in depression, but as results stand it is too early to make conclusions about the genetic association between overgeneral memory and depression. A small association with common genetic variants cannot be ruled out (due to the aforementioned power issues) and no work has investigated rare genetic burden for depression and overgeneral memory. Although early research found few rare variants associated with depression (Flint & Kendler, 2014), more recent research using larger samples has proved promising in identifying Copy Number Variants (CNVs) linked to the disorder (Kendall et al., 2018). Exploring the link between overgeneral memory and these rare CNVs would be the natural progression for Chapter 5 but this was not possible within the timeframe of the PhD and the evidence to support such a study has only very recently come to light. Furthermore, there have been no twin studies or genetic epidemiological studies examining the genetic (and environmental) basis of the association between overgeneral memory and depression. Without these studies, it is unclear what role genetic variants may play in the link between overgeneral memory and depression.

Power may have also been an issue in the neuroimaging study (Chapter 6). It is likely the neuroimaging analyses were underpowered to detect smaller effects or

effects following correction for multiple comparison as seen with the whole-brain TBSS analyses. However, the study was theory-driven – depression is considered a disorder of connections (Hulvershorn et al., 2011; Keedwell & Linden, 2013) and very few studies have examined brain connectivity in relation to overgeneral memory in depression (see Chapter 6, section 6.1 for a review). This is the first study to examine the relationship between structural connectivity (i.e. white matter tracts), depression and overgeneral memory. This examination can be seen as a feasibility study that can lead to a larger, better-powered study in the future and is the first step in building the literature in this area. Nevertheless, results from this chapter should be interpreted with caution.

Attrition and missing data are often issues to consider in longitudinal studies (Gustavson, von Soest, Karevold, & Røysamb, 2012; Sterne et al., 2009). Analyses in this thesis did not account for missing data which would have been a particular issue in chapters using the ALSPAC sample as this sample had greater attrition than EPAD (see Methods and Figures 3.1, 5.1 and 5.2), and missing data has little impact in EPAD (Collishaw et al., 2016). When comparing ALSPAC participants *with* versus *without* complete data available for contemporaneous and prospective analyses in Chapter 3, there were a number of differences in sociodemographic factors measured at baseline, and depressive and cognitive factors measured later in life (Appendix 3.1). Specifically, individuals included in analyses in Chapter 3 were more likely to come from families with mortgaged or owned accommodation (as opposed to renting/other), fewer financial difficulties, fewer siblings, and higher maternal education. Furthermore, the adolescents included in analyses were more likely to be female, achieve 5 A*s to Cs at GCSE, have higher IQ, have fewer depressive symptoms at follow up (16.5 years), retrieve fewer overgeneral AMs and retrieve more specific AMs than adolescents with missing data. However, there were

no differences in depressive symptoms at baseline (12.5 years). Given the large sample size, it is unsurprising that differences for those with versus without complete data for analyses were significant. However, the differences tended to be small (Appendix 3.1); for instance, in prospective analyses, the mean difference for depression symptoms (possible range 0-26) at follow up was 0.32 (not missing mean = 5.72 (SD = 5.44) vs missing mean = 6.04 (SD = 5.8)), and mean difference for specific AM (possible range 0-12) was 0.39 (not missing mean = 3.98 (SD = 2.49) vs missing mean = 3.59 (SD = 2.51)). Work in this thesis therefore used a sample with less social disadvantage and better cognitive ability than might be found in the general population which is consistent with other studies in ALSPAC (Boyd et al., 2013). Results from these analyses are therefore less generalisable and effects are also likely to be attenuated as the sample is more homogeneous on sociodemographic, cognitive and psychiatric variables, which in turn may reduce the power for detecting effects (Lundberg, Damström Thakker, Hällström, & Forsell, 2005; Martin et al., 2016). This attrition could potentially introduce bias (Martin et al., 2016; Sterne et al., 2009) although mean level differences do not necessarily mean that the association between overgeneral memory and depression will be biased (Gustavson et al., 2012). Additional work using statistical techniques that can account for missingness (such as multiple imputation (Sterne et al., 2009) and sample weights (Seaman & White, 2013)) can assess the impact of sample bias on the patterns of associations observed. Previous studies in ALSPAC have reported that associations with depression do not change after taking missingness into account using approaches such as multiple imputation and inverse probability weighting (Crane et al., 2016; Pearson et al., 2018; Rice et al., 2018), suggesting that attrition may not have had a major impact on current findings.

Comparison of the EPAD and ALSPAC cohorts was somewhat limited by the different measures and informants. For instance, EPAD parents and adolescents reported depressive symptoms on the long version of the MFQ, whereas in ALSPAC depressive symptoms were self-reported by adolescents on the short version of the MFQ. In the EPAD sample, parent and child responses were combined as this is best practice in clinical settings (NICE, 2005). It was not possible to combine parent and adolescent responses in ALSPAC as both respondents did not report on symptoms at the same time points. However, older children are considered reliable reporters of their own symptoms (Grills & Ollendick, 2003; Lewis et al., 2012). The contemporaneous and prospective relationships between OGMneg and depressive symptoms in ALSPAC were replicated with parent-reported depression outcomes (Chapter 3, section 3.3.8.1) suggesting informant differences are unlikely to have affected the results. Different methods of measuring AM were also apparent as EPAD used an oral version of the AMT which included interviewer prompts when necessary and time limits for responses, whereas ALSPAC used an unsupervised written version of the AMT with no time limits. Nevertheless, as a prospective relationship between OGMneg and depressive symptoms was evident using different methods and different reporters, it gives greater confidence in the results.

In Chapter 6 I based my tract-specific hypotheses on white matter identified by whole brain analysis approaches in the literature. This was to ensure all tracts were included for consideration and, in part, due to the paucity of good-quality tract-specific papers that used a clinical interview to ascertain diagnosis of depression, controlled adequately for multiple comparisons and had sample sizes larger than 20 patients and 20 controls (see Chapter 6, section 6.1). However, there are inherent differences in the methodologies of tract-specific and whole brain analyses. For instance, tract-specific analyses look at microstructural properties across the entire

white matter tract, investigating the connection between one area of the brain to another, whereas whole brain voxel-based approaches examine microstructural properties in each small voxel or segment within white matter. Thus, a tract implicated with reduced FA in MDD in tract-specific analysis is more meaningful than a voxel of white matter not necessarily connected to another area of white matter that is altered in whole brain analyses. Furthermore, tract-specific analyses take into account the entirety of the tract whereas whole brain analyses typically only include the central part of the tract, or the tract skeleton. Thus, hypotheses based on white matter associated with MDD from whole brain approaches may be measuring different white matter areas than were assessed in tract-specific analyses. Based on this I would have expected a stronger association in the exploratory TBSS analysis but the meaning of this lack of association is not clear. As TBSS controls for the thousands of tests that assess the relationship between overgeneral memory and every white matter voxel in the brain, lack of power is likely to have prevented any small associations between overgeneral memory and white matter reaching statistical significance. An a priori tract-specific approach has fewer comparisons as it assesses the relationship with whole white matter tracts rather than thousands of voxels so has better power to detect potential small effects, thereby highlighting the benefit of choosing this as my primary approach for a small feasibility study. Future research increasing the sample size is one way power can be increased for TBSS analysis of the relationship between overgeneral memory and depression.

All analyses adjusted for IQ. This was done as not accounting for IQ in analyses has been identified as a limitation of the previous research (Williams et al., 2007), and because lower IQ is associated with depression (Zammit et al., 2004) as well as with reduced AM specificity and increased overgeneral AM (Heron et al., 2012; Park et al., 2002). IQ was considered as a proxy for cognitive ability as it

encompasses a wide range of factors including processing speed, working memory, perceptual reasoning, verbal comprehension (Wechsler, 1991, 2003). Failing to adjust for IQ may result in observed associations between overgeneral memory and depression to be attributable to low IQ or reduced cognitive ability. However, it is possible that reading and language difficulties may have affected the results in that young people with difficulties in these domains may struggle with the demands of the AMT but have IQ scores within the normal range. Although full scale IQ on the WISC encompasses verbal comprehension (word similarities, vocabulary and comprehension; Wechsler, 1991, 2003), this does not necessarily equate to language and reading difficulties. As difficulties with language and reading are associated with depression (Cederlöf, Maughan, Larsson, D'Onofrio, & Plomin, 2017; Francis, Caruana, Hudson, & McArthur, 2019; Maughan & Carroll, 2006; Maughan, Rowe, Loeber, & Stouthamer-Loeber, 2003), and the AM tasks used are likely reliant on language and reading, these factors could account for some of the findings in this thesis. Nevertheless, a prospective relationship between OGMneg and depressive symptoms was present in ALSPAC, which used a written AMT (Chapter 3), as well as in EPAD which used an oral AMT (Rawal & Rice, 2012b). The procedure for the oral AMT in EPAD is likely to have placed less burden on individuals with reading and language difficulties as participants did not need to read the instructions themselves, instead interviewers gave the instructions verbally, gave three practice trials to ensure participants understood the task, gave definitions of cue words when required, and prompted participants to be specific for non-specific responses. Similar results from ALSPAC and EPAD despite the differences in task burden for reading and language gives greater confidence in the prospective association. Nevertheless, effects of reading and language difficulties on the results cannot be ruled out.

In all empirical chapters I performed initial correlational analyses on a large number of variables without controlling for the number of tests run. The purpose of these correlations was to observe initial associations and I mainly focused on effect sizes (which would not change) within each chapter. However, results noted as significant should be treated with caution as not all relationships would remain significant if control for multiple comparisons were implemented.

Finally, I focused on overgeneral memory as an individual risk factor despite MDD having a multifactorial aetiology (Rice & Rawal, 2011; Sullivan et al., 2000; Thapar et al., 2012). I chose to focus more on one factor in depth rather than multiple factors in little detail as before overgeneral memory can be considered as part of depression's multifactorial aetiology it must first be identified as a causal risk mechanism for depression (Academy of Medical Sciences, 2007). I chose to investigate overgeneral memory as risk factor and risk mechanism for a number of reasons. Firstly, overgeneral memory is in line with overgeneralisations that are common in depression (Beck, 2008; Thew et al., 2017) and there is very strong evidence for memory biases in depression (see Introduction, section 1.2.3.2). Furthermore, evidence has suggested overgeneral memory is likely to be a risk factor for adult depression (Sumner et al., 2010; Williams et al., 2007) and emerging evidence suggests it may be a risk factor for early-onset depression in adolescence (Hipwell et al., 2011; Rawal & Rice, 2012b; Sumner et al., 2011). Finally, overgeneral memory is modifiable (Hitchcock et al., 2017; Williams et al., 2000) making it a good target for interventions (Garber, 2006). Chapters assessing the relationship between overgeneral memory and individual known risk factors for depression have begun to examine how overgeneral memory is associated with SLEs, PRS and white matter differences that lead to depression. However, further

research is required looking at the relationship between overgeneral memory and other important risk factors involved in depression but not examined in this thesis.

7.8. Future research

Research in this thesis suggests several important areas for further research. Firstly, the prospective relationship between OGMneg and depressive symptoms was present over a period of three years (Chapter 3) but it is not clear whether this relationship would extend further into young adulthood. Young adulthood is a key risk period for the onset of depression (Rohde et al., 2013; Weissman et al., 2006) so is a particularly important period to examine if overgeneral memory is thought to be a risk factor or risk mechanism for the disorder. Chapter 6 and previous meta-analyses in adults (Liu et al., 2013; Ono et al., 2015) suggest depression is associated with positive AM specificity in young adulthood. It is not clear whether the difference in AM measure associated with depression in adolescence and adulthood reflects a developmental change or methodological differences and limitations. Consequently, work investigating the longitudinal relationship between overgeneral memory and depression considering AM valence and definition is necessary.

Secondly, more understanding of the mechanisms underlying the development of overgeneral memory, and how overgeneral memory affects depression, is needed. Current research on the aetiology of overgeneral memory in adolescents is limited to rumination, functional avoidance and executive function due to the prominent CaR-FA-X model (Williams et al., 2007), so exploration of alternative mechanisms is required. Findings in Chapter 5 suggest that association between common genetic risk for depression and overgeneral memory is likely to be small, thus it is important to investigate environmental and social factors in the development of overgeneral memory and depression. OGMneg could be a risk factor

for depressive and psychotic-like symptoms (Chapter 3), therefore further research into whether the underlying mechanisms of the association with overgeneral memory differ by disorder would be beneficial for understanding the aetiology of each condition. The current understanding of how overgeneral memory affects depression and associated impairment is disparate, with evidence pointing to several different pathways; for instance, emotion regulation, negative self cognitions, social problem solving, and social functioning, (see Introduction section 1.3.3). Efforts to develop this research, particularly into a unified theory based on current evidence, would enhance understanding of cognition in the aetiology of depression.

Although this thesis has begun to look at overgeneral memory in relation to other risk factors for depression (Chapters 4-6), further research should be conducted examining a number of risk factors simultaneously based on theory. This thesis has found that gender, age and IQ are important covariates, but it is also known that other factors that are associated with overgeneral memory, such as executive functioning, rumination, social problem-solving, social functioning, emotion regulation, and sense of self (Askelund et al., 2019; Conway & Pleydell-Pearce, 2000; Goddard et al., 1996, 1997; Harris et al., 2008; Joormann & Siemer, 2004; Joormann et al., 2007; Williams et al., 2007), are also important. Given lower-level cognitive biases are thought to feed into and build these higher level cognitive, affective and social processes (Jacobs et al., 2008; Roiser et al., 2012), research into how overgeneral memory contributes to these factors, and how they might lead to depression, is vital.

The work in this thesis provides preliminary evidence of a link between overgeneral memory and white matter microstructure but was limited by sample size and cross-sectional design. Studies with larger samples sizes assessing the relationship between overgeneral memory, white matter and depression over time are

required to fully understand how overgeneral memory and white matter contribute to the aetiology of depression. There is a general paucity of neuroimaging studies assessing structural and functional connectivity in individuals before the onset of depression (Dohm et al., 2017). Longitudinal neuroimaging studies that assess clinical characteristics, cognition and other potential risk factors are much needed to provide a more complete picture of the multifactorial aetiology of depression. However, scanning a large number of people repeatedly over time is very costly. Studies that have assessed the development of white matter in childhood and adolescence (see (Blakemore, 2012; Schmithorst & Yuan, 2010) for reviews) have tended to focus on cross-sectional comparisons that do not account for individual differences in participants. Emerging evidence from a longitudinal population-based sample indicates that baseline psychiatric problems are associated with subsequent reduced white matter FA (Muetzel et al., 2018), but it is unclear how these are associated with cognitive biases and deficits. Consequently further longitudinal work is necessary. Following high-risk groups (such as offspring of depressed parents) that result in a higher incidence of disorder over a shorter time period may offer a more cost-effective method than following individuals with typical-risk of developing depression.

Work in this thesis has found that the relationship between overgeneral memory and depression is complex and is partly based on AM definition and valence. In Chapter 3 both overgeneral AM to negative cues and specific AM to negative cues were associated with contemporaneous depressive symptoms, whereas in Chapter 6 specific AMs cued with positive memories and specific AMs that were positive in content were associated with depressive symptoms. Although overgeneral AM and specific AM are not opposite ends of the same continuum (Sumner, 2012), they are likely tapping the same underlying construct (Askelund et al., 2019). Future

work should be mindful that AM definition and valence are important when looking at the relationship between overgeneral memory and depression. However a strict rule determining an AM definition and valence to adopt in all studies may not be appropriate, instead the index of overgeneral memory should be chosen based on theory and aim of the research. For instance, research on treatment may benefit from focusing on specific positive AMs as recalling these may act as an emotion regulation strategy (Joormann & Siemer, 2004; Joormann et al., 2007; Ramirez et al., 2015), whereas research on the phenomenon of overgeneral memory in the onset of depression may do better to focus on negative overgeneral AMs as theory suggests overgeneral memory may develop first for negative events/memories before becoming generalised to positive memories (Sumner, 2012; Williams et al., 2007).

Although this thesis has taken the first steps to assess the longitudinal relationship between overgeneral memory and depression, further work assessing causation is required to support overgeneral memory as a risk mechanism involved in the aetiology of depression. Throughout the thesis an observational design has been used but this design has inherent threats to causal inference such as confounding, reverse causation, and selection bias (Rutter, 2007; Thapar & Rutter, 2019). In order to provide greater confidence that overgeneral memory is a causal risk mechanism for depression, a number of techniques and designs should be used to assess the relationship with convergence or "triangulation" of findings from different types of study designs with different inherent sources of bias indicating that causality is more likely (Munafo & Davey Smith, 2018; Thapar & Rutter, 2019). For instance, should SNPs for overgeneral memory be identified through a GWAS, Mendelian randomisation could be used to test whether overgeneral memory is causally associated with depression (Pingault et al., 2018). A twin study investigating the association between overgeneral memory and depression would be able highlight the

genetic and environmental basis of this association (Thapar & Rutter, 2019). A number of RCTs have begun to look at targeting overgeneral memory as a treatment for depression (Hitchcock, Werner-Seidler, Blackwell, & Dalgleish, 2017; section 7.6). These RCTs in combination with aforementioned approaches would provide greater confidence that overgeneral memory is a causal mechanism through which depression develops.

Finally, as work in this thesis has suggested overgeneral memory is likely to be a risk factor for depression, a thorough assessment of overgeneral memory as a potential target for treatment and prevention of depression is required. Preliminary interventions targeting overgeneral memory in adults has found overgeneral memory is malleable (Hitchcock et al., 2017; Williams et al., 2000) and effective at reducing depressive symptoms over shorter periods of time (Hitchcock et al., 2017). However, further work is needed assessing the long-term effectiveness of interventions targeting overgeneral memory and the effectiveness of interventions in adolescent samples as these areas have received little attention in the literature. As well as assessing reduction in depressive symptoms, studies should strive to ensure that effects are clinically meaningful and assess subsequent functioning in other related domains, e.g. social functioning and relationships (Harris et al., 2008). Social functioning outcomes may be particularly important given AM is linked to social functioning and social problem solving (see Introduction, section 1.3.3) and depression is the leading global cause of years lived with a disability (Friedrich, 2017; World Health Organization, 2017). As work in Chapter 6 found overgeneral memory was associated with white matter, in the future one potential therapeutic intervention in the future could involve a form of neural brain training (Linden, 2014; Marzbani, Marateb, & Mansourian, 2016), as white matter is also amenable to change (Hofstetter, Tavor, Tzur Moryosef, & Assaf, 2013; Sampaio-Baptista &

Johansen-Berg, 2017) and may be a mechanism through which the reduction in depressive symptoms occurs.

7.9. Conclusions

Work in this thesis has added to knowledge on overgeneral memory as a risk factor and potential risk mechanism for depression in adolescents. Results show a complex relationship between overgeneral memory and depression, with differences based on AM definition and valence. OGMneg is likely to be a risk factor for adolescent depression as it is associated with subsequent depression, thereby displaying temporal precedence to the disorder. However, OGMneg does not act as a mediator for SLEs or genetic risk for depression, and these factors seem likely to exert independent effects on subsequent depression. In young adults OGMneg was not associated with white matter previously linked to depression but overgeneral memory associated with current depression (reduced AM specificity that was positive in content) was. Taken together, these findings suggest OGMneg is likely to be a risk factor for adolescent depression but whether OGMneg could be risk mechanism is less clear. Definition and valence of AM is an important consideration given the inconsistencies in the literature and that work in this thesis finds depression and associated white matter tracts are not associated with OGMneg in young adults. Longitudinal work assessing overgeneral memory indices in conjunction with other risk factors is needed to unpick this relationship further. This research has the potential to improve understanding of the role of cognition in the development of depression, and offers opportunities for strengthening the evidence for causal mechanisms to target in interventions and preventative measures.

8. References

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9. Appendices

Appendix 2.1: ALSPAC Autobiographical Memory Test instructions
taken from Data Dictionary available at www.bristol.ac.uk/alspac/researchers/access/

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Appendix 2.2: EPAD neuroimaging subsample MRI screening forms

CUBRIC, CARDIFF UNIVERSITY - MAGNETIC RESONANCE IMAGING UNIT INITIAL SCREENING FORM

NAME OF PARTICIPANT …… Sex: M / F
Date of birth…… CUBRIC UNIQUE IDENTIFIER:

Please read the following questions CAREFULLY and provide answers. For a very small number of individuals, being scanned can endanger comfort, health or even life. The purpose of these questions is to make sure that you are not such a person. You have the right to withdraw from the screening and subsequent scanning if you find the questions unacceptably intrusive. The information you provide will be treated as strictly confidential and will be held in secure conditions.

If you are unsure of the answer to any of the questions, please ASK the person who gave you this form or the person who will be performing the scan. Definitions of some of technical terms are given overleaf.

Please answer all questions	*Circle answer*
1. Have you been fitted with a pacemaker, or any other implanted device?	YES/NO
2. Have you any surgical clips, aneurysm clips, shunts or stents in your body?	YES/NO
3. Have you had a heart valve replacement	YES/NO
4. Have you ever had any metal fragments in your eyes?	YES/NO
5. Have you had a cochlear implant fitted	YES/NO
6. Do you wear a hearing aid?	YES/NO
7. Do you have any other mechanical/electrical or magnetically operated devices in or on your body?	YES/NO
8. Have you ever had any metal fragments, e.g. shrapnel in any other part of your body?	YES/NO
9. Have you any surgically implanted metal in any part of your body (e.g. joint replacement or bone reconstruction, pins, rods, screws, nails, clips, plates, wires).	YES/NO
10. Have you ever had any surgery that might have involved metal implants of which you are not aware?	YES/NO
11.Do you have a catheter fitted?	YES/NO
12.Do you have any intra-venous devices fitted (including stents and filters)	YES/NO
13. Do you have any Tattoos?	YES/NO
14. Is there any possibility that you might be pregnant?	YES/NO
15. Have you been sterilised using clips?	YES/NO
16. Do you have a contraceptive coil (IUD) installed?	YES/NO
17. Do you have **any** dental work (including dentures, crowns, bridgework, braces) in your mouth, other than simple fillings?	YES/NO
18. Have you ever suffered from any of: epilepsy, diabetes or thermoregulatory problems?	YES/NO

19. Have you ever suffered from any heart disease?	YES/NO
20. Do you have any permanent eye makeup?	YES/NO

CUBRIC, CARDIFF UNIVERSITY - MAGNETIC RESONANCE IMAGING UNIT
SECOND SCREENING FORM

This form should be completed and signed immediately before your scan, after removal of any jewellery or other metal objects and (if required by the operator) changing your clothes.

NAME OF PARTICIPANT …… Date of birth……Sex: M / F

STUDY TITLE: ……
FOR STAFF USE: CUBRIC UNIQUE IDENTIFIER:……

Today's Weight in kg…… or Stones/lbs ……

Please read the following questions CAREFULLY and provide answers. For a very small number of individuals, being scanned can endanger comfort, health or even life. The purpose of these questions is to make sure that you are not such a person.

You have the right to withdraw from the screening and subsequent scanning if you find the questions unacceptably intrusive. The information you provide will be treated as strictly confidential and will he held in secure conditions.

BEFORE YOU ARE TAKEN THROUGH FOR YOUR SCAN IT IS ESSENTIAL THAT YOU REMOVE ALL METAL OBJECTS INCLUDING: WATCHES, PENS, LOOSE CHANGE, KEYS, HAIR CLIPS, ALL JEWELLERY, BRASSIERES WITH METAL FASTENERS, METALLIC COSMETICS, CHEQUE/CASH POINT CARDS.

Please answer all questions	*Circle your answer*
1. Are you wearing or carrying any metal items such as those listed above?	YES/NO
2. Have your answers to any of the questions in the initial screening form changed? (The initial screening form must be shown to you before you answer this question.)	YES/NO
3. Have you been fitted with a pacemaker, artificial heart valve, cochlear implant or any other implanted device?	YES/NO
4. Is there any possibility that you might be pregnant?	YES/NO
5. Are you currently feeling unwell (colds, flu etc.) or have you been unwell in the last week?	YES/NO
6. Are you wearing metallic nail polish?	YES/NO

I have read and understood the questions above and have answered them correctly.

SIGNATURE…… DATE……

Appendix 3.1: Assessment of attrition in contemporaneous and prospective depression analyses

		N (row %) or mean (SD)							
		Tenure (n = 13,501)		**Financial difficulties (n = 11,260)**	**Maternal parity (n = 13,124)**			**Maternal education (n = 12,493)**	
		Rent/ other	*Mortgage /owned*		*0*	*1*	*2+*	*<= GCSE*	*>= A level*
Contemporaneous analysis (n = 3,154)	*Not missing*	393 (12.6)	2717 (87.4)	2.69 (3.33)	1552 (50.0)	1086 (35.0)	465 (15.0)	1568 (50.1)	1563 (49.9)
	Missing	3223 (31.0)	7168 (69.0)	3.40 (3.69)	4321 (43.1)	3501 (34.9)	2198 (21.9)	6515 (69.6)	2847 (30.4)
Test statistic		**$\chi^2(1) = 412.38$, $p < .001$**		**$t(6150.29) = -9.79$, $p < .001$**	**$\chi^2(2) = 81.56$, $p < .001$**			**$\chi^2(1) = 391.04$, $p < .001$**	
Prospective analysis (n = 2,345)	*Not missing*	262 (11.3)	2051 (88.7)	2.54 (3.27)	1181 (51.1)	793 (34.3)	335 (14.5)	1080 (46.3)	1255 (53.7)
	Missing	3354 (30.0)	7834 (70.0)	3.37 (3.67)	4692 (43.4)	3795 (35.1)	2328 (21.5)	7003 (68.9)	3155 (31.1)
Test statistic		**$\chi^2(1) = 340.04$, $p < .001$**		**$t(3939.37) = -10.57$, $p < .001$**	**$\chi^2(2) = 72.11$, $p < .001$**			**$\chi^2(1) = 427.90$, $p < .001$**	

Results significant at $p < .05$ indicated in bold.

Appendix 3.1: Assessment of attrition in contemporaneous and prospective depression analyses continued

		N (row %) or mean (SD)								
		Child sex (n = 14,854)		**Child 5 A*s to Cs (n = 12,278)**		**Child depressive symptoms age 12.5 (n = 6,761)**	**Child depressive symptoms age 16.5 (n = 5,088)**	**Child IQ (n = 7,347)**	**Overgeneral AM (n = 5,788)**	**Specific AM (n = 5,788)**
		M	*F*	*0*	*1*					
Contemporaneous analysis (n = 3,154)	*Not missing*	1410 (44.7)	1744 (55.3)	491 (17.9)	2245 (82.1)	3.94 (3.75)		107.47 (15.68)	2.51 (2.07)	3.84 (2.49)
	Missing	6225 (53.2)	5475 (46.8)	4498 (47.1)	5044 (52.9)	4.01 (3.98)		101.34 (16.68)	2.68 (2.19)	3.63 (2.53)
Test statistic		**$\chi^2(1) = 320.16$, $p < .001$**		**$\chi^2(1) = 751.21$, $p < .001$**		t(6759) = -0.734, p = .463		**t(6994.08) = 16.13, p < .001**	**t(5479.64) = -3.06, p = .002**	**t(5786) = 3.28, p = .001**
Prospective analysis (n = 2,345)	*Not missing*	952 (40.6)	1393 (59.4)	259 (12.9)	1750 (87.1)	3.94 (3.66)	5.72 (5.44)	108.76 (15.52)	2.50 (2.05)	3.98 (2.49)
	Missing	6683 (53.4)	5826 (46.6)	4730 (46.1)	5539 (53.9)	4.00 (3.99)	6.04 (5.80)	101.74 (16.53)	2.65 (2.18)	3.59 (2.51)
Test statistic		**$\chi^2(1) = 130.1$, $p < .001$**		**$\chi^2(1) = 766.33$, $p < .001$**		t(5151.59) = -0.616, p = .538	**t(5043.55) = -2.03, p = .042**	**t(4856.77) = 17.70, p < .001**	**t(5228.30) = -2.61, p = .002**	**t(5786) = 5.78, p < .001**

Results significant at p < .05 indicated in bold.

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Appendix 4.1: Correspondence between cue and researcher-rated valence in the EPAD sample

		Memory valence		
		Positive	*Neutral*	*Negative*
Cue valence	*Positive*	90.881%	4.368%	4.751%
	Negative	5.056%	3.599%	91.345%

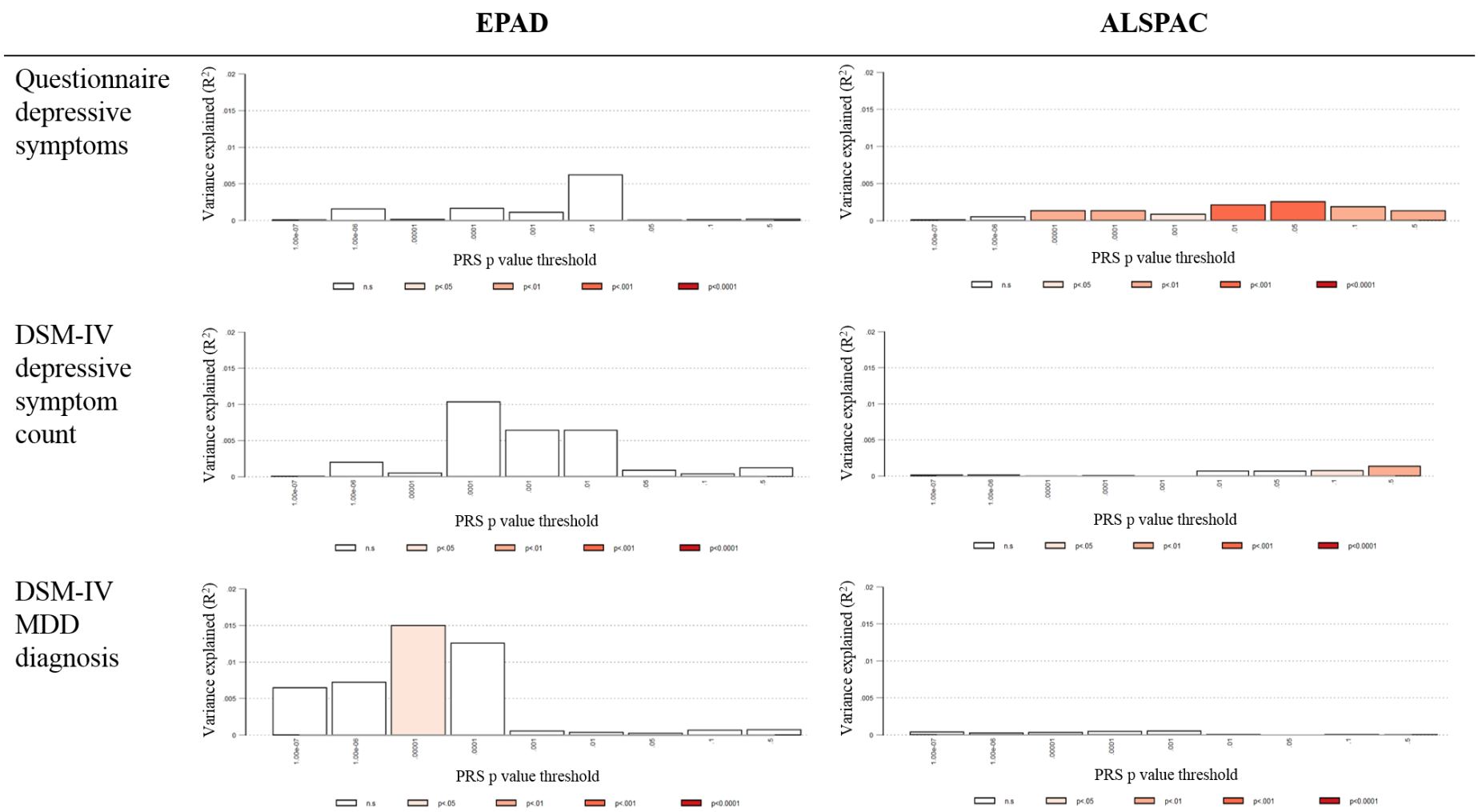
Percent of memories recalled (positive, neutral, negative) for each cue valence.

Appendix 4.2: Mean autobiographical memory for all participants completing the AMT in EPAD (n = 257) and ALSPAC (n = 5,785)

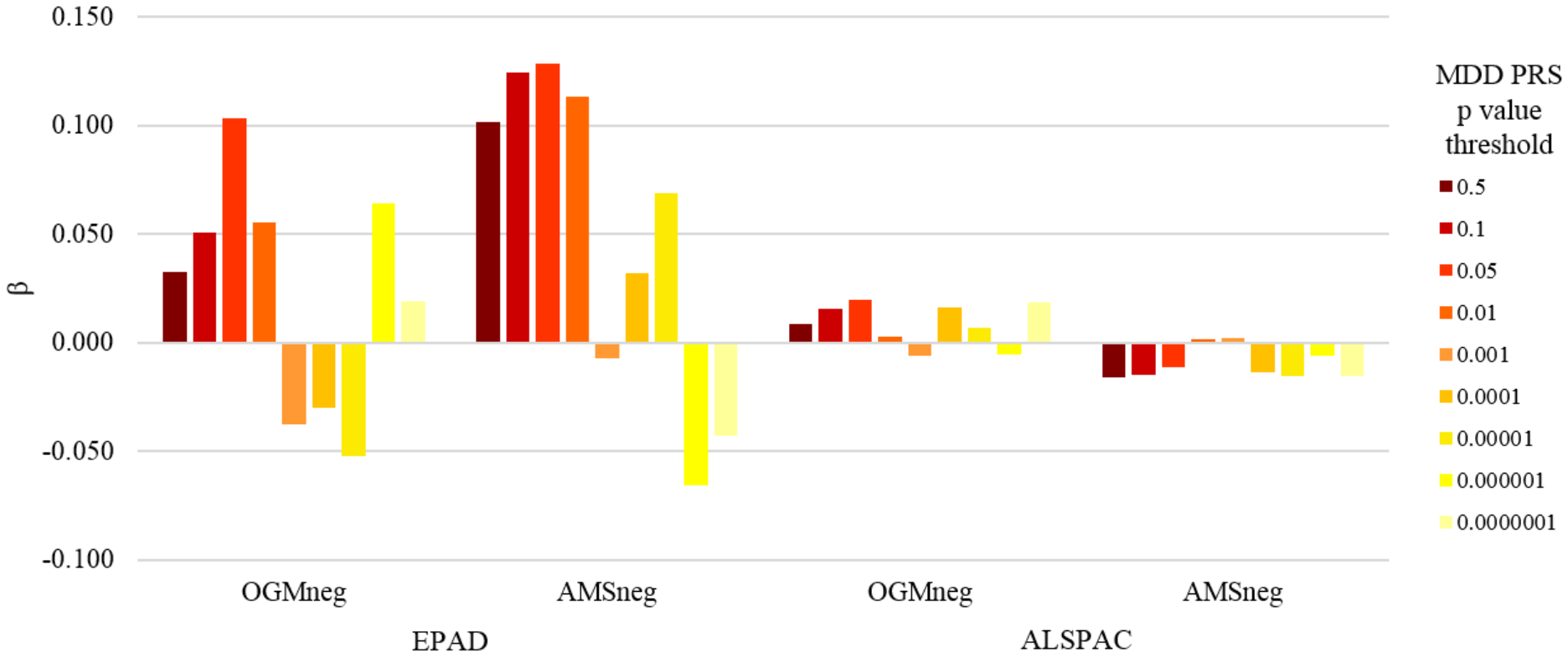
AM measure	EPAD mean (SD)	ALSPAC mean (SD)
OGMneg	.930 (1.126)	1.328 (1.239)
OGMpos	1.109 (1.144)	1.259 (1.229)
AMSneg	3.230 (1.691)	1.351 (1.343)
AMSpos	3.518 (1.623)	2.395 (1.485)

AMSneg - specific AM to negative cues; AMSpos – specific AM to positive cues; OGMneg – overgeneral AM to negative cues; OGMpos – overgeneral AM to positive cues.
AM indices in EPAD possible range 0-6; AM indices in ALSPAC possible range 0-5.

Appendix 5.1: Variance in depression phenotype explained by MDD polygenic risk scores at a number of p value thresholds in EPAD and ALSPAC



Appendix 5.2: Associations between depression polygenic risk scores and autobiographical memory using a range of p value thresholds from the MDD discovery sample



ALSPAC – Avon Longitudinal Study of Parents and Children; AMSneg – specific autobiographical memories to negative cues; EPAD – Early Prediction of Adolescent Depression; MDD – Major Depressive Disorder; OGMneg – overgeneral autobiographical memory to negative cues; PRS – polygenic risk score. No associations were significant at $p < .05$.

Appendix 6.1: Correspondence between cue and participant-rated memory content valence in the neuroimaging sample

		Memory valence		
		Positive	*Neutral*	*Negative*
Cue valence	*Positive*	84.768	5.298	9.934
	Neutral	59.333	16.000	24.667
	Negative	9.859	10.563	79.577

Percent of memories recalled (positive, neutral, negative) for each cue valence.