Overgeneral Autobiographical Memory and Executive Functioning in Adolescent Depression

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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Abstract

Depression often emerges in adolescence; however, current psychological therapies for adolescents with depression are modest at best. A better understanding of mechanisms that cause and maintain depression could lead to significant improvements in the effectiveness of treatment. A core cognitive process in depression is Overgeneral Memory (OGM). OGM appears to play a role in maintaining depression, increasing the risk of relapse, and may also be implicated in aetiology. The CaR-FA-X model proposes three mechanisms that may cause OGM (rumination, functional avoidance and reduced executive control). There is some empirical support for each component, but no study has explored all three mechanisms in adolescent depression. The aim of this thesis was to assess OGM and the CaR-FA-X mechanisms in adolescent depression and to investigate potential ways to enhance working memory. Paper 1 investigated OGM and the components of the CaR-FA-X model in adolescents with elevated depression symptoms and compared findings to youth with low depression symptoms. Adolescents with elevated depression retrieved fewer specific memories, ruminated more, and had poorer working memory and verbal fluency. Post hoc analysis also revealed that OGM was associated with higher levels of rumination and poorer working memory and verbal fluency. Paper 2 recruited adolescents with a diagnosis of depression and those with an anxiety disorder and compared them to a matched non-clinical control group. OGM and working memory deficits were specific to the depression group. Anxious and depressed participants had impaired inhibition and rumination compared to the non-clinical controls. OGM was associated with increased rumination and reduced working memory and inhibition performance. These findings suggest that working memory is a potential target for prevention and treatment interventions for depression. Paper 3 systematically reviewed meta-analyses of the effectiveness of working memory training. This demonstrated that working memory training has limited effects and effects do not generalise to ‘real life’ tasks. There is emerging evidence that dietary flavonoids may enhance executive control and mood. Therefore paper 4 reports a double-blind randomised controlled trial comparing effects of a chronic flavonoid supplementation and a placebo on mood and executive functioning in young people. Following the flavonoid intervention, depression symptoms, but not cognition, improved. Taken

together, this body of work provides valuable insight into depression-specific working memory deficits in adolescents, which has important implications for therapeutic and school environments.

Declaration

I confirm that this is all my own work and use of all the material from other sources has been properly and fully acknowledge. With regards to paper 4, Sundus Khalid contributed equally in the data collection, analysis and the write up from the manuscript.

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1 Chapter 1 Thesis Outline

1.1 Thesis Overview

The focus of this doctoral thesis was to assess overgeneral autobiographical memory (OGM) and explore cognitive processing in adolescents with depression symptoms. The thesis consists of 4 manuscripts. OGM appears to play a role in both the onset and maintenance of depression in adolescents, however the mechanisms underlying OGM require further investigation. The CaR-FA-X model (Williams et al., 2007) proposed 3 mechanisms that may cause OGM (capture and rumination, functional avoidance, and reduced executive control). Therefore, the first 2 studies assessed overgeneral memory and investigated the potential underlying mechanisms in community adolescents with elevated depression symptoms (Chapter 3), and adolescents with a clinical diagnosis of depression (Chapter 4). In both studies, adolescents experiencing depression symptoms had deficits in both autobiographical memory retrieval and working memory. The findings suggested that working memory could be a potential target for prevention and treatment interventions for adolescent depression. A possible strategy to target working memory deficits could be working memory training. Therefore, in paper 3 (chapter 5), the meta-analyses that examine the effectiveness of working memory training were reviewed. The meta-meta review demonstrated that working memory training provides limited effects and importantly does not generalise to 'real life' tasks (e.g., academic performance). However, there is emerging evidence in children and adults that dietary flavonoids potentially improve both executive control and mood, although no study had assessed the effects of chronic flavonoid supplementation in adolescents. The final papers (Chapter 7 and 8) reported a

randomised control trial assessing the effect of a blueberry rich flavonoid supplementation on both mood and executive functioning. Each chapter of the thesis will be described below.

1.2 An outline of Chapter 2 – an introduction to the thesis

The key background literature for the thesis will be discussed in detail in Chapter 2. This section will introduce each part of the literature review. The literature review is separated into 4 parts.

Part 1: Adolescent depression. This section includes an introduction to depression in adolescence, discussing the prevalence, symptoms, and the many negative life-long impacts. Depression is often co-morbid with symptoms of anxiety and therefore the relationship between anxiety and depression in youth will be introduced. This is important because comparing anxious and depressed adolescents may help to understand deficits in cognitive processes that are specific to depression. Finding mechanisms that are specific to depression may help to improve current psychological therapies. Although current treatments for depression in adolescence are moderately effective, this effectiveness appears to be decreasing over time (Weisz et al., 2017). This section will therefore also discuss why new interventions are needed.

Part 2: The unique adolescent brain. This section describes how adolescence is a unique and important period. Adolescence is marked by the development of brain structures and cognitive functioning (Paus, Keshavan & Giedd, 2008; Steinberg, 2005). This is important for two reasons. First, depression often emerges in adolescence and is therefore considered a period of risk. It has been hypothesised that the maturation of brain regions associated with higher level cognition, joint with stressors during

adolescence, may help to account for the peak in depression onset in adolescence (Fuhrmann, Knoll & Blakemore, 2015; Steinberg, 2008). Second, the developmental changes in the brain indicate that the adolescent brain is functionally different compared to an adult brain (Puffier & Blakemore, 2012) and that such developmental changes may alter the relationship between brain circuits, information processing and symptoms of depression (Oliver, Pile, Elm & Lau, 2019). This highlights the need to assess potential mechanisms for the onset and maintenance of depression in adolescence, and to not presume that mechanisms of depression are the same for adults and adolescents. Part 2 will also describe in more detail how the developing adolescent brain differs from the adult brain and introduce potential vulnerability factors for developing depression.

Part 3: Cognitive theory of depression. This section introduces the cognitive theory of depression. The cognitive theory of depression (Beck, 1967; 1979) proposed that negative cognitions influence how an individual thinks, feels, and behaves and how they interpret situations. A key element of this model is the biased acquisition and processing of information, this includes attention, interpretation and memory biases. Part 3 will provide an overview of cognitive bias studies in depressed adolescents, with a focus on studies assessing memory bias. Several researchers have proposed the potential role of cognitive control in relation to biased information processing and have speculated that brain structures associated with cognitive control and cognitive biases could emerge and contribute to depression in adolescence (LeMoult & Gotlib, 2018; Gotlib & Joorman, 2010; Orchard, Pass & Reynolds, 2016). Therefore, cognitive control will be described, and the potential relationship between cognitive control and depression will be introduced.

Part 4: Overgeneral autobiographical memory. This section focuses on the problematic autobiographical memory processing in depression. Across the lifespan, depression is associated with impaired recall of significant personal memories (Williams et al., 2007). This is referred to as overgeneral memory (OGM) and is considered a core cognitive process in depression. Autobiographical memory will be introduced, and the process of retrieving specific memories described to help understand how the memory search process may be disrupted. The most prominent model to explain OGM is the CaR-FA-X model (Williams et al., 2007). Williams et al. (2007) hypothesised that 3 cognitive processes (i.e., Capture and Rumination, Functional Avoidance and Reduced Executive Control) working together, or in isolation, interfere with the retrieval of specific memories and cause OGM. This section also reviews the background literature relating to The CaR-FA-X model and depression in youth.

1.3 Chapter 3 (study 1)

This study has been published in "Memory" and is entitled "A test of the CaR-FA-X mechanisms and depression in adolescents". The study assessed overgeneral memory, and explored associated cognitive processes, rumination, functional avoidance and executive functioning in a community group of adolescents with elevated symptoms of depression and compared findings to teenagers with very low levels of depression symptoms. Adolescents with elevated depression symptoms retrieved fewer specific memories, ruminated more, and had poorer working memory and verbal fluency than adolescents with minimal depression. Understanding key psychological mechanisms associated with depression, such as executive control and rumination, has the potential to inform prevention and treatment strategies for depression. Assessing

these cognitive processes in young people with a clinical diagnosis is essential. Further, it is important to include a clinical control group to examine which cognitive processes may be specific to depression symptoms.

1.4 Chapter 4 (study 2)

This study has been submitted to "the Journal of Abnormal Child Psychology" and is entitled "Overgeneral memory bias and the CaR-FA-X mechanisms in depressed and anxious adolescents". The study investigated overgeneral memory and the CaR-FA-X mechanisms in three groups of young people; adolescents with a primary diagnosis of depression, a primary diagnosis of an anxiety disorder (but not depression), and non-clinical controls. The key findings in this study were that young people with a diagnosis of depression had significant impairments in autobiographical memory processing and working memory compared to community and clinical controls. This suggests that overgeneral memory and reduced working memory may be specific to depression.

1.5 Chapter 5 (study 3)

This chapter is a systematic meta-meta review of the current meta-analyses that examine the effectiveness of working memory training (WMT) in children and young people. This paper is entitled "What are the effects of working memory training on children and adolescents? A meta-meta review." The findings from studies 1 and 2 led us to consider the idea that improving working memory deficits may have a positive effect on depression. Researchers have speculated that working memory training enhances working memory capacity and has the potential to improve broader skills e.g., academic performance (Jaeggi, Buschkuehl, Jonides & Perrig, 2008; Pearson, 2016).

However, before assessing the effectiveness of WMT in adolescents with depression symptoms it was necessary to evaluate the previous literature of the efficacy of WMT. Consequently, we systematically searched and reviewed the meta-analyses that had tested the effectiveness of WMT in youth. It was concluded that although near-transfer effects are reported after training (i.e., to other working memory tasks) there was no robust evidence to support that training skills improved other cognitive domains (i.e., skills do not transfer to 'real life 'such as academic performance). Therefore, as working memory training was less effective than expected, alternative interventions were considered.

1.6 Chapter 6: an introduction to dietary flavonoids

This chapter is an introduction to flavonoids (a nutritional compound), and the literature that reports potential benefits of dietary flavonoids on both cognition and mood will be critically evaluated. Researchers have hypothesised that flavonoids enhance mood and boost executive functioning, however the majority of research in this area has been conducted with children or adults, not adolescents. The literature regarding the beneficial effects of flavonoids on executive functions, and the research suggesting that flavonoid intake improves mood, provided a rationale to examine the effects of flavonoids on executive functioning and depression symptoms. This leads to paper 4, which is discussed in the next section.

1.7 Chapter 7 (study 4)

This study has been published in "The British Journal of Nutrition". This was a double-blind, placebo-controlled, experimental study entitled "Effects of 4 weeks daily wild blueberry supplementation on depression in adolescents". The emerging evidence

(as discussed in Chapter 6) demonstrating potential beneficial effects on both executive functioning and mood provided a rationale for examining wild blueberry supplementation (high in flavonoids) in healthy adolescents. The effects of the supplementation on depression symptoms and transient affect are reported in this chapter. Findings demonstrated that adolescents who received the chronic flavonoid supplementation reported a significant decrease in depression symptoms compared to those who received the matched placebo. Although these findings need to be replicated and future trials require both at-risk and clinical populations, they provide a promising justification for future research on the effects of blueberry flavonoids on depression symptoms.

1.8 Chapter 8

Chapter 8 consists of an addendum to paper 4 and describes the effects of chronic wild blueberry supplementation on cognition i.e., working memory and inhibitory control. Executive functioning was measured as part of the hypothesis that wild blueberry supplementation may increase mood through enhancing cognition. In this study, no significant improvements in executive functions were found in youth that had received the flavonoid supplementation compared to those who had the matched placebo. The results will be discussed with implications for future research.

1.9 Chapter 9

This chapter consists of the general discussion for the thesis. This chapter begins by summarising the results in each paper and strengths and limitations for each study will be discussed. Following this, broader implications of the thesis findings and ideas for future research will be described.

Chapter 2: Literature review

1.10 Literature review part 1: Adolescent depression

1.10.1 Adolescent depression

Depression is a chronic and disabling disorder that affects over 300 million people worldwide (World Health Organization, 2017) and adolescence is the period of greatest risk for the development of depression (Rao, Hammen & Poland, 2010). Worldwide approximately 2.6% of young people experience an episode of depression at any one time (Polanczyk, Salum, Sugaya, Caye & Rohde, 2015). In pre-pubertal children depression is uncommon and prevalence rates increase steeply between the ages of 13 and 18 years, with markedly greater increases in females compared to males (Avenevoli, Swendsen, He, Burnstein & Merikangas, 2015).

Depression in adolescence is associated with a wide range of long-term negative impacts. These include repeated episodes of depression and increased severity of depression symptoms, other mental health problems, and suicide thoughts, suicide plans, suicide attempts and completed suicide (Johnson, Dupuis, Piche, Claybourne & Colman, 2018; Nock et al., 2013). Adolescent depression also predicts poor physical health and low levels of social support in later life (Naicker, Galambos, Zeng, Senthilselvan & Colman, 2013). A recent meta-analysis by Clayborne, Varin and Colman (2019) found that experiencing a depressive episode during adolescence was significantly associated with educational underachievement, unemployment, and greater likelihood of pregnancy/parenthood. It is therefore crucial to prevent or treat depression as soon as possible to avoid the multiple negative lifelong impacts described above.

Nine symptoms of depression are used to make a diagnosis of depression; low mood (and in adolescents, irritability), anhedonia (a loss of interest and/or pleasure), suicidal ideation, sleep disturbance, feelings of worthlessness or negative self-perceptions, difficulty concentrating or making decisions, fatigue, psychomotor changes and changes in appetite (DSM-5; APA, 2013). To meet diagnostic criteria for Major Depressive Disorder (MDD), an individual must present symptoms of either low mood (or irritability if an adolescent) or anhedonia, and at least five other symptoms. Additionally, these symptoms must be present for at least 2 weeks and cause clinically significant impairment or distress in important areas of functioning (DSM-5; APA, 2013).

1.10.2 Sub-threshold symptoms of depression

Although symptoms of depression can be viewed as a continuum of increasing severity, as indicated above, mood disorders, including major depressive disorder (MDD) is diagnosed using a categorical system. Therefore, some adolescents can experience depressive symptoms but not meet full criteria for a diagnosis of MDD (Lewinsohn, Solomon, Seeley & Zeiss, 2000). For example, young people may experience dysphoria, a mood state characterised by depressed mood, anxiety and/or irritability (DSM-5; APA, 2013) yet do not qualify for a MDD diagnosis. Although sub-threshold symptoms of depression are less severe than MDD, they are associated with significant impairment and often precede the onset of MDD (Wesselhoeft, Soren, Heiervan & Bilenberg, 2013). Sub-threshold levels of depression are also associated with elevated risk of depression and suicidal behaviours in adulthood (Fergusson, Horwood, Ridder & Beautrais, 2005) and impaired social development, leading to increased levels of loneliness and poor social functioning e.g., difficulties with family

and romantic relationships (Allen, Chango, Szwedo & Schad, 2014). Consequently, this highlights the need to understand symptoms of depression in young people (even if a clinical diagnosis of major depressive disorder is not met) to mitigate adverse outcomes.

1.10.3 The relationship between anxiety and depression

Depression and anxiety are both 'internalising disorders' and depressive disorders are often co-morbid with anxiety disorders in adolescents (Avenevoli et al., 2015). Anxiety disorders in children and young people include separation anxiety, social anxiety disorder, generalised anxiety disorder, panic disorder and agoraphobia (DSM-5; APA, 2013). Anxiety and depression also share some of the same symptoms (e.g., fatigue, low concentration, and sleep disturbance). Anxiety is more common than depression in youth, with a worldwide prevalence estimated of 6.5% of adolescents experiencing anxiety at one time (Polanczyk et al., 2015). Young people with anxiety are at increased risk of developing depression (Costello et al., 2003) and childhood anxiety symptoms have been found to predict depression symptoms in adolescents (Cohen, Andrews, Davis & Rudolph, 2018). Although there is a clear relationship between anxiety and depression, distinguishing differences in the aetiology and maintenance factors between anxiety and depression may have the potential to inform treatment. For example, both overlaps and differences have been found in cognitive and neural processing in anxiety and depression during adolescence (Beesdo et al., 2009; Etkin & Schatzberg, 2011; Thomas et al., 2001). These data suggest that there are differences between the two disorders. Further, the most recent meta-analysis testing psychological treatment effects in youth reported that effect sizes were higher for anxious adolescents than depressed adolescents (Weisz et al., 2017). This is important

because the reason for this is unknown and studying this has the potential to change treatment for depression. Additionally, Weisz et al. (2017) reported that multi-method treatments (i.e., treatments that do not have a specific target but treat anxiety and depression together) have poor outcome effects. This indicates a need for specific treatment packages; however, to be able to develop these it would be helpful to understand what teenagers with depression need. As a result, it is important that research considers both anxiety and depression symptoms within the same study to help explore differences between the disorders in adolescence, which in turn may inform clinical practice.

1.10.4 Treatment of depression in adolescents

Psychological therapies are offered as first line treatments for depression in children and young people such as individual Cognitive Behavioural Therapy (CBT) and family therapy (National Institute of Health and Excellence, 2015). Evidence from a recent meta-analysis, which included research from the last 50 years, found that outcomes from psychological therapy in youth are moderate at best, particularly in the treatment for depression (Weisz et al., 2017), and that treatment effect sizes have reduced over time, i.e., therapy appears to be becoming less effective. Moreover, recent trials have reported significant drop-out levels in CBT and other therapies (Goodyer et al., 2017) and evidence-based treatments may not meet the needs of many depressed youth (Pass, Lejuez & Reynolds, 2018). Waiting times in children and adolescent mental services can be variable (National Society for the prevention of Cruelty to children, 2015), and can also be lengthy (House of Common Health Committee, 2014; Docherty & Thornicroft, 2015). For these reasons, there is now emerging evidence into

novel ‘low-intensity’ therapies that can be administered by non-specialties (i.e., more affordable and the ability to train more people).

Brief Behavioural Activation is an example of a ‘low-intensity’ treatment for adolescent depression. Behavioural activation (BA) is one of the components of CBT; however, as an intervention on its own it uses learning theory to find out what might be reinforcing and maintaining depressed mood. BA proposes that the initial withdrawal from activities and other people leads to reduced positive reinforcement and low mood, leading to a cycle that is hard to break. Pass, Lejuez & Reynolds, (2018) conducted a pilot study of Brief BA and found that the effect on depression symptoms was large. Most participants did not require another intervention at the end of treatment. Other novel interventions for treating depression in young people include targeting specific cognitive impairments in depression, such as improving memory specificity and enhancing executive control (Dalgleish & Werner-Seidler, 2014).

There is emerging evidence for targeting impaired memory specificity (i.e., OGM) (Jing, Madore & Schacter, 2016; Hitchcock, Werner-Seidler, Blackwell & Dalgleish, 2017). Interventions that improve an individual’s access to specific memories could lead to therapeutic benefits by alleviating the negative consequences associated with OGM (Hitchcock et al., 2017). For example, an adolescent study found that depression symptoms can be alleviated following Memory Specificity Training (MEST) (Neshat-Doost et al., 2014). Although this research is at an early stage, this brief treatment for depression (5 weeks) does not require extensive therapist training and may potentially be an attractive intervention for adolescent depression.

There are several other novel interventions that aim to improve mood and/or cognitive processes by improving executive control (Dalgleish & Werner-Seidler,

2014). These include working memory training (Sala & Gobet, 2017; Dalgleish & Werner-Seidler, 2014), attention-bias modification (Micco, Henin & Hirshfeld-Becker, 2014) and nutritional supplementation interventions (Busch, Taylor, Kanarek & Holcomb, 2002; Khalid, Williams and Reynolds, 2016). However, further evaluation is necessary to understand these potential additive or adjunctive therapies and their potential benefits for young people with depression.

1.11 Literature review part 2: The unique adolescent brain

1.11.1 The developing adolescent brain

Adolescence is the time between childhood and adulthood and is characterised by hormonal, physical, psychological and social changes (Ernst & Mueller, 2008; Sebastian, Burnett & Blakemore, 2008). During this transitional period, adolescents begin to differentiate from their parents, create new friendships and explore their identity (Sebastian, et al., 2008). These changes are often accompanied with heightened emotionality and occur in parallel with biological and physical changes i.e., brain development and the onset of puberty.

Neuroimaging studies demonstrate that the brain undergoes extensive and rapid neurological development during adolescence (Blakemore 2012; Blakemore & Mills, 2014; Fuhrmann, Knoll & Blakemore, 2015). This normative period of brain development has therefore been suggested as a potential "window of risk" (Steinberg, 2008). The evidence of the reorganisation of brain structure architecture has led researchers to propose that adolescence is a particularly sensitive period because of heightened neural plasticity (i.e., the way the brain adapts to internal or external stimuli), rendering the adolescent brain uniquely sensitive to influences in the

environment (Blakemore & Mills, 2004; Anderson & Teicher, 2008). For example, salience is heightened to environmental events (Lichenstein, Verstynen, & Forbes, 2016), peer relationships (Kilford, Garrett, & Blakemore, 2016) and rewarding stimuli such as drugs, alcohol & novelty seeking (Steinberg, 2008). Adolescence is also a life period that presents with numerous new stressors that could influence brain development, such as school pressure, the increased importance of peer relationships and the beginning of puberty (Blakemore, 2012).

Researchers have suggested that this 'window of risk' is because of a developmental imbalance between brain regions that are involved in emotion reactivity (e.g., the amygdala in the limbic system), and areas involved in emotion regulation and complex cognition e.g., reasoning (the prefrontal cortex) (Casey & Lee, 2015; Casey, Jones & Hare, 2008; Powers & Casey, 2015). The pre-frontal cortex is the last brain region to reach full maturation and is an area that has been associated with complex cognitive analysis (e.g., planning and decision making), cognitive control of emotions, abstract thought, and evaluation of risk versus reward (Blakemore & Choudhury, 2006; Powers & Casey, 2015). Conversely, the limbic system, which is involved in interpreting and expressing emotions, develops early in adolescence (Casey, Jones & Somerville, 2011). Importantly, the above research suggests that the adolescent brain is functionally different to the adult brain. This is important as it confirms that adult models of depression should not be routinely applied to young people without evidence that this would be appropriate.

1.11.2 Vulnerability factors for developing depression

The development of brain structures is part of normative development and not every adolescent develops depression, therefore other factors must influence the

development of the disorder. There are many potential factors suggested to be involved in why some adolescents develop depression, including, genetic, biological, cognitive, and environmental factors (Alloy, Abramso, Walshaw & Neeren, 2006; Dunn et al., 2011; Jacobs et al., 2015; Joormann, 2010). For example, depression is a familial disorder, with children of depressed parents being 3 to 4 times more likely to develop depression than offspring of non-depressed parents (Garber, 2006; Rice & Rawal, 2012a). A review of genetic epidemiology of depression concluded that although depression was a familial disorder, its development was complex, in that genetic and environmental influences are likely to interact with each other (Sullivan, Neale and Kendler, 2000). Evidence of the interaction between genetics and the environment is supported in genotype studies with adults and adolescents (Vrshek-Schallhorn et al., 2014). The aetiology of depression is clearly complex and both genetic and environmental influences can alter brain development leading to reduced capacity to regulate emotions, and an increased risk for developing psychopathology (Casey & Lee, 2015). The role of cognition as a risk and maintenance factor for depression will be discussed below in more detail as the cognitive theory of depression is most relevant to the current thesis.

1.12 Literature review part 3: The role of cognitive processes in depression

1.12.1 The Cognitive model

The Cognitive Model of depression (Beck, 1967) is an influential and widely used model. Beck based his cognitive model on examination of the clinical material from 50 depressed patients who had received psychotherapy. After comparing patients to healthy controls, it was concluded that a key difference between the individuals were

patterns in negative thinking. The cognitive theory aims to account for, and explain the development and maintenance of depression, and is the basis of a leading evidence-based treatment for depression - Cognitive Therapy (CT) or Cognitive Behaviour Therapy (CBT).

A key element of the cognitive model was the causal role of negative depressogenic beliefs (Beck, 1967). The model proposed that negative thinking was a causal factor in depression, rather than simply a consequence, in that biased acquisition and processing of negative information affects the development and course of depression. Beck, (1967) argued that early life adversity plays an important role in the development of depressive schemas, which can later be activated by internal and external negative events (i.e., negative schemas can lay latent until activated). Beck also suggested that depressed cognitions can be activated in response to an interpretation of an event, rather than the event itself. Beck, (1967) grouped depressed individuals' negative thoughts into three areas; negative thoughts about the self, the future and the world. The 'self' refers to how an individual thinks about themselves i.e., as worthless or inadequate. The component 'the future' refers to negative thinking patterns that a patient has about their future i.e., being full of suffering. The component 'world' refers to how an individual interprets the world around them in their day-to-day life i.e., their life being full of defeat and continuous obstacles.

The presence of a negative view of the self is supported in depressed youth. For instance, depressed adolescents endorse more negative self-referential adjectives than healthy participants (Auerbach, Stanton, Proudfit & Pizzagalli, 2015; Orchard, Pass & Reynolds, 2016), indicating that depressed adolescents have a negative view of themselves, thus supporting this aspect of the cognitive model.

Negative cognitions of the self, the world and the future (i.e., the negative cognitive triad) in depression are thought to drive negative thinking and other cognitive biases (i.e., dysfunctional information processing) seen in depressed individuals, including biases in autobiographical memory processing (Beck, 1967; Dalgleish & Werner-Seidler, 2014).

1.12.2 Information processing biases in depression

Cognitive models of depression (e.g., Beck, 1967; Beck & Bredemeier, 2016; LeMoult & Gotlib, 2018) have proposed that depression impairs the information-processing system, and depression is characterised by a range of information processing biases including domains of interpretation, attention and memory (Clark, Beck & Alford, 1999). The way individuals' process information can influence their emotional responses. Biased processing of emotional material ("cognitive biases") and deficits in processing non-emotional information ("reduced cognitive control") are hypothesised to play a role in the aetiology of depression (Joorman & Gotlib, 2008; Joorman 2010; Oliver et al., 2019). A range of negative cognitive biases in depression have been reported across the lifespan (Gotlib & Joorman, 2010; Platt, Waters, Schulte-Koerne, Engelmann and Salemink, 2017; Oliver, Pile, Elm & Lau, 2019).

Platt et al. (2017) and Oliver et al. (2019) reviewed empirical research on information processing biases in young people with depression and found the most consistent evidence for interpretation biases, attention bias and difficulty retrieving specific autobiographical memories.

Interpretation bias refers to the tendency to interpret ambiguous cues in a negative way. For example, adolescents with depression are more likely to interpret ambiguous scenarios as negative compared to healthy controls (e.g., Orchard, Pass &

Reynolds, 2016) suggesting that, in line with the cognitive model, depressed children and adolescents show a negative interpretation bias. Interpretation biases have also been positively correlated with the severity of depression symptoms in youth (Reid, Salmon & Lovibond 2006; Micco, Henin & Hirshfeld-Beck, 2014**)**. However, it has been suggested that some of these findings may be because of anxiety rather than depression symptoms (Platt et al., 2017; Oliver et al., 2019).

Attention bias refers to the tendency to attend to, or have difficulty disengaging from, negative information. Although earlier studies found limited support for attention bias in adolescents (e.g., Dalgleish et al., 2003), it has been suggested that this may be due to limited sample sizes (Platt et al., 2017). More recent studies suggest that depressed youth (when compared to non-depressed youth) show an attention bias to negative (mostly sadness related) stimuli but do not have an attention bias to neutral stimuli (e.g., Hankin, Gibb, Abela & Flory, 2010).

Platt and colleagues (2017) reviewed evidence for memory bias in depressed youth. They found that most studies examining memory bias used free-recall or recognition tasks to assess if youth with depression tend to recall negative (versus positive) stimuli from a previous encoded set of words (or stories). The majority of these studies used a self-referent encoding task which involves presenting participants with a list of positive and negative adjectives and asking them to rate how much each word describes them. Participants are then asked to recall as many of the words as possible in a given timeframe. Some studies have tested free recall memory using emotional words (i.e., depression or threat related words) or used recognition tests of emotional stories (i.e., depressed teenagers were hypothesised to recognise more negative than positive stories). Overall, they reported inconsistent findings across a

range of studies examining memory biases towards negative information. An early study found support for memory bias, children and adolescents with depression had increased recall of negative (versus positive) self-referent adjectives (Zupan, Hammen & Jaenicke, 1987). Neshat-Doost et al. (1998) assessed memory bias through both a recall task and a recognition task. A bias in memory recall of negative adjectives (versus positive) was found in depressed youth, however there was no evidence of memory bias during the recognition task. Further, Gencoz et al. (2001) assessed recall of adjectives in youth who had been admitted to a psychiatric hospital and found that lower recall of positive adjectives (but not enhanced recall of negative adjectives) predicted depression symptoms. Three studies in depressed youth found no evidence of memory bias (Hammen & Zupan, 1984; Dalgleish et al., 2003; Timbremont, Braet, Bosmans & Van Vlierberghe, 2008). For example, Timbremont et al. (2008) assessed free recall of self-referent words in currently, previously, and never depressed children and adolescents following a mood induction procedure and reported no group differences. Further, Dalgleish et al. (2003) found no evidence of memory bias for negative words in a sample of clinically depressed compared to non-depressed youth. Consequently, the evidence provides a mixed picture for memory bias to negative adjectives.

A memory bias that is better supported by empirical evidence in both depressed adults and adolescents is overgeneral autobiographical memory. Autobiographical memory is a different type of memory, referred to as episodic memory. This is memory for past events and personal knowledge about such events e.g., places, events, and associated emotions. This memory bias is the focus of the first two studies in this thesis and thus will be described in more detail in section 2.3.2.

1.12.3 The role of cognitive control and depression

More recently cognitive researchers have recognised a relationship between general cognitive deficits (i.e., deficits in executive control) and cognitive biases (i.e., the biased processing of emotional information) and depression (e.g., Kaiser et al., 2003; Joormann, 2005; LeMoult & Gotlib, 2018).

Cognitive control or executive control, which is largely influenced by the development of the prefrontal cortex, is essential for optimal functioning and develops throughout childhood and adolescence. Executive control is an umbrella term for cognitive processes that are needed to govern behaviour and control emotions (Snyder, Miyake & Hankin, 2015). Cognitive control involves 'executive' functions that are required to process information and moderate behaviour. Miyake et al. (2000) proposed a model of executive functioning comprising of three separate (but related) elements; i.e., inhibition, working memory and shifting. 'Inhibition' refers to the ability to deliberately suppress pre-potent (dominant) responses to achieve a more appropriate task-relevant response. 'Updating/monitoring working memory representations' refers to the monitoring of incoming information while evaluating the relevance of information and discarding of old information. 'Shifting 'or 'cognitive flexibility' refers to the ability to switch between tasks (Miyake et al., 2000) and is thought to require both inhibition and working memory (Diamond, 2013).

A recent review by Oliver et al. (2019) found limited evidence that young people with depression symptoms had a general cognitive deficit (i.e., in executive functions); however, study findings are inconsistent and need further investigation. For example, a review of the executive control literature concluded that further studies were needed to assess potential difficulties in working memory, sustained attention, planning

and decision making (Vilgis, Silk & Vance, 2015). The mixed results in this area have been suggested to be due to differences in depression severity levels (Oliver et al., 2019). This is illustrated by Holler, Kavanaugh & Cook (2014), who compared findings in executive functioning in depressed adolescents to a clinical control group. Young people were classified as either having 'major depression' (i.e., severe MDD) or 'minor depression' (i.e., less severe MDD), and executive function outcomes were compared to an outpatient control group (i.e., a group of adolescents with other diagnoses such as anxiety and ADHD). Adolescents in the major depression group had significantly lower performance scores on measures of both working memory/simple attention and cognitive flexibility, whereas adolescents in the minor depression group had lower performance on only the working memory/attention task, compared to controls. These findings suggest that executive dysfunction increases as depression severity increases (Holler, Kavanaugh & Cook, 2014).

Furthermore, it has been hypothesised that difficulty controlling negative information in working memory may underlie the cognitive biases and maladaptive emotion regulation strategies (such as rumination) that are commonly found in depression (Joorman & Gotlib, 2010; LeMoult& Gotlib, 2018). Executive control plays a key role in determining the information entering and being discarded from working memory. Therefore, for optimal working memory functioning, flexible control over information in working memory is required by limiting initial access into working memory (inhibition) and expelling information that is no longer relevant (updating). The biased acquisition and processing of information has been suggested to influence the aetiology and the course of depressive episodes (Beck 1967; LeMoult & Gotlib 2018). However, the causal and maintaining role of cognitive biases and other cognitive

deficits needs to be better understood (Orchard, Pass & Reynolds, 2016; Synder, 2013; Synder et al, 2015). A greater understanding of the potential role of executive control in adolescents with depression may help to explain why cognitive biases develop or are maintained in depression.

1.13 Literature review part 4: Overgeneral autobiographical memory bias and potential underlying mechanisms

1.13.1 Overgeneral autobiographical memory

Overgeneral autobiographical memory (OGM) refers to the difficulty of retrieving details of personal events stored in autobiographical memory. Autobiographical, or personal memories are essential for adaptive functioning because they are needed to regulate emotions and to develop and consolidate self-identity (e.g., Bluck, Alea, Habermas & Rubin, 2005). Specific memories are used when thinking about difficult situations, in order to help problem-solving and make plans for the future (Jing, et al., 2016). OGM in adults has been associated with several impairments in depression including problem solving, difficulty imagining future events and greater rumination (Dalgleish & Werner-Seidler, 2014). Because adolescence is a critical period for developing the sense of self, planning for the future, and pursuing goals relating to these plans, it is likely that disruptions in retrieving autobiographical memories during this period may have particularly adverse impacts on current and future well-being.

Autobiographical memory has been conceptualised as a system that provides access to personally relevant episodic memories from the past and to self-related semantic knowledge (Conway & Pleydell-Pearce, 2000). The self-memory model

(Conway & Pleydell-Pearce, 2000) describes the processes involved in the construction and recall of an autobiographical memory. This model describes an interaction between the knowledge base (self-related event information stored in memory that is built over a lifetime) and the 'working self' (an executive process that guides information encoding and retrieval depending on current goals) to influence what information is encoded and retrieved. According to the self-memory model (Conway & Pleydell-Pearce, 2000), this knowledge base is organised hierarchically into 'levels', with each level differing in its degree of abstraction and detail. Information within each level is activated to form a memory (Figure 1). The broadest (top) level consists of general knowledge about a time in an individual's life (e.g., "when I was at university"). Subsequent levels include more detailed events (e.g., "attending first year seminars"), until it reaches the most event-specific knowledge (e.g., "the time when we had to measure ourselves and I was the shortest in my seminar group").

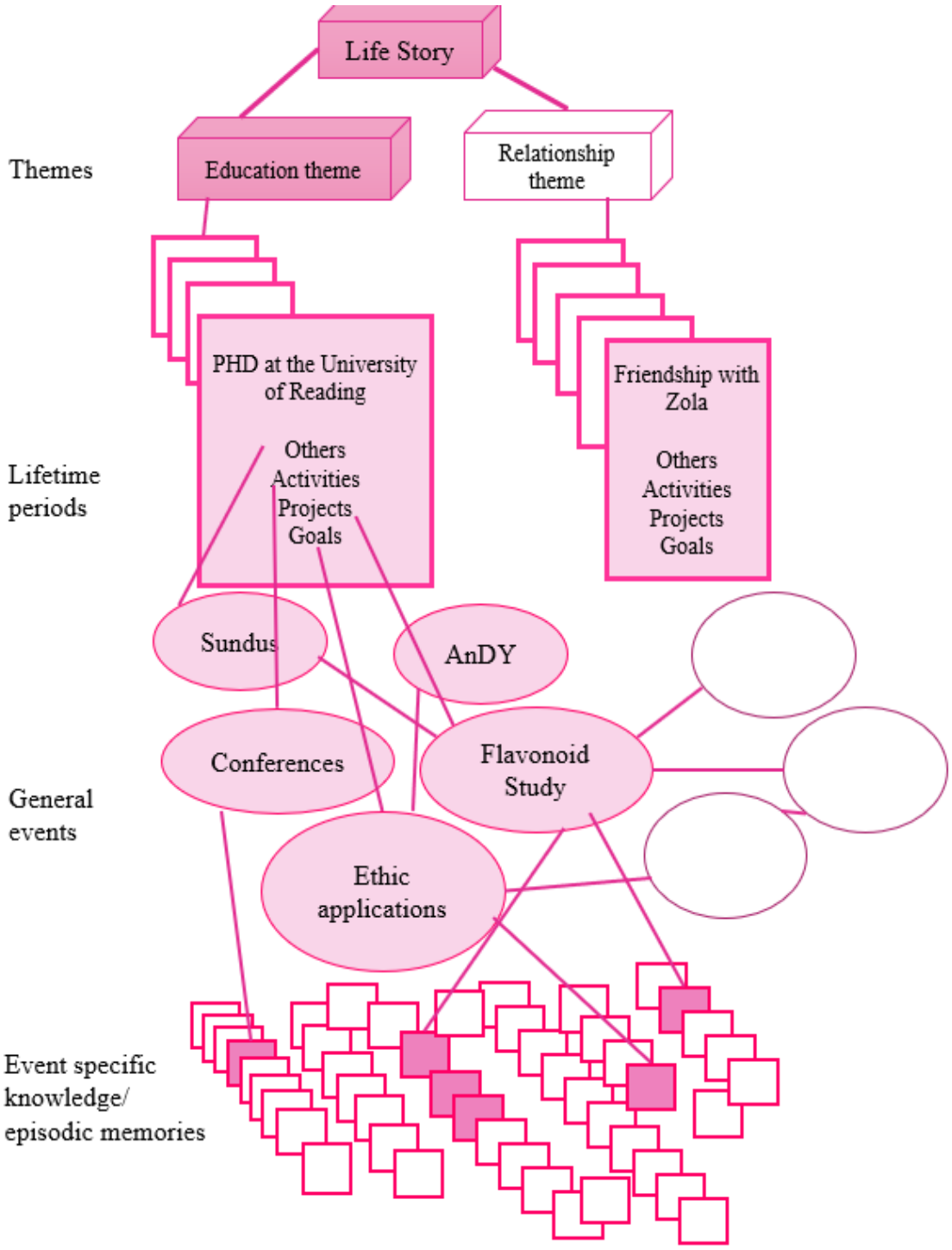

Figure 1. The self-memory model. The image is re-constructed from Conway & Pleydell-Pearce (2000).

The hierarchical organisation of autobiographical knowledge allows memories to be retrieved and combined in several ways. For instance, a specific autobiographical memory can be retrieved through directive or generative retrieval (Conway & Pleydell-Pearce, 2000). Directive retrieval occurs when a cue in the environment is sufficient to immediately activate event-specific knowledge. Generative retrieval, on the other hand, requires an effortful 'top-down process', in order to retrieve a specific autobiographical memory. During this effortful search, broad information is first activated (e.g., the lifetime period in which the event is likely to have occurred), followed by general information (a body of events that fall into the search category e.g., occasions when I have felt isolated), which then (typically) activates event-specific self-knowledge (Conway & Pleydell Pearce, 2000). Thus generative retrieval of a specific autobiographical memory is influenced by cognitive and motivational processes (Rawal & Rice, 2012b). For instance, higher cognitive (or executive) processes (e.g., working memory and inhibitory control) influence the likelihood that activated representations are consistent with search criteria (e.g., to the cue word "party"). According to the self-memory model (Conway & Pleydell-Pearce, 2000) OGM occurs if a generative search is disrupted before activation is able to reach the bottom, most content-specific level and episodic level, of the hierarchy.

1.13.2 Assessing overgeneral memory

OGM has been assessed in several, diverse ways. For instance, in non-clinical participants, the Minimal Instructions Autobiographical Test (Mi-AMT) (Debeer, Raes & Hermans, 2009) is often used because of its reported sensitivity in finding OGM in non-clinical groups (for a full review of all OGM tests please see Griffith et al., 2012). However, the Autobiographical Memory Test (AMT) (Williams & Broadbent, 1986) is

the most common method for assessing OGM in clinical populations (Ros et al., 2018). Although other variations exist, the original AMT consists of participants being presented with 10 cue words (5 positive and 5 negative). Participants are asked to recall a specific autobiographical event that the word reminds them of within 60 seconds. Participants are told that the memory can be important or not, and from a long time ago or recently. However, the event they remember must have happened on one day only. From the memories that each participant recalls, OGM can be assessed as an index of the number of memories that do not include specific details. Overgeneral memories are then also coded as either being 'categoric' or 'extended' memories. Categoric memories are events that have occurred on multiple occasions, and extended memories are memories of events that lasted longer than a week. 'Reduced autobiographical memory specificity' (rAMS) can also be recorded, which refers to autobiographical memories with limited details.

1.13.3 OGM and adolescent depression

There is robust evidence that OGM is a stable characteristic in adolescents at risk of depression, in those with current depression and in those who have repeated episodes of depression (Hitchcock, Nixon & Weber, 2014a). Hitchcock et al. (2014a) systematically reviewed 17 studies of OGM in children and young people with elevated symptoms of depression. Most (i.e., 14 of the 17 studies) found evidence of a positive relationship between OGM and depression symptoms with moderate to large effect sizes overall (Hitchcock et al., 2014a). In addition to this a recent review of cognitive processing difficulties in adolescent depression found that OGM had the most robust support out of the various information processing deficits that characterise depression in youth (Oliver et al., 2019).

Early research on OGM and depression in teenagers compared young people with depression or another mental health difficulty to a 'healthy' control group. For example, Swales, Williams and Wood, (2001) recruited 26 adolescents from an inpatient unit with a mixture of different diagnoses (e.g., conduct disorders, depressive disorder, social phobia and anorexia nervosa), and compared them to a control group of 24 healthy adolescents. OGM was significantly greater in the clinical group and the level of depression symptoms was significantly correlated with OGM. Vrielynck, Delpus & Philippot (2007) assessed OGM in 15 clinically depressed 9-13-year-olds, 25 with a history of any psychiatric disorder and 20 with no history of a psychiatric disorder. Depressed youth had significantly higher OGM than those with other or no psychiatric disorders when controlling for depression symptoms, lifetime traumatic events, verbal IQ and verbal memory.

1.13.4 OGM and youth at-risk of developing depression

There is evidence that adolescents who are at risk of developing depression have difficulty retrieving specific autobiographical details. This has been replicated in a number of at-risk samples, such as those with a history of depression (Park, Goodyear & Teasdale, 2002; Kuyken & Dalgleish, 2011a), individuals at familial risk (Rawal & Rice, 2012a) and adolescents with high neuroticism scores (Kuyken & Dalgleish, 2011b). Kuyken and Dalgleish (2011a) recruited adolescents who had recovered from depression and found that they retrieved more overgeneral memories to negative cue words than never-depressed adolescents, groups were matched for gender, age and current depression symptoms. This suggests that OGM may be a trait, rather than state, feature of depression. Similarly, Sumner et al. (2011) found that in teenagers aged 16-18 years with a history of depression and reduced memory specificity, predicted

depression symptoms following an interpersonal stressor over a period of 16 months. Their findings highlight the importance of OGM in recurrent depression but only in the context of high levels of chronic interpersonal stress, thus some of the effects of OGM may be strongest in higher levels of stress.

Rawal and Rice (2012a) reported that increased OGM predicted the onset of depressive symptoms one year later in a large group of teenage girls with familial risk of depression. Kuyken and Dalgleish (2011b) identified an 'at-risk' sample, on the basis of their scores on a measure of neuroticism in 179 community adolescents. Adolescents with high neuroticism scores recalled a greater proportion of overgeneral compared to specific memories to negative cue words (Kuyken & Dalgleish, 2011a). Moreover, the severity of depression symptoms mediated the relationship between neuroticism and OGM retrieval, indicating that OGM is present in adolescents at risk of developing depression (Kuyken & Dalgleish, 2011). OGM, therefore, may be a trait-like vulnerability to developing depression rather than being a consequence of depression. This means that examining the mechanisms of OGM, especially in adolescence (a period of heightened risk for depression) may help to understand cognitive processes that maintain the disorder, and have the potential be used to prevent or treat depression.

1.13.5 The CaR-FA-X model (Williams et al., 2007)

Based on the self-memory model Conway and Pleydell-Pearce (2000), Williams et al. (2007) proposed that OGM is caused by and maintained by three mechanisms: capture and rumination (CaR), functional avoidance (FA), and impaired executive control (X). Studies that have tested the CaR-FA-X mechanisms in adolescents are discussed below. The CaR-FA-X model (see figure 2) was first developed to explain OGM in clinically depressed adults (Williams et al., 2007) however, most of the

research that has been conducted to understand the CaR-FA-X model in adolescents has been with community samples.

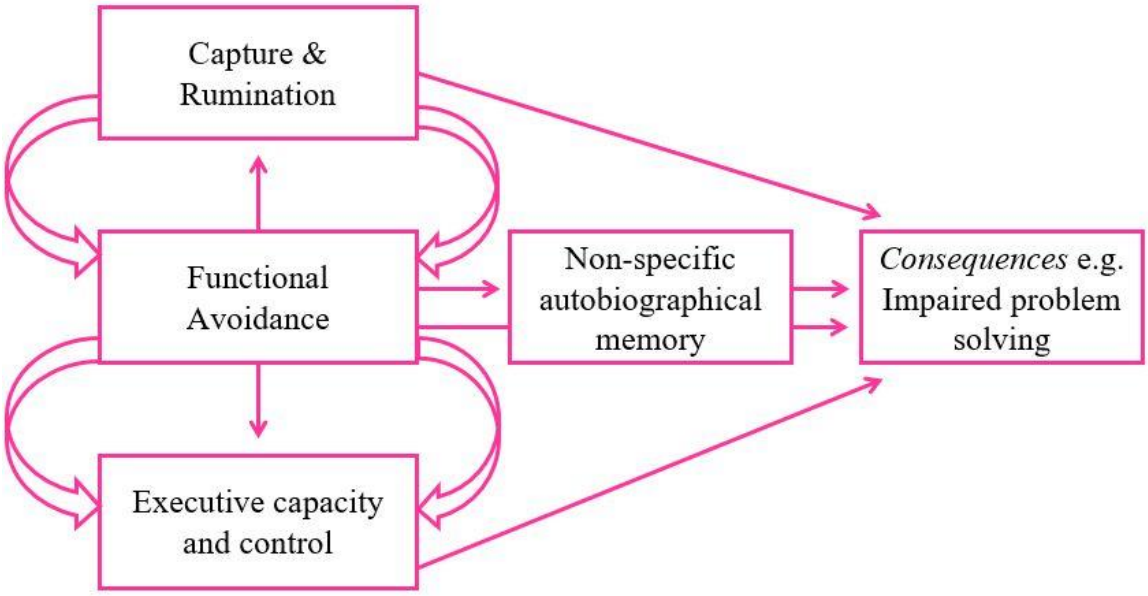

Figure 2. The CaR-FA-X model. The image is re-constructed from Williams et al., (2007).

1.13.6 Capture and Rumination (CaR)

Capture and rumination (CaR) refer to the idea that information that is relevant to the self tends to capture our attention, is distracting, and can lead to thinking about the information in a repetitive, circular or 'ruminative' way. Rumination is a strategy that people with depression often use to regulate their emotions (Compare, Zarbo, Shonin, Van Gordon, & Marconi, 2014). Williams et al. (2007) proposed that capture of attention and/or rumination uses up executive resources and therefore interferes with the ability to retrieve autobiographical memories and thus leads to overgeneral memory.

'Capture' of attention tends to be attracted to emotionally rich information (e.g., I am / was sad) which is typically stored at the top of the self-memory model hierarchy (Conway & Pleydell-Pearce 2000; Williams et al., 2007). If attention is captured in this way, then information is activated across the hierarchy rather than down (Sumner, 2012), which has been referred to as 'mnemonic interlock' (Williams, 1996). Specifically, this is when abstract general self-representation activates other general self-representations rather than activating specific episodic details.

The capture of attention of negative information (e.g., I am / was sad) may also activate ruminative processes (Williams et al., 2007). In addition, individuals who tend to ruminate are more likely to become 'captured' and remain at an early stage of retrieval, thus resulting in the retrieval of an OGM (Williams et al., 2007). Rumination also disrupts the autobiographical retrieval process because activating high level general memories (rather than specific memories) results in the search for a specific memory being terminated (Williams et al., 2007). Further, rumination leads to a fixation on problems and their consequences rather than active problem solving (Nolen-Hoeksema, 1991; Nolan-Hoeksema, 2000). Rumination then prevents individuals from activating adaptive strategies to repair mood (Donaldson & Lam, 2004). In the non-clinical populations rumination increases from late childhood into adolescence, and females may have a tendency to ruminate more than males (Rood, Roelofs, Bogels, Nolen-Hoeksema, & Schouten, 2009).

Rumination has been associated with the onset, maintenance, and severity of depression both in children and adolescents (Abela, Brozina & Haigh, 2002; Kuyken, Watkins, Holden & Cook, 2006). Although often measured as one construct, there are thought to be at least two sub-types of rumination that differ in terms of adaptiveness.

The first is brooding rumination, which is drawing attention to problems and their consequences (Treynor, Gonzalez & Nolan-Hoeksema, 2003). Treynor et al. (2003) suggest that brooding is a maladaptive strategy associated with higher levels of depression. Reflective pondering, on the other hand, is a more adaptive problem-solving strategy i.e., actively thinking about and understanding problems (Treynor et al., 2003). The depression literature suggests that in clinical populations reflective pondering and brooding ruminative thinking perpetuate each other, minimising any difference between them (Joorman, Dkane & Gotlib, 2006). Therefore, the majority of studies in this area tend to examine rumination as one construct, measuring both brooding and reflective pondering.

There is evidence to suggest that the rumination element of the CaR mechanism may be specific to OGM in depression. This stems from studies indicating that, 1) capture, but not rumination, affects memory specificity in healthy adolescents (e.g., Schoofs, Hermans & Raes, 2012) and, 2) rumination is related to OGM in adolescents with, but not without, depression symptoms.

1.13.6.1 Capture and Rumination in non-clinical participants

Schoofs et al. (2012) found support for the capture, but not the rumination element in healthy teenage community adolescents. To test if self-evaluative information captured attention, either low or high discrepant cue words (i.e., words that were self-descriptive) were used for autobiographical memory generation. Brooding rumination was measured via a questionnaire (Ruminative Responses Questionnaire; Treynor, Gonzalez, & Nolen-Hoeksema, 2003). They found that in two groups (i.e., from two separate studies), a lower proportion of specific memories to high discrepant

cue words compared to low discrepant, and more categoric memories in response to high, compared to low, discrepant cues. This suggests that when cues were relevant to the self, attention was captured thereby resulting in OGM, thus supporting the capture element of the CaR mechanism. However, memory specificity did not differ between low and high ruminators (Schoofs et al., 2012a.b). Whilst these results offer support for the capture, but not the rumination element of the CaR mechanism, this might be because this study examined healthy, and not depressed, adolescents.

1.13.6.2 Capture and Rumination in adolescents with depression symptoms

In a sample of 123 young people Smets, Griffith, Wessel, Walschaerts and Raes, (2013) found evidence to support the rumination element of the CaR-FA-X model in young people with high levels of depression (depression was measured via the Beck Depression Inventory II; Beck, Steer & Brown, 1996). Participants with low and high levels of depression completed the AMT before and after a self-discrepancy induction. The self-discrepancy induction involved participants rating 50 single-word characteristics. They were asked to rate each word for the degree to which they would like to possess the characteristic and subsequently the extent to which they currently possess the characteristic. Self-discrepancy induced rumination was significantly correlated with OGM but only in the high depression group. These findings suggest that participants with elevated depression symptoms became more overgeneral in their memories after self-evaluative information captured their attention and that this activated ruminative processes.

Park, Goodyer & Teasdale, (2004) assessed adolescents with current MDD or in partial remission from MDD (n=75), non-depressed psychiatric participants (n=26) and

community controls (n=33). They assessed depression symptoms and OGM following an induced rumination condition and a distraction condition. Following rumination, the severity of depressed mood (measured via the Mood and Feelings Questionnaire; Costello & Angold, 1988) increased in both the MDD group and the control group. However, rumination increased the number of overgeneral memories only in the depression group and this effect was only seen in response to negative cue words, suggesting that, in the depressed participants, rumination increased negative overgeneral autobiographical memories (Park et al., 2004).

Taken together, the evidence suggests that the capture element of the CaR mechanism is found in healthy adolescents and that the rumination element might be specific to depression (Park et al., 2004). However, given the limited number of studies that have explored the relationship between CaR and OGM in adolescents with depression symptoms further studies are needed to clarify this relationship.

1.13.7 Functional Avoidance (FA)

Functional avoidance refers to a cognitive avoidance strategy that minimises negative affect (Williams, 1996; Sumner, 2012). The CaR-FA-X model proposed that when the specific details of an event evoke negative emotions depressed individuals will then avoid further exploration of that event (Williams et al., 2007). Williams et al. (1996) suggested that this might initially occur in response to a traumatic event and then become habitual and generalise to other memory searches, be they positive or negative (Williams et al., 2007). Functional avoidance may therefore take time to develop and be helpful (in terms of avoiding distressing memories) for some individuals. It may also become inflexible and a habitual response (Williams et al., 2007). The role of functional avoidance has mostly been inferred by the finding that

OGM is impaired in individuals who have experienced trauma or stressful life events, and thus may suggest that functional avoidance develops as a coping strategy (Warne, Collishaw & Rice, 2019). This means that rather than measuring avoidance directly, researchers examining functional avoidance have measured trauma and assumed that OGM following trauma is indicative of functional avoidance.

A recent systematic review (Stewart, Hunter & Rhodes, 2017) evaluated the CaR-FA-X mechanisms and trauma exposure in children and adolescent populations. Sixteen studies examined whether exposure to trauma was associated with OGM. The results from 11 relevant studies supported the hypothesis that adolescents who had experienced trauma were more likely to retrieve overgeneral memories than those who had not been exposed to trauma (Stewart, Hunter & Rhodes, 2018). However, because the results of five studies did not support the hypothesis that adolescents exposed to trauma have OGM, this suggests that OGM (and functional avoidance) is not always a consequence of exposure to trauma. Furthermore, Kuyken, Howell and Dalgleish (2006) assessed OGM in depressed adolescents with a history of trauma, depressed adolescents without a history of trauma, and never depressed adolescents but with a trauma history. Both of the two depressed groups retrieved significantly more overgeneral memories than the never depressed group. However, depressed adolescents with a reported trauma history retrieved fewer overgeneral memories than those young people with depression with no reported history of trauma. Therefore, exposure to trauma alone may not explain the development of OGM in depression (Moore & Zoellner, 2007) and OGM can be a function of depression over and above the influence of an early trauma (Kuyken et al., 2006).

Unfortunately, very few studies have directly assessed functional avoidance in adolescents with depression symptoms. Of these, Gutenbrunner, Salmon and Jose, (2019) examined OGM and the CaR-FA-X model in a longitudinal study of 323 community youth. Their participants completed measures of depression, OGM and avoidance each year for four years. At time point 1 the mean age of participants was 12.8. They were split into sub-groups dependent on their trajectories of change on a depression measure across four testing points. Two groups were formed, a 'low symptoms group' (N = 176) and a group with elevated symptoms of depression that increased over time (N =147), referred to as the 'medium increasing group'. Originally the authors had a separate group of adolescents with higher symptoms of depression but as this was only 26 young people they were included in the medium group. For young people in the 'medium increasing group', higher avoidance at time point 3 predicted a higher proportion of overgeneral memories at time point 4. While this supports the hypothesis that functional avoidance of specific memories is used to regulate affect, it is important to note that across participant groups depression levels were low. This study highlights the importance of testing functional avoidance through a more objective measure (i.e., as a measure of general avoidance) in adolescents with a higher severity of depression symptoms to confirm a relationship between OGM, cognitive avoidance and depression.

Overall, the role of functional avoidance needs further examination in adolescent depression to understand the potential relationship between OGM and functional avoidance in youth with depression symptoms and adolescents with clinical depression.

1.13.8 Reduced Executive Control (X)

Williams et al. (2007) argued that difficulties in executive control can hamper an autobiographical search strategy at several different levels of retrieval. This mechanism of the CaR-FA-X model may be of particular importance in adolescent depression because deficits in cognition are common symptoms of major depressive disorder (Orchard, Pass, Marshall & Reynolds, 2017). The components of executive control (i.e., working memory and inhibition) are explained in section 2.3.3. For the successful retrieval of specific autobiographical memories, working memory and inhibition skills are needed (Conway & Pleydell-Pearce, 2000). Reduced working memory can reduce the ability to hold and update autobiographical information that has been retrieved. Impaired inhibition may make it more difficult to filter out irrelevant autobiographical material, which in turn is likely to capture attention, thus prematurely truncating the memory search (Conway & Pleydell-Pearce, 2000; Williams et al., 2007). When assessing executive control and OGM many researchers have tested verbal fluency (i.e., a broad measure of executive control; Dalgleish et al., 2007). Both working memory and inhibitory control are required for this task because it requires the ability to organise retrieval, initiate and maintain a search, as well as the ability to inhibit irrelevant responses (e.g., Swan & Carmelli, 2002).

1.13.8.1 Reduced executive control in participants recruited from the community

Most research with adult participants supports the hypothesis that there is reduced executive control and that this often leads to problems in recalling specific autobiographical memories (Sumner, 2012). Impairments in working memory, inhibition, and verbal fluency have been related to OGM across a variety of tasks and

populations (Dalgleish et al., 2007; Sumner, 2012). Current studies that have tested executive control mechanisms have used very broad executive functioning tests. There is suggestion that separate sub-components of executive control may impact memory retrieval differently (Dalgleish, 2007; Kuyken, Howell & Dalgleish, 2006). For example, difficulty retrieving specific events could be a function of deficits in the ability to inhibit distracting information (Engle, Conway, Tuholski & Shisler, 1995), e.g., inhibiting negative self-relevant information that may be cued by the words given in the autobiographical memory task (i.e., capture errors). Alternatively, OGM could be caused by a difficulty maintaining task goals and updating information in working memory when faced with distracting information (Engle et al., 1999; Dalgleish et al., 2007). Therefore, it is important to understand which specific sub-components are associated with OGM and depressed youth, or if general cognitive control is causal of OGM. This is important because by narrowing down the mechanisms underlying OGM, a more specific potential target for the prevention or treatment of depression may be found.

Almost all studies with young people that investigate the relationship between executive control, OGM, and depression symptoms have recruited participants from the general community. Raes, Verstraeten, Bijttebier, Vasey and Dalgleish (2010), for example, found that inhibitory control mediated the relationship between depression symptoms and OGM in a community group of 10-year-olds. While this provides support for the executive control measure of the CaR-FA-X model, inhibition was measured via a temperament questionnaire. Factor analyses suggest that questionnaires and behavioural executive function tasks do not tap into the same constructs (Samyn, Rowyers, Bijttebier, Rosseel & Wiersena, 2015; Snyder, Miyake & Hankin, 2015) and,

therefore, a behavioural inhibition task might have been a more appropriate measure (Stewart, Hunter & Rhodes, 2017). Hitchcock et al. (2014b) used a behavioural inhibition task in youth who had recently experienced a trauma and found no relationship between depression symptoms, inhibitory control and OGM. They also reported no relationship between OGM and working memory, or verbal fluency. This study recruited youth that had experienced a recent trauma, however, only 3 of the 56 adolescents were above the clinical cut-off for depression. In young people with high depression symptoms, the findings relating to depression, OGM and executive control may be very different.

1.13.8.2 Reduced executive control in young people recruited from clinical services

Valentino, Bridgett, Hayden and Nuttall (2012) tested executive control and OGM in a group of 49 adolescent inpatients. The sample included participants with various primary disorders including major depressive disorder, PTSD and behavioural disorders. Different components of executive functioning were measured using well established behavioural tasks. Inhibition was tested using a colour word interference task (Delis, Kramer, Kaplan & Holdnack, 2004), switching using the Wisconsin Card Sorting Test (Heaton, Chelune, Talley & Kay, 1993) and verbal fluency using both letters and categories (Delis et al., 2004). Severity of depression symptoms significantly predicted OGM. Category fluency was negative correlated with OGM, but contrary to the CaR-FA-X model, switching, letter fluency and inhibition were not correlated with OGM. Valentino et al. (2012) also found that category fluency did not mediate the relationship between depression symptoms and OGM but significantly predicted OGM in isolation i.e., executive control was associated with OGM separately from

depression. This study, therefore, provides partial evidence for the executive control mechanism of the CaR-FA-X model. However, the mixed diagnostic groups make it difficult to infer if any deficits are specific to depression. Kuyken et al. (2006) found no evidence for the executive control mechanism using a measure of verbal fluency. Depressed adolescents retrieved more overgeneral memories than controls but did not differ on verbal fluency.

Overall, there is mixed support for the role of deficits in executive control as mechanisms of OGM and it is unclear which, if any, executive control components underpin OGM. Therefore, more research is required in this understudied area and specifically in depressed samples of adolescents.

1.13.9 Studies that test interactions of mechanisms (CaR-FA-X)

As discussed above, each mechanism of the CaR-FA-X model has often been examined in isolation. However, the CaR-FA-X model proposes that the three mechanisms can work together or in isolation to predict OGM (Williams et al., 2007). Four studies recruited large samples and thus had sufficient power to explore the interactions between components of the CAR-FA-X model. However, it is important to note that the participants of these well powered studies were recruited from non-clinical setting and therefore the results may not generalise to participants who have a diagnosis of depression.

There is evidence that the CaR-FA-X mechanisms do not operate in isolation from each other. For instance, Rawal and Rice (2012a) found that young people at familial risk of depression, who had high rumination and low executive control, were more likely to exhibit OGM one year later (Rawal & Rice, 2012a). This suggests an interaction between rumination and the executive control mechanisms of the CaR-FA-X

model. However, these researchers measured executive control was non-specific (i.e., operationalised as 1 SD below the mean on a block design task) and therefore did not examine specific components of executive control (e.g., working memory or inhibition) that are implicated in the CAR-FA-X model. In contrast, Stewart, Hunter and Rhodes (2018) examined the interaction between rumination and executive control in a group of healthy adolescents. Executive control was negatively associated with OGM but only in individuals with high levels of reflective pondering. This suggests that reflective pondering may have acted as a protective factor between executive control and OGM. Differences in the participants recruited in each study may explain the inconsistent findings. Although both samples were non-clinical, Rawal and Rice (2012b) recruited healthy, but 'at-risk' adolescents who had a parent who had a history of depression. This group have been found to have less specific retrieval than youth with parents with no history of depression (Woody, Burkhouse & Gibb, 2015). Thus this might explain why Rawal and Rice (2012b) found a significant interaction between rumination and executive control and Stewart et al. (2018) did not. Furthermore, two studies in non-clinical youth reported no interaction effects between rumination, and measures of working memory capacity and working memory updating (Hitchcock et al., 2014b). However, OGM as a function of depression may have different underlying mechanisms than in non-clinical studies (Dalgleish et al., 2005) and therefore further work is necessary in adolescents with depression symptoms, and those young people with a clinical diagnosis of depression.

Only one study has assessed all three components of the CaR-FA-X model in adolescents. Gutenbrunner et al. (2019) examined OGM and the CaR-FA-X components 4 times over 4 years in 323 community youth. The sample was split into

depression trajectory groups, with youth that had low or that had medium-high depression symptoms over the four time points. Participants completed the written AMT-I, and the measures for depression symptoms, avoidance and cognitive control were all self-report questionnaires. No longitudinal interactions were reported between the mechanisms in this study and only the functional avoidance mechanism was supported (see description above in section 2.4.7).

The most recent review of the CaR-FA-X model in youth/adolescence (Stewart, Hunter & Rhodes, 2017) concluded that data support the detrimental role of the capture of attention and trauma exposure in OGM. However, support for rumination, avoidance and impaired executive control in youth populations is limited. The high heterogeneity between studies, such as the population, participant ages and various measures, makes it difficult to draw clear conclusions. This is exacerbated by the limited number of studies that have recruited clinically depressed adolescents or adolescents experiencing elevated depression symptoms. Importantly, the CaR-FA-X mechanisms may vary as a function of the type of psychopathology being studied (e.g., Dalgleish et al., 2007) and, due to the differential findings in different populations, it has been suggested that the CaR-FA-X model is not necessarily a 'one-size-fits-all' model (Barnhofer, Crane, Spinhoven & Williams, 2007). The research evidence therefore highlights the need to examine the relationship between OGM and depression in adolescents more specifically. Specific studies that explore and critically test the assertions of the CaR-FA-X mechanisms in adolescents experiencing or at risk of depression will enhance understanding of OGM, the CaR-FA-X model and depression in adolescents.

1.14 Thesis Aims

The aim of this thesis is to contribute to the empirical research literature examining OGM and exploring the underlying cognitive processes that are hypothesised to interfere with the ability to retrieve specific autobiographical memories in adolescents, thereby extending pre-existing evidence of the mechanisms of the CaR-FA-X model in OGM and adolescent depression, which is currently predominantly based on studies with adults (Williams et al., 2007). As identified above, very few studies have tested the CaR-FA-X mechanisms in adolescents, in particular few have assessed all three mechanisms within the same study (i.e., capture and rumination, functional avoidance and reduced executive control), and no published study has, to date, reported a study that assesses the three mechanisms either in adolescents with elevated levels of depression, or in young people with a diagnosis of depression. Consequently, it is unclear which of the underlying cognitive processes may be important to OGM and depression in young people. Furthermore, it has been suggested that sub-components of cognitive control (i.e., working memory and inhibition) may have different contributions to OGM in depression (Dalgleish et al., 2007). However, as illustrated above, the research on OGM in young people has resulted in conflicting results and has inadequately assessed the executive functioning component of the CaR-FA-X model. Therefore, the research reported in this thesis aims to explore the sub-components of executive control in adolescent depression and thereby expand current knowledge of this disorder in youth and help inform new prevention and treatment strategies.

Four papers are included in this thesis. Although the initial aim was to test OGM and explore the potential underlying mechanisms proposed by the CaR-FA-X model,

the research reported in Papers 1 and 2 identified both OGM and working memory processing as a specific deficit in young people with elevated depression symptoms and youth with a diagnosis of depression. Therefore, working memory impairment could be a target for prevention and treatment of depression in adolescents and this led to a secondary aim, i.e., to explore potential ways to enhance working memory in adolescents.

1.15 Principle Questions

1.15.1 Is there empirical support for the CaR-FA-X model of over general memory in adolescents?

Paper 1: A Test of the CaR-FA-X Mechanisms and Depression in Adolescents Published in Memory.

As discussed above (section 2.4.1), there is evidence to suggest that adolescents with high levels of depression retrieve more overgeneral memories than healthy controls. However, all three mechanisms of the CaR-FA-X model have not yet been explored together in youth who have both elevated depression scores and difficultly producing specific memories. Therefore, in Study 1 young people with elevated and low levels of depression were recruited. They were assessed on measures of rumination (both brooding and reflective pondering sub-types), functional avoidance and executive control (i.e., working memory, inhibition and verbal fluency). Based on previous research and in line with assumptions from the CaR-FA-X model (Williams et al., 2007),

the study hypotheses were;

i) OGM will be significantly higher in the elevated group compared to adolescents with minimal symptoms of depression. If this hypothesis is supported then,

ii) One or more of the cognitive processes that are described in the CaR-FA-X model of OGM (i.e. rumination, functional avoidance of negative affect, and impaired executive control) will be significantly higher in the elevated group compared to age and gender matched controls with low levels of depression.

1.15.2 2.6.2 Is there empirical support for the CaR-FA-X model of overgeneral memory in adolescents with a diagnosis of depression?

Paper 2: Overgeneral Memory Bias and the CaR-FA-X Mechanisms in Depressed and Anxious Adolescents

Manuscript submitted to Journal of Abnormal Child Psychology.

There is limited evidence to support the application of the CaR-FA-X model in children and adolescents. The results are inconsistent, samples do not include young people with a diagnosis of depression and, critically, no study has included a clinical control group. Including a clinical control group is a stronger test of the model because young people who are recruited with elevated symptoms of depression, or who are 'at risk' of depression, are very likely to include individuals who have, or are at risk of, other mental health problems. In particular, depression is often co-morbid with anxiety disorders (Tharpar, Collishaw, Pine & Tharpar, 2012) and OGM is specific to depression and not anxiety (Rawal & Rice, 2012a). It is therefore important to test the model in a sample of young people with depression and one with anxiety disorders.

Therefore, in Paper 2 all components proposed by the CaR-FA-X were assessed in adolescents with a diagnosis of major depressive disorder who also had difficulty retrieving specific memories. Non-specific effects of distress and related mental health problems were controlled by comparing the depressed young people to two control groups, one with a diagnosis of one or more anxiety disorders (but not depression), another who were a 'healthy' community group of young people with very low self-reported levels of depression.

Two hypotheses were tested in this study;

i) OGM will be significantly higher in the depressed group than in the clinically anxious or community control groups. If this hypothesis is supported then,

ii) One or more of the cognitive processes that are described in the CaR-FA-X model of OGM (i.e. rumination, functional avoidance of negative affect, and impaired executive control) will be significantly higher in the depressed group than in the anxious control and the non-clinical control groups.

1.15.3 2.6.3 Paper 3: What are the effects of working memory training on children and adolescents? A review of meta-analyses

Paper 3: A meta-meta review of the effectiveness of working memory training in children and adolescents.

Manuscript in preparation.

The findings from studies 1 and 2 identified a depression-specific deficit in working memory. It is possible therefore that improving working memory deficits could be a potential avenue for helping depressed youth. One way to do this could be to enhance working memory through working memory training; however, it was firstly important to evaluate the effectiveness of this type of intervention. Therefore, in Paper

3 we wanted to evaluate the efficacy of working memory interventions in children and young people. Studies that have tested the effectiveness of working memory training in young people are typically small and underpowered, and the findings are inconsistent. There are several meta-analyses of the effectiveness of working memory training. These vary in important ways including the criteria used to select studies, which studies were included, and the outcome variables that were tested. Therefore, in Paper 3 we conducted a meta-meta review i.e., a review of existing meta-analyses. This allowed for stronger conclusions about the effectiveness of working memory training for children and young people and provided a clearer understanding of whether cognitive functioning improved following training, and which variables potentially moderate the effects of training. Therefore, the purpose of Paper 3 was to review, critically evaluate and discuss the methods and results of existing meta-analyses of the effectiveness of working memory training with children and adolescents. Additionally, the review includes an evaluation of the current meta review and includes suggestions for future research.

1.15.4 What is the effect of a 4-week dietary supplement of wild blueberries on the symptoms of depression in young people?

Paper 4: Effect of 4 weeks daily wild blueberry supplementation on symptoms of depression in adolescents

Published in The British Journal of Nutrition.

Based on the conclusions of Paper 3 (i.e., the limited effects following working memory training), we assessed another way that may have the potential to improve working memory in youth. There is evidence in both children and adults to suggest that

dietary flavonoid intake has beneficial effects on executive control (e.g., Lamport, Dye, Wightman, 2012; Barfoot et al., 2019).

Moreover, a recent review concluded a potential association between diet and depression in adolescents (Khalid, Reynolds & Williams, 2016), and there is emerging evidence for a potential relationship between flavonoid intake and mood. It has been suggested that this possible relationship may be mediated through the enhancing effects of flavonoids on executive control (Vauzour, Vafeiadou, Rodriguez-Mateos, Rendeiro, & Spencer, 2008). However, as highlighted in Chapter 6, all of the studies assessing the effects of flavonoids on mood or cognition have been completed with either children or adults.

Therefore, we conducted a randomised, double-blind, placebo-controlled experiment to test the effect of consuming a flavonoid-rich wild blueberry drink daily for 4 weeks on symptoms of depression, anxiety, transient affect and executive control (i.e., working memory and inhibition performance) in healthy adolescents.
Two hypotheses were tested in this study;

i) Participants in the flavonoid condition would report decreased depression symptoms and increased positive affect (i.e., transient mood) compared to adolescents in the placebo condition.

ii) Adolescents in the flavonoid condition would show increased cognitive performance on working memory and inhibition tasks compared with a placebo control group (while controlling for baseline cognition performance).

The findings from this study are presented in separate sections; the results for Hypothesis 1 (i.e., the effects on mood) are reported in Paper 4 (Chapter 7) and the

results for Hypothesis 2 (i.e., the effects on cognition) are presented in an addendum (Chapter 8).

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2 Chapter 3 Paper 1: A test of the CaR-FA-X mechanisms and depression in adolescence

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A Test of the CaR-FA-X Mechanisms and Depression in Adolescents

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Abstract

People who have depression have difficulty recalling specific autobiographical information (Sumner, 2012). This is called overgeneral autobiographical memory (OGM) and is associated with the development and persistence of depression. To replicate and extend previous research OGM was assessed in youth with elevated depression and findings compared to healthy adolescents. Williams and colleagues (2007) proposed that OGM is maintained by three mechanisms: capture and rumination (CaR), functional avoidance (FA), and impaired executive control (X), and integrated these into the CaR-FA-X model. There is limited and inconsistent evidence for the applicability of the CaR-FA-X model in youth with depression symptoms. We hypothesised that adolescents with elevated symptoms of depression who also had reduced memory specificity would also show evidence of one or more of the CaR-FAX mechsnims compared to community controls. We recruited 29 young people aged 12-17 with elevated symptoms of depression and 29 with minimal symptoms of depression, matched for gender and age. After controlling for IQ, adolescents with elevated depression retrieved fewer specific memories, ruminated more, and had poorer working memory and verbal fluency than adolescents with minimal depression. The groups did not differ on measures of inhibition or functional avoidance. Additional analysis revealed that greater overgeneral memory recall was associated with higher levels of rumination and poorer working memory and verbal fluency performance. These results confirm that there is a relationship between low mood and OGM in young people. Findings also suggest that youth with OGM also show impaired working memory and verbal fluency and may have cognitive interference due to rumination.

Key words: overgeneral memory, memory specificity, adolescents, CaR-FA-X, depression

Introduction

Depression is a common mental health problem across the life span (Angold, Costello, Worthman, 1998) and the incidence of depression appears to peak during adolescence (Green, McGinnity, Meltzer, Ford & Goodman, 2005). Depression during this period of life is associated with many adverse impacts e.g., impaired social functioning, (Groeben, Perren, Stadelmann & von Klitzberg 2011) and poor academic achievement (Fergusson, Boden & Horwood, 2007; Verboom, Sijtsema, Verhulst, Penninx, & Ormel, 2014). Further, experiencing depression in adolescence is related to long term health difficulties including repeated episodes of depression (Lewinsohn, Allen, Seeley & Gotlib, 1999) and future development of mental health problems (Boden, Fergusson, & Horwood, 2007). For these reasons, it is important to establish if and how depression in adolescence is distinctive from depression that occurs later in life.

Across the lifespan, depression is associated with impaired recall of significant personal memories (Williams et al., 2007). Personal, or 'autobiographical' memories are important to our well-being and functioning; they help develop our sense of identity, identify goals and make decisions (Conway & Pleydell-Pearce, 2000). In addition, it has been proposed that the ability to retrieve specific autobiographical memories guides present and future thoughts and behaviours, and helps us regulate emotions (Raes, Hermans, de Decker, Eelen & Williams 2003). Because adolescence is a critical period for developing our sense of self, to make plans for the future, and to pursue goals relating to these plans, we expect that disruptions in retrieving autobiographical memories during this period may have particularly salient impacts on current and future well-being.

The inability to retrieve specific memories is termed overgeneral memory (OGM: Williams and Broadbent, 1986). Overgeneral memories can be split further into 'extended' memories that last longer than a day (e.g., "on my holiday in Spain") and 'categoric' memories, which are a group of repeated events (e.g., "parties with friends"). The association between OGM and depression in adults has been replicated many times (Sumner, 2012). There is a standard method of assessing OGM through the use of the Autobiographical Memory Test (AMT) (Williams & Broadbent 1986). Participants are asked to retrieve a specific memory in response to a cue word (Williams et al., 2007) e.g., 'happy'. In adults, OGM predicts the course of depression independent of current depression and is associated with longer recovery time (Brittlebank, Scott, Williams & Ferrier, 1993; Herman et al., 2008) Individuals in remission of depression also retrieve more overgeneral memories than never-depressed controls (Williams et al., 2007). OGM is therefore considered an important cognitive marker in depression and has led clinical researchers to speculate about potential interventions to improve memory specificity (Dalgleish & Werner- Seidler 2014; Oliver, Pile, Elm & Lau, 2019). Moreover, specific memories are also used when thinking about difficult situations, to problem-solve, and make plans for the future thus finding ways to help ensure retrieval of specific memories has many positive impacts (Jing, Madore & Schacter, 2016).

OGM is also observed in depressed young people (e.g., Park, Goodyer & Teasdale, 2002; Swales, Williams, & Wood, 2001) and may increase vulnerability for the development and reoccurrence of depression (Kuyken & Dalgleish, 2011; Park et al., 2002). For example, in girls with a family history of depression, OGM predicted the onset of depressive symptoms one year later (Rawal & Rice, 2012a). Similarly, Sumner et al. (2011) found that in teenagers, aged 16-18 years with a history of depression,

reduced memory specificity predicted the reappearance of symptoms following an interpersonal stressor over a period of 16 months. Therefore, assessing depression-related OGM and investigating the possible underlying cognitive processes could be important in youth depression research and inform if the original CaR-FA-X model can be applied to youth. For example, if we can identify cognitive deficits in depressed youth who also have reduced memory specificity, these deficits could be a focus for larger studies that aim to test relationships between OGM and the CaR-FA-X components.

The self-memory model (Conway and Pleydell-Pearce 2000) describes the processes involved in the construction and recall of an autobiographical memory. The model describes an interaction between a knowledge base (information stored in memory that is built over a lifetime) and the "working self" to influence what is encoded and retrieved. The knowledge base is organised in a hierarchy. The broadest (top) level of the hierarchy consists of general knowledge about a time in an individual's life (e.g., when I was at secondary school). Subsequent levels include more detailed events (e.g., attending psychology classes at school) and event-specific knowledge (e.g., when my psychology teacher told us about when she studied psychology at university). This organization of personal knowledge allows memories to be extracted and combined in many ways (Conway & Pleydell–Pearce 2000). The working self is an executive process that guides information encoding and retrieval depending on our current goals. For example, the goal in the Autobiographical Memory Test is to find a specific memory relevant to the cue word, the working self therefore interacts with the knowledge base to retrieve the required information.

A specific autobiographical memory can be retrieved through both directive and generative retrieval (Conway and Pleydell-Pearce 2000). Directive retrieval occurs

when a cue in the environment immediately activates event specific knowledge. Generative retrieval requires an effortful 'top-down' process firstly activating broad information then general, which then activates event specific self-knowledge. According to the self-memory model (Conway and Pleydell Pearce 2000), OGM occurs if the search is disrupted before activation is able to reach event specific knowledge.

Generative retrieval is when, in response to a request to retrieve a specific memory to a cue word, the individual forms a mental model of that request and then compares and evaluates memories activated during the against the model (Birch & Davidson, 2007). This effortful process of retrieving a specific autobiographical memory is influenced by cognitive and motivational processes (Rawal & Rice, 2012b). Higher cognitive (or executive) processes (e.g., working memory, inhibition) influence the likelihood that activated representations are consistent with the search criteria (e.g. a cue word "party"). Generative retrieval requires both the capacity to search for memory representations and to evaluate these against the memory model. Therefore, information needs to be held and updated in working memory and any irrelevant search information needs to be ignored (Conway & Pleydell-Pearce 2000; William et al., 2007). The most comprehensive model to explain why this generative search process gets truncated at more general levels for people with depression is the CaR-FA-X model (Williams et al., 2007).

Based upon the self-memory model (Conway & Pleydell Pearce, 2000) Williams et al. (2007) developed The CaR-FA-X model to help explain OGM in adult depression. This proposed that three mechanisms, not necessarily mutually exclusive, interfere with the retrieval of specific memories and therefore cause may OGM. The key aim of this study is to explore these mechanisms in youth with who have difficulties retrieving specific memories, and depression symptoms, to clarify if the

concept of the CaR-FA-X model translates to younger populations. These are 'capture and rumination' (CaR), 'functional avoidance' (FA), and reduced executive control (X). Capture and rumination (CaR) refers to the idea that self-relevant information 'captures' cognitive resources and activates ruminative processing. Rumination involves focusing on abstract thoughts about the self in a repetitive way and is a common maladaptive emotion regulation strategy in depression (Schafer, Naumann, Holmes, Tuschen-Caffier & Samson, 2017). Although often measured as one construct, there is evidence of two sub-types of rumination (brooding rumination and pondering rumination) that differ in terms of adaptiveness. Treynor, Gonzalez and Nolen-Hoeksema (2003) suggest that brooding is a maladaptive strategy associated with higher levels of depression, and that reflective pondering is a more adaptive, problem-solving strategy. In relation to the self-memory model (Conway, Playdell & Pearce, 2000) rumination uses cognitive resources and is, thus hypothesised to interfere with the ability to retrieve specific information about the past (Nolen-Hoeksema 2000; Treynor et al., 2003). Functional avoidance (FA) is a method of affect regulation since general memories are thought to result in less affect than specific memories. This mechanism is similar to those proposed in previous theories of OGM, where OGM was a strategy used by children who have experienced negative events as a way of avoiding the negative affect by avoiding autobiographical content associated with distress (Williams, 1996; affect regulation theory). Executive control (X) refers to a broad range of cognitive strategies used to manage, focus on, plan and carry out tasks (Roberts, 1998). Executive functions are required for successful cognitive control (Funahashi and Andreau, 2013). Miyake et al. (2000) proposed a model of executive functioning comprising of three separate (but related) elements, i.e., inhibition, working memory and shifting. 'Inhibition' refers to the ability to deliberately suppress pre-potent

(dominant) responses to achieve a more appropriate task-relevant response, 'updating and monitoring working memory representations' refers to the monitoring of incoming information while evaluating the relevance of information and discarding of old information (i.e., updating the current information stored in working memory), and 'shifting' relates to the switching between tasks (Mikaye et al., 2000). Deficits in executive control are hypothesised to interfere with the retrieval of specific autobiographical memories because of the need to hold information in mind (updating working memory) and ignore irrelevant information (inhibition). Therefore, if these skills are impaired the memory search is more likely to truncate before retrieving the requested specific autobiographical information (Conway & Pleydell-Pearce 2000; Williams et al., 2007).

The majority of research assessing the CaR-FA-X mechanisms and OGM are large community studies that allow examination of relationships between OGM and CaR-FA-X components. It has been suggested that 250 participants is an adequate sample size to detect small effects in these types of studies (Austin, Raes & Takano, 2018). However, these large studies use self-report measures of key variables and recruitment is most often restricted to participants from the community who are not experiencing elevated depression symptoms. This latter point is particularly important because there is evidence that OGM is only associated with future depression in young people who are at risk of depression (Crane et al. 2016; Gutenbrunner et al., 2018). An alternative strategy, and one which we use in this paper, is to assess memory specificity and the CaR-FA-X components in young people who have elevated depression symptoms. Logically, if reduced memory specificity is caused by one or more cognitive processes outlined in the CaR-FA-X model (Williams, et al., 2007) depressed young people who have OGM will report high levels of rumination, avoid distressing

autobiographical memories, and have executive functioning deficits. Whilst this research design makes it more difficult to recruit large samples, smaller samples make it feasible to administer more precise measures of key CaR-FA-X components (e.g., executive functioning) and thus avoid the methodological problems associated with self-report. Therefore, by conducting this exploratory study we may learn about beneficial procedures for assessing depression, OGM and the associated cognitive mechanisms.

Consistent evidence supports the components of the CaR-FA-X model in adults with OGM and depression, and individuals who have experienced trauma (Sumner et al., 2012). However, relatively few studies have explored the mechanisms in adolescents and those that have, produce mixed findings (Stewart, Hunter & Rhodes, 2017). Most youth research has been conducted with healthy youth, and no study has explored the three mechanisms together in adolescents with elevated depression symptoms who also have difficulty retrieving specific memories. Therefore, preliminary findings may help pave with way for larger future studies. The few studies that investigate the relationship between OGM and the CaR-FA-X elements in youth with depression symptoms will be reviewed below.

One experimental study with 134 youth with depression symptoms reported evidence for the Capture and Rumination mechanism. Authors, experimentally induced rumination which lead to increased OGM in depressed adolescents but not in a non-depressed control group (Park, Goodyer and Teasdale 2004). Smets, Griffith, Wessel, Walschaerts & Raes (2013) compared capture and rumination in 246 non-clinical community youth people with high and low levels of depression symptoms. Participants completed the AMT before and after a self-discrepancy induction. Following the experimental induction, rumination was significantly correlated with

OGM only in the high depression group. Participants with higher depression symptoms became more overgeneral in their memories after self-discrepant information captured their attention.

Functional avoidance (of a detailed memory) is hypothesized to emerge as a way of coping with negative emotions associated with exposure to a traumatic event. Memories are thought to be retrieved in a less specific manner to avoid the emotions triggered by recalling negatively charged autobiographical information (Williams, 2007). Therefore, the memory search stops at the general level to avoid activation of negative emotion (Conway and Playdell Pearce 2000; Williams, 2007). Over time this emotion regulation strategy becomes habitual and occurs for all memories, whether positive or negative (Williams et al., 2007). In adolescents, Functional Avoidance has been associated with OGM in traumatic situations though not necessary in youth with depression symptoms (Neshat Doost, Yule, Kalantari, Rohollah, Dyregrov & Jobson, 2014; Ogle et al., 2013). Young people who had direct exposure to early trauma retrieved more OGM compared to young people who did not have exposure to early trauma (Hitchcock, Nixon and Weber 2014). However, Kuyken, Howell and Dalgleish (2006) found that OGM can also occur in the absence of trauma. They compared autobiographical memory retrieval between three groups: depressed adolescents with a history of trauma, depressed adolescents without a history of trauma, and never depressed adolescents. Depressed young people without a history of trauma had more OGM than either of the other groups, suggesting that exposure to trauma alone does not explain the development of OGM. Few studies have assessed the role of functional avoidance in youth depression and the measurement is imperfect. Some researchers (e.g., Gutenbrunner et al., 2019) have used self-report questionnaires to assess functional avoidance; however, this requires participants to be aware that they are using

cognitive avoidance strategies, which seems problematic. Other researchers deduce that functional avoidance is associated with OGM because memory retrieval is impaired in individuals who have experienced trauma and are thus assumed to avoid trauma memories (Warne, Collishaw & Rice, 2019). However, functional avoidance can occur in the absence of trauma which makes this method flawed (Kuyken, Howell and Dalgleish, 2006). As far as we are aware, no previous study with adolescents has investigated the relationship between OGM and a more general cognitive avoidance strategy in youth with elevated depression symptoms, although avoidance i.e., of internal psychological events, is a maladaptive emotion regulation strategy in young people with depression symptoms (Schafer, Naumann, Holmes, Tuschen-Caffier & Samson, 2017). In the current study we assess functional avoidance as a cognitive avoidance strategy (Sumner, 2012; Williams 2007) by evaluating the level of negative autobiographical material recalled in response to the Autobiographical Memory Test.

Research on executive control (X) and OGM in adolescents with depression is inconclusive (Hitchcock et al., 2014). Deficits in executive functioning are of particular interest as difficulties with inhibition and working memory have been associated with depression in youth (Baune, Czira, Smith, Mitchell & Sinnamon, 2012) and are associated with adverse changes in thoughts, emotions and behaviour (Diamond 2013; Joormann & D'Avanzato, 2010). Further, executive control deficits are related to depression-related information processing biases and maladaptive emotion regulation strategies (LeMoult & Gotlib, 2019). Therefore, identifying cognitive deficits in youth with depression may develop our understanding of general cognitive processing in depression, and thus help understand problems with autobiographical memory retrieval. In relation to memory retrieval, Raes, Verstraeten, Bijttebier, Vasey and Dalgleish (2010) found that inhibitory control (a subcomponent of executive control) mediated

the relationship between depression symptoms and OGM in a community group of 135 10 year old's. Inhibition was measured via a temperament questionnaire, but for a clearer understanding of the mechanism of impaired executive control studies need to include a behavioral inhibition task (Stewart, Hunter & Rhodes, 2017), and to examine executive control in older adolescents. Additionally, conflicting evidence concerning which aspects of executive functions affect memory retrieval. For example, Kuyken et al. (2006) found no relationship between verbal fluency and OGM whereas Valentino et al., (2012) reported no connection with OGM and inhibition (via a colour word inference task) in trauma related youth. Thus, further work is needed to understand which aspects of executive functioning are reduced in depression as these may be driving memory difficulties in depressed youth.

There is some evidence that the components of the CaR-FA-X model may not operate in isolation from each other. Rawal and Rice (2012a) found that young people at familial risk of developing depression who had high rumination and low executive control were more likely to exhibit OGM one year later (Rawal & Rice 2012a). However, the measure of executive control used was generic and did not examine unique components of executive control that are thought to influence specific memory retrieval, including updating information in working memory and inhibiting irrelevant thoughts and memories (Sumner, 2012). Another recent study by Stewart, Hunter & Rhodes (2018) examined the interaction between rumination and executive control in a group of 149 healthy adolescents. Executive control was negatively associated with OGM but only in individuals with high levels of reflective pondering. These findings highlight the notion that different sub-types of rumination may play diverse roles in autobiographical memory retrieval and should be assessed separately in the community. No study has yet included all components of the CaR-FA-X model with young people

in one study, and more research is needed in both clinical and nonclinical youth populations (Stewart, Hunter, & Rhodes, 2017). Therefore, the current study is to explore the CaR-FA-X cognitive mechanisms in community teenagers with depression symptoms and OGM, compared to community teenagers with very low levels of depression symptoms who do not have difficulty retrieving specific memories.

The current evidence investigating OGM and the CaR-FA-X mechanisms in youth is limited; the results are inconsistent; studies do not include all three mechanisms or separate executive control components. Moreover, self-report measures are commonly used, and rumination sub-types are seldom included, and data have rarely been collected from youth with depression symptoms. Overall, there is not sufficient evidence to suggest the CaR-FA-X model of OGM can be applied to depressed youth who have difficulty retrieving specific personal memories. Therefore, research needs to firstly obtain proof that the dysfunctional cognitive processes posited to cause OGM are exhibited in adolescents with depression symptoms. Although unlike most studies described above, the current study cannot directly test OGM and the CaR-FA-X components (due to inadequate power), however investigating all three mechanisms in youth with OGM may be informative for several reasons. 1) findings may highlight important cognitive deficits in youth with OGM and depression, 2) current procedures may detect important methodological factors that can inform future research (e.g., which measures to use) and 3) discover potential targets for prevention and treatment strategies for depression.

In this study our primary aim was to explore the cognitive processes highlighted by the CaR-FA-X model (rumination, functional avoidance, and executive functioning) in adolescents who have elevated symptoms of depression and have difficulty retrieving autobiographical memories. Multiple components of executive functioning (working

memory, verbal fluency, and inhibition) were also included. The components chosen for testing are directly related to the retrieval of overgeneral memory i.e., the ability to inhibit irrelevant thoughts and memories while monitoring and updating information relevant autobiographical knowledge while keeping task instructions in mind.

Based on previous studies of OGM in depression, and considering mechanisms in CaR-FA-X model the study hypotheses are:

i) Adolescents with elevated symptoms of depression will report more overgeneral autobiographical memories than adolescents with minimal symptoms of depression. If this hypothesis is supported then,

ii) One or more of the cognitive processes that are described in the CaR-FA-X model of OGM (i.e., rumination, functional avoidance of negative affect, and impaired executive control) will be significantly higher in adolescents with elevated symptoms of depression.

Method

Design

This was a between-groups design with adolescents recruited from the community. The independent variable was level of depression symptoms ('elevated' or 'low' based on self-reported symptoms). The dependent variables were the number of overgeneral memories retrieved, rumination, functional avoidance, and three aspects of executive control - verbal fluency, inhibitory control (reaction time and errors), and working memory updating. A brief measure of IQ was used as a covariate. For the first hypothesis, the sample size for each group was determined by a power analysis. Power was calculated using a planned analyses using the statistical programme G * power. Based upon the mean between-group effect size of d = 0.86 on overgeneral memory

(i.e. Vrielynck. Delpus & Philippot, 2007; Park et al. 2004), 28 participants were needed in each group. For the second hypothesis, the sample size for each group was determined by a power analysis. A total sample size of 40 gave 80% power to detect a medium effect size (F = 0.4) with multiple comparisons (for the CaR-FAX mechanisms) and three groups. Thus, there was adequate statistical power to detect mean group differences. Therefore, the study is sufficiently powered for both hypotheses.

Participants

Adolescents (N=58) aged 12-18 years were recruited from a pool of 215 participants who were pupils at a high school in England and who completed a measure of depressive symptoms (MFQ; Costello & Angold 1995). Participants were recruited at the screening session if they scored over 27 on the MFQ (5 male, 24 female) or below 12 on the MFQ (5 male, 24 female). Depression symptoms were measured a second time at the testing session using the Brief MFQ. Participants who scored 27 or above at the screening session (via the full MFQ) and scored 13 or above on the brief MFQ were allocated to "elevated depression" group. Participants who scored 12 or below on the full MFQ at the screening session and scored below 13 on the brief MFQ at the testing session were allocated to the "low levels of depression" group. Depression measures were taken twice as the was approximately 2 weeks between screening and testing thus depression scores could have change within this time. All participants remained in the same groups from screening to testing. The mean group scores for both the full and for the Brief MFQ can be found in Table 2 with the other experimental variables.

Groups were also matched on age, t (56) - 0.46, p = 0.65, gender χ^2 (1) = 0, p = 1 and ethnicity, χ^2 (1) = 0.47, p=0.48 and IQ scores t (56) .53, p = .97 (see Table 1).

Table 1

Demographic and descriptive statistics for elevated and healthy community comparison

Characteristic	Group	
	Healthy community (n=29)	Elevated community (n=29)
Age (*M*, SD)	14.65 (1.52)	14.83 (1.36)
Gender (percent female)	82.8%	82.8%
Ethnicity (percent White British)	86.2%	89.7%
IQ scores	93.21 (8.39)	92.00 (8.83)

Measures

Self-report questionnaires

The Mood and Feelings Questionnaire (MFQ; Costello & Angold, 1988). This was used to screen participants and determine eligibility for the study and group allocation. The MFQ is a 33 item self-report measure of depression in children and adolescents with good reliability and moderate validity (Burleson Daviss et al., 2006; Kent, Vostanins, & Feehan, 1997; Wood, Kroll, Moore &Harrington 1995). Each item is rated on a 3-point scale; 0 (not true) to 2 (true). Internal consistency was high (MFQ α= 0.96). A cut off of 27 and above was used to identify clinically significant levels of depression (Wood et al.,1995) and thus membership of the elevated group. MFQ scores of below 12 were used to identify a low depression group. This lower cut off was based on data from a clinical sample of 467 young people with a diagnosis of major

depression (Goodyer et al., 2017) in which no participant with a diagnosis of major depression scored below 13 on the MFQ.

The Brief Mood and Feelings Questionnaire (BMFQ: Angold et al., 1995) This is a 13 item self-report questionnaire to measure depression in children and adolescents. By the time of the research assessment (approximately 2 weeks from the screening participant) it was necessary to measure current symptoms of depression and confirm the allocation to the low depression and high depression groups were correct.

The Rumination Response Scale (RRS; Nolen-Hoeksema & Morrow, 1991). This is a 22-item questionnaire asking participants what they habitually think, do or feel when they experience low mood. The measure has been validated for use with adolescents (Kuyken, Watkins, Holden, & Cook, 2006). Internal consistency was high (RRS α= 0.96). The RRS includes two 5 item sub-scales 'Brooding' and 'Reflective Pondering' that are suggested to measure the two different sub-types of rumination (Treynor, Gonzalez, Nolen-Hoeksema, 2003).

Measures administered by the researcher

The Autobiographical Memory Test (AMT; Williams & Broadbent, 1986). This is a standardised test of autobiographical memory. Participants were asked to provide specific autobiographical memories in response to 10 emotional cue words (Loved, Excited, Relaxed, Lucky, Relieved, Angry, Failure, Hopeless, Lonely, Sad) that were presented in a random order.

Participants were told that the event they remembered could be important or trivial, recent or from a long time ago, but that the memory should be something that happened at a particular place and time. All participants were given an example before starting the test. They were told that if they were given the word 'party', it would be

fine to say: ‘I had a great time at Sara’s party last Saturday’ but that ‘When I go to parties I have a good time’ was not acceptable (because it did not specify a particular place and time). Two practice items were given (happy and sad) to make sure that participants understood the instructions.

The words were adapted from Heron et al., (2012) who carried out research on the psychometric properties of the test. They chose 5 positive and 5 negative words that were judged to be familiar to adolescents. The words were matched for familiarity using the University of Essex Children’s Printed Word Database (Lovejoy, 2003). Positive words were; happy, excited, relaxed, lucky, relieved. Negative words were bored; failure, hopeless, lonely, sad. Heron et al., found that ‘happy’ and ‘bored’ showed poor discrimination in OGM. In this study ‘happy’ and ‘bored’. were replaced with ‘loved’ and ‘angry’ as used by Kuyken and Dalgleish (2011).

Generated memories were tape-recorded and transcribed. Coding was based on the method used by Kuyken & Dalgleish (2011). Two researchers, who were blind to participant’s MFQ score, coded all the memories from each participant from transcripts. Specific memories were defined as events that lasted less than a day. Non-specific memories included extended memories (events that lasted a distinct, but prolonged period of time) and categoric memories (events that had occurred on multiple occasions with no defined time frame). Answers that did not refer to the past and non-responses were coded as ‘not a memory’. Inter-rater reliability between two independent coders, who were blind to group membership of participants, was good $\kappa = 0.78$. Discrepancies were discussed and an agreed code allocated.

Assessment of Functional Avoidance

To assess functional avoidance, memories generated in the autobiographical memory test were coded for positivity and negativity on a Likert scale (-3 for very

negative, 0 for neutral, and +3 for very positive). This index of functional avoidance is based on the hypothesis that functional avoidance is a cognitive strategy used to regulate emotions (Sumner, 2012). Williams et al. (2007) originally defined functional avoidance as "when episodic material threatens to cause affective disturbance" (p.122), and functional avoidance research in adult PTSD shows that OGM is positively correlated with several cognitive avoidance strategies, such as, avoidance of private personal experiences (Schonfeld & Ehlers, 2006). Therefore, theoretically if youth are using OGM as a cognitive strategy to regulate emotions, it is plausible that they may avoid negative autobiographical material, as this is also likely to cause affective disturbance. Further, trauma related research reveals that OGM is positively correlated with several cognitive avoidance strategies, such as, avoidance of private personal experiences (Schonfeld & Ehlers, 2006). It this possible that depressed youth may also be using similar cognitive avoidance strategies. Functional avoidance would therefore be indicated by recall of more positively valenced and fewer negatively valenced memories.

Williams et al. (2007) stated that functional avoidance can occur in response to positive and negative cues; therefore, the valence of response to both positive and negative cue words on the AMT were included. Functional avoidance is therefore indicated by recall of more negatively valanced memories to both negative and positive cue words. Functional avoidance would therefore be indicated by recall of more positively valenced and fewer negatively valenced memories.

Inter-rater reliability between two independent coders, who were blind to group membership of participants, was high κ=0.84. There was no difference in the valence of memories recalled in response to positive and negative cue words so the mean valence across all 10 cue words was used as an index of functional avoidance. The Likert scale

included both positive and negative numbers; therefore 7 was added to all scores to provide data suitable for statistical analysis.

Assessment of IQ

The Wechsler Abbreviated Scale of Intelligence (WASI II; Wechsler, 2011). The WASI II is a brief, well-standardised assessment of intellectual abilities for 6 to 89-year-olds. Two subtests (Vocabulary and Matrix Reasoning) were used to provide an estimate of full-scale intelligence quotient (FSIQ). In the vocabulary subtest, participants were required to define a word that was presented to them orally. The Matrix Reasoning consisted of 30 incomplete matrices presented in a stimulus book. Participants were asked to look at each incomplete matrix and choose one item from a selection of five figures at the bottom of each page to correctly complete the matrix. The WASI has strong psychometric properties, including good test- retest reliability and internal and concurrent validity (Garland, 2005; McCrimmon & Smith, 2013).

Executive function tasks

The Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1976). This was used to measure verbal fluency. Participants were asked to list as many words as possible in 60 seconds that begin with the letters F, A and S. The task requires the ability to organise verbal information, to initiate retrieval, and maintain a search set in working memory and inhibit inappropriate responses (Swan & Carmelli, 2002). Verbal fluency is a standard measure of neuropsychological assessment, with good levels of test-re-test reliability and validity (Harrison, Buxton, Hussain & Wise, 2000).

The Hayling Sentence Completion task (HSC; Burgess & Shallice, 1996). This is a measure of inhibition that detects difficulties in suppressing pre-potent responses. The task involves asking participants to listen to incomplete sentences read by the

researcher (e.g., “London is a very big – ”) and then provide a word that completes the sentence either appropriately (e.g., ‘city’; Part A) or inappropriately (e.g., ‘banana’; Part B). The task has moderate validity and reliability (Strauss et al., 2006) and has been used with adolescents (Robinson, Goddard, Dritschel, Wisley, & Howlin, 2009).

Inhibition in this test is measured in two ways - the number of errors and reaction time. Errors include word endings that finish the sentences appropriately or are associated with the meaning of the sentence. To analyse both measures, raw scores were converted into scaled scores, 8 indicating “good performance” and 1 indicating signs of cognitive impairment (Burgess & Shallice 1996).

The Keep track task (KTT; originally adapted by Miyake et al., (2000) from Yntema (1963)). This is a reliable and valid measure of updating working memory (Thompson & Gathercole, 2006; Conway et al., 2005). Participants were shown a list of six target categories (e.g. animals, furniture, fruit) and exemplars (dog, table, apple), compiled using an updated and extended version of Battig and Montague (1969) norms (Overschelde, Rawson, & Dunlosky, 2004). They were asked to familiarise themselves with the words and make sure they know which exemplar belongs to each category. At the beginning of each trial a single tone was played and several target categories were displayed on the lower half of the computer screen. Fifteen words, including 2 or 3 exemplars from each of six possible categories were then presented serially in a pseudo-randomized order for 2 seconds per word. Target categories remained on the screen during the trial. The task was to recall the last word presented in each of the target categories. Thus participants have to continuously update their working memory for the target categories. After each trial, participants were asked to recall the exemplars used in that trial.

Before the task, participants practiced on two trials with three target categories.

The task itself consisted of four trials with three target categories, four trials with four target categories and one trial with five target categories. The total number of words presented was 33 and the percentage of words recalled correctly was the measure of interest.

Procedure

Two hundred and fifteen students completed the MFQ and rumination questionnaire in their classroom (i.e., the screening session) and indicated that they were willing to take part in further research (126 students from an original screening number of 341 did not want to be involved in future research). Seventy-two students who scored 12 or below, or 27 or above on the MFQ were invited to take part in the research of whom 58 agreed to take part. The interval between screening and testing was approximately 1 to 2 weeks. If adolescents scored 27 or above on the MFQ they were allocated to the "elevated depression group' at the screening section. If they scored 12 or below, they were allocated into the 'low levels of depression' group. Depression scores were assessed again at the start of the testing sessions to confirm young people were in the correct group. To measure depression symptoms at the research session, the Brief MFQ was used as this is shorter and saved time. If participants in the elevated group continued to have elevated depression scores (indicated by Brief MFQ scores above 13) at the testing session, they could continue the study and remained in the same group. If participants in the "low levels of depression" group score below 13 on the brief MFQ at the testing session, they could stay in the same group and continue with the study. All participants remained in the same groups. Please find the descriptive statistics in Table 2.

Individual meetings were arranged with each participant in a quiet room at school, during the school day. Administration of the tasks took between 45-55 minutes.

Participants completed the brief MFQ first. The cognitive tests were then administered in a standardised order; Verbal Fluency, Hayling Sentence Completion Task, Keep Track task, Autobiographical Memory task and the WASI II. All adolescents who completed the research tasks were entered into a prize draw to win a £10 Amazon voucher.

Ethics

The University of Reading Research Ethics Committee provided ethical approval for this study. Written informed consent was obtained from all participants over 16 years, and parental informed consent and adolescent assent were obtained for all participants under 16 years.

Information about the study was given to young people and their parents. All students who agreed to be contacted, met study criteria, and had parental consent (or were over 16 years and consented for themselves) were invited to take part. Before testing began, the study was explained to each adolescent by the researcher. As agreed with the school and with young people and their parents, and in line with the school safeguarding procedures, young people who reported elevated symptoms of depression were identified to a nominated member of pastoral care.

Results

Preliminary Analyses and Analytic Plan

Continuous data were screened in relation to the assumptions of parametric tests (Tabachnick & Fidell, 2007). Where assumptions were violated, confirmatory analyses were conducted by running analyses with 1000 bootstrap samples. All results were consistent, suggesting that the original analyses were robust to the violations of assumptions, so the results based on the original (non-bootstrapped) analyses are

presented for simplicity.

To confirm that young people with elevated depression symptoms at screening were still reporting similar symptom levels at the next research session, depression scores on the Brief MFQ were examined. All participants had levels of depression that were consistent with their screening MFQ scores. Group differences in OGM were examined using an independent samples t-test. Next, group differences on each mechanism of the CaR-FA-X model were examined using multivariate (MANCOVA) analyses of variance, controlling for multiple tests. Group (low depression vs elevated depression) was the independent variable, and executive function, rumination and functional avoidance measures were dependent variables. Because IQ is associated with executive control (Mahone et al., 2002; Arffa 2007), the WASI II IQ was assessed between-groups to ensure any deficits could be attributed to executive control difficulties.

Between group differences in symptoms of depression and IQ

Mean levels of depression symptoms in the elevated group were significantly higher than in the control group (see Table 1). The mean MFQ score in the elevated groups was similar to that reported in a clinical sample of depressed adolescents (Goodyer et al., 2017). The mean IQ score in both groups was average (Shaw et al., 2006) this is illustrated in Table 1.

Table 2

Means and standard deviations for all measures

Measure	Healthy (n = 29)	Elevated symptoms (n = 29)
	M (SD)	*M* (SD)
MFQ (full version)	7.45 (4.27)[a]	37.76 (8.66)[b]
MFQ (brief version)	1.97 (1.45)a	14.93 (3.55)b
OGM	1.59 (1.40)a	3.41 (1.82)[b]
Verbal fluency	31.83 (10.94)[a]	24.93 (8.13)[b]
Working memory	22.21 (4.21)[a]	18.45 (3.96)[b]
Inhibition error	6.41 (1.60)[a]	6.10 (1.86)[a]
Inhibition RT	5.93 (0.26)[a]	5.62 (0.78)[a]
RRS = Brooding	7.76 (2.56)[a]	13.41 (3.32)[b]
RRS = Reflective Pondering	6.31 (1.86)[a]	11.31 (3.86)[b]
FA	7.2 (4.44)[a]	5.6 (2.57)[a]

Note. Corresponding superscripts represent groups that are significantly different, $p<0.05$, same letter subscripts show null significance. MFQ = Mood and Feelings Questionnaire; OGM =

overgeneral autobiographical memory, RT = reaction time, RRS = Ruminative Response Scale, FA = functional avoidance.

Hypothesis testing

The first hypothesis was that adolescents with elevated symptoms of depression would retrieve more overgeneral autobiographical memories than adolescents with low levels of depression. There was a significant between-groups difference in the number of overgeneral memories retrieved, t (56) = 1.37, $p < .001$, d=1.1. As expected, adolescents with elevated depression symptoms retrieved more overgeneral memories than those with low levels of depression (see Table 2). For the second hypothesis, the sample size for each group was determined by a power analysis. A total sample size of 40 gave 80% power to detect a medium effect size (F = 0.4) with multiple comparisons (for the CaR-FAX mechanisms) and three groups. Thus, there was adequate statistical power to detect mean group differences. Therefore, the study is sufficiently powered for both hypotheses.

Descriptive statistics for all measures assessing components of the CaR-FA-X model are presented in Table 2. The CaR-FA-X model was tested in a MANCOVA with group as the independent variable, functional avoidance, rumination and three variables measuring executive control as dependent variables and WASI II as covariate. There was a significant multivariate effect of group F (6, 450) = 7.63, $p < .001$ showing that the depressed and the non-depressed groups significantly differed on the CaR-FA-X components. This was followed up with univariate F tests to examine each element of the CaR-FA-X model separately. There was a significant effect of group on brooding rumination, F (1, 55) = 7.32, $p < .001$ and reflective pondering rumination F (1, 55) = 7.32, $p < .001$; both types of rumination were higher in the group with elevated depression. There was no significant effect of group on functional avoidance, F (1, 55)

= 3.41, *p*=.07). In response to both positive and negative the cue words, adolescents in the elevated depression group did recalled similar levels of positive or less negative autobiographical material compared to those in the low depression group. Participants in both groups provided a wide range of positive and negative memories in response to both positive and negative cue words. There was a significant univariate effect of group on verbal fluency F (1, 55) = 7.32, p = .009, the elevated depression group produced significantly fewer words than the low depression group. There was also a significant group difference in working memory F (1, 55) = 11.90, p = .001; adolescents with elevated symptoms of depression had poorer working memory than the low depressed group. Contrary to the hypothesis there was no significant difference in inhibition between groups, either for the number of errors made F (1, 55) = .450, p =. 51, or for reaction time, F (1, 55) = 3.86, p = .06.

Post-hoc analysis

We also explored associations between the CaR-FA-X components and OGM. There was a significant difference between the healthy and elevated groups regarding the number of overgeneral memories (i.e., the 'healthy' group produced very few overgeneral memories) and therefore OGM was significantly skewed. Therefore, data from both groups (n=58) were combined so that data were more normally distributed and better suited for correlational analysis. Table 3 shows that OGM was positively correlated with rumination (both 'brooding' and 'reflective pondering'), working memory and verbal fluency. There was no association between OGM and functional avoidance. All significant Pearson effect sizes were medium-sized, with the association between working memory and OGM having the largest effect size.

Table 3

Pearson Correlations for total Overgeneral Memories retrieved, Brooding rumination, Reflective Pondering rumination, Functional Avoidance, Working memory score, Inhibition errors scores, Inhibition reaction time scores, and Verbal Fluency.

Variable	*n*	*M*	*SD*	1	2	3	4	5	6	7	8	9
1. Total OGM	58	2.50	1.86	_								
2. Working memory	58	20.34	4.47	-.46**	_							
3. Verbal Fluency	58	28.38	10.17	-.36*	-.31*	_						
4. Inhibition-errors	58	6.36	1.51	-.23	.20	.18	_					
5. Inhibition -RT	58	5.78	.59	-.17	-.01	.18	.50**	_				
6. Functional Avoidance	58	6.43	3.69	-.11	.21	.06	.01	-.09	_			
7. RRS-Brooding	58	10.59	4.10	.35*	-.23	-.09	.01	-.29*	-.46**	_		
8. RRS – reflective pondering	58	8.81	3.92	.36*	-.32*	-.29*	-.10	-.39*	-.29*	.72**	_	

Note. Pearson correlations between total overgeneral memories retrieved, each CaR-FA-X measure and depression symptoms for all participants are presented above (n=58). RRS = Ruminative Response Scale. RT = reaction time. M= mean. SD = standard deviation. * = $p<0.05$. ** = $p<0.001$.

Discussion

This study is the first to explore each mechanism highlighted by the CaR-FA-X model of OGM in the same study with adolescents with high symptoms of depression. As predicted, young people with elevated depression symptoms recalled significantly fewer specific memories than the low depression group. In line with our first hypothesis and previous research (e.g., Hitchcock et al., 2014), young people with higher depression symptoms retrieved a higher number of overgeneral memories compared to a control group. However, they had no deficits in inhibition and there was no evidence of functional avoidance, i.e. they did not report fewer negative or more positive autobiographical memories than young people without depression symptoms. Therefore, the CaR-FA-X model was partly supported.

We also completed exploratory analysis to directly assess potential associations between OGM and the mechanisms, however the sample was underpowered for this analysis so findings should be interpreted with caution. Overgeneral memory retrieval was associated with higher depression symptoms, increased rumination, and poorer working memory.

Both 'brooding' and 'reflective pondering' rumination were associated with OGM retrieval. The CaR-FA-X model does not differentiate between the different aspects of rumination and studies have rarely assessed both types in relation to OGM. However, a recent study in healthy adolescents reported that 'reflective pondering' (not 'brooding') was a moderator in the relationship between executive control and OGM (Stewart, Hunter & Rhodes, 2018**).** However, there was no distinction between the two types in this study which could reflect the sample population. Healthy adolescents within this study showed low levels of rumination in general, thus despite the sub-type it appeared that they did not engage in ruminative thinking. Whereas, although our

depressed group were recruited from the community, they showed clinical levels of depression as measured by the MFQ. Brooding rumination has shown associations with depressive disorders as well as sub-clinical symptoms of depression in adolescence (Burwell & Shirk, 2007; Gibb, Grassia, Stone, Uhrlass, & McGreary, 2012). Therefore, it could be argued that reflective pondering and brooding rumination perpetuated each other within youth experiencing high levels of depression, thus concealing any distinction between them (Joorman et al., 2006).

The associations between OGM and the measures of executive control suggest that retrieval of overgeneral memories were related to poorer working memory and fluency thus supporting the impaired executive control mechanism of the CaR-FA-X model.

To investigate the executive control component of the CaR-FA-X model, we included a broad measure of executive control, verbal fluency, and two sub processes of executive control thought to be involved in the retrieval of a memory search, updating working memory and inhibition (Conway and Pleydell-Pearce 2000). This selection of different executive components reflects the notion that separate executive function components may have different influences on the retrieval search of autobiographical memories (Rawal and Rice 2012b). For example, to retrieve a specific memory it is necessary to inhibit irrelevant memories that come to mind and keep in mind instructions and the aim of the search, thus working memory must be used and updated (Williams et al., 2007). Adolescents who had high depression symptoms had poorer verbal fluency and were less able to update working memory than young people with low depression. The elevated depression group did not differ from the low depression group in their ability to inhibit a verbal response, suggesting that inhibitory control did not interfere with the memory search. This is not consistent with Raes et al., (2010)

who found that self-reported inhibition mediated the relationship between depression symptoms and OGM. However, in the current study, both groups performed well on the measure of inhibition and there was a possible ceiling effect. When participants were asked to give a word that did not make sense at the end of a sentence both groups used similar, successful strategies to help inhibit their initial responses i.e., such as scanning the room for random items.

Inhibition is not a unitary construct (Nigg, 2000) and can be split into behavioural inhibition (the ability to resist acting impulsively) and cognitive inhibition (the inhibition of prepotent mental representations including thoughts and memories). Here we found no group difference on a behavioural inhibition task and previously Valentino et al., (2012) found no association between cognitive inhibition and OGM (on the colour word inference task. However, Raes and colleagues (2010) did report a significant association between overgeneral memory and inhibition as assessed on a self-report questionnaire. Therefore, the relationship between inhibition and OGM in depressed adolescents needs to be investigated further with a more sensitive measure that capture all elements of the construct.

Common symptoms of depression in adolescents include a lack of motivation, concentration and increased fatigue (Goodyer et al, 2017, Orchard, 2016). These more general symptoms of depression are a plausible explanation for deficits in cognitive tasks, including autobiographical memory recall, and executive functioning tasks, which typically require effort and concentration. However, in this study there were no between group difference in IQ, suggesting that deficits in executive control and autobiographical memory specificity were not explained by a lack of motivation, poor concentration, or fatigue.

There was also support for the rumination mechanism of the CaR-FA-X model.

Ruminating (i.e., repetitive and circular thinking about one's problems) uses cognitive resources that are believed to compete with the resources needed to retrieve specific memories. This finding is in line with previous research (Park, Goodyer, Teasdale, 2004) supporting the rumination mechanism within the CaR-FA-X model. There are two types of rumination: 'brooding' and 'reflective pondering'. In our sample adolescents with elevated symptoms of depression engaged more in both forms of rumination compared to healthy controls. Previous research has suggested an interaction between executive control and rumination i.e., when adolescents with familial risk of developing depression had lower executive control and ruminated more, they recalled less specific memories on the AMT (Rawal and Rice, 2012b). We were not able to test the relationship between rumination and executive control due to limited sample size. However, the group differences on rumination and executive control suggests that future work looking at the relationship between these two mechanisms in adolescents with low mood would be worthwhile.

There was no evidence that functional avoidance (i.e., avoiding negative memory content as a cognitive strategy to decrease exposure to negative feelings) was higher in adolescents with elevated depression symptoms. Functional avoidance was measured by coding the valence of the memories retrieved on the Autobiographical Memory Task; if depressed young people were avoiding negative autobiographical content as a way of managing negative affect, we would expect to see less negative content recalled. There was no difference between the groups in terms of memory valence. Therefore, we did not find support for the hypothesis that adolescents with high depression symptoms were functionally avoiding negative material to dampen negative affect. The method used to assess functional avoidance in this study is a new and untested way to assess functional avoidance without validated psychometric

properties. The measure was based on the original definition of functional avoidance, and previous functional avoidance research in Post-Traumatic Stress Disorder (PTSD) patients. Please see page 103 in the methods section for further explanation. Our justification for this functional avoidance measure was that adolescents who use OGM as a cognitive avoidance strategy would also avoid negative memory content, as this is likely to cause affective disturbance and presumably youth would want to avoid this also. Rating the emotional valance of autobiographical memories has good face validity but ratings made by participants of their own memories would improve the measure substantially.

We did not directly measure participants' experience of trauma; to do so in a community sample would present considerable ethical challenges. It is possible that functional avoidance is a specific mechanism only associated with experience of severe trauma – and this is best examined in a clinical setting where appropriate therapeutic support is available if required. We also did not measure for lifetime exposure to negative or positive experiences, which might plausibly differ between the elevated and low risk groups. Specifically, because of increased exposure to negative life events (including possible trauma) young people in the elevated depression group may have had a larger mental 'catalogue' of negative experiences to draw on, and thus their retrieval of memories that did not differ in affective tone from the non-depressed group may reflect a positively biased retrieval. In future, adolescents could be asked to rate the memories themselves in terms of how positive or negative they believe their recollection to be in comparison to other memories they have. This would provide a more precise insight into whether adolescents were avoiding negative autobiographical content. Further, it would be advised for future researchers to include a supplementary strategy to assess cognitive avoidance, such as, a behavioural avoidance questionnaire

to explicitly measure the young person's general avoidance behaviour. Further, including a measure of lifetime exposure to trauma would be a good adjunctive measure to assess functional avoidance such as 'the life's events questionnaire', or 'the impact of events scale to measure' (Stewart, Hunter & Rhodes, 2017).

This study is the first to explore the three components suggested by the CaR-FA-X model with adolescents with elevated depression symptoms, to measure separate executive functions likely to be involved in the impaired executive control mechanism, and to measure both sub-components of rumination. Participants were recruited from a non-clinical population of young people aged 13 to 18 years old so were not help seeking or diagnosed with depression. However, they were assessed using a well-established self-report measure of depression and the groups were clearly distinct in relation to symptom severity but matched well on other salient variables. The elevated depression group reported very high depression symptoms, similar in severity to levels reported in clinical samples (e.g., Orchard et al, 2016), therefore the current results are likely to generalise to other adolescents with high levels of depression symptoms. Well-established measures of rumination, autobiographical memory, and elements of executive control were used. Although a well-established measure was used to assess inhibition, it is important to note recent concerns about the sensitivity of the task, (i.e., the Hayling Sentence Completion Test) that were developed for use with neuropsychological groups, to detect potentially less marked deficits in clinical disorders (Synder et al., 2015). Therefore, possible deficits with inhibitory control should be explored further using more specific and sensitive tests of inhibition e.g., the Stop Signal task (Verbruggen et al, 2008).

The results of this exploratory study make a worthy contribution to OGM research in youth with depression symptoms by complementing pre-existing evidence

which may pave the way to larger more advanced studies. Evidence that youth who have high depression scores and difficulties retrieving specific memories, also have high levels of rumination and deficits in working memory and verbal fluency (thus assessing executive functions associated with OGM and depression may be valuable). Therefore, these preliminary findings suggest that larger more advanced studies that can directly test relationships and potential interactions between depression symptoms, OGM and the CaR-FA-X mechanisms in youth are warranted.

For instance, recruiting larger samples and longitudinal designs, would allow future studies to investigate important research questions. For example, with adequate power, testing multivariate causal relationships through analysis such as structural equation modelling may help identify causal mechanisms between variables. Directly assessing the relationships between cognitive processes (i.e., rumination, functional avoidance, and multiple components of executive control) in youth with depression symptoms would identify if mechanisms caused OGM in isolation, or if interactions between components are disrupting the autobiographical memory search. For example, Rawal and Rice (2012) reported that higher rumination predicted reduced memory specificity but only in youth with low executive control. Although informative, Rawal and Rice (2012) recruited an at-risk sample who were not currently experiencing depression symptoms and used a measure of IQ to assess executive control. Given the current findings of executive control it would be recommended that separate components of executive control are assessed, especially working memory. Moreover, by employing a longitudinal design and recruiting youth with elevated depression symptoms (so that findings are generalisable to a depression population), cognitive processes can be tested at multiple time points. This future research is important because 1) it may provide a better understanding of OGM in adolescent depression i.e.,

by identifying underlying OGM mechanisms that may contribute to the development and maintenance of depression, and 2) has the potential to inform prevention or treatment strategies e.g., interventions targeting working memory may have the potential to reduce depression symptoms and/or rumination.

Additionally, given the limitations of the current functional avoidance measure, an alternative or supplementary measure of cognitive avoidance would be recommended. For example, to explicitly measure general avoidance, researchers could use a behavioural avoidance questionnaire together with the measure used in the current study. However, participants should rate their own memories for how positive or negative they are in comparison to their other memories. An assessment of lifetime trauma exposure and individuals' reactions to those events would also strengthen the assessment of functional avoidance e.g., the life's events questionnaire, or the impact of events scale (Stewart, Hunter & Rhodes, 2017).

Overall, the findings are of theoretical interest because this developmental period marks the onset of most first episodes of depression (Costello, Erkanli & Angold, 2006) as well as significant cognitive development, including the maturation of the prefrontal cortex (Paus, Keshavan, Giedd, 2008; Steinberg 2005). Therefore, understanding key psychological mechanisms associated with depression, such as executive control and rumination, is particularly important because they may also inform the development of new interventions to prevent or treat depression. If impaired cognitive processes and impaired autobiographical memory constitute a vulnerability for the development of depression early identification of these difficulties and targeted interventions may prevent future onset of depression. Likewise, because cognitive processes such as concentration, attention and memory are so critical to educational and occupational functioning and are clearly impaired during episodes of depression these

outcomes should be assessed before and after treatment to ensure that adolescents with depression are fully recovered. If cognitive processes do not improve after routine treatment for depression it may be necessary to develop additional or adjunctive treatments to target these areas alongside interventions designed to improve emotional symptoms of depression.

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3 Chapter 4 Paper 2: Overgeneral Memory Bias and the CaR-FA-X Mechanisms in Depressed and Anxious Adolescents

Overgeneral Memory Bias and the CaR-FA-X Mechanisms in Depressed and Anxious Adolescents

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Abstract

Young people and adults with depression tend to have problems remembering specific autobiographical memories – this is known as overgeneral memory (OGM). OGM may maintain episodes of depression and increase the risk of relapse (Hitchcock, Nixon & Weber, 2014), and improving autobiographical specificity may help reduce depression (Dalgleish et al., 2007). Three cognitive processes are posited to underpin OGM – Capture and Rumination (CaR), functional avoidance (FA), and executive functioning (X) (Williams et al., 2007). There is limited and inconsistent evidence for the applicability of the CaR-FA-X model in youth and this is based mainly on self-report data from participants recruited from the community. We hypothesised that for adolescents with depression and reduced memory specificity, one or more components of the CaR-FA-X model would be elevated, compared with non-clinical controls and anxious controls. We separately assessed OGM and investigated each CaR-FA-X component; rumination, functional avoidance and three aspects of executive functioning in 30 young people with Major Depressive Disorder, 22 with an anxiety disorder (but not depression), and 29 non-clinical controls. As expected, depressed youth had significantly higher OGM than anxious and non-clinical controls. Depressed adolescents ruminated more and had poorer working memory than anxious and non-clinical controls. Depressed and anxious young people had longer reaction times on an inhibition task than non-clinical controls. The three groups did not differ on inhibition errors, functional avoidance or verbal fluency. Therefore, only working memory problems and rumination were specific deficits in young people with depression and OGM. Post-hoc analysis revealed that working memory and rumination significantly predicted OGM independently, however this model was underpowered thus findings should be interpreted with caution. Interventions to improve working memory deficits

and reduce rumination may therefore be valid targets for prevention and treatment of adolescent depression.

Introduction

Depression often emerges during adolescence (Thapar, Collishaw, Pine & Thapar, 2012). Worldwide it is estimated that 2.6 % of young people aged 12-17 years have an episode of depression each year (Polanczyk, Salum, Sugaya, Caye & Rode, 2015). Depression in adolescence is associated with many negative long-term impacts such as increased risk of later episodes in adult life (Johnson, Dupuis, Piche, Claybourne & Colman, 2018), educational underachievement, lower income levels (Claybourne, Varin & Colman, 2019) and suicidal ideation, attempt and completion (Nock et al., 2013). For these reasons, identifying plausible ways to identify those vulnerable to depression and developing targeted prevention and early interventions are priorities for clinical researchers.

A prominent psychological process, which may help inform new interventions for preventing or treating depression is overgeneral memory (OGM; Williams and Broadbent, 1986). OGM refers to difficulty retrieving specific details of autobiographical memories and is a characteristic of adults and young people with depression (Sumner, 2012). A specific memory is a memory of a particular event that does not last longer than a day e.g. "I felt happy when I was dancing with my friends at my 18th birthday party". Two types of OGM have been identified; 'extended' memories (e.g. "on my holiday in Spain") and 'categoric' memories, which are a group of repeated events (e.g. "parties with friends"). OGM interferes with adaptive functioning because specific autobiographical memories are needed to regulate emotions and to develop and consolidate self-identity (Bluck, Alea, Habermas, & Rubin, 2005). Specific memories are also used when thinking about difficult situations, to problem-solve, and make plans for the future (Jing, Madore & Schacter, 2016).

OGM is also associated with the onset and course of depression. Understanding how OGM develops and is maintained is therefore important because this might help inform psychological interventions to prevent or treat problems with OGM. Adolescence is a distinct period of rapid cognitive and emotional development and susceptibility to new mental health problems; therefore, it cannot be assumed that the results of research with adults can be generalised to young people. Most evidence relating to OGM has been collected from adult participants (e.g., Sumner et al., 2012). OGM is also associated with depression in adolescents and may increase the risk of developing depression (Rawal & Rice, 2012a) and the risk of reoccurrence (Park, Goodyer & Teasdale, 2002). Therefore, assessing depression related memory specificity difficulties and investigating the possible underlying cognitive processes, could be important in youth depression research, and help to understand if the CaR-FA-X components are present in youth. For example, if we can identify cognitive deficits in depressed youth who also have reduced memory specificity, larger studies could focus on these cognitive mechanisms when testing relationships between depression, OGM and the CaR-FA-X components.

Conway and Pleydell-Pearce (2000) proposed that autobiographical memories are stored hierarchically, with the most general memories at the top (i.e., most easily accessible level) and with more specific memories organised beneath in layers of increasing specificity. For example, general memories relating to "When I was at school' are higher in the organisation and easier to access than specific memories, (e.g., 'the emotion I felt when I opened the envelope with the results of my final school exams').

OGM is typically assessed by the Autobiographical Memory Test (Williams & Broadbent, 1986). Participants are presented with cue words one at a time and for each

they are asked to remember a particular autobiographical event related to the word (i.e., a specific memory). To recall a relevant autobiographical memory the individual must hold the cue word in mind, form a mental model of the request, search for, retrieve, compare and evaluate memories that are activated, and then select a memory that fits the request. Therefore, information needs to be held and updated in working memory and irrelevant search information needs to be ignored (Conway & Pleydell-Pearce 2000; Williams et al., 2007). This process is called generative retrieval (Conway & Pleydell-Pearce 2000) and requires an effortful 'top-down' process that is influenced by cognitive and motivational processes (Rawal & Rice, 2012b). In OGM, this generative search process gets truncated at more general levels of autobiographical memory. The most comprehensive model to explain why this is the case is the CaR-FA-X model (Williams et al., 2007).

Based upon the self-memory model (Conway & Pleydell Pearce, 2000) Williams et al. (2007) developed The CaR-FA-X model to help explain OGM in adult depression. This proposed that three mechanisms, not necessarily mutually exclusive, interfere with the retrieval of specific memories and therefore cause difficulties retrieving specific memories. By exploring these mechanisms in youth with a depression diagnosis who have trouble retrieving specific memories, may help to clarify if The CaR-FA-X model generalises to adolescents with depression. The mechanisms within The CaR-FA-X model are 'capture and rumination' (CaR), 'functional avoidance' (FA), and 'reduced executive control' (X). Rumination is typically elevated in young people and adults who have depression (e.g., Schafer et al., 2017). In relation to retrieving autobiographical memories it is thought that self-relevant information 'captures' cognitive resources and activates ruminative processing which then derails memory retrieval. 'Functional Avoidance' (FA) refers to a cognitive avoidance strategy

(Sumner, 2012), whereby to regulate mood and minimise negative affect, individuals avoid remembering things that have been aversive, traumatic or otherwise distressing (Hallford, Austin & Takano, 2018). Williams et al. (2007) suggest that this avoidance of negative memories interferes with the individual's ability to retrieve specific memories. Finally, problems with 'Executive' control interfere with recall of specific autobiographical memories (Williams et al., 2007). Reduced executive resources have been proposed to disrupt remembering specific autobiographical memories. Impaired *inhibition* makes it difficult to filter out irrelevant autobiographical material and focus only on relevant material (Conway & Pleydell-Pearce, 2000; Williams et al., 2007). Problems with *working memory* reduce the ability to hold the request in mind and continuously update relevant autobiographical information.

The CaR-FA-X model was originally developed to explain OGM in depression and trauma related psychopathology (Williams et al., 2006; Williams et al., 2007) thus the model is not specific to depression and mechanisms may vary as a function of the type of psychopathology being studied (e.g., Dalgleish et al., 2007). Differential findings across populations (e.g., depression, trauma related OGM and healthy individuals, Sumner et al., 2012), suggest that the CaR-FA-X model is not necessarily a 'one-size-fits-all' model (Barnhofer, Crane, Spinhoven & Williams, 2007). This therefore highlights the need to explore OGM and the underlying components in depressed adolescents specifically. Specific studies that investigate the assertions of the CaR-FA-X mechanisms in adolescents experiencing depression will heighten understanding of OGM, the CaR-FA-X model, and depression in adolescents.

Less research has examined the CaR-FA-X model in relation to young people (compared to adults) and only a subsample has focused on young people with depression symptoms (Hitchcock, Nixon & Weber, 2014). Further, no study has

explored the mechanisms together in adolescents with clinical depression or compared to a clinical and community control. As in research with adults, most studies examine one or two components rather than all three mechanisms. For example, Park, Goodyer and Teasdale (2004) induced rumination in depressed and non-depressed adolescents and found that this increased OGM only in depressed participants. Rawal and Rice (2012) assessed rumination and executive control in adolescents who were at familial risk of depression. Rumination predicted later OGM, but only in those with low executive control. There is weak support for the role of inhibition in OGM with one study reporting that inhibitory control in children (measured via a questionnaire) mediated the relationship between depression symptoms and OGM (Raes, Verstraeten, Bijttebier, Vasey & Dalgleish, 2010). Few studies have assessed the role of functional avoidance in youth depression and measurement is imperfect. Some researchers (e.g., Gutenbrunner et al., 2019) have used self-report questionnaires to assess functional avoidance; this requires participants to be aware that they are using cognitive avoidance strategies, which seems problematic. Other researchers deduce that functional avoidance is associated with OGM because memory retrieval is impaired in individuals who have experienced trauma and are thus assumed to avoid trauma memories (Warne, Collishaw & Rice, 2019). However, functional avoidance can occur in the absence of trauma which makes this method flawed (Kuyken, Howell, & Dalgleish, 2006). Thus overall, the measure of functional avoidance is varied and inconsistent.

Two studies with young people have examined all three of the CaR-FA-X mechanisms. Gutenbrunner, Salmon and Jose (2018) recruited a large community sample of 269 youth who completed self-report questionnaires annually for four years (mean age at year 1 was 12.8). Functional avoidance in year 3 predicted OGM in year 4, but only in those who reported increasing depression symptoms across the four

assessments. There was no evidence that rumination or executive control were related to OGM either cross-sectionally or prospectively. The longitudinal design and large community sample studies are very important as it allowed the authors to test interactions between OGM and the CaR-FA-X components. However, most participants did not report elevated symptoms of depression, and all variables including executive functioning and functional avoidance, were measured by self-report.

Fisk, Ellis and Reynolds, (2019) assessed OGM and explored each CaR-FA-X mechanism in adolescents with elevated depression symptoms. In line with previous evidence (Hitchcock, Nixon & Weber, 2014) Fisk et al. (2019) found that teenagers with high depression symptoms retrieved a significantly higher number of overgeneral memories compared to teenagers with very low levels of self-report depression symptoms. Each CaR-FA-X component was also examined in both groups. Youth with elevated depression symptoms who also retrieved more overgeneral memories, ruminated more, had lower verbal fluency and poorer working memory than controls; there were no differences in inhibition or functional avoidance. Unfortunately, this study was underpowered to directly test relationships however post-hoc analysis revealed that across all participants, higher rumination and poorer working memory were associated with higher retrieval of overgeneral memories. Fisk et al. (2019) used behavioural measures to assess executive functioning and functional avoidance to avoid problems associated with of self-report. However, self -report measures were used to identify young people with elevated symptoms of depression and thus the 'depressed' group is likely to be over-inclusive. This is essential because recruitment of participants who report elevated symptoms of depression, or who are 'at risk' of depression will very likely include individuals who have, or are at risk of, other mental health problems that share genetic risk or symptoms (e.g. fatigue, poor sleep, social withdrawal).

The current evidence for overgeneral memory retrieval and the CaR-FA-X mechanisms in young people is limited and results are unclear, particularly in relation to depression. For example, data have typically not been collected from young people with depression symptoms or a diagnosis of depression. Further, the specificity of memory retrieval and CaR-FA-X components in depression, as opposed to other common comorbid mental health conditions is unclear. In addition, measures have often been self-report rather than objective measures of the CaR-FA-X components, and critically, no studies have included a clinical control group. Finally, although large community studies allow examination of relationships between the ability to retrieve specific memories when cued, and the CaR-FA-X components, they are particularly limited in recruitment of participants from the community, who are not depressed or at risk of depression. This latter point is particularly important because there is evidence that OGM is only associated with future depression in young people who are at risk of depression (Crane et al. 2015; Gutenbrunner et al., 2018). Further, measures in these studies use measures of self-report for key variables (e.g., executive function). Understanding OGM as a cognitive marker in depression and thus exploring the CaR-FA-X components is crucial when thinking about identifying plausible ways to identify those vulnerable to depression and developing targeted prevention and early interventions. Although the current research is essentially a proof-of-concept study (i.e., exploring the mechanisms executive control, rumination, and functional avoidance in youth with reduced memory specificity), it will help identify if these cognitive processes are problematic for depressed youth with OGM. This may potentially provide evidence that larger more complex studies of the CaR-FA-X model and youth depression are warranted, and whether the model can be applied to young people with depression.

In this study our primary aim was to overcome the limitations of previous research by exploring each component of the CaR-FA-X model young people with a diagnosis of depression and difficulties retrieving specific autobiographical memories. Critically, behavioural measures were used for executive functioning and several components of executive control were assessed to better understand this mechanism. To be confident that cognitive processes were specific to depression it was necessary to recruit a clinical control group (to control for non-specific distress and difficulties in mental health) and a community control group. A clinically anxious group (with low depression symptoms) was thought to be appropriate based on evidence that clinically depressed youth have difficultly retrieving specific memories when compared to clinically anxious groups (Rawal & Rice, 2012).

Based on previous research and the CaR-FA-X model of OGM we tested the following hypotheses:

i) The proportion of specific autobiographical memories will be significantly lower (i.e., higher OGM) in the depressed group than in the clinically anxious or community control groups. The proportion of overgeneral autobiographical memories will be significantly higher in the depressed group than in the clinically anxious or community control groups. If this hypothesis is supported then,

ii) One or more of the cognitive processes that are described in the CaR-FA-X model of OGM (i.e., rumination, functional avoidance of negative affect, and impaired executive control) will be significantly higher in the depressed group than in the anxious control and the non-clinical control groups.

Method

Participants

Clinical sample. Adolescents aged 12-18 were recruited through an NHS funded university clinic. Adolescents were recruited through an NHS funded University clinic. Clinical referrals for Anxiety and Depression in Berkshire are sent to 'The Common Point of Entry', this can be described as the front door to mental health services across Berkshire. (e.g., referrals from general practitioners and other services are sent here). Referrals for Anxiety and Depression are discussed within the Anxiety and Depression NHS pathway, and diagnostic assessments that are considered appropriate (e.g., low risk youth and cases that were not considered 'complex') are sent to the Anxiety and Depression in Young People Clinic (Andy; our research clinic at the University of Reading). Post graduate research assistants (most also often students) and trainee NHS Child Well-being Practitioners (CWP's) complete the anxiety and depression diagnostic assessment (please see the measures section (page 31 underneath the subtitle The Diagnostic Interview), for a more detailed description of the assessment interview). Patients are briefly approached after their assessment interview to be asked if they were interested in taking part in research (a brief description of the research study was described by the researcher in charge of the study). Potential participants were then contacted at a later date to arrange a research meeting.

We recruited two groups: those who met criteria for a primary diagnosis of major depressive disorder (n = 30) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and those who met criteria for one or more anxiety disorders *and did not have a diagnosis of depression* (n = 22). Primary anxiety disorders were social anxiety disorder (n = 11), generalised anxiety disorder (n = 6),

specific phobia (*n* = 2), agoraphobia (*n* = 1), panic disorder (*n* = 1), and separation anxiety disorder (*n* = 1). Eighteen adolescents in the depressed group had one or more co-morbid anxiety disorders but none of the anxious adolescents had a diagnosis of co-morbid depression. Further, no participants had a diagnosis of Post-Traumatic Stress Disorder (PTSD). No participants in the anxious or depressed groups were prescribed anti-depressant medication or were (yet) receiving treatment for mental health problems. There were no significant age differences between the groups.

C**ommunity sample**. Adolescents (*n* = 29) aged 12-18 years were recruited from a pool of 215 students at a high school in England. They were screened with the Mood and Feelings Questionnaire (MFQ; Costello & Angold, 1988) and included in this study if they scored 12 or below when the MFQ was administered at screening and when the MFQ was re-administered as part of a battery of measures. The cut-off was based on MFQ data from 467 young people with a diagnosis of major depression (Goodyer et al., 2017); in this sample no participant scored below 13 on the MFQ. These participants are the same group of 'low risk' adolescents in the Fisk et al. (2019) study. The demographic information for each group can be found in table 1. There were no significant differences between groups for age, gender, ethnicity or IQ.

Table 1

Demographic characteristics of community, anxious and depressed groups

Mean (SD) (Range)	Community Control (*n* = 29)	Anxious (*n* = 22)	Depressed (*n* = 30)	Statistics
Age (years)	14.56 (1.46)[a] (13-17)	14.45 (1.47)[a] (12-17)	15.07 (1.51)[a] (12-17)	*F (2,78) = 1.37, p=0.26*

Gender (%female)	76%	86%	83%	χ^2 (4) = 2.35, p=0.67
Ethnicity (% White British)	86%	91%	80%	χ^2 (6)= 5.35, p=0.55
IQ	90.94 (15.96)[a]	94.41(13.38)[a]	95.95 (8.44)[a]	F(2,78)=1.15, p=.321

Note: Corresponding superscripts represent groups that are significantly different, p<0.05, same letter subscripts show null significance.

Measures

The diagnostic interview. Participants in the two clinical groups were assigned diagnoses based on gold standard diagnostic interviews; the Anxiety Disorder Interview Schedule for DSM-IV for children, child and parent versions (ADIS-C/P; Silverman, 1996) and the Kiddie Schedule of Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997). Both are semi structured diagnostic interviews based on DSM-IV. Minor amendments were made to the interview schedules to enable diagnoses consistent with DSM-5 diagnostic criteria. The ADIS was used to report on anxiety disorders and behavioral disorders, and the K-SADS was used to report on depressive disorders. Interviews were conducted with young people and their caregivers separately. Seven participants were assessed using only the K-SADS (i.e., both depression and anxiety sections of the interview). The other clinical participants were assessed using the K-SADS (for depression) and the ADIS (for anxiety disorders). The change of the interview routine was due to a restructure in the university research clinic.

The assessors, all psychology graduates, were trained to administer and score

the ADIS-C/P and K-SADS through verbal instruction, listening to assessment audio-recordings, role-play, and taking part in diagnostic consensus discussions. Assessor competence was evaluated using an observed structured clinical assessment, which was scored by the trainers. All assessments were discussed in supervision with an experienced member of the assessment team, to agree on consensus diagnoses. For the K-SADS, as is standard, diagnoses were based on the combined information obtained from interviews with the young person and their parent(s). Inter-rater reliability for presence of a K-SADS depression diagnoses was k = 1.00. For the ADIS-C/P, as is standard, overall diagnoses and clinical severity ratings (CSRs) were assigned if the child met diagnostic criteria on the basis of either the child or parent report, and the higher CSR of the two was taken. Reliability for presence or absence of anxiety diagnosis on the ADIS-C/P was $\kappa = 1.00$, and CSR ICC = 0.93.

Following discussions with researchers and clinical psychologists within the AnDY University clinic it was agreed that the change in interview strategy was unlikely to affect diagnoses for those participants recruited before versus after the clinic restructure. This is because both interviews are gold standard research diagnostic interviews that both contain reliable questions to gain information on clinical information and symptoms. (ADIS-C/P; Silverman, 1996; K-SADS; Kaufman et al., 1997) Further, all training, assessor competence monitoring and supervision procedures remained the same.

The Mood and Feelings Questionnaire (MFQ; Costello & Angold, 1988). The MFQ is a 33 item self-report measure of depression in children and adolescents with good reliability and moderate validity (Burleson Daviss et al., 2006). Each item is rated on a 3-point scale; 0 (not true) to 2 (true). Internal consistency for this measure is high (MFQ $\alpha = 0.93$; George & Mallory, 2003).

Revised Child Anxiety and Depression Scale (RCADS; Chorpita, Yim, Moffitt, Umemoto & Francis, 2000). The RCADS total Anxiety subscale (37 items) was used to assess anxiety symptoms. The RCADS has good construct validity (Chorpita, et al., 2000) and the total anxiety subscale has excellent internal consistency (RCADS-Total Anxiety α=.84 George & Mallory, 2003).

The Rumination Response Scale (RRS; Nolen-Hoeksema & Morrow, 1991). This was used to assess the Capture and Rumination aspect of the CaR-FA-X model. The RRS is a 22-item questionnaire asking participants whether they repetitively think about their problems and consequences. Internal consistency for this measure is high (α=0.95; George & Mallory, 2003). This measure can be split into sub-scales (e.g., Brooding rumination and Reflective Pondering rumination), however, premlininary tests found no differences between the subtypes in each group, thus the total score of the questionnaire was used in the final analysis.

The Autobiographical Memory Test (AMT; Williams & Broadbent, 1986). This is a standardised test of autobiographical memory. Participants were asked to provide specific autobiographical memories in response to 10 emotional cue words presented in a random order. Participants were told that the event they remembered could be important or trivial, recent or from a long time ago, but that the memory should be something that happened at a particular place and time. All participants were given an example before starting the test, and they were given two practice items (happy and bored) to make sure that they understood the instructions.

The words were adapted from Heron et al. (2012) who carried out research on the psychometric properties of the test. They chose 5 positive and 5 negative words that were judged to be familiar to adolescents. The words were matched for familiarity using the University of Essex Children's Printed Word Database (Lovejoy, 2003).

Positive words were; happy, excited, relaxed, lucky, relieved. Negative words were bored; failure, hopeless, lonely, sad. Heron et al. (2012) found that ′happy′and ′bored′ showed poor discrimination in OGM. Therefore, following Kuyken and Dalgleish (2011) ′happy' and ′bored′ were replaced with ′loved' and ′angry'.

Administration of the test was tape-recorded and then transcribed and coded following Kuyken & Dalgleish (2011). 'Specific' memories were defined as events that lasted less than a day. Non-specific (or 'overgeneral') memories included 'extended' memories (events that lasted a distinct, but prolonged period of time) and 'categoric' memories (events that had occurred on multiple occasions with no defined time frame). E.g., the cue word 'lucky', a specific memory was "When I told my mum when I came out, and the first thing that she said to me was "I don't really mind Dean because you will always be my Dean" and then I felt lucky because you know not everybody gets that, so". Overgeneral memories can be 'categorical' or 'extended'. An example of a categorical memory was "I feel lucky if I get a good score on my tests". An example of an extended memory was "I felt really lucky when I was allowed to go to a music festival for the weekend, it was so much fun". The proportion of specific to overgeneral memories were calculated and answers that did not refer to the past and non-responses were coded as 'not a memory' thus were not included in the analysis. Data reported in tables is the proportion of autobiographical memories that were 'specific. Two researchers, who were blind to the group membership of the participant, coded all the transcribed memories from each participant. Inter-rater reliability was good $\kappa = 0.78$. Discrepancies between raters were discussed and an agreed code allocated.

Functional Avoidance. To assess functional avoidance, the valance of autobiographical memories generated on the autobiographical memory test were coded on a seven-point Likert scale (-3 for very negative, 0 for neutral, and +3 for very

positive). Therefore, avoidance is indicated by recall of more positively valenced and fewer negatively valenced autobiographical material.

This index of functional avoidance is based on the hypothesis that functional avoidance is a cognitive strategy used to regulate emotions (Sumner, 2012). Williams et al. (2007) originally defined functional avoidance as "when episodic material threatens to cause affective disturbance" (p.122) and functional avoidance research in adult PTSD shows that OGM is positively correlated with several cognitive avoidance strategies such as avoidance of private personal experiences (Schonfeld & Ehlers, 2006). Therefore, theoretically if youth using OGM as a cognitive strategy to regulate emotions, we thought youth may avoid negative autobiographical material, as this is also likely to cause affective disturbance. Also, trauma research reveals OGM is positively correlated with several cognitive avoidance strategies, such as, avoidance of private personal experiences (Schonfeld & Ehlers, 2006).

Williams et al. (2007) stated that functional avoidance can occur in response to positive and negative cues; therefore, the valence of response to both positive and negative cue words on the AMT were included. Functional avoidance is therefore indicated by recall of more negatively valanced memories to both negative and positive cue words.

Inter-rater reliability of functional avoidance between two independent coders, who were blind to group membership of participants, was high (κ=0.84). The Likert scale included both positive and negative numbers; therefore seven was added to all scores to provide data suitable for statistical analysis.

The Wechsler Abbreviated Scale of Intelligence (WASI II; Wechsler, 2011). The WASI II is a brief, well-standardised assessment of intellectual abilities for 6 to 89-year-olds. Two subtests (Vocabulary and Matrix Reasoning) were used to provide an

estimate of full-scale intelligence quotient (FSIQ). The WASI has strong psychometric properties, including good test-retest reliability and internal and concurrent validity (McCrimmon & Smith, 2013).

The Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1976). This was used to measure verbal fluency i.e., a classic measure of executive control (Rosen & Engle, 1997). Participants were asked to say as many words as possible in 60 seconds that began with a specific letter. The letters F, A and S were used and the total score was calculated across the three trials. Verbal fluency is a standard measure of neuropsychological assessment, with good levels of test-re-test reliability and validity (Harrison, Buxton, Hussain & Wise, 2000).

The Hayling Sentence Completion task (HSC; Burgess & Shallice, 1996). This is a measure of inhibition. The task involves asking participants to listen to incomplete sentences read by the researcher (e.g., "London is a very big – ") and then to provide a word that completes the sentence either appropriately (e.g., 'city'; Part A) or inappropriately (e.g., 'banana'; Part B). The task has moderate validity and reliability (Strauss et al., 2006). Inhibition is measured in two ways - the number of errors and reaction time. Errors include word endings that finish the sentences appropriately or are associated with the meaning of the sentence.

The Keep track task [KTT; originally adapted by *from Yntema (1963)].* This is a reliable and valid measure of updating working memory (St Thompson & Gathercole, 2006). his KTT is also used for assessing impairments on neuropsychological measures of executive function in depression (Snyder, 2013). Participants were shown a list of six target categories (e.g. animals, furniture, fruit) and exemplars (dog, table, apple). Fifteen words, including two or three exemplars from

each of six possible categories were then presented serially in a pseudo-randomised order for two seconds per word. Target categories remained on the bottom of the screen. The task was to recall the last word presented in each of the target categories. Thus, participants had to continuously update their working memory for the target categories. After each trial, participants were asked to recall the exemplars used in that trial. Participants practiced on two trials with three target categories. The task itself consisted of four trials with three target categories, four trials with four target categories and one trial with five target categories. The total number of words out of 33 recalled correctly was the measure of interest.

Procedure

The study was approved by the Berkshire Local Research Ethics Committee and the University of Reading Research Ethics Committee. Adolescents aged between 16-18 years provided consent for themselves, while adolescents aged between 12-15 years required parental consent as well as providing assent themselves.

The administration of tasks (in the clinic or at school) took between 45-55 minutes. The cognitive tests were administered in a standardised order; Verbal Fluency, Hayling Sentence Completion Task, Keep Track Task, Autobiographical Memory task and the WASI II. In the clinical groups, adolescents took part in a research assessment two weeks after the diagnostic assessment. Adolescents in the community control group took part during the school day. They first completed the MFQ, RCADS and rumination questionnaire in their classroom and later completed the research tasks and another MFQ (to check low mood was stable across administrations) in a separate room with the researcher.

Data Analytic Plan

For hypothesis one, power (80%) was calculated using a planned analysis using the statistical programme G * power. Based upon the mean between-group effect size of d = 0.71 on overgeneral memory (i.e., Nixon, Ball, Sterk, Best & Beatty, (2013); Park et al., (2004)), 21 participants were needed in each group. For example, the Nixon et al., 2013 study included in this power analysis assessed OGM in 3 groups; high acute stress group *(n*=11), low acute stress (*n*=11), and a hospital control group (*n*=32). For hypothesis 2, a total sample of 27 gave 80% power to detect a medium effect size (F = 0.4) with multiple comparisons (for the CaR-FAX mechanisms) and three groups. Thus, there was adequate statistical power to detect mean group differences. Therefore, the study is sufficiently powered for both hypotheses.

Continuous data were screened in relation to the assumptions of parametric tests (Tabachnick & Fidell, 2007). Where assumptions were violated, confirmatory analyses were conducted by running analyses with 1000 bootstrap samples. All results were consistent, suggesting that the original analyses were robust to the violations of assumptions, so the results based on the original (non-bootstrapped) analyses are presented for simplicity.

We conducted preliminary analyses to explore between group differences on IQ, depression and anxiety symptoms using one-way Analysis of Variance (ANOVA). Means, SDs and *F* values are shown in Table 2. IQ was a potential confound as measures of executive function and IQ are highly correlated (Diamond, 2013). We examined group means on the RCADS and MFQ (anxiety and depression symptoms) to confirm expected differences between diagnostic groups and between the community group and the clinical groups. We also examined the number of co-morbid diagnoses in the clinical groups to exclude the possibility that between-group differences were

attributable to overall severity of mental health problems.

To test our hypotheses, we examined between group differences in our key variables. OGM was compared using a one-way between-groups Analysis of Variance (ANOVA) followed by corrected pairwise comparisons. Next, group differences on each mechanism of the CaR-FA-X model were examined using Multivariate Analysis of Variance (MANOVA). Group (depressed vs anxious vs community control) was the independent variable, and executive function, rumination and functional avoidance measures were dependent variables.

The sample size in this study was underpowered to reliably test direct associations between overgeneral memory proportions and the CaR-FA-X components. For instance, according to power analysis, to conduct correlational analysis a sample size of 134 is needed, and to test interactions between OGM and the CaR-FA-X mechanisms a sample size of 92 was required for a multiple regression analysis. However, for exploratory analysis we also conducted post-hoc correlation and multiple regression analyses.

Results

Preliminary Analysis

There were no significant differences between the groups for IQ score (see Table 1), therefore IQ was not added as a covariate when testing the CaR-FA-X mechanisms. As expected, the depressed group had significantly higher MFQ scores than both the anxious group and the community control group. MFQ scores were also significantly higher in the anxious group than in the community control group (see Table 2). There was no significant difference in severity of anxiety symptoms between the anxious and depressed clinical groups and both clinical groups reported significantly more symptoms of anxiety than the community control group. The

RCADS also contains ten questions that refer to depression symptoms only, we therefore thought it necessary to remove these to make sure findings were not influenced by answered to depression questions but a more specific measure of anxiety symptoms. The overall findings were the same this is unsurprising given the number of depressed participants who had a co-morbid anxiety disorder. There was no significant difference in the number of co-morbid disorders in the anxious group and the depressed groups.

Table 2

Clinical characteristics of participants

Measure	Community Control (*n* = 29)	Anxious (*n* = 22)	Depressed (*n* = 30)	Main effects
	M (SD) (Range)	*M* (SD) (Range)	*M* (SD) (Range)	
MFQ	7.41 (4.27)[a] (0-13)	25.82 (14.92)[b] (2-60)	37.03 (14.28)[c] (12-57)	*F*(2,78)=43.61, *p*<.001
RCADS (full version)	42.10 (7.60)[a] (34-67)	70.27 (13.40)[b] (47-92)	74.27 (14.72)[b] (47-106)	*F(*2,78)=31.94, *p*<.001
RCADS (anxiety questions only)	42.10 (7.60)[a] (34-61)	70.27 (13.40)[b] (47-92)	74.20 (14.72)[b] (47-106)	*F(2,78)* = 58.30, *p*<.001
N co-morbid disorders	n/a	1.73 (3.04)[a]	1.57 (1.49)[a]	*t* (50)=.252, *p*=.35

Proportion of specific memories	.89 (.02)[a]	.85 (.04)[a]	.58 (.27)[b]	*F(2,78)=20.03, p<0.001*
Proportion of overgeneral memories	.09 (.11)[a]	.16 (.19)[a]	.41(.29)[b]	*F(2,78)=18.98, p<.001*

Note. MFQ= Mood and Feelings Questionnaire; RCADs = Revised Child Anxiety and Depression Scale. Corresponding superscripts represent groups that are significantly different, p<0.05, same letter subscripts show null significance.

Hypothesis testing

Consistent with hypothesis one, depressed adolescents retrieved significantly lower proportion of specific autobiographical material and a significantly higher proportion of overgeneral autobiographical memories (table 2) i.e., young people with a diagnosis of depression had reduced memory specificity and higher OGM compared to both community (p<.001) and anxious (p<.001) groups of adolescents. There was no significant difference in memory specificity between anxious young people and community controls (p=.427). We assessed each CaR-FA-X model component in each group (i.e. hypothesis 2) using a MANOVA with group as the independent variable, and dependent variables of functional avoidance, rumination and three measures of executive control (i.e. verbal fluency, inhibition and working memory). There was a significant multivariate effect of group F (12, 148) = 8.94, p <.001, indicating that depressed, anxious and the community control groups significantly differed. This was followed up with univariate F tests to examine each component of the CaR-FA-X model separately. Corrected pairwise comparisons were then used to identify which

group(s) differed from each other. Bonferroni adjustment for multiple comparisons was used for all post hoc analyses.

Figure 1 shows the group differences on dependent variables i.e., the mechanisms suggested by the CaR-FA-X model. Descriptive data for figures are provided in supporting materials (Table S1). Corrected pairwise comparisons found that the depressed group ruminated more than the anxious group (p=.002) and the community control group (p<.001), and that the anxious group ruminated more than the community control group (p<.001). There was no group difference in functional avoidance i.e., in the valence of the memories recalled in each group. Some aspects of executive functioning did differ. Depressed young people had significantly greater deficits in working memory than those with anxiety disorders (p=.003) and those recruited from the community (p=.004). Anxious and control participants did not differ on working memory performance. There was no significant effect of group on verbal fluency or for the number of errors made on the inhibition task. However, on the inhibition task, participants in the depressed and anxious groups were significantly slower than participants in the community group (p=.006) and did not significantly differ from each other.

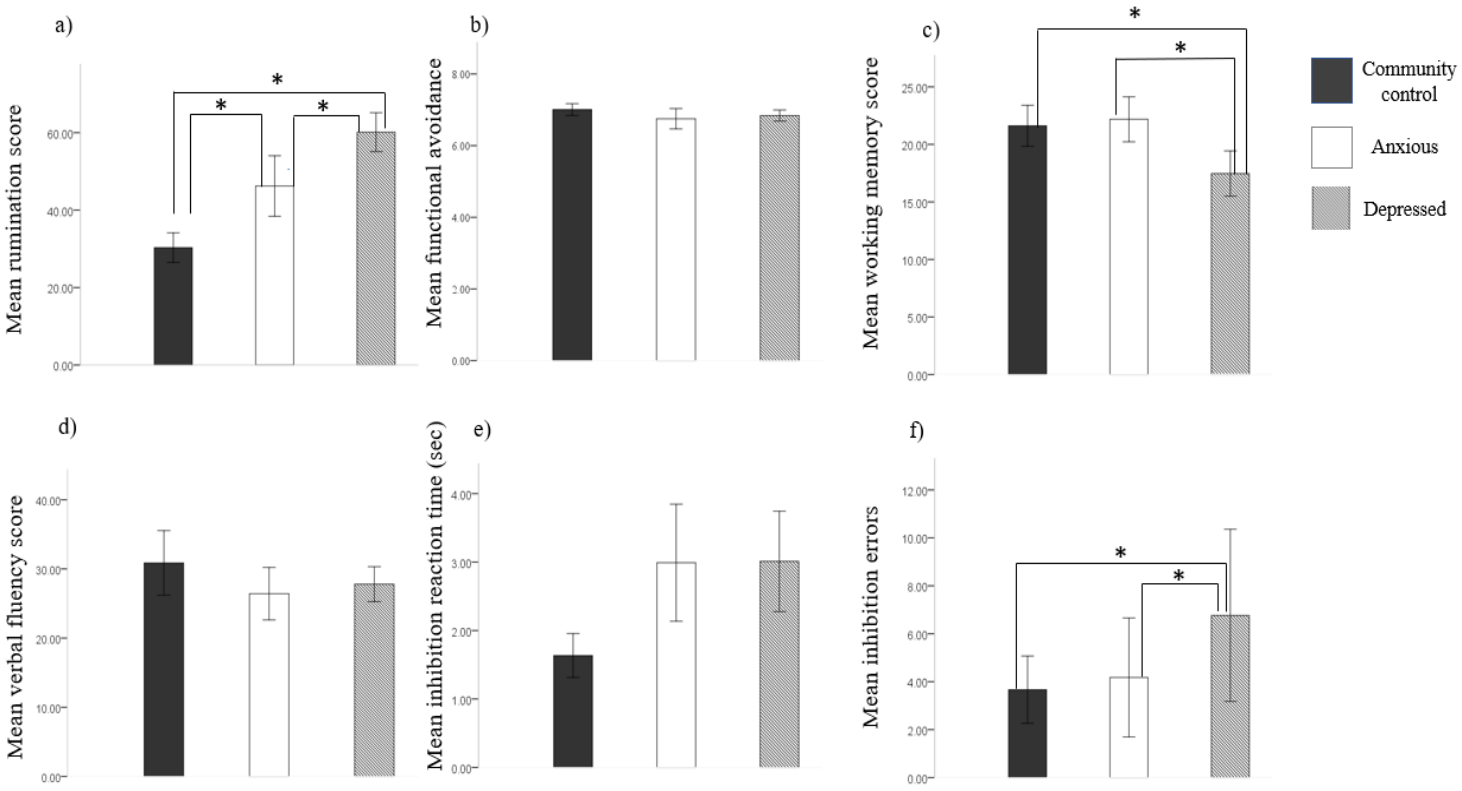

Figure 1. The mean scores for each CaR-FA-X mechanism a) mean rumination score for each group b) mean functional avoidance score for each group c) mean working memory score for each group d) mean verbal fluency score for each group d) mean reaction time for each group on the inhibition task e) mean number of errors made in each group on the inhibition task – reaction time. f) mean number of errors made in each group on the inhibition task – errors. Error bars show 95% confidence intervals.

Post hoc analysis

Exploratory post hoc analysis was conducted to test the CaR-FA-X model by examining associations between the individual components of the CaR-FA-X model and memory specificity. The sample size of each group in our study limited power to examine associations within each group and overgeneral memory was uncommon in anxious and control participants, meaning that within these groups this variable was skewed. Combining the data from the three groups increased power and resulted in a normal distribution of overgeneral memory so correlational analysis was appropriate.

Across the three groups, recall of specific memories was negatively correlated with ruminate and positively correlated with working memory. Recall of specific memories was not correlated with any other of the CaR-FA-X variables.

Table 3

Pearson Correlations for Proportion of specific to overgeneral memories, RRS, Functional Avoidance, Working memory score, Inhibition errors, Inhibition RT, Verbal Fluency.

Measure	1	2	3	4	5	6	7	*M*	*SD*
1. Proportion specific to OGM	1								
2. RRS	.49**	1	.01	.36**	.29*.	25*	-.11	46.43	17.60
3. Functional Avoidance	-.05	.01	1	.11	-.01	.03	.10	7.00	.39
4. Working memory	.50**	.36**	.11	1	-.02	.02	.18	20.44	5.16
5. Inhibition errors	.01	.29*	-.01	-.02	1	.48**	.02	4.95	6.97
6. Inhibition RT	-.12	.25*	.03	.02	.48**	1	.20	2.56	1.73

7. Verbal fluency	.21	-.11	.10	.18	.02	-.20	1	29.06	.38

*Note. Pearson correlations between proportion of specific to OGM and each CaR-FA-X measure for all participants are presented above (n=81). RRS = Ruminative Response Scale. RT = reaction time. M= mean. SD = standard deviation. * = p<0.05. ** = p<0.001.*

To examine multivariate relationships between overgeneral memory, working memory and rumination, we entered working memory and rumination as independent predictors of overgeneral memory in a multiple regression. This was significant; both variables were significantly associated with overgeneral memory (see Table 4). Adding the interaction of working memory and rumination at step 2 was not significant (see Table 4). Therefore, there was no evidence that an interaction of working memory and rumination was associated with the recall of specific memories.

Table 4

Predictors of proportion of specific to overgeneral memories

	Proportion of specific to memories		
	Model 1 *B*	Model 2	
Variable		*B*	95% CI
Constant	.77	.78	[.27, .81]
Working Memory	.02	.02	[.01, .03]
Rumination	-.01	-.01	[.01, .00]

Working memory *		.00	[.00, .00]
Interaction			
R^2	.33	.34	
F	19.50	13.19	
R^2 change		.01	
F change		.70	

Note. N=81. CI= confidence interval.

Discussion

This study is the first study to explore each mechanism highlighted by the CaR-FA-X model of OGM with clinically depressed adolescents who had difficulties retrieving specific personal memories. It was also the first to compare youth with a diagnosis of depression to both a community and clinical control group. In line with our first hypothesis and previous research (e.g., Hitchcock et al., 2014), young people with depression recalled a significantly lower proportion of specific autobiographical memories **(**and a significantly higher proportion of overgeneral memories) compared to young people with anxiety disorders and a community control group (Rawal & Rice, 2012; Hitchcock et al., 2014). We also found that depressed young people had poorer working memory and higher rumination than the other two groups. Anxious and depressed adolescents had longer inhibition reaction times than the community control group. There were no differences between any groups for functional avoidance (i.e., recall of negative autobiographical material), verbal fluency or inhibition errors. OGM therefore appeared to be a specific difficulty in depression that is not observed in young people who have anxiety disorders (Rawal & Rice, 2012a). Working memory deficits may also be specific to depression and the results here are consistent with Fisk et al.,

(2019) who also reported both OGM and working memory deficits in young people with elevated symptoms of depression.

Additionally, exploratory tests found that across participants retrieval of specific memories were associated with higher working memory scores and lower levels of rumination, these findings support the CaR-FA-X theory. Working memory performance and rumination levels independently predicted specific memory retrieval. This contradicts previous findings that an interaction between working memory and rumination are associated with OGM (Rawal & Rice, 2012b; Sumner, Griffith & Mineka, 2011). For example, Rawal and Rice (2012b) found that overgeneral memory retrieval was predicted when adolescents ruminated more, but only in the context of lower executive control. This disparity in findings may reflect methodological differences in participants. For example, we recruited young people with a diagnosis of depression, whereas Rawal and Rice (2012b) recruited children who were 'at risk', and Sumner, Griffith and Mineka, (2011) recruited adults. It may also reflect measurement differences. For example, Rawal and Rice (2012b) used a measure of IQ to assess executive control whereas we assessed independent elements of executive control. The findings from tests within the post-hoc analyses should be interpreted with caution as the study lacked adequate power, however they are important as they justify the need for larger studies to help better understand the relationships between depression, OGM and the CaR-FA-X components.

We also found deficits in inhibitory control (assessed by reaction times) in both the anxiety and depressed groups. From these data we can infer two things. First, given that both groups were experiencing symptoms of anxiety, it is plausible that anxiety, rather than depression symptoms, were driving this cognitive deficit. Second, considering that only the depressed group had difficulty retrieving specific memories it

is unlikely that inhibition was driving a disruption in the autobiographical memory search. This inference is supported by the exploratory post-hoc tests, in that, no relationship was found between inhibition and OGM.

We also did not find a relationship between functional avoidance and OGM. However, measuring functional avoidance is not straightforward. We measured functional avoidance by coding the valance of memories elicited by the Autobiographical Memory Test. This did not equate the experience of trauma with avoidance or require that the individual was aware of avoiding negative memories. However, it did require us to infer that depressed young people have memories of negative events, and that, if they do not recall these when prompted, avoidance could be taking place. One idea to improve the current measure, would be to ask participants to rate their own memories in comparison in other memories they have stored. Until a more independent and precise measure of functional avoidance is available, that does not rely on self-report, any conclusions we draw about the role of functional avoidance in OGM recall must be highly provisional.

The findings partly support the CaR-FA-X model of OGM and importantly pave the way for larger studies by, for example, highlighting the potential role of working memory and rumination in the retrieval of specific autobiographical material in depressed youth, and emphasizing the idea that different elements of executive control may impact memory retrieval. It is necessary to assess OGM and each cognitive mechanism specifically in young people with current Major Depressive Disorder (MDD) for two key reasons. Firstly, rapid cognitive and emotional development during adolescence means research with adults cannot be assumed to generalise to young people (Blakemore, 2012). Second, the contributions of each CaR-FA-X mechanism is thought to differ in different populations. For example, in adult research, functional

avoidance primarily explains OGM in trauma-exposed individuals, whereas impaired executive control primarily causes OGM in adults with depressive symptoms (Sumner et al., 2014).

The design of our study helps us exclude important alternative explanations. For example, because the onset of depression is uncommon before adolescence, the specific cognitive difficulties of this group are unlikely to be due to repeated episodes or prolonged periods of depression. None of the participants were taking anti-depressant medication and therefore this cannot account for the differences between the groups or for any specific problems with working memory. Our design also allows us to exclude some plausible alternative explanations for this specific impairment in working memory i.e., IQ and motivation, because the three groups of young people were well matched for IQ.

It was important to compare findings to both a clinical and community control group. The clinical control group was important to control for non-specific difficulties related to emotional distress and to demonstrate whether findings were driven by depression. A clinically anxious group (with low depression symptoms) were thought to be an appropriate control group as previous evidence found that clinically depressed youth have difficulty retrieving specific memories when compared to clinically anxious groups (Rawal & Rice, 2012). Findings suggest that both OGM and working memory deficits were specific to adolescents within our depressed group, compared to the anxious and healthy controls. However, it is important to highlight that the depressed group were also experiencing some symptoms of anxiety. As such, it could be argued that findings (i.e., reduced working memory) could be an artefact of the combined anxiety and depression rather than a specific feature of depression symptoms. However, because working memory deficits were not present in the anxiety-only control group, it

is plausible that depression symptoms, rather than anxiety symptoms, were driving working memory problems. Nevertheless, whether cognitive deficits were caused by depression symptoms, or co-morbid anxiety and depression, the depressed sample were comparable to a typical group of depressed teenagers. For example, Anxiety and Depression often co-occur in adolescents (Avenevoli et al., 2015) and approximately 75% of young people with depression experience symptoms of anxiety (Essau & Chang, 2009). This is important because if we want to better understand depression and inform intervention strategies it is crucial that information is applicable to adolescents in the real world.

Despite the strengths of this paper, some features of our design were sub-optimal. For example, in line with epidemiological data (Tharpar et al., 2012) and typical referral practices in the UK, there were fewer boys than girls in our depressed and anxious clinical groups. Furthermore, we could not carry out diagnostic assessments with the community control group and therefore cannot rule out the possibility that some young people in this group had mental health problems. This study was designed and powered to examine between group differences; therefore, it was not powered to test associations or interactions between different elements of the CAR-FA-X model and OGM. Despite this, some exploratory post-hoc analyses were conducted to test potential relationships between memory specificity and the CaR-FA-X mechanisms generally. Findings suggested that further investigations, particularly testing rumination and executive control, are required using much larger samples. For example, Hallford, Austin, Raes and Takano, (2018) recommend that a minimum of 250 participants is required to detect a small effect when testing interactions between CaR-FA-X mechanisms using multiple regression models.

Most research investigating the CaR-FA-X model has done so by recruiting large non-clinical samples which provides greater power to test associations and interactions between OGM and the CaR-FA-X mechanisms. These studies are very important to help us understand underlying mechanisms of the autobiographical memory search in general.

To learn about OGM in adolescent depression we selected a different but complementary approach to exploring the mechanisms of the CaR-FA-X model. Logically, if cognitive processes associated with the CaR-FA-X model (Williams et al., 2007) are specific to OGM in depressed teenagers compared to control groups we would expect depressed youth to report one or more cognitive deficits proposed by The CaR-FA-X model i.e., report high levels of rumination, avoid distressing autobiographical memories, and have executive functioning deficits compared to control groups. The findings from this study supported this notion. Therefore, offering preliminary proof that the CaR-FA-X mechanisms are present in youth with depression and who also have difficulties retrieving specific memories. Additionally, further research in this area will be valuable for understanding depression, memory retrieval and cognitive processing. Future work however would require larger samples of depressed youth to ensure adequate power to directly assess relationships and potential interactions between depression, OGM and the CaR-FA-X mechanisms. The use of correlations and multiple regression models or statistical equation modeling would help gain a better understanding of the mechanisms directly associated with depression levels (e.g., MFQ scores), OGM, rumination, functional avoidance, and executive control components. Interactions between CaR-FA-X mechanisms would help gain a better understanding of whether mechanisms work together or in isolation to cause OGM in depression.

Whilst it is realised this research design (i.e., including clinical participants) makes it more difficult to recruit large samples, smaller samples make it feasible to administer more precise measures of key CaR-FA-X components (e.g., executive functioning) and thus reducing methodological problems associated with self-report. For instance, evidence suggests that measuring executive control through self-report does not tap into the same constructs as behavioural tasks (Snyder, Miyake & Hankin, 2015). This also allowed us to examine multiple aspects of executive control (e.g., updating working memory and inhibition) which has been noted as necessary to improve understanding of the role of executive control in OGM (e.g., Dalgleish, 2007, Sumner, 2012).

A further limitation was the measure of functional avoidance as this was a novel measure and without validated psychometric properties. For an additional explanation of this choice of measure please refer to the methods section (please see page 135). Our justification for this functional avoidance measure was that adolescents who use OGM as a cognitive avoidance strategy would also avoid negative memory content, as this is likely to cause affective disturbance. However, a key weakness with this, was that we did not measure lifetime exposure to negative or positive experiences, which might plausibly differ between the groups. Specifically, because of increased exposure to negative life events (including possible trauma) young people in the depression group may have had a larger mental 'catalogue' of negative memories to draw on, and thus their retrieval of memories that did not differ in affective tone may reflect a positively biased retrieval. In future, adolescents could be asked to rate the memories themselves, in terms of how positive or negative they believe their recollection to be in comparison to other memories they have. This would provide a more precise insight into whether adolescents were avoiding negative autobiographical content. Including a

supplementary strategy to assess cognitive avoidance would also be advised for future work, such as, a cognitive avoidance questionnaire to explicitly measure the young person's general avoidance (e.g., The cognitive avoidance questionnaire; Sexton & Douglas, 2008).

The cross-sectional design of the study means that we cannot infer the direction of causality i.e., were working memory deficits present before the onset of depression or did depression symptoms influence the deficits? OGM and working memory deficits may increase the risk of developing depression (Kuyken & Dalgleish, 2011; Zukerman et al., 2018) but this is not conclusive (Scult, Paulli, Mazure, Moffit, Hariri & Strauman, 2017). If these impaired cognitive processes are risk factors, then they could possibly be targeted early, potentially preventing the onset of depression. To assess this, a longitudinal approach, a larger sample, and multivariate statistical analysis could help identify relationships between depression, OGM and the CaR-FA-X mechanisms, in community at-risk adolescents could be used. For instance, adolescents at familial risk of depression but who are not currently depressed, could be assessed on depression symptoms, OGM, and the CaR-FA-X mechanisms over time. Also, a more explicit measure of functional avoidance could be used (e.g., an avoidant behavior questionnaire or a cognitive avoidance questionnaire) in addition to our method. However, with inclusion of adolescents rating the positivity or negativity of their memories in comparison to other experiences they have. This research could help to determine if working memory deficits and/or rumination and/or functional avoidance predict OGM and thus help to identify potential vulnerability factors in youth depression.

Overall, the current findings are important for two key reasons. First, memory problems, especially working memory problems, are associated with many difficulties

in learning and daily functioning (Diamond, 2013). For young people with depression, memory problems are likely to amplify other symptoms of depression, including negative self-evaluation and low mood due to negative material capturing attention or entering working memory and the reduced ability to use positive specific memories to repair negative moods (LeMoult & Gotlib, 2018). Second, memory processes may offer a direct target for preventing and treating depression (Barry et al., 2019). There is an extensive literature on working memory training, but this has largely failed to show significant or lasting benefits to 'real life' (Sala & Gobet, 2017). However, the absence of specific positive autobiographical memories may maintain low mood (Dalgleish & Werner-Seildler, 2014) and training positive memory specificity may reduce vulnerability to depression in adolescents (Askeland, Schweizer, Goodyer & van Harmelen, 2018).

The identification of working memory problems as a difficulty in clinically depressed adolescents provides a potentially important 'marker' that could be used to identify and assess depression in young people (Oliver et al., 2019). It also has promise as a potential target to prevent and treat adolescent (and adult) depression. This potential new avenue for intervention is particularly important because of evidence that the outcomes of psychological treatment for depression are moderate (at best) and may be deteriorating (Weisz et al., 2017). To make significant advances in psychological treatments we need to identify specific psychological mechanisms that cause and maintain adolescent depression, and then work out how to change them.

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Supplementary materials - Online resource 1

Means, standard deviations and univariate F values for the CaR-FA-X mechanisms

Measure	Community Control (*n*= 29)	Anxious (*n*=22)	Depressed (*n*=30)	Main effects
	M (SD)	M (SD)	M (SD)	
RRS	30.31 (13.46)[a]	46.23 (17.62)[b]	60.13 (13.46)[c]	*F*(2,78)=35.05, *p*=.000*****
FA	7.07 (.30)[a]	7.03 (.24)[a]	6.92 (.38)[a]	*F*(2,78)=1.12, *p*=.330
Working memory	22.21 (4.21)[b]	21. 95 (4.83)[b]	17.70 (5.52)[a]	*F*(2,78)=5.83, *p*=.001*****
Verbal fluency	30.86 (12.26)[a]	26.14 (8.57)[a]	27.80 (6.77)[a]	*F*(2,78)=3.47, *p*=.229
Inhibition RT	1.64 (.85)[a]	2.99 (1.93)[b]	3.01 (1.96)[b]	*F*(2,78)=6.48, *p*=.002*****
Inhibition error	3.67 (3.71)[a]	4.18 (5.59)[a]	6.77 (9.62)[a]	*F*(2,78)=1.67 *p*=.194

Note. FA= Functional Avoidance RT= Reaction Time RRS=Rumination Response Scale Corresponding superscripts represent groups that are significantly different p<0.05 same letter subscripts show null significance *****= significant *p* value same letter subscripts show null significance.

4 Chapter 5 : Paper 3: What are the effects of working memory training in children and adolescents – a meta-meta review.

Manuscript in preparation

What are the effects of working memory training on children and adolescents? A review of meta-analyses.

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Abstract

Working memory is a core executive function and an integral part of critical cognitive processes, such as planning and reasoning and encoding and storing memories (Baddeley 1992; Diamond, 2013). Working memory develops in childhood and adolescence and reaches full capacity in early adulthood. Deficits in working memory in children and adolescents are associated with impairments in academic skills (e.g., reading and mathematics) and with a number of mental health disorders, including depression and ADHD (Diamond, 2013). Working memory training (WMT) has been developed with the aim of improving working memory itself and also other global cognitive abilities (e.g., attention and intelligence) and academic achievement. A number of meta-analyses of the effectiveness of WMT have included studies with children and adolescents. However, the aims of these differ and thus they are often hard to compare, given differences in sampling, evaluation of variables to test near and far-transfer, and the range of moderators thought to influence the effectiveness of training. The aim of this systematic review was to collate and evaluate evidence from all published meta-analyses of working memory training with children and young people and to synthesise their findings. Ten meta-analyses and one second-order meta-analysis were identified following a systematic literature search. They were assessed for quality and overall effect sizes. The data suggests that WMT does result in short term improvements in working memory. However, there is insufficient evidence to conclude that WMT results in the improvement of other cognitive abilities or impacts daily life e.g., academic achievement or behaviour. Therefore, future research should consider different interventions to improve working memory which have more global effects or discover ways to support working memory impairment (e.g., teaching strategies) rather than continuing to focus on WMT.

Introduction

Working memory (WM) is a capacity limited system that allows temporary storage and manipulation of information needed for cognition in the present moment (Van Bastian & Oberauer, 2014). It is needed for planning, reasoning, learning, encoding, and storing memories (Baddeley 1992; Diamond, 2013). The capacity of WM is typically 2-5 chunks of information (Cowan, 2010) but differs between individuals and is influenced by the type of information being processed (e.g., verse or pictures). Baddeley and Hitch (1974) developed a comprehensive model of WM. They proposed that WM consists of a central executive control system that monitors two sub-systems; the visuo-spatial sketchpad (i.e., for spatial information processing) and the phonological loop (i.e., for verbal information processing). Based on this model, tasks that assess working memory are usually split into visuo-spatial WM and verbal WM tasks (Baddeley & Hitch, 1974).

Working memory is often thought to be stable (Blasiman & Was, 2018) and reduced capacity is associated with impairments in educational related skills such as reading (Swanson, Howard & Sáez, 2006), mathematics (Passolunghi, Vercelloni & Schadee, 2007) and language (Archibald & Gathercole, 2006). However, Klingberg, Forssberg and Westerberg (2002) suggested that it might be possible to improve working memory through training and this may have positive effects on related tasks e.g., academic achievement and general intelligence (Shipstead, Redick & Engle, 2010; for a summary see Barrett, Tugade & Engle, 2004).

Working Memory Training (WMT) is typically delivered via computerised programs and has been proposed to work via two potential mechanisms. First, WMT increases WM capacity (i.e., the number of items that can be held simultaneously in WM) and second, it enhances the efficiency of WM (e.g., by training how to process

information more quickly). Several programmes have been developed (e.g., 'Cogmed'; Klingberg, Forssberg & Westerway, 2002) and are based on the foundation that by repeatedly performing WM tasks, participants will develop different strategies that may enhance their working memory performance. For example, Cogmed WMT (Klingberg, Forssberg & Westerway, 2002) is a computerised training programme that uses a game-like interface, and targets both storage and processing components of working memory. Training happens over a 5-week period; with trials individualised to the participant's capacity, and difficulty adjusted on a trial-by-trial basis (i.e., if children respond correctly in trials, the following trials become more difficult, however if the trial is completed incorrectly, the next trails decrease in difficulty, requiring less working memory load). Reinforcement is integrated within the programme, such as earning small rewards after a week of successful training. Such programmes are called "implicit" WMT. In contrast, "explicit WMT" participants are asked to repeat WM tasks and are also instructed in different memory strategies (e.g., memory booster; St Clair Thompson, Stevens, Hunt & Bolder, 2010).

The success of WMT is measured by performance on both WM tasks and on tasks that are related to WM but have not been trained (i.e., transfer of WM skills). Generally, there are two ways to measure if improvements in WM have been transferred. *Near-transfer* is the transfer of skills to related domains (e.g., a different working memory task). *Far-transfer* is the transfer of skills to weakly related domains (e.g., general intelligence). Far-transfer effects are essential for demonstrating that WMT has any practical or clinical application (Melby-Lervåg & Hulme, 2013) and can only be inferred if near-transfer has also been demonstrated. For example, in the absence of near-transfer effects, any observed change in far-transfer must be due to

factors such as practice or expectancy effects. This is because far-transfer is capped at the magnitude of near-transfer (Shipstead, Redick & Engle, 2012).

Working memory training has shown some efficacy in specific populations. For example, Klingberg et al. (2002) tested WMT in 17 young people aged between 7 and 15 years old with Attention Deficit/Hyperactivity Disorder (ADHD). Seven were assigned to working memory training, which consisted of a computerised program of 30 trials lasting approximately 25 minutes, daily for 24 days. The control group completed a version of the working memory training that had just 10 trials. At the end of training those in the WMT group, had significantly better WM performance (near-transfer) than the control group and significantly improved non-verbal IQ (far-transfer). Although these results were promising, this study was underpowered, allocation to treatment and control groups was not randomised and the control group had significantly less intervention time. Similarly, many of the WMT trials that have been published since have been underpowered to detect anything other than a large effect size (e.g. d=0.80 – 0.90; Sala et al., 2019). Based on a more realistic effect size of d=0.3, Sala et al. (2019) calculated that effectiveness trials would need a minimum group size of 175, compared to the typical group size of 20.

Meta-analyses can help synthesise the results of multiple underpowered studies and provide an estimate of the probable effect size of the intervention. The analysis can also asses the overall strength of the relationships between variables (e.g., the relationship between child age and the effectiveness of working memory training; Shorten & Shorten, 2013). However, the methods of meta-analyses are varied and, as a result, their results and conclusions are also varied. For example, when assessing the effect of WMT on near-transfer, the majority of meta-analyses compute an overall effect size for both visuospatial and verbal working memory (e.g., Melby-Lervåg &

Hulme, 2013). Alternatively, the overall effects of far-transfer have been calculated in a range of ways. For example, Sala and Gobet, (2017) calculated an overall effect size for 'cognitive performance' whereas Melby-Lervåg and Hulme (2013) calculated separate effect sizes for different categories of cognitive performance (e.g., for Maths and English). The average length of the follow up period and the total number of estimated effect sizes calculated also differs across meta-analyses. For example, some meta-analyses report both immediate (i.e., straight after the intervention) and sustained (i.e., after a follow up period) effects, and others provide just immediate effects. Therefore, reviewing findings across meta-analyses could be helpful to gain a clearer picture of the efficacy of WMT.

Meta-analyses include a diverse range of moderators including age, learning disability status, duration of training and type of control group. Reviewing multiple meta-analyses may allow for a broader consideration of the influence moderators have on the effectiveness of WMT. The common moderators (e.g., age, learning disability status, study design) that are typically used in meta-analyses within this review will be described here. Age is taken as a proxy of development. Lövdén, Bäckman, Lindenberger, Schaefer, and Schmiedek (2010) argued that, because of development of the pre-frontal cortex (the area of the brain related to cognition), younger people might be more receptive to WMT than adults and older adolescents. Conditions which effect learning such as ADHD, global learning difficulties and traumatic head injury may moderate WMT outcomes. It has been suggested that participants who have cognitive deficits may benefit from WMT to a greater extent because there may be more capacity for improvement (Melby-Lervåg, Redick & Hulme, 2016). WMT studies also differ regarding the type of control group chosen. Trials that do not control for non-specific treatment effects (e.g., those with a passive control group) may have inflated results due

to confounds such as differences at baseline, non-randomisation of the treated sample, and placebo effects (Melby-Lervåg, Redick & Hulme 2016). Therefore, reviewing multiple moderator effects across multiple meta-analyses allows for a wider understanding of specific influences on the effectiveness of WMT.

Meta-analyses also differ regarding the technique used to assess publication bias. Publication bias occurs when only studies with significant results or large effects are published, or because researchers only report data from variables with significant effects (Schwaighofer et al., 2015). To overcome publication bias, researchers should contact authors about unpublished studies and estimate the likelihood of publication bias. The inclusion of grey literature (i.e., unpublished literature) and the tests used for estimating publication bias (e.g. *p* curve analysis) differ between meta-analyses, and some tests are suggested to be better than others, again highlighting the need to review multiple meta-analyses.

The varied methods and analyses used in different meta-analyses make it difficult to reach a reliable conclusion about the short- and longer-term effectiveness of WMT on near and far-transfer, as well as about variables that may moderate their effectiveness. The aim of this meta-analytic review is therefore to critically evaluate and then synthesise all available meta-analyses of WMT with children and young people. This will allow us to (i) establish whether WMT with children and young people improves working memory (near-transfer), or related cognitive or psychological variables (far-transfer); (ii) how long any effects last, and (iii) which, if any, variables are associated with larger or more enduring effects of training.

Method

Literature search and Inclusion Criteria

A systematic search of 2 databases (Web of Science and Psychinfo) and references from previous reviews (Table 1) was conducted. Details concerning the method of the literature search are shown in Figure 1. To be included in this review, the meta-analyses was required to (i) analyse the effectiveness of WMT to both near and far-transfer, and (ii) include children and young people under 18 years, such that included studies recruited only children and young people *or* included age as a moderator in the meta-analysis (i.e. so that we would know if effect sizes were significantly different in youth compared to other populations). The search terms used were, 'working memory train* OR cognitive train* OR train* working memory OR Cogmed' AND 'meta-analysis'.

Each meta-analysis was assessed for quality using the 'Assessing the Methodological Quality of Systematic Reviews' (AMSTAR; Shea et al., 2007) tool. The quality of each meta-analysis was evaluated by the 1st author, and a randomly selected 50% of the reviews were evaluated by the 2nd author. There was a moderate level of agreement between the raters (Cohens k = 0.63). Disagreements were discussed and resolved. The quality score and details of the key methodological characteristics of each meta-analysis can be found in Table 1. The outcomes assessed in each meta-analysis and their adjusted effect sizes are shown in Table 2 (near-transfer) and Table 3 (far-transfer).

Methodological strengths and limitations of each meta-analysis as well as significant effect sizes for near and far-transfer, and significant moderators are highlighted below in individual reviews (non-significant effects are shown in Table 2).

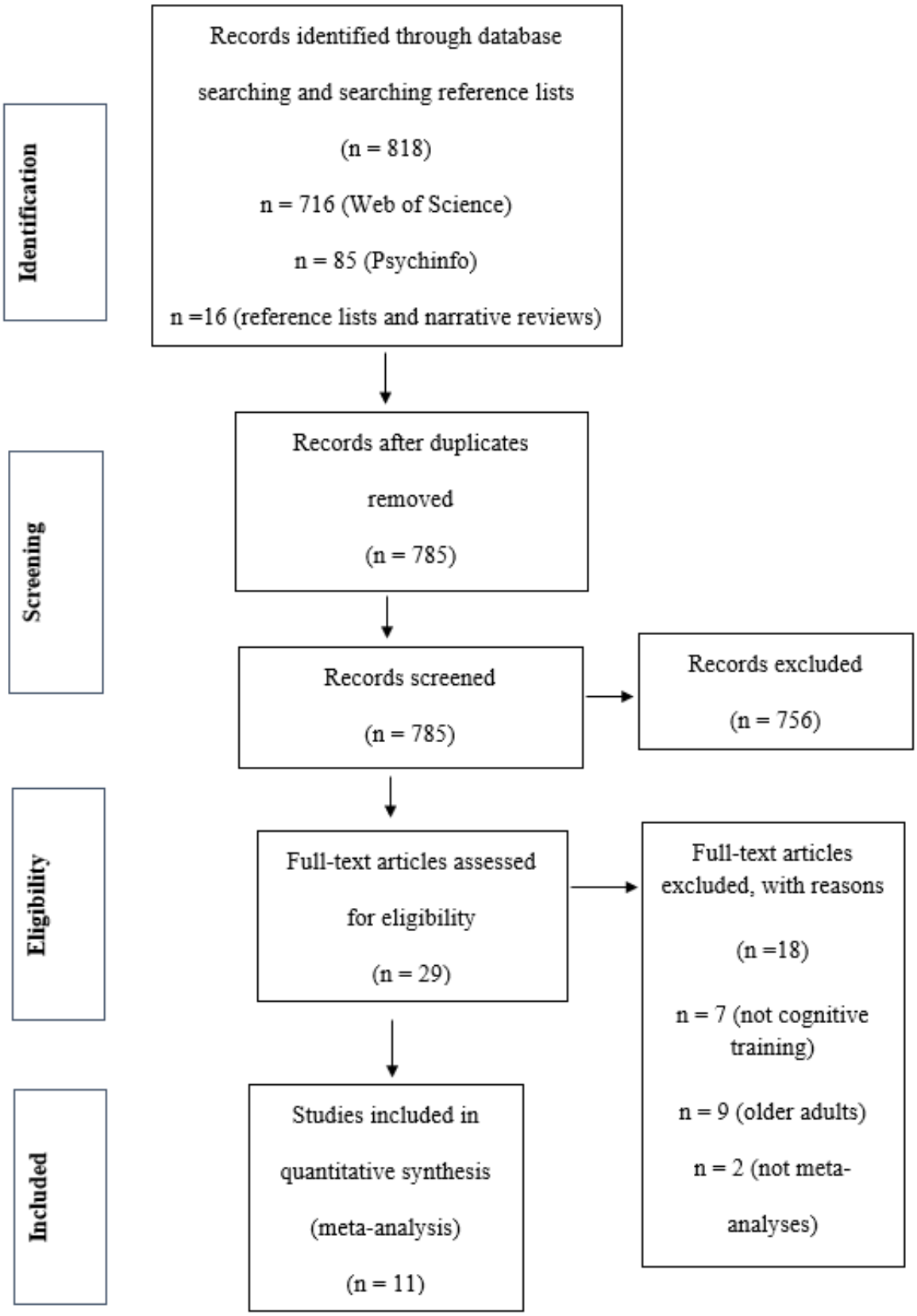

Figure 1. A flow diagram for the search of meta-analyses included in this review.

Table 1

Key characteristics of each meta-analysis and the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) total score

Studies (authors, date)	N of studies (N group comparison)	Age Ranges	Sample characteristics	Moderators (i.e., variables for sub-group analyses)	AMSTAR quality rating
Melby-Lervag and Hulme (2013)	23 (30)	Children (aged 4.3 -18 years) Adults (aged 19 -71 years)	Typically developing Learning disorder	- Age* - Training dose* - Design type* - Control group* - Learner status - Intervention type*	11/11

Rapport, Orban, Kofler and Friedman (2013)	25 (636)	Children and adolescents (No age range provided)	Primary diagnosis of ADHD Youth experiencing significant or documented attention/ hyperactivity/impulsivity problems by teacher and/ or parent rating scale report	-	Blind/unblinded raters* Training target Control group Treatment intensity	9/11

Spencer -Smith & Kilngberg (2015)	11 (12)	Children/ adolescents (aged 5-17 years), Adults (aged 34-70 years)	Healthy ADHD diagnosis At-risk of WM impairment	- Age (children, adolescents, adults) - Specific or general measure of inattention in daily life - Type of control group - Learning status (e.g. healthy or ADHD)	10/11

Schwaighofer, Fischer and Buhner (2015)	47 (65)	Children/ adolescents (aged 4-18 years) Adults (aged 19-71 years)	Typically developing Patients with learning difficulty	- Age - Type of control group - Learner status - Training dose* - Session duration* - Training frequency - Trained modality of WM - Supervisor presence* - Training location* - Instructional support - Feedback given	9/11

Cortese et al. (2015)	15	Children (aged 6 -10 years)	Clinical cut off for ADHD diagnosis	-	Control group - Training target - Blinded or unblinded rater - Greater than 30% on ADHD medication	10/11
Melby-Lervag, Redick and Hulme (2016)	87 (145)	Children/ adolescents Adults Older adults	Typically developing Patients with a learning difficulty	-	Age* - Learning status* - Training dose* - Intervention type* - Publication type (e.g. journal, chapter, peer reviewed)	10/11

Peijnenborgh, Hurks, Aldenkamp, Viles & Hendriksen (2016)	13 (610)	Children/ adolescents (aged 6-17 years)	Learning disorders (i.e. ADHD, Low IQ, working memory deficits)	-	Age* Study design* Session duration Control group Type of learning difficulty Training intervention Adaptive or non-adaptive program	5/11

Weicker, Villringer and Thöne-Otto (2016)	103 (112)	No age ranges available	Typically developing children and healthy adults Children and adolescents with WM deficits Adult patients with acquired brain injuries Adult patients with other diagnoses Older adults with mild cognitive impairment	- Study design* (type of control group & use of adaptive intervention in control group) - Duration of training* (number of sessions and total hours) - Intervention type*	5/11

Gobet and Sala (2017)	25	Children/ adolescents (aged 4-14 years)	Typically developing	-	Age* Control group* Randomisation* Training duration	7/11
Aksayli, Sala and Gobet (2019)	50	Children (aged 5-18 years) Adults (aged 18-70 years)	Typically developing Clinical conditions (e.g., ADHD) and learning disabilities	-	Randomisation Control group (passive or active) Age * Population Outcome measure Baseline difference Criterion (similarity of near-transfer tasks to those used in training) *	8/11

Sala, Aksayli, Tatlidil, Tatsumi, Gondo and Gobet, (2019a) Model 1 Near transfer	50	Children/ adolescents Adults (age ranges not available)	Typically developing children Children with learning disabilities Healthy Adults Older adults with mild impairment	-	Age Control group Randomization Learning status	9/11
Sala, Aksayli, Tatlidil, Tatsumi, Gondo and Gobet, (2019b) Model 2 Far transfer		Children/ adolescents Adults (age ranges not available)	Typically developing children Children with learning disabilities Healthy Adults Older adults with mild cognitive impairment	- - - -	Age Control group Randomization Learning status Measure of far transfer	9/11

Note. ADHD = Attention Deficit/Hyperactivity Disorder, TD=typically developing, WM= working memory, *= significant moderator

Rapport, Orban, Kofler and Friedman (2013). This meta-analysis aimed to test the efficacy of executive function training (referred to as 'cognitive training') for children with ADHD symptoms (but not necessarily with a diagnosis of ADHD). Most of the included studies were randomised control trials however five of the 25 did not include a control group (e.g., single group design studies were included). Those with control groups included either an adaptive control group, non-adaptive control group (i.e., passive), or wait-list controls. All but six of the cognitive training interventions targeted working memory, however some studies were included that aimed to improve either inhibition or set-shifting (these are components of executive control).

Overall, the meta-analysis found that WMT had significant near-transfer effects and remained significant at between 3- and 6-months follow-up. Notably, effects on the separate types of near-transfer were not investigated in this meta-analysis (Melby-Lervåg & Hulme, 2013). The significant follow-up effects were based on data from just three studies thus the authors suggest that their findings should be interpreted with caution (Rapport et al., 2013).

Small far-transfer effects of cognitive training were reported to cognitive tasks (i.e., tasks that were dissimilar to the training tasks), and effects were sustained over time. However, there were no significant effects on academic achievement.

Significant improvements in behaviour ratings (i.e., far-transfer) were reported following cognitive training, however this was only when behaviour had been rated by un-blinded raters. This highlights the need for blinded raters in studies to avoid the risk inflated effect sizes due to expectancy effects. Data from seven studies was used to calculate long term far-transfer effects (i.e., between 2 and 4 months) however no long-term significant effects were reported to cognitive tasks, academic tasks or behaviour.

Melby-Lervåg and Hulme (2013). This was the first meta-analysis to evaluate the effectiveness of WMT on near and far-transfer across age groups and learning difficulties. Both RCTs and quasi-experiments were included, with both active and passive control groups. Large near-transfer effects were reported for verbal WM, with larger gains in studies with younger children (below 10 years old) compared to those with older children (11-18 years old). However, these effects were not maintained at follow up, suggesting that beneficial effects following WMT do not last over time on tasks measuring verbal WM. Moderate transfer effects were reported on visuo-spatial WM tasks and this effect was maintained approximately five months post-intervention. Further investigation revealed that the commercial training program 'Cogmed' demonstrated higher effect sizes compared to four non-commercial programs.

Small far-transfer effects were reported to non-verbal ability tasks (i.e., tasks that measured problem solving without relying on language) but only in non-randomised studies with passive control groups. Notably, several research groups reported significant transfer effects to non-verbal ability when WMT was compared to an untreated control group yet could not replicate findings when they compared WMT to a treated control group (Melby-Lervåg & Hulme, 2013), thus highlighting the need for independent studies to include control groups to avoid overestimated effect sizes. Importantly, sub-group analysis also revealed that effects to non-verbal ability were highest in the 'young adults' age category (18- 51 years old) and when they trained for 9 hours or more i.e., these far-transfer effects are because of studies in young adults rather than in children and adolescents.

The finding that non-randomised studies with passive control groups significantly influenced effect sizes is important as it suggests that the use of randomised control groups and comparison to a treated (active) control group is essential to provide unambiguous evidence for the effects of WMT (Melby-Lervåg & Hulme, 2013).

Spencer-Smith and Klingberg (2015). The aim of this meta-analysis was to assess the transfer effects to inattention in daily life following 'Cogmed' WMT in both children and adults. The inclusion criteria for this meta-analysis were fairly strict in comparison to other meta-analyses within this review. To be included, the

intervention study had to have assessed the full 'Cogmed' training programme (i.e., 20 sessions) and include an intervention and control group (randomised or non-randomised). The control group had to either be passive, or an intervention that did *not* train a cognitive domain closely related to WM. Each study also had to include a measure of 'inattention to daily life' and this included self, parent and teacher reports on behaviour (e.g., an ADHD rating scale). These were therefore all subjective ratings.

Moderate immediate effects were found to both verbal WM and visuospatial WM. Far-transfer, measured through reduced inattention to daily life, had a significant moderate effect which was sustained 2-4 months after training. Moderator analysis was completed to test if effects were present in children and adolescent studies only (i.e., to check that effects were not solely driven by adult studies). This revealed moderate immediate transfer to inattention for children and adolescents; however, there were too few studies in youth to analyse sustained transfer effects to (i.e., after a follow-up period) in youth only samples.

Notably over half of the included studies had untreated control groups and given that passive controls are associated with overestimated effect sizes the findings should be interpreted with caution. Further, inattention was measured through subjective rating tools (completed by either teachers or parents in youth studies) yet

the likelihood of expectancy effects were not controlled for in this analysis thus this should be considered when interpreting findings.

Schwaighofer, Fischer and Buhner (2015). This was an update of Melby-Lervåg and Hulme (2013) examining the effectiveness of WMT to near and far-transfer. Schwaighofer et al. (2015) made slight variations to Melby-Lervåg and Hulme (2013) by examining 7 additional moderators. The meta-analysis included RCTs and quasi-experiments that used either a passive or active control group.

Moderate effect sizes were found for immediate and sustained (8 months) near-transfer effects for verbal and visuo-spatial short-term memory and for verbal and visuo-spatial WM. Age was not a significant moderator (i.e., effects in youth and adult studies did not appear to vary); therefore, further analysis of just youth studies was not available. Moderation analysis revealed that supervised training yielded greater effect sizes i.e., training in the presence of others. Longer training sessions for verbal short-term memory were more effective and a higher training dose for visuospatial short-term memory. The location of where participants trained was also a significant moderator however no clear pattern emerged i.e., training at home yielded higher effects for visuospatial short-term memory, training at school was more effective for verbal WM, and training in a laboratory yielded higher effects to non-verbal ability.

Far-transfer effects were reported for verbal and non-verbal ability but were small and not maintained at follow up. The only significant moderator was intervention type, with 'Cogmed' training yielding smaller effect sizes than an n-back training intervention.

Cortese et al. (2015). The objective of this meta-analysis was to establish the effectiveness of cognitive training on symptoms and academic achievement in children that either had a diagnosis of ADHD, or had met clinical cut off criteria for a diagnosis of ADHD on validated rating scales. Across 15 RCTs different types of cognitive training were evaluated with six studies focusing on WMT, four that trained WM and another cognitive domain, four on attention training and one training general executive functioning. Multiple analyses were performed and five separate effect sizes (when 5 or more trials were available) for each transfer outcome were provided. The five different effect sizes were 1) the effect size calculated when all studies were included, 2) the effect size calculated when the outcome was given by the rater most proximal to the treatment setting i.e., typically unblinded, 3) the effect calculated when the rater was 'probably blinded', 4) when just WMT studies were included and 5) only trials where <30% of participants were treated with ADHD medication.

Moderate effect sizes were reported for near-transfer to both verbal and visual WM, and on reduction of total ADHD symptoms/inattention symptoms (i.e, far-transfer). Moderate effects remained to verbal and visual WM when just 'WMT-

only' studies were analysed, and when active control studies were analysed. However, effects were no longer significant for ADHD symptoms when active control only, WMT-only, and trials including participants on <30% medication were analysed separately.

Additionally, effect size reduced from moderate to small for ADHD symptoms when the 'probably blinded' trials were analysed and became non-significant for inattention only symptoms. Thus, although at first effects appeared promising, once more stringent criteria for analyses were completed, the significant effects reduced or disappeared. Follow up data were not reported because, as the authors noted, not enough studies included long term outcomes. Importantly, findings again highlight the need for blinded raters when using subjective tools to assess far-transfer to avoid overestimated effect sizes due to potential bias.

Melby-Lervåg, Redick and Hulme (2016). The objective of this paper was to report an updated meta-analysis of the current evidence of WMT. It aimed to build upon Melby-Lervåg and Hulme (2013) and Schwaighofer et al. (2015) by including the most recent WMT RCTs or quasi-experiments with various ages, learning status and training types. In the same way as the previous studies, the focus was on evidence of near and far-transfer following WMT. A second objective was to examine the relationship between near and far-transfer. This would help confirm whether far-transfer effects were the direct result of near-transfer or were influenced by other

factors e.g. non-specific treatment effects. Given the consistent finding in previous meta-analyses that treated (or active) and untreated (or passive) trials affect effect sizes, the two types of study designs were analysed separately in this meta-analysis.

WMT resulted in improved verbal and visuo-spatial WM. These effects were moderate in size when WMT was assessed in studies with passive control groups, and small in studies with active control groups. Effects were larger in children and older adults compared to younger adults. At follow up, effects were only sustained for visuo-spatial working memory.

Small far-transfer effects were reported for reading comprehension, mathematics, and non-verbal abilities immediately after training. These effects were further investigated. The far-transfer effect to reading comprehension was, however, believed to be due to a measurement error. This was because in a small number of studies, the control groups had decreased reading comprehension from pre-test to post-test and theoretically there is no reason to expect a decrease as reading is a relatively stable construct (Melby-Lervåg et al., 2016). Therefore, authors suggested that the reading transfer effect was because of unexplained decreases in reading in the control groups rather than increased reading skills in WMT groups. Moreover, once these studies were removed the effect size in the analysis became trivial ($g = 0.08$).

Further examination of the non-verbal ability transfer effect revealed that effects were highest in n-back training studies. However, the studies that had the

largest effect sizes had very small sample sizes, used only one measure of non-verbal ability and has unexplained pre to post decreases in the control groups. Similarly, the far-transfer effect for maths was driven by 3 comparisons across 2 studies (Alloway, Bibile, & Lau, 2013; Nussbaumer, Grabner, Schneider, & Stern, 2013) where again there were unexplained decreases in the control groups score form pre to post test. When these studies were excluded, the effect size became much smaller (g = 0.14). Overall, the positive far-transfer effects following WMT appear to be due to shortcomings in study methodology rather than true effects (Melby-Lervåg et al., 2016).

Importantly, mediation analyses revealed that near-transfer (i.e., change in WM) was not related to changes in far-transfer. This suggests that although some far-transfer was observed, WMT is unlikely to have been the mechanism of change. This begs the question of what did cause changes in measures of non-verbal abilities, mathematics and reading or if they were indeed because of the methodological problems discussed above.

Peijnenborgh, Hurks, Aldenkamp, Vles and Hendriksen (2016). This meta-analysis aimed to test the effectiveness of WMT in 13 studies with children who had learning difficulties. WMT resulted in improved verbal and visuospatial WM, with moderate effect sizes and effects lasted overtime (approximately 8 months). Far-transfer immediate and sustained effects were also reported for word decoding tasks.

However, this was based on just three studies and unlike Melby-Lervåg et al. (2016) there was no further investigation into these effects. This would have been informative given that these beneficial effects have been rare or better explained by methodological problems in previous meta-analyses.

Peijnenborgh et al. (2016) also reported that older children (11 years or above) were more likely to benefit from WMT than younger children. Notably, 10 studies included children or adolescents with ADHD and there were too few studies with other populations (i.e., referred to as learning disorders unspecified in the study) to compare the effectiveness of WMT with children who had a different diagnosis to youth with ADHD.

Weicker, Villringer and Thöne-Otto (2016). This study examined the effectiveness of WMT in children and adolescents with WM deficits, healthy children, healthy adults and adult patients with acquired brain injury. Various study designs were included such as RCTs, quasi-experiments, matched groups and within group designs (i.e., randomised or not, passive or active control type). Near and far-transfer to cognitive domains and to participants' quality of life (measured via questionnaires) following training were analysed. Effect sizes for adult patients with brain injury were analysed separately but as these were only adults we do not focus on these effects. To identify if WMT was more effective for a specific population, a sub-

group analysis was completed. When separate effect sizes for either healthy children or children with WM deficits were provided, these were reported in tables 2 and 3.

Moderate near-transfer effects on WM were reported for all groups, and single group analyses revealed that children and adolescent had the highest effects (i.e., comparative to adult samples). These near-transfer effects were sustained for up to 8 months but only for children with WM deficits.

Moderation analysis also revealed a number of significant moderators across studies. Adaptive training tasks (i.e., when they increase in difficulty over time), studies using 'Cogmed', and interventions with 25 or more sessions had the highest effects.

Small far-transfer effects were reported for all studies. However, transfer to reasoning and intelligence tasks were exclusively from adult studies i.e., no significant transfer to reasoning and intelligence was reported in youth. There were no significant differences in effect sizes between populations for cognitive control, attention and long-term memory i.e., exact effect sizes for children and adolescents were not reported for these domains. Small, sustained transfer to everyday functioning was reported for youth with WM deficits ($g = 0.24$), however study design (e.g. passive or active control group) and blinding status of the parent/teacher providing behavioural reports were not controlled for. Notably, there was significant heterogeneity between the studies for reasoning and intelligence, cognitive and

everyday functioning effects and thus effects were likely overestimated (Weicker et al., 2016).

Sala and Gobet (2017). The objective of this meta-analysis was to examine if WMT enhances cognitive and academic skills in typically developing children and adolescents. All studies were either RCTs or quasi-experiments. To calculate far-transfer, the authors computed an overall effect size for near-transfer and then used moderation analysis to assess transfer of WMT to academic performance and to crystallised and fluid intelligence. There was a moderate effect of WMT on near-transfer at post-test and at follow up. The length of the follow up period however was not reported. There was a small effect of WMT on far-transfer that was specific to mathematics; however, this was thought to be because of study methods rather than a true effect. Type of control group was a significant moderator, studies that used non-randomised group allocation or a passive control group yielded higher effect sizes than those that were randomised and/or used active controls. Sala and Gobet (2017) therefore concluded that currently WMT should not be offered as an educational tool.

Aksayli, Sala and Gobet (2019). This meta-analysis aimed to examine the effectiveness of 'Cogmed' on near and far-transfer. **'**Cogmed' is a commercially available WMT program that has claimed to increase performance in academic, social, and professional settings (Pearson, 2016). The previous meta-analyses that examined 'Cogmed' reported far-transfer to measures of everyday functioning,

however only subjective measures were used (Spencer-Smith & Klingberg, 2015). Aksayli et al. (2019) included updated evidence and analysed far-transfer to objective measures (e.g., attentional skills). They included RCTs and quasi-experiments and excluded the use of subjective ratings as measures for transfer. One of the moderators was whether the experimental task resembled one or more of the training tasks in 'cogmed' *(very near transfer)* or, was a different task *(lesser near transfe*r). This moderator was significant i.e., showing an overlap between the experimental tasks and 'Cogmed' tasks thus separate analysis was completed for *'very near-transfer'* measures and *'lesser near-transfer'* measures. WM tasks that were very similar to training tasks produced moderate near-transfer effect sizes, whereas the effect was small for less similar tasks. Effect sizes were larger in child studies compared to adults and small sustained near-transfer effects were reported between 2-12 months. No far-transfer effects were revealed, thus Aksayki et al. (2019) concluded that 'Cogmed' does not lead to enhanced cognitive function, and improvements in WM performance may be because of task similarity rather than enhanced WM.

Sala et al. (2019). This was a 'second order' meta-analysis of cognitive training on immediate near and far-transfer. A 'second order' meta-analysis is essentially a meta-analysis of meta-analyses i.e., it compares meta-analyses effect sizes rather than individual study effect sizes (Sala et al., 2019). The main objective was to test the impact of WMT and the moderating effect of age.

They tested near-transfer and far-transfer in 2 separate models. Model 1 analysed immediate near-transfer effects of WMT and model 2 analysed immediate far-transfer effects. Sala et al. (2019) included 4 meta-analyses, which they proposed were the 'most comprehensive' previous meta-analyses. The meta-analyses that were selected needed to include studies that trained cognitive skills on objective measures (i.e., not subjective measures), the meta-analysis had to be recent (published in 2015 or later) and it had to measure both near and far-transfer. They included the following: typically developing child studies from Sala and Gobet (2017), a sub-sample of studies with healthy adults and children with a learning disability from Melby-Lervåg et al. (2016), and a sub-sample of older adults with and without mild cognitive impairment from Sala, Aksayli, Tatlidil, Gondo and Gobet (2018). This paper is important to include as it adds to the previous meta-analyses in that it provides a more robust statistical analysis; however, it does not include all of the meta-analysis in the current review and did not analyse sustained effects.

The analyses of Model 1, which included 99 studies of near-transfer effects of WMT found that WMT leads to small effects on other measures of WM. Effect sizes were larger for children than adults. Analysis of Model 2, which included 119 studies of far-transfer effects found no significant transfer effects. Sala et al. (2019) did not distinguish between different domains of WM and although they reported to be comprehensive regarding decisions about which studies to include and exclude, it

was ‘arbitrary’. Despite these concerns, their conclusion that whilst there is some evidence that WMT can improve performance on WM-specific tasks, these improvements do not transfer to other areas of cognitive performance, reflect the largest synthesis of research, and confirm the conclusions of previous meta-analyses.

Table 2
Outcome variables and significant adjusted effect sizes for each meta-analysis for both near immediate and near sustained transfer.

Study (authors, date)	Immediate near-transfer	N participants in analysis WMT (control) *or* total k	Length of follow-up across studies	Sustained near - transfer	N participants in analysis WMT (control)
Melby-Lervag and Hulme (2013)	VWM: d = 0.79	707(641)	9 months	VWM: ns	135(118)
	VSWM: d = 0.72	610(469)	5 months	VSWM: d = 0.41	102(954)

Rapport, Orban, Kofler and Friedman (2013)	WM: d = 0.23	Not available	3-6	Not available	WM: d=0.71
Spencer Smith & Klingberg (2015)	VWM: SMD = 0.40	257(229)	Not analysed		
	VSWM: SMD = 0.67	257(229)	Not analysed		
Cortese et al. (2015)	VWM: SMD = 0.52	k = 8	Not analysed		

Active control only: SMD = 0.58	k = 5	Not analysed
WMT only: SMD = 0.57	k = 5	Not analysed
VSWM: SMD = 0.47	k = 5	Not analysed
WMT only: SMD = 0.47	k = 5	Not analysed

Schwaighofer, Fischer and Buhner (2015)	VWM: g = 0.50	k = 42	M = 8.36	VWM: g = 0.35	k = 11
	VSWM: g = 0.63	k = 19	M = 6.83	VSWM: g = 0.63	k = 19
	VSTM: g = 0.37	k = 39	M = 8.11	VSTM: g = 0.22	k = 9
	VSSTM: g = 0.72	k = 25	M = 4.86	VSSTM: g = 0.78	k = 7
Peijnenborgh, Hurks, Aldenkamp, Viles & Hendriksen (2016)	VWM g = 0.64	229(204)	M = 8	VWM: g = 0.54	150(156)
	VSWM: g = 0.63	246(230)	M = 8	VSWM: g = 0.39	150(156)
Weicker, Villringer and	All studies WM: g = 0.37	2426 (2061)	M = 5	WM: g = 0.51	728(582)

Thöne-Otto (2016)	WM deficits: g = 0.43	Not available	M = 5	WM deficits: g = 0.73	Not available
	Healthy: g = 0.49	Not available	M = 5	Healthy children: g = 0.76	Not available
Melby-Lervag, Redick and Hulme (2016)					
Passive control groups only	VWM: g = 0.42	k = 38	Not available		
	VSWM: g = 0.51	k = 25	Not available		
Active control groups only	VWM: g = 0.31	k = 60	Not available		
	VSWM: g = 0.28	k = 40	Not available		

All studies included				VWM: g = 0.28 VSWM: g = 0.4	k = 10 k = 9
Akayli, Sala and Gobet (2019)					
	WM: g = 0.43	k = 247	2-12 months	WM: g = 0.44	k = 102
	Very near transfer g = 0.45	k = 152			
	Lesser near transfer: g = 0.25	k = 92			
Sala and Gobet (2017)	WM: g = 0.46	k = 30	Not available	WM: g = 0.33	k = 74

Sala, Aksayli, Tatlidil, Tatsumi, Gondo and Gobet (2019a)					
Effect sizes from passive control studies	TD children: g = 0.43	k = 16	Not available	TD children: *ns*	k = 25
	LD children: g = 0.32	k = 16	Not available	LD children: *ns*	k = 18
	Adults: g = 0.18	k = 31	Not available	Adults: *ns*	k = 44
	Older adults: g = 0.17	k = 34	Not available	Older adults: *ns*	k = 31
Effect sizes from active control studies	TD children: g = 0.35	k = 11	Not available	TD children: *ns*	k = 15
	LD children: g = 0.23	k = 13	Not available	LD children: *ns*	k = 12
	Adults: g = 0.17	k = 20	Not available	Adults: *ns*	k = 27
	Older adults: g = 0.17	k = 19	Not available	Older adults: *ns*	k = 16

Note. D = cohen's d, g = hedges g, LD = learning disability, k = total studies included, LTM = long term memory, M = mean, *ns* = non-significant effect, TD = typically developing, SMD = standardised mean difference, VWM = verbal working memory, VSWM = visuo-spatial working memory, VSTM = verbal short term memory, VSSTM= visuo-spatial short term memory, WM= working memory.

Table 3

Outcome variables and significant effect sizes for each meta-analysis for far immediate and far sustained transfer

Study (authors, date)	Immediate far transfer	N participants in analysis WMT(control) or k	Length of follow-up across studies (months)	Sustained far transfer	N participants in analysis WMT(control)
Melby-Lervag and Hulme (2013)	Nonverbal ability: d= 0.19	628(528)	7.8	Nonverbal ability: *ns*	138 (120)
	Verbal ability: *ns*	317(215)	5	Verbal ability: *ns*	102 (94)
					91 (84)
	Decoding: *ns*	197(196)	3.7	Decoding: *ns*	108 (76)
	Maths: *ns*	198(188)	3.3	Maths: *ns*	
	Inhibition: *ns*	194(168)			

Rapport, Orban, Kofler and Friedman (2013)	Cognitive: d=0.14 Academic: *ns* Blinded ratings: *ns* Unblinded ratings: *ns*	Not available	2-4	Cognitive: *ns* Academic: *ns* Blinded ratings: *ns* Unblinded ratings: *ns*	Not available
Spencer Smith & Klingberg (2015)	Inattention in daily life: SMD = -0.47	259 (229)	2-4	Inattention in daily life: SMD = - 0.33	146(133)
Cortese et al. (2015)	ADHD total all studies included: SMD = 0.37	k = 14	Not analysed		

ADHD total ‘probably blinded’: SMD = 0.2	k = 11
ADHD total active control only: SMD = ns	k = 7
Inattention all studies: SMD = 0.47	k = 11
Inattention ‘probably blinded only’: SMD = ns	k = 9
Inhibition all studies included: SMD = ns	k = 6
Attention all studies: SMD = ns	k = 7
Reading: SMD = ns	k = 5

	Maths: SMD = ns	k = 5			
Schwaighofer, Fischer and Buhner (2015)	Verbal ability: g = 0.16	k = 29	M = 12.8	Verbal ability: *ns*	k = 5
	Nonverbal ability: g = 0.14	k = 45	M = 6.54	Nonverbal ability: *ns*	k = 11
	Decoding: *ns*	k = 14	M = 6.20	Decoding: *ns*	k = 5
	Maths: *ns*	k = 15	M = 6.13	Maths: *ns*	k = 8
Peijnenborgh, Hurks, Aldenkamp, Viles & Hendriksen (2016)	Nonverbal ability: *ns*	k = 4	2-8	Nonverbal ability: *ns*	k = 2
	Verbal ability: *ns*	k = 3		Verbal ability: *ns*	k = 1
	Decoding: g = 0.36	k = 4		Decoding: g = 0.48	k = 3
	Maths: *ns*	k = 2		Maths: *ns*	k = 2
	Inhibition: *ns*	k = 4		inhibition: *ns*	k = 2

Weicker et al (2016)	Reasoning: g = 0.23	1719(1554)	M = 5	Reasoning g = 0.20	472 (427)
	Executive function: g = 0.20	1535(1558)	M = 5	Executive function g = 0.20	464(428)
	Attention: g = 0.18	1080(944)	M = 5	Attention: *ns*	286(220)
	LTM: g = 0.18	678(490)	M = 5	LTM: ns	160(139)
	Everyday functioning: g = 0.29	797(490)	M = 5	Everyday functioning: g = 0.14	797(642)
Melby-Lervag, Redick & Hulme (2016)	Nonverbal ability: g = 0.20	k = 53	M = 5	Nonverbal ability: *ns*	k = 7
Passive control comparisons only	Verbal ability: *ns*	k = 16	M = 5	Verbal ability: *ns*	k = 2
	Decoding: *ns*	k = 7	M = 5	Decoding: *ns*	k = 2
	Maths: g = 0.12	k = 14	M = 5	Maths: *ns*	k = 6

	Reading: *ns*	k = 7	M = 5	Reading: *ns*	k = 2
Active control comparisons only	Nonverbal ability: *ns*	k = 67	M =5	Nonverbal ability: *ns*	k = 12
	Verbal ability: *ns*	k = 22	M = 5	Verbal ability: *ns*	k = 3
	Decoding: *ns*	k = 10	M = 5	Decoding: *ns*	k = 3
	Maths: *ns*	k = 15	M = 5	Maths: g = 022	k = 10
	Reading: 0.05	k = 19	M = 5	Reading: *ns*	k = 1
Gobet and Sala (2017)	Overall WM: g = 0.12	k = 74	Not reported	Overall WM: *ns*	k = 24
	Literacy: *ns*	k = 17	Not analysed		
	Fluid intelligence: *ns*	k = 14	Not analysed		
	Cognitive control: *ns*	k = 3	Not analysed		

	Crystallised intelligence: ns	k = 2	Not analysed		
	Science: *ns*	k = 2	Not analysed		
	Maths: g = 0.18	k = 17	Not analysed		
Aksayli, Sali & Gobet (2019)	Overall WM: *ns*	k = 194	2-12 months	Overall WM: *ns*	k = 91
Sala, Aksayli, Tatlidil, Tatsumi, Gondo and Gobet (2019a)					
Effects sizes from studies with passive control groups.	TD children: *ns*	k = 25	Not analysed		
	LD children: *ns*	k = 18	Not analysed		

	Adult: *ns*	k = 44	Not analysed
	Older adults: *ns*	k = 31	Not analysed
Effects sizes from studies with an active control group.	TD children: *ns*	k = 15	Not analysed
	LD children: *ns*	k = 12	Not analysed
	Adult: *ns*	k = 27	Not analysed
	Older adults: *ns*	k = 16	Not analysed

Note. D = cohen's d, g = hedges g, LD =learning disability, k = total studies included, LTM = long term memory, *ns* = non-significant effect, TD = typically developing, SMD = standardised mean difference, WM = working memory

Discussion

The objective of this review was to provide a summary and evaluate the evidence from multiple meta-analyses that have assessed the efficacy of WMT in children and adolescents. We did this to establish if WMT enhances working memory in youth (near-transfer) and, importantly, if skills transferred to other cognitive or psychological domains (far-transfer). The following sections aim to describe the effectiveness of WMT and whether effects change in different populations. Following this, evaluations of the meta-analyses, and how methodological differences may impact effect sizes will be discussed.

The effects of WMT on near and far-transfer

Reviewing both near and far-transfer effects is essential as the magnitude of far-transfer is capped at the magnitude of near-transfer (Shipstead, Redick & Engle, 2012). As such, any far-transfer effects should be similar to, or less than, the effects found on WM tasks (i.e., near-transfer) otherwise WM is unlikely to be the cause of any far-transfer effects seen. Far-transfer effects are critical to demonstrate the practical or clinical applicability of WMT on cognitive and behavioural outcomes (Melby-Lervåg & Hulme, 2013). A summary of the findings for near and far-transfer will be described including how WMT effects may differ across populations.

Near-transfer

There was consistent evidence across meta-analyses of significant moderate effects to WM tasks following WMT. This effect was demonstrated to both verbal and

visuospatial WM tasks (e.g., Melby-Lervåg et al., 2016). Aksayli et al. (2019) reported moderate near-transfer effects to WM tasks that were most similar to training tasks, yet small effects to WM tasks less similar. This may suggest that, in part, significant near-transfer effects may be due to variables such as practice effects, rather than enhanced working memory (Aksayli et al., 2019). When sustained near-transfer was measured, the length of follow-up time varied between meta-analyses (1-12 months). This makes it difficult to accurately conclude if effects last over time and for how long. However, most effects either reduced over time or became non-significant (Melby-Lervåg & Hulme, 2013; Rapport et al., 2013; Schwaighofer et al., 2015; Peijnenborugh et al., 2015).

Far-transfer

Far-transfer is presented differently across meta-analyses, therefore reviewing multiple meta-analyses was helpful to gain a wider understanding of far-transfer effects. Both subjective tools (e.g., behaviour ratings) and objective measures (e.g., maths performance) were used to assess far-transfer. Subjective measures are often self-reports or interviews, and for children and adolescents they are usually completed by parents or teachers. These types of measures are good indicators for how WMT may have impacted everyday life. However, subjective measures can be sensitive to expectancy effects and therefore are most reliable when the person completing the report is blind to the treatment condition (Cortese et al., 2015).

Evidence of far-transfer to cognitive and behavioural changes through subjective measures were reported in four meta-analyses (Rapport et al., 2013; Cortese et al., 2015; Spencer-Smith & Klingberg, 2015; Weicker et al., 2016). However, once Rapport et al. (2013) and Cortese et al. (2015) analysed blinded measures only, far-transfer effects became non-significant. Neither Spencer-Smith and Klingberg, (2015) or Weicker et al. (2016) controlled for the potential influence of expectancy effects, thus any far-transfer effect to 'everyday functioning' may be the subject of bias.

Far-transfer was assessed in several ways across meta-analyses using objective measures. Small transfer effects were reported for cognitive control (e.g., when measured via the Stroop task), however this effect was calculated from a small number of studies and was driven by effects in adult populations (Melby-Lervåg & Hulme, 2013; Weicker et al., 2016). Seven meta-analyses reported small effects immediately post WMT. However, three of these effects were better explained by study methodology or measurement error (Melby-Lervåg & Hulme, 2013; Melby-Lervåg et., 2016; Sala & Gobet, 2017).

Four meta-analyses reported significant sustained far-transfer effects to one or more cognitive domains. Crucially, as described in the independent reviews, both Melby-Lervåg et al. (2016) and Rapport et al. (2013) highlighted problems with the findings, thus rendering them unreliable. Consequently, only two meta-analyses from the original 11 reported sustained far-transfer. Further, the small effect to 'word

decoding' tasks in Peijnenborogh et al. (2016) came from a small number of studies that were both non-randomised designs and had passive control groups. Additionally, the far-transfer effect size was greater than the near-transfer effect, which is incongruent with the 'transfer' theory (Shipstead et al., 2012). Therefore, this far-transfer effect should be interpreted with caution.

It should be noted that there were substantially fewer studies measuring far-transfer which may have impacted the paucity of significant findings.

WMT effects in different populations

When observing the findings in this review, two populations were commonly analysed across meta-analyses. These were the learning status of participants (e.g., typically developing, learning disabilities, children with ADHD symptomology) and the age of participants. Although the focus of this review was to identify the effectiveness of WMT in youth, some meta-analyses did include adult studies (e.g., Melby- Lervåg et al. 2016).

The impact of learning status on near-transfer effects

Both typically developing youth, and participants experiencing a learning disorder or ADHD symptomology exhibited immediate and sustained near-transfer following WMT (e.g., Melby- Lervåg et al., 2016). Studies that separated effect sizes by learning status reported similar effect sizes for both groups (e.g., Weicker et al., 2016; Sala et al., 2019a). Melby- Lervåg et al. (2016) found higher effect sizes in participants with a learning disorder, however this effect size included both youth and

adult studies therefore it was unclear which studies were driving the effect. Meta-analyses that focused on one population, e.g., Sala and Gobet (2017), included only studies with typically developing children and adolescents. They found moderate near-transfer effect sizes both immediately after training and after a follow up period. These effects were similar to meta-analyses that included only youth with ADHD symptoms (Rapport et al., 2013; Cortese et al., 2015), or youth with a learning disorder (Peijnenborgh et al., 2016). Overall, it appears WMT effects for near-transfer were similar for typically developing youth, and those with learning or behavioural difficulties (Melby-Lervåg & Hulme, 2016; Spencer-Smith & Kingberg, 2015; Schwaighofer et al., 2016; Melby- Lervåg et al. 2016; Weicker et al., 2016; Aksayli et al., 2019; Sala et al., 2019a).

The impact of age on near-transfer effects

Four meta-analyses (e.g., Spencer-Smith & Klingberg, 2015; Schwaighofer er al., (2015); Sala et al., 2019) found no significant differences between age groups. Whereas Melby-Lervåg et al. (2016), Aksayli et al. (2019) and Sala et al. (2019) reported larger near-transfer effect sizes for children/adolescents compared to adults.

When focusing on age differences in youth, inconsistent findings were reported. Melby-Lervåg and Hulme (2013) found that younger children (age 10 and below) performed better than older children after training, whereas Peijnenborgh et al. (2016) reported that older children (over 11) exhibited higher effects than younger children. Other meta-analyses either found no differences in youth age or did not

analyse youth studies separately. Overall, there is not enough evidence to conclude if WMT efficacy is higher for younger children compared to older. Nonetheless, all youth did improve on near-transfer tasks after WMT across meta-analyses, and the evidence does suggest that WMT may be more effective for younger populations compared to adults (e.g., Sala et al., 2019a).

The impact of age and learning status on far-transfer

Most meta-analyses measuring sustained far-transfer found non-significant results for both various ages and learning status (Melby-Lervåg & Hulme 2013; Rapport et al., 2013; Cortese et al., 2015; Schwaighofer et al., 2015; Gobet & Sala, 2017; Sala et al., 2019b).

One meta-analysis that focused on youth with learning difficulties (Spencer Smith & Klingberg, 2015) reported far-transfer to inattention to daily life (measured via a questionnaire), however, this effect is questionable because the meta-analysis did not control for unblind raters, thus expectancy effects may have impacted the outcome.

Overall, the effectiveness that WMT had on various far-transfer measures to distal cognitive and behavioural measures was disappointing across the age span and for both typically developing participants and those with a learning difficulty (e.g., Spencer-King & Klingberg, 2015; Melby-Lervåg et al., 2016).

Evaluation of the Mata-analyses that were included in the Meta-Review

Each meta-analysis was rated for methodological quality using the AMSTAR rating scale (Shea et al., 2007) (please see appendix 4). The tool measures if necessary methodological stages had been carried out for each meta-analysis. For example, whether a comprehensive literature search was conducted or whether publication bias was assessed. All meta-analyses used three or more databases to search for studies except for Spencer-Smith and Klingberg (2015), who only used two databases. Most authors also conducted additional searches, such as, scanning reference lists from relevant journals (Schwaighofer et al., 2015; Melby- Lervåg et al. 2016; Gobet & Sala 2017; Aksayli et al., 2019; Sala et al., 2019a; Sala et al., 2019b), or emailing authors in the field for unpublished data (e.g., Melby-Lervåg & Hulme, 2013; Rapport et al., 2013). Only Spencer-Smith and Klingberg (2015), Peijnenborgh et al., (2016) and Weicker et al., (2016) used a database search only. Notably, these 3 studies were included in the few that reported far-transfer effects. It is possible that this may have impacted effect sizes, as appropriate studies could have been missed. This could also perhaps be a reason for why Spencer-Smith and Klingberg (2015), Peijnenborgh et al., (2016) had the least studies in their analyses.

The assessment of publication bias is another important methodological step when conducting meta-analyses. All but one meta-analysis used common strategies, such as funnel plots and fill/trim analysis, to assess this (although, notably, these procedures become less reliable when there are few studies; Cooper, Hedges, &

Valentine, 2009). Melby- Lervåg et al. (2016) used an alternative method (i.e., p curve analysis), which is suggested to overcome weaknesses with the funnel plot/trim-and-fill analysis (Simonson, Nelson & Simmons, 2014). This may imply that their assessment of publication bias may be more accurate and, in turn, their findings more reliable.

On a similar note, four of the meta-analyses did not include grey literature (i.e., unpublished data), increasing the risk of publication bias (Cortese et al., 2015; Peijnenburgh et al., 2016; Spencer-Smith & Klingberg, 2015; Weicker et al., 2016). Cortese et al. (2015) included only published studies, however each study was assessed for risk of bias by two researchers. Importantly, the other meta-analyses that included only published literature did not report doing an independent assessment of risk and were also the only three meta-analyses that concluded that WMT skills transferred to everyday life. This suggests that these outcomes should be considered with caution.

After evaluating each meta-analysis for methodologic quality, those meta-analyses with the lowest quality ratings were also those reporting significant far-transfer effects following WMT (Weicker et al., 2016; Peijnenborgh et al., 2016; Spencer-Smith & Klingberg, 2015). Importantly, those with high quality ratings concluded that WMT does not transfer to other tasks that assess cognition or behavioural symptoms (Aksayli et al., 2019; Cortese et al., 2015; Melby-Lervåg & Hulme, 2013; Melby-Lervåg et al., 2016; Rapport et al., 2013; Sala & Gobet, 2017;

Sala et al., 2019). This suggests that those meta-analyses reporting significant effects were less robust and thus findings that WMT transfers to 'real life' should be interpreted with caution.

When observing the factors that may affect effect sizes, it was apparent that the quality of the individual studies that were selected for analyses, and how these influences were controlled, likely affected the final outcomes. Differences in individual studies highlighted that significant far-transfer effects were mostly found among studies with non-randomised conditions, studies using passive control groups, or studies using subjective tools used by unblinded raters to assess behaviour or symptom change.

It has been argued that only studies using treated control groups provide adequate control for non-specific treatment effects (e.g., familiarity of being assessed on a computer; Shipstead et al., 2012). Meta-analyses managed the potential effects of 'type control group' used in different ways. Most meta-analyses controlled for this by including the control type as a moderator in their analyses. This was done either by checking if effects from active control group comparisons significantly differed from passive controls (e.g., Melby-Lervåg & Hulme, 2013; Schwaighofer et al., 2015) or by analysing active and passive groups separately (Melby-Lervåg & Hulme, 2016; Sala et al., 2019a). For example, Melby-Lervåg & Hulme (2013) found that studies with a passive control group yielded significantly greater effects than studies with

active control groups. This suggests some of the significant far-transfer effects may be due to flaws in study design.

Randomisation is generally accepted to be the best way to ensure that the results of an intervention reflect a causal effect, because it verifies that pre-existing individual differences cannot explain differences in outcomes between groups (Shadish, Cook & Campbell, 2002). All but one meta-analysis included studies using quasi-experimental design and thus it was important to consider if the lack of randomisation in individual studies influenced effects. Effects were smaller in randomised designs (Melby-Lervåg & Hulme, 2013; Melby- Lervåg et al. 2016; Sala & Gobet, 2017). Crucially, the two meta-analyses reporting consistent far-transfer effects did not take randomisation into account (Weicker et al., 2016; Spencer-Smith & Klingberg, 2015), which reduces the reliability of their findings.

Furthermore, both objective and subjective tools were included as measures of far-transfer in their individual studies. However, Rapport et al. (2013) and Cortese et al. (2015) demonstrated that significant effects were not maintained when only effect sizes from blinded raters were included in analyses, highlighting the importance of blind trials in individual studies.

It was also worth noting, meta-analyses with fewer studies were often those to report far-transfer. For example, Spencer-Smith & Klingberg (2015) had 11 studies, Peijenburgh et al. (2015) had 13, and Cortese et al. (2015) had 16. Whereas those meta-analyses that included a greater number of studies reported less or no significant

far-transfer effects (Schwaighofer et al., 2015; Melby- Lervåg et al., 2016). Therefore, the number of studies included in the analysis has an evident effect on overall transfer effect sizes.

In some meta-analyses, effect sizes for specific groups of interest were analysed and presented separately. This allowed for a more accurate assessment of transfer effects within meta-analyses that took this approach. For example, Aksayli et al. (2019) distinguished near-transfer by 'very near-transfer' and 'lesser near-transfer', revealing smaller effects when tasks were less similar to the training tasks. This questions if the similarity of training and experimental tasks may have affected other meta-analyses effect sizes. Other meta-analyses split their findings by the learning status of participants (Weicker et al., 2016; Sala et al., 2019) and by studies with passive and active control groups (Melby- Lervåg et al. 2016; Sala et al. 2019). By splitting effect sizes into categories to control for certain factors, more specific effect sizes for areas of interest, such as age, can be assessed more clearly.

Another observation that influences the understanding of the findings was the level of further investigation completed by authors when significant far-effects were calculated (i.e. if effect sizes appeared to be inconsistent with previous literature, or if authors had reason to be cautious). For example, far-transfer to 'maths' in Melby-Lervåg et al. (2016) was driven by unexplained decreases in control groups rather than improvement in the WMT groups. Conversely, Peijnenborgh et al. (2016), did not report any further examination of their far-transfer to decoding. Given that this

was the only meta-analysis to report beneficial effects to decoding tasks and considering their far-transfer effect was greater than their near-transfer effect, a further investigation into which independent studies had found beneficial effects would have been pertinent, to clarify if effects were reliable. When taking a closer look at this finding, it appeared that 4 individual studies were driving the effect to decoding tasks. Each were small studies with passive control groups (Alloway, 2012; Alloway, Bibile & Lau 2013; Dahlin, 2011; Engeland, Aarlien & Saunes, 2013). For example, Alloway et al. (2012) had just 8 participants in their experimental group. Additionally, three of these studies were included in a higher quality meta-analysis (Melby-Lervåg et al., 2016), which also measured WMT effects to 'de-coding' and found no significant transfer. Therefore the 'decoding' transfer finding from Peijnenborgh et al. (2016), should be interpreted with caution.

Evaluation of the Meta- Review and Future Suggestions

The review emphasised that the quality of the individual studies included in each analysis had effects on outcomes (e.g., passive control groups in individual studies lead to inflated effect sizes) and helped identify ways to manage this. For instance, analysing studies with passive control groups versus active control groups separately. Recognising different methods of analysing and presenting data differently provided useful ideas for future meta-analyses, such as, assessing verbal and visual working memory to 'lesser near' and 'nearer near' transfer dependent on how similar the eperimental tasks were to the training tasks (Aksayli et al., 2019). The review also

highlighted the importance of measures that should be included (e.g., potentially analysing only objective measures to reduce bias or ensure the use of subjective measures had bind raters).

Although the review was valuable there were a number of sub-optimal elements. It was not possible to directly compare the meta-analyses as they are different in many ways (e.g., inclusion criteria, how far-transfer was categorised). Most importantly is the problem of interdependence i.e., many meta-analyses included the same studies, and the review could not account for this. This is a key limitation because certain studies may have critical influencing effects. For instance, if a particular individual study(s) reported very high or low effect sizes, then this would influence total effect sizes across multiple meta-analyses, thus influencing overall conclusions of both these meta-analyses and therefore this review. For example, Rapport et al. (2013) found immediate and sustained near-transfer. However, sustained effects were driven by three studies thus authors suggested results should be interpreted with caution (Rapport et al., 2013). Therefore, if these three studies were included in other meta-analyses the same problem would occur, i.e., an over estimation of sustained near-transfer. Conversely, given the multiple findings of no significant far-transfer, it would be optimal to investigate if any particular studies were driving this across the multiple meta-analysis. A more efficient way of managing this and to ensure no study is used more than once would be to conduct a stronger meta-analysis using the information from the review. Alternatively, to

conduct a second order meta-analysis including youth studies only, in a similar way to Sala et al. (2019).

For future researchers interested in WMT effects in youth, a meta-analysis could be conducted using the evaluation of the previous meta-analyses. For example, by using only youth studies, and separating analysis by both study design (i.e., passive/active control groups), control group (randomised/ non-randomised) and by age. None of the previous meta-analyses looked specifically at whether there was a difference between younger children and adolescents. Given that this is a major period of developmental change (i.e.., the continuous development of the prefrontal cortex which is essential for optimal cognitive functioning including working memory; Blakemore & Choudary, 2006), it would be of interest to assess if WMT effects change between children and adolescents. Other factors which would strengthen future meta-analyses would be to separate effect sizes into 'lesser' and 'nearer' near-transfer depending on how close the experimental tasks were to the training tasks (Aksayli et al., 2019), grey literature, and a strict search criterion based on the quality of selected studies. In addition, future work would benefit from either excluding subjective measures of WM or only including studies whereby participants were blind to the intervention. Further, future researchers should conduct further investigations for any effect sizes that may be questionable.

Alternatively, future research could concentrate on other interventions that may have more global effects beyond increasing short-term performance on WM tasks.

Concluding remarks

This review was helpful for a number of reasons, such as, gaining a better understanding of WMT efficacy and whether these effects differ across populations. It also revealed important variables (e.g., quality of individual study selection) that may influence effect sizes. Overall, the review suggests that WMT leads to near-transfer effects, to both verbal and visuo-spatial WM tasks across all age groups. However, there was a consistent pattern of effects reducing over time. Most importantly, to demonstrate whether WMT has any clinical or practical application, meta-analyses need to report significant far-transfer effects. Unfortunately, the evidence from the higher quality meta-analyses in particular, currently suggests that WMT does not produce far-transfer effects to other cognitive or behavioural domains (e.g., Melby-Lervåg & Hulme, 2016; Sala & Gobet, 2017; Aksayli et al., 2019; Sala et al., 2019b). Specifically, evidence suggests that WMT does not enhance measures that assess academic achievement, behaviour or general intelligence in either healthy youth or children or adolescents with a learning disability.

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5 Chapter 6: An Introduction to flavonoids

5.1 Introduction to the chapter

Owing to the limited effects of working memory training on cognition, as highlighted in paper 3, additional research was completed to find an alternative strategy to enhance executive control. Evidence has found that flavonoids can increase ability on several cognitive functions (e.g., working memory), and research suggests that flavonoid supplementation is also beneficial for mood. It has been proposed that flavonoid intake increases blood flow to the brain. This is important because brain regions such as the pre-frontal cortex (the area of the brain associated with executive functioning) are rapidly maturing throughout adolescence and into early adult years, thus increased blood flow to this area may help strengthen neural circuitry. With this in mind it has been hypothesised that increasing cognition via flavonoid intake has the potential to lead to improved mood (Vauzour, Vafeiadou, Rodriguez - Mateos, Rendeiro & Spencer, 2008).

Therefore, this chapter will introduce dietary flavonoids, and discuss the evidence that suggests flavonoids can have beneficial effect on cognition and mood. Studies that assess the effects of flavonoids have rarely used adolescents, therefore this chapter focuses on research that has been completed with children and young adults (i.e., rather than older adults) as it is likely that these studies are the most relevant to the current thesis. This chapter will also describe the potential mechanisms that have been

hypothesised to underlie the beneficial effects of flavonoids on improved cognition and mood.

5.2 What are flavonoids?

Flavonoids are a large subgroup of polyphenols. There are many different types of polyphenols, of which flavonoids are the second most common in the human diet (Probst, Guan & Kent, 2018). Polyphenols are phytochemicals that are found abundantly in plant-based products and are receiving increasing interest due to the positive association between health benefits and polyphenol-rich food i.e., fruit and vegetables. They are known to have antioxidant properties and play a potential role in the prevention of various diseases such as cancer, cardiovascular and neurodegenerative diseases (Manach, Scalber, Morand, Remesy & Jimenez, 2004).

Flavonoids are a micronutrient found in various concentrations in plant-based foods such as berries, tea, cocoa, soybeans and grains (Spencer, 2008). Flavonoids are split into 12 sub-categories based on their molecular structure, however six of these are of dietary significance. The dietary flavonoid sub-classes are; flavonols, flavones, isoflavones, flavanols, flavanones and anthocyanidins. Anthocyanidins are found in fruits and vegetables; their pigments are purple, red and blue and are usually found in berries (e.g., blueberries, strawberries and red grapes) and vegetables that are red or purple in colour (e.g., red cabbage and aubergines). Flavonols are also found in vegetables (e.g., onions) and small amounts can be found in blueberries and blackberries. Flavanols are most commonly found in cocoa (e.g., dark chocolate) and green and black tea. Flavanones can be found in citrus-based fruits such as grapefruits

and oranges. Lastly, isoflavones can be found in soy products (e.g., soy beans) (Spencer, 2008).

Both epidemiological and clinical studies have found evidence to suggest that increased levels of dietary flavonoid elicit health benefits by reducing the risk factors associated with several diseases such as, cardiovascular disease, stroke & cancer (Basu, Rhones & Lyons, 2010; Novotny, Baer, Khoo, Gebauer & Charron, 2010; Del-Rio et al., 2013). More recently there is growing interest on the effects of flavonoid consumption and cognitive benefits e.g., improved executive functioning performance. This evidence is reviewed in detail below (6.3).

5.3 The effects of flavonoids and executive functioning performance

5.3.1 Can a healthy diet improve cognition?

Diet and nutritional intake have a positive effect on both development and cognitive performance in humans and animals (Benton, 2008; Gomez-Pinilla, 2008). For example, a recent meta-analysis evaluated the impact of eating a healthy diet (e.g., grains, fish, fruits and/or vegetables) on executive functioning in children and adolescents aged between 6-18 years. Twenty-one studies were included that measured food quality, micronutrient intake and long-term diet and executive function. Overall, there was a positive association between healthier food consumption and executive functioning, and less-healthy food patterns were inversely associated with executive functioning (Cohen, Gorski, Gruber, Kurdziel & Rimm, 2016). This meta-analysis, therefore, highlights the potential benefits of dietary interventions on improving executive function in children and adolescents. A healthy diet would be rich in

flavonoids, and there are accumulating studies examining the potential effects of flavonoids on cognition.

In nutritional studies two methods are commonly used, ‘acute’ and ‘chronic’ supplementation. Acute supplementation refers to when one, short dose of supplementation is given, and effects are measured after a given time. For example, the peak absorption and metabolism of anthocyanins occurs in a 2-hour interval (Rendeiro et al., 2012), therefore acute effects are often measured 2 hours post supplementation in flavonoid studies. Whereas chronic supplementation occurs over a longer period, this could be days, weeks, or years.

5.3.2 Can flavonoids enhance executive functioning?

Several chronic and acute studies have examined the effects of dietary flavonoids across various age groups. Acute supplementation refers to participants receiving one dose of the chosen supplementation (e.g., drink or tablet) before tests are completed, whereas chronic studies assess the effects of continuous supplementation over time. Lamport, Dye, Wightman and Lawton (2012) completed a systematic review exploring the chronic and acute effects of flavonoids and other polyphenols (e.g., Ginkgo Biloba) on executive functioning (i.e., immediate verbal working memory, delayed spatial working memory and category fluency) in adults. Cognitive improvements after supplementation were reported on immediate verbal working memory, delayed spatial working memory and other executive function tasks e.g., category fluency. They concluded that additional polyphenols consumption in the diet can lead to cognitive benefits; however, the effects observed were small.

Although informative, this review only included adult studies and many samples were with older aging adults, thus to gain a better understating of potential flavonoid effects on executive functioning in adolescents, reviewing research in youth and young adults may be more appropriate.

The majority of studies that have investigated the effects of flavonoids on executive functioning have used cocoa (rich in flavanol) or berries (a source of anthocyanins). Research assessing the effects of flavonoids on executive functioning in adolescents appears to be non-existent thus the following sections will focus on the studies that have been completed with young adults (i.e. below 35 years) and children (i.e. below 12 years).

5.3.3 The effects of flavonoids on executive functioning in young adults

Sholey et al. (2010) conducted an acute, double-blind crossover study with 30 young adults to assess the effects of two different doses of cocoa flavanol on executive function tasks. Participants' working memory performance improved following 520mg of cocoa flavanol and improved to attention tasks post a higher dose of 994mg. A similar study conducted with 18-30-year olds (n=30), compared a dark chocolate bar containing a 773mg dose of flavanols, to a low flavanol white chocolate control. Improvement in visual spatial working memory, and reduced reaction times to a choice reaction time task were reported after the high dose chocolate. However, these results should be interpreted with caution as the two types of chocolate were not matched for levels of caffeine or theobromine thus effects may not have been due to flavanol intake alone (Field, Williams & Butler, 2011). When assessing the effects of nutritional

supplementation, it is important to check that the control intervention is matched for levels of other ingredients that may influence findings. For example, sugars (e.g., glucose and fructose) provide extra energy, which may cause enhanced cognitive performance (Busch, Taylor, Kanarek & Holcomb, 2002).

Several studies have used berry anthocyanins when examining the effects of flavonoids on executive functions in young adults. A randomised cross-over design study assessed the acute effects of a blueberry drink (containing 579mg of flavonoids) on working memory in 19 healthy young adults. Cognitive performance was measured at baseline, two- and five-hours post drink. Working memory performance was significantly increased 5 hours post blueberry consumption (Dodd, 2012). A larger study (n=36) examined the effects of blackcurrant anthocyanins on tasks assessing executive function through a double-blind controlled crossover design. Compared to a control condition, participants' performance increased on a task that measured sustained attention and working memory. It is hard to evaluate the potential effects of flavonoids by comparing these studies due to study differences, such as flavonoid type, method of flavonoid consumption and dose, and the different executive function tasks used. However there appears to be promising preliminary findings that flavonoids benefit cognitive functioning i.e., working memory performance.

5.3.4 The effects of flavonoids on executive functioning in children

All of the studies in young adults assessed cognitive function following acute supplementation. However, one study in children assessed the effects of a chronic flavonoid supplementation. Calderon-Garcidueanasn et al. (2013) carried out a pre/post

design, chronic supplementation study with cocoa flavonoids. They recruited 18 children (mean age 10.5 years) and all participants were asked to avoid flavonoid-rich food for 15 days prior to the intervention. They were then given a cocoa flavonoid drink supplementation, of 680mg of coco-flavanols, over an average of 10 days (the minimum number of days was 9 and the maximum 24). Participants completed two short-term working memory tasks (a letter span task and an object span task) before and after the intervention to measure executive functioning. Fifteen, of the 18 children, showed significant individual improvement from pre to post intervention in a short-term memory task. However, this was not a randomised control trial and the duration of the intervention differed between participants. Further, the second (and final) testing session was completed four hours after the final dose of cocoa and children were able to add as much sugar as they wanted to their drinks. Therefore, the observed working memory improvements could have been from either chronic or acute flavonoid effects, or from additional sugar, as sugar is known to impact cognitive performance in children (Busch, Taylor, Kanarek & Holcomb, 2002).

All other research on flavonoids with children has examined the effects of acute supplementation. Whyte and Williams (2015) tested the effects of acute blueberry supplementation in a small sample of 8-10-year olds. Using a crossover design, 14 children were given a blueberry drink on one day and a matched placebo drink on another. Cognitive testing was completed 2 hours post-consumption of the drink. After consumption of the blueberry drink (and not after the placebo drink) children significantly improved on an auditory verbal learning task. The improvement in delayed

word recall post-flavonoid consumption suggests that children were encoding memory items more effectively after the blueberry drink. However, no beneficial effects were seen on tasks measuring attention, inhibition or visuo-spatial working memory. This, however, could have been due to power given the small sample size (Whyte & Williams, 2015). The same research group then completed a larger double-blind cross-over study, investigating different doses of anthocyanin supplementation on cognition in 21 children (aged 7-10 years). Each participant was involved in three full days of testing that included tests at baseline, 1.15 hours, 3 hours and 6 hours post their supplementation drink (which was 15g of wild blueberries/127mg anthocyanins, 30g of wild blueberries containing 253mg anthocyanins or a vehicle-only drink). The washout period in-between testing was 7 days. The highest dose of flavonoids resulted in significant improvement in immediate word recall 1.25 hours after drink consumption, and in delayed word recognition 6 hours post intervention. This suggests that at this time point and at the 30g dosage, children were encoding words more effectively after the blueberry drink. Significant improvements in accuracy on an inhibition and attention task (i.e., a modified flank task) were also seen 3 hours post the 30g blueberry drink, indicating that flavonoid supplementation may be beneficial for executive control processes in children (Whyte, Shafer & Williams, 2016).

The above studies indicate that flavonoid consumption may improve some areas of executive function. However, it is important to examine whether improvement in executive function transfers to everyday cognition. Barfoot et al. (2018) completed a randomised, single-blind, parallel-groups study. They recruited 54 typically developing

children (aged 7-10 years) to test whether an acute supplementation of a flavonoid-rich blueberry drink boosted executive function performance and reading ability. Children were given a blueberry rich drink (containing 253mg anthocyanins) or a matched placebo drink. Executive function tasks were completed 2 hours post-consumption to ensure optimum absorption of the flavonoids. Two tasks were used to assess executive function, an auditory verbal learning task and an attention task measuring vigilance, selective attention and inhibition. Children in the blueberry supplementation group exhibited improved verbal learning and quicker reaction times to the attention/inhibition task compared to the placebo group. Because there was no difference in accuracy, this suggests that increased speed on the attention task following blueberry supplementation was without cost on accuracy. The study did not find any improvement on reading abilities, however, Barfoot et al. (2018) suggested that a chronic flavonoid supplementation may have a greater benefit and generalise to more global functioning (i.e., reading). This suggests that future studies should assess chronic (i.e., for a longer period of time) interventions on executive functioning.

The above research presents promising findings for both acute and chronic flavonoid intervention in children. However, the majority of the studies have assessed executive functioning following acute flavonoid intervention, and no study has included an adolescent sample. This is important because brain regions involved in cognitive processing are developing in adolescents thus it is crucial to assess the effects of flavonoids on cognition independently in adolescence.

5.4 The potential mechanisms underlying the beneficial effects of flavonoids on executive functions

The potential underlying mechanisms that cause flavonoids to impact executive functioning are still being investigated. However, it is hypothesised that flavonoids impact on neuroplasticity (the formation of new connections in the brain) by increasing blood flow to the brain (Francis, Head, Morris & Macdonald, 2006). Increased cerebral blood flow protects against neuronal stress, either by lowering oxidative stress or inflammation, both of which increase cell survival and support cognitive functioning (Miller & Shukitt-Hale, 2012). Increased cerebral blood flow and strengthened neural activity in areas such as dorsolateral prefrontal cortex, a brain region associated with executive functioning and emotion regulation (Miller, 2000). This could be especially important in adolescence when the brain is rapidly maturing. Another possible mechanism is through the stimulation of neuronal signalling pathways, in particular hippocampal Brain-Derived Neurotropic Factor (BDNF). Flavonoid interventions appear to have positive effects on BDNF (Hariri et al., 2003) and, crucially, BDNF plays an important role in the neuroplasticity underlying memory formation and learning at the synaptic level (Bekinschtein, Cammarota, Izquierdo, Medina 2008; Tyler, Alonso, Bramham & Pozzo-Miller, 2002). For example, Hariri et al. (2003) assessed memory performance in a brain imaging study and found BDNF modulated hippocampal acting during encoding and subsequent memory performance, thus improved BDNF-related neuronal signalling may explain why cognition (e.g., memory processes) improves following flavonoid consumption.

5.5 The effects of flavonoids on mood

In addition to the accumulating evidence that flavonoid intake may have a beneficial impact on executive functioning, there is independent research investigating the effects of flavonoids on mood. Given the importance of the potential relationship between nutrition and mood to this thesis, the evidence will be discussed below.

5.5.1 The assessment of mood

Examining the potential effects of flavonoids on mood can be complicated due to the different ways that 'mood' and 'depression' have been defined and assessed. 'Mood' is often conceptualised as a transient state that has been triggered by an external cue and is often short-lived. This can sometimes be referred to as 'mood state' or 'affect' e.g., transient mood states could be when one feels sad, angry or tense. 'Mood' in this sense is often measured via rating scales whereby participants rate how much a certain emotion describes their current feeling (e.g. happy). However, 'mood' in the context of depression is a longer lasting affective disturbance (Schore, 1994). For example, a core symptom of depression is 'low mood', and for a diagnosis of major depressive disorder, this continuous mood state must last two weeks or longer (DSM-5;APA 2013). Therefore, tools that assess 'mood' either target a specific transient affective state (e.g. positive or negative affect) or assess a broad dimension of emotion (i.e. low mood). Some of the studies described below have used tools that measure current transient mood (i.e. affect). This is important to mention because measures of affect are different to those that measure sustained low mood in the context of depression. Thus to make valid inferences about the relationship between dietary

flavonoids and symptoms of depression, a tool that assesses the affective and cognitive components of depression is required.

5.5.2 The effects of a high flavonoid diet on mental health in adults

Independent of the research suggesting that there are positive effects of flavonoids on executive functioning, recent evidence has also focused on the beneficial impact of a healthy high-flavonoid diet on mental health and wellbeing (Khalid, Williams & Reynolds, 2017). Most of this research has focused on the effects of eating patterns and the whole diet on mental health (Khalid et al., 2017) For example, a large well-controlled epidemiological study involving 82,643 women examined associations between habitual intakes of dietary flavonoids (calculated through food frequency questionnaires) and depression (Chang et al., 2016). They found that individuals, particularly older women, who consumed diets high in flavonoids presented a lower depression risk (Chang et al., 2016). A similar study investigated the dietary polyphenol intake and demographic characteristics of 1572 adults living in southern Italy (Godos, Castellano, Ray, Grosso & Galvana, 2018). Overall polyphenol intake was not associated with depression symptoms however flavanones and anthocyanins consumption were inversely associated with depression symptoms. Jacka et al. (2018) found more direct support of a causal relationship between flavonoids (through fruit and vegetable intake) and depression. They conducted a controlled trial with 67 adults with moderate to severe depression who were randomized to receive either an adjunctive dietary intervention or social support. The dietary intervention included 7 individual consultations with a clinical dietician promoting a healthy diet (i.e., at least 9

portions of fruit and vegetables each day). After 12 weeks those in the dietary condition had improved significantly more on a depression rating scale than those in the social support group. Overall, there is growing evidence for the anti-depressant role of flavonoids, however because of distinct differences between adults and youth it is crucial to evaluate evidence in both age groups.

5.5.3 The effects of a high flavonoid diet and depression in children and adolescent

Khalid, Williams and Reynolds (2017) completed a systematic review of 20 studies that examined the relationship between diet and mental health in children and adolescents. Their conclusions supported previous studies, in that healthy dietary patterns/consumption (i.e., fruits and vegetables) were associated with lower levels of depression, and unhealthy diets (i.e., junk foods and saturated fats) were associated with greater mental health difficulties. However, the relationship between diet and depression is complex and potentially bidirectional (Murakami & Sasaki, 2010). To test causality, well designed intervention studies are needed that are informed by theory about mechanisms (Khalid, Williams & Reynolds, 2017). For example, a well-designed nutritional study should include a matched placebo supplement. This refers to placebo interventions being matched in all nutritional ingredients that may influence findings except the key ingredient being tested e.g., flavonoid content. This is important to control for the potential effects other ingredients may have.

5.5.4 The effects of a high flavonoid diet on transient mood in children and young adults

The only intervention study to examine flavonoid-specific effects on mood in younger people is by Khalid et al. (2017). In part one, 21 young adults (aged 18-21 years) were assessed after consuming a flavonoid-rich wild blueberry drink and a matched placebo drink, separated by a 3-7-day washout period. Part two included 50 children (7-10 years old) who were randomly assigned to either a blueberry drink condition or matched placebo drink condition. Both groups had their mood assessed 2 hours post-consumption of the drink using the Positive and Negative Affect Schedule (Watson, Clark & Tellegen, 1988), a self–report measure of current positive or negative affect. Both groups reported enhanced positive affect after consuming the flavonoid-rich wild blueberry drink. This suggests that the acute flavonoid supplementation had a beneficial influence on transient mood in both children and young people, and future work with an adolescent group would be worthwhile.

6.5.5 The effects of flavonoids on both executive functioning and transient mood in young adults

Only one study has measured the effects of flavonoids on both transient mood (i.e., affect) and executive functioning in youth. Haskell-Ramsay, Stuart, Okello and Watson (2017) conducted a randomised, control, double-blind crossover design study. They assessed the effects of grape juice (high in polyphenols) on episodic memory, working memory, attention and transient mood in healthy young adults (aged 18-30 years). There was a significant improvement in attention and positive affect after

drinking the anthocyanins-rich juice. Affect in this study was measured through a tool whereby participants rated how much they felt a certain emotion e.g., relaxed/tense. Whilst this study demonstrated that flavonoids can improve attention and transient mood, future studies should consider using measures that assess the emotional and cognitive components of mood.

It is important to clarify that all previous studies suggesting that dietary flavonoids have beneficial effects on mood have used tools that assess 'transient mood' or 'affect' i.e. measures of 'transient mood' reflect fleeting emotions rather than sustained mood. Although effects from these studies have been promising and provide evidence for improved transient mood, the inclusion of tools that assess sustained mood are crucial.

5.6 The potential mechanisms underlying the beneficial effects of flavonoids on mood

There are several plausible explanations of why flavonoids might have a beneficial effect on mood. The first is the indirect effect of increased blood flow to the frontal cortex (as discussed above). The pre-frontal cortex is involved in cognitive function and emotion regulation (Miller, 2000). This area of the brain is still maturing throughout adolescence and into early adult years, therefore increased blood flow to this area may help strengthen neural circuitry (Rodriguez-Mateous et al., 2013). Cognitive deficits are a common disabling symptom of depression (Orchard, Pass, Marshall & Reynolds, 2017), and executive functioning is impaired in depression (Wagner, Müller, Helmreich, Huss & Tadić, 2015). Improving cognitive deficits may therefore improve these symptoms of depression. A second possible mechanism relates to the

neurotransmitters associated with depression. Monoamine Oxidase (MAO) inhibitors have an anti-depressant effect (Watson, Haskell-Ramsay & Kennedy, 2015). Anthocyanins are suggested to have MAO inhibitory effects that may reduce oxidative stress and lead to increased concentration of neurotransmitters involved in depression (e.g., serotonin, dopamine and noradrenaline). Therefore, consuming flavonoids could reduce MAO activity, thus increasing monoamines in the brain and elevating mood (Watson et al., 2015).

5.7 Conclusion

Overall, flavonoids appear to have beneficial effects on executive functions and there is emerging evidence that they may also have benefits for depression symptoms and transient mood. It is plausible that both are related. Cognitive deficits are a common problem in depression; therefore, if flavonoid intake increases executive functioning, then this may in turn reduce depression symptoms. There is not yet a study that has tested flavonoid supplementation on both executive control and depression symptoms in teenagers and considering that adolescence is a critical period for both cognitive development and depression onset, future studies with this age group would be important.

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6 Chapter 7 Paper 4: Effect of 4 weeks Daily Wild Blueberry Supplementation on Symptoms of Depression in Adolescents

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Effect of 4 weeks daily wild blueberry supplementation on symptoms of depression in adolescents

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Abstract

Adolescence is an important period for cognitive maturation and emotional regulation and this age group is particularly vulnerable to developing depression. Diets rich in fruits and vegetables have been associated with decreased risk of developing depressive disorders across the lifespan, an association that may be due to the high flavonoid content of these foods. Previously we have shown increases in transient positive affect in both children and young adults two hours after administration of a wild blueberry intervention. Here, using a randomized double-blind, placebo-controlled trial, we investigated the effects of four weeks, daily wild blueberry supplementation (containing ~253mg anthocyanins) on transient and chronic mood in adolescents. Healthy 12-17-year old (N = 64, 35 females) were recruited and randomly assigned to receive either a wild blueberry or matched placebo. Depression and anxiety symptoms were assessed before and after the intervention period using the Mood and Feeling Questionnaire and Revised Child Anxiety and Depression Scale. Transient affect was assessed before, two weeks, and at four weeks using Positive and Negative Affects. Following the intervention period there were significantly fewer self-reported depression symptoms in participants who were supplemented with the wild blueberry intervention compared to those who received the matched placebo ($p = 0.02$, 95 % CI -6.71 to -5.35). There was no between group effect on anxiety symptoms or on transient affect. Further investigation is required to identify specific mechanisms that link flavonoids consumption and mood. If replicated, the observed effects of wild blueberry

supplementation may be a potential prevention strategy for adolescent depression and may have benefits for public mental health.

Introduction

Puberty is a complex biologically driven process that has an impact on emotional and behavioural well-being, resulting in a period with increased risk of developing emotional disorders and risk-taking behaviour. The brain undergoes cognitive maturation via synaptic remodeling well into the 20s. The limbic system, responsible for governing reward processing, appetite and pleasure seeking, matures before the prefrontal cortex, which is responsible for executive functioning such as problem solving, planning, emotional regulation and multitasking. This difference in cortical maturity is hypothesised to create a developmental imbalance, making teens vulnerable to behavioural and mental health problems, such as depression (Hawton, Saunders & O'Connor, 2012).

An episode of major depressive disorder (MDD) during adolescence is a major personal and public health problem across the world (World Health Organisation, 2017). Depression has many acute and long-term adverse consequences on adolescents' education and occupational success, relationships and family life and on their future physical and mental health (Clayborne, Varin & Colman, 2019). Each year around 7.5% of adolescents aged 13 to 18 years' experience an episode of major depression (Avenonoli, Swendsen, Burstein, & Merikangas, 2015; Polanczyk et al., 2015; Costello, Erkanli & Angold, 2006). Symptoms of depression are distressing and include sleep and cognitive problems, low mood, irritability, feelings of worthlessness and lack of pleasure. Sub-clinical MDD is even more common: recent surveys in the UK suggest that ~25% of young people report elevated symptoms of depression in any given year

(Avenonoli et al. 2015; UK Parliament , 2018) including depressive symptoms that are not sufficient in number or severe enough to meet diagnostic criteria. Sub-clinical symptoms have a major impact on daily functioning and are associated with increased risk of developing the disorder (Avenonoli et al. 2015).

Treatment for depression in this age group includes psychological therapies and anti-depressant medication; however, these are only moderately effective and are often inaccessible to young people due to limited public health service resources (UK Parliament 2018; National Institute for Health and Care Excellence, 2015). A recent meta-analysis of psychological treatments for children and young people with mental health problems found that the effect size of treatment for depression was small (d = 0.29) and was lower than effects of treatment for other common mental health problem (National Institute for Health and Care Excellence, 2015). For these reasons many depressed young people do not receive an evidence-based treatment and the prevention of adolescent depression is, therefore, a highly valued goal (Children's Society, 2008).

One potential way to prevent the onset of depression and sub-clinical depression is through diet. Diet and depression are significantly associated in adults, although this relationship is complex and potentially bidirectional, i.e. unhealthy diet leading to low mood and vice versa (Murakami & Sasaki, 2010). A recent systematic review of the association between depression symptoms and diet in adolescents found that 'healthy' diets (i.e. consumption of fruits and vegetables) were associated with lower depression symptoms; whilst 'unhealthy' diets (i.e. consumption of junk foods and saturated fats) were associated with higher depression symptoms (Khalid, Williams & Reynolds,

2016). A large well-controlled epidemiological study examining associations between habitual intakes of dietary flavonoids and depression risk showed that individuals consuming diets higher in flavonoids presented a lower depression risk, particularly amongst older women (Chang, Cassidy & Willet, 2016). A similar study assessed symptoms of depression and the total habitual intake of polyphenols among the participants and found that higher dietary intake of flavonoids was inversely associated with depressive symptoms (Godos, Castellano & Ray, 2018). Thus, diets rich in fruits and vegetables are associated with low depression symptoms. Dietary flavonoids are present in substantial concentrations in commonly consumed fruits and vegetables and may be a potential mediator for the anti-depressant action of diets rich in fruits and vegetables.

The hypothesis that there is a causal relationship between diet and depression symptoms and the onset of MDD has recently been strengthened by number of intervention studies. Acute purple grape juice intervention resulted in increase in self-reported ratings of ‘calm’ in healthy young adults (Haskell-Ramsay, Stuart, Okello & Watson, 2017). Similarly, acute consumption of flavonoid-rich wild blueberry improved short-term positive mood in children aged 7-10 years and in young adults aged 18-25 years (Khalid et al., 2017). In a recent randomized controlled trial with 67 depressed adults (Jacka et al., 2017) participants randomized to an intervention promoting a healthy diet with at least nine portions of fruit and vegetables each day reported significantly less depression at twelve weeks than those randomized to receive social support.

Anti-depressive effects of flavonoid rich plants and their extracts have also been investigated. *Hypercium perforatum* extract (also known as Saint John's wort, derived from a flowering plant in the Hypericaceae family) intervention studies show its effectiveness as treatment for mild/moderate depression when compared to placebo and having similar effects to pharmacological treatments (Brattström, 2009; Clement, Coverston, Johnson & Dearing, 2006; Kasper, Anghelescu, Szegedi, Dienel & Kieser, M, 2006; Mannel, Kuhn, Schmidt, Ploch, & Murck, 2010). Similarly, saffron (*Crocus sativus*, derived from the saffron spice of the flowering plant of Crocus genus)) extract consumption had equivalent effects as pharmacological treatment for depression and was significantly more effective than the matched placebo (Moshiri et al., 2006; Noorbala, Akhondzadeh, Tahmacebi-Pour & Jamshidi, 2005; Shahmansouri et al., 2015).

The specific effects of sustained wild blueberry flavonoid consumption on symptoms of depression in adolescents have not yet been tested. Here, we designed a double-blind, placebo-controlled experiment to test the effect of consuming a flavonoid-rich wild blueberry intervention for four weeks on symptoms of depression, anxiety and transient affect in healthy adolescents. Participants were randomly assigned to a wild blueberry or a matched placebo drink with transient affect and symptoms of depression and anxiety assessed before and after the four-week intervention period.

Method

Ethics

This research was reviewed and given a favourable ethical opinion for conduct by the University of Reading Research Ethics Committee (UREC 16/55). The study was registered at clinicaltrials.gov NCT03119597.

Participants

An *a priori* power analysis (using G Power 3.1.9.2) based on data from a previous study (Khalid et al., 2017) revealed that 24 participants per group were required to achieve power of 0.8 with alpha set at 0.5 level. Students, aged 11-17 years of varying ethnicity, from four schools in Reading Berkshire, UK were invited to take part in this study. We recruited 82 participants of whom 18 dropped out after the first session and were excluded from the study. This resulted in 64 participants (N=5 who missed the last session) that were included in the analysis. A post hoc power analysis conducted using G Power 3.1.9.2 to conduct power value for significant treatment related result revealed a power of 0.69. All parents or legal guardians provided informed written consent for young people under the age of 16. Participants under the age of 16 provided written assent and those over 16 gave written consent. All participants were screened for any health conditions (including mental health), any treatment they were receiving and food related allergies that would exclude them from the study. Participants were randomly assigned to either a wild blueberry drink or a matched placebo drink. The randomised allocation of participants to treatment was generated using Excel. The groups were coded A and B and the sequence was saved in

a password protected spreadsheet. Both the researchers and the participants were blind to treatment group and participants were told the study was investigating effects of different fruit drinks so were not aware of the study hypothesis.

Interventions

Both interventions (wild blueberry and placebo) were measured and packaged into silver opaque sachets at the University of Reading. Sachets were identical for the wild blueberry and the placebo drink and neither the researchers nor the participants knew what their sachets contained. Wild Blueberry Association of North America provided the blueberry powder whilst the matched sugars and vitamin C (placebo) was obtained from Bulk Powders. This was to control for potential effects of increased sugars or vitamin C on findings. The packets of wild blueberry contained 13g of freeze-dried wild blueberry (WBB) powder (containing ~253mg anthocyanins). Placebo packets were matched to the WBB for sugars (4.52g glucose and 4.79g fructose) and vitamin C (4 mg). Each participant was given 14 days' supply of their requisite intervention, along with written and video instructions for their parents/guardians on how to prepare the intervention. Each intervention was prepared daily, by adding 30 ml of low-flavonoid 'Rock's Organic Orange Squash' and 170 ml of water and the contents of the sachet to the opaque cup provided. Each participant was given a checklist to record the dates and times when they consumed the drink each day and the name of the person who prepared the drinks. Participants were also asked to bring back their used sachets after two weeks as a measure of compliance. The remaining 14 days' supply of each intervention was given to the participants two weeks

into the intervention period. The true aim of the study was not disclosed to the participants, they were informed that it was a fruit drink study, to avoid revealing the contents of the drink.

Measures

The Mood and Feelings Questionnaire (MFQ) was used to measure symptoms of depression (Costello & Angold, 1988). The MFQ is considered to be the gold standard self-report measure for depression in young people (NICE, 2015). It is a standardized and well-validated 33-item self-report measure of the severity of depression symptoms in adolescents. Each item relates to a symptom or experience associated with depression. Participants are asked to rate each item in relation to their symptoms in the past 2 weeks on a 3-point Likert scale (not true = 0, sometimes = 1, true = 2). Total MFQ scores range from 0 to 66 where higher scores indicate greater risk of depression. The clinical cut off for the MFQ is 27, with scores above 27 indicating significant risk of a diagnosis of MDD **(**Angold, Costello & Messer, 1995).

Anxiety symptoms were assessed using the anxiety sub-scale of the Revised Child Anxiety and Depression Scale (RCADS; Chorpita, Yim, Moffitt, Umemoto & Francis, 2000), a standardized and validated measure of anxiety symptoms in young people used routinely in UK NHS mental health services. The anxiety sub-scale of RCADS consists of 37 items, each rated on a 4-point Likert scale (never =1, sometimes = 2, often = 3, always = 4). Total scores range from 37 to 148 with higher scores indicating increased risk of an anxiety disorder. Again, participants were asked to rate the items keeping the past two weeks in mind.

Current mood (i.e., transient affect) was assessed using the Positive and Negative Affect Schedule-NOW (PANAS-NOW) at screening, and at two and four weeks. As the term suggests, this is a measure of transient mood. The PANAS is a valid and reliable 20 self-report measure of positive affect (PA – 10 items) and negative affect (NA - 10 items) that can be used on multiple test occasions (Watson, Clark & Tellegen 1988; Crawford & Henry, 2004). Participants rated the degree to which they were currently experiencing each item on a 5-point Likert scale ranging from 'very slightly' to 'extremely'. Ratings of positive and negative items were summed to calculate an overall positive affect and overall negative affect score, each ranging from 10-50 where lower scores indicate lower levels of positive or negative affect.

Habitual fruit and vegetable consumption were assessed using EPIC-Norfolk food frequency questionnaire, a semi-quantitative paper-based questionnaire, which includes 130 food items, each rated on 9-point Likert scale (never or less than a month-1 to 6+ perday-9). FETA software was used to analyse the data collected to calculate 46 nutrient and 14 food group values including average daily fruit and vegetable intake (Mulligan et al., 2014).

Procedure

As outlined in Figure 1, participants were seen by the researchers four times across a five weeks period. Research sessions took place either at the University of Reading or at the participant's school. Sessions were scheduled at the same time of day for each participant. The first two sessions, scheduled 48 hours apart, were screening sessions where participants completed a battery of questionnaires: MFQ, RCADS,

(screening session 1) PANAS, EPIC- Norfolk food frequency questionnaire and a questionnaire about their health status (screening session 2). Screening sessions were limited to 30 minutes to fit with the school timetable and to maintain high levels of participant engagement in both sessions. Parents were also asked to complete a demographic questionnaire. Participants started the intervention the day after the second screening session was completed. Two weeks later they returned their used drink sachets, were given a new checklist and completed the PANAS (Test session 1). Participants were also asked if they were experiencing any adverse effects of the drink and feedback on its palatability. They then returned two weeks later (Test session 2), returned their drink sachets, completed the PANAS, MFQ and RCADS and were debriefed. For each test session, participants were instructed not to consume their allocated intervention before the test session to ensure that chronic, not acute, effects of the intervention were being measured.

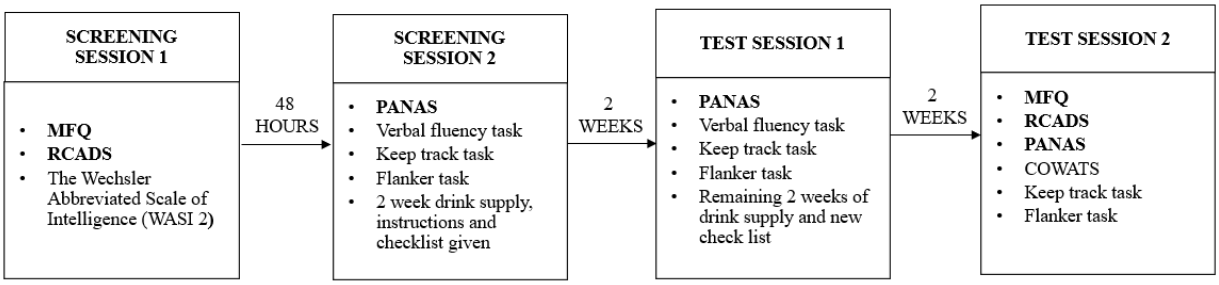

Figure 1. A Schematic of the Study Procedure. The measures reported in Chapter 7 are highlighted in bold font.

Statistical Analysis

Statistical analyses were conducted using IMB SPSS version 22. T-tests were used to investigate differences in symptoms of depression, anxiety and fruit and vegetable intake between the two groups at baseline. Effects of intervention on transient affect was analysed using Linear Mixed Modelling (LMM) using an unstructured covariance matrix to model successive repeat test sessions, with subjects included as random effects. Data from two weeks and four weeks measures of the PANAS and treatment group were included as fixed factors, with baseline PANAS scores included as a covariate. LMM deals with data that is missing at random and with multiple measurement points, giving unbiased estimates of each of the means. To test the effects of the intervention on anxiety and depressive symptoms at four weeks, data were analysed using Analysis of Covariance (ANCOVA) with drink (Placebo, WBB) as an independent variable and MFQ and RCADS scores at 4 weeks as dependent variable. Baseline measures of depression and anxiety were used as covariates and Bonferroni corrected T-tests were used to investigate all fixed effects and interactions.

Results

Sample characteristics

Sixty-four participants were recruited (35 females, 29 males) aged 12-17 years (M=14.20 SD=1.71). Thirty-five participants were randomly allocated to receive the placebo drink and twenty-nine to the WBB intervention. 25.7% in the placebo group

and 20.7% in the intervention group had MFQ scores above 27 indicating that these participants' depressive symptoms were above the clinical cut-off. However, no significant differences of participants with depressive symptoms between the two groups t (62) = 0.47, p = 0.64. Participants' demographic data, baseline mood scores and habitual fruit and vegetable intakes are reported in table 1. There were no significant differences between groups in the amount of daily fruit t (51) = 0.14, p = 0.89 or vegetable t (51) = 1.45, p = 0.15 consumed. One sample t-test revealed that the mean fruit and vegetable consumption by the participants was significantly lower than the 400g per day as recommended by WHO, Fruit: t (52) = 11.20, $p<0.005$, Vegetable: t (52) = 7.12, $p<0.005$.

Table 1.

Demographic details, mean fruit and vegetable intake and mean depression and anxiety scores at baseline for both intervention groups.

	PLACEBO GROUP	WILD BLUEBERRY GROUP	P VALUES
MEAN AGE	14.5 (SD=1.804)	13.82(SD=1.54)	P=0.11
MALE %	48.6	41.4	P=0.57
FEMALE %	51.4	58.6	P=0.57
BRITISH %	60	52.4	P=0.52
ASIAN%	11.4	12.5	P=0.52
MIXED%	5.8	12.6	P=0.52
AFRICAN	2.9	8.3	P=0.52
CHINESE	2.9	4.2	P=0.52
MEAN FRUIT INTAKE (GRAMS/DAY)	188 (SD=168.26)	176 (SD=97.96)	P=0.89
MEAN VEGETABLES (GRAMS/DAY)	257.61 (SD= 186.99)	187.53 (SD=144.62)	P=0.15
MEAN DEPRESSION (MFQ) SCORE	13 (SD= 9.97)	11.257 (SD= 8.54)	P=0.55

MEAN ANXIETY (RCADS) SCORE	24.2 (SD= 14.90)	22.27 (SD=13.00)	P=0.66
MEAN POSITVE AFFECT SCORE	28.03 (SD=7.72)	25.28 (SD=7.98)	P=0.17
MEAN NEGATIV E AFFECT SCORE	15.09 (SD=5.24)	14.10 (SD=4.38)	P=0.98

At baseline mean depression and anxiety scores were 12.35 (SD = 9.31) and 23.19 (SD = 13.80) respectively, both below the clinical threshold. There was no significant group difference in symptoms at baseline; MFQ t (60) = 0.60, p = 0.55, RCADS t (40) = 0.45, p=0.66 and no group difference in mean positive and negative affect; t (62) = 1.40, p=0.17 and t (62) =0.80, p=0.98 respectively. 11.4% in the placebo group and 3.4% in the intervention groups scored above 27 on the MFQ, indicating depressive symptoms above the clinical cut-off. No participants reported a diagnosis of depression or anxiety, or that they were receiving treatment for these disorders. A minority of participants (9.38%) reported depression symptoms above the clinical cut-off of 27 on the MFQ. No participants reported anxiety symptoms above the clinical threshold.

Hypothesis testing

As shown in Figure 2a, after four weeks of the intervention, the mean MFQ score for participants who consumed WBB was significantly lower than the mean MFQ score for participants who consumed the placebo drink. This was significant F (1,57) = 5.52, p = 0.02 95 % CI -6.71 to -5.35 with a medium effect size (d = 0. 65). The change in the depression scores for each participant including a regression line for both treatments is shown in figure 3. There was no significant effect of WBB on symptoms of anxiety (Figure 2b) after four weeks of supplementation F (1,34) = 2.1, p=0.16;

mean RCADS score for participants in the WBB group was 13.90, (SD = 8.39) and the mean RCADS for the placebo group was 19.3, (SD = 11.31).

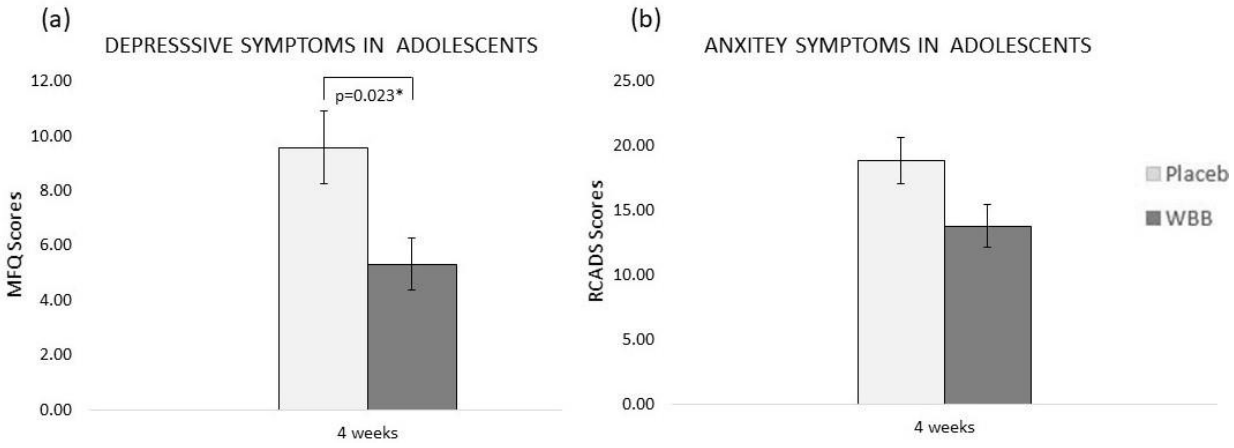

Figure 2. Mean scores (± standard error of the mean) in adolescents aged 11-17 years (**a**) Mean MFQ scores after 4 weeks consumption of placebo and intervention drinks. (**b**) Mean RCADS scores after 4 weeks consumption of placebo and intervention drinks.

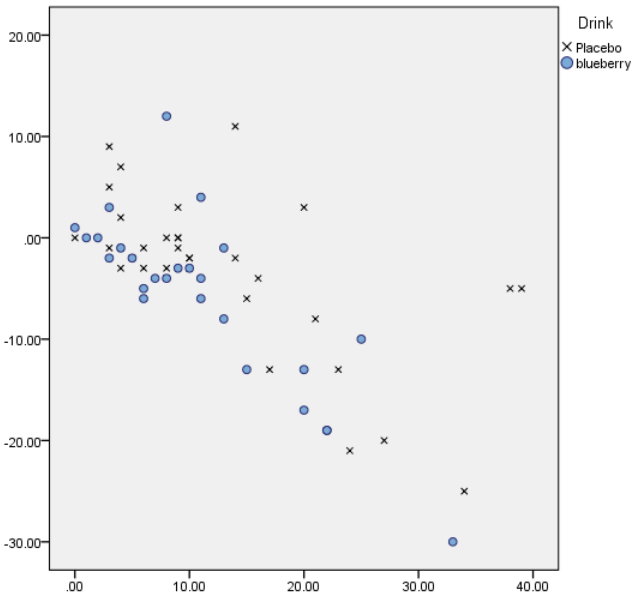

Figure 3. Scatterplot showing the MFQ scores at baseline and 4-week post intervention.

We also examined the effect of intervention on positive affect and negative affect (PANAS) after two and four weeks (see Figure 3). There was no significant effect of Drink F (1, 64.33) = 0.26, p = 0.62, Repeated trial, F (1, 62.22) = 2.95, p = 0.09, or any Drink x Repeated trial interaction F (1, 62.22) = 3.686, p = 0.06 on transient positive affect. Figure 4a shows the mean PA scores following intervention of WBB and placebo drink at drink at two weeks was 25.55 (SD = 9.71) and at four weeks was 23.04 (SD = 8.07), and following the placebo drink at two weeks was 25.86 (SD = 7.69) and at four weeks was 26.30 (SD = 7.54). There was also no significant effect of the intervention on NA; Repeated trial, F (1, 59.3) = 0.66, p = 0.42, Drink, F (1, 63.79) = 0.24, p = 0.63 or Repeated trial × Drink interaction, F (1, 59.30) = 1.17, p = 0.28. As shown in Figure 4b, NA was not significantly different after consuming the WBB drink at 2 weeks: M = 13.69, SD = 4.02, and 4 weeks: M = 13.19, SD = 5.55, or the placebo drink at 2 weeks: M = 13.4, SD = 3.96 and 4 weeks M = 14.24, SD = 5.24.

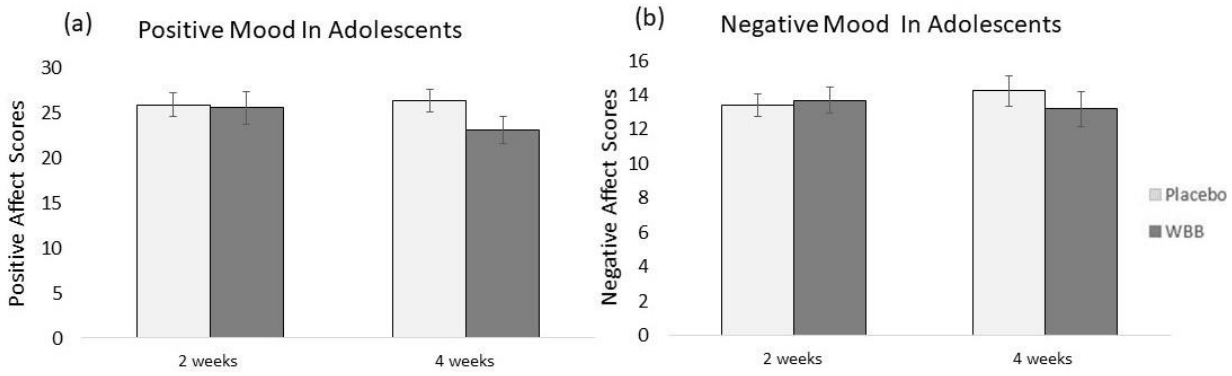

Figure 4. Mean PANAS-NOW Mood scores (± standard error of the mean) in adolescents aged 11-17 years: (a) Mean PA scores 2- and 4-weeks post-consumption of placebo and intervention drinks. (b) Mean NA scores 2- and 4-weeks post-consumption of placebo and intervention drinks.

Discussion

This randomized, placebo controlled, double blinded trial investigated the effects of 4 weeks of consumption of a flavonoid-rich WBB drink on symptoms of depression and anxiety and on transient affect in a community sample of healthy 12-17-year-old. The results demonstrated that after four weeks of daily WBB intervention there was a between groups difference in self-reported depressive symptoms; participants randomised to the WBB intervention reported significantly lower scores on the measure of depression symptoms than participants who were randomised to the placebo drink. There was no significant effect of the intervention on anxiety symptoms or on positive affect or negative affect (i.e., transient affect). The data suggest that flavonoid supplementation may be beneficial in reducing depressive symptoms in healthy adolescents. This is, to our knowledge, the first randomized double blinded study to show the effects of chronic WBB flavonoids on depression symptoms in teenagers. The participants in the study were healthy but at baseline assessment were consuming sub-optimal habitual levels of flavonoids, i.e. their daily consumption of fruit (44.87%) and vegetable (57.46%) was well below the WHO recommended amount of 400g/day (World Health Organization 2017; Vereecken et al., 2015). This is consistent with the typical diet of young people in the UK, where only 18% of adolescents meet the recommended daily requirement, and the average daily consumption within this age group is 256g (3.5 portions) of fruit and vegetables (NHS digital, 2017). Levels of depression and anxiety were similar to community norms, and importantly about a quarter of the sample had symptoms that were at or above the clinical cut-off for depression. It is also important to note that the depression and anxiety symptoms were assessed by self-report. Diagnosis of depression is made by

clinical interview and thus scores above the clinical cut off indicate that the participant is at increased risk of a diagnosis but are not equivalent to receiving a diagnosis. As the intervention effects were observed in a community sample, these effects cannot necessarily be generalised to adolescents who have a diagnosis of depression.

The effect size of the flavonoid intervention compared to the control group on the gold standard self-report measure of depression symptoms (the MFQ) was d = 0.65, a medium effect size. To put this into context, two recent meta-analyses have examined the effects of psychological treatments for depression and the prevention of depression. Ecksthtain et al., (2019) concluded that the treatment effect size of psychological treatments for adolescents with depression was d = .36. In a review of interventions to prevent depression Ssegonia et al., (2019) reported an effect size of d = .22. Further the reduction of the 4 points on the MFQ scores in the intervention group indicates complete amelioration of 2 items on the scale or a reduction (from 2 to 1, or 1 to 0) of 4 items. Because each item reflects a symptom or adverse effect of depression clinically this would be likely to reflect a meaningful reduction in the impact of depression on the young person (McCarty et al., 2013).

Previously the effects of flavonoids from different sources such as apples, cocoa and grape juice showed no effects on depression in healthy adults (Khan, Perviz, Sureda, Nabavi, & Tejada, 2018; Hendrickson,& Mattes, 2008; Bondonno et al., 2014). However, our results are consistent with previous animal and epidemiological studies that suggest anti-depressive effects of a flavonoid rich diet (Chang et al., 2016; Scholey et al., 2009; Mihrshahi Dobson, & Mishra, 2015; Pase et al., 2013; Bouaved, 2010; Brattström, 2009). They also are in keeping with experimental data on the acute effects of WBB on positive mood in children and young adults (Haskell-Ramsay et al., 2017;

Khalid et al., 2017) and the acute effect of grape juice on mood in healthy adults (Haskell-Ramsay et al., 2017). Unlike a previous acute intervention study, we did not observe a significant effect of WBB on momentary mood (i.e., transitory affect). However, the interval between consuming the WBB drink and assessing negative affect and positive affect was variable, unlike the standard 2-hour interval used in previous studies. In addition, the four-week assessment (our end point) was conducted during the first week of school after the summer holidays. Unlike symptoms of depression (and anxiety) which were measured over a minimum two-week period and which are conceptualised as relatively stable, positive and negative affect are conceived as short-lived events that have rapid decay after elicitation (Qiao-Tasserit et al., 2017). It is therefore possible that this external event (returning to school) had a measurable impact on participants' momentary affect.

Although anxiety and depression are frequently co-morbid in young people and share some symptoms (e.g., fatigue, low concentration and sleep disturbances), the results of this intervention study suggest that flavonoids may reduce symptoms that are more prominent in depression than anxiety, e.g., low mood, anhedonia, feelings of guilt, and worthlessness and do not reduce anxiety specific symptoms. It is also possible that the effect of flavonoids on anxiety is smaller than the effect on depression and that a larger sample, with greater power, might result in a significant effect.

Some authors have proposed that flavonoids increase cerebral blood flow to the dorsolateral prefrontal cortex, a site that is highly associated with cognitive and emotional regulation, including rumination, a cognitive process of repetitive thinking that may exacerbate feelings of guilt and worthlessness (Vauzour, Vafeiadou,Rodriguez-Mateos, Rendeiro & Spencer, 2008; Miller, 2000; Schore, 2016).

This suggests that there may be an indirect pathway between flavonoid consumption and depression whereby flavonoid consumption enhances cerebral blood flow, which boosts executive functioning; in turn improved executive functioning helps to enhance cognitive control, inhibits rumination and thus reduces depression. Adolescents with depression have impaired executive function compared to non-depressed and anxious young people (Fisk, Ellis & Reynolds, 2019) and therefore the benefits of flavonoid consumption may be more prominent in these young people. However, potentially any positive effects of flavonoid consumption on executive function would have benefits for more young people because executive function is critical for academic achievement (St Clair-Thompson & Gathercole, 2006).

A plausible direct pathway between flavonoid consumption and mood is the effects of flavonoids on Monoamine Oxidase (MAO). MAO inhibitors have been used to treat mood disorders and flavonoids may mimic their effects (Watson et al., 2015). A recent study showed that consuming fruits high in flavonoids i.e. blackcurrants, significantly reduces MAO activity and increases the circulating monoamines and thereby elevates mood (Watson et al., 2015).

Another possible mechanism by which flavonoids may affect mood is by mimicking anxiolytic-like effects by binding to benzodiazepine receptors, enhancing the effect of GABA via GABAA receptors (Khan et al., 2018; Hanrahan, Chebib & Johnston, 2011; Wasowski & Marder 2012). However, in line with a previous study (Khalid et al., 2017) that showed no changes in negative affect (an indicator of anxiety) after acute flavonoid intervention, here there was no significant effect of flavonoid consumption on anxiety.

Although the mechanisms of action require further investigation there is accumulating evidence of a causal relationship between flavonoid consumption and depression symptoms. This evidence has been published by independent research groups using different research designs, including epidemiology, clinical trials and experiments. However, the research is preliminary and requires robust replication and extension, with larger samples, longer timescales and careful tests of mechanisms of action. Our study examined the effects of flavonoids on healthy young people, some of whom had elevated symptoms of depression. We did not have adequate power to conduct sub-group analysis but clearly it is important to identify if the change in depression symptoms is driven by improvements in those with elevated symptoms, or if the effects are similar across all levels of baseline depression. This distinction is important because flavonoids may have the potential to prevent depression in those at risk (i.e. those with elevated symptoms) or may have a more general effect. The former would suggest that dietary interventions could be used for early intervention in those exhibiting symptoms of depression; the latter that dietary interventions could have a broader benefit to public mental health.

Conclusion

This randomised double-blind study demonstrated the chronic effects of wild blueberry flavonoid consumption on reducing symptoms of depression in a community sample of adolescents. Dietary flavonoid interventions may have potential to reduce symptoms of depression in adolescents. This study requires replication, not only in healthy participants, but also in clinically referred samples to assess the potential of flavonoids to be used as a practical and cost-effective intervention. In addition to this,

studies focused on investigating biochemical changes and investigating the mechanistic pathways in which flavonoids decrease depressive symptoms in humans is essential.

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7 Chapter 8 Addendum for paper 4: Effect of 4 Weeks Daily Wild Blueberry Supplementation on Executive functioning in Adolescents

Introduction

In Chapter 7 (paper 4) an experimental test of the effect of flavonoid consumption on affect and symptoms of depression in adolescents was presented. In this double-blinded randomised, placebo-controlled experiment the effects of the intervention on executive functioning performances were also assessed, and these data are presented in this chapter.

Chapter 6 (section 6.3) provides a critical evaluation of previous research on the effects of flavonoids on executive control performance in children and young adults. Generally acute supplementation has resulted in improved cognitive functioning performance on the same day as the flavonoid supplementation was taken. For example, Barfoot et al. (2018) assessed acute cognitive performance and reading ability in children, 2 hours post a blueberry supplementation. They reported improved memory and attentional components of executive functioning in children (7-10 years old) but no change in reading ability. Barfoot et al. (2018) hypothesised that chronic supplementation of blueberry flavonoids might be more appropriate to elicit benefits to real-word scenarios (i.e., such as reading). Only one study has examined the effects of chronic flavonoid supplementation in children. Participants were given a cocoa flavonoid supplement for an average of 10 days and working memory was assessed pre and post the intervention (Calderón-Garcidueñas et al., 2013). Although performance improved on working memory tasks, the final testing session was completed 4 hours post the last high flavonoid drink thus it was not clear if improved performance was due to an acute or chronic effect. Therefore, future studies are required to assess the effects of chronic flavonoid supplementation.

There is accumulating evidence that acute supplementation of flavonoids

enhanced transient mood (e.g., Khalid et al, 2018). Further, a systematic review by Khalid et al. (2016) and the results of Chapter 7, suggest that chronic flavonoid intake may have beneficial effects on depression symptoms in youth. A possible mechanism to explain how flavonoids may improve mood is through enhancing executive functioning. For instance, a common symptom of depression in adolescents is reduced concentration (Orchard, Pass, Marshall & Reynolds, 2017) and impaired executive functioning impacts on the ability to concentrate (Diamond, 2013).

Furthermore, reduced executive functions, such as inhibitory control and updating information in working memory are associated with cognitive deficits in both adults and adolescent depression. Critically, evidence suggests that these problematic cognitive processes exacerbate and sustain the negative mood that typifies depression**.** In addition, research signifies that diminished cognitive control is associated with negative information processing biases and increases the use of maladaptive emotion regulation strategies, such as rumination. (for review, LeMoult & Gotlib, 2018). Therefore, discovering ways to enhance executive control and the associated cognitive processing deficits is imperative and could inform depression treatment.

Crucially, beneficial effects of flavonoids have been found in several executive functions that are impaired in depression, such as working memory, inhibition and verbal fluency (e.g., Lamport et al., 2012; Snyder, Miyake & Hankin, 2015). Therefore, it is plausible that if flavonoids boost executive functioning (thus cognitive control) this may consequently alleviate cognitive-related symptoms of depression and potentially begin to relieve information processing difficulties associated with the disorder.

Based on previous research in adults and young people we expected to find improved performance on executive control tasks that assessed working memory and

inhibition in the blueberry drink intervention group compared to the control group. These executive function tasks were both central to the study.

Method

Ethics, participants, and intervention

Please see paper 4 (chapter 7) for details about the study design, ethical issues, participants and the intervention. In the same way as paper 4, there were two researchers that carried out the collection of executive control data, myself and Sundus Khalid (both first authors on paper 4).

Executive control tasks

Modified Attention Network Task (MANT): The Modified Attention Network Task assesses inhibitory control, selective attention and reaction times (RTs; with RTs<100ms removed as it may have been intended for previous stimuli). Participants' accuracy and reaction time were measured at baseline, 2-week post intervention and 4-week post intervention. In accordance with Whyte et al. (2016) stimuli load, duration and cueing were manipulated to modify the cognitive demands. Five arrow symbols "<" and ">" were presented in white against a black background. The centre arrow was either congruent (i.e. <<<<< or >>>>>) or incongruent (i.e. <<><< or >><>>) with pairs of arrows on either side (please see figure 1 for further illustration). One hundred trials were presented, with the direction of the arrow and congruence randomized and appearing with equal probability. The stimulus was displayed for 120ms and then followed by a pseudo-random stimulus interval of 1000, 1300 or 1500ms. Participants were instructed to use the left and right keys on the keyboard to indicate the direction of the presented stimuli (i.e. the

centre arrow). Accuracy and response times for both congruent and incongruent trials were measured separately.

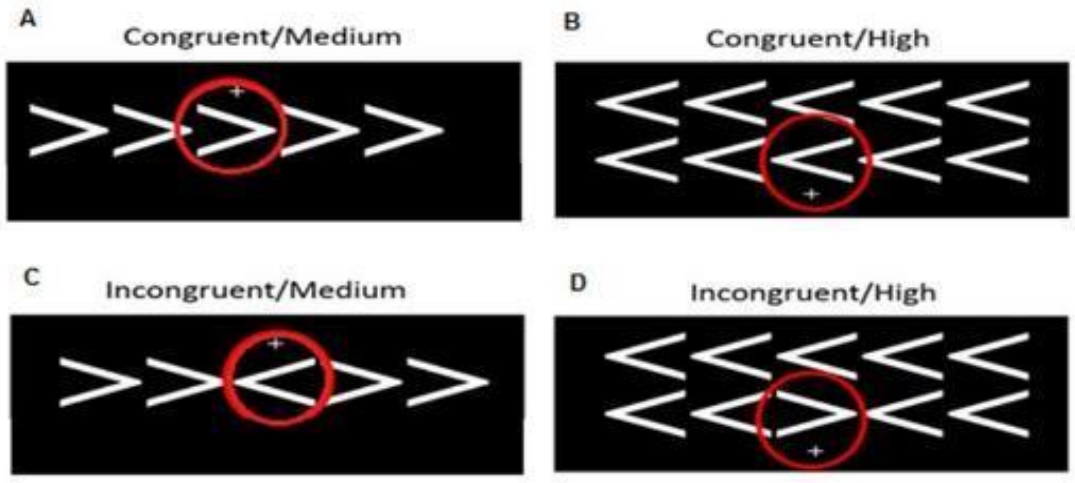

Figure 1. (A) shows congruent stimuli at medium difficulty load (B) shows congruent stimuli at high difficult load (C) shows incongruent stimuli at medium difficulty load and (D) shows incongruent stimuli at high difficulty load.

The Keep track task (KTT; originally adapted by Miyake et al., (2000) from Yntema (1963): This is a reliable and valid measure of updating working memory (Synder, Miyake & Hankin, 2015). This was an adapted version of the keep track working memory task used in paper 1 and 2. Participants were shown a list of six target categories (e.g., animals, furniture, fruit) and exemplars (e.g., dog, table, apple), compiled using an updated and extended version of Battig and Montague (1969) norms (Overschelde, Rawson, & Dunlosky, 2004). Participants were asked to familiarise themselves with the words and to make sure that they knew which exemplar belonged to which category. At the beginning of each trial a single tone was played, and several

target categories were displayed on the lower half of the computer screen. Fifteen words, including 2 or 3 exemplars from each of six possible categories were then presented serially in a pseudo-randomized order for 5 seconds per word. Target categories remained on the screen during the trial. The task was to recall the last word presented in each of the target categories. Thus, participants have to continuously update their working memory for the target categories. After each trial, participants were asked to recall the exemplars used in that trial. This was done by participants writing down their responses on a work sheet. Before the task, participants practised on two trials with three target categories. The task itself consisted of four trials with three target categories, four trials with four target categories and one trial with five target categories. The total number of words presented was 33 and the number of words recalled correctly was the measure of interest.

The Wechsler Abbreviated Scale of Intelligence (WASI II; Wechsler, 2011). The WASI II is a brief, well-standardised assessment of intellectual abilities for 6 to 89-year-olds. Two subtests (Vocabulary and Matrix Reasoning) were used to provide an estimate of full-scale intelligence quotient (FSIQ). In the vocabulary subtest, participants were required to define a word that was presented to them orally. The Matrix Reasoning consisted of 30 incomplete matrices presented in a stimulus book. Participants were asked to look at each incomplete matrix and choose one item from a selection of five figures at the bottom of each page to correctly complete the matrix. The WASI has strong psychometric properties, including good test- retest reliability and internal and concurrent validity (Garland, 2005; McCrimmon & Smith, 2013).

Procedure

As outlined in Figure 1, participants were assessed by the researchers four times across a five-week period. Research sessions took place either at the University of Reading or at the participant's school. Sessions were scheduled at the same time of day for each participant. The first two sessions, scheduled 48 hours apart, were screening sessions where participants completed 2 cognitive computerised tasks (i.e. the MANT & the KTT) at each session with the addition of the WASI-2 at the first session (completed in person, individually, with a researcher).

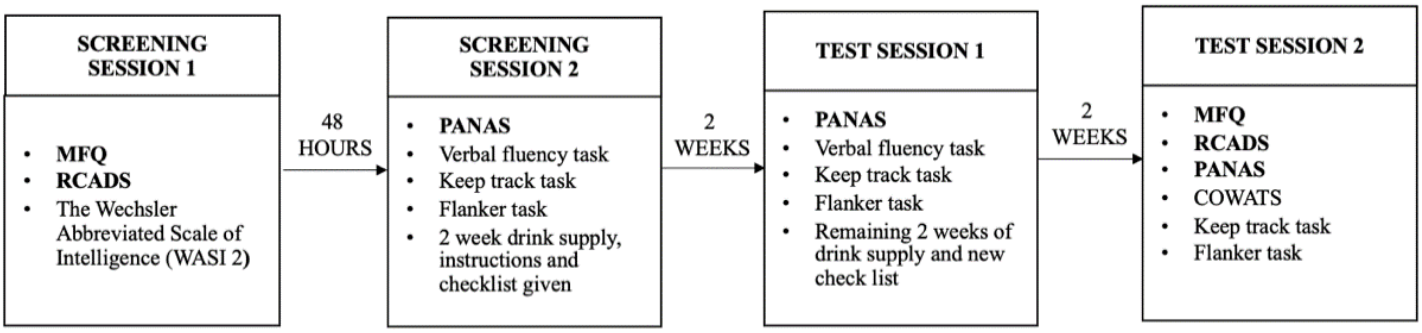

Figure 2. Diagram of study procedure. The results for the measures highlighted in bold are reported in the Results section of chapter 7.

Results

Data analytic plan

Preliminary analysis was completed using an independent sample t test to assess IQ between the blueberry and placebo intervention groups. IQ was a potential confound as measures of executive function and IQ are highly correlated (Diamond, 2013).

The effects of the chronic flavonoid intervention on executive control were analysed using Linear Mixed Modelling (LMM) using an unstructured covariance matrix to model successive repeat test sessions, with subjects included as random effects. Data from two-weeks and four-week measures of cognition, (i.e. MANT, KTT) and treatment group were included as fixed factors with baseline scores of all the executive control measures included as covariate to account for group baseline variations.

Preliminary Analysis

There were no significant differences between the intervention groups for IQ score tested by an independent samples t test, therefore IQ was not added as a covariate when testing the effects of flavonoid supplementation on executive control, t (72,70) = -0.56, p = 0.56.

Hypothesis testing

In contrast to the hypothesis, no significant effect of blueberry flavonoids was found on either working memory or inhibition. These findings for are reported below.

Working memory

We assessed effects of chronic wild blueberry supplementation on the ability to update and monitor information in working memory using the Keep Track Task, and data was analysed using LMM and baseline scores were added as a covariate. The group mean scores at baseline and post 2- and 4-week intervention can be found in figure 3. Using baseline scores as a covariate there were no significant effects for Drink F (1, 59.51) = 0.83, p = 0.37, Session F (1, 59.5) = 2.21, p = 0.14 or Drink x Session F (1,59.52) = 1.6, p = 0.211.

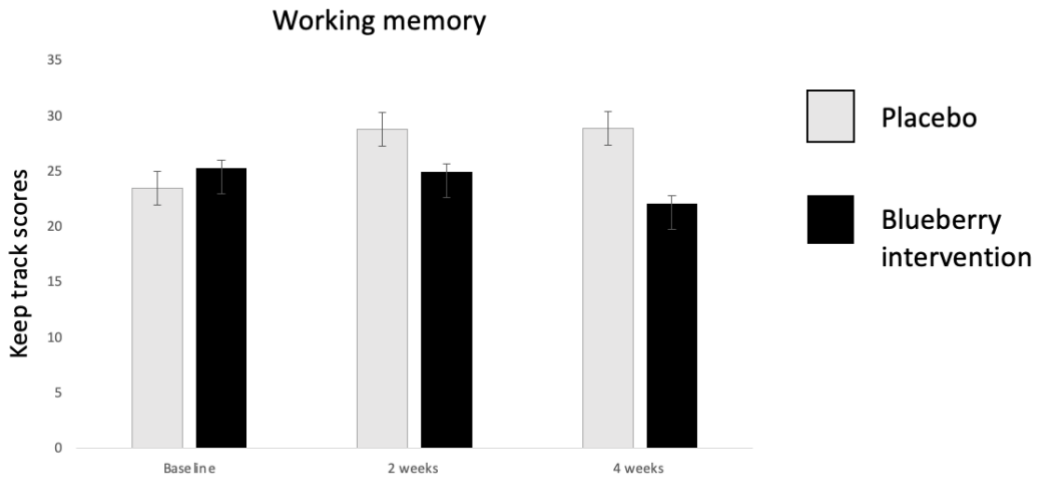

Figure 3. The group mean scores (+ standard error of mean) of the total words remembered on the keep track task, at baseline, week 2 and week 4 post consumption of either placebo or blueberry intervention.

Inhibition

LMM was also used to examine the effects of wild blueberry and the placebo interventions on performance on the MANT (i.e., a measure of attentional and inhibition aspects of executive control) with baseline scores added as a covariate. Inhibition was assessed in two ways; reaction time and accuracy. The task included congruent and incongruent trials, that had either a medium or high cognitive load. In the following section 'session' refers to week 2 and 4 post intervention, 'drink or intervention' refers to either the wild blueberry flavonoid condition (intervention) or placebo (drink), 'congruency' refers to whether the trial was congruent (i.e., when the target arrow faces the same way as other arrows on the screen) or incongruent (i.e., when the target arrow faces the opposite way to the other arrows on the screen). 'Cognitive load' refers to the difficultly of the trials i.e., medium load (one line of

arrows) or high load (2 lines of arrows). Examples of what the task looks like can be found in figure 1, although baseline was added as a covariate within the analysis, group means were included in the graph.

Figure 2 depicts the mean accuracy scores for congruent and incongruent trials at both medium and high levels of difficulty (i.e., cognitive load). As before, baseline cognitive scores were included as a covariate within analysis. There was no significant main effect of session, F (1,511) = 2.49, p = 0.115, on adolescents' accuracy. However, there was a significant main effect of drink intervention F (1,511) = 1.17, p = 0.001, congruency F (1,511) = 12.47, p<0.05 and load F (1,511) = 31.32, p<0.005. Pairwise comparisons demonstrated that participants who were assigned to the placebo group (M = 0.88, SD = 0.29), were more accurate than those in the blueberry group (M = 0.83, SD = 0.22) when presented with a high cognitive load i.e., participants in the placebo group were more accurate than those in the blueberry group at testing session 4 compared to testing session 2 (with baseline scores added as a covariate). Both groups (Placebo and Blueberry intervention) were more accurate when presented with a medium cognitive load trial (M= 0.89, SD=0.26), compared to a high cognitive load trial (M = 0.82, SD = 0.27). Similarly, both groups were more accurate on the trials with congruent stimuli (M = 0.88, SD = 0.23) compared to incongruent stimuli (M = 0.83, SD = 0.28) i.e., accuracy decreased for more difficult trials.

There was no significant interaction between drink x session F (1,511) = 0.14, p = 0.71, session x congruency F (1,511) = 0.15, p = 0.70, or session x load F (1,511) = 0.08, p = 0.77 on the number of accurate responses on the MANT. However, significant interactions were found for drink intervention x congruency F (1,511) = 14.93, p<0.005, drink x load F (1,511) = 16.49, p<0.005, session x congruency x cognitive

load F (2,511) = 5.47, p = 0.004, and drink x session x congruency x cognitive load F (4,511) = 5.04, p = 0.001. Corrected pairwise comparisons identified the differences between the groups. Adolescents in the placebo group (M = 0.88, SD = 0.29) were more accurate when presented with incongruent stimuli than adolescents in the blueberry group (M = 0.79, SD = 0.25). Again, adolescents in the placebo group (M = 0.86, SD = 0.29) were more accurate in the high load trials compared to the blueberry group. (M = 0.77, SD = 0.24), i.e., participants in the placebo group were more accurate than those in the blueberry group between week 4 testing compared to week 2 testing, with baseline scores added as a covariate to control for individual differences at baseline.

We also examined differences in accuracy scores between high and medium load trials (i.e., to assess if the difficulty of the task was associated with accuracy). Pairwise comparisons revealed that adolescents in the blueberry intervention group (M = 0.89, SD = 0.21) were significantly more accurate in the medium cognitive load trials compared to the high cognitive load trials (M = 0.77, SD = 0.24), i.e., participants showed increased accuracy for easier trials.

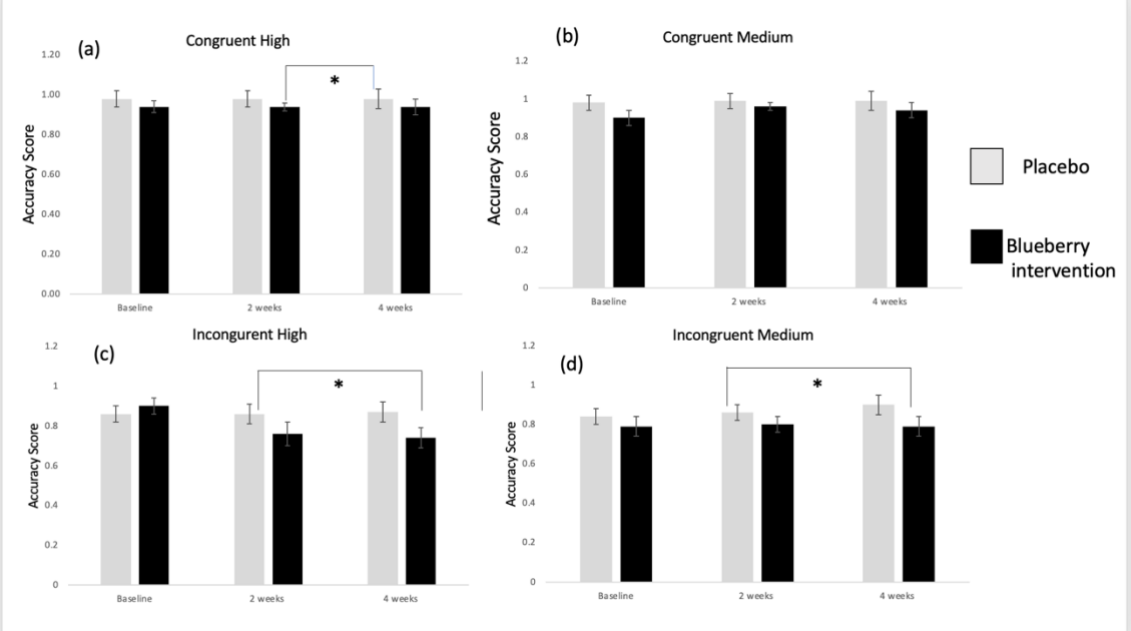

Figure 4. Mean (+ standard error of mean) Accuracy score on MANT at baseline, week 2 and week 4 consumption of placebo and intervention drinks in adolescents aged 11-17 years: (a) Mean Accuracy score when congruent/high stimuli were presented. (b) Mean Accuracy score when congruent/medium stimuli were presented. (c) Mean Accuracy score when incongruent/high stimuli were presented. (d) Mean Accuracy score when incongruent/medium stimuli were presented. Asterisks with this graph show significant differences between 2 week and 4-week post-intervention.

We also analysed the effects of the drink intervention on reaction time on the MANT and found no significant main effects of drink intervention, F (1,512) = 0.42, p = 0.52 or cognitive load, F (1,512) = 0.02, p = 0.88, on adolescents' reaction time. There was however a significant main effect of session F (1,512) = 26.0, p<0.005 and congruency F (1,512) = 0.022, p = 0.018, on reaction time. Inhibition response time significantly decreased between 2-weeks (M = 463.04, SD = 75.92) and 4-weeks (M = 415.49, SD = 144.04) thus adolescents (across both groups) were quicker at week four compared to week two (taking into account baseline as a covariate). All participants reaction times were also significantly quicker when they were presented with congruent

stimuli (M = 427.35, SD = 103.75) compared to incongruent stimuli (M = 451.17, SD = 123.89) i.e., all adolescents were faster when the task was easier.

Group mean reaction times (for both placebo and blueberry intervention interventions) for congruent and incongruent stimuli trials, at high and medium cognitive load are presented in Figure 4. No significant effects on reaction time were revealed for the following; drink intervention x session F (1,512) = 0.11, p = 0.75, drink x congruency, F (1,512) =0.11, p = 0.811, drink x cognitive load F (1,512) = 0.057, p = 0.81, session x congruency F (1,512) = 0.43, p = 0.52, session x load F (1,512) =0.005, p = 0.95, session x congruency x cognitive load F (2,512) = 0.22, p = 0.80 or drink intervention x session x congruency x cognitive load F (4,512) = 0.22, p= 0.93. As before, all analyses used the baseline measure as a covariate to control for individual differences at baseline.

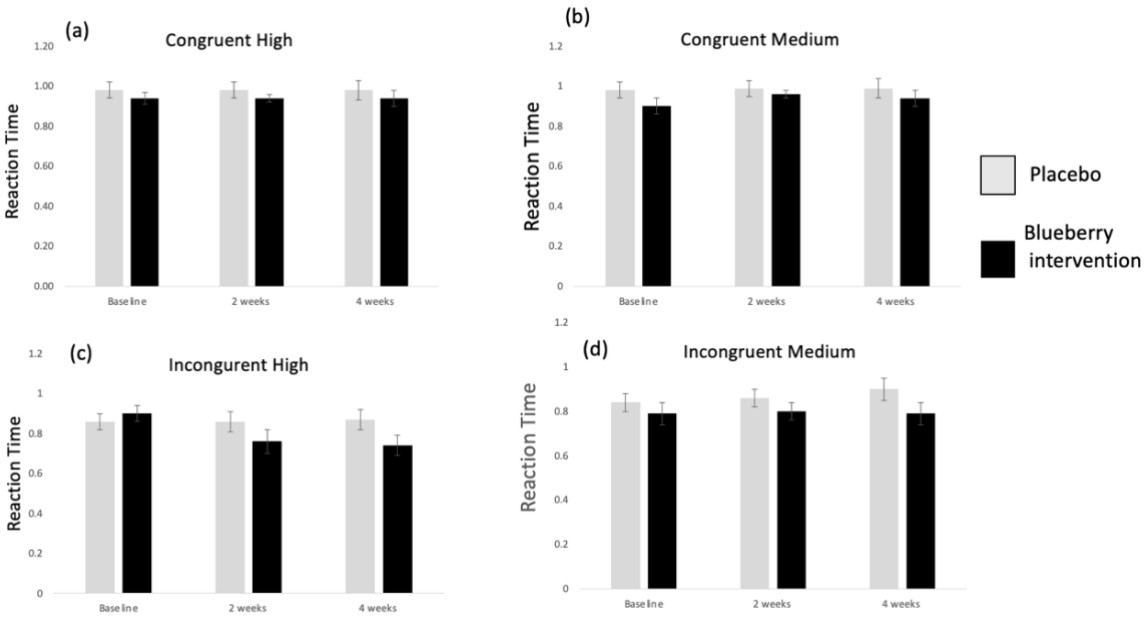

Figure 5. Mean (+ standard error of mean) reaction time on MANT at baseline, week 2 and week 4 consumption of placebo and intervention drinks in adolescents aged 11-17 years: (a) Mean reaction time when congruent/high stimuli were presented. (b) Mean reaction time when

congruent/medium stimuli were presented. (c) Mean reaction time when incongruent/high stimuli were presented. (d) Mean reaction time when incongruent/medium stimuli were presented. Asterisks with this graph show significant differences between 2 week and 4-week post-intervention.

Discussion

This randomised, placebo controlled, double blinded trial was the first to examine the effects of chronic flavonoid supplementation on executive function performance. Based on research with adults and children (e.g., Khalid et al., 2017, please see chapter 6 for full review of studies), we hypothesised that flavonoid supplementation would enhance adolescents' cognitive performance compared to a placebo control. Contrary to the hypotheses, there were no between group differences in executive functioning performance (i.e., working memory or inhibition/attention) between the blueberry and control intervention groups. This finding was surprising because (as reported in Chapter 7) adolescents in the blueberry intervention had significantly lower levels of depression symptoms at 4 weeks than those in the placebo group. Thus, based on research suggesting that anti-depressant effects following flavonoid consumption may be because of increased blood flow to brain areas associated with executive functioning, we postulated that lower symptoms of depression may be related to enhanced executive functioning (e.g., Spencer, 2008). The analysis also revealed that response interference (i.e., on the inhibition task) was evident, in that adolescents' performance was reduced on high load, incongruent trials i.e., performance was worse when trials were more cognitively demanding. However, there were no between group differences for inhibition on accuracy or reaction time.

There are several potential explanations for these findings. For example, due to

their levels of difficulty, the executive control tasks may have been insensitive to changes over time in healthy adolescents. The modified flanker task had been previously used at the University of Reading with 7 to 10-year-old children (Whyte, Schafer & Williams, 2016; Barfoot et al., 2018) and may not have been cognitively demanding enough for teenagers. Therefore, a more age-appropriate task (i.e., a more difficult task) may be better at detecting cognitive changes in adolescents. Further, although the working memory task was the same as that used in papers 1 and 2 (i.e., the KTT), it had been adapted for the current study because adolescents were tested in a group as individual testing was not possible. Owing to this adaptation, exemplar words in the task (that are expected to be updated and held in working memory) were presented on the computer screen for longer (i.e., from 2 seconds in paper 1 & 2, to 5 seconds in the current study). This modification of the task likely reduced the difficulty of the task and thus potentially made it less sensitive to working memory improvements. To explore if the adapted task was less sensitive, we looked at the keep track task data across the studies. From this we inferred that accuracy was quite likely higher in papers 1 and 2 (i.e., healthy adolescents having lower scores) compared to paper 4 and therefore the current task may have had reduced sensitivity.

Furthermore, the length of the intervention may explain the lack of effects. It is possible that 4 weeks is not long enough to observe the impact of a chronic supplementation on cognitive performance. For example, one study in older adults found improved performance on a spatial working memory task after a 3-month intervention (Ryan et al., 2008). Similarly, a 12-week intervention of berry juice (Kirkorian, Nash, Shidler, Shukitt-Hale & Joseph 2010; Krikorian et al., 2010) improved verbal memory acquisition in older adults with cognitive difficulties.

Therefore, 4 weeks may be too short a timeframe to demonstrate an observable change in executive functioning.

Given the potential insensitivity of both cognitive tasks for this age group, and previous evidence of cognitive improvements in children and adults following flavonoid supplementation, future studies should replicate the current study but use tasks with increased difficulty. Alternatively, recruiting adolescents with depression or cognitive impairment (or both) would be of interest as flavonoid-related cognitive improvement may be observed if there is 'more room for improvement'. Further, there has been suggestion that improvements in cognition following flavonoid intake is associated with increased cerebral blood flow (Spencer, 2008; Bell, Lamport, Butler & Williams, 2015). The role of cognition and cognitive control on the onset and maintenance of depression is long acknowledged, and cognitive control requires executive functions i.e., working memory and inhibition (Mikaye 2000; Snyder, Miyake & Hankin, 2015, LeMoult & Gotlib, 2018). If, as posited, increased blood flow to the brain, potentially strengthens executive control (e.g., Miller, 2000) it may have beneficial cognitive effects for those with depression. Individuals may become more resilient when controlling negative information, thus cognitive factors associated with depression (i.e., cognitive biases and maladaptive emotion regulation strategies) may reduce which in turn may elevate mood. To assess if changes in cognitive functioning impact depression, future research should directly analyse the relationship between flavonoid intake, depression, cognitive control and depression related factors associated with cognitive control deficits. This would help to better understand if and how they are related. It's important to note that definitive mechanisms underlying enhanced cognition in flavonoid supplementation studies are unknown. Therefore, additional

research investigating cognitive processing and the bioavailability of flavonoids within child and adolescent bodies could help explore these potential mechanisms of action.

The absence of cognitive functioning changes across Chapters 7 and 8 suggest that the reduction of depression symptoms may not (as hypothesised) have been instigated by enhanced blood flow to the prefrontal cortex, thus consequently not boosting executive function. This may suggest that an alternative mechanism could underlie flavonoid intake and the anti-depressant effects. A more direct pathway between flavonoid consumption and mood is the effects of flavonoids on Monoamine Oxidase (MAO). This is because anthocyanins (i.e., the flavonoid found in blueberries) are suggested to have MAO inhibitory effects that may reduce oxidative stress and lead to increased concentration of the neurotransmitters involved in depression. Some of which are neurotransmitters involved in the regulation of mood (e.g., serotonin, dopamine, and noradrenaline). MAO inhibitors have been used to treat mood disorders. Therefore, consuming flavonoids could reduce MAO activity, thus increasing monoamines in the brain and elevating mood (Watson et al., 2015). Hence the consumption of fruits high in flavonoids, may significantly reduce MAO activity, thereby increasing circulating monoamines, and elevating mood (Vauzour, Vafeiadou, Rodriguez - Mateos, Rendeiro & Spencer, 2008). Crucially, this appears to be a healthy alternative compared to taking pharmaceuticals, with a bonus of improving general health by consuming healthy food. To test this theory, future studies would also have to longitudinally use biochemical analysis to assess MAO activity, test key executive functions (working memory and inhibitory control), and depression.

To conclude, although no significant improvements were found for either

inhibition or working memory performance in healthy adolescents following chronic flavonoid intervention, further research with different executive function tasks and depressed youth populations is recommended as the current findings cannot be generalised to clinical samples.

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8 Chapter 9 General Discussion

Depression is characterised by problematic information processing, specifically in the domains of attention, interpretation and memory. A recent review of information processing difficulties in adolescent depression concluded that studies of overgeneral memory provide the most consistent data (Oliver, Pile, Elm & Lau, 2019). However, the mechanisms underlying OGM in teenagers with depression symptoms are not well understood (Hitchcock, Nixon & Weber, 2014). The aim of this thesis was to assess overgeneral memory (OGM) and explore the potential underlying mechanisms in adolescent depression.

The CaR-FA-X model is the most prominent model to account for OGM and focuses on three key mechanisms that may interrupt a retrieval search; capture and rumination, functional avoidance and impaired executive control (Williams et al., 2007). No study had yet investigated all three mechanisms in adolescents with elevated symptoms of depression (paper 1) or adolescents with a clinical diagnosis of depression (paper 2). Based upon the CaR-FA-X model (Williams et al., 2007), it was hypothesised that youth with elevated depression symptoms and adolescents with a formal diagnosis of depression would have higher rumination scores, avoid negative memory content as a form of functional avoidance, and have reduced executive functioning, when compared to young people at low-risk of depression. It was also important to compare findings to a clinical control group to control for non-specific effects of distress and related mental health problems. Therefore, paper 2 also compared findings to a group of adolescents with a clinical diagnosis of anxiety (but not depression).

The key finding in both paper 1 and 2 was that overgeneral memory and working memory deficits were present in community teenagers with elevated depression symptoms and adolescents with a clinical diagnosis of major depressive disorder. Exploratory analysis also revealed that poor working memory was directly related to OGM in both papers. Therefore, the next step was to examine if it was possible to improve working memory. One potential strategy was to use working memory training, however given the disappointing effects of this type of training (reviewed in paper 3), an alternative strategy to target cognitive functioning was needed.

As discussed in Chapter 6, an alternative intervention to enhance cognition was dietary flavonoid intake. As a result, we tested a 4-week supplementation of a high flavonoid drink on mood and cognition in healthy adolescents (paper 4).

This discussion will describe and integrate findings from each of the papers in this thesis and evaluate their strengths and limitations. The implications for research, clinical practice and future work will be considered.

8.1 Overview of findings

8.1.1 Chapter 3 (Paper 1): A test of OGM and the CaR-FA-X mechanisms in adolescents with low mood.

The potential underlying mechanisms that affect an autobiographical memory search are not well understood in adolescent depression and have not yet been explored in the same in the same study. The CaR-FA-X model proposes that three different mechanisms account for why the search of a specific memory is prematurely interrupted (Williams et al., 2007; Conway & Pleydell-Pearce, 2000). Therefore, paper 1 assessed OGM and each of the CaR-FA-X mechanisms in community adolescents

with elevated depression symptoms (n=30) and compared results to teenagers with very low levels of depression symptoms (n=29). Depression symptoms were measured using a valid and reliable measure of depression symptoms; The Mood and Feelings Questionnaire (MFQ; Costello & Angold, 1988).

The executive control component has previously been measured using a broad measure of executive control (e.g., Rawal and Rice, 2012). However, both 'updating working memory' and 'inhibition' are postulated to be important in autobiographical memory retrieval (Conway & Pleydell-Pearce, 2000). Therefore, it was important to examine both constructs to assess which (or both) are reduced in adolescent depression thus may cause OGM.

Based on the CaR-FA-X model, it was hypothesised that adolescents with elevated symptoms of depression would retrieve more overgeneral memories, and if this was true we expected that to either have higher rumination scores, retrieve less negative memory content (indicating avoidance to reduce negative affect), and have reduced executive functioning, compared to the group with low depression scores. Additionally, a recent study with healthy adolescents (Stewart, Hunter & Rhodes, 2018) demonstrated a difference between brooding and reflective pondering rumination and therefore these constructs were analysed separately.

As expected, after controlling for IQ, adolescents with elevated depression symptoms retrieved more overgeneral memories, ruminated more (both brooding rumination and reflective pondering), and had poorer working memory and verbal fluency, than adolescents with minimal depression symptoms. However, contrary to the hypothesis the groups did not differ on measures of inhibition or functional avoidance and potential reasons for this are discussed in Chapter 3. Overall, the findings suggest

that reduced working memory, verbal fluency and rumination may be involved in OGM retrieval in youth with high depression symptoms. Exploratory analysis using correlational analysis also revealed that OGM retrieval was associated with higher levels of rumination and reduced working memory and verbal fluency performance.

The young people in this study were from a non-clinical population. Although mood symptoms were measured via a valid and reliable measure of depression symptoms (i.e., the MFQ), it was essential to replicate these findings within a clinically diagnosed population.

8.1.2 Chapter 4 (Paper 2): A test of OGM and the CaR-FA-X mechanisms in clinically anxious and depressed adolescents.

Paper 2 followed directly from paper 1 by assessing OGM and investigating the CaR-FA-X mechanisms in adolescents with a clinical diagnosis of depression (n=30) adolescents with a primary diagnosis of anxiety but not depression (n=22) and a community control group (n=30). It was important to have a clinical control group to control for any non-specific effects relating to mental health difficulties. Adolescents with a primary clinical diagnosis of depression and adolescents with a primary diagnosis of anxiety (with no depression diagnosis) were recruited from an NHS funded research clinic. Both clinical groups were also compared to a community control group that had very few symptoms of depression (measured via the MFQ) and anxiety (measured via the Revised Child Anxiety and Depression Scale (RCADS); Chorpita, Yim, Moffitt, Umemoto & Francis, 2000). The three groups were matched for age and IQ.

Based on the CaR-FA-X model, it was hypothesised that adolescents with clinical depression would retrieve more overgeneral memories, if this was true, the

study could continue and it was thought that depressed youth may also have either higher rumination scores, retrieve less negative memory content (indicating avoidance to reduce negative affect), and/or have reduced executive functioning, compared to both control groups.

As expected, depressed adolescents retrieved significantly more overgeneral memories compared to both anxious and community adolescents. However, there was no significant difference in the number of overgeneral memories recalled between anxious and community adolescents. This suggests that the maladaptive retrieval of overgeneral autobiographical memories is specific to depression (i.e., not anxiety).

Depressed young people had significantly higher rumination scores than both anxious and community samples, and anxious adolescents ruminated significantly more than the community group. There were no significant differences in the number of errors made on the inhibition task between the three groups. However, both depressed and anxious adolescents were significantly slower when inhibiting prepotent responses compared to the community group. Only young people with a depression diagnosis had significant impairments in working memory, suggesting that difficulty updating information in working memory may be a problem specific to adolescent depression. However, we cannot completely rule out that the cognitive dysfunction was influenced by a combination of depression and anxiety symptoms (i.e., youth with a diagnosis of depression did also experienced anxiety symptoms). Although it should be noted that the anxiety groups retrieved very few overgeneral memories which may indicate that in relation to which cognitive components were underlying OGM, it is possible that the depression symptoms were driving this. Finally, there were no between group differences in functional avoidance or verbal fluency between the 3 groups.

Exploratory analysis also revealed that OGM retrieval was associated with higher levels of rumination and reduced working memory. Post-hoc analysis revealed that working memory and rumination separately predicted OGM, however this model was underpowered thus findings should be interpreted with caution.

These findings replicate those from study 1 and demonstrate that adolescents with a clinical diagnosis of depression potentially have specific deficits in autobiographical memory processing and working memory. Therefore, working memory could be a potential strategy for prevention or treatment in adolescent depression and a logical next step was to examine potential strategies to enhance working memory.

8.1.3 Chapter 5 (paper 3): A review of meta-analyses examining the near and far-transfer effects of working memory training.

Deficits in working memory appear to be specific to adolescents with depression symptoms (from the community and from the clinical population, respectively) thus targeting working memory could be a potential intervention strategy. One way to target working memory would be through working memory training (WMT) programmes. These programmes aim to enhance working memory by engaging in cognitively demanding tasks (Strobach & Karbach, 2016). It has been hypothesised that boosting one cognitive domain (e.g., working memory) will impact other cognitive domains and 'real life' skills (e.g. Jaeggi, Buschkuehl, Jonides & Perrig, 2008; Jerrim, Macmillan, Micklewright, Sawtell & Wiggins, 2016). Several meta-analyses have been completed that examine the effectiveness of working memory training (WMT) in youth populations and thus paper 3 reviewed the current evidence.

A systematic search for meta-analyses found 10 meta-analyses and 1 second order meta-analysis. Each meta-analysis was reviewed, evaluated and rated for quality. The review concluded that working memory training improved performance on working memory tasks (i.e., near-transfer), with a range of small to medium effect sizes; however, these effects diminished over time. Importantly there was no robust evidence that trained skills transferred to other cognitive domains or 'real life' tasks. Therefore, it was important to research alternative interventions that target cognition. The evaluation of the review also focused on how WMT effected different populations, evaluated the review itself and considered future research.

8.1.4 Chapter 7 (paper 4): Effect of 4 weeks daily wild blueberry supplementation on symptoms of depression and cognition in adolescents.

As reviewed in Chapter 6, there is emerging evidence to suggest that a nutritional diet (a high-flavonoid diet of fruit and vegetables) may have promising effects on cognition by enhancing executive functions. There is also separate accumulating evidence to suggest a relationship between flavonoid intake and improved mood. Based on this literature we therefore proposed two hypotheses. The first, we expected adolescents in the flavonoid condition would report decreased depression symptoms and increased positive affect (i.e., transient mood) compared to adolescents in the placebo condition. The second, we expected adolescents in the flavonoid condition would show increased cognitive performance on working memory and inhibition tasks compared with a placebo control group.

To test these two hypotheses we completed a randomised, double-blind, placebo-controlled trial to assess whether a chronic 4-week supplementation of a high-flavonoid blueberry drink improved depression symptoms and executive functions in community

adolescents. Sixty-four young people were recruited from 4 local secondary schools. The first two sessions, scheduled 48 hours apart, involved the first practice session and a baseline session. Young people completed the MFQ and the RCADs at the beginning of the intervention and again at the last session (4 weeks later). At each time of the 4 time points, participants completed computerised executive function tasks (to assess working memory and inhibition). Momentary mood (i.e., affect) was also measured at each time point through the Positive and Negative Affect Schedule-NOW (Watson, Clark, Tellegen, 1988). Following the intervention, a significant decrease in self-reported depression symptoms was found in participants within the blueberry, but not the placebo, intervention. There were no significant effects found for either momentary mood or executive functioning. The absence of cognitive effects may have been due to the choice of cognitive tasks (further explanation in chapter 8). Nevertheless, our preliminary results indicate that further research is warranted to explore the effects of flavonoid supplementation on depression symptoms, and that increasing the level of flavonoids in diet (i.e., through additional fruit and vegetable intake or supplementations) could be a potential strategy to prevent the development of depression symptoms in youth.

8.2 Findings in relation to cognitive theories in depression

The findings from papers 1 and 2 of overgeneral retrieval and impaired executive functioning, support core aspects of cognitive theories of depression i.e., biased autobiographical memory and impaired cognitive control. Cognitive theories propose that the way in which information is processed influences emotional responses, and therefore biased processing of emotional material (i.e., “cognitive biases”) and

impaired processing of non-emotional information (i.e., “reduced cognitive control”) maintain depression in young people and increase the risk of depression onset in vulnerable populations (Oliver et al., 2019).

8.2.1 Overgeneral autobiographical memory

The findings from studies 1 and 2 support previous literature, in that the retrieval of autobiographical material is retrieved in an overgeneral way (Williams et al., 2007). A new discovery however was that this disruption in autobiographical memory retrieval is potentially caused by deficits in working memory, as both OGM and impaired working memory were specific to depression symptoms (when compared to both community and clinically anxious adolescents). From these findings, it may be beneficial for future research aiming to better understand the relationship between OGM and depression to focus on working memory processing. Notably, rumination was also significantly higher in depressed individuals in paper 2, and therefore further research should examine the potential relationship between rumination, deficits in working memory, and depression in adolescents. For instance, if impaired working memory is driving ruminative processing in adolescent depression, then targeting working memory may also impact (i.e., reduce) the tendency to engage in this maladaptive thinking process. To unravel this relationship, larger studies are needed with adequate statistical power to test the relationships between cognitive processes in depression. For exploratory analysis we conduced post-hoc analysis in papers 1 and 2. Although both studies had inadequate power for these tests so findings should be interpreted with caution, interesting findings were revealed. In paper 1, OGM was associated with working memory, rumination, and verbal fluency. In paper 2, OGM

was associated with working memory and rumination. Tests also revealed that working memory and rumination predicted OGM in isolation.

8.2.2 Impaired executive control

Findings from papers 1 and 2 support the view proposed by cognitive researchers that executive control is impaired in depression (e.g., LeMoult & Gotlib, 2018). Both papers 1 and 2 demonstrated that adolescents with depression symptoms also had reduced executive function performance i.e., the higher order cognitive processes needed for successful executive/cognitive control. Paper 1 found reduced working memory and verbal fluency in community youth with elevated depression symptoms, whereas paper 2 found reduced working memory in depressed adolescents, and impaired inhibitory control in both anxiety and depression groups.

These findings suggest that cognitive dysfunction is present in adolescents with a depression diagnosis and is thus in line with adult depression research, that has consistently found that adults with depression have impaired executive functioning (Synder, 2013). The findings from empirical evidence have been mixed in youth depression. One review reported little support for executive function deficits (Vigis, Silk & Vance, 2015), whereas another found pronounced deficits in youth with depression (Wagner, Müller, Helmreich, Huss & Tadić, 2014). However, it has been argued that the null results in some studies may have arisen because of power limitations in the studies due poor task sensitivity and/or a small sample size (Snyder, Miyake & Hankin, 2015). Another proposed reason for the mixed findings is because of the paucity of studies that have used executive control tasks with emotional stimuli, and evidence suggests that executive control impairments are more prominent when processing emotional information (Joorman & Gotlib, 2010).

Importantly, the impaired executive function findings (i.e., in paper 1 and 2) provide justification for further assessment of executive control processes, and specifically working memory functioning, in adolescents with depression. The research in this thesis suggests that adolescents with depression symptoms have specific processing difficulties when updating information in working memory. This impairment was present with non-emotional stimuli thus deficits were global and therefore likely to impact multiple areas of everyday life (Snyder, Miyake & Hankin, 2015), which further highlights the need for future work to focus on working memory in adolescent depression.

8.3 Strengths and Limitations of the thesis

8.3.1 Strengths and limitations of paper 1 and 2

A strength of both paper 1 and 2 was that all three mechanisms of the CaR-FA-X model were explored in adolescents with depression symptoms. The previous studies that tested all three mechanisms in adolescents have been with healthy community populations (e.g., Gutenbrunner, Salmon & Jose, 2018; Stewart, Hunter & Rhodes, 2017). It was important to investigate the CaR-FA-X mechanisms in young people with depression symptoms, to be certain that findings can be generalised to this specific population. For instance, mechanisms such as rumination and impaired executive control are likely to have a greater impact on cognitive processes (e.g., such as autobiographical memory retrieval) in adolescents with depression comparative to healthy youth. This is because both rumination and impaired executive control have been suggested as potential cognitive factors in depression (Oliver et al., 2019; Stewart, Hunter & Rhodes, 2017).

Although we studied the 3 mechanisms, a limitation was the measure for functional avoidance as this was a novel measure without validated psychometric properties. To assess functional avoidance of autobiographical retrieval, the memories recorded from the autobiographical memory task were rated by the researcher for negativity and positivity on a 7-point Likert scale. The measure was based on the original definition of functional avoidance, and previous functional avoidance research in Post-Traumatic Stress Disorder (PTSD) patients. Williams et al. (2007) defined functional avoidance as "when episodic material threatens to cause affective disturbance" (p.122). Further, research assessing functional avoidance in adult PTSD found that OGM was positively correlated with several cognitive avoidance strategies such as thought suppression, dissociation, and avoidance of private personal experiences (Schonfeld & Ehlers, 2006). Therefore, the justification for our functional avoidance measure was that adolescents who use OGM as a cognitive avoidance strategy would also avoid negative memory content, as this is likely to cause affective disturbance. However, a key weakness with this, was that we did not measure lifetime exposure to negative or positive experiences, which might plausibly differ between the groups. Specifically, because increased exposure to negative life events (including possible trauma) in young people in the depression group may indicate that they have had a larger mental 'catalogue' of negative memories to draw on, and thus their retrieval of memories that did not differ in affective tone may reflect a positively biased retrieval. In future, adolescents could be asked to rate the memories themselves, in terms of how positive or negative they believe their recollection to be in comparison to other memories they have. This would provide a more precise insight into whether adolescents were avoiding negative autobiographical content. An additional or

adjunctive strategy to assess cognitive avoidance would be to include an avoidance questionnaire to explicitly measure the young person's general avoidance behaviour.

A main strength of paper 2 was the inclusion of a clinically depressed group of young people and a clinical control group. Both groups were assessed using gold-standard, standardised, semi-structured interviews for anxiety and depression (ADIS-C/P; Silverman, 1996; K-SADS; Kaufman et al., 1997). Including a clinical control group is particularly important because disruptions in the information processing system are a general characteristic of psychopathology (Beck & Alford, 2009). Although the nature of dysfunctional thinking varies between disorders some studies have found that certain cognitive biases (e.g., attention bias) may be better explained by anxiety (Reid, Salmon & Lovibond, 2006). Therefore, it is important to include clinical control groups to a) control for non-specific distress and difficulties in mental health and b) to demonstrate whether findings are potentially specific to a depression of depression. However, recruitment of clinical samples within clinical research is challenging, and although depression symptoms were only experienced in the depression group (i.e., depression symptoms were significantly higher on a self-report measure compared to both the anxious group and the clinical control group, and no youth in the other groups has a diagnosis of depression). Adolescents with a diagnosis of depression were also experiencing symptoms of anxiety. Although only those in the depression group revealed cognitive deficits such as OGM and Working Memory, some may argue that findings were influenced by a combination of anxiety and depression symptoms in the depressed group. However, co-morbidly in anxiety and depression is extremely high in adolescents e.g., anxiety is the most common co-morbid mental health problem in young people with depression (Angold, Costello, & Erkanli, 1999).

Therefore, findings in the current thesis likely reflect a true clinical sample. For future researchers that want to investigate cognitive deficits in depression, to be certain that cognitive functions are associated with depression specifically, anxiety symptoms could be controlled for within their analysis. Despite this, because cognitive impairments such as OGM and working memory were not a difficulty in the anxiety only group, it is plausible that depression symptoms were driving cognitive processing deficits in both autobiographical memory retrieval and working memory processing.

The sample sizes for papers 1 and 2 were determined by an a priori power analysis to test for differences between groups. Although our papers were adequately powered to test for group differences, there was inadequate power for additional statistical analyses of the relationships between the CaR-FA-X mechanisms. A larger sample would be needed to firstly, run correlations between the total number of overgeneral memories retrieved and each CaR-FA-X mechanism in each group, to clarify that each mechanism was directly correlated with OGM. Second, to test for potential interactions between the CaR-FA-X mechanisms. This is expected to be important because Rawal and Rice (2012b) found that, in a sample of 259 at-risk adolescents, OGM was predicted in the context of high rumination and low executive control. A much larger sample is needed for this type of analysis, for example, Hallford, Austin, Raes and Takano, (2018) reported that a minimum of 250 participants is necessary to detect a small effect. The ability to recruit larger samples was beyond the scope of this project, due to the need of a greater capacity of time and resources but would be advised for future research. However as previously mentioned (and although tests were underpowered) post-hoc analyses were conducted. For example, in paper 1, OGM was associated with working memory, rumination, and verbal fluency. Similarly,

OGM was associated with working memory and rumination in paper 2. Additionally, tests also revealed that working memory and rumination predicted OGM in isolation in the clinical paper.

Unlike most studies examining OGM and executive control, papers 1 and 2 assessed subcomponents of executive control that are involved in the search for a specific autobiographical memory (i.e., working memory and inhibition). A potential limitation however is that the current thesis only assessed non-emotional information processing and it is hypothesised that problematic cognitive processing in depression is more severe when emotional stimuli are involved (Oliver et al., 2019). Some studies have assessed executive function while using emotional stimuli (also referred to as 'hot' executive control tasks) and have found that youth are more likely to allocate their attention to negative stimuli compared to controls, thus affecting task performance (Kyte, Goodyer & Sahakion, 2005; Ladouceur et al., 2006; Maalouf, Clark, Tavilian, Sahakian, Brent & Philips, 2012). The use of non-emotional task stimuli may account for the absence of inhibition deficits in paper 1, and the mixed findings in paper 2. Both studies hypothesised that depressed adolescents would have impaired inhibition. Thus, the inconsistent findings were surprising, as inhibitory control is hypothesised to underpin biases in memory and attention in depression and set the stage for rumination of negative events and negative mood states (Joorman, 2005; Joorman & Gotlib, 2010). However, The Hayling Sentence Completion Task used non-emotional stimuli. Therefore, it is possible that non-emotional stimuli did not impact the information processing system to the degree that emotional stimuli may have, e.g., negative self-relevant stimuli may have captured the attention of young people to a greater extent, thus using more cognitive resources and therefore reducing task ability.

8.3.2 Strengths and limitations of paper 3

This was the first paper to review the findings from all meta-analyses that examined the efficacy of working memory training in youth. However, a limitation was the absence of data for affective working memory training in adolescents, and studies that assess far-transfer to questionnaires that measure depression symptoms. Affective working memory training refers to training programs that use emotional stimuli rather than the global non-emotional stimuli that is used in most training programs, i.e., the working memory training regimes reviewed in paper 3 involved challenging cognitive tasks usually using numbers. The inclusion of a meta-analysis for affective working memory training, or for data of far-transfer to depression, was not possible due to the paucity of research assessing this in youth. Because of this, it could be argued that although working memory training is ineffective for improving other cognitive domains and academic tasks, it does not rule out the possibility of far-transfer to depressionogenic symptomology (Beloe & Derakshan, 2018), yet there is currently not enough available research in youth to examine this.

8.3.3 Strengths and limitations of paper 4

This was the first chronic trial to assess effects of a high-flavonoid blueberry supplementation on mood and executive functioning in adolescents. Importantly, in relation to measuring 'mood' it was also the first trial to use a standardised measure of depression symptoms rather than a measure of affect (i.e., transient mood). Previous studies have used measures that ask individuals to score how much they are feeling a certain emotion at that moment in time e.g., 'how enthusiastic or afraid do you feel right now'. For example, Khalid et al. (2017) used the Positive and Negative Affect scale (Watson, Clark & Tellegen, 1988) to measure 'affect'. They found that following

an acute dose of a high-flavonoid blueberry drink, both children and young adults had increased positive affect. Although this was an important finding, any inferences made about depression (i.e., referred to as 'sustained mood' in paper 4) are inappropriate, as all previous studies have only measured fleeting emotional states. Whereas paper 4 used the MFQ (Costello & Angold, 1995), which is a validated screening tool for depression and thus more accurate inferences on the effects of flavonoids on emotional, cognitive and physical symptoms of depression can be made.

The main limitation of this paper was the potential insensitivity of the cognitive tasks. The inhibition task (a modified flanker task) had previously been used to assess cognitive function in children, and the working memory task (the keep track task) had been adapted so that it could be used without a researcher present, which consequently reduced the task difficulty. Another shortcoming of paper 4 was it was split into two chapters, (i.e., Chapter 7 reported flavonoid supplementation on mood, whereas Chapter 8 described findings to executive functions). Due to this, there were missed opportunities to investigate the potential relationship between executive function performances and mood, particularly as flavonoid supplementation may improve mood through potential flavonoid effects on executive control (such potential links are discussed in more detail within the introduction and discussion sections in Chapter 8). Despite the absence of executive function differences between the flavonoid intervention group compared to the placebo group, the hypothetical relationship between mood and executive function could have been investigated further. The potential relationship between flavonoids, cognition and depression symptoms needs to be reassessed using more challenging cognitive tasks, and relationships between mood, cognitive performance (and depression related cognitive processing difficulties

associated with poor executive control) should be an avenue for future studies. This may help understand if increased cerebral blood flow from flavonoid intake enhances executive functions, improves cognitive control, and consequently impacts mood and depression related cognitive factors. Therefore, future research continuing in this direction is warranted and is further discussed in section 9.4.2.

8.4 Broader implications and recommendations for future research

8.4.1 Implications and future research for The CaR-FA-X model

8.4.1.1 Are deficits of working memory, inhibition and rumination risk factors for developing depression or are they a consequence of depression symptoms?

The findings in both papers 1 and 2 found specific deficits in working memory, and increased levels of rumination in adolescents with depression symptoms. This suggests that rumination and impaired working memory may be underlying mechanisms of OGM for those experiencing depression symptoms. However due to the cross-sectional nature of the studies, it is not known if these deficits were a consequence of depression symptoms or acted as a vulnerability factor for the onset of depression symptoms.

This would be important to understand because if these impaired cognitive processes are risk factors, then they could possibly be targeted early, potentially preventing the onset of depression. Further, as the brain is undergoing rapid development in this period (Blakemore, 2012) it is important to assess cognitive processes across adolescence, as the relationship between cognitive processes and depression symptoms may change throughout development.

Therefore, one possible suggestion for future research would be to assess the model using a longitudinal design, in community at-risk adolescents. For instance, adolescents at familiar risk of depression but who are not currently depressed could be recruited and assessed on depression symptoms, OGM, and the CAR-FA-X mechanisms over time. Although papers 1 and 2 did not find evidence for the functional avoidance mechanism, this may have been due to the measure rather than an absence of functional avoidance (see section 9.3.1), thus this should also be assessed in future work. The cognitive processes could be re-tested annually over adolescence (e.g., over a 4-year period). Additionally, it would be advised that all executive control tasks are interactive (i.e., not questionnaires), as it had been suggested that behavioural executive functioning tasks and questionnaires do not tap into the same constructs (Samyn, Rowyers, Bijttebier, Rosseel & Wiersena, 2015; Snyder, Miyake & Hankin, 2015). Moreover, a more explicit measure of functional avoidance compared to that used in papers 1 and 2 (e.g., an avoidant behaviour questionnaire) should be implemented. Using more advanced statistical analysis than conducted in the current thesis, an approach such as structure equation modelling or mediation modelling may help identify causal mechanism between variables. This research could help to determine if working memory deficits and/or rumination and/or functional avoidance predict depression symptoms and thus help to identify potential vulnerability factors in youth depression. This is important because finding vulnerability factors may help to inform intervention strategies for adolescents to prevent the onset of depression.

8.4.1.2 Do the CaR-FA-X mechanisms interact and does one predict another in adolescent depression?

An additional question that requires an answer is if the CaR-FA-X mechanisms interact with each other over time in adolescent depression, e.g., does impaired working memory predict rumination? A much larger sample than the current studies would be necessary to complete this type of study (i.e., to obtain adequate power for statistical analysis). For example, Rawal and Rice (2012) examined the relationship between memory specificity, rumination and executive control in a large sample of adolescents (n = 259). They reported that in youth at familial risk of depression, higher rumination predicted reduced memory specificity but only in youth with low executive control. This suggests an interaction between the executive control and rumination mechanisms. Although informative, Rawal and Rice (2012) recruited an at-risk sample (rather than depressed) and used a measure of IQ to assess executive control. A future longitudinal design could recruit a large sample of adolescents experiencing elevated depression symptoms (so that findings are generalisable to a depression population) and assess the CaR-FA-X mechanisms at least at 2 time points (e.g., with a year follow-up period). This future research is important because 1) it may provide a better understanding of OGM in adolescent depression i.e., by identifying underlying OGM mechanisms that may contribute the development and maintenance of depression, and 2) has the potential to inform prevention or treatment strategies e.g., interventions targeting working memory may have the potential to reduce depression symptoms and/or rumination.

8.4.2 Implications and future research for dietary flavonoids, depression and cognition.

Considering the promising finding of reduced depression symptoms on the MFQ in community adolescents following a chronic (4-week) supplementation of high-flavonoid blueberry drink in paper 4, further investigation into the effects of chronic flavonoid supplementation on depression symptoms is warranted. Replication of the current findings is required, for instance in depressed or at-risk adolescents. Crucially, the inclusion of methods to help identify the underlying mechanisms of change that may be causing the reduction of depression symptoms is required. As discussed in chapter 8, no significant improvements on measures of executive function were found following the flavonoid supplementation. There are a number of reasons for this, including the limitations to the current cognitive tasks (Chapter 8 and section 9.3.3) or that cognitive improvement may be found in a depressed sample because they are more likely to experience cognitive deficits thus may be more likely to benefit from supplemental intervention. However, it does also potentially suggest that depression symptoms did not improve as a by-product of enhanced executive functioning and may transpire through alternative mechanisms. For example, it has been suggested that flavonoids mimic the effects of monoamine oxidase inhibitors, leading to an increased concentration of neurotransmitters known to be associated with depression e.g., serotonin, dopamine and noradrenaline (Watson, Haskell-Ramsay & Kennedy, 2015). This might be one mechanism that could explain how flavonoids improve mood but to investigate this theory it would be vital to longitudinally use biochemical analysis to assess MAO levels. Nevertheless, when considering the literature that associates enhances executive functioning following healthy diets (i.e., rich in flavonoids) and studies that report cognitive function increases following flavonoid intervention (for the full literature review please see chapter 6), it is still a possibility that boosting executive

functioning could be an indirect mechanism for decreasing depression symptoms. Although improved executive functioning was not observed following the flavonoid supplementation in paper 4, this was thought to be because of the insensitive cognitive tasks (see limitations in Chapter 8 and section 9.3.3). Moreover, several authors have proposed that flavonoids increase cerebral blood flow to the dorsolateral prefrontal cortex (e.g., Spencer, 2008). This is a site that is highly associated with executive functioning and emotional regulation processing, including rumination (LeMoult & Gotlib, 2018; Oliver et al., 2019; Miller, 2000). Therefore, it is hypothesised that increasing blood flow to this brain area will positively impact the depression-linked cognitive processes and emotional regulation that are associated with this area i.e., the prefrontal cortex (Miller, 2000).

Consequently, future studies should consider three core proposals. First, future research should examine chronic flavonoid supplementations in youth with elevated depression symptoms to assess the effects of flavonoid intake on depression symptoms. Especially as, it is plausible that youth with elevated symptoms of depression, or youth with clinical depression may experience greater effects from flavonoid intake. This is because executive function deficits are evidenced in adolescent depression (Wagner et al., 2015; Fisk, Ellis & Reynolds, 2019), and therefore there may be more room for cognitive improvement compared to the healthy adolescents in study 4. This research would be imperative as improving diet could be an accessible and cost-efficient way to reduce depression symptoms. Second, to select executive function tasks that are more sensitive compared to those used in study 4 to reduce any potential ceiling effects and to be certain that tasks are sensitive enough to detect cognitive deficits in youth, and therefore be more likely to identify possible improvement after a flavonoid

intervention. Third, further research should directly assess potential relationships between depression, executive processes, and flavonoid intake. Notably, this could also help discover if the executive functions that can be improved by flavonoid intake are the same as those that may potentially have a positive impact on depression symptoms. These studies may be instrumental in recognising whether increased executive functioning could be a potential mechanism of change between consumption of flavonoids and reduction in depression symptoms. Furthermore, currently, in the UK, only 18% of adolescents meet the recommended daily requirement of fruit and vegetables (NHS Digital, 2017). Therefore, replication of our findings in paper 4, could have extensive value to public mental health through advising dietary interventions.

8.4.3 Implications of impaired working memory processing in educational settings

Difficulties in monitoring and updating information in working memory is likely to have a large impact on academic life and achievements, thus findings should be shared with educational departments. This is because school work may be harder to process, require more time to work on and ultimately remember. There is evidence that supports the potential relationship between educational achievement and working memory abilities. For example, working memory performance has been found to be a significant predictor for academic achievement (Peng et al., 2018; Peng, Namkung, Barnes & Sun, 2016) and lower working memory capacity correlates with poorer academic achievement (Passolunghi, 2006). Therefore, disseminating this information to schools would be beneficial to inform academic staff and to encourage schools to consider potential ways to adapt the school environment to help those young people with depression related cognitive dysfunction e.g., offering additional support or extra

time for projects, or teaching compensatory strategies that might help with day to day school tasks (compensatory strategies are discussed in more detail in section 9.4.4.2).

8.4.4 Clinical implications and recommendations for future research

8.4.4.1 Improving treatment response

Based on the evidence of impaired working memory in depression (i.e., from studies 1 and 2), it is likely that engaging in cognitive techniques within psychological therapies could be very challenging. This is because deficits in working memory affect a young person's ability to hold information in their mind, relating one thing to another and using information to problem solve (Diamond, 2013). Therefore, cognitive techniques (like those found in Cognitive Behavioural Therapy; CBT) such as identifying and monitoring thoughts, restructuring cognitions, and searching memories to find evidence to evaluate core beliefs, require abstract reasoning skills that may be impaired due to deficits in working memory. This has recently been considered in adults with depression and it was found that certain aspects of cognitive functioning, in particular executive function, may be useful in predicting treatment response (Groves, Douglas & Porter, 2018). For example, one study reported that higher baseline executive functioning predicted more successful treatment from cognitive behavioural therapy (Kundermann et al., 2015) In contrast, lower executive function predicted better response to cognitive remediation therapy (designed to improve attention, working memory and cognitive flexibility), problem-solving therapy and supportive therapy (Groves et al., 2018). Importantly, assessing if baseline working memory predicts treatment response in adolescents could be informative for clinical practice. With this in mind there are three important suggestions that should be considered. The first, would be to assess if young people with impaired working memory respond more successfully

to certain treatments. This could be investigated by measuring working memory functioning before treatment and examining if higher or lower pre-treatment working memory predicts treatment response. Two youth adolescent depression treatments that could be included in this potential research are Behavioural Activation (BA) and Cognitive Therapy. The reason why cognitive therapies (e.g., CBT) might be a good choice for a treatment response study is because a number of cognitive treatment techniques employ working memory skills, such as cognitive restructuring. Whereas BA involves learning through positive reinforcement that mood states can improve following a healthy behaviour, such as activity with friends, thus it is likely to be easier to comprehend, compared to evaluating cognitions. Therefore (although research is needed), it is possible that an intervention that involves focusing on behaviours, using concrete concepts (rather than abstract), and simple, easy to grasp instructions may be most appropriate for adolescents with impaired executive control, and ultimately may be a more efficient treatment for this group (Pass, Lejuez & Reynolds, 2017).

8.4.4.2 Teaching compensatory strategies for working memory deficits

Another option for helping young people with impaired executive functioning that could be implemented before or during treatment, could be to teach compensatory strategies that aim to make day to day life easier. This idea comes from cognitive rehabilitation interventions that have mostly been used with individuals that have sustained brain damage. However, there is emerging evidence that similar techniques (e.g., goal management training) may be beneficial for people with psychopathology (Snyder, Miyake & Hankin, 2015). Essentially, these techniques aim to compensate for poor executive functioning by teaching ways to make everyday tasks feel easier and manageable. For example, strategies such as using lists and cues in day to day life, and

dividing tasks into smaller steps may help goals feel more manageable (Snyder et al., 2015).

8.4.5 Implications for directly targeting impaired cognitive processing in depression

A third suggestion would be to directly target the impaired cognitive processes found in papers 1 and 2 to improve depression symptoms. Two options worth considering would therefore be by directly targeting OGM, or by directly targeting working memory deficits. These will be discussed in more detail below.

Given that both paper 1 and paper 2 found OGM to be a specific problem in adolescents with depression, an option for preventing or treating depression symptoms would be by directly challenging OGM through therapeutic strategies that aim to increase memory specificity (e.g. Nesha-Doost et al., 2012; Pile et al., 2018). A recent meta-analysis reviewed studies that had assessed memory specificity training (MeST) and analysed the ability of MeST to increase memory specificity and reduce symptoms in various emotional disorders. They found that, in comparison to control groups, MeST was associated with substantial improvement in memory specificity and reduction of depression symptoms. Although the improvements were not sustained after a follow up period, authors proposed that this may be due to inadequate statistical power (Barry, Szem & Raes, 2019). Only one small study in this meta-analysis was completed with adolescents (Neshat-Doost et al., 2012) however preliminary findings were promising and suggested that future research with larger samples and a more rigorous design (e.g., a randomised control trial) is warranted. On this note, a more recent protocol for a randomised control trial has been published, and Pile et al. (2018) are currently conducting the ‘IMAGINE’ trial. This is a brief, manualised and structured intervention

that combines techniques of memory specificity training, image rescripting of negative events and image generation of positive events. Therefore, the findings from this trial, when it is complete, will be extremely relevant for the field of adolescent depression.

Another potential intervention strategy to prevent or treat depression symptoms would be to directly target impaired executive control, particularly working memory. Reduced cognitive functioning is a common symptom in adolescent depression (Orchard, Pass, Marshall & Reynolds, 2017) and executive control (specifically working memory) is clearly impaired in youth experiencing depression symptoms (as seen in papers 1 and 2). Therefore, targeting this cognitive deficit may have beneficial effects for either preventing the onset or alleviating current depression symptoms. However, given the current lack of evidence for effective transfer of working memory training to everyday life (paper 3), novel research is required to find other beneficial approaches to boost executive functions.

The current thesis attempted to do did this by assessing the effects of flavonoid supplementation on both executive control and mood separately (paper 4). Notably, no beneficial effects were found on executive functioning following blueberry supplementation, however as discussed in more detail in chapter 8 and section 9.4.2, the relationship between dietary flavonoids, executive functioning and depression symptoms needs further examination.

8.4.6 Implications and future research for cognitive and affective development

Research conducted in adolescents with depression is limited in comparison to adults research and other adolescent mental health research. Importantly, because the brain is still developing (Blakemore, 2012), adult models of depression should not be routinely applied to young people without evidence. However, the evidence in this

thesis is consistent with previous findings in adult depression research in many ways. For example, previous evidence (e.g., Oliver, Pile, Elm & Lau, 2019) and the findings in paper 1 and 2 support the phenomenon of OGM in depression, in that, adolescents experiencing depression symptoms, and teenagers with a clinical diagnosis of depression have difficultly retrieving specific memories. Also, when exploring the cognitive mechanisms suggested by the CaR-FA-X model, the evidence suggests that in youth with depression symptoms and OGM, they also have higher levels of rumination and deficits in working memory. Additionally, exploratory post hoc analysis revealed that both working memory and rumination were associated with OGM. Therefore, this is consistent with adult research that suggests reduced executive control and rumination (not functional avoidance) are key mechanisms in explaining OGM in adults with depression (Sumner, 2012). Further, there was no evidence that functional avoidance was present in either paper 1 or 2, which supports most adult research that functional avoidance is unlikely to be driving OGM in adults with depression (Sumner, 2012; Dalgleish, 2007).

When beginning this research, it was unclear whether cognitive findings would be consistent with those found in adults because the brain is developing in youth and therefore cognitive processing could have differed in adolescents. Similarities between the findings in this thesis and previous research may be because the cognitive processes assessed in this thesis are simply similar for both adults and adolescents i.e., cognitive functions were close to, or had fully developed thus were affected in the same way as in adults. However, it should be noted that many adolescents in these studies were reaching later adolescence. For instance, in paper 1 and 2 over half of participants were between the ages of 15-18. Therefore, it is plausible that this impacted findings as

developmental changes across adolescence may alter the relationship between brain circuits, cognitive processing, and symptoms of depression. For instance, research has found that both decision making skills, and acquisition of fully coordinated executive functioning occurs later in adolescence (Steinberg, 2005). Therefore, future research should assess cognitive processes and depression throughout adolescence to capture developmental changes. To do this, researchers could a) split adolescents into 2 categories (i.e., 13 to 15 and 16-18), or b) conduct longitudinal work that allows multiple assessments over adolescent years.

Further research should also consider assessing the potential bidirectional relationship longitudinally between depression and cognitive processing i.e., does having executive functioning deficits in adolescence relate to poorer cognitive functioning and/or increased likelihood of depression onset in adulthood? This would help us better understand the key psychological mechanisms associated to depression and may inform the development of new interventions to prevent or treat depression.

8.5 Conclusion

Depression is a chronic and disabling disorder that often emerges during adolescence and understanding core cognitive aspects of depression may help inform the development of new interventions to prevent or treat adolescents with depression.

Overgeneral memory is a proposed cognitive marker in depression and it has been found to increase the risk of depression onset and reoccurrence in adolescents (Hitchcock et al., 2014). The CaR-FA-X model (Williams et al., 2007) proposed three underlying mechanisms that cause and maintain OGM (capture and rumination, functional avoidance and reduced executive control). These mechanisms were yet to be

explored together in either community adolescents with elevated depression symptoms or in clinically depressed youth and was thus the aims of paper 1 and paper 2, respectively.

Additionally, since no study had examined the different sub-components of executive control (working memory and inhibition), OGM and depression in youth, we examined these components separately. As expected, both elevated community and clinically depressed adolescents retrieved a greater number of overgeneral memories compared to adolescents with very low levels of depression. Moreover, since clinically depressed youth also retrieved more overgeneral memories than young people with a diagnosis of anxiety (without depression), this suggested that OGM is specific to depression symptoms (and not anxiety). Overall, the findings of these studies provided partial support for the CaR-FA-X model. There were no differences in functional avoidance between groups in both studies, suggesting that this mechanism might not underlie OGM in youth depression. However, this finding should be interpreted with caution as the measure of functional avoidance may have influenced this null finding (as discussed in section 9.3.1). Both the community elevated depression group and the clinically depressed adolescents had higher rumination and poorer working memory in both studies, supporting that these two mechanisms might cause and maintain OGM in depression. With regards to executive control, the main and novel finding was that working memory performance was reduced in both community youth with elevated depression scores, and adolescents with depression, compared to community controls and clinically anxious adolescents. This indicates deficits in working memory as an important potential 'marker' for identifying and assessing depression.

Considering the importance of impaired working memory for both community teenagers with elevated depression symptoms and clinically depressed youth, the logical next step was to investigate if working memory could be enhanced, and if so, how. Therefore, paper 3 reviewed meta-analyses that had examined the effectiveness of working memory training in children and young people. The review indicated that working memory training does not appear to be a successful solution. This is because although near-transfer effects were consistent across studies, there was no robust evidence to suggest that trained skills transfered to wider domains such as other cognitive tasks or academic performance. In paper 4, we assessed the effects of a different intervention with the aim of enhancing executive functioning. Following research that suggests flavonoid intake can lead to improvements in both cognition (Barfoot et al., 2018) and mood (Khalid et al., 2017), we tested whether a chronic supplementation of flavonoid-rich blueberry drink improved mood and cognitive functioning compared to a placebo control. No improvements were seen for executive control tasks following flavonoid supplementation, however a decrease in depression symptoms were found in the blueberry drink group compared to the placebo group. Paper 4 therefore provides promising results for reducing depression symptoms in adolescents via a dietary intervention, however the mechanism of change needs further investigation.

Taken together, these findings highlight the importance of overgeneral memory and working memory deficits in adolescent depression, and thus may inform prevention and treatment strategies in adolescents at-risk of, or experiencing, depression symptoms. The evidence that working memory is impaired in depression is important for clinicians, teachers and researchers, as such deficits are likely to influence multiple

contexts of life such as clinical and school environments. Future experimental and longitudinal research is required to help identify the specific psychological mechanisms and potential relationships between them, that cause and maintain adolescent depression, and then we can work out the best way to change them.

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Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: current status and future directions. *Annual review of clinical psychology*, *6*, 285-312.

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9 Chapter 10 Appendices

9.1 Appendix 1: Mood and Feelings Questionnaire

9.2 Appendix 2: Response Rumination Scale

9.3 Appendix 3: Revised Child Anxiety and Depression Scale

Appendix 4: Assessment Quality Rating Scales (AMSTAR)

AMSTAR – a measurement tool to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided?
The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

□ **Yes**
□ No
□ Can't answer
□ Not applicable

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2. Was there duplicate study selection and data extraction?
There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

□ **Yes**
□ No
□ Can't answer
□ Not applicable

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3. Was a comprehensive literature search performed?
At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.

Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).

□ **Yes**
□ No
□ Can't answer
□ Not applicable

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4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

□ **Yes**
□ No
□ Can't answer
□ Not applicable

---

5. Was a list of studies (included and excluded) provided?
A list of included and excluded studies should be provided.

□ **Yes**
□ No
□ Can't answer
□ Not applicable

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

---

6. Were the characteristics of the included studies provided?

In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.

□ **Yes**
□ No
□ Can't answer
□ Not applicable

Note: Acceptable if not in table format as long as they are described as above.

---

7. Was the scientific quality of the included studies assessed and documented?

'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

□ **Yes**
□ No
□ Can't answer
□ Not applicable

---

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.

□ **Yes**
□ No
□ Can't answer
□ Not applicable

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9. Were the methods used to combine the findings of studies appropriate?

For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).

Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.

□ **Yes**
□ No
□ Can't answer
□ Not applicable

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10. Was the likelihood of publication bias assessed?

An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).

Note: If no test values or funnel plot included, score "no". Score "yes" if mentions that publication bias could not be assessed because there were fewer than 10 included studies.

□ **Yes**
□ No
□ Can't answer
□ Not applicable

---

11. Was the conflict of interest included?

Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

Note: To get a "yes," must indicate source of funding or support for the systematic review AND for each of the included studies.

□ **Yes**
□ No
□ Can't answer
□ Not applicable

Shea *et al. BMC Medical Research Methodology* 2007 **7**:10 doi:10.1186/1471-2288-7-10

9.4 Appendix 5: Ethic Approvals for all experimental studies (papers 1, 2 and 4)

9.4.1 University of Reading ethics approval for paper 1

University of Reading

Coordinator for Quality Assurance in Research
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Professor Shirley Reynolds
School of Psychology and Clinical Language Sciences
University of Reading
RG6 6AL

17 April 2015

Dear Shirley

UREC 15/13: Does mood impact memory retrieval and executive functioning in adolescents? *Favourable opinion*

Thank you for the response (email dated 31 March 2015 from Jennifer Fisk, including attachments, refers) addressing the issues raised by the UREC Sub-committee at its March 2015 meeting. On the basis of these responses and the revised documentation, I can confirm that the Chair is pleased to confirm a favourable ethical opinion.

The response from Jennifer was very clear, thorough and well-argued. The UREC sub-committee did still, on further review, have concerns about one or two of the more contentious issues (in particular the Study 1 'opt out' provisions) but – on balance – were minded to approve the project as amended.

Please note that the Committee will monitor the progress of projects to which it has given favourable ethical opinion approximately one year after such agreement, and then on a regular basis until its completion.

Please also find attached Safety Note 59: Incident Reporting in Human Interventional Studies at the University of Reading, to be followed should there be an incident arising from the conduct of this research.

9.4.2 University of Reading ethics approval for paper 2

University of Reading

Coordinator for Quality Assurance in Research
Dr Mike Proven, BSc(Hons), PhD

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Professor Shirley Reynolds
School of Psychology and Clinical Language Sciences
University of Reading
RG6 6AL

7 April 2016

Dear Shirley

UREC 16/13: Overgeneral autobiographical memory and executive function in adolescent depression. *Favourable opinion*

Thank you for the response (emails dated 6 April 2016 from Jeni Fisk, including attachments, refers) addressing the issues raised by the UREC Sub-committee at its March 2016 meeting. On the basis of these responses and the revised documentation, I can confirm that the Chair is pleased to confirm a favourable ethical opinion.

Please note that the Committee will monitor the progress of projects to which it has given favourable ethical opinion approximately one year after such agreement, and then on a regular basis until its completion.

Please also find attached Safety Note 59: Incident Reporting in Human Interventional Studies at the University of Reading, to be followed should there be an incident arising from the conduct of this research.

The University Board for Research and Innovation has also asked that recipients of favourable ethical opinions from UREC be reminded of the provisions of the University Code of Good Practice in Research. A copy is attached and further information may be obtained here:

http://www.reading.ac.uk/internal/res/QualityAssuranceInResearch/reas-RSqar.aspx .

Yours sincerely

Dr M J Proven
Coordinator for Quality Assurance in Research (UREC Secretary)
cc: Dr John Wright (Chair); Dr Laurie Butler (Head of School); Ms Jeni Fisk (PhD student)

9.4.3 NHS and HRA ethics approval for paper 2

NHS
Health Research Authority

South Central - Berkshire B Research Ethics Committee

Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

29 November 2016

Prof Shirley Reynolds
Department of Psychology
Earley Gate
Whiteknights Road
RG6 6AL

Dear Prof Reynolds

Study title:	**Overgeneral memory bias and executive functioning in adolescent depression**
REC reference:	**15/SC/0670**
Amendment number:	**3.0**
Amendment date:	**07 November 2016**
IRAS project ID:	**189280**

The above amendment was reviewed at the meeting of the Sub-Committee held on 29 November 2016 via correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter_031112]		03 November 2016
Non-validated questionnaire [CAMHS prescreen_version 2]	2.0	03 November 2016
Non-validated questionnaire [CAMHS prescreen_version 2_clean document]	2.0	03 November 2016
Notice of Substantial Amendment (non-CTIMP) [AmendmentForm_amendment3]	3.0	07 November 2016
Other [NHSProposal_version4]	4.0	03 November 2016
Other [NHSProposal_version4]	4.0	03 November 2016
Other [NHSProposal_version4_clean document]	4.0	03 November 2016

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

15/SC/0670:	**Please quote this number on all correspondence**

Yours sincerely

Ms Helen Sivey
REC Assistant

pp. Mr Mike Arnott
Chair

E-mail:

SJ

STRICKLAND, Joanna (HEALTH RESEARCH AUTHORITY) <jo
anna.strickland@nhs.net>

Thu 15/12/2016 14:28

Jennifer Fisk <J.Fisk@pgr.reading.ac.uk>; Shirley Reynolds; Mike Proven +2 others

Dear Jennifer

Further to the below, I am pleased to confirm that HRA Approval has been issued for the referenced amendment, following assessment against the HRA criteria and standards.

The sponsor should now work collaboratively with participating NHS organisations in England to implement the amendment as per the below categorisation information. This email may be provided by the sponsor to participating organisations in England to evidence that the amendment has HRA Approval.

Please contact for any queries relating to the assessment of this amendment.

Kind regards
Joanna

Joanna Strickland | Assessor
Health Research Authority
London HRA office, Skipton House, 80 London Road
London, SE1 6LH
E:
www.hra.nhs.uk

Please note working days: Mon, Wed, Fri

Would you like to receive the latest updates on HRA work? Sign up here

For more information on the HRA Approval process Click here

9.4.4 University of Reading ethics approval for paper 4

University of Reading

Coordinator for Quality Assurance in Research
Dr Mike Proven, BSc(Hons), PhD

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Professor Shirley Reynolds
School of Psychology and Clinical Language Sciences
University of Reading
RG6 6AL

28 November 2016

Dear Shirley

UREC 16/55: The Effects of Blueberry Anthocyanin Intervention on Cognitive functioning and Mood. *Favourable opinion*

Thank you for the application (email dated 15 September 2016 from Sundus Khalid and

The University Board for Research and Innovation has also asked that recipients of favourable ethical opinions from UREC be reminded of the provisions of the University Code of Good Practice in Research. A copy is attached and further information may be obtained here:

http://www.reading.ac.uk/internal/res/QualityAssuranceInResearch/reas-RSqar.aspx

Yours sincerely

Dr M J Proven
Coordinator for Quality Assurance in Research (UREC Secretary)
cc: Dr John Wright (Chair); Professor Claire Williams (Co-supervisor) Dr Laurie Butler (Head of School); Sundus Khalid (PhD student)

9.5 Appendix 6: Adolescent information sheets for papers 1, 2 and 4.

9.5.1 Adolescent information sheet age 13-15 for paper 1 for questionnaires

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

Project Title: Does Mood Affect Thinking in Adolescents? (Study 1)
INFORMATION FOR ADOLESCENTS aged 13-15

Hello,

We are inviting you to take part in a research study.

Why is this project being done?

We want to find out how mood affects teenagers' identity and their thoughts and experiences.

Why have I been asked to take part?

You have been asked to take part because your school has agreed to help us with this project. We are inviting you because you are aged between 13 and 15 years old and this is the age group we are interested in.

Do I have to take part?

No. Whether or not you take part in this study is **completely up to you**. You do not have to do this. Also, if you decide to take part and then change your mind, this won't matter at all. You won't have to give us a reason.

What will happen to me if I take part in the project?

We would like you to complete some worksheets in your mentoring sessions. They will take about 20-30 minutes. They include questions about your feelings, thoughts and experiences. We will also ask you to come up with some statements that describe you.

Might anything about the research upset me?

Some of the questions about your thoughts and feelings might remind you of both happy and sad feelings. This is

completely normal and OK. If you want to stop at any time, or take a break this will be fine. We can talk about this at the time or you might want to talk to your friends or a teacher or parent about it.

Will my information be kept private if I take part? Will anyone else know I'm doing this?

Everything you tell us as part of this project is treated as confidential; this means that nobody other than us will ever know what you have told us. All your answers will be kept in locked cabinets and nothing will have your name on it. Audio-recordings will be kept on the computer and will need a password to get into them. Once we have finished the project all the questionnaires will be shredded and computer files will be deleted. The only exception is if something you tell us puts you or someone else at risk. This would include answers on our questionnaires that make us worried about your safety. If this happened we would talk to you first, straightaway.

Did anyone else check the project is okay to do?

Before any research is allowed, it has to be checked by a group of people called an Ethics Committee. They make sure the research is safe. This study has been looked at by the Reading University Ethics Committee and they were happy for it to go ahead. Everyone working on this study has been through the formal Criminal Records Bureau Disclosure process and has been approved by the School of Psychology of the University of Reading to work with young people.

What if I have more questions?

If you have any questions about our study, either now or later, please feel free to email us or phone to speak to us. You have a right to know everything and we will be happy to tell you everything. Also, please discuss this with your parents, friends or teachers.

Thank you very much,

Jeni Fisk (Researcher) □ j.fisk@pgr.reading.ac.uk
Prof Shirley Reynolds (Supervisor) □ s.a.reynolds@reading.ac.uk □ 0118 378 8525

Website: andyresearchclinic.com

9.5.2 Adolescent information age 16-18 sheet paper 1 for questionnaires

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

Project Title: Does Mood Affect Thinking in Adolescents? (Study 1)

INFORMATION FOR ADOLESCENTS AGED 16-18

Hello,

We are inviting you to take part in a research study.

Why is this project being done?
We want to understand mood problems in adolescents and to examine how mood is linked with adolescents' thoughts, experiences and self-identity.

Why have I been asked to take part?
You have been asked to take part because your school has agreed to help us with this project. We are inviting you because you are aged between 16 and 18 years old.

Do I have to take part?
No. Whether or not you take part in this study is **completely up to you**. You do not have to do this. Also, if you decide to take part and then change your mind, this won't matter at all. You won't have to give us a reason.

What will happen to me if I take part in the project?
We would like you to complete some questionnaires in your mentoring session. They will take about 20-30 minutes. They include questions about your feelings, thoughts and experiences. We will also ask you to come up with some statements that describe you.

Might anything about the research upset me?
Some of the questions about your thoughts and feelings might remind you of both happy and sad feelings. This is completely normal and OK. If you want to stop at any time, or take a break this will be fine. We can talk about this at the time or you might want to talk to your friends or a teacher or parent about it.

Will my information be kept private if I take part? Will anyone else know I'm doing this?
Everything you tell us as part of this project is treated as confidential; this means that nobody other than us will ever know what you have told us. Your answers will be kept in locked cabinets and nothing will have your name on it. Once we have finished the project the questionnaires will be shredded. The only time we would not be able to keep information confidential is if you tell us something which puts someone else at

risk or if you score highly on one of our questionnaires and we are worried about your safety. If this were to happen we would talk to you first straightaway.

Did anyone else check the project is okay to do?
Before any research is allowed, it has to be checked by a group of people called an Ethics Committee. They make sure the research is safe. This study has been looked at by the Reading University Ethics Committee and they were happy for it to go ahead. Everyone working on this study has been through the formal Criminal Records Bureau Disclosure process and has been approved by the School of Psychology of the University of Reading to work with young people.

What if I have more questions?
If you have any questions about our study, either now or later, please feel free to email us or phone to speak to us. You have a right to know everything and we will be happy to tell you everything. Also please take the opportunity to discuss this study with your friends, parents and/or teachers.
Thank you very much,

Jeni Fisk (Researcher) email: j.fisk@pgr.reading.ac.uk
Prof Shirley Reynolds (Supervisor) email: s.a.reynolds@reading.ac.uk tel: 0118 378 8525

Website: andyresearchclinic.com

9.5.3 Adolescent information sheet age 13-15 paper 1 for experimental tasks

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

University of Reading

Project Title: Does Mood Affect Thinking in Adolescents? (Study 2)
INFORMATION FOR ADOLESCENTS aged 13-15

Hi,

We are inviting you to take part in a study we are doing.

Why is this project being done?

1. To help us better understand problems with mood in teenagers

2. To investigate how mood relates to how teenagers remember information

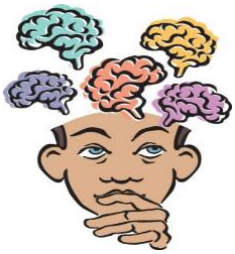
3. To investigate the relationship between memory and thinking processes

Why have I been asked to take part?
You took part in Study 1 in your classroom and filled out some questionnaires. You told us that you were interested in taking part in Study 2. Now we are inviting you to Study 2, which will involve 42 students.

What do I gain if I take part?
If you agree to take part you will automatically be entered into our prize draw; 10 students will win an Amazon voucher worth £10

Do I have to take part?

No. Whether or not you take part in this study is **completely up to you**. You do not have to do this. Also, if you decide to take part and then change your mind, this won't matter at all. You won't have to give us a reason.



What will I be asked to do if I take part in Study 2?

Tasks

In Study 2 we want to work with young people individually. There will be a brief questionnaire about your mood. We would then like you to complete some short tasks with the researcher. These include a memory task and some puzzles. The short tasks also include solving some picture puzzles, giving definitions for different words, thinking of words that begin with certain letters, finishing sentences, and a short memory task on the computer. Some of the tasks are timed and we will audio record our meeting to help us collect accurate data and to use in supervision.

Might anything about the research upset me?
Some of the questions about your thoughts and feelings might remind you of both happy and sad feelings. This is completely normal and OK. If you want to stop at any time, or take a break this will be fine. We can talk about this at the time or you might want to talk to your friends or a teacher or parent about it.

Will my information be kept private if I take part? Will anyone else know I'm doing this?

Everything you tell us is treated as confidential; this means that nobody other than us will ever know what you have told us. The only <u>exception</u> to this is if you tell us something which puts you or someone else at risk, or if you score highly on one of our questionnaires and we are worried about your safety. If this were to happen we would talk to you first straightaway. Your answers will be kept in locked cabinets and nothing will have your name on it. Audio-recordings will be kept on the computer and will need a password to get into them. Once we have finished the project all of the questionnaires will be shredded.

Did anyone else check the project is okay to do?

Before any research is allowed, it has to be checked by a group of people called an Ethics Committee. They make sure the research is safe. This study has been looked at by the Reading University Ethics Committee and they were happy for it to go ahead. Everyone working on this study has been through the formal Criminal Records Bureau Disclosure process and has been approved by the School of Psychology of the University of Reading to work with young people.

What if I have more questions?

If you have any questions about our study, either now or later, please feel free to email us or phone to speak to us. You have a right to know everything and we will be happy to tell you everything. Also please discuss this with your parents, teachers and/or your friends.

Thank you very much,

Jeni Fisk (Researcher) j.fisk@pgr.reading.ac.uk
Prof Shirley Reynolds (Supervisor) s.a.reynolds@reading.ac.uk 0118 378 8525

Website: andyresearchclinic.com

9.5.4 Adolescent information sheet age 16-18 paper 1 for experimental tasks

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

Project Title: Does Mood Affect Thinking in Adolescents? (Study 2)
INFORMATION FOR ADOLESCENTS aged 16-18

What is the purpose of the study?
To help us better understand mood problems in adolescents; to understand the impact of mood on adolescents' memory and thinking abilities. We are interested in a specific kind of thinking used every day for planning, solving problems and organising things. This is called 'Executive Functioning'.

Why have I been asked to take part?
You have been asked to take part because your school have agreed to help us with this project and your questionnaire scores in the previous study means we would like you to take part in our second study too.

What do I gain if I take part?
If you agree to take part you will automatically be entered into our prize drawer where you could win a £10 of Amazon voucher.

Do I have to take part?
Whether or not you take part in this study is **completely up to you**. You do not have to do this. Also, if you decide to take part and then change your mind, this won't matter at all. You won't have to give us a reason.

What will I have to do id I take part in the study?
Tasks:
Firstly, we would like you to fill out a short questionnaire about your feelings. We would then like you to complete some short tasks with the researcher. These include a memory task and some puzzles. The short tasks also include solving some picture puzzles, giving definitions for different words, thinking of words that begin with certain letters, finishing sentences, and a short memory task on the computer.
In these tasks, your answers will be audio-recorded so that the researcher can listen to them later.

Might anything about the research upset me?
Some of the questions about your thoughts and feelings might remind you of both happy and sad feelings. This is completely normal and OK. If you want to stop at any time, or take a break this will be fine. We can talk about this at the time or you might want to talk to your friends or a teacher or parent about it.

Will my information be kept private if I take part? Will anyone else know I'm doing this?
Everything you tell us as part of this project is treated as confidential; this means that nobody other than us will ever know what you have told us. The only exception to this

is if you tell us something which puts you or someone else at risk or if you score highly on one of our questionnaires and we are worried about your safety. If this were to happen we would talk to you first straightaway. All your answers will be kept in locked cabinets and nothing will have your name on it. Audio-recordings will be kept on the computer and will need a password to get into them. Once we have finished the project all the questionnaires will be shredded and computer files will be deleted.

Did anyone else check the project is okay to do?

Before any research is allowed to happen, it has to be checked by a group of people called an Ethics Committee. They make sure the research is okay to do. This study has been looked at by the Reading University Ethics Committee and they were happy for it to go ahead. Everyone working on this study has been through the formal Criminal Records Bureau Disclosure process and has been approved by the School of Psychology of the University of Reading to work with children and adolescents.

What if I have more questions?

If you have any questions about our study, either now or later, please feel free to email us or phone to speak to us. You have a right to know everything and we will be happy to tell you everything.

Thanks

Jeni Fisk (Researcher) email: j.fisk@pgr.reading.ac.uk

Prof Shirley Reynolds (Supervisor) email: s.a.reynolds@reading.ac.uk Tel: 0118 378 8525

9.5.5 Adolescent information sheet age 13-15 paper 2

INFORMATION ABOUT THE RESEARCH FOR YOUNG PEOPLE

Project Title: How Does Low Mood Affect Thinking in Young People

Hi,

We are inviting you to take part in a study we are doing. Jeni Fisk, a student, who is studying at the University of Reading, is doing this research as part of her studies.

Why is this project being done?

❶ To help us better understand problems with mood in teenagers

❷ To investigate how low mood relates to thinking in teenagers

Why have I been asked to take part?

You have been asked to take part because you have come to our clinic for help with low mood.

Do I have to take part?

Whether or not you take part in this study is **completely up to you**. You do not have to do this. If you decide not to take part you will still get the usual help that we give to young people. Also, if you decide to take part and then change your mind, this won't matter at all. You won't have to give us a reason.

What do I gain if I take part?

There is no direct health benefit if you take part, however you will be helping researchers to learn about how low mood affects young people, and this may help to develop better treatments for other young people in the future. If you agree to take part you will receive £10 payment for your time.

What will happen to me if I take part in the project?

Interactive thinking tasks and questionnaires:

You will be asked to complete some short questionnaires, interactive tasks, and puzzles with the researcher. They will take about 60 minutes. The short tasks include solving some picture puzzles, telling us what certain words mean, thinking of words that begin with certain letters, finishing sentences, and a short task on the computer. You will also be asked some questions about your feelings and what you sometimes might think about. Some of the tasks are timed and ~~we~~ they will be audio recorded so that they can be listened to later.

Memory task:

You will be asked to remember different times in your life. They will be audio recorded so that they can be listened to later.

Might anything about the research upset me?

Some young people might get upset when they think about their feelings. The people at the clinic will be able to help if this is the case.

Will my information be kept private if I take part? Will anyone else know I'm doing this?

Everything you tell us as part of this project is treated as confidential; this means that nobody other than us will ever know what you have told us. The only time we would tell someone is if we thought someone might get hurt. If this were to happen we would talk to you straightaway. All of your answers will be kept in locked cabinets and nothing will have your name on it. Audio-recordings will be kept on the computer and will need a password to get into them. Once we have finished the project all of the questionnaires will be shredded and computer files will be deleted.

What other information will be used in the research?

If you agree, information from your assessment interview and the routine questionnaires you are asked to complete will also be used for the research. This information will not have your name on it.

Did anyone else check the project is okay to do?

Before any research is allowed to happen, it has to be checked by a group of people called an Ethics Committee. They make sure the research is okay to do. This study has been looked at by the South Central – Berkshire B Research Ethics Committee and the Reading University Ethics Committee and they were happy for it to go ahead. Everyone working on this study has been cleared to work with young people.

What if there is a problem?

If you have any worries about any part of this study then please contact the researcher or their supervisor. Their contact details are below. If you want to make a complaint about it, there are some people who can help you with this. They are the Patient Advice and Liaison Service (PALS), who you can call on or email

What if I have more questions?

If you have any questions about our study, either now or later, please feel free to email us or phone to speak to us. You have a right to know everything and we will be happy to tell you everything.

Thanks,

Jeni Fisk (Researcher) j.fisk@pgr.reading.ac.uk

Prof Shirley Reynolds (Supervisor) s.a.reynolds@reading.ac.uk 0118 378 8525

9.5.6 Adolescent information sheet age 16-18 paper 2

INFORMATION ABOUT THE RESEARCH FOR YOUNG PEOPLE (16-18)

Project Title: How Does Low Mood Affect Thinking in Young People?

What is the purpose of the study?

To help us better understand mood problems in adolescents; to understand the impact of low mood on young people's memory and thinking abilities. We are interested in a specific kind of thinking used every day for planning, solving problems and organising things. This is called 'Executive Functioning'.

Why have I been asked to take part?

You have been asked to take part because you have come to our clinic for help with low mood.

Do I have to take part?

Whether or not you take part in this study is **completely up to you**. You do not have to do this. If you decide not to take part you will still get the usual help that we give to young people. Also, if you decide to take part and then change your mind, this won't matter at all. You won't have to give us a reason.

What do I gain if I take part?

There is no direct health benefit if you take part, however you will be helping researchers to learn about how low mood affects young people, and this may help to develop better treatments for other young people in the future. If you agree to take part you will receive £10 payment for your time.

What will I have to do if I take part in the study?

Interactive thinking tasks and questionnaires:

You will be asked to complete some short questionnaires, interactive tasks, and puzzles with the researcher. They will take about 60 minutes. The short tasks include solving some picture puzzles, telling us what certain words mean, thinking of words that begin with certain letters, finishing sentences, and a short task on the computer. You will also be asked some questions about your feelings and what you sometimes might think about. Some of the tasks are timed and they will be audio recorded so that they can be listened to later.

Memory task:

You will be asked to remember different times in your life. They will be audio recorded so that they can be listened to later.

Might anything about the research upset me?

Some young people might get upset when they think about their feelings. The people at the clinic will be able to help if this is the case.

Will my information be kept private if I take part? Will anyone else know I'm doing this?

Everything you tell us as part of this project is treated as confidential; this means that nobody other than us will ever know what you have told us. The only time we would tell someone is if we thought someone might get hurt. If this were to happen we would talk to you straightaway. All of your answers will be kept in locked cabinets and nothing will have your name on it. Audio-recordings will be kept on the computer and will need a password to get into them. Once we have finished the project all of the questionnaires will be shredded and computer files will be deleted.

What other information will be used in the research?

If you agree, information gathered from your assessment interview, the routine questionnaires you are asked to complete and the demographic information your parents have been asked for, will also be used for the research. This information will be anonymised using a participant ID and will be used in this study and in routine clinical care, by the clinical care team.

Did anyone else check the project is okay to do?

Before any research is allowed to happen, it has to be checked by a group of people called an Ethics Committee. They make sure the research is okay to do. This study has been looked at by the South Central – Berkshire B Research Ethics Committee and the Reading University Ethics Committee and they were happy for it to go ahead. Everyone working on this study has been cleared to work with young people.

What if there is a problem?

If you have any worries about any part of this study then please contact the researcher or their supervisor. Their contact details are below. If you want to make a complaint about it, there are some people who can help you with this. They are the Patient Advice and Liaison Service (PALS), who you can call on or email .

What if I have more questions?

If you have any questions about our study, either now or later, please feel free to email us or phone to speak to us. You have a right to know everything and we will be happy to tell you everything.

Thanks,

Jeni Fisk (Researcher) email: j.fisk@pgr.reading.ac.uk
Prof Shirley Reynolds (Supervisor) email: s.a.reynolds@reading.ac.uk Tel: 0118 378 8525

9.5.7 Adolescent information sheet paper 4

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

Information for Young People

Project title: **The Effects of Blueberry Anthocyanin Intervention on Cognitive functioning and Mood.**

Hello,

We are inviting you to take part in a research project we are doing at your school.

Why is this project being done?

In this study, we want to explore the effects of Blueberry Flavonoids on health and wellbeing in adolescents. Flavonoids are naturally occurring compounds that are widely distributed in plants and plant-based foods and beverages (e.g. pulses, fruits such as apples or blueberries, cocoa etc.).

Why have I been asked to take part?

You have been invited to take part because your school has agreed to help us with this project and because you are aged between 12-17 years, the age group we are interested in working with.

Do I have to take part?

Whether or not you want to take part in this project is completely up to you. You do not have to do this. Also, it is completely OK if you chose to take part and then change your mind. You can withdraw from the project any time you like without having to give us a reason.

What will happen if I take part in this project?

We will come to your school and ask you to complete some questions about your mood and feelings. If you have trouble reading them, we will be able to help you. You would do the research in class, in a group.

A group of you will then be invited to the second part of the study were your parents will prepare a drink for you every morning for 4 weeks. You will be asked to fill a short questionnaire to let us know your fruit and vegetable intake and complete a few computerised cognitive tasks and mood measures on the first day, two weeks and four weeks of intervention at PCLS laboratory in University of Reading or your school.

Might anything about the project upset me?

The questions about your feelings may remind you of both happy and sad feelings. This is completely OK and normal. If you want to take a break or stop at any time, that is OK. We can talk about this at the time. You might also want to talk to your teachers or friends or parents about it.

Will my information be kept private if I take part?

Everything you tell us as part of this project will be confidential and no one other than us will know what you have told us. The only exception is if you tell us anything that we think puts you or someone else at risk. If that happens, we would follow your school's procedures to keep you safe.

If you have any worries you can talk to us straight away. No paperwork will have your name on them. Everything you write will be kept in locked cabinets. Once we are done with our project, all the questionnaires will be shredded.

Did anyone else check if the project is OK to do?

Before any research project is allowed to take place, it is checked by a group of people called an Ethics Committee. They make sure the project is ok to do. This project is looked at by the University of Reading Research Ethics Committee and they are happy for us to go ahead. Everyone working on this study has been through the formal Criminal Records Bureau Disclosure process and has been approved by the School of Psychology of the University of Reading to work with children and adolescents.

What if I have more questions?

If you have any questions about this project, now or later, feel free to email or call us. You have the right to know everything and we are happy to tell you what you need to know.

Thanks,

Researcher:

Jennifer Fisk Email: J.Fisk@pgr.reading.ac.uk

Sundus Khalid Email: Sundus.Khalid@pgr.reading.ac.uk Phone: 0118 378 7928

Supervisors:

Prof Claire Williams Email: claire.williams@reading.ac.uk Phone: 0118 378 7540

Prof Shirley Reynolds Email: s.a.reynolds@reading.ac.uk Phone: 0118 378 8525

9.6 Appendix 7: Parent information sheets (paper 1, paper 2 and paper 4)

9.6.1 Parent information sheets for paper 1

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

INFORMATION ABOUT THE RESEARCH FOR PARENTS

Project Title*: *Does Mood Affect Thinking in

What is the purpose of the study?

To help us better understand mood problems in adolescents; to understand the impact of mood on adolescents' own thoughts, experiences and self-identity.

Why are we inviting your son/daughter to take part?

Your son/daughter has been invited to take part because their school has agreed to take part in this project. Your child is aged between 13 and 18 and therefore in the age group we are working with.

Does my child have to take part?

It is up to you and your son/daughter to decide whether to join the study. If you agree to take part, you are still free to withdraw at any time without giving any reason.
This is an opt-out study. This means that if your child is under 16 and you **DO NOT** want them to take part, please sign and return the attached form. If you do not return this form we will assume that you are happy for your child to take part in this research. Your child will also be asked if they are happy to take part – they are free to opt out themselves.

What will happen if my child takes part?

Your son/daughter will complete some questionnaires in their timetabled mentoring sessions. The questions will ask about feelings, thinking processes and self-concept.

What are the possible disadvantages and risks of taking part?

We do not expect there to be any disadvantages or risks involved in taking part in this research. Some of the tasks involved will require answering questions about feelings, and it is possible that some adolescents may find this upsetting. Some of the questions are personal and ask about feelings of being unhappy and feeling worthless. It is important to highlight that many of these questions are unlikely to be relevant to the young person, however if they are, it is important for us to know this. However, if anyone was upset by any of the questions we would offer to stop the research immediately. During the research we will adhere to all school safeguarding and child protection policies. Additionally, all children will be given a resource list to keep. The list contains helpful resources for those who want to learn more about mental health, who want to get involved in volunteering opportunities or would like to seek advice. As the research will be carried out in school we do not require you or your child to come to the University at any point during the research. The study will be carried out on whole classes therefore your child will not miss any teaching.

What are the possible benefits?

Taking part will contribute to our gaining a greater understanding of how teenagers think and remember, and how this may relate to how they are feeling. Research investigating low mood in adolescents is limited and we hope to use this information to evaluate and understand how clinical treatments should be specifically designed for this age group.

What if there is a problem?

If you have any concern about any aspect of the study, you should ask to speak to Jeni Fisk, the researcher of the project. Please see the last page for contact details. If you remain unhappy and wish to complain formally, you can contact the supervisor of this research, Prof Shirley Reynolds, who will discuss any concerns you may have.

Will our taking part in the study be kept confidential?

All the information provided will be kept confidential. The only exception to this is if your child tells us something, which puts them, or someone else at risk. The information we collect (questionnaire answers) will not have any names on and will be

kept strictly confidential in locked cabinets in a password-protected area of the university. All the information collected for the project will be destroyed as soon as they are no longer needed. The consent forms, however, will be kept for 5 years before disposal.

What will happen to the results of the research study?

The information we collect will be analysed and written up as part of a doctoral thesis (2017). We also hope to write these results up for publication in a scientific journal and at professional academic conferences. When we do this, no personal information will be given and if we quote anything that has been said by people taking part in the study, this will be anonymous and will not be traceable to a particular person. If you would like a report of the findings of our study, we will be happy to provide it. Please note that the publication of any such data may take a year or more after the completion of the study.

Who has reviewed the study?

All research at the University of Reading is reviewed by an independent group of people, called a Research Ethics Committee, to protect your interests. This application has been reviewed and given a favourable opinion by the University of Reading Research Ethics Committee. Everyone working on this study has been through the formal Criminal Records Bureau Disclosure process and has been approved by the School of Psychology of the University of Reading to work with children and adolescents.

Will there be any further studies?

We would like to invite some young people who take part in this study to take part in a future study. This would take about 55 minutes and your child would be interviewed individually at school. We would send you information about this separately, and we would ask you to send back a consent form, giving permission. **Do we have to take part?**

Participation in this research is entirely voluntary. If you have any questions please do not hesitate to contact us by phone or email. We will be happy to tell you more about the research and to discuss any questions or concerns you might have.
Thank you very much,

Jeni Fisk (Researcher) email: j.fisk@pgr.reading.ac.uk
Prof Shirley Reynolds (Supervisor) email: s.a.reynolds@reading.ac.uk tel: 0118 378 8525

Website: andyresearchclinic.com

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

INFORMATION FOR PARENTS

Project Title: Does mood affect thinking in adolescents? (Study 2)

Dear parent,

Your son or daughter has already helped us with our research. They completed questions about their mood and feelings during a classroom period in (name month). Now we would like to invite them to take part in another study. This information sheet is to help you decide if you are happy for them to take part. We have tried to include the most important information here – if you have any questions that are not answered here, or if you just want to know more please get in touch with us. Our contact details are at the end of this information sheet.

What is the purpose of the study?

The aim of this study is to improve our understanding of mood problem in young people. In particular we want to examine how mood affects young people's memory and thinking abilities. We are interested in a specific kind of thinking that we all use every day to plan, solve problems and organise things. We hope that this understanding will help develop and improve treatment for depression in young people.

Why are we inviting your son/daughter to take part?

Lodge Park Academy has agreed to help us with this research. Your son/daughter took part in a previous study and filled in some questionnaires. Their answers to those questionnaires mean that they are eligible to take part in Study 2.

Does my child have to take part?

No. It is up to you and your son/daughter to decide whether to join the study. If you agree that they may take part, you are still free to withdraw your permission at any time, without giving any reason.

This is an opt-in study. This means that if you **agree that** your child can take part, please sign and return the attached form. We cannot include any child under 16 if their parent does not give written consent. Your child will also be asked if they are happy to take part – they are free to opt out themselves.

What will my child gain from taking part?

If your son/daughter takes part in this study they will be entered into our prize draw, where 10 young people will win a £10 Amazon voucher. Most young people enjoy the research tasks and they will also have an important opportunity to experience a real research study. If you or they would like to find out more about our results or our other research we will be happy to give you a summary.

What will happen if my child takes part?
Your son/daughter will complete some tasks with the researcher. These include a memory task and some puzzles. The short tasks also include solving some picture puzzles, giving definitions for different words, thinking of words that begin with certain letters, finishing sentences, and a short memory task on the computer. Your son/daughter will also be asked to complete a short questionnaire about their mood and feelings. This questionnaire also helps identify self harm in young people. We have tried to make the tasks as short and enjoyable as possible

What are the possible disadvantages and risks of taking part?
We do not expect there to be any disadvantages or risks involved in taking part in this research. Some of the tasks require answering questions about feelings, and it is possible that some adolescents may find this upsetting. If this did happen we would offer to stop the research immediately. The researcher has experience working with adolescents in the NHS and of dealing with distress.

As the research will be carried out in school we do not require you or your child to come to the University at any point during the research.

What are the possible benefits?
There is no direct benefit to your son or daughter beyond the experience of the research and their opportunity to win a £10 Amazon voucher. If we identify any young person who is experiencing high levels of distress we will discuss this with them and work with the school to provide appropriate support and information for them. We hope that the research findings will help us to develop new treatment and to improve current treatments of depression in young people.

What if there is a problem?
If you have any concern about the study, please contact Jeni Fisk, the researcher. Her contact details are at the end of this information sheet. If you remain concerned, please contact the supervisor of this research, Professor Shirley Reynolds, -her contact details are also at the end.

Will the information provided be kept confidential?
All the information provided will be confidential. The only exception to this is if your child tells us something that puts them, or someone else at risk. In this case we will follow the School's safeguarding procedures. The information we collect (questionnaire answers) will include any names and will be kept in locked cabinets in a password-protected area of the university. All papers collected for the project will be destroyed as soon as they are no longer needed. The consent forms, however, will be kept for 5 years before disposal.

What will happen to the results of the research study?
The results will be analysed and written up as part of a doctoral thesis (2017). They will also be published in a scientific journal and presented at academic conferences. No personal information will be given. If you would like a report about the study results, we will be happy to provide it. However, it can take up to a year to complete and write up the study.

Who has reviewed the study?
All research at the University of Reading is reviewed by an independent group of people, called a Research Ethics Committee, to protect your interests. This application has been reviewed and given a favourable opinion by the University of Reading Research Ethics Committee. Everyone working on this study has been through the formal Criminal Records Bureau Disclosure process and has been approved by the School of Psychology of the University of Reading to work with children and adolescents.

If you have any questions please contact us by phone or email. We will be happy to tell you more about the research and to discuss any questions or concerns you might have. Thank you very much for your help,

Jeni Fisk (Researcher) email: j.fisk@pgr.reading.ac.uk
Prof Shirley Reynolds (Supervisor) email: s.a.reynolds@reading.ac.uk tel: 0118 378 8525

Website: andyresearchclinic.com

9.6.2 Parent information sheets for paper 2

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

INFORMATION ABOUT THE RESEARCH FOR PARENTS

***Project Title*: How Does Low Mood Affect T** University of Reading **escents**

What is the purpose of the study?

To help us better understand mood problems in adolescents, and to understand the impact of mood on adolescents' memory and thinking processes. Jeni Fisk, the lead researcher, is currently working on her PhD and this research forms part of her doctoral qualification. The data collected will be compared to other non-depressed young people.

Why are we inviting you and your child to take part?

You and your child have been invited because they are aged between 12 and 18 years and have been referred to the Anxiety and Depression Pathway (a Child and Adolescent Mental Health service) for treatment. 40 adolescents referred to the clinic will take part in the study.

Does my child have to take part?

If your child is between **12-15**: If you **and your child agree** to take part, we will then ask you to sign a consent form and **your child to assign an assent form**.

If you child is between **16-18**: If your child agrees to take part, we will ask them to sign a consent form.

You and your child are free to withdraw at any time, without giving any reason. This would not affect in any way the standard of care or the treatment you and your child will receive.

What will happen if we take part?

Your child will complete some questionnaires. The questions will ask about feelings, and things that your child might sometimes think about. They will be asked to complete a selection of short interactive tasks. The short tasks include solving some picture puzzles, giving definitions for different words, thinking of words that begin with certain letters, finishing sentences, and a short task on the computer. They will be asked to think of and describe some memories relating to words that the researcher will show them. In some of the tasks your child's answers will be audio-recorded so that the researcher can listen to them later. The study will last about 60 minutes.

What are the possible disadvantages and risks of taking part?

We do not expect there to be any disadvantages or risks involved in taking part in this research. Some of the questionnaires involve answering questions about thoughts and feelings, and one of the tasks requires thinking about memories, it is possible some people may find this upsetting. However, if this was to happen we would offer to stop the research immediately. Furthermore, the researcher involved in the assessment will be experienced at dealing with distress.

What are the possible benefits?

Taking part will contribute to our gaining a greater understanding of low mood in adolescents. Research investigating low mood in adolescents is limited and we hope to use this information to evaluate and understand how clinical treatments should be specifically designed for this age group.

Will my child be paid for participating?

All participants will receive a £10 cash payment for their time.

If you or your child decide it is easier to come back to help with the research on an alternative day travel expenses will be reimbursed.

What if there is a problem?

If you have any concern about any aspect of the study, you should ask to speak to Jeni Fisk, the researcher of the project. If you remain unhappy and wish to complain formally, you can contact the supervisor of this research, Prof Shirley Reynolds, who

will discuss any concerns you may have. If you remain unhappy and wish to make a formal complaint then you can obtain details about the NHS Complaints Procedure from the Patient Advice and Liaison Service (PALS), on 0118 960 5027 or via BHT@berkshire.nhs.uk.

Will our taking part in the study be kept confidential?

All the information provided will be kept confidential. However, if during the study you or your child gave us any information that suggested that anyone was at risk of harm, it may be necessary for us to contact other agencies in order to keep everyone safe. The information we collect (questionnaire answers) will not have any names on and will be kept in a secured area at the University. The audio recordings will be stored anonymously in a password-protected computer file, and will be listened to by members of the research team only. All the information collected for the project will be destroyed as soon as they are no longer needed at the end of the study. The consent forms, however, will be kept for 5 years before disposal.

What other information will be used for the research?

If you and your child agree, information gathered from your child's assessment appointment (the interview), the routine questionnaires you and your child are asked to complete, and the demographic information will also be used for the research. This information will be kept anonymous using a participant ID and will be used in this study and in routine clinical care, by the clinical care team.

What will happen to the results of the research study?

The information we collect will be analysed and written up as part of a doctoral thesis (end of 2017). We also hope to write these results up for publication in a scientific journal and present them at professional academic conferences. When we do this, no personal information will be given and if we quote anything that has been said by people taking part in the study, this will be anonymous and will not be traceable to a particular person. If you would like a report of the findings of our study, we will be happy to provide it. Please note that the publication of any such data may take a year or more after the completion of the study.

Who provides insurance and compensation arrangements for this study?

The University of Reading has insurance policies that provide cover for the activities of employees and registered students. This cover compensates for damages, which are deemed to be legally liable from the University and includes Claimant's costs and expenses and Defence Costs.

Who has reviewed the study?

All research at the University of Reading is reviewed by an independent group of people, called a Research Ethics Committee, to protect your interests. This application has been reviewed and given a favourable opinion by the South Central – Berkshire B Research Ethics Committee and the Reading University Ethics Committee. Everyone working on this study has been cleared to work with children and adolescents.

Any Questions?

If you have any questions please do not hesitate to contact us. We will be happy to tell you more about the research and to discuss any questions or concerns you might have.

Contact Details:

Researcher: Jeni Fisk
Email: j.fisk@pgr.reading.ac.uk

Supervisor: Prof Shirley Reynolds
Email: s.a.reynolds@reading.ac.uk
Phone: 0118 378 8525

Many thanks for your help

Yours sincerely,
On Behalf of the Research Team at the University of Reading

9.6.3 Parent information sheet for paper 4

Department of Psychology and Clinical Language Sciences
University of Reading

Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

Information about the Research for Parents

Project title: **The Effects of Blueberry Anthocyanin Intervention on Cognitive functioning and Mood.**

Purpose of the research:

Flavonoids are naturally occurring compounds that are widely distributed in plants and plant-based foods and beverages (e.g. pulses, fruits such as apples or blueberries, cocoa etc.). Research has shown that short-term flavonoid intake improves cognition and wellbeing in both adults and children, however, no research has been carried out in adolescents. In this study, we want to explore the effects of Blueberry Flavonoids on health and wellbeing in adolescents.

Why are we inviting your children to take part?

Your child will be invited to take part in this study because their school has agreed to take part in this project, and they are aged between 13-16 years.

What will happen if my child takes part?

Part 1: Your child will be asked to complete some questionnaires about their mood and feelings in class. We will then invite around 120 boys and girls to the second part of this study.

Part 2: At this stage, your child will be randomly be assigned to either placebo or blueberry intervention. You (parent) will be given packs either blueberry powder or match placebo and instructions (written and video) on how to create the drink. You will be asked to prepare the drink for your child to consume every morning for four weeks. Your child will be asked to fill a short questionnaire to let us know their fruit and vegetable intake and complete a few cognitive tasks and mood measures on the first day, two weeks and four weeks of intervention at PCLS laboratory in University of Reading or their school, discussed with you in advance.

Does my child have to take part?

No. If you and your child want to take part, that's great. For the first part of this study, you don't have to do anything else. If your child does not want to take part, they can tell us when we visit the school, or they can ask you to let us know now. If your child is under 16 years and **you do not** want your child to take part in the study, please let us know.

Part 1 is an **OPT-OUT** study. Therefore, if you **DO NOT** want your child to take part in this study, please sign and return the attached form or contact your child's school or us, either by email, phone, text, or in writing. Our contact details are at the end of this letter. If you do not return this form or contact us it will be assumed that you are happy for your child to participate.

The part 2 of this study you will be sent a separate **OPT-IN** consent form which we will require you to sign if you and your child would like to take part.

You or your child can choose to opt out of the study at any time. If you decide you do not want your child to be involved – just let us know and we will destroy any information they have given us.

What are the possible disadvantages and risks of taking part?

If they take part your child will answer questions about their mood and feelings. It is possible that for some young people this might draw their attention to their feeling, and they might find this upsetting. We will work with the school to make sure that if any child becomes upset that they are supported. In such a situation we would offer to stop the research immediately. The researcher who will be working with each class of children, under the supervision of the class teacher, is experienced at working with young people, has experience of working in an NHS clinic for children and young people, has full DBS clearance, and will receive regular supervision at the university. The research will be carried out in school time with the whole class together during an appropriate period (e.g. PHSE or lunch break). Your son or daughter will not miss any lessons or spend time alone with the researcher.

What are the possible benefits?

We hope that young people who take part in this research will enjoy the experience of being involved in a science project. After we do the research, we are happy to visit the

school and talk about the research and the general effects of nutrition and exercise on health. In addition, taking part in this research will help us understand more about how food and diet affect the health and well-being of young people. This is important to help us improve their health and promote well-being. This school-based research will support the research we are doing in the NHS with young people who seek help for depression and anxiety. This research improves our understanding of depression in young people and how to prevent and treat depression.

What if there is a problem?

If you have any concerns about any aspect of this study, you can ask to speak with any of the researcher, the researcher. If you remain unhappy, you can contact one of the supervisors of this research. You can also make a formal complaint if you are not satisfied by our response. Please see the last page for all of our contact details.

Will taking part in the study be kept confidential?

Yes. All information provided will be kept confidential. Questionnaires and other data will be identified by number only and kept in locked cabinets. Children's names or other identifying information will not be sorted by the researcher. Data entered into the computer will be anonymised and password protected. All paper records will be destroyed as soon as they are no longer needed with the exception of consent forms, which will be kept for 5 years before disposal.

Who has reviewed this study?

To protect your interest, all research at the University of Reading is reviewed by an independent group of people called a Research Ethics Committee. Application for this research had been reviewed and approved by the University of Reading Research Ethics Committee. Everyone working on this study has been through the formal Criminal Records Bureau Disclosure process and has been approved by the School of Psychology of the University of Reading to work with children and adolescents.

Contact details:

Researcher:

Jennifer Fisk Email: J.Fisk@pgr.reading.ac.uk

Sundus Khalid Email: Sundus.Khalid@pgr.reading.ac.uk Phone: 0118 378 7928

Project supervisors:

Prof Claire Williams Email: claire.williams@reading.ac.uk Phone: 0118 378 7540

Prof Shirley Reynolds Email: s.a.reynolds@reading.ac.uk Phone: 0118 378 8525

If you have any questions, please do not hesitate to contact us. We will be happy to tell you more about the research and to discuss any questions or concerns you may have. Thank you for your time and cooperation.

Kind regards,

On Behalf of the Research Team at the University of Reading.

9.7 Appendix 8 – School information sheets (papers 1 and 4)

9.7.1 School information sheet paper 1

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

Project Title*: *Does Mood Affect Thinking in Adolescents?

INFORMATION FOR HEADTEACHERS

What is the purpose of the research?

This study has a number of aims:

1. To help us better understand depression and low mood in adolescents;
2. To understand how depression and low mood affect adolescents' memory of their past
3. To understand the relationship between low mood, memory and executive functioning in young people

Who do we want to recruit?

We want to recruit 500 young people, aged 13-18 years.

What will be involved?

Study 1:

In the first study, students will complete questionnaires during a tutorial period with the class teacher present. This will take about 20-30 minutes. The questionnaires will assess students' current mood and feelings and their self-concept (how they view themselves). A researcher will be present to explain what is involved and to answer any questions as well as to administer and collect the questionnaires.

Study 2:

Adolescents who take part in the first study may be invited to take part in a second study, which will take place on a different day. They will be asked to complete brief questionnaires about their mood followed by a series of interactive tasks with the researcher. This includes a brief measure of cognitive ability and a memory task. They will complete three tasks that measure different types of thinking; how well they can focus on a task, their ability to manage complicated information, and to inhibit irrelevant information. All the tasks have been tried out with young people to make sure that they are suitable. They are generally enjoyed by most young people. We will audio record the interaction with the students to help with data collection and supervision.

All students who take part in study 2 will be entered into a prize draw for 10 Amazon vouchers worth £10.

How will adolescents and parents provide consent?

To take part in this research, adolescents aged 13-15 years will require parental consent. Adolescents aged 16-18 years will not require parental consent. All adolescents will only take part in the research if they have given consent (or assent for under 16s).
For Study 1 all pupils will be invited to take part. For students under 16 years, parents/guardians will be sent information sheets describing the study with a form regarding opt-out consent. Adolescents will also be given age appropriate information sheets. For the Study 1 parents will be deemed to have given consent if they do not return the opt-out form. All efforts will be taken to make parents aware of the study and what is involved. With the permission of the school we will make information about the study available on the school website, in newsletters and in any other media that parents have access to.
For Study 2, we wish to recruit 42 young people. This will involve the researcher working individually with young people. Young people and parents will receive information about the study. We will ask parents to provide 'opt-in' consent for any young person under 16 years. This means that parents will be required to return the

consent form if they are happy for their child to take part. If we do not receive the consent forms from parents for Study 2, young people under 16 will not be able to take part. Young people over 16 can give consent; we will provide information about the study to their parents and will encourage them to discuss this. All young people will be given the chance to ask questions and will be asked to give written consent (or assent if under 16) before the research starts.

Where will the research take place?

Study 1

This will take place in classrooms, with the whole class during an appropriate lesson, for example, PSHE, tutor period or free periods. The research will take approximately 20-30 minutes. Young people who do not wish to take part, or for whom parental consent has not been given will be given a parallel task that looks like the research task but includes irrelevant (to the research) information that will be destroyed by the researcher. This will ensure that young people can be discrete if they do not wish to take part or do not have parental consent.

Study 2

This will take part individually in a quiet room in school. By agreement with the student and their form teacher we will ask remove the young person from the classroom for a school period i.e. 50 minutes.

Your school's involvement

If you would be interested in working with us, it would be great if you could help us in the following ways:

1. Send out information sheets and consent forms to the children and their parents

2. Nominate a staff member with whom we can liaise to organise the best time to administer Study 1 (to classes) and Study 2 (with individual pupils).

Will information be kept confidential?

The information provided for research purposes will be kept confidential. The only exception to this is if a child tells us something which puts them or someone else at risk. In this case we will follow a procedure which we will agree with you in advance. All information provided by young people (e.g. questionnaires, audio recordings) will be identified only by identification numbers (not names). They will be stored in locked cabinets in a password-protected area of the university and on a password-protected computer drive with restricted access. Consent forms will have individual names and will be kept separately, in locked cabinets in a second part of the university. In accordance with ethical guidelines they will be kept for 5 years before disposal.

What will happen to the results of the research?

The information will be analysed and written up as part of a PhD due to be completed in 2017. We also hope to publish the results in a scientific journal and present them at academic conferences. When we do this, no personal information will be given. We would like to provide a report of the study finding to the school and if wished would be happy to discuss this with staff, parents and/or students. It can take a year or more to analyse and report the finding of the study.

Who has reviewed the study?

This application has been reviewed and approved by the University of Reading Research Ethics Committee. Everyone working on this study has been through the formal Criminal Records Bureau Disclosure process and has been approved by the School of Psychology of the University of Reading to work with children and adolescents.

Many thanks for your help

Yours sincerely,

Thank you very much,

Jeni Fisk (Researcher) email: j.fisk@pgr.reading.ac.uk

Prof Shirley Reynolds (Supervisor) email: s.a.reynolds@reading.ac.uk tel: 0118 378 8525

Website: andyresearchclinic.com

9.7.2 School information sheet paper 4

School Information Sheet

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

Information for Head Teachers

Project title: **The Effects of Blueberry Anthocyanin Intervention on Cognitive functioning and Mood.**

Why are we doing this research?

Depression and low mood is a common problem for young people and it is important to find ways to increase resilience and reduce the risk of depression. Research with adults suggests that some nutrients such as flavonoids found in our diets are associated with low mood and depression. Flavonoids are naturally occurring compounds that are widely distributed in plants and plant-based foods and beverages (eg pulses, fruits such as apples or blueberries, cocoa etc). Research also suggests that short-term flavonoids intervention improve cognitive functions such as attention, visuospatial and working memory. This is also thought to help improve mood. The aim of this research is to examine the effects of blueberry flavonoids on cognition and mood in adolescents. This could be a useful way to prevent depression, but we know less about this relationship between flavonoid cognition and mood in young people. In this study, we want to examine how mood, cognition, and flavonoids are related.

Who are we recruiting?

We want to recruit young people between ages of 13-16 years old who are attending schools.

What will be involved?

There are two parts to this study. In Part 1, around 600 students will be asked to complete standardised questionnaires about their mood and general health. This will take about 20-25 min.

We will then invite a subgroup (approximately 120, based on the responses in part 1) to take part in the next step. They will be randomly be assigned to either placebo or blueberry intervention. Parents will be given packs of blueberry powder or match placebo and instructions (written and video) on how to create the drink. Participants will be asked to consume the drink every morning for four weeks.
They will be asked to complete a few cognitive tasks and mood measure on the first day, two weeks and four weeks of intervention at PCLS laboratory in University of Reading or their school, discussed with you and the participants in advance. On the 1st session, they will also be asked to fill in a short questionnaire to let us know their fruit and vegetable intake so that typical levels of flavonoids in their background diet can be ascertained.

How will parents and adolescents provide consent?

Students aged 16 years do not require parental consent and can consent on their own behalf. Students aged 13-15, do require parental consent to take part in this research.
Subject to your approval we propose to use an 'opt-out' consent method for parents of students under 16 years for Part 1. This is a low-risk study and we believe that this method minimises the disruption and burden of research on schools, gives most students an opportunity to take part in scientific research, reduces inequality, and will provide a much better and more representative sample of students. We are happy to discuss this with you and to see how this would work in your school, with your staff, parents, and pupils.

We propose to use a traditional 'opt-in' consent method for part 2 of the study. This part of the study is more time consuming and requires commitment from parents and the participants.

Regardless of age, all participants will only take part if they also have consented or given assent. All students taking part will have information about the study.

Where will the research take place?

Part 1 would ideally be conducted in school, during an appropriate lesson such as PSHE or a free period, or during lunch. It will take approximately 20-25 min.

Your School's Involvement

If you are interested in working with us, we would really appreciate it if you would help in the following ways:

- Send out the information sheets and consent forms to students and their parents (or give us information so that we can do this).

- Nominate a staff member who we can coordinate with regarding the best time to see classes.

In return, we are very happy to contribute to the school in a number of ways. We can offer work experience to psychology A-level students, support EPQ project work, talk to student, staff or parents about mental health in young people, or contribute to biology or PHSE teaching. We will be very happy to discuss this with you and see what would work best for your school.

Will the information be kept confidential?

We will keep all information confidential unless we become aware that a child or someone else is at risk. We will follow school safeguarding procedures and will discuss this with you in advance.

All data will be kept in locked cabinets in a password protected area of the university. Students who take part in Study 2 will provide contact information. This will be kept separate from the questionnaire data, linked with a unique ID to the questionnaire data, and password protected.

All research data will be kept confidential. Paper forms will be destroyed at the end of the with the exception of consent forms, which will be kept for 5 years before disposal.

Who has reviewed this study?

All research at the University of Reading is reviewed by an independent group of people called a Research Ethics Committee. Application for this research had been reviewed and approved by the University of Reading Research Ethics Committee. Everyone working on this study has been through the formal Criminal Records Bureau Disclosure process and has been approved by the School of Psychology of the University of Reading to work with children and adolescents.

Contact details:

Researcher:

Jennifer Fisk
Email: J.Fisk@pgr.reading.ac.uk
Phone:

Sundus Khalid
Email: Sundus.Khalid@pgr.reading.ac.uk
Phone: 0118 378 7928

Project supervisors:

Prof Claire Williams
Email: claire.williams@reading.ac.uk
Phone: 0118 378 7540

Prof Shirley Reynolds
Email: s.a.reynolds@reading.ac.uk
Phone: 0118 378 8525

Thank you for your time and cooperation.

Kind regards,
On Behalf of the Research Team at University of Reading

9.8 Appendix 9: Debrief sheets for experimental studies papers 1, 2 and 4

9.8.1 Adolescent debrief for paper 1

University of Reading

ADOLESCENT DEBRIEF SHEET

Project Title*: *Does Mood Affect Thinking in Adolescents? (Study 1)

Project Supervisors: Prof Shirley Reynolds: s.a.reynolds@reading.ac.uk
Prof Judi Ellis: j.ellis@reading.ac.uk
Researcher: Jeni Fisk: j.fisk@pgr.reading.ac.uk

The aim of this study was to investigate how your mood relates to how you think about yourself.

Your results will be anonymously compared with those of other participants taking part in the study. If at any point you wish to withdraw your results or ask any questions about this study please email the me or my supervisors (contact details above). The project was approved by the University of Reading research Ethics Committee

The different questionnaires about mood and worries tell us about how you have been feeling. Everyone's feelings go up and down from time to time. This is perfectly normal and nothing to worry about. Sometimes we do go through times when we feel down for quite a while. If you, or a friend, are feeling down there are lots of places that can help. Usually people you already know can help; for example, your parents, other family, a teacher, or a friend. Sometimes it's useful to talk to someone else so we have included information about other organisations that can help young people. Do have a look at this. If you feel that you definitely would like some help you can also talk to your house manager at school.

Thank you very much for helping us with this research. We hope you have found it interesting. If you would like to know more about our results please let your teacher know and we would be happy to come back and tell you want we found out. If you

would like us to send you a brief summary of what we found you can email us at this address j.fisk@pgr.reading.ac.uk (it will be ready in about 6 months).

University of Reading

ADOLESCENT DEBRIEF SHEET

Project Title*: *Does Mood Affect Thinking in Adolescents?

Project Supervisors: Prof Shirley Reynolds: s.a.reynolds@reading.ac.uk

Prof Judi Ellis: j.ellis@reading.ac.uk

Researcher: Jeni Fisk: j.fisk@pgr.reading.ac.uk

The aim of this study was to investigate how your mood relates to your memory and thinking processes. We are interested in a specific kind of thinking used every day for planning, solving problems and organising things. This is called 'Executive Functioning'. The project has been approved by the University of Reading Research Ethics Committee.

The questionnaire that you completed assessed your current mood. The different tasks that you did with Jeni allowed us to measure different types of thinking processes. We are interested to see if these are affected by your mood and have compared students with different levels of mood

Your results will be anonymously compared with those of other students. If, at any time, you would like to withdraw your results or ask any questions about the research please contact me (Jeni Fisk) or my project supervisors (our contact details are above).

Thank you very much for helping us with this research. We hope you have found it interesting. If you would like us to send you a brief summary of what we found you can email me j.fisk@pgr.reading .ac.uk It will be about 6 months before this is ready.

9.8.2 Adolescent debrief for paper 2

YOUNG PERSON DEBRIEF SHEET

Project Title*: *Does Low Mood Affect Thinki

Project Supervisor: Prof Shirley Reynolds: s.a.reynolds@reading.ac.uk

Researcher: Jeni Fisk: j.fisk@pgr.reading.ac.uk

The aim of this study was to investigate how your mood relates to your memory and thinking processes. We are interested in a specific kind of thinking used every day for planning, solving problems and organising things. This is called 'Executive Functioning'.

The different questionnaires that you completed regarding mood and thinking helped us to understand how you have been feeling. The memory test that you completed allowed us to see how you remember events from your past. The different interactive tasks allowed us to measure different types of thinking processes.

Your results will be anonymously compared with those of other participants taking part in the study. If at any point you wish to withdraw your results or ask any questions about the study please email the researcher or project supervisor (contact details above).

Thank you very much for helping us with this research. We hope you have found it interesting.

9.8.3 Adolescent debrief for paper 4

Department of Psychology and Clinical Language Sciences
University of Reading

Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

Debriefing information: The Effects of Blueberry Anthocyanin Intervention on Cognitive functioning and Mood.

Thank you very much for taking part in this study. Our aim was to examine how flavonoids, which are found in many plants and fruits, especially blueberries, influence our thinking and mood. We want to understand more about any benefits of flavonoids in our diet on our mood and feelings and if this is related to improvements in our ability to solve problems. We hope that this study will help us better understand the impact of what we eat and how we think on our mood and well-being. This is because it is important to understand more about lifestyle factors that might promote well-being and prevent ill-health and diet is a very important part of this. Our hypothesis is that flavonoids have an effect on mood through their impact on executive functioning – something that is itself associated with low mood and depression. In the information sheet that we gave you before you and your parents took part in the study, we did not specifically describe our interest in mood at the start of the study. This was done to avoid the influence of social desirability or demand characteristics which may have influenced the results.

Again, thank you for your time and cooperation. If you have any questions regarding this study, please feel free to contact us.

Contact details:

Researcher:

Jennifer Fisk Email: J.Fisk@pgr.reading.ac.uk

Sundus Khalid Email: Sundus.Khalid@pgr.reading.ac.uk Phone: 0118 378 7928

Project supervisors:

Prof Claire Williams Email: claire.williams@reading.ac.uk Phone: 0118 378 7540

9.9 Appendix 11: Adolescent assent and consent forms for experimental studies papers 1,2 and 4

9.9.1 Parent OPT OUT consent form questionnaires in paper 1 for questionnaires

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

OPT-OUT FORM

Title of Project: Does mood affect thinking in adolescents?

Researcher: Jeni Fisk

Supervisor: Prof. Shirley Reynolds

Please only complete and return this form if you DO NOT want your child to take part in this research.

I **do not** agree to my child participating in this research.

Your child's name: _____

Your Name: _____ Date: _____

Signature: _____

9.9.2 Adolescent consent aged 16-18 paper 1 for questionnaires

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

CONSENT FORM FOR ADOLESCENTS

(To be completed by the adolescent)

Study One: Mood and Thinking in Adolescents

Please circle all you agree with:

Have you read (or had read to you) the information about this project?

YES/NO

Has somebody explained this project to you?

YES/NO

Do you understand what this project is about?

YES/NO

Have you asked all the questions you want?

YES/NO

Have you had your questions answered in a way you understand **YES/ NO/no questions**

Do you understand it's OK to stop taking part at any time? **YES/ NO**

Are you happy to take part? **YES/ NO**

If any answers are ‘no’ or you **don’t** want to take part, **don’t** sign your name!

If you **do** want to take part, please write your name and today’s date:

Your name _____ Date _____

Date of Birth: Male/female (please circle)

The person who explained this project to you needs to sign too:

Print name _____

Sign _____

Date _____

9.9.3 Adolescent consent form for questionnaires for adolescents aged 16-18 paper 1

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

CONSENT FORM FOR ADOLESCENTS aged 16-18
(To be completed by the young person)
Study 1: Does mood affect thinking in adolescents?

Please circle all you agree with:

Have you read (or had read to you) the information about this project? **YES/ NO**

Has somebody explained this project to you? **YES/ NO**

Do you understand what this project is about? **YES/ NO**

Have you asked all the questions you want? **YES/ NO**

Have you had your questions answered in a way you understand **YES/ NO/no questions**

Do you understand it's OK to stop taking part at any time? **YES/ NO**

Are you happy to take part? **YES/ NO**

If any answers are 'no' or you **don't** want to take part, **don't** sign your name!

If you **do** want to take part, please write your name and today's date:

Your name _____ Date _____

Date of Birth: Male/female (please circle)

The person who explained this project to you will also sign this

Print name _____
Sign _____
Date _____

9.9.4 Adolescent assent form for questionnaires for adolescents aged 13-15 paper 1 for questionnaires

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

ASSENT FORM FOR ADOLESCENTS aged 13-15 years
Study 1: Does mood affect thinking in adolescents?

Please circle all you agree with:

Have you read (or had read to you) the information about this project? **YES/ NO**
Has somebody explained this project to you? **YES/ NO**
Do you understand what this project is about? **YES/ NO**
Have you asked all the questions you want? **YES/ NO**
Have you had your questions answered in a way you understand **YES/ NO/no questions**
Do you understand it's OK to stop taking part at any time? **YES/ NO**
Are you happy to take part? **YES/ NO**

If any answers are 'no' or you **don't** want to take part, **don't** sign your name!
If you **do** want to take part, please write your name and today's date:

Your name _____ Date _____

Date of Birth: _____ Male/female (please circle)

The person who explained this project to you needs to sign too:

Print name _____

Sign _____

Date _____

9.9.5 Parent opt in consent form paper 1 for experimental tasks

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

PARENT CONSENT FORM
Does mood affect thinking in adolescents?

Researcher: Jeni Fisk
Supervisor: Prof. Shirley Reynolds

(Please initial each box)

1. I confirm that I have read and understand the Information Sheet for the above study and that I have had the opportunity to consider the information. ☐

2. I understand that my son/daughter's participation is voluntary and that we are free to withdraw at any time ☐

3. I agree that my child can be audio-recorded. I understand that this recording will be heard only by members of the research team and they will be destroyed at the end of the research study. ☐

4. I agree for my son/daughter to take part in the above study. ☐

The study was reviewed and given a favourable ethical opinion for conduct by the University of Reading Research Ethics Committee.

Your child's name: _____

Your Name: _____ Date: _____

Signature: _____

Name of Researcher: _____ Date: _____

Signature: _____

9.9.6 Adolescent consent form paper 1 aged 16-18 for experimental tasks

Department of Psychology and Clinical Language Sciences

University of Reading

Harry Pitt Building

Whiteknights Road

Reading RG6 6AL

ADOLESCENT CONSENT FORM

Does mood affect thinking in Adolescents? (Study 2)

Please initial each box:

Have you read (or had read to you) the information about this project?	☐
Has somebody explained this project to you?	☐
Do you understand what this project is about?	☐
Have you asked all the questions you want?	☐
Have you had your questions answered in a way you understand?	☐
Do you understand it's OK to stop taking part at any time?	☐
Is it ok to audio tape the session?	☐
Are you happy to take part?	☐

If any answers are 'no' or you **don't** want to take part, **don't** sign your name!

If you **do** want to take part, please write your name and today's date:

Your name _____ Date

_____

The person who explained this project to you needs to sign too:

Print name _____

Sign _____

Date _____

9.9.7 Adolescent consent form for adolescents aged 16-18 paper 2

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

University of Reading

CONSENT FORM FOR YOUNG PEOPLE (1

How Does Low Mood Affect Thinking in Young People?

Please initial each box:

Have you read (or had read to you) the information about this project?	
Has somebody explained this project to you?	
Do you understand what this project is about?	
Have you asked all the questions you want?	
Have you had your questions answered in a way you understand?	
Do you understand it's OK to stop taking part at any time?	
Are you happy for the research team to have access to the symptom measures, demographic information and assessment findings gathered as part of your routine assessment and treatment at the Child and Adolescent Mental Health Service? *(All information used for research is anonymised using an ID number)*	
Are you happy to be audio-recorded?	
Are you happy to take part?	

If any answers are 'no' or you **don't** want to take part, **don't** sign your name!

If you **do** want to take part, please write your name and today's date:

Your name _____ Date

_____

Please tick this box if you would like to hear about the study's results in the future

If you have ticked this box please provide us with your contact details e.g email address

……

……..

The person who explained this project to you needs to sign too:

Print name _____

Sign _____

Date _____

9.9.8 Adolescent assent form adolescents aged 12-15 paper 2

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

ASSENT FORM FOR YOUNG PEOPLE (12-15)
How Does Low Mood Affect Thinking in Young People?

Please circle all you agree with:

Have you read (or had read to you) the information about this project? **YES/ NO**

Has somebody explained this project to you? **YES/ NO**

Do you understand what this project is about? **YES/ NO**

Have you asked all the questions you want? **YES/ NO**

Have you had your questions answered in a way you understand **YES/ NO/no questions**

Do you understand it's OK to stop taking part at any time? **YES/ NO**

Are you happy for the research team to have access to the symptom

measures, demographic information and assessment findings gathered as part of your routine assessment and treatment at the Child and Adolescent Mental Health Service?*(All information used for research is kept private using an ID number and so your name will not be on this)* **YES/ NO**

Are you happy to be audio-recorded? **YES/ NO**

Are you happy to take part?

If any answers are 'no' or you **don't** want to take part, **don't** sign your name!

If you **do** want to take part, please write your name and today's date:

Your name _____ Date _____

Your parent or guardian must write his/her name here too if s/he is happy for you to do the project:

Print name _____ Date _____

Sign _____

Please tick this box if you would like to hear about the study's results in the future ☐
If you have ticked this box please provide us with your contact details e.g email address

……
……..

The person who explained this project to you needs to sign too:

Print name _____
Sign _____
Date _____

9.9.9 Parent consent form for adolescents aged 12-15 paper 2

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building

Whiteknights Road
Reading RG6 6AL

PARENT CONSENT FORM

How Does Low Mood Affect Thinking in Adolescents

(Please initial each box)

1. I confirm that I have read and understand the Information Sheet for the above study. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily. ☐

2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected. ☐

3. I agree for members of the research team to have access to the symptom measures, demographic information and assessment findings gathered as part of my child's routine assessment and treatment at the Child and Adolescent Mental Health Service, and be used for research purposes. *(All information used for research is anonymised using an ID number)* ☐

4. I agree for my child to be audio-recorded. ☐

5. I agree for my child to take part in the above study. ☐

Your child's name: _____

Your Name: _____ Date: _____ Signature: _____

Name of Researcher: _____ Date: _____

Signature:_____

Please tick this box if you would like to hear about the study's results in the future ☐

If you have ticked this box please provide us with your contact details e.g email address

……
……

9.9.10 Adolescent consent form aged 16- 17 paper 4

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

CONSENT FORM FOR Young People
(To be completed by young people over 16 years)

Project Title: The Effects of Blueberry Anthocyanin Intervention on Cognitive functioning and Mood

Please circle all you agree with:

Have you read (or had read to you) the information about this project?
YES/ NO

Has somebody explained this project to you? **YES/ NO**

Do you understand what this project is about? **YES/ NO**

Have you asked all the questions you want? **YES/ NO**

Have you had any questions answered in a way you understand **YES/ NO**

Do you understand it's OK to stop taking part at any time?
YES/ NO

Are you happy to take part?
YES/ NO

If any answers are 'no' or you **don't** want to take part, **don't** sign your name!

If you **do** want to take part, please write your name and today's date:

Your name:
Date:

The person who explained this project to you needs to sign too:

Print name:	Sign:
Date:	

9.9.11 Adolescent assent form for aged 12-15 paper 4

ASSENT FORM FOR YOUNG PEOPLE

University of Reading

(To be completed by young people less than 16 years of age)

Project Title: The Effects of Blueberry Anthocyanin Intervention on Cognitive functioning and Mood

Please circle all you agree with:

Have you read (or had read to you) the information about this project? **YES/ NO**

Has somebody explained this project to you? **YES/ NO**

Do you understand what this project is about? **YES/ NO**

Have you asked all the questions you want? **YES/ NO**

Have you had your questions answered in a way you understand **YES/ NO**

Do you understand it's OK to stop taking part at any time? **YES/ NO**

Are you happy to take part? **YES/ NO**

If any answers are 'no' or you **don't** want to take part, **don't** sign your name!

If you **do** want to take part, please write your name and today's date:

Your name:
Date:

The person who explained this project to you needs to sign too:

Print name:	Sign:

9.9.12 Parent consent form for adolescents aged 12-15 paper 4

Department of Psychology and Clinical Language Sciences
University of Reading
Harry Pitt Building
Whiteknights Road
Reading RG6 6AL

PARENT CONSENT FORM

Title of Project: The Effects of Blueberry Anthocyanin Intervention on Cognitive functioning and Mood (Part 2)

Researcher: Jennifer Fisk, and Sundus Khalid

Supervisors: Prof. Claire Williams & Prof. Shirley Reynolds

Dear Parent,

We would like to invite your son or daughter to Part 2 of our research. Part 2 would involve you (parent) making drinks (blueberry or matched placebo) for your child to consume every morning for 4 weeks. completing questionnaires about their diet and physical activity. Your child will be asked to fill a short questionnaire to let us know their fruit and vegetable intake and complete a few cognitive tasks and mood measures on the first day, two weeks and four weeks of intervention at PCLS laboratory in University of Reading/ their school.

(Please initial each box)

I confirm that I have read and understand the Information Sheet for the above study and that I have had the opportunity to consider the information. ☐

I understand that my son/daughter's participation is voluntary and that we are free to withdraw at any time. ☐

I agree for my son/daughter to take part in the above study. ☐

I would **NOT** like my child to be contacted further for any related study ☐

The study was reviewed and given a favourable ethical opinion for conduct by the University of Reading Research Ethics Committee.

Your child's name:

Your name:

Date:

Signature: Name of Researcher:

Signature: