Investigating the relationship between emotion and cognition during adolescence : genes and behaviour

Investigating the relationship between emotion and cognition during adolescence: genes and behaviour

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Declaration

I, Georgina Donati, hereby declare that, except where explicit attribution is made, the work presented in this thesis is entirely my own.

Exceptions:

BSc student Maria Giannakidou collected the data for Chapter 4. Many thanks for her work.
Data for the other five chapters was drawn from the Avon Longitudinal Study of Parents and Children (ALSAPC).

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Publications

The work presented in Chapter 3 and 7 have been accepted for publication:

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Abstract

Emotions provide the motivational aspect to conscious, goal-directed cognition. When they become disruptive, interfering with attainment or well-being, we rely on the ability to regulate them, facilitated by cognitive control. Exactly how emotion and cognition relate to each other is still unclear, particularly during adolescence, a time when structural and hormonal changes may accentuate the importance of their interactions. This thesis explores the relationship between emotion and cognition during adolescence using the Avon Longitudinal Study of Parents and Children, a longitudinal population-based cohort. **Chapter 3** characterises cognitive ability and emotional behaviour across adolescence, finding modest associations between constructs, the largest being between externalising and working memory. Using an independent adult sample, **Chapter 4** finds emotional behaviours to be differently related to emotion regulation strategies, and, using an emotional variant of the N—back, that externalising again associates with working memory, and internalising with emotional distraction**. Chapter 5** employs a longitudinal design to assess directional associations and finds that early adolescent externalising and internalising predict later adolescent working memory. **Chapter 6** reports six genome-wide association studies evaluating genetic relationships between cognitive and emotion measures; phenotypic relations between working memory and externalising replicate genetically, but a contrasting relationship is found with internalising. **Chapter 7** investigates whether these measures predict academic achievement and find working memory to be a robust predictor, while emotion measures explain small amounts of unique variance. **Chapter 8** reports the first genome-wide association study of national standardised school assessments of English, maths and science attainment and finds strong genetic contributions to attainment from cognitive measures and differential relationships with emotion measures. Across studies cognitive and emotional behaviour measures emerged as independent and diverse, highlighting the importance of considering specific roles of cognitive and emotional processes in academic achievement and mental health, as well as investigating their unique genetic bases.

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List of Abbreviations

AA	Academic Achievement
ADHD	Attention Deficit Hyperactivity Disorder
ALSPAC	Avon Longitudinal Study of Parents and Children
CD	Conduct Disorder
CERQ	Cognitive Emotion Regulation Questionnaire
DLPFC	Dorsolateral Prefrontal Cortex
EF	Executive Function
EFNBACK	Emotional Face N-Back
ER	Emotion Regulation
ERQ	Emotion Regulation Questionnaire
fMRI	Functional Magnetic Resonance Imaging
GCSE	General Certificate of Secondary Education
GCTA	Genome-wide Complex Trait Analysis
GTEx	Genotype-Tissue Expression
GWAS	Genome-Wide Association Study
IC	Inhibitory Control
KS	Key Stage
LD	Linkage Disequilibrium
LDSC	Linkage Disequilibrium Score Regression
MDD	Major Depressive Disorder
mPFC	Medial Prefrontal Cortex
ODD	Oppositional Defiant Disorder
PCA	Principal Component Analysis
PFC	Prefrontal Cortex
PS	Processing Speed
SATs	Standardised Assessment Tests
SDQ	Strengths and Difficulties Questionnaire
SEM	Structural Equation Modelling
SES	Socio-Economic Status
SNP	Single Nucleotide Polymorphism
vmPFC	Ventromedial Prefrontal Cortex
WM	Working Memory

1. Introduction

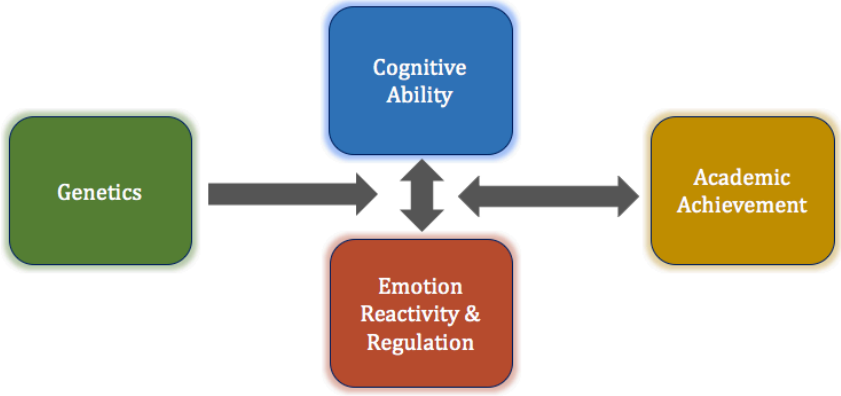


Figure 1.1: *A schematic showing how this thesis aims to investigate how emotion relates to cognitive ability, whether there exists a genetic basis for this relationship, and how they predict academic achievement.*

Emotions play an important role in carrying out everyday activities. On the one hand they provide both the motivational aspect of cognition in conscious, goal-directed problem-solving (Zelazo & Cunningham, 2007) and in helping organise our thinking, learning and action (Carlson & Wang, 2007; Garcia-Andres, Huertas-Martínez, Ardura, & Fernández-Alcaraz, 2010). On the other hand, emotions can also negatively influence our cognitive capacities. In such situations, we rely on our ability to regulate emotions, facilitated by executive functions (EF). EFs are the cognitive tools by which we carry out goal-directed actions. However, exactly how emotion and cognition relate to each other is still unclear. Literature examining the relationship between emotion and EF starts in early development and focuses on self-regulation and effortful control, both of which emerge around 5 years of age (Zelazo & Cunningham, 2007). Further development of emotion regulation occurs during adolescence coinciding with frontal brain maturation and increased social pressures which require more complex emotion regulation (ER) strategies (Yap, Allen, & Sheeber, 2007). Neuroimaging studies measuring ER strategies report that good functional and structural prefrontal – amygdala connectivity is paramount to successful regulation. Structural and hormonal changes in both of these brain areas during adolescence, coupled with the fact that this developmental period is a key time for the onset of mental health issues (Giedd, Keshavan, & Paus, 2008), make it crucial to understand how cognition and emotion interact during this period of human development. Clinical studies show a persistent and pervasive coincidence of

psychopathology and EF deficits (Snyder, Miyake, & Hankin, 2015). In fact, emotion dysregulation and EF are increasingly recognised as transdiagnostic features of many psychopathologies (Gratz & Roemer, 2004; Nolen-Hoeksema & Watkins, 2011). Transdiagnostic factors are considered to be key to creating better models of mental health (both clinical and non-clinical) and understanding the interaction between risk factors at various levels, from genetics to behaviour (Nolen-Hoeksema & Watkins, 2011). Twin studies, as well as candidate gene and imaging-genetics studies have provided evidence for genetic influences on individual differences in ER. However, replication of molecular findings has been difficult and as yet there have been no well-powered quantitative genetic (i.e., twin studies) or molecular genetic studies (i.e., Genome-Wide Association Studies; GWAS) aimed at comprehensively examining genetic contributions to ER. Understanding the genetic basis of individual differences in ER/EF would provide vital insights into the origins of their relationship. It would also help to map risk leading to maladaptive behaviours that have a negative influence on personal relationships, academic performance, career success, and general well-being (Graziano, Reavis, Keane, & Calkins, 2007; Gross & Munoz, 1995). This thesis will explore the relationship between emotion and cognition, focusing on the period of adolescence and using for the most part the Avon Longitudinal Study of Parents and Children (ALSPAC), a longitudinal population-based cohort.

1.1 Adolescence

Adolescence is a developmental period beginning at the onset of puberty and ending when an individual takes on a position of responsibility within their society (Crone & Dahl, 2012). Accordingly, on the one hand adolescence will vary widely between cultures and across history, but on the other hand certain factors appear to remain constant even across species. Specific behaviours such as increased novelty seeking, or risk-taking have been referenced over the centuries (Shakespeare, 2001), in a range of countries and cultures (Duell et al., 2018) and across different species (Brenhouse & Andersen, 2011; Laviola, Macrı, Morley-Fletcher, & Adriani, 2003; Spear & Varlinskaya, 2010).

In terms of the brain, the adolescent period in humans is characterised by changes in the prefrontal cortex (PFC), which is key for executive abilities, and in subcortical structures, key for emotional processing. Structural changes occur across most of the brain during adolescence, with an increase in white matter volumes continuing until the mid-twenties, and a decrease in cortical grey matter volumes plateauing in the early twenties (Mills et al., 2016). Cortical thickness in all lobes was found to decrease more rapidly during adolescence than during childhood and adulthood (Zhou, Lebel, Treit, Evans, & Beaulieu,

2015). The frontal and temporal lobes, in particular the superior temporal sulcus, are thought to be the last regions of the brain to go through this grey - white matter reorganisation which progresses from lower-order somatosensory cortices to higher order association cortices (Gogtay et al., 2004). This is believed to represent a process of synaptic specialisation (rapid synaptogenesis followed by synaptic pruning of weaker or unused connections) and the reinforcement of long range connections (myelination of axons) making them faster and more reliable (Huttenlocher, 2002; Petanjek et al., 2011) although there is some suggestion that the calculable reduction in grey matter is only relative to the increase in white matter (Sowell, Trauner, Gamst, & Jernigan, 2002). These structural developments coincide with parallel changes in functional connectivity which sees a decrease in short range and an increase in long range functional connectivity facilitating increased integration between different brain regions (Vogel, Power, Petersen, & Schlaggar, 2010).

The structural changes mentioned above are largely age-dependent. However the onset of puberty, signalled by hormone release, shows both independent and interactive effects with age on the volume of subcortical regions (Goddings et al., 2014). Other important changes to occur as a result of puberty include a re-wiring of the dopamine projections to the prefrontal cortex resulting in an increase in dopamine release regulating emotional arousal, pleasure and reward, and learning (Blakemore, Burnett, & Dahl, 2010; Luna, Marek, Larsen, Tervo-Clemmens, & Chahal, 2015; Steinberg, 2008).

There are also numerous behavioural characteristics associated with adolescence including a social shift towards peers (Brown, 2004), increased self-awareness (Sebastian, Burnett, & Blakemore, 2008), risk-taking and reward-seeking (Steinberg, 2008). These are believed to be connected to changes in frontal and subcortical areas (discussed later in this chapter). Together, all of these factors make adolescence a crucial period in development for the investigation of the interaction between cognition and emotion.

1.2 Executive function in adolescence

EFs are a set of cognitive processes, partially distinct from IQ (Friedman & Miyake, 2017; Friedman et al., 2006; Lehto, Juujärvi, Kooistra, & Pulkkinen, 2003), which are necessary for the voluntary control of behaviour and the successful achievement of goals. Within the field of cognitive neuroscience/neuropsychology, the debate as to whether this constitutes one general control mechanism or multiple separable mechanisms goes back as far as the field of executive functions itself. However current dominant adult EF

frameworks, such as the Miyake-Friedman model (2000), distinguish between a) working memory (WM), the ability to hold and manipulate information in mind; b) shifting, the ability to flexibly switch attention between different tasks, rules, or mental states; and c) inhibitory control (IC), the ability to suppress distracting information and unwanted responses; as key aspects of executive functioning, which, although correlated when measured experimentally, can also be separated (Lee, Bull, & Ho, 2013; Miyake et al., 2000). More recently this model has been adapted to represent the correlated variance between measures as a separate factor: 'Common EF'. This common EF factor, which could be considered as a general control mechanism, absorbs all of the variance explained by IC, but remains distinct from WM, shifting and other cognitive constructs such as processing speed (PS) and IQ (Friedman et al., 2008).

Developmentally, there appears to be a pattern of increasing specialisation from unity to diversity. A number of studies consistently find a unitary model of EF in early childhood (Wiebe, Espy, & Charak, 2008; Wiebe et al., 2011), whereas by late childhood/early adolescence the picture is more variable. Some studies find evidence to support three separable but highly correlated traits in 8 – 13 year olds (Lehto et al., 2003) and others find that in 5 – 13 year olds a two-factor model of EF fits the data best and it is not until age 15 that a three-factor model emerges (Lee et al., 2013). Huizinga et al. (2006), found shifting and WM latent factors in 7 – 21 year olds, but not a clear IC latent measure, instead the three IC measures loaded separately.

There is evidence that the above mentioned EFs continue to improve into adolescence and have distinct developmental trajectories (Huizinga, Dolan, & van der Molen, 2006; Kail, 2000). As demonstrated by the Huizinga et al. (2006) study, IC is potentially less uniform in nature than working memory or shifting. Some elements of inhibitory control develop early, such as performance on the Simon Says task which is generally mastered by the age of 5 (Jones, Rothbart, & Posner, 2003) or inhibiting outward expression of disappointment by 7 years (Garcia-Andres et al., 2010). Motor and oculo-motor inhibition tasks such as the Stop-signal and Erikson Flankers continue to improve until 15 years and semantic inhibition such as that found with the Stroop continue until age 21 (Huizinga et al., 2006). WM ability in terms of performance on gradually more complex tasks, continues to develop linearly until late adolescence. For example, children as young as six years can hold up to three items in mind, whereas the number of items individuals can keep in WM beyond this continues to develop until 17 years old (Conklin, Luciana, Hooper, & Yarger, 2007; Dumontheil et al., 2011). Shifting ability, exemplified by the Wisconsin Card Sorting Task, is the most complex of the three as it requires both WM and IC. Shifting requires an individual to hold in mind more than one rule and to be able to

move flexibly between rules or learn a new one as appropriate, and inhibit the rule which is not currently applicable (Best & Miller, 2010). Shifting, as WM, continues to change behaviourally and neurally into the mid to late teens (Crone, Donohue, Honomichl, Wendelken, & Bunge, 2006; Crone, Richard Ridderinkhof, Worm, Somsen, & van der Molen, 2004).

While EFs continue to improve over adolescence, there is also evidence that individual differences in EF remain relatively stable over this time, and that this stability is mediated by genetic factors (Friedman, Miyake, Robinson, & Hewitt, 2011; Miyake & Friedman, 2012).

1.3 Early developmental associations between executive function and emotion

Studies looking at the relationship between EF and emotion across development have found that changes in this relationship co-occur with structural developments in the prefrontal cortex (PFC). Further development of both the PFC and social-emotional systems during adolescence potentially signal another important stage of development in emotional regulation (Yap et al., 2007). It has also been proposed that strengths and weaknesses in different EFs may result in diverse emotional outcomes. However, disentangling executive-function driven emotion regulation from emotion reactivity has presented a challenge.

Temperament research posits that the voluntary control of behaviour (effortful control) first emerges around the age of 5 years and coincides with significant developments in the PFC (Zelazo & Cunningham, 2007). Many early ER studies focus around the development of IC, e.g. the disappointing gift paradigm (Saarni, 1984) and show high correlations between executive ability and emotion regulation (Carlson & Wang, 2007). However Rothbart and colleges argue that low negative affect is maintained by high attentional control (Rothbart, Derryberry, Posner, & others, 1994), attention being the mechanism by which perceived stimuli are selected from all sensory inputs. Orienting attention away from unpleasant or distressing stimuli allows for successful ER (Posner & Rothbart, 2000). Eisenberg et al. (2001) found that 4 – 8 year old children with low attentional control were more likely to experience internalising difficulties, and those with low IC were more likely to experience externalising problems. Eisenberg and Fabes (1992) propose a tripartite ER-EF model where children with low ER and IC are impulsive, intense and prone to aggression, while children with high IC and poor cognitive flexibility are withdrawn, sad and anxious. The optimally-regulated children are

somewhere in the middle (Eisenberg & Fabes, 1992). Other studies have supported the idea that high levels of IC lead to a rigid cognitive approach and make children more susceptible to internalising disorders (Carlson & Wang, 2007; Fox, 1994; Nigg, 2000). Carlson and Wang tested this model by comparing linear and quadratic models of hierarchical regression with ER scores as the criterion and found that the quadratic model explained an extra 9.5% of the variance in ER and confirmed that "medium" IC resulted in optimal ER.

This pattern continues into adolescence. A longitudinal twin study by Friedman and colleagues found that those who were high in self-restraint in childhood, were high in self-restraint as teenagers, and had lower cognitive flexibility. They also found that IC was primarily genetic in nature but that cognitive flexibility was the result of both genetic and environmental effects (Friedman et al., 2011). This adds some support to Eisenberg and Fabes' theory and suggests that some early EF differences may persist into adolescence, but they may be balanced by or influence the development of other EFs. Forty years after the initial marshmallow experiment, Casey et al., (2011) followed up participants and found that those who had better delayed gratification at nursery, were also better at an affective go-no-go task as adults. However they were only better when supressing happy faces, not sad ones, perhaps supporting evidence that regulating positive emotion (happy face, eating marshmallow) may be differently mediated than regulating negative emotion (Gross & John, 2003)[1]. These studies together suggest, that higher levels of certain EFs does not necessarily imply better regulation.

A distinction exists between measuring emotion and inferring levels of regulation, and actually measuring ER itself (Cole, Martin, & Dennis, 2004). Many of the studies reviewed above are not able to differentiate between ER and emotional reactivity. For example, it is not known whether children who are good at the disappointing gift task are better at regulating, or simply not disappointed by the gift. Likewise, we are not able to tell whether those who have low anxiety are good regulators, or whether they are less emotionally reactive. However, if it is the case that emotion and EF interact during the course of development then a possible consequence of this will be that those who regulate better, are less emotionally reactive.

[1] Note that others have not found such large effects using this paradigm, in particular when controlling for socio-economic status (Watts, Duncan, & Quan, 2018). Watts and colleagues (2018) found the majority of the variance in later adolescent achievement, explained by the task at 4yrs, came from the child being able to wait at least 20 seconds.

The studies mentioned so far find a relationship between EF and emotional outcomes. They hypothesise that particular executive strengths and weaknesses have an effect on how emotions are regulated and expressed. This relationship, if causal, could plausibly function in either direction or have bi-directional and reciprocal effects across development. There are as yet no longitudinal studies in adolescence investigating these hypotheses.

1.4 Emotion regulation: mechanism of interaction

As mentioned above, there are difficulties disentangling regulation and reactivity. Almost all of the studies mentioned above infer regulation from the relationship between cognitive control and emotional outcomes. The implied mechanism of ER takes many forms. Some of these will be unconscious behavioural types of regulation such as self-soothing or distraction, while others will come in the form of cognitive or attentional biases which alter conscious information processing or interpretation. Presumably those that are related to EF will be effortful cognitive processes and the following section explores some of the more common theories.

In the last 15 years ER has become a popular field of research particularly due to a recognition that it may have an underlying role in a range of clinical conditions (Aldao, Gee, De Los Reyes, & Seager, 2016; Aldao & Nolen-Hoeksema, 2010). There is much debate about how to define ER and a range of questionnaires have been developed measuring different aspects of ER or taking different approaches to the topic. Some authors focus on the ability to modulate emotional experience, where ER is something which arises either as a result of emotion or in anticipation of an emotion (Gross, 1998). Other theorists suggest that the ability to experience/recognise a range of emotions is just as important as the modulation process, making emotional awareness a key part of regulation and therefore that methods which encourage emotional acceptance and valuing such as mindfulness are important. They argue that responding negatively to your own emotions is maladaptive and can cause greater difficulties (Gratz & Roemer, 2004).

One of the most influential models of ER is Gross's *Process Model* of ER and the accompanying Emotion Regulation Questionnaire (ERQ). The process model asserts that there is a time-course over which emotions are generated and that the emotional outcome depends on the time point at which you begin to deploy a strategy (Gross, 1998). The emotion generative process can be divided into: situation selection, situation modification, attention deployment and cognitive change (or reappraisal) and response modulation. It is possible to use ER strategies at any point during this process but

reappraisal, defined as the attempt to alter the meaning and emotional impact of a situation, is deployed during cognitive change and suppression, the attempt to inhibit or reduce emotion-expressive behaviour is a type of response modulation. Reappraisal is antecedent-focused thereby changing the course of the emotion experience, and suppression is response-focused and therefore tries to stop the expression of the feeling once it has already arisen. Gross asserts that both strategies are used regularly by adults, can be experimentally manipulated and one is generally adaptive and the other maladaptive (Gross & John, 2003). Gross and John (2003) showed participants a 'negative emotion-eliciting film' and asked one group to suppress negative emotion, another to reappraise the experience and a final group to simply watch the film. Participants in the reappraisal group reported experiencing less negative emotion, whereas those in the suppression group reported equal negative emotion to those in the control group. A functional Magnetic Resonance Imaging[2] (fMRI) study with a similar paradigm but with all participants asked to suppress or reappraise a series of images found confirmation that reappraisal recruits PFC earlier than suppression and in doing so successfully down-regulates amygdala and insula activity whereas suppression leads to this down-regulation initially but not in a sustained manner (Goldin, McRae, Ramel, & Gross, 2008).

Use of reappraisal has been found to be negatively associated with depression, but positively associated with the number of relationships one has, the closeness of the relationships and being liked by others. Suppression on the other hand is associated with reduced well-being, self-esteem and optimism (Gross & John, 2003) and increased rumination (Balzarotti, John, & Gross, 2010), a major diagnostic factor in many psychopathologies (Nolen-Hoeksema & Watkins, 2011). This is particularly interesting in the context of adolescence where young people are becoming more reliant on their peer relationships for reward and identity (Crone & Dahl, 2012; Gardner & Steinberg, 2005; Sebastian et al., 2008; Sebastian et al., 2011). People who use suppression are less likely to experience positive emotion. Gullone, Hughes, King, and Tonge (2010) looked at use of suppression in children and adolescents aged 9 – 15 yrs. in a longitudinal study and found that suppression decreased over time (Gullone, Hughes, King, & Tonge, 2010).

The Cognitive Emotion Regulation Questionnaire (CERQ; Garnefski & Kraaij, 2007) is one of the first questionnaires to bring together cognitive ER strategies from different traditions in order to understand more broadly the relationship between strategies and

[2] fMRI is a neuroimaging technique which measures the flow of oxygenated blood in the brain as an indicator of neuronal activity.

emotional well-being. In the creation of CERQ the authors sought to establish a measure of cognitive ER strategy use which could characterise an adolescent's 'style' of responding to a stressful situation. Strategies include catastrophizing, reappraisal, rumination, self-blame, other-blame, positive refocusing, refocus on planning and putting into perspective. In validating the CERQ it was found that rumination and self-blame were the most significantly positively correlated to depression and anxiety, in contrast to reappraisal and refocusing, which had the most significant negative correlations with depression and anxiety. However, these negative correlations only appeared after controlling for the other strategies, as previously they were positively correlated. The authors conclude that 1) strategies are used in combination with each other, and some combinations produce positive effects and others negative; 2) that the strategies themselves are not clearly adaptive or maladaptive; 3) adaptiveness may be more related to how strategies are deployed (Garnefski & Kraaij, 2007) .

Gratz and Roemer (2004) developed the Difficulties in Emotion Regulation Scale (DERS) with young adults with the aim of incorporating factors influencing degrees of emotion dysregulation (Gratz & Roemer, 2004). They define ER as the ability to control impulses and modulate emotions so as to be able to meet self-directed goals. The questionnaire includes emotional awareness and understanding, acceptance and impulse control. Gratz and Roemer critique previous ER measures which assign strategies to the categories of adaptive or maladaptive and argue that the appropriateness of ER strategies depends on context and a person's ability to use strategies appropriately, or flexibly. This questionnaire involves six scales: Non-Acceptance; Clarity; Goals; Impulse; Strategies; and Awareness.

Some developmentalists have argued that it is the flexible and appropriate use of executive regulation of emotion that is key (Carlson & Wang, 2007). Likewise ER researchers increasingly argue that particular strategies may be less relevant than the context in which they are used (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Aldao & Tull, 2015; Gratz & Roemer, 2004), and that cognitive flexibility is more important than being particularly good at any one strategy (Gratz & Roemer, 2004). On the other hand, Aldao and Nolen-Hoeksema (2010) argue that whereas this may be the case on an individual basis or within the typical population, when comparing clinical and non-clinical populations, particular strategies such as rumination and suppression are positively related to depression, anxiety and eating disorders, and others are not.

Out of the questionnaires reviewed above, the ERQ has been the most widely used in cognitive neuroscience. For example, Drabant and colleagues (2009) used the ERQ to

assess the extent to which adult participants ordinarily use reappraisal or suppression. They also took control measures of trait anxiety and neuroticism to assess emotional reactivity and predicted that those who habitually used reappraisal would better down-regulate amygdala activation even after controlling for emotional reactivity, IQ and Socio-Economic Status (SES). They found a significant negative relationship between reported reappraisal use and bilateral amygdala activation during an emotion regulation task, and a significantly positive relationship between reappraisal use and activation in the dorsomedial PFC, dorsolateral PFC and orbital frontal cortex. They also found that neuroticism, but not anxiety, independently predicted amygdala and parietal (Brodmann area 40) activation. This suggests that regulation and reactivity may be independent, although the authors do not report the behavioural correlation between the emotion regulation and reactivity measures (Drabant, McRae, Manuck, Hariri, & Gross, 2009).

Neuroimaging studies have shown an association between better down-regulation of emotions, measured behaviourally, and a greater inverse functional connectivity between the amygdala and parts of the PFC while regulating emotion (Lee, Heller, van Reekum, Nelson, & Davidson, 2012). A meta-analysis of 44 neuroimaging studies looking at the down-regulation of emotion consistently showed decreased activation in the amygdala, parahippocampal gyrus and left inferior parietal lobule alongside increased activation in the inferior, middle and superior frontal gyri and the left anterior cingulate cortex during emotion regulation (Frank et al 2014). Those with high levels of anxiety have been found to have decreased structural connectivity between the PFC and limbic regions (Kim & Whalen, 2009; Kim et al., 2011) and reduced functional connectivity between these regions in adolescents at risk of psychosis (Gee et al., 2012).

The common finding throughout the cognitive neuroscience ER literature is the role of the amygdala in emotional reactivity, and of the PFC in down-regulating this reactivity. The research also draw links between successful ER and better mental health and wellbeing (Gross & John, 2003; Gross & Munoz, 1995). These results are interesting in regard to adolescence, which is characterised by a period of great change in these two brain areas.

1.5 Adolescent Vulnerability

During adolescence the neural circuity implicated in ER undergoes significant changes (Mills, Goddings, Clasen, Giedd, & Blakemore, 2014; Prencipe et al., 2011). There are both structural (Gogtay et al., 2004; Mills et al., 2016; Zhou et al., 2015) and functional (Crone & Dahl, 2012) changes in the frontal-parietal executive networks. Structural

(Goddings et al., 2014) and functional (Hare et al., 2008) changes are also present in subcortical areas. Hormonal influences on the limbic system are believed to make adolescents more emotionally reactive and sensitive to factors such as social rejection. Furthermore, the 'flexible' or relatively less developed state of the PFC has been suggested as a risk factor for adolescent mental health problems.

During adolescence the amygdala increases in volume (Goddings et al., 2014) and reactivity in response to emotion regulation tasks (Hare et al., 2008) and fearful faces (Guyer et al., 2008). This increased activity has been associated with an increased risk of anxiety, depression (Yang et al., 2010) and behavioural problems (Viding et al., 2012). However, findings in regards to amygdala reactivity are not always consistent and some find no changes or particular differences during adolescence (Del Piero, Saxbe, & Margolin, 2016). Yurgon-Todd and Killgore (2006) for example looked at the development of the role of the PFC in implicit emotion regulation by assessing changes in PFC activation across adolescence in response to fearful vs happy faces. Although they found increasing PFC activation with age, they did not find the expected age-related reductions in amygdala activity (Yurgelun-Todd & Killgore, 2006).

There is evidence that adolescents struggle to integrate cognitive and emotional information at adult levels in decision-making tasks. This has been shown most clearly by performance in the Iowa Gambling Task, which presents participants with four decks of cards. Participants are required to select cards from the decks and in doing so they either win or lose money. Of these decks, two are 'good', in that they show lower rewards but a decreased risk of loss, and two are 'bad' decks, these have high rewards and high losses. Overall selecting from the good decks is more beneficial. Six to nine year-olds choose indiscriminately from the decks, 10-15 year-olds show a very slight preference for the good decks, but only 18-25 year olds consistently prefer the good decks (Crone & van der Molen, 2004). Furthermore, performance on this task (reliant on ventromedial PFC) and a go/no-go and digit span task (reliant on dorsolateral PFC) were not correlated in adolescents suggesting that 'hot' and 'cool' executive functions may be functioning via different mechanisms which, at least during adolescence, are not necessarily related (Hooper, Luciana, Conklin, & Yarger, 2004). Hot EF tasks are those which are emotionally or motivationally salient, whereas cool tasks are not. Zelazo and Carlson (2012) argue that during adolescence 'hot' and 'cool' EF develop separately and adult levels of cool EF may be reached sooner than hot EF (Zelazo & Carlson, 2012). Affective theory of mind (ToM) tasks, whereby individuals are asked to reflect on their own or other people's feelings and emotions, also require the integration of cognitive and affective information, and are supported by the vmPFC. In one study, adolescents made more

errors than adults in the affective theory of mind conditions but not in cognitive theory of mind or causal conditions, and also showed more vmPFC activation than adults in the affective ToM condition compared to the physical causality condition (Sebastian et al., 2012). These studies support other evidence that adolescents can perform at adult levels on 'cool' executive function tasks, but differ from adults on 'hot' tasks.

From research looking specifically at emotion regulation however, there is evidence that ER and cool EF are correlated. Using the Behavior Rating Inventory of Executive Function-Self-Report Version (Guy, Gioia, & Isquith, 2004) to measure EF, and the ERQ to measure ER, Lantrip and colleagues (2015) found that a greater use of reappraisal in adolescence was associated with better EF (Lantrip, Isquith, Koven, Welsh, & Roth, 2015). Adult studies have also found a positive association between reappraisal and WM (McRae, Jacobs, Ray, John, & Gross, 2012; Pe, Raes, & Kuppens, 2013; Schmeichel, Volokhov, & Demaree, 2008), although not necessarily IQ (Drabant et al., 2009).

Developmental change in performance on tasks involving emotion and EF is not necessarily always linear. Burnett et al. (2010) used a probabilistic gambling task to test risky-decision making in more or less emotional contexts and found that the peak in risk taking was at 14.38 yrs. of age, with an inverted U-pattern where adolescents at this age took more risks than those younger (from age 9) or older (up to age 35) (Burnett, Bault, Coricelli, & Blakemore, 2010). In a laboratory driving-game, adolescents take more risks when in the presence of their peers (Gardner & Steinberg, 2005) and during peer observation have higher activation in reward-related brain regions than adults and younger children and recruit cognitive control areas less (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011). McRae and colleagues (2012) looked at both linear and quadratic models of reappraisal across childhood (10-13yrs), adolescence (14-17yrs) and adulthood (18-23ys). They found a negative linear relationship between age and reactivity in the left ventromedial PFC and a positive linear correlation between age and reappraisal in the left ventrolateral PFC and inferior frontal gyrus. U-shape effects were found in the superior temporal gyrus, left insula, left parahippocampal gyrus and cingulate cortices in the contrast relating to emotional reactivity meaning that adolescents recruited these regions less than children or adults. In contrast, adolescent recruitment of the posterior cingulate, medial PFC and temporal lobes during reappraisal, was higher than in the other two age groups. Reactivity was measured as the difference between passively looking at a negative vs. a neutral picture, and reappraisal as the difference between passively looking at negative pictures and being told to down-regulate response to negative pictures. They found no age-related increases in emotion reactivity, but they did find both linear and quadratic relationships between age and reappraisal. They conclude that this

is due to the different maturational timings of different cognitive abilities relating to ER (McRae, Gross, et al., 2012). This research suggests that it is not just that 'hot' EF takes *longer* to develop, but that there are adolescent-specific changes in 'hot' EF.

It has been proposed that changes to subcortical areas influencing arousal and motivation come about before the further development of regulatory elements in the PFC, making adolescents more vulnerable to developing ER difficulties (Steinberg, 2005). These findings provide the basis for the developmental mismatch theory of adolescence (Casey, Getz, & Galvan, 2008), which focuses on the relationship between the relatively matured limbic system and the maturing PFC. The theory states that risky, reward- and sensation-seeking behaviours are driven by the limbic system. Where in adults impulses are subject to PFC top-down control, ensuring the completion of long-term goals, planning and inhibition, this is not yet available to adolescents (Casey et al., 2008). This theory is appealing in its simplicity, however many argue that this dichotomy between emotions and reasoning are not based in biological fact (Pfeifer & Allen, 2012). Crone and Dahl (2012) state that too much emphasis has been put on the PFC's inability to inhibit behaviours leading to undesirable consequences. They suggest that findings regarding cognitive control vary, and could therefore reflect a more flexible control system depending on the degree of engagement, rather than an unreliable control system. When sufficiently motivated, adolescents are able to perform extremely well on cognitive tasks (Crone & Dahl, 2012). Some have proposed that a re-modelling of dopamine systems may be responsible for adolescent-specific reward-seeking behaviours (Steinberg, 2008; Sturman & Moghaddam, 2011). Dopamine projections begin in the ventral tegmental area and substantia nigra and terminate in various structures of the limbic system, the medial PFC and other cortical regions. Dopamine initiates exploratory behaviours such as risk-taking, sensation-seeking, novelty-seeking and increased independence. It is thought that adolescence is a period of particularly high concentrations of dopamine predominantly in the PFC (Wahlstrom, Collins, White, & Luciana, 2010). Since the biological task of an adolescent may be to develop good social skills, attention will be orientated towards social interactions and captured by social context when available (Mills et al., 2014), in the same way that infants focus on visual stimuli and actions during visual or motor sensitive periods.

To summarise, there are adolescent-specific changes in structure and functional processing in areas involved in emotional and cognitive tasks which influence the integration of these two types of information. Adolescents do not perform at adult levels in such tasks possibly due to a slower development of 'hot' executive function (Zelazo & Carlson, 2012), or perhaps because adolescents simply give more weight to social and

emotional information (Steinberg, 2005). Either way, the proposal is that this renders them more vulnerable to emotion regulation difficulties and to developing mental health problems.

1.6 Clinical associations between executive functions and poor mental health

It has been suggested that EF deficits may represent transdiagnostic risk that contributes to commonalities and comorbidities between emotional, behavioural, and psychotic disorders (Aldao & Nolen-Hoeksema, 2010; Benca et al., 2016; Huang-Pollock, Shapiro, Galloway-Long, & Weigard, 2017; Snyder et al., 2015) and some researchers have even suggested the existence of a common psychopathology latent factor or 'p' factor (Caspi et al., 2014), which is related to EF (Martel et al., 2017). However, studies comparing models associating EF with either a general 'p' factor, an internalising-externalising model, or as separate behavioural disorders have been inconsistent in their findings (Bloemen et al., 2018; Hatoum, Rhee, Corley, Hewitt, & Friedman, 2017; Huang-Pollock et al., 2017).

Cross-sectional clinical and non-clinical studies of adults have found deficits across the spectrum of internalising and externalising disorders in almost all neuropsychological EF tasks (Snyder, 2013). For example, De Lissnyder and colleagues found impairments in shifting between items held in WM in those with depression (De Lissnyder et al., 2012). Poor IC has been associated with depression as well as rumination in the general population (Hilt, Leitzke, & Pollak, 2014; Joormann, Yoon, & Zetsche, 2007; Whitmer & Banich, 2007); depressed adult patients are generally slower and make more errors in IC tasks (Gohier et al., 2009). Attention-Deficit Hyperactivity Disorder (ADHD) and other externalising behaviours, have been associated with small to medium sized deficits in shifting, IC and WM (see Ogilvie, Stewart, Chan, & Shum, 2011 for meta-analysis). Anxiety-related disorders are associated with problems in shifting (Mantella et al., 2007), inhibiting competing responses (Snyder et al., 2010), and visuospatial working memory (Boldrini et al., 2005). Impairments in the Stop Signal IC task and ER have been found in substance abuse (Li et al., 2008), remitted Major Depressive Disorder (MDD) patients (Aker, Bø, Harmer, Stiles, & Landrø, 2016) and in ADHD (Dimoska, Johnstone, Barry, & Clarke, 2003) although this may vary between children and adults (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005). On the basis of these neuropsychological and neuroimaging results it has been suggested that poor EFs might contribute to poor emotional regulation via poor top-down regulation of subcortical regions (Frank et al., 2014; Zelazo & Cunningham, 2007).

Based on the widespread clinical findings of the co-occurrence of psychopathology and EF deficits, emotion dysregulation and EF have been proposed as transdiagnostic risk factors for developing mental health issues. Such transdiagnostic risk factors are appealing candidates for endophenotypes in genetic research, but, more importantly, investigating genetic effects on EF and ER could help us understand the origins of their relationship and possible shared genetic mechanisms.

1.7 Genetics of EF and ER

Genetic methods have been used to study the origins of individual differences in higher level cognitive traits and behaviours traits using family and twin studies, followed by molecular genetic strategies to identify specific genetic variants and/or candidate genes. Specifically, classical twin studies use inferred genetic relatedness between pairs of related individuals to quantify the genetic and environmental origins of individual differences (Plomin, DeFries, McClearn, & Rutter, 1997). Genetic association approaches (either whole genome or candidate gene scale) using very large samples of unrelated individuals seek to uncover which genes and where, and delineate the functional and biological pathways linking genes, brain and behaviour.

1.7.1 Twin studies

Twin studies capitalise on the known genetic relatedness between monozygotic (100% genetic similarity) and dizygotic (share ~50% of segregating alleles) twins to untangle the relative contributions of genes and environment on behaviour. Results of twin studies provide estimates of the percentage variance accounted for by A (additive genetic influences), C (environmental influences causing twins to correlate) and E (environmental influences causing twins not to correlate). Over two decades of twin studies have consistently shown that (1) most human complex traits are 30% - 70% heritable, (2) heritability for cognitive traits increases over time, most probably due to increasing gene-environment correlation, and (3) most behavioural traits share a significant proportion of their genetic effects (Plomin, DeFries, Knopik, & Neiderhiser, 2016).

As with other cognitive functions, twin studies have demonstrated that EFs are heritable with estimates of latent EF factors ranging between 76 and 100% (Friedman et al., 2011, 2008), both overlapping and independent genetic effects across specific EFs, and much lower estimates for individual as opposed to latent measures (0% - 36%) (Friedman et al., 2008). A number of twin studies have estimated that Common EF, the factor

representing shared variance between EFs, has a high heritability of ~99%. In contrast, individual differences in some specific EFs are also influenced by non-shared environment (Engelhardt, Briley, Mann, Harden, & Tucker-Drob, 2015; Friedman et al., 2008). The finding of high heritability for common EF is replicated in older populations, but not necessarily that of a distinct genetic contribution for distinct EFs (OATS Research Team et al., 2012). Evidence from longitudinal twin studies suggests that genetic effects contributing to individual differences in EF increase between the ages of 5 and 12yrs (working memory = 55% – 73%, sustained attention = 59% – 63% and selective attention = 52% – 63%) (Polderman et al., 2007) and then stabilise from 17 to 23yrs (common EF = 81%, shifting = 79% and updating = 99%) (Friedman et al., 2016).

In contrast, studies investigating internalising and externalising behaviours suggest that genes play a lesser role in explaining individual differences in internalising behaviours over time. In a study involving 3,620 twin pairs, genetic factors were found to explain three quarters of the variance in girls' and half of the variance in boys' externalising problems, whereas genetics explained approximately two thirds of the variance for both genders in internalising. Shared environment also played a part in boys' externalising behaviours only (van der Valk, Verhulst, Stroet, & Boomsma, 1998). However, although genetics play a key role in the stability of internalising and externalising behaviours over childhood (explaining 51% - 57% of the correlation between age 3 and age 7 in internalising and externalising behaviours), the total amount of variance explained by genetics decreases for internalising (59% - 40%) but stays consistent for externalising (51% - 52%) during childhood (Verhulst & Boomsma, 2003). This reduced estimate of genetic influence in internalising is explained by an increase in shared environment (10% - 31%) showing the opposite trend to cognitive traits that generally increase in heritability and have relatively little variance explained by shared environment (Verhulst & Boomsma, 2003). A series of meta-analyses of anxiety disorders found modest twin heritability of between 30% - 40%, dependent on the specific disorder (Hettema, Neale, & Kendler, 2001).

Well-powered quantitative genetic studies investigating emotion regulation are sparse. The available twin research suggests a moderate heritability for ER of ~40% (Hawn, Overstreet, Stewart, & Amstadter, 2015; Wang & Saudino, 2013). Wang and Saudino (2013) examined toddlers' ER, measured by the Bayley's behaviour rating scale and WM, measured by a pictorial memory span task and found a significant phenotypic and genotypic correlation between ER and WM. Individual differences in ER were significantly influenced by genetic factors and accounted for 43% of the variance in the model, shared environmental effects were only 9%, with 48% of variance accounted for

by non-shared environment. They found a high genetic correlation between traits (r_g = .76 - 86) and non-significant environmental effects suggesting that it is mostly genetic factors that contribute to covariation between EF and ER (Wang & Saudino, 2013). A significant genetic covariance between EFs and psychopathologies has also been found (Johnson, Whisman, Corley, Hewitt, & Friedman, 2014).

1.7.2. Candidate genes

The candidate gene approach is a hypothesis-driven method that identifies theoretically plausible genes based on known biological relationships or previous linkage with the trait of interest, and investigates the effect of variation that this gene has on behaviour. Popular candidate genes for behavioural studies have been part of the monoaminergic systems – primarily dopamine and serotonin – as these systems are known to regulate cognition, emotion, arousal and certain types of memory (Hawn et al., 2015; Robbins & Arnsten, 2009). The literature in this field is too vast to summarise fully but primarily candidate gene studies have reported associations between the repeat variant 5-HTTLPR located in the gene SLC6A4 – a gene modulating serotonin transcription – and anxiety, increased amygdala activation, neuroticism and harm avoidance (Hariri & Holmes, 2006; Heinz et al., 2007; Lesch et al., 1996; Whalen & Davis, 2001). Different interpretations of these results have been put forward: (1) that individuals with reduced transcriptional activity (short allele carriers) preferentially engage systems which enhance the fear response when exposed to stress (Drabant et al., 2012; Whalen & Davis, 2001); (2) that they have a tonic heightened sense of vigilance (Heinz et al., 2007); or (3) that gene-environment interactions mean that insecurely attached short allele carriers develop poor ER abilities, while those who are securely attached develop as good regulatory ability as long allele homozygotes (Kochanska, Philibert, & Barry, 2009).

Dopamine-related genes have also been popular candidates for investigation (Gadow, Pinsonneault, Perlman, & Sadee, 2014). The gene encoding monoamine oxidase A enzyme (MOA-A) which regulates the breakdown of serotonin and dopamine has been associated with aggressive behaviour (Buckholtz & Meyer-Lindenberg, 2008; Buckholtz et al., 2007; Caspi et al., 2002) and working memory ability, which in turn predicted externalising behaviour (Ziermans et al., 2012). Genetic variants of catechol-O-methytransferase (COMT; an enzyme affecting dopamine levels in the PFC) have been associated with individual differences in verbalising of emotions, emotional awareness (Swart et al., 2011), anger perception bias (Gohier et al., 2014), and also cognitive functioning (Dumontheil et al., 2011; Egan et al., 2001).

However candidate gene studies have struggled to consistently replicate findings (Beevers, Wells, & McGeary, 2009; Buckholtz & Meyer-Lindenberg, 2008; Canli & Lesch, 2007; Hariri & Holmes, 2006) and selected variants have rarely emerged as robustly significant associations in later unbiased whole-genome based approaches, leading to caution when interpreting these results (Hirschhorn, Lohmueller, Byrne, & Hirschhorn, 2002). These more recent studies have also highlighted how intricate the genetic architecture contributing to complex traits is and how little knowledge we have of how genes (or non-coding variants) affect these traits, making it likely that even if these candidate genes are legitimate associations, they will probably only contribute a very small amount of variance to a trait (Hariri & Holmes, 2006). As such there has been a move away from candidate gene studies towards data-driven hypothesis-free genome-wide association (GWA) analyses.

1.7.3 Genome-Wide Association Studies (GWAS)

GWA is a population-based approach that characterises common genetic variation distributed throughout the human genome in order to identify specific common genetic variants that contribute to the trait of interest. In the GWA approach, 1+ million common genetic variants – typically single nucleotide polymorphisms (SNPs)[3] – are characterized in very large samples of unrelated individuals, and each SNP is systematically tested for association with the measured trait or outcome (Hirschhorn & Daly, 2005). Because the SNP tested has already been mapped to a specific chromosomal location, identification of a statistically significant signal immediately indicates the genomic location of the genetic variant(s) and allows researchers to hone in on the associated biological pathways and functions (Visscher, Brown, McCarthy, & Yang, 2012). Crucially, this approach requires no prior hypotheses or assumptions about the chromosomal location or biological function of SNPs that influence the trait, and instead allows researchers to systematically search the entire genome in an unbiased manner. However, this 'atheoretical' approach comes at a cost; due to the large number of SNPs being tested for association in a GWA study, a stringent p value of $p \leq 5 \times 10^{-8}$ has been established as the threshold for statistical significance (Dudbridge & Gusnanto, 2008). This is to guard against chance findings that fail to replicate in subsequent studies and avoid the proliferation of 'false positive' results. Since 2005, GWAS have shown that complex traits are highly polygenic, that is there are many alleles influencing behavioural traits - and that effects sizes of associated variants are generally very small (typically <0.5% per variant) (Visscher et al., 2012).

[3] Single nucleotide polymorphisms, most commonly known as SNPs, are single base changes in the DNA sequence contributing to variation between individuals

The data generated by GWA analyses also allow for gene-based association testing, estimation of SNP heritability (h^2_{SNP}), and generation of polygenic risk scores (PRS). SNP heritability is the amount of variance in a phenotype explained by summing all the individual SNP effects in a GWA analysis. The two most popular methods for estimating SNP heritability are (1) genome-based restricted maximum likelihood (GREML) and linkage disequilibrium[4] (LD) score regression. GREML uses whole-genome genotyping data to create a genetic relatedness matrix for the sample and then uses a mixed linear model to estimate SNP heritability (Yang, Lee, Goddard, & Visscher, 2011). In contrast, LD score regression side-steps the requirement for raw genotype data and instead uses GWAS summary statistics and the expected relationship between the effect size of a SNP and its LD score to estimate inflation caused by genetic association (Bulik-Sullivan, Loh, et al., 2015). Other methods based around these two approaches are also available, and are reviewed here (Dudbridge, 2016). Polygenic risk scores (Dudbridge, 2013) are typically used to demonstrate polygenic influence on a trait. They do this by examining the extent to which genetic risk for one trait (the 'discovery' or 'training' GWAS) can predict phenotypic variance in second independent sample for the same trait ('target' sample) or a related different trait. The latter comparison allows for the assessment of pleiotropic effects. PRS's are created using the summary statistics from well-powered discovery GWAS and the genome-wide data from an independent 'target' sample. GWAS summary statistics provide information about each SNP in the study regarding the effect allele (that which is contributing to an increase in phenotype) and the size of the effect. This information can then be used to create an aggregate score for each individual, based on his or her own genetic information.

1.7.3.1 GWAS of cognitive abilities

Well-powered molecular genetic studies of cognition have tended to focus on general cognitive ability or 'g', which is the first principal component derived from a range of neurocognitive tasks and often includes working memory, fluency, processing speed and declarative memory tasks. The first sizable GWAS of general cognitive ability used 7,100 participants and failed to find any genome-wide significant associations. However, they were able to estimate a SNP heritability of 35% (Kirkpatrick, McGue, Iacono, Miller, & Basu, 2013) demonstrating that although common genetic variants were able to explain a considerable amount of the variance in cognitive ability, individual effect sizes would

[4] Linkage disequilibrium is the genetic correlation between SNPs which represents the non-random association of alleles. Generally, alleles that are closer together are inherited more frequently together than those further apart.

likely be very small, which by this time was an increasingly common finding in behavioural genetics (Davies et al., 2011). A large meta-analysis of GWAS across 24 cohorts (N= 35,298) by the Cognitive Genetics Consortium (COGENT) consortium succeeded in uncovering two independent SNP associations in the genes *CENPO* and *LOC105378853*. They also estimated a slightly smaller SNP heritability of 22% (Trampush et al., 2017). A larger meta-analysis of 31 GWAS cohorts (N = 53,949) found three independent genome-wide significant associations close to the genes *MIR2113*, *AKAP6* and *APOE/TOMM40*. They also found one significant gene-based association with *HMGN1*. Gene-based analyses are a type of secondary analysis which combines individual SNP effects across a gene. SNP heritability was estimated at 28-29% and a PRS was able to predict ~1.2% of the variance in cognitive ability in an independent sample. The same study also performed 29 hypothesis-driven tests for genes that had been previously associated with Alzheimer's disease and replicated associations for the genes *TOMM40, APOE, ABCG1* and *MEF2C* (Davies et al., 2015). The most recent GWAS meta-analysis of 78,308 individuals found 18 SNP associations and 30 gene-based associations, and a h^2_{SNP} estimate of 20% (Sniekers et al., 2017). This study has since been combined with one examining the correlated phenotype 'Years in Education', which increased the sample size to 248,482 and found 187 independent SNP based associations and 538 gene-based associations (Hill et al., 2018). Together these studies demonstrated that with very large (>30,000) samples associations can be found, but it is worth noticing that as sample sizes increase, SNP heritability estimates reduce as the phenotypes used become increasingly impoverished and inevitably absorb more noise.

Only a handful of GWAS studies have investigated associations with specific EFs due to the large sample sizes necessary. A small series of studies have looked at latent measures of processing speed across four cohorts (N = 305 – 1,659). Each cohort used different visuospatial and verbal speeded tasks with key press responses to create their processing speed phenotype measure. A number of suggestive associations ($p < .1E^{-5}$) were found in genes including *DCDC2*, *TRIB3* and *NFKBIL1* (Luciano et al., 2011) however the small sample size means results should be interpreted with caution. Using multiple measures to create specific latent processing speed factors however may help to boost power as has been found in the twin literature. A much larger sample (N = 32,070) using only a single measure of processing speed subsequently found one significantly associated SNP in the *CADM2* gene. The same study failed to find any associations with the inhibitory control Stroop task (N = 12,866), two trail-making switching tasks (N = 5,429, N = 6,210) or two verbal IQ tasks (N = 13,454, N = 6,383) (Ibrahim-Verbaas et al., 2016).

There have also been some attempts at studying well established discrete working memory measures, which have found bigger SNP heritability estimates than the larger studies (Davies et al., 2016). In a sample of 2,298 individuals, heritability of single measures of the N-back working memory task ranged between 24% (2-back RT) to 41% (2-back-0-back accuracy) (Vogler et al., 2014). This demonstrates how SNP heritability estimates can be influenced by the reliability of a measure. Small samples often have better phenotypes but larger standard error, whereas larger samples have reduced estimates, but also reduced standard error. Separate GWAS of verbal-numerical reasoning, short-term memory and reaction time were performed in the large UK Biobank sample (N = 112,151). Three independent significant associations were uncovered with verbal-numerical reasoning and two with reaction time, but no associations were found with short-term memory. SNP-based heritabilities were estimated at 31% for verbal-numerical reasoning, 5% for memory and 11% for reaction time (Davies et al., 2016). This SNP-based heritability for short-term memory was significantly lower than the n-back measures and so emphasises the need both for reliable measures and large samples.

Smaller GWAS have employed more complex study designs that incorporate neuroimaging as an intermediary phenotype. For instance, a GWAS study of N-back related fMRI activation that used a 2back>0back contrast in 46 regions of interest from 679 healthy twins and siblings (of which 97 participants formed a replication sample) failed to identify any significant associations. However, a suggestive signal was reported for a SNP located in the *BANK1* gene, which is linked with the regulation of the dopamine-signalling pathway and associated with signal change in the left supra-marginal gyrus (Blokland et al., 2016). The association between *BANK1* and cognitive ability was recently replicated in the previously discussed meta-analysis on intelligence, suggesting that it is not a false positive finding (Hill et al., 2018). A small GWAS of only 333 individuals examined immediate recall/short-term memory, and found a suggestive association ($p < 5 \times 10^{-5}$) with the SNP rs10930201 located in the *SCN1A* gene, which has previously been associated with seizures (Parihar & Ganesh, 2013). The gene was also examined in a small neuroimaging study (N = 24) that found differences in frontal activation between homozygote major allele carriers and heterozygotes during the N-back task (Papassotiropoulos et al., 2011). However, suggestive findings from these smaller studies require caution in interpretation until they are rigorously replicated.

1.7.3.2 GWAS of traits related to emotional regulation

To the best of our knowledge there have been no GWAS performed that focus specifically on ER, however there have been studies focused on related traits. For example, a recent

UK Biobank study (N = 157,366) assessing both anxiety within the normal range as well as clinical anxiety found that heritabilities ranged widely from 4% for population level anxiety traits, to 32% for predicted generalised anxiety disorder, which is very close to the twin estimate (Hettema et al., 2001). They also found three independent SNP associations for generalised anxiety, but none for anxiety in the general population, although the two phenotypes were significantly genetically correlated 20% - 30% (Purves et al., 2017). A meta-analysis of anxiety disorders across nine cohorts (N= ~18,000 individuals) found two further SNP associations and four gene-based associations (Otowa et al., 2016). They performed SNP heritability analyses in one of the samples using two phenotypes and two methods. The first compared those with an anxiety disorder with 'supernormal' controls (case-control approach, N = 7,832), the second used a continuous confirmatory factor analysis score of anxiety (N = 5,379). The case-control and GREML method yielded the highest estimates in both scenarios (case-control: GREML 14%, LDscore 10%; factor-score GREML 11%, LDscore 7%) demonstrating that although latent traits may be more powerful than single measures, they are not necessarily more powerful than case-control designs.

GWAS investigating temperament-based measures of emotional reactivity and regulation (traits) have been more fruitful than those using state-based measures. For example, a study looking at proneness to anger (N=8,747) using angry temperament and angry reaction as phenotypes (i.e. state and trait measures) demonstrated that angry temperament had more power (greater inflation in the Q-Q plot), but that the sample size still only allowed for one association with temperament ($p = 4.6 \times 10^{-7}$) (Mick et al., 2014). Cloninger's temperament scales, which have an estimated twin heritability of between 30-60%, are believed to be the basic biologically-driven traits that underlie variation in personality. These traits include harm avoidance, novelty seeking, reward dependence and persistence. The scales were investigated in a GWAS of 5,117 individuals but no significant association was found (Verweij et al., 2010). Other attempts to use more biologically-driven phenotypes such as a case (N = 39) control (N = 29) GWAS of amygdala activation in youths with bipolar disorder (BD) have shown some promise (Liu et al., 2010). Right amygdala activation when participants rated how hostile a series of emotional and neutral faces were (vs. how wide the face's nose was) most strongly associated with a SNP in *DOK5* (rs2023454, $p = 4.9 \times 10^{-7}$). The SNP accounted for 33% of the variance in amygdala activation in youths with BD and 12% of the variance in healthy controls (Liu et al., 2010).

A genome-wide association study performed in 1,249 adults with externalising disorders was used to create polygenic risk scores to predict externalising behaviours in young

adults, and was found to explain 6% of the variance (Salvatore et al., 2015). A GWAS meta-analysis of preschool aggressive behaviour found SNP heritabilities ranging between 10 - 54% (Pappa et al., 2016), whilst another GWAS of preschool internalising found a similar range of estimates from 13 - 43% (Benke et al., 2014). Neither study identified genome-wide significant SNP associations. There have been large GWAS of other traits related to emotion such as subjective well-being (N = 298,420), depressive symptoms (N = 161,460) and neuroticism (N = 170,911). These found three variants associated with subjective well-being, two with depressive symptoms and 11 with neuroticism (Okbay, Baselmans, et al., 2016).

1.7.3.3 Polygenic risk scores investigating associations between phenotypes

Studies have started to used polygenic risk scores (Dudbridge, 2013) to look at the extent to which genetic risk for one trait can predict phenotypic variance in another to test the genetic relatedness between correlated traits. Benca et al. (2016) hypothesised that if EF deficits are a risk factor for psychiatric disorders then genetic risk for disorders should predict experimental measures of EF in a non-clinical population (a so-called 'reverse phenotype' approach). They created polygenic risk scores for a number of psychiatric disorders using publicly available GWAS summary statistics and used these to predict executive function ability in their sample. The sample size was modest (N=386) and they performed a large number of tests, and after correction for multiple testing no robustly significant results remained. However there were indications of positive associations between Major Depressive Disorder (MDD) and common EF, between Attention-Deficit and Hyperactivity Disorder (ADHD) and schizophrenia and updating, and a negative association between schizophrenia and IQ (Benca et al., 2016).

Martin et al. (2014) created an ADHD polygenic risk score to predict IQ (derived from the short form WISC-III), WM (digit span and counting span at age 10), IC (Opposite worlds task) and facial emotion recognition (DANVA) in the ALSPAC sample with the hypothesis that genetic risk for ADHD would be related to the lower end of the normal distribution of cognitive traits. A latent trait score of 'ADHD-ness' was created using the inattention and hyperactive-impulsive scales of the Development And Well-Being Assessment (Goodman, Ford, Richards, Gatward, & Meltzer, 2000), the Skuse social disorders communication checklist, and the Children's communication checklist (Bishop, 1998). The ADHD polygenic risk score was associated with lower IQ (R^2 = .003), and WM (R^2 = .001) performance. No relationships between IC or emotion recognition were found (Martin, Hamshere, Stergiakouli, O'Donovan, & Thapar, 2014).

In summary, EF and affective traits are heritable (Friedman et al., 2008; Polderman et al., 2007) and, on the whole, share a significant proportion of their genetic variance (Wang & Saudino, 2013) However, these are complex traits and therefore highly polygenic, with likely small effects sizes of common individual genetic variants. Molecular studies examining cognition have tended to focus on general cognitive ability, and report SNP heritability estimates of up to 35% (Kirkpatrick et al., 2013). All EF GWA studies reported to-date have been limited to small sample sizes or individual EF measures (i.e. not latent measures). No GWAS of ER has been reported in the literature, but temperament-based trait-like measures have identified some promising individual SNP associations (Okbay, Baselmans, et al., 2016). In order to be able to understand relationships between EF and emotion-related traits, it is important to understand how they relate genetically, as this provides clues as to their origins and to helps us understand the development of maladaptive behaviours (Graziano et al., 2007; Gross & Munoz, 1995).

1.8 Academic Achievement

As demonstrated by the schematic presented at the beginning of this chapter, one aim of this thesis was to bridge levels of investigation of individual differences in EF and ER. Specifically, we aimed to consider the relationships between EF and ER during adolescence, the genetic predictors of EF and ER, and how genetic, cognitive and behavioural data could improve our understanding of individual differences in academic achievement - a specific example of a real-life outcome. In this section the literature on the cognitive, affective and genetic predictors of academic achievement will be reviewed.

1.8.1 Cognitive predictors of academic achievement

A number of cognitive abilities have been proposed to explain individual differences in academic achievement (AA), including IQ, EFs and attention (Best, Miller, & Naglieri, 2011; Cragg & Gilmore, 2014; St Clair-Thompson & Gathercole, 2006).

Intelligence is the most well-established predictor of AA, with correlations ranging from .3 to .7 (see Roth et al., 2015 for review). The close relationship between AA and non-verbal IQ has been replicated in at least 40 countries across the world (Lynn & Mikk, 2007). A meta-analysis of 162 studies with an international sample of more than 100,000 individuals (mean age of 13.9 years) found an overall correlation of .54 between IQ and AA, across academic subjects and ages. Moderator analyses indicated that verbal IQ was a higher predictor (.53) than non-verbal IQ (.44), and that the association between IQ and

academic attainment was lower in elementary (.45) than Middle and High school (.54 and .58 respectively), which did not differ (Roth et al., 2015). These findings have been replicated in other large cohort studies (Laidra, Pullmann, & Allik, 2007). Furthermore verbal and non-verbal IQ tend to show slightly different associations with different academic subjects, with highest correlations between maths and non-verbal IQ, and between English and verbal IQ (Alloway & Alloway, 2010).

EFs have been shown to predict academic achievement independently of IQ both through individual task measures and latent factors (Alloway & Alloway, 2010; Cragg & Gilmore, 2014; Rhodes et al., 2016). A large number of cross-sectional studies have provided evidence that WM and inhibitory control account for unique variance in arithmetic, beyond variance explained by IQ, age, processing speed or reading, in a wide range of age groups (e.g. Monette, Bigras, & Guay, 2011; Bull & Scerif, 2001; see Cragg & Gilmore, 2014 for review). In general, associations between WM and maths and literacy have tended to be more consistent across ages, while IC may be a stronger predictor of pre-school (Blair & Razza, 2007; Espy et al., 2004), but not necessarily later primary school, maths and literacy (Bull & Scerif, 2001). Evidence is more limited regarding predictors of science attainment. However, using a large task battery including measures of both response and semantic inhibition, a cross-sectional study in 10 and 11 year-olds found a relationship between English, maths and science attainment and IC (St Clair-Thompson & Gathercole, 2006). Some of the associations between EFs and academic attainment are observed across cultures. For example, Lan et al. (2011) recruited 119 Chinese and 139 American children and found that while WM was the best predictor of complex maths and reading tasks in pre-schoolers, IC (measured with a response inhibition task) predicted basic maths tasks such as counting abilities (Lan, Legare, Ponitz, Li, & Morrison, 2011).

There are few longitudinal studies of EFs as predictors of academic attainment, but the results that are available support the cross-sectional data, with WM and IQ found to uniquely predict maths and reading outcome in primary and secondary school (Alloway & Alloway, 2010; Dumontheil & Klingberg, 2012; Mazzocco & Kover, 2007). However, as these studies have tended not to control for early academic attainment, it is unclear whether EFs and IQ continue to uniquely influence academic outcomes beyond early effects. One study by Stipek and colleagues suggest that on the contrary, although working memory and attention are important in early attainment, there is a 'fade-out' by adolescence (Stipek & Valentino, 2015). This is an important issue, as a better understanding of the predictors of learning and academic attainment throughout the school years could inform the potential of targeted interventions beyond the early years (Heckman, 2006).

While the studies reviewed above collected various measures of academic attainment, few have systematically investigated the specific influence of IQ and EFs across academic subjects. In their large meta-analysis, Roth et al. (2015) found that across age groups IQ predicted maths and science attainment and languages and social sciences to a similar extent, with correlations of .43 - .49. Best and colleagues found that while the relationships between EF and academic attainment changed over time between 5 and 17 yrs of age, the pattern of these correlations was similar for maths and reading, leading the authors to conclude that a domain-general mechanism must be operating across academic subjects (Best et al., 2011). In contrast, Latzman et al. (2010) found different associations between cognitive abilities and different academic subjects in a sample of 11-16yrs males. Using the Delis-Kaplan Executive Functions System (Delis, Kaplan, & Kramer, 2001), the study tested the association between three derived EF variables (monitoring, conceptual flexibility and inhibition) and reading, maths, social studies and science attainment, covarying for IQ. Monitoring was found to be related to reading and social studies, conceptual flexibility to reading and science, and inhibition to maths and science, suggesting some specificity of the relationship between cognition and individual academic subject attainment (Latzman, Elkovitch, Young, & Clark, 2010).

In summary, IQ reliably predicts achievement across cultures (Lynn & Mikk, 2007), explains more variance with age (Laidra et al., 2007; Roth et al., 2015) and highest correlations are reported between non-verbal IQ and maths, and between verbal IQ and English (Alloway & Alloway, 2010). EFs also predict academic attainment independently of IQ, both through individual task measures and latent factors (Cragg & Gilmore, 2014; Rhodes et al., 2016) with working memory and inhibitory control predicting arithmetic, beyond IQ, age, processing speed or reading (e.g. Monette, Bigras, & Guay, 2011; Bull & Scerif, 2001) and across cultures (Lan, Legare, Ponitz, Li, & Morrison, 2011). Associations between WM, maths and literacy are found cross-sectionally (Blair & Razza, 2007; Espy et al., 2004) and longitudinally (Dumontheil & Klingberg, 2012; Mazzocco & Kover, 2007). However, it is unclear whether EFs and IQ continue to uniquely influence academic outcomes beyond early effects, and if they do whether these effects are similar across academic subjects (Best et al., 2011) or specific (Latzman, Elkovitch, Young, & Clark, 2010).

1.8.2 Affective predictors of AA

The research looking at the role of emotion and ER in academic attainment is rather more mixed. Rationale for the role of ER in the classroom is strong: individuals who are overcome or distracted by their emotions are unlikely to be able to concentrate on the

teacher or their work (Graziano et al., 2007). However, depending on how ER is measured, the extent to which it remains predictive of AA after controlling for cognitive variables varies. Brock and colleagues looked at the differential contributions of 'hot' and 'cool' EF in kindergarten. Hot EF was measured by two tasks involving a motivationally salient object such as a toy that children should attend to but not engage with, 'cool' EF was measured by an inhibitory control and a sustained attention task. They compared a one-factor EF model with a two-factor 'hot' and 'cool' EF model and the two-factor model fit better, with a moderate correlation (r = .50) found between factors. 'Hot' EF was less correlated with academic outcomes (r = .12 - .19) than 'cool' EF (r = .37 - .46), and when modelled together, only 'cool' EF predicted academic outcomes (Brock, Rimm-Kaufman, Nathanson, & Grimm, 2009). A study by Howse and colleagues looked at kindergarten AA, ER and self-regulation. They found that lab-based measures of ER did not correlate with AA but parent–report measures did. However, after controlling for self-regulation, using a questionnaire which asked teachers questions about the child such as "likes to do challenging tasks", "concentrates well and is not easily distractible when doing a task", ER no longer predicted AA (Howse, Calkins, Anastopoulos, Keane, & Shelton, 2003).

EF and self-regulation are tightly related concepts and self-regulation is sometimes thought of as a broader umbrella term under which EF and ER sit (Barkley, 2001). The studies summarised above suggest that the relationship between ER and AA may function via cognitive control. On the other hand, Graziano and colleagues found that after controlling for IQ, ER as measured by the Emotion Regulation Checklist (Shields & Cicchetti, 1997) remained a significant predictor of early years AA in maths and literacy. They had hypothesised that this would be mediated by teacher interaction or behavioural problems but found this not to be the case (Graziano et al., 2007). This suggests that either IQ is not explaining the same variance as ER and EF, or perhaps that this measure of ER is assessing something beyond EF.

It is commonly found that externalising but not necessarily internalising behaviours uniquely predict under-achievement across school age children (6-18 yrs) (Nelson, Benner, Lane, & Smith, 2004; Risi, Gerhardstein, & Kistner, 2003). However it has been shown that externalising behavioural problems, such as conduct disorders, are often comorbid with ADHD, and that individuals with externalising behavioural problems but without ADHD, and specifically without attentional problems, do not under-achieve (Frick et al., 1991). A large study using six population-based cohorts in the United States, Britain and Canada looked at the best predictors of schooling outcomes during childhood (primary school) including prior attainment and measures of attention and socioemotional behaviours (including measures of internalising and externalising). They

found that prior school attainment measures were the best predictors, that attention had much smaller but significant effects but that emotional measures predicted only ~0.01% variance and were non-significant (Duncan et al., 2007). Others have argued that although inattention may be the main link between externalising and under-achievement during childhood, by adolescence a relationship can also be found with aggressive behaviour (Hinshaw, 1992). A longitudinal study looking at 205 children over four time points found that early externalising, predicted later under-achievement in adolescence and under-achievement predicted subsequent internalising behaviours (Masten et al., 2005). Therefore, it could be that the mechanism by which emotion interferes with AA changes over development.

Anxiety, although often categorised within internalising, has also been studied separately in regard to education and could be argued to play either a facilitating or debilitating role in achievement, much like stress. Again this is hypothesised to function via its impact on cognition; either positively by focusing attention (Wang et al., 2015), or negatively by decreasing attentional control (Eysenck, Derakshan, Santos, & Calvo, 2007). Both state and trait anxiety have been associated with poorer performance in English, maths and science (Rajchert, Zoltak, & Smulczyk, 2013). However, when other factors are considered (such as motivation), this potentially alters the relationship. For example, studies focused on maths anxiety found an inverted U-type relationship where no anxiety or high anxiety states are detrimental to maths performance, but where some maths anxiety can be beneficial in directing attention but only when individuals are sufficiently motivated (Wang et al., 2015). The effect of specific maths anxiety appears to be separate from trait anxiety (Wang et al., 2014).

Another way in which emotion is thought to influence attainment is via more 'approach' like behaviours which contribute to a social attitude that positively engages teachers and encourages more attention (Blair, 2002; Eisenberg, Sadovsky, & Spinrad, 2005). However there is little evidence to show this is the case and if anything extraversion is often negatively associated with attainment (Chamorro-Premuzic & Furnham, 2003b; O'Conner & Paunonen, 2007). Conscientiousness on the other hand has been shown to positively predict achievement. After controlling for the other big five personality dimensions, conscientiousness and ER predicted school attainment outcome. Conscientiousness and ER showed a similar pattern of correlations with school outcomes although only a correlation r =.30 with each other (Ivcevic & Brackett, 2014). Similar results were found by Rimfeld and colleagues, who found conscientiousness predicted GSCE scores (Rimfeld, Kovas, Dale, & Plomin, 2016).

To summarise, the role of emotion in AA is rather more mixed than that of IQ and EF. There is evidence that the relationship may be mediated by cognitive ability (Brock et.al., 2009; Howse et.al., 2003) or moderated by motivation (Wang et al., 2015) or that in some instances academic under-achievement may be the cause of emotional problems (Masten et al., 2005). Some have found evidence for the role of emotion regulation in early years AA (Graziano et.al., 2007) but again these studies do not compare differential effects of emotion on different subjects.

1.8.3 Genetic Research of Academic Attainment

The molecular genetic study of AA and the overlap with cognitive and emotional variables is still very much in its infancy, and GWASes of individual academic subjects are sparse. The first GWAS of mathematical ability, the most studied academic subject, looked at high versus low ability using a sample of 2,365 individuals and found no significantly associated SNPs, and one suggestive association on chromosome 11 (rs10501162) (Docherty et al., 2010). The second study followed a similar process of looking at high and low mathematical ability with a smaller sample of 602 participants, controlling for verbal ability. Again this study failed to find any genome-wide significant associations (Baron-Cohen et al., 2014). In the same year, Davis et al. (2014) carried out a GWAS and multivariate twin study of both mathematical and reading ability in a sample of 2,794 12-year-olds. No genome-wide significant associations were found, however the twin study estimated a 66% and 51% heritability for reading and maths respectively, and SNP-based heritability estimates of 27% for reading and 52% for maths. Phenotypically the two traits were correlated ~0.60, and had a bivariate twin heritability of 0.64 (0.56-0.72) and bivariate SNP heritability of 0.74 (0.32 - 1) – that is, of the estimated heritability, just over half was shared between the two subjects (Davis et al., 2014). Overall these results indicate high heritability, polygenicity, as well as significant contribution of common genetic variation between the two academic subjects and unique genetic effects. All of the studies discussed have been performed on Western populations, which limits the generalisability of the findings to non-Caucasian populations. This was recently addressed in a GWAS of a Chinese sample (n= 998), with the use of a small sample justified by the potential insights gained by examining a population with a different ancestral history. The authors report several associations with maths attainment, but these need to be evaluated with caution due to the small sample size (Chen et al., 2017). However, the premise of the study raises some interesting questions about population-specific variants and how the genetic architecture of AA may differ across populations.

English ability has been studied less as an academic subject and more in terms of reading and language ability and disability. Gialluisi et al. (2014) used two samples, one smaller

sample of 1,862 of people with language difficulties and their siblings, and a larger 6,434 typical population-based sample, to look at genetic correlates of language ability. They used the first principal component from a PCA performed on a collection of language tests and as with the maths studies summarised above, they failed to find any genome-wide significant SNPs (Gialluisi et al., 2014). On the whole, these studies have been fairly small, (< 3,000) and have not looked at population-based standardised assessments of school level English or maths ability.

In the last few years there has been a move away from looking at specific academic subjects or abilities and towards a more general educational attainment phenotype. There are a number of reasons for this. Firstly, early studies showed that effect sizes for educational and cognitive traits were likely to be small requiring large sample sizes to uncover significant associations (Davies et al., 2011). Secondly, both twin and early molecular studies showed that there was a large amount of overlap between genes for different academic subjects and cognitive ability, which were titled 'generalist genes' (Kovas & Plomin, 2007). With the advent of large population-based genetic collection such as in the UK Biobank, researchers were in search of phenotypes that could characterise this generalist nature and give large sample sizes, allowing the detection of smaller effects and so began a series of studies looking at demographic variables such as 'number of years in education', now labelled for GWAS purposes "Educational Attainment".

The first large Educational Attainment (EA) GWAS (N=126,559) found three independent genome-wide significant SNPs with small estimated effects sizes of approximately 1 month of schooling per allele. Genes near the associated loci had been previously associated with health and cognition (Rietveld et al., 2013), demonstrating overlaps between education, cognitive ability and health (Trampush et al., 2015). This was followed three years later by a study in 293,723 individuals, more than doubling the first study, and this found 74 loci associated with years in education. A large number of these loci were found in regions involved in regulating gene expression in the foetal brain development (Okbay, Beauchamp, et al., 2016). This year the EA GWAS had a sample of over 1 million participants, finding 1,271 independently associated loci and explaining 11-13% of the variance in educational attainment, and 7-10% of the variance in cognitive performance. This study identified genes expressed postnatally in the central nervous system and involved in functions such as neurotransmitter secretion and synaptic plasticity. The other interesting finding was that although the polygenic risk score created from this GWAS predicted up to 13% of the variance in AA in a white Western population, in an African American population this dropped significantly to 1.6% (Lee et al., 2018).

Beyond cognitive performance, the EA GWAS genetically correlates with or predicts affect-related traits, including SDQ scores on the Strength and Difficulties questionnaire (Goodman, 1997), depressive symptoms, callous and unemotional traits and ADHD (Krapohl et al., 2015; Zeeuw et al., 2014).

However, despite the success of these studies looking at common variance, and the strong evidence for generalist genes playing a large part in academic attainment, cognitive ability and affective behaviour, there is also evidence for specificity in the genetic profile of individual subjects and cognitive ability. When controlling for IQ, bivariate twin estimates of English, maths and science, suggest that just over half of the remaining heritability was shared between subjects (Maths - English (0.54), Science - English (0.64), Science - Maths (.69)) (Rimfeld, Kovas, Dale, & Plomin, 2015), meaning that just under half is not shared across subjects. When controlling for general intelligence as well as reading ability, maths still retains a heritability of .44 (Tosto, Malykh, Voronin, Plomin, & Kovas, 2013), again suggesting a significant amount of variance not shared between subjects.

Although there is strong evidence for a great deal of common genetic variance between EFs, there is also evidence for specificity (Friedman et al., 2008). Health, well-being and personality among other factors have all been shown to genetically influence achievement over and above intelligence and may contribute to shared or specific variance between subjects (Krapohl et al., 2014). As yet there have been no genome-wide association studies looking at the genetic differences between subjects and how these differences may be mediated by different cognitive or emotion-related genetic effects.

1.9 Thesis overview

This thesis explores the relationship between emotion and cognition focusing on the adolescent period, using (for the most part) the Avon Longitudinal Study of Parents and Children (ALSPAC) – a longitudinal population-based cohort. The thesis includes four chapters which investigate the relationship between emotion and cognition during adolescence and two chapters which examine how these interact in a context in which both are considered to be important: AA. The overarching goal of the thesis was to test, in a large representative sample, some of the hypotheses in the literature regarding the impact of EF on emotional behaviour across adolescence. The aim was to understand how EFs relate to emotional behaviours at this time, what the direction of this effect may be and whether this relationship can be traced to common genetic underpinnings.

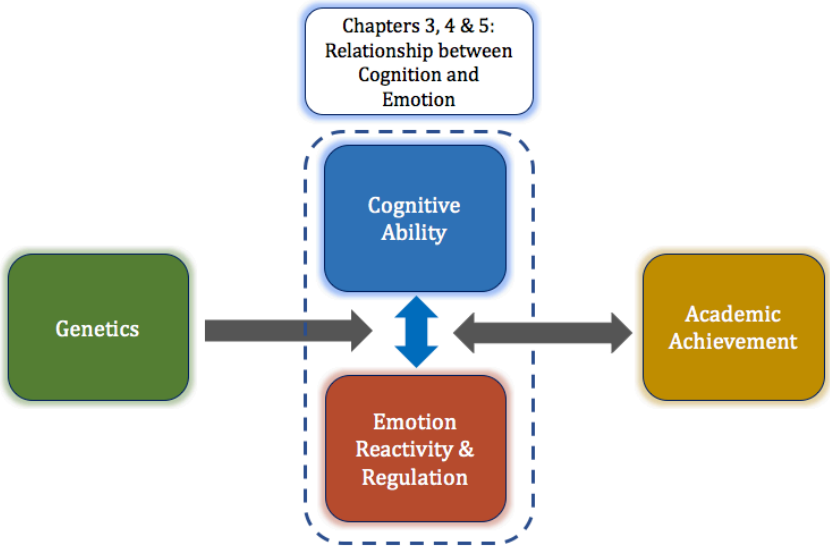


Figure 1.2: *shows how Chapters 3, 4 and 5 relate to the main thesis schematic plan. These chapters aim to understand the relationship between cognitive and emotional and behavioural regulation measures during adolescence. Blue arrows indicate the relationships that are assessed and grey arrows indicate those that are not.*

1.9.1 Chapter 3

The first study sought to broadly characterise cognitive ability and trait-like emotional behaviour across adolescence using a dimension reduction method. The aims of this study were to:

1) understand the main axes of variance in a range of different and repeated questionnaires measuring different aspects of emotion and regulation.
2) assess the relationship between variation in cognitive ability and emotional outcomes during adolescence by testing both linear and quadratic patterns of associations.

1.9.2 Chapter 4

An independent adult sample was used in this chapter to model the relationship between emotion traits from Chapter 3, established models of ER, and an emotional n-back task. The aims of this study were to:

1) validate our emotion measures against established ER strategies

2) establish whether the relationship been emotion measures and EF was stronger in a condition where there were emotional distractors
3) test whether ER strategies were more associated with EF than emotion measures

1.9.3 Chapter 5

This chapter tested the directionality of the correlations between IC and WM on one hand and internalising and externalising behaviours on the other during adolescence. This chapter employed a longitudinal cross-lag design, which controls for within time covariance, in order to assess the directionality of adolescent-specific changes in emotion and executive function. The aims of this study were to:

1) test whether associations between emotion and EF were stronger when using single measures rather than latent models
2) assess which measures predicted each other over time between early and late adolescence or whether there were bi-directional effects
3) investigate how internalising and externalising change over time during adolescence.

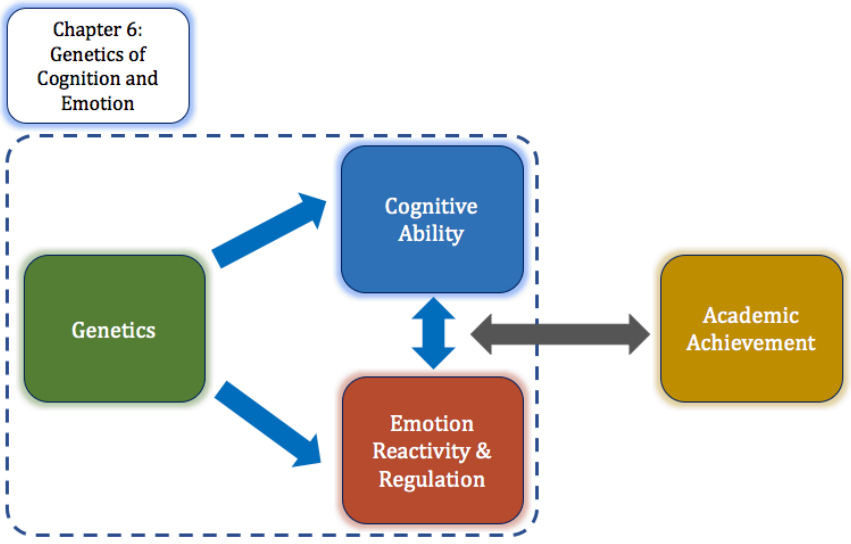


Figure 1.3: *shows how Chapter 6 relates to the main thesis schematic plan. This chapter aims to uncover genetic variation associated with cognitive and emotional and behavioural regulation traits. Blue arrows indicate the relationships that are assessed and grey arrows indicate those that are not.*

1.9.4 Chapter 6

In this chapter, six genome-wide associations studies of the cognitive and emotion traits established in Chapter 3 were performed in order to assess their genetic relationships, in

addition to evaluating their relationship with related traits using publicly available GWAS summary statistics. The aims of this study were to:

1) perform the first GWAS of latent executive function measures
2) perform possibly the largest GWAS of internalising and externalising behaviours
3) estimate genetic relationships within and across cognitive and emotional traits in order to understand the extent to which phenotypic covariation is genetically mediated.

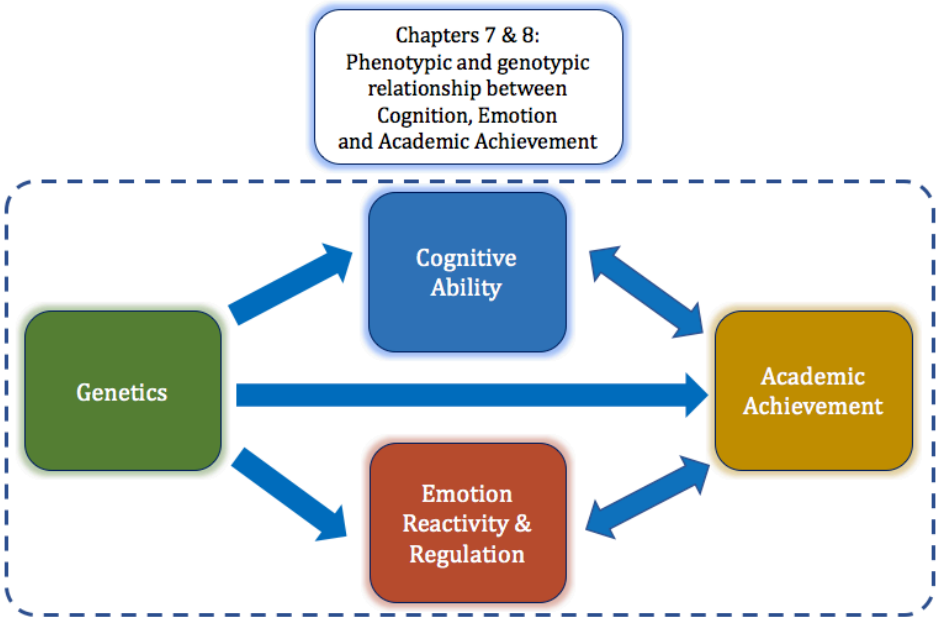


Figure 1.4: *shows how Chapters 7 & 8 fit into the main thesis schematic plan. These chapters aim to understand how emotion and cognition might influence academic outcomes both genetically and phenotypically. Blue arrows indicate the relationships that are assessed.*

1.9.5 Chapter 7

In this chapter, structural equation modelling was used to perform a phenotypic analysis of the relationship between cognitive and emotion traits identified in Chapter 3 and AA in adolescence. The aims of this study were to:

1) test whether, when controlling for prior attainment, cognitive ability accounted for variance in improvements in academic attainment between ages 11 and 16 years old
2) test whether a model using separate executive functions and separate academic attainment was better than one using common EF or common AA latent measures.
3) assess whether emotion traits added significant variance to the best model selected from above (i.e., once EF had been considered).

1.9.6 Chapter 8

In this final experimental chapter, following from Chapter 7, genome-wide association studies were used to perform a genotypic analysis of the relationship between cognitive and emotion traits identified in Chapter 3 and AA in adolescence. The aims of this study were to:

1) perform the first GWAS of English and maths and the first GWAS of science attainment, using standardised national assessments.
2) use GWA data to assess the SNP heritability of English, maths and science attainment
3) use GWA data to estimate genetic correlations between English, maths and science and related cognitive and emotional traits in both ALSPAC (Chapter 3 EF measures) and independent samples.

2. Methods

2.1 The ALSPAC Sample

The Avon Longitudinal study of Parents and Children (ALSPAC) (http://www.bristol.ac.uk/alspac/) is an on-going, trans-generational and longitudinal observational study investigating factors influencing development and health across the life span. Data have been collected across many levels of description and include genetic and epigenetic, biological and psychological, and social and environmental measures. Initial recruitment began between 1990 and 1992 and included 14,541 mothers with 13,988 children alive at age one. Another round of recruitment at age 7 left the total sample size for data collected after this age at 15,247 (Boyd et al., 2013). Attrition rates were highest during infancy and late adolescence.

Chapters 3, 5, 6, 7 and **8** use data from three ALSPAC data collection waves which broadly span the period of adolescence from 10 to 20 years of age. Measures were selected using the downloadable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). During this period, participants were sent 20 questionnaires (nine of which data were selected from) and were invited to six clinical assessment visits (five of which data were selected from). **Table 2.1** summarises the measures used in the thesis. In **Chapter 7** and **8** linkage to education records were accessed to capture children's national standardised exam results (N=10, 008 – 12, 542). Finally, in **Chapters 6** and **8** genome-wide genotyping data available for 8,941 children were incorporated.

Table 2.1: Summary of ALSPAC data collection time points, measures and sample sizes used in the thesis.

	Data Type	File Name	Time Point (months)	Age (years: months)	Completed	Cognitive Data	Emotion QAs
7 <13 years of age	Clinic	F@10	120	10	7,557	Counting Span, Stop Signal	Moods and Feelings Questionnaire, Antisocial Activities Protocol
	Parent report	KV	128	10:8	7,851		Development And Well-Being Assessment, Social Cognition Scale
	Clinic	F@11	132	11	7,153	TEACh	Sensation Seeking, Borderline Personality Disorder
	Parent report	KW	140	11:8	7,478		Strengths and Difficulties Questionnaire, Moods and Feelings Questionnaire
	Clinic	TF1	144	12	6,832		Moods and Feelings Questionnaire. Antisocial Activities Protocol, Bullying
>=13 years and <=16 years of age	Clinic	TF2	156	13	6,141	Digit vigilance, RT measures	Moods and Feelings Questionnaire, Dating Violence, IPIP, Sensation Seeking
	Parent report	TA	157	13:1	7,159		Strengths and Difficulties Questionnaire, Moods and Feelings Questionnaire, Eating
	Parent report	TB	166	13:10	7,108		Development And Well-Being Assessment, Social Cognition Scale
	Child report	CCP			6,905		Self Image
	Clinic	TF3	180	15	5,509	Stop Signal, IQ test	Development And Well-Being Assessment ESYTC
>16 years and <=18 years of age	Parent report	TC	198	16:6	5,720		Strengths and Difficulties Questionnaire, Moods and Feelings Questionnaire, Social Cognition Scale
	Child report	CCS			5,126		Strengths and Difficulties Questionnaire, PLIKS, Sensation Seeking, Eating & Self Harm
	Clinic	TF17	204	17:0	5,196	N-Back	Dysfunctional Attitudes Scale, Cognitive Styles Questionnaire, Anxiety-Sensitivity Index
	Child report	CCXD	210	17:6	4,497		Moods and Feelings Questionnaire, Bachman, Warwick-Edinburgh Mental Well-Being scale
	Child report	CCT	222	18:6	3,355		Eating, Sensation Seeking

2.2 Measures

2.2.1 Demographics

Socio-economic status (SES) was calculated using the mother and partner's occupational social classes as classified by the Office of Population Census and Surveys (OPCS). Scores were reversed so that the higher the occupational status, the higher the score (i.e., 6 = professional, 5= managerial and technical, 4= skilled non-manual, 3 = skilled manual, 2 = partly skilled, 1 = unskilled labour ; OPCS, 1990). Measures of SES were taken at three time points. The first was taken from the mother only, before the birth of the child. The second was taken from both parents when the child was four years of age. Finally, at eight years of age the SES measure was collected from the mother's partner only. For each child, an average score was created from all parental scores across the three time points.

2.2.2 Cognitive Measures

The data dictionary was used to identify cognitive measures available during adolescence, broadly defined for this thesis as between the ages of 10 and 20 yrs, with a focus on measures of IQ, EF, attention and processing speed. Measures from the affective Go/No-go task were considered but excluded as the literature has mainly found this task to measure positive/negative bias rather than response inhibition, shifting or emotion regulation (Erickson et al., 2005). Also excluded was the Probability Reversal Learning task due to the amount of missing data. The final set of cognitive measures were derived from ten tasks across five time points.

2.2.2.1 Counting Span task

The Counting Span task (Case, Kurland, & Goldberg, 1982), performed at 10 yrs., is a WM task which requires processing, storing as well as an element of updating information. The child is shown a series of screens comprising of red and blue dots and is asked to count out loud only the red dots (processing element). At the end of each block the participant is asked to recall in order the number of red dots presented on each trial of that block (storage and updating). The participant had two practice blocks of two screens, then three experimental blocks with two, three, four and five screens allowing a maximum score of 42.

2.2.2.2 Stop Signal task

The Stop Signal task (Logan & Cowan, 1984) was performed at 10 and 15 yrs. This is a computerised measure of motor response inhibition. Participants are asked to fixate on

a smiley face in the middle of the screen. An X or O eventually appears and the child must respond as quickly as possible by pressing a key corresponding to X or O as quickly as possible (Go trials). This establishes a mean RT baseline and familiarises the child to the task; the child performs 30 of these trials (15 X and 15 O). Stop trials are then introduced in subsequent blocks. On Stop trials a beep was played randomly 150ms or 250ms before the participant's baseline RT indicating that the participant should refrain from responding. Participants then performed 24 practice trials with 8 Go trials and 16 Stop trials. Finally, there were two experimental blocks consisting of 48 trials in total, 16 of which were Stop trials. At 15 years the task was repeated with the same practice and test blocks but slightly different delay times between stimulus and stop signal presentations for different participants, hence a residual score covarying for delay duration was calculated for the age 15 scores of this measure.

2.2.2.3 Tests of Everyday Attention for Children

At age 11 three attention tasks from the Tests of Everyday Attention for Children (adapted from Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996) were performed. The *Sky Search task* assesses selective attention and motor control. Participants had to circle pairs of identical spaceships from a large number of similar pairs (distractors) as quickly as possible. The *Dual task* assesses divided attention. Participants were required to repeat the task above while counting spaceship noises played throughout the task. Finally, the *Opposite Worlds task* involves two conditions: in the same world condition participants have to read aloud a sequence of 1s and 2s, while in the opposite world condition participants have to say 1 for the number 2 and 2 for the number 1.

2.2.2.4 Digit Vigilance Task

At age 13 years participants were assessed on the Cognitive Drug Research (CDR) computerised cognitive assessment system (Simpson, Surmon, Wesnes, & Wilcock, 1991). Participants performed the Digit Vigilance task, which measures sustained attention. A number was shown on one side of the screen and remained constant while a sequence of different numbers was shown in the middle of the screen. Participants pressed a key when the side and middle numbers matched. There were a total number of 30 targets to be matched and 88 other numbers shown.

2.2.2.5 Reaction Time measures

Also at age 13 participants undertook two reaction time tasks. A *Simple RT task* where they were required to press a key labelled YES every time the world YES appeared on the

screen. In the *Choice RT task*, participants had two keys, YES and NO and were required to press the key corresponding to the word presented on the screen. Tasks included 30 trials.

2.2.2.6 Wechsler Abbreviated Scale of Intelligence

Vocabulary and *Matrix Reasoning* raw scores were taken from the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999) at age 15. The WASI was assessed during an interview session. In the vocabulary subtest participants were asked the meaning of a list of gradually more complex words. They began with 'car' and 'short' and ended with words such as 'impertinent' and 'panacea'. The Matrix reasoning subtest consisted of a multiple choice visual puzzle in which the participants were presented with a series of pictures and had to choose the missing image.

2.2.2.7 N-Back Task

A visual-spatial N-back task was used at 17 yrs. to test WM, more specifically updating. Participants were presented one by one with numbers 0-9 on a screen for 500ms and then had 3000 ms to judge whether the current number was the same as the number shown either two or three screens previously.

2.2.3 Emotion Measures

There were no specific emotion regulation questionnaires in the ALSPAC sample and it was not clear from the questionnaires and interviews administered that any particular one would best characterise how adolescents experience and regulate their emotions. Therefore, a number of questionnaires were selected on the basis that they would be representing (i) a cognitive approach to emotional situations, (ii) the experience or behavioural expression of emotions (iii) factors to do with relationships and personality. Detailed rationale for each questionnaire is provided in **Chapter 3.1.3.2**). Overall, the measures selected were taken across the period of adolescence at one or more time points (**Table 2.2**).

Table 2.2: Summary of emotion-related questionnaire measures selected and age at collection

Measure	Rationale	Age in months												
		120	128	132	140	144	156	157	166	180	198	204	210	222
Development and Well-Being Assessment	ii		P						P	Cl				
Skuse Social Cognition Scale	ii		P						P		P			
Moods and Feelings Questionnaire	ii	Cl			P	Cl	P	Cl			P		C	
Strengths and Difficulties Questionnaire	ii		T		P		P				P C			C
ALSPAC Eating questions	ii						P				C			C
ALSPAC Self Harm questions	ii										C			
Semi-structured Psychosis-like symptoms interview (PLIKS)	ii										C			
Locus Of Control Scale	i										C			
Arnett Inventory of Sensation Seeking	ii			Cl				Cl			C			C
Self-image	i								C					
Bachman revision of Rosenberg's Self-Esteem Scale	i												C	
Warwick-Edinburgh Mental Well-Being scale	i												C	
Antisocial Activities Protocol	ii	Cl				Cl								
Borderline Personality Disorder assessment	ii			Cl										
Friends and Peers interview	iii					Cl								
Dating Violence questionnaire	ii							Cl						
International Personality Item Pool	iii							Cl						
Edinburgh Study of Youth Transitions and Crime misbehaviour sub scale	ii									Cl				
Dysfunctional Attitude Scale	i											Cl		
Anxiety Sensitivity Index	ii											Cl		
Cognitive Styles Questionnaire Short Form	i											Cl		

P = questionnaires completed by parents about the child, C = questionnaires completed by child, T = questionnaires completed by teacher, Cl = questionnaires and interviews carried out at clinic. Rationale for including questionnaire: (i) a cognitive approach to emotional situations, (ii) the experience or expression of emotions and (iii) factors to do with relationships and personality

2.2.3.1 Development and Well-Being Assessment (DAWBA)

The Development And Well-Being Assessment (Goodman, Ford, Richards, Gatward, & Meltzer, 2000) is a questionnaire, administered in person or online, allowing for the assessment of children from 2-17 year olds, for up to 17 psychiatric disorders. These are broadly considered either conduct, emotional or hyperkinetic disorders under the DSM IV diagnoses (DSM-IV, 1994) criterion. The questionnaire was created for epidemiological purposes but also aims to have clinical utility. From the DAWBA, 157 questions were included that referred to conduct and emotional disorders.

2.2.3.2 Strengths and Difficulties Questionnaire (SDQ)

The Strengths and Difficulties Questionnaire is a behavioural screening questionnaire designed for researchers, clinicians and educationalists. The SDQ was designed as a tool to detect emotional and behavioural difficulties in children. It was based on Rutter parent questionnaire (Elander & Rutter, 1996), but developed with the aim of having more contemporary questions, fitting only on one page, having formats for parents/teachers as well as for children themselves, and including behavioural strengths as well as difficulties (Goodman, 1997). The questionnaire has 25 questions and can either be divided into five scales or two. The five scales represent: emotional problems (e.g. "often unhappy, downhearted"), conduct problems (e.g. "often fights with other children"), hyperactivity (e.g. "constantly fidgeting or squirming"), peer problems (e.g. "rather solitary, tends to play alone") and prosocial behaviour (e.g. "considerate of other people feelings"). However, the SDQ can equally be organised into the dimensions of internalising and externalising, where internalising is a combination of peer and emotional problems, and externalising is a combination of conduct problems and hyperactivity. The internalising-externalising dimensions were used in the analyses presented in **Chapter 5**. The SDQ was collected in subsamples using teacher, parent and child based questionnaires.

2.2.3.3 Short Moods and Feelings Questionnaire (SMFQ)

The Short Moods and feelings Questionnaire was designed as a short questionnaire for epidemiological studies for the purpose of assessing depressive symptoms in children and adolescents (Angold, Costello, Messer, Pickles, et al., 1995). It is sensitive enough to discriminate between children with and without depressive disorder across development (Messer, Angold, Costello, Loeber, & et al, 1995). It was completed at seven time points, but at 198 months was adapted to include additional "happy" questions after feedback from the cohort's "Teenage Advisory Panel". Example questions from the SMFQ include "child has been feeling miserable or unhappy in the last two weeks", "Child has hated

themselves in the last two weeks", "Child has cried lots in the last two weeks". This questionnaire had 17 items including happy items.

2.2.3.4 Warwick-Edinburgh Mental Well-Being scale (WEMWBS)

The Warwick-Edinburgh Mental Well-Being scale (Tennant et al., 2007) was developed to assess mental well-being and its contribution to all aspects of life at a population level. It focuses entirely on the positive aspects of mental health and correlates well with other measures of mental health and well-being but less well with measures of overall physical health. The WEMWBS includes items such as "I've been dealing with problems well", "I've been feeling relaxed" and "I've been feeling optimistic about the future". The WEMWBS has 14 items in total.

2.2.3.5 Cognitive styles questionnaire short form (CSQ-SF)

The Cognitive styles questionnaire short form measures a 'negative inferential style' or cognitive vulnerability. This is a cognitive style which interacts with negative life events and it thought to increase the likelihood of developing depression (Haeffel et al., 2008). The questionnaire orientates around nine hypothetical situations relating to failures in academic achievement, work and relationships. Participants are asked to imagine this has happened to them and to judge the likely cause of the event by rating eight possible statements. The possible causes are classified as internal (e.g. "It is my fault if I am getting along badly with my parents"), stable (e.g. "The reason for getting along badly will stop me from getting along well with my parents in the future"), global (e.g. "The reason I get on badly with my parents causes problems in all areas of my life") and self-worth (e.g. "Getting along badly with my parents means there is something wrong with me as a person"). Participants rated the extent to which they agreed with each statement. Higher scores indicate a more negative cognitive style and overall there are 72 items.

2.2.3.6 International Personality Item Pool (IPIP)

The IPIP is based on the five-factor model of personality (Goldberg, 1992), and provides dimensional measures of extraversion, neuroticism, agreeableness, conscientiousness and openness to experience (Goldberg, 1999). ALSPAC selected 50 statements from the IPIP that the participants rated on a 5 point Likert scale ranging from "very like me" to "not at all like me". Items for extraversion include "I am the life of the party", neuroticism "I get stressed out easily", agreeableness "I am relaxed most of the time", conscientiousness "I pay attention to details" and openness to experience "I have a vivid imagination".

2.2.3.7 Semi-structured Psychosis-like symptoms interview (PLIKS)

The semi-structured PLIKS interview assesses psychosis-like symptoms and is based on DISC-IV assessment criteria for children (Shaffer, Fisher, Lucas, Dulcan, & Schwab-stone, 2000). For this thesis only the negative symptoms, i.e. those relating to flattened affect or depression rather than positive symptoms relating to psychosis such as hallucinations have been selected. Questions included "I felt lacking in get up and go in the last month", "I felt guilty in the last month", "I felt there is no future for me in the last month". There are 17 items overall.

2.2.3.8 Edinburgh Study of Youth Transitions and Crime misbehaviour sub scale (ESYTC)

The Edinburgh Study of Youth Transitions and Crime was developed in response to a rise in misconduct and ordinary crime mostly carried out by young people (Smith, McVie, Woodward, Shute, & McAra, 2001). This scale is part of a broader programme of longitudinal research which aims to understand the causes of criminal and risky behaviours in young people. The general programme asked questions about a range of factors including family structure, relationships, health and friends. Here we use a self-report misbehaviour subscale which asks questions about the young person's behaviour in general such as "Young person has had temper outbursts in the past 6 months", "Young person often did things to annoy other on purpose in the past 6 months", "Young person often blamed others for their own mistakes or bad behaviour over the past 6 months". They also ask about specific criminal behaviour such as stealing, starting fires and destroying property. This scale includes 56 items.

2.2.3.9 Shortened Nowinicki-Strickland Internal/External Locus of control scale (LOCS)

The aim of the Locus of control scale was to look at the extent to which participants believe there is a causal relationship between themselves and things that happen to them (Nowicki, Strickand, & Bonnie, 1971). It is considered a measure of resilience and based on the theory that reinforcement is a key determinant of behaviour and learning. However, reinforcement, or reward, is only successful if the individual sees a relationship between their behaviour and the reward or punishment and this questionnaire measures the extent to which this is true. It is a 13-item scale which asks the participants to state whether they believe statements are true or false. Statements include "Do you think preparing for things is a waste of time?", "Do you usually do badly in your schoolwork even when they try hard?", "When you get into an argument or fight, is it the other person's fault?".

2.2.3.10 Arnett Inventory of Sensation Seeking (AISS)

Sensation seeking has been mostly commonly defined as "the need for varied, novel and complex sensations and experiences and the willingness to take physical and social risks for the sake of such experiences" (Zuckerman & Neeb, 1979) and is often associated with risk-taking and externalising behaviour. This thesis uses the ALSPAC modified version of Arnett's Inventory of Sensation Seeking (AISS) (1994) which seeks to assess sensation seeking behaviour in the children and adolescents. The original version of the AISS contains 20 questions, 11 of these were chosen for inclusion in the ALSPAC scale and a further 9 more age appropriate questions were designed by Dieter Wolke and Andrea Waylen and incorporated (Arnett, 1994) (**Supplementary Table 2.1**).

2.2.3.11 Anxiety Sensitivity Index (ASI)

Two nine-item subscales of the Anxiety Sensitivity Index (Reiss, Peterson, Gursky, & McNally, 1986) were used to assess physical and mental concerns about the types of sensations experienced during a period of anxiety. The questions focus around the response to bodily sensations of anxiety such as "Young person is scared when their heart beats fast" or "When young person's stomach hurts, they worry that they might be really sick". The other section is mental response to anxiety including "Young person does not want other people to know when they feel afraid", "It is important for the young person to stay in control of their feelings".

2.2.3.12 Bachman revision of Rosenberg's Self-Esteem Scale (RSE-B)

This is taken from the Bachman revision (called RSE-B) (Bachman, 1970) of the Rosenberg's Self-Esteem Scale designed for adolescents (Rosenberg, 1965, 2015). Participants have to rate items on a 5-point Likert scale from "Almost always true" to "Never true". It includes statements such as "I feel that I have a number of good qualities", "I am able to do things as well as most other people" and negatively coded "I feel I do not have much to be proud of". This questionnaire has 10 questions.

2.2.3.13 Dysfunctional Attitude Scale (DAS-SF)

The Dysfunctional Attitude Scale – Short Form is a self-report questionnaire containing nine items taken from the original Dysfunctional Attitude Scale (Weissman, 1979). The DAS-SF measures core beliefs about the world, relationships with others and their approval as well as judgments on their own performance. Dysfunctional attitudes are thought to be stable and consistent across situations. They are involved in assigning

meaning to stressful situations related to the self. Participants rated from 1-5 the extent to which they agree with nine statements including "Young person feels that they should be able to please everybody", "Young person's life is wasted unless they are a success" and "Turning to someone else for help or advice is an admission of weakness". Higher scores reflect more dysfunctional attitudes.

2.2.3.14 Borderline Personality Disorder assessment (DSM-IV face-2-face interview)

The Childhood Interview for DSM-IV Borderline Personality Disorder (CI-BPD) is a semi-structured interview designed to assess BPD in children and adolescents developed by Mary Zanarini (Zanarini, 2003) and adapted by Jeremy Horwood and Dieter Wolke for ASLPAC for the purpose of assessing the prevalence of BPD-related behaviours and emotions rather than diagnosis. Borderline Personality disorder is assessed along three main dimensions: (1) affective stability - the extent to which one is able to control extreme feelings; (2) interpersonal relationships - efforts to prevent abandonment, experiences that the self or the world is not real; and (3) impulsivity - impulsive self-destructive or otherwise harming behaviours. Included were 42 questions focused around the frequency and intensity of anger, emptiness and impulsivity as well as items such as "I managed to hide (my anger)", "I threatened to physically harm someone", "I ate so much I had to throw up".

2.2.3.15 Skuse Social Cognition Scale (SCS)

The Skuse Social Cognition Scale is a parent report measure designed to summarise the dominant features of social cognition in children (Skuse et al., 1997). Parents must rate 12 statements as either being "not at all true of my child", "quite or sometimes true of my child" or "very or often true of my child". The questions focus around an awareness of others' thoughts/feelings such as "My child does not realise when others are angry or upset" and a difficulty co-operating with others "my child does not respond to commands" or "my child is difficult to reason with when upset".

2.2.3.16 Dating Violence questionnaire

The Dating Violence questionnaire measures the extent to which an individual is aggressive towards and has experienced aggressive behaviour from a partner. It was completed through a face-to-face interview adapted for adolescents by Arriaga & Foshee (2004) from the Conflict Tactics Scale (Straus, 1979), the most commonly used assessment of intimate partner violence. It was included as a measure of externalising behaviour. This questionnaire focuses on adolescent dating expectations of violent

behaviour to try to understand the origins of interpersonal violence (Arriaga & Foshee, 2004). The questionnaire asks whether teenagers have intentionally hurt or been hurt by someone they have been out with, how they felt afterwards and whether they told anyone. It also asks questions addressing their general attitude towards violence such as whether it is okay to use violence to get what they want and how they might respond when violence is directed towards them, for example whether the teenager believes they should break up with partner when that person hits them. Overall this there were 44 questions on attitudes to violence in a relationship.

2.2.3.17 Antisocial Activities Protocol

The Antisocial Activities Protocol was administered as a semi-structured interview where the questions were adapted from a large-scale study into antisocial activities carried out in Germany by Dieter Wolke. There were 11 questions regarding antisocial activities; Adolescents are asked if they have been told off by their teacher, if they have destroyed or broken something for fun, if they get into fights or have been arrested. If children answer yes to any of these they are subsequently asked about the frequency.

2.2.3.18 General questions developed by ALSPAC

ALSPAC also included some general questions about problematic eating habits, social skills, behaviour and self-image (**Supplementary Table 2.2).** These measures were collected by parent report at 160 months and subsequently by the children themselves at 166 and 198 months.

2.2.3.19 Friends and Peers interview

The Friends and Peers interview was adapted from a version by Wolke and colleagues (Wolke, Woods, Stanford, & Schulz, 2001) to identify bullying and victimisation. The interview questions are listed in **Supplementary Table 2.3** and include 35 items in total.

2.2.4 Academic Achievement

Academic achievement (AA) was assessed using national curriculum standardised tests at 11, 14 and 16 years of age (**Table 2.3**). At age 11 (end of Key Stage 2) and age 14 (end of Key Stage 3), national exams, known as the Standardised Assessment Test (SATs), were obligatory in schools across the UK when this data was collected. At age 16 (end of Key Stage 4), adolescents again take a set of national exams to obtain General Certificates of Secondary Education (GCSE) in a range of subjects, of which English, maths and science

are obligatory. At Key Stages 2 (age 11) and 3 (age 14) children are given a curriculum level from 1-9, this score was used directly. GCSEs were scored from 1-9 representing GSCE grades U-A* (U=1, G=2, F=3, E=4, D=5, C=6, B=7, A=8, A*=9).

2.2.4.1 Academic achievement in English

At age 11 and 14, SAT English exams assess reading, grammar, punctuation and spelling as well as understanding and interpretation of a studied text. Age 16 the GCSE English exam includes a language test to assess reading and writing ability, and a literature test that examines knowledge and understanding of a novel or play, poetry and a previously unseen text. For English at age 16, an average score of the GCSE exams in literature and language were used for each individual.

2.2.4.2 Academic achievement in Maths

Maths is assessed in all three exam types (SATs at 11 and 14yrs and GSCEs at 16yrs) with written tests that cover all areas of mathematics including conceptual understanding, mathematical reasoning and problem solving. The age 11 SAT maths assessment also includes a 'mental maths' component in which the children are asked questions orally and under timed conditions they must write down their answers having worked them out in their heads.

2.2.4.3 Academic achievement in Science

The SAT science exams at age 11 and 14 assess the development of scientific thinking and knowledge, experimental skills and strategies, analysis and evaluation as well as scientific vocabulary, units, symbols and nomenclature. Science at GCSE level (16yrs) are either taken as three separate subjects (chemistry, physics and biology), or as one condensed subject (**Table 2.3**). Individuals who took the three science subjects separately were given an average score, and those who did single science kept this score. These two measures were considered equivalent due to the extra teacher time and curriculum cross-over between the three separate subjects.

Table 2.3: List of the raw Standardised Assessment Tasks (SATs) scores available in the ALPSAC sample.

					Standardised residual scores[c] (mean)	
EA variable	Test	N	Mean	Range	Males	Females
English age 11	Key Stage 2 National Curriculum SATs English	11,778	5.14	3 - 6	-0.112	**0.111***
English age 14	Key Stage 3 National Curriculum SATs English	10,008	5.32	3 - 7	-0.178	**0.169***
English age 16[a]	English Literature GCSE	9,683	6.23	1 - 9	-0.287	**0.263***
	English Language GCSE	11,337	6.06	1 - 9	-0.296	**0.291***
Maths age 11	Key Stage 2 National Curriculum SATs Maths	11,823	6.13	4 - 8	**0.039***	-0.039
Maths age 14	Key Stage 3 National Curriculum SATs Maths	10,577	6.80	3 - 9	0.018	-0.018
Maths age 16	Maths GCSE	11,231	5.79	1 - 9	-0.028	0.028
Science age 11	Key Stage 2 National Curriculum SATs Science	12,165	6.38	4 - 7	-0.000	0.000
Science age 14	Key Stage 3 National Curriculum SATs Science	10,623	6.35	3 - 8	0.011	-0.011
Science age 16[b]	Single Science GCSE	7,319	5.75	1 - 9	-0.063	**0.062***
	Chemistry GCSE	1,588	7.33	4 - 9	-0.048	0.055
	Physics GCSE	1,596	7.31	4 - 9	-0.060	**0.072***
	Biology GCSE	1,696	7.23	1 – 9	-0.014	0.019

[a] For all participants English Literature and Language GCSE scores were averaged into a single score. [b] Participants who took science subjects separately were given an average score across the three subjects. * Indicates this score is significantly better than the other ($p<.05$). [c] Scores are the saved residuals from a regression analysis performed with age at time of testing. These data represent the sample used in Chapter 7 (N = 5,838).

2.3 Structural Equation Modelling

Structural equation modelling (SEM) is a general modelling framework allowing the combination of a range of statistical methods including latent variable modelling, path analysis and multiple regression. SEM is well suited to modelling psychological constructs that inevitably suffer from measurement error and which SEM is able to estimate. It also allows for the modelling of systems of relationships, where multiple predictors and multiple outcomes are all related to each other either directly or via mediation or moderation. SEM is generally represented using a path diagram that

consists of circles, boxes and arrows each with a specific meaning (**Figure 2.1** and **2.2**). Various combinations of path and/or latent analyses are used in **Chapters 4, 5** and **7**.

2.3.1 Latent analysis

Latent variable analysis, or factor analysis, is a type of measurement model. A latent measure is something that cannot be measured directly but is considered to cause the behaviours that we can measure. For example, we are able to use various tests to estimate working memory capacity, however not all the variation in performance is attributable to working memory capacity; it includes factors associated with the experimental design, room temperature, and participant-specific factors like processing speed and tiredness to name a few. In this situation factor analysis can use multiple indicators or measures to model measurement error and extract a latent working memory factor, with more accurate effect sizes and smaller standard errors. There are two main approaches to factor analysis: exploratory and confirmatory. Exploratory methods such as EFA and PCA are data-driven hypothesis-free methods, which attempt to find the best model fit for the data. Confirmatory methods are theory-driven and aim to test the theory against the data. In exploratory methods, all of the variables are allowed to correlate with the factors, whilst in confirmatory analyses restrictions are placed on these correlations. Figure 2.1 shows a CFA model where the first three measures are only allowed to correlate with latent trait 1 and the second three measures with latent trait 2. In contrast, an exploratory model would have arrows leading from both latent traits to all six measures.

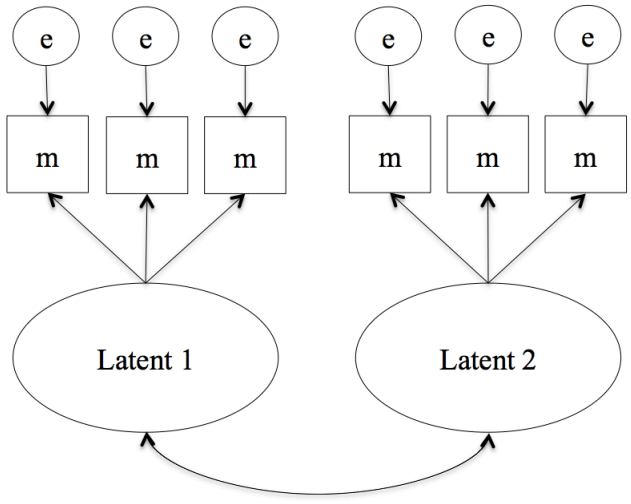


Figure 2.1: *Here the large circles represent latent measures, and the small circles represent error terms (e). Error terms are round like the latent variables as they are also estimated rather than measured. The curved double-headed arrow indicates covariance between factors but does not provide information about the direction of the relationship. The arrows go from the latent traits to the measured traits (m) as it is assumed the measured traits are caused by the underlying latent trait.*

2.3.2 Path Analysis

Path analysis enables the modelling of complex regression relationships between specific variables. Traditional path analysis uses only measured variables but allows for the measurement of direct (**Figure 2.2**) and indirect effects. An indirect effect would have a third box mediating the relationship between X and Y. SEM allows us to bring together and model latent variables into multiple regression path models.

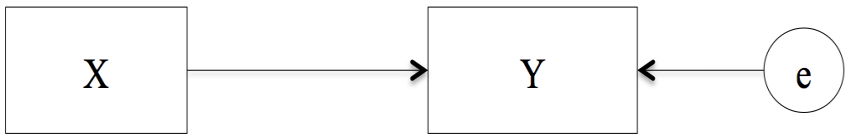


Figure 2.2: *The rectangular boxes represent two measured variables and the small circle is the error term. Straight single headed arrows indicate that it is a directional path, i.e. X predicts Y.*

2.3.3 Assessment of Model fit

Unlike some other types of analysis, a SEM creates a model variance/covariance (var/covar) matrix to compare the model fitted against the raw var/covar matrix to assess goodness of fit. The variance in this case is the covariance of a variable with itself. SEM estimates the unknown parameters in a model (i.e. the betas), using Maximum Likelihood (ML) which iterates through different possible L's (L= joint probability of continuous sample observations) until it reaches the maximum likely beta score. ML is unbiased and efficient: if the sample is large then estimates will converge well on the real values, as long as the data has come from a normal distribution of continuous variables.

Because a model will be unlikely to fit the data perfectly, fit indices measure the difference between the model and the observed data using residuals. The χ^2 static is an index of 'absolute fit' and can be assessed using the (log)likelihood of our model against the observed data. If $p > .05$ then we prefer the SEM model which has fewer parameters than the observed data and is therefore the more parsimonious model. However, χ^2 is sensitive to the number of parameters estimated and therefore isn't favoured with larger models as p is rarely non-significant. Another index of 'absolute fit' is the Root Mean Square Error of Approximation (RMSEA). RMSEA is able to take into account parameters but will favour the more parsimonious model. The ML based Standardised Root Mean squared Residual (SRMR) is another similar model fit which works well with all sample sizes. RMSEA and SRMR give a model fit value between 0 and 1, with a better model fit having smaller values. A good fitting model has an RMSEA $\leq$ 0.06 or SRMR $\leq$ 0.08 (Hu & Bentler, 1999). An alternative method of estimating model fit is to compare a model to

the worst fitting model using a 'relative fit index'. The mostly commonly used approaches are the Comparative Fit Index (CFI) and the Tucker-Lewis Index (TFI). Again fit values are between 0 and 1 but a better fit is indicated by a higher value and an acceptable fit is ≥ .09 (Hu & Bentler, 1999). It is commonplace to look at all of the above model fit indices to assess your model fit. The model fit can only be estimated if the model is over-identified, i.e. there are more defined parameters, than the number of parameters to be estimated. To help with this some parameters can be constrained, not estimated, or more information can be added to the model.

Comparing different SEM models (as opposed to the SEM model with the observed data) requires the models to be nested, i.e. the models are the same but they have different parameters. Models with different variables cannot be directly compared.

2.4 Genetic Methods

Chapters 6 and **8** of this thesis use genome-wide data to estimate heritability and perform a series of genome-wide association studies (GWAS). GWA is a population-based approach using common genetic variation to identify specific genetic variants contributing to the trait of interest. Common genetic variation is distributed throughout the human genome – typically single base changes in the DNA sequence (Single Nucleotide Polymorphisms: SNP). GWAS uses unrelated individuals to uncover associations between variation in phenotypes and base changes in DNA sequence allowing the biological underpinnings of common human variation to be mapped. A necessary precondition of GWA studies is that the phenotype being examined is under genetic influence – i.e. it must be heritable. Heritability is a population-based statistic that indexes the extent to which, genetic factors contribute to individual differences in the measured phenotype. It is population and context specific. Heritability can be estimated using familial studies or DNA-based approaches. Classical twin studies estimate heritability by exploiting the fact that identical (monozygotic or 'MZ') and non-identical or fraternal twins (dizygotic or 'DZ') share the same family environmental experiences but differ in their genetic similarity. Specifically, MZ twins share 100% of their DNA sequence, while DZ twins share on average 50% of their segregating genes. Working under the assumption that environmentally caused similarity is equivalent for both types of twin pairs, genetic influence can be quantified by the extent to which MZ twins are more similar for a trait than DZ twins (Plomin et al., 1997). In contrast, DNA-based approaches utilise measured genetic variation in large samples of unrelated individuals to estimate the total amount of variance explained by common genetic variation captured by the genotyping platform (h^2_{SNP}). Therefore, in order to assess h^2_{SNP} one must first run a GWA

analysis to estimate effect sizes for each SNP. The process by which data are cleaned and prepared for GWA analysis is described in the figure and descriptions below (**Figure 2.3**)

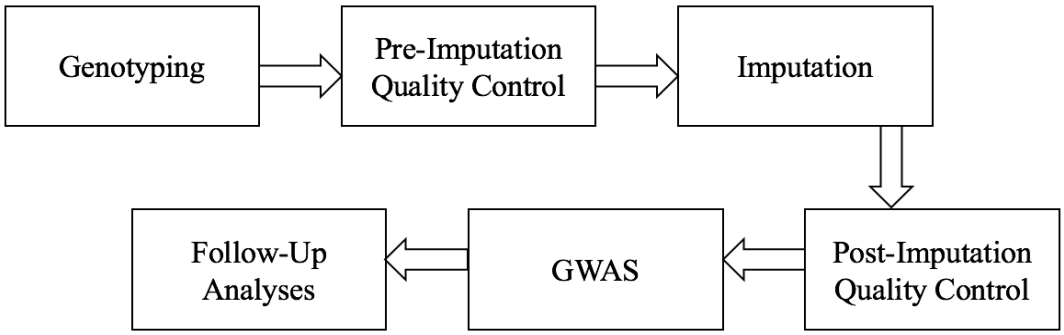


Figure 2.3: *This figure shows the quality control and analysis pipeline of a genome-wide association study (GWAS).*

2.4.1 Genotyping and imputation

Genotyping is typically performed using microarray technology, which allows for the alleles of a particular SNP be read or 'called' using molecular probes and the SNP genotype determined. This approach usually calls approximately 500,000 SNPs distributed throughout the 3 billion bases of the human genome, but from these data, additional (non-genotyped) SNP genotypes can be derived or 'imputed' using haplotype reference panels. Haplotype reference panels map whole-genome variation in samples of individuals with different ancestral backgrounds. This provides a reference panel of haplotypes, which are short segments of the genome containing multiple alleles in linkage disequilibrium (LD) with each other. LD is the genetic correlation (measured with R^2 - which takes into account allele frequency, or D') between markers representing the non-random association of alleles at two or more loci such that they are inherited together more frequently than expected by chance. If two SNPs are physically close to each other on the genome, there is more chance that they will be continually inherited together and therefore in general, although not always (Price et al., 2008), LD between SNPs decreases with physical distance on the genome. The strength of LD varies across the human genome, but where it is strong, fewer SNPs are needed in order to characterise allelic variation. As a consequence, carefully selected genotyped SNPs can be combined with an appropriate haplotype reference panel to impute the 'best guess' allelic variation in the un-genotyped regions of an individual's genome. Haplotypes are population specific as they vary based on recombination rate, mutation rate, population size and natural selection, but imputation with European reference haplotype panels are currently able to determine alleles for ~ 39,000,000 common SNPs (Haplotype Reference Consortium et al., 2016).

2.4.2 Quality control measures

Quality control is performed after genotyping using SNP microarray platforms, and repeated following imputation. Both processes orientate around the same basic principles, which are now described.

2.4.2.1 Hardy-Weinberg equilibrium

Hardy-Weinberg equilibrium (HWE) is a principle that assumes that both allele and genotype frequencies remain constant in a population over generations. For instance, if in the first generation you have four 'aa' homozygotes, two 'AA' homozygotes and three 'aA' heterozygotes, the allele frequency will be a=11, A=7 and HWE assumes that the ratio between the minor and major allele will remain stable in subsequent generations. There are many instances in which this does not hold, for example due to migration or immigration, selection, mutation, non-random mating and inbreeding. During quality control it is standard practise to use a χ^2-test of association to test for deviances from the expected allele frequencies (Reed et al., 2015). However due to the fact that we expect deviations from HWE due to the reasons stated above, the stringency for the p-value significance threshold has been relaxed over the years to $< 5 \times 10^{-7}$ (Anderson et al., 2010).

2.4.2.2 Minor Allele frequency

The minor allele frequency (MAF) is a percentage of how often the less frequent allele of a bi-allelic SNP occurs in a population of individuals. For example if an (A/G) SNP is genotyped in 1,000 people and 550 individuals are homozygous 'A/A', 400 are A/G and 50 are G/G), then the 'G' allele, which is less common, is considered the minor allele and the MAF is (400+100)/2000 = 0.25. During quality control, it is usual to remove alleles that have a minor allele frequency < 0.01. This threshold is applied for two reasons: (1) extremely low MAF is more likely to be a genotyping error, and (2) the smaller the MAF, the less likely it is to reflect differences in common variation, which is the general purpose of genome-wide association studies.

2.4.2.3 SNP genotype reliability

Info score, SNP call rate and missing data are three indexes that provide information about the reliability of the genotype calls for the directly measured and imputed SNPs. Call rate is the proportion of individuals for each SNP for whom the maximum genotype probability > 0.95 (Reed et al., 2015) and indicates sample quality. 'Missingness' or 'sample level call rate' is the proportion of individuals with missing genotype data across

a sample. Maximum missingness is generally set at 10%, so that individuals with more than 10% missing genotype calls across all SNPs are removed. Info score is a metric between 0 – 1 indicating the level of certainty in the imputed SNP genotypes with 1 indicating no uncertainty and 0 indicating complete uncertainty. There is no consensus on info score thresholds and studies use metrics varying from 0.3 - 0.9 (Verma et al., 2014). This is because as the MAF decreases, so does the imputation certainty thereby reducing power to detect associations, a particular problem for smaller samples. A more liberal threshold of .4 has been adopted for this thesis as it is deemed appropriate for smaller samples ('Genotype imputation and genetic association studies of UK biobank', 2015). Therefore, genotypes with an INFO score ≤ 0.4 were removed from downstream analysis.

2.4.2.4 Population stratification

Assessing for evidence of population stratification is a necessary step in running genome-wide association studies to minimise conflating associations that are culturally rather than genetically driven. As shown on Figure 2.4, populations that are geographically closer to each other are also genetically closer, but they may also have more cultural factors in common. A problem arises if certain phenotypes and genetic structures are more present in a particular population; here GWAS will falsely find this association to be trait-related. The most famous illustration of this problem was conceived by Lander and Schork in their example of the chopstick gene. They invite you to imagine a GWAS looking at the genetics of chopstick use in a mixed population of Europeans and Asians. The GWAS would likely find spurious associations between chopstick use and variants more common in the Asian population, such as HLA-A1 (Lander & Schork, 1994). In order to overcome this problem, genome-wide association studies tend to be performed 'within' populations and principal component analysis is performed on the genetic data to identify genetic outliers and to generate latent component scores for use as covariates in the association analysis (Price et al., 2006).

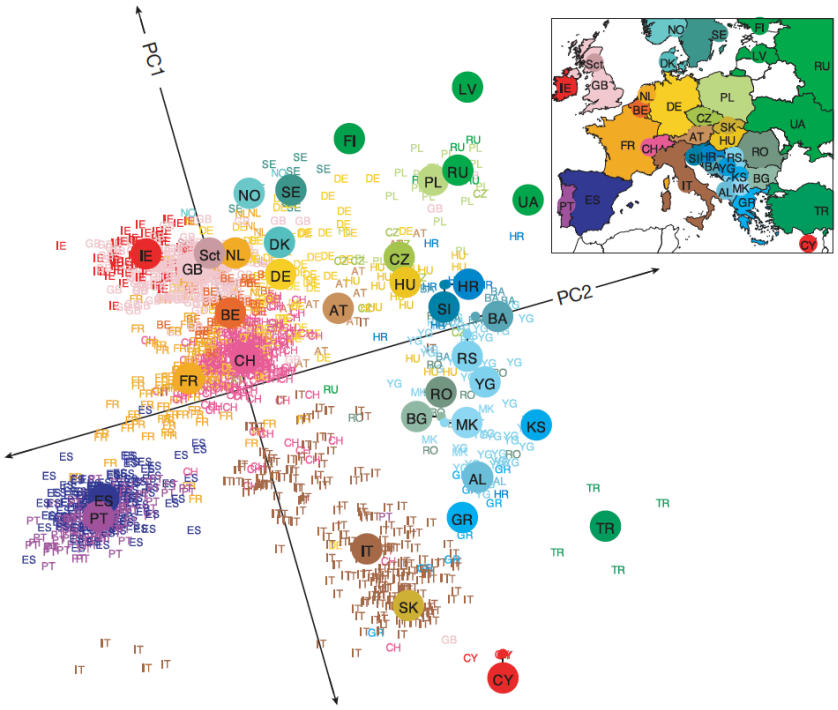


Figure 2.4: *Figure mapping the first two components of a principal component analysis of genetic data (N=3,000) where the first component represents the largest amount of variance in the data set. Figure taken from Novembre et al., (2008).*

2.4.3 Statistical Analysis

2.4.3.1 Genome-Wide Association

Genome-wide association use genome-wide SNP data to test for statistical associations between individual SNPs and the selected phenotype. For studies presented in **Chapters 6** and **7** univariate genotype-phenotype analyses were performed with imputed dataset using the software SNPTest v.2, implemented in bash. SNPTEST can be found at (https://mathgen.stats.ox.ac.uk/). As is standard, all GWAS were performed using an additive model, which assumes a linear model whereby if T is the risk allele, AA=0, AT=1 and TT=2. Alternative models are recessive, whereby AA=0, AT=0, TT=2, i.e. two T alleles are necessary to see the effect, or dominant AA=0, AT=2, TT=2, i.e. one allele is sufficient to see the effect and two alleles are not associated with a greater effect. Genotype dosage scores, which use imputation probability estimates, were used to increase power. Genotype dosage scores vary between 0-1 and represent the confidence that the imputed allele is the true allele. Using dosage (or probability scores) is preferable to the alternative, which is to remove all SNPs with a probability <.9 and treat those >.9 as real genotype calls.

2.4.3.2 Gene-Wide Association

GWA tests associations between the chosen trait and each individual SNP. However, SNPs are not independent and it is possible to combine individual SNPs within each gene or gene region, and run fewer gene-based analyses. This approach can offer more statistical power as fewer tests are performed, and (smaller) individual effects of each SNP are aggregated across a gene. Gene-based association analyses were performed using Multi-marker Analysis of GenoMic Annotation (MAGMA) within the FUMA programme (Watanabe, Taskesen, Bochoven, & Posthuma, 2017) using the summary statistics from each individual GWA analysis. MAGMA uses a multiple linear principal component regression-based technique allowing for the incorporation of LD between SNPs, and applies a F-test to calculate per gene p-values (Leeuw, Mooij, Heskes, & Posthuma, 2015). SNPs were assigned to genes based on the NCBI 37.3 build with a +/- 10kb annotation window, resulting in 17,226 genes being tested for association and corrected for multiple testing using Bonferroni correction.

2.4.3.3 SNP Heritability Estimates

For this thesis SNP heritability (h^2_{SNP}) was estimated using LD score regression, a GWAS summary statistic-based method (Bulik-Sullivan, Loh, et al., 2015). Heritability is calculated based on the assumption that a SNP's effect size (χ^2) is positively correlated with LD score but not ancestry, and therefore the extent to which effect sizes are higher than the expected represents inflation due to polygenicity (the multiple variants influencing a trait).

LD score regression can either be performed using LD hub (http://ldsc.broadinstitute.org) or manually with python, which allows more control over the arguments used. For example, using python it is possible to constrain the LD score intercept if there is high confidence that there is no population sub-structure, which reduces the standard error on heritability estimates. This can also be done for genetic correlations provided there is no overlap in participants between the two studies or the overlap is known. The advantage of LD hub is that it stores the GWAS summary statistics of 832 traits allowing for the easy estimation of genetic correlations with independent samples (Zheng et al., 2017).

2.4.3.4 Genetic Correlations

Genetic correlations allow for the assessment of the extent to which the DNA sequence variants contributing to one trait also contribute to another trait. Genetic correlations (r_g)

vary between ~ 0 – 1, regardless of the h^2_{SNP} of the individual traits. For this thesis, genetic correlations were estimated using LD score regression; this method operates under the same principle as h^2_{SNP} estimates explained above but replaces the χ^2 with the product of z-scores from two separate GWAS studies (Bulik-Sullivan, Finucane, et al., 2015).

3. Characterising latent measures of cognition and emotion in adolescence

There is a large body of literature looking at the relationship between cognitive ability and emotional outcomes both in children and adults. In order to explore this relationship in adolescence, this first set of analyses reduces numerous measures of cognition and emotion taken across adolescence in the ALSPAC study into latent measures which broadly characterise individual differences in these areas during adolescence. The study aimed to: (1) try to understand the main axes of variance in a range of different and repeated questionnaires taken across adolescence measuring different aspects of emotion and behavioural regulation; and (2) assess the relationship between variation in cognitive ability and emotion-based traits testing linear and quadratic hypotheses. The PCAs identified three cognitive components: working memory, inhibitory control and processing speed and five emotion components: externalising, internalising, anxiety, extraversion and conscientiousness. Small associations where observed between the cognitive and emotion measures, with stronger associations between higher levels of problem behaviours and lower cognitive abilities.

3.1 Introduction

3.1.1 Executive function

Executive functions (EFs) are the processes by which we control and direct our behaviour. As such they regulate lower level processes such as emotion. EFs have been proposed by many people as being the mechanism by which we are able to down-regulate unpleasant, unwanted or un-helpful emotions (Hankin, Snyder, & Gulley, 2016; Hofmann, Schmeichel, & Baddeley, 2012; Zelazo & Cunningham, 2007), which is thought to be crucial in good mental health (Gross, 2002). Associations between poor mental health and deficits in EF are common in both clinical (Snyder et al., 2015) and non-clinical populations (Kim & Whalen, 2009).

Dominant adult EF frameworks such as the Miyake-Friedman model emphasize both the unity and diversity of executive functions distinguishing between updating, shifting and inhibitory control, which, although correlated when measured experimentally, can also be separated (Lee et al., 2013; Miyake et al., 2000). More recent work suggests that IC may function as part of a common factor as it is required for success in the other two areas (Friedman & Miyake, 2017). Developmentally there appears to be a shift from a more general executive control process in younger children to more specialized and separable processes into adolescence (Lee et al., 2013; Wiebe et al., 2008). Importantly, for the topic of emotion regulation, there is a suggestion that different executive functions contribute or are related differently to psychological and behavioural traits. Hofmann and colleagues suggest that working memory directs attention towards desirable stimuli, suppresses ruminative thoughts and down-regulates affect as well as holding personal goals in mind. Inhibitory control on the other hand prevents mindless, habitual behaviours and switching allows for one to move between different ways of achieving the same goal, or moving between goals (Hofmann et al., 2012).

3.1.2 Executive function and emotion dysregulation

Although working memory deficits are often widespread across different forms of psychopathology, there also appears to be some disorder-specificity with the largest effect sizes for individuals with schizophrenia, moderate for those with attention deficit and bipolar disorders, and small for those with depression and obsessive compulsive disorder with slightly larger effects for depression in verbal working memory manipulation (Snyder et al., 2015). Problems with attention are most commonly found in attention deficit and hyperactivity disorder (ADHD), here individuals struggle specifically with sustained attention rather than selective (Huang-Pollock, Nigg, & Carr, 2005).

Developmental work suggests that although inhibitory control (IC) is important for early emotion regulation, high levels of IC can also lead to a rigid cognitive approach and make children more susceptible to internalising disorders (Carlson & Wang, 2007; Fox, 1994; Nigg, 2000). Children with low inhibitory regulation on the other hand, are more likely to experience externalizing problems (Eisenberg et al. (2001). These behaviours appear relatively stable with high levels of in self-restraint in childhood often leading to high in self-restraint as teenagers, together with lower cognitive flexibility (Friedman et al., 2011). Hofmann and colleagues however propose that executive functions could be associated with emotion regulation in a number of ways: as direct predictors/regulators (EF down-regulates emotions), as mediators or moderators, by influencing each other (e.g. as above high inhibitory control reduces cognitive flexibility) or as an outcome of regulation (emotion regulates executive function) (Hofmann et al., 2012).

3.1.3 Emotion and emotion regulation

There are various ways of approaching the measurement of emotion regulation. Much research looks at emotional outcomes, inferring a lack of regulation from negative outcomes. Common measures include measures of internalising or externalising behaviours which are predictive of developing an internalizing pathology such as depression or BPD, or an externalizing pathology such as conduct disorder or ADHD (Snyder et al., 2015), or actual measure of psychopathology. An alternative approach is to look at specific cognitive regulation strategies. Some authors focus on the ability to modulate emotional experience, here ER is something which arises either as a result of emotion or in anticipation of an emotion, such as in the influential 'Process Model' (Gross, 1998) which asserts that emotions are generated over a time-course and regulation can occur at any point with earlier regulation (such as reappraisal) as more successful than later (such as suppression). Other models use a broader range of strategies or response types to stressful situations such as the Cognitive Emotion Regulation Questionnaires (Garnefski & Kraaij, 2007). Other researchers assert that methods which encourage emotional acceptance and valuing, such as mindfulness, are important. They argue that responding negatively to your own emotions is maladaptive and can cause greater difficulties (Gratz & Roemer, 2004). Emotion regulation questionnaires validate themselves on their ability to predict a variety of emotional states. The ERQ for example has been validated on its ability to predict depression, well-being, self-esteem, optimism, likability, extraversion, neuroticism, inauthenticity and rumination (Balzarotti et al., 2010; Gross & John, 2003). DERS predicts generalised anxiety disorder (GAD), Post-traumatic stress disorder (PTSD) and 'delinquent behaviour' in an adolescent sample (Neumann, 2010).

3.1.4 The present study

The present study sought to broadly characterise cognitive and emotional experience, approaches and behaviours from a series of measures collected during adolescence in the ALSPAC sample, and to investigate associations between these cognitive and emotional composite measures during adolescence.

3.1.3.1 Cognition

The data dictionary was used to identify cognitive measures available during adolescence, broadly defined for this study as between the ages of 10 and 20 yrs., with a focus on measures of EF, attention and processing speed, with the exclusion of the Probability Reversal Learning task due to the amount of missing data. The final set of cognitive measures was derived from ten tasks across five time points. Measures were taken across adolescence. Other than one repeated measure, all tasks measured slightly different aspects of executive function and were taken at different ages. Our aim was to broadly characterise executive functioning during adolescence with the available measures and therefore decided to use a data reduction technique, principal component analysis, with the aim of obtaining more general latent measures from (i) variety of tasks (ii) over ages. Furthermore, the study aimed to test whether variables would be related along constructs, tasks or age at time of testing. Although the process was exploratory, we did expect that there would be some kind of working memory component due to the presence of the N-back and the Counting Span task. We also expected there to be an inhibitory control component due to there being two measures of the Stop signal task, a standard motor inhibition task. Other tasks less obviously measured distinct executive functions: the opposite worlds task and digit vigilance, which are both attention tasks, and two reaction time only measures. It was unclear as to whether the processing speed and attentional measures would load alongside the other measures or as their own distinct measures. However, including them allowed the potential identification of more the general cognitive components, processing speed and attention which are both correlated with, and distinguishable from other EFs (Awh & Jonides, 2001; Friedman et al., 2008).

3.1.3.2 Emotion

There were no specific emotion regulation questionnaires in the ALSPAC sample and it was not evident from the questionnaires and interviews available that any particular one would best characterise a broad understanding of how adolescents in general experience and regulate their emotions.

A number of questionnaires were selected on the basis that they would be representing a cognitive approach to emotional situations and their emotions. The *Cognitive Styles Questionnaire Short Form* (Haeffel et al., 2008) presents hypothetical negative events and respondents answer questions about what they believe the cause, consequences, and self-worth implications of the event would be. The *Dysfunctional Attitude Scale* (D'Alessandro, 2005; Weissman, 1979) measures how individuals assign meaning to stressful situations related to the self (Weissman & Beck, 1978). The *Shortened Nowinicki-Strickland Internal/External Locus of control scale* (Nowicki et al., 1971) measures the extent to which an individual believes there is a causal relationship between their actions, positive or negative and the outcome. Believing that behaviour has consequences is a requirement for motivation in regulating emotion. The *Warwick-Edinburgh Mental Well-Being* scale (WEMWBS) to measure mental-health and well-being and measures both cognitive statements "I've been dealing with problems well" and "I've been able to make up my own mind about things" as well as emotional well-being, "I've been feeling loved" and "I've been feeling good about myself". The Bachman revision of *Rosenberg's Self-Esteem Scale* (RSE-B) measures general self-esteem, "I feel I have a number of good qualities" (Bachman, 1970).

Some of the more common measures of 'emotional outcomes' are (i) symptoms of depression or internalizing as measured by the *Moods and feelings Questionnaire* (MFQ) (Angold, Costello, Messer, & Pickles, 1995; Messer et al., 1995), a scale from the *Strengths and Difficulties Questionnaire* (Goodman, Lamping, & Ploubidis, 2010) and negative symptom items from the *Semi-Structured Psychosis-like symptoms interview* (PLIKS), (ii) anxiety measures, such as the *Anxiety Sensitivity Index* (ASI), (iii) externalizing behaviours, as measured by the second scale of the Strengths and Difficulties Questionnaire, *Self-reported anti-social behaviour for young children questionnaire* (adapted from a large study into anti-social activities by Wolke), *Dating Violence questionnaire* (Questions adapted from the Conflict Tactics Scale), and *Edinburgh Study of Youth Transitions and Crime* school misbehaviour sub scale (ESYTC). Sensation seeking, defined as the need for novel and intense stimulation, has also been associated with externalizing behaviours (Arnett, 1994) and reduced emotion regulation (Joseph, Liu, Jiang, Lynam, & Kelly, 2009) and so the *Arnett Inventory of Sensation Seeking (AISS)* was included. Also included are the *Borderline Personality Disorder* assessment (DSM-IV face-2-face interview) and the *Skuse Social Cognition Scale* (SCS) which measures social and emotional understanding thought by some to be an important element of emotion regulation (Gratz & Roemer, 2004). There are also general questions on problematic eating habits, self-harm and self-image that were questions included by ALPSAC, but not part of standard questionnaires.

Finally as certain dimensions of personality have been associated with regulation and emotion types (Balzarotti et al., 2010; Gross & John, 2003), and items from *The International Personality Item Pool* (IPIP) had strong overlap with items from other relevant questionnaires, this was also included. And as peers are particularly relevant to adolescents and their emotional state (Sebastian, Viding, Williams, & Blakemore, 2010), questions about their feelings about their relationships with the peers from the Friends and Peers interview were also included.

This first study will look at behaviours across adolescence attempting to capture more trait-like measures of habitual regulation and see how these relate to general measures of cognition. Principal component analysis will be performed on the selective cognitive and questionnaire data separately in order to create cognitive and affective factors. Next linear and quadratic associations between the cognitive and affective factors will be examined and regression models will be used to assess to cumulative variance explained. We predict that (1) we will extract a measure of working memory (WM) and a measure of inhibitory control (IC) from the cognitive data; (2) from the emotion questionnaires we will derive a measure related to antisocial behaviours and depressive or anxious behaviours as these are most commonly represented in the questionnaires; (3) that we will find associations between these four factors in that lower cognition lead to higher antisocial and depressive tendencies.

3.2 Methods

3.2.1 Study cohort

This first set of analyses uses the ALSPAC sample, and includes 5,838 participants (2,784 males) aged 9yrs 10m to 20yrs for the EF analysis and 6,876 participants (3,252 males) aged 9yrs 10m to 20yrs 1m for the ER analysis. The process of selection from the full sample is described below.

3.2.2 Cognitive Measures

3.2.2.1 Age 10

The **Counting Span task** (Case et al., 1982) (N = 5,347) is a WM task where at the end of each block the participant is asked to recall in order the number of red dots presented on each trial of that block. A *Counting Span score* was calculated from the number of blocks where the information was correctly recalled (M = 18.9, range = 0 – 42).

The **Stop Signal task** (Logan & Cowan, 1984) is an IC task where the participant must respond to X's and O's on the screen by pressing the corresponding button as quickly as possible (Go trials). This establishes a mean RT baseline. On Stop trials a beep played randomly 150ms or 250ms before the participant's baseline RT indicates the participant should refrain from responding. The task started with two practice blocks: first a block of 30 Go trials, then a block of 16 Go trials and eight Stop trials. There were then two experimental blocks of 48 trials, 16 of which were Stop trials (33%). As the number of correct Stop trials in the 150ms and 250ms delay conditions were highly correlated, an average *Stop Signal number of correct Stop trials* across delays was calculated for each individual (N = 5,266) (*M* = 13, range = 4 – 16). The *Stop Signal number of correct Go trials* (N = 5,280) (*M* = 54, range = 23 – 64) and the *Stop Signal Go trials RT* (N = 5,307) (*M* = 599 ms, range = 388 – 818 ms) were also included in our analyses to reflect performance on this task more broadly (for example to consider potentially trade-offs between speed, correct stops and correct key presses) and feed into a potential processing speed component.

3.2.2.2 Age 11

At age 11 three attention tasks from the **Tests of Everyday Attention for Children** (adapted from Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996) were performed. The **Sky Search task** (N = 5,587) assesses selective attention and motor control. Participants had to circle pairs of identical space ships from a large number of similar pairs (distractors) as quickly as possible. The *Selective attention speed* was calculated as the average time spent trying to find a pair minus a motor score, estimated by having asked participants to circle pairs of space ships with no constraints (*M* = 3.5 s, range = −0.4 – 7.8 s). The **Dual task** assesses divided attention (N = 5,534). Participants were required to repeat the task above while counting spaceship noises played throughout the task. A *Dual task decrement score* was calculated as the difference in numbers of pairs correctly identified in the Dual task compared with the Sky Search task (*M* = 0.9, range = −7.2 – 21.6). Finally, the **Opposite Worlds task** assesses attentional control (N = 5,431) (Strauss, Sherman, & Spreen, 2006). In the same world condition participants have to read aloud a sequence of 1s and 2s, while in the opposite world condition participants have to say 1 for the number 2 and 2 for the number 1. Participants read four sequences of 24 numbers each in the order: same world, opposite world, opposite world, same world. The *Opposite World RT cost* was calculated as the proportional difference between opposite and same world RTs and represents the cost of the verbal/visual interference, controlling for same world RT (*M* = 0.3 s, range = −0.2 – 0.8). For these three measures, higher values correspond to poorer attentional control.

3.2.2.3 Age 13.5

At age 13.5 years participants were assessed on the Cognitive Drug Research (CDR) computerised cognitive assessment system (United BioSource Corporation). Participants performed the **Digit Vigilance task** which measures sustained attention. A number was shown on one side of the screen and remained constant while a sequence of different numbers was shown in the middle of the screen. Participants pressed a key when the side and middle numbers matched. A total of 450 numbers were presented over 3 minutes, with 45 targets (10%). Measures on this task were the *Digit Vigilance accuracy* (z-score target detection rate – z-score of false alarms rate) (N = 5,030, *M* = 0.1, range = −5.5 – 1.8) and *Digit Vigilance RT* (N = 5,072, *M* = 428 ms, range = 303 – 572 ms) for correctly detected targets. In the **Simple RT task** (N = 5,041), participants pressed a key labelled YES every time the world YES appeared on the screen. There were 30 trials, presented with varying inter-stimulus intervals. In the **Choice RT task** (N = 5,030), participants pressed keys labelled YES or NO depending on which word was presented on the screen. There was an equal probability of YES/NO trials, with 30 trials presented with varying inter-stimulus interval. Measures were respectively *Simple RT* (*M* = 294 ms, range = 209 – 486 ms), *Choice RT* (*M* = 443 ms, range = 260 – 660 ms) and *Choice RT task number of correct* (*M* = 27, range = 21 – 30)

3.2.2.4 Age 15.5

The **Stop Signal task** from age 10 was repeated, with the same practice and test blocks but slightly different delay times between stimulus and stop signal presentations for different participants. A residual score covarying for delay duration was therefore calculated for the purpose of this study. As at age 10, the measures included in our analyses were *Stop Signal number of correct Stop trials (residual)* (N = 4,769, *M* = 0.1, range = −7.1 – 2.6). *Stop Signal number of correct Go trials* (N = 4,811, *M* = 50, range = 10 - 64), and *Stop Signal Go RT* on correct trials (N = 4,831, *M* = 566 ms, range = 309 – 818 ms). *Verbal IQ* (N = 4,859, *M* = 45.7, range = 8 – 71) and *Matrix Reasoning IQ* (N = 4,854, *M* = 24.7, range = 5 – 80) raw scores were taken from the **Wechsler Abbreviated Scale of Intelligence** (WASI, Wechsler, 1999) interview performed at age 15 (*M* = 15 years 5 months, range=14 years 3 months – 17 years 5 months).

3.2.2.5 Age 17

The **N-back** task, used at age 17 years, is a test of WM, more specifically updating. Participants were presented with numbers 0-9 for 500 ms and had 3000 ms to judge

whether the current number was the same as the number shown either 2-back or 3-back. The practice block consisted of 12 trials with two targets, and there were single blocks of the 2-back and 3-back conditions each consisting of 48 trials with eight targets. Measures on this task were *2-back accuracy* (N = 3,230, *M* = 77%, range = 15% – 100%) and *2-back RT* (N = 3,226, *M* = 680 ms, range = 82 – 1385 ms). In addition, as with the Opposite Worlds task, additional scores were created to represent the added WM cost of 3-back in relation to 2-back. *Accuracy 3-back - 2-back* (N = 3,048, *M* = –10%, range = –60% – 46%) and *RT (3-back – 2back)/2-back*, a proportional difference score which controls for a baseline reaction time and looks at proportionally how much slower each participant is in the harder condition (N = 3,041, *M* = 0.1, range = –0.9 – 1.1).

Gender differences were found in some of the cognitive tasks (**Table 3.1**) and therefore variance explained by gender was removed from the tasks along with age at time of testing.

Table 3.1 Gender differences in the cognitive tasks. Scores are age-regressed to account for the fact that participants completed the tasks at different ages.

Age (y)	Measure	Standardised residual scores[a] (Mean)	
		Males	Females
10	**Counting Span task:** *Score*	-0.159	0.166
10	**Stop Signal task:** *Number of correct Stop trials*	-0.029	0.026
	Stop Signal task*: Number of correct Go trials*	-0.170	0.152
	Stop Signal task: *Go trials RT*	**-3.724***	3.557
11	**Sky Search task**: *Selective attention speed*	0.233	**-0.223***
	Dual task: *Decrement score*	0.086	**-0.082***
	Opposite Worlds task: *RT cost*	0.008	**-0.008***
13.5	**Digit Vigilance task**: *Accuracy (targets – false-alarms)*	-0.177	**0.167***
	Digit Vigilance task: *RT*	**-1.596***	1.541
13.5	**Simple RT task:** *Simple RT*	**-1.653***	1.560
	Choice RT task: *Choice RT*	**-6.807***	6.432
	Choice RT task: *Number of correct trials*	-0.346	**0.329***
15	**WASI subtest:** *Vocabulary*	**0.389***	-0.344
	WASI subtest: *Matrix Reasoning*	0.013	-0.012
15.5	**Stop Signal task:** *Number of correct Stop trials*	**-0.154***	0.140
	Stop Signal task: *Number of correct Go trials*	0.289	-0.265
	Stop Signal task: *Go trials RT*	**-4.472***	4.066

17	**N-back task:** *2-back accuracy*	**0.011**	-0.009
	N-back task: *2-back RT*	-4.715	3.568
	N-back task: *Accuracy 3-back - 2-back*	-0.004	0.003
	N-back task: *RT (3-back – 2back)/2-back)*	0.028	**-0.022***

* Indicates this score is significantly better than that of the other gender (p< .05)
[a] Scores are the saved residuals from a regression analysis performed with age at time of testing.

3.2.3 Emotion Measures

The data dictionary was used to identify measures relating to emotional expression, regulation and awareness available during adolescence. These could be behavioural expressions of emotion such as "Often fights or bullies other teenagers", "Is often unhappy, down-hearted, tearful", or regulation strategies "Teenager avoids thinking about traumatic event", "Teenager usually thinks when bad things happen to them it is somebody else's fault". These were taken from a range of questionnaires (**Table 3.2**).

Table 3.2: Summary of emotion related questionnaires

Questionnaire & Reference	Description
3.2.1 Development and Well-Being Assessment (DAWBA) (Goodman, Ford, Richards, Gatward, & Meltzer, 2000)	Assessment of children from 2-17year olds, for up to 17 psychiatric disorders
3.2.2 Strengths and Difficulties Questionnaire (SDQ) (R. Goodman, 1997)	Assessment of behavioural strengths as well as difficulties five scales represent: emotional problems, conduct problems, hyperactivity, peer problems and prosocial behaviour
3.2.3 Short Moods and Feelings Questionnaire (SMFQ) (Angold, Costello, Messer, Pickles, et al., 1995)	Assesses depressive symptoms in children and adolescents
3.2.4 Warwick-Edinburgh Mental Well-Being scale (WEMWBS) (Tennant et al., 2007)	Assesses mental well-being and its contribution to all aspects of life
3.2.5 Cognitive styles questionnaire short form (CSQ-SF) (Haeffel et al., 2008)	Measures a 'negative inferential style' or cognitive vulnerability
3.2.6 The International Personality Item Pool (IPIP) (Goldberg, 1999)	Provides dimensional measures of extraversion, neuroticism, agreeableness, conscientiousness and openness to experience
3.2.7 Semi-structured Psychosis-like symptoms interview (PLIKS) (Shaffer et al., 2000)	Assesses negative symptoms (depressive) and is based on DISC-IV assessment criteria for children
3.2.8 Edinburgh Study of Youth Transitions and Crime school misbehaviour sub scale (ESYTC) (Smith et al., 2001)	Aims to understand the causes of criminal and risky behaviours in young people
3.2.9 Shortened Nowinicki-Strickland Internal/External Locus of control scale (Nowicki et al., 1971).	Assesses the extent to which participants believe there is a causal relationship between themselves and things that happen to them (measuring resilience)

Questionnaire & Reference	Description
3.2.10 Arnett Inventory of Sensation Seeking (AISS) (Arnett, 1994)	Assesses sensation seeking behaviour in the children and adolescents
3.2.11 Anxiety Sensitivity Index (ASI) (Reiss et al., 1986)	Assesses physical and mental concerns about the types of sensations experienced during a period of anxiety
3.2.12 Bachman revision of Rosenberg's Self-Esteem Scale (RSE-B) (Bachman, 1970)	Self-Esteem Scale designed for adolescents
3.2.13 Dysfunctional Attitude Scale (DAS) (Weissman, 1979)	Measures core beliefs about the world, relationships with others and their approval as well as judgments on their own performance
3.2.14 Borderline Personality Disorder assessment (Zanarini, 2003)	Assesses affective stability, interpersonal relationships and impulsivity. Adapted from the DSM-IV face-2-face interview for the assessment of behaviours in general rather than diagnosis
3.2.15 Skuse Social Cognition Scale (SCS) (Skuse et al., 1997)	Assesses the dominant features of social cognition in children
3.2.16 Dating Violence questionnaire (Arriaga & Foshee, 2004)	Measures extent to which an adolescent is aggressive towards and has experienced aggressive behaviour from a partner
3.2.17 Self-reported anti-social behaviour for young children questionnaire (ASLAPC/Wolke)	Individuals asked if they get into trouble at school or with police, get into fights or destroy things for fun.
3.2.18 There are also general questions on behaviour social skills, eating habits, self-harm and self-image.	Positive aspects of self-image and social skills, maladaptive eating and other behaviours and self-harm. See **Supplementary Table 2.2** for full list of questions.
3.2.19 Friends and Peers interview (Wolke et al., 2001)	Assesses bullying and victimisation either directed at or by, child/adolescent

Items that were repeated over time were averaged. For example, items such as "Child has bullied or threatened people" appeared at seven different time points or "In the past two weeks I felt miserable or unhappy" appeared at nine time points and therefore a mean score was taken from all occurrences. This left 579 items, with high levels of missing data (26-100%). In order to prepare the dataset for imputation (section 3.2.4) it was necessary to reduce the data to a set of variables which had at least 50% of the data per participant and per variable, retaining key variables where possible. It was possible of course to just restrict the data immediately to variables which had 50% data available but this was undesirable for a few reasons. Firstly, it is not entirely clear whether one should do this from the perspective of participants or variables first. This would have meant prioritising individuals or variables with more data, which in the case of individuals would have automatically meant a skewed sample (**Table 3.3**) and in the case of variables this would have been skewed towards variables measured early in adolescence as drop out increased over age (**Chapter 2.1**), furthermore it would not necessarily have resulted in the most

informative variables. The optimum solution would be 50% complete data of the most desirable variables with the largest range of participants possible. Therefore, first, variables with such high levels of missing data that it was not possible to perform PCA were removed, second, a missing data matrix identified other variables with particularly low response rates. Third, an initial PCA was performed to guide variables for exclusion. Finally, participants missing more than 50% of variables were excluded at this stage (**Figure 3.1**).

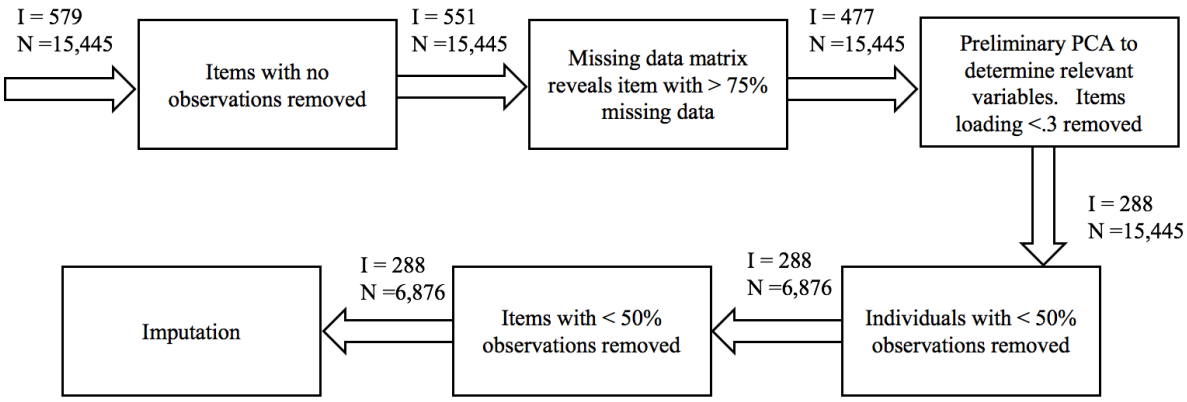


Figure 3.1: *Schematic representation of the process by which emotion items were selected for imputation. I = number of items, N = number of individuals*

Items without any observations or too few to correlate with other items were removed from further analysis leaving 551 items. A missing data matrix allowed us to establish that 74 variables had more than 75% missing data (<4,000 observations) and were therefore also removed further analysis leaving 477 items. In order to determine which variables were most relevant for analysis a preliminary PCA was then performed with items loading under 0.3 removed from further analysis[5]. The scree plot indicated that a 6-factor solution would be best however the 6th factor largely double loaded with another factor whereas the 5-factor solution had clear and distinct interpretable factors with a similar model fit to 6 (5-factor fit=.87 RMSR=.04, 6-factor fit=.89 RMSR=.03). Therefore, the more parsimonious model was selected. The factor fit is calculated by dividing the sum of the squared residuals, by the sum of the squared correlations, and then subtracting this number from 1 thereby giving you a number between zero and one.

[5] Note that although it is possible to perform as PCA based on a correlation matrix and therefore complete data is not necessary, it is not possible to compute factor scores without complete data.

In the next step, 189 variables were removed for not loading onto the 5-factor solution, leaving 288 for imputation. Evidence shows that there are some differences between how males and females regulate their emotions (Balzarotti et al., 2010; Bender, Reinholdt-Dunne, Esbjørn, & Pons, 2012; Brody & Hall, 2008). In order to ensure that the factors were not being driven by sex differences, a complete case principal component analysis was then performed separately for males (N=303) and females (N=447) to assess whether there were any differences in the factors derived. The factors derived were the same and the loadings very similar. Therefore, all participants were analysed together with sex regressed out to remain consistent with the EF measures.

3.2.4 Imputation

Missing data is an inevitable problem when working with longitudinal data due to participant drop-out or non-response. Restricting analyses to only children with complete data risks introducing potential biases (Schafer & Graham, 2002) and greatly reduces statistical power due to reduced sample size. Furthermore, we were interested in using the measures in genetic analyses and therefore needed the largest possible sample size. In the present study 1,070 participants had complete EF data, and 750 participants had complete ER data, both sample sizes too small for a genetic study. The missing cognitive data proportion was significantly correlated with SES, IQ and academic achievement (Table 2) making the data not missing completely at random (MCAR). The fact that there was systematic bias in the missing data made it appropriate to impute missing data. This is because using only complete case data would mean excluding those with lower cognitive ability and SES, however including these variables in our imputation model allows us to model these differences and estimate their scores.

Table 3.3: Correlations between percentage of missing cognitive and emotion data and attainment, other cognitive phenotypes and socio-economic status

	Verbal IQ	Matrix IQ	SES	Age 11 English	Age 14 English	Age 11 Maths	Age 14 Maths	Age 11 Science	Age 14 Science
% of missing EF data	-0.16***	-0.04*	-0.15***	-0.25***	-0.26***	-0.25***	-0.33***	-0.29***	-0.34***
% of missing ER data	-0.09**	-0.03	-0.14***	-0.15***	-0.19***	-0.14***	-0.19***	-0.16***	-0.20***

Pearson's correlation *p<0.01, **p<.001, ***p<1e^{-10}. Correlations were carried out on full sample of 15,445.

The decision was made to impute missing data using the current best method (Schafer & Graham, 2002), multiple imputation using chained equations, for participants with > 50% complete data and with the constraint that each variable < 50% data missing (Buuren & Groothuis-Oudshoorn, 2011; White, Royston, & Wood, 2011). Many of our variables were not normally distributed and so we considered it preferable to impute based on raw rather than normalized data and use predictive mean matching ('meth = pmm'), which is

considered the best imputation method in this scenario (Azur, Stuart, Frangakis, & Leaf, 2011; White et al., 2011). Imputed and non-imputed distributions were compared and then variables were rank normalised (Beasley, Erickson, & Allison, 2009; Bishara & Hittner, 2012; Schafer & Graham, 2002; Solomon & Sawilowsky, 2009). Imputation was performed separately for the emotion and cognitive data. Measures of IQ (2.2.2.6), SES (2.2.1), AA (2.2.4) were included in both imputation models. The emotion imputation also included the already imputed cognitive variables. Additional missing data from cognitive variables were not imputed to avoid imputing individuals who lacked raw cognitive data. Including covariates and outcome measures in the imputation model is important in addressing the missing at random (MAR) assumption and improves the imputation model (Buuren & Groothuis-Oudshoorn, 2011; White et al., 2011). All subsequent results using imputed data (cognitive data, N = 5,478, emotion data, N=6,876) were compared with analyses of the complete case data (cognitive data, N = 1,070, emotion data, N=750). Pre- and post-imputation distributions were compared as were correlations between variables.

3.2.5 Statistical analysis

Principal component analysis (PCA) was used to identify measures that could be combined into latent measures of EF, processing speed, attention, or other aspects of cognition. A cut-off criterion for item loading was fixed at 0.3 and with the condition that the overall and individual Kaiser-Meyer-Olkin (KMO) values, a measure of sampling adequacy, were over 0.5. Oblimin oblique rotation was used as previous studies indicate it is appropriate when the inter-correlation between components is high (Field, Miles, & Field, 2012). All statistical analyses were conducted using R (R Core Team, 2013) using the 'psych' package (Revelle, 2018). Missing data was imputed using the 'mice' package (Buuren & Groothuis-Oudshoorn, 2011; White et al., 2011).

As expected all measures were correlated with age at time of testing and some measures also showed associations with gender (**Table 3.1**). Therefore, all measured were regressed on age and gender. Outliers further than 3.29 SD from the mean for each cognitive measure were excluded, removing 806 data points across 18 variables. These points were treated as missing data and imputed. Multiple regression analyses were used to assess the variance explained in the cognitive data by the emotion measures and vice versa.

3.3 Results

3.3.1 Principal component analyses

3.3.1.1 Cognitive Data

The Bartlett's test of sphericity, performed with all 19 cognitive variables, indicated that correlations between items were sufficiently large for PCA (χ^2 (171) = 23069.04, p < .001). The *Accuracy 3-back – 2-back* measure (age 17) was removed from the analysis as it had a KMO value of less than 0.5, this left an overall KMO of 0.68. The first two factors explained the most variance and although the scree plot was unclear, it suggested a 5-factor solution and so we compared solutions between 2 and 5. The 3-factor solution had the best fit statistics and retained the most number of variables (2-factor fit= .64 RMSR=.11; 3-factor fit= .80 RMSR=.08; 4-factor fit= .78 RMSR=.08; 5-factor fit= .66 RMSR=.10) and was therefore selected.

In a second stage, *Opposite World RT cost* at age 11 was removed as it did not load onto any of the three factors above 0.3 and *Stop Signal number of correct Stop trials* at age 10 was removed as it loaded both on the second and third components. Finally, *2-back RT* (age 17) and *Choice RT task number of correct trials* (age 13) were removed from the analysis for double loading on components one and two. Fourteen variables were retained for a final three-component solution which explained 45% of the variance in the data and had a model fit of 0.80 with correlations between principal components one and two being r = 0.4, between one and three r = -0.2, and finally between two and three r = -0.02. **Table 3.4** shows the final component loadings after rotation.

The first component (PC1) consisted of positive loadings of RT measures across tasks and ages with low RTs associated with a high PC1 score, we named this component *Processing Speed*. The second component (PC2) included measures from the N-back and Counting Span tasks, which are both WM tasks. Digit vigilance is a sustained attention task primarily, however much literature argues that attention and WM are overlapping concepts (e.g. Awh & Jonides, 2001; Fougnie, 2008; Wendelken et al., 2011). Finally, the Dual task could also be conceptualised as reflecting WM abilities, as participants needed to keep and update a number in verbal WM while performing a visuospatial task. This component was therefore named *Working Memory*, with a high PC2 score reflecting better WM. Variables constituting the last component (PC3) all came from the Stop Signal task administered at age 15. Within this component the highest loading variable quantified the ability to 'Stop' when a beep was heard, followed by a slow RT in Go trials and poorer accuracy in Go trials, reflecting the common result of slowing responses to increase stopping accuracy (Verbruggen & Logan, 2009). We therefore named this component *Inhibitory Control*, where a high measure reflects better inhibitory control.

Table 3.4: Component loadings in the final cognitive measures PCA. PC: principal component

Variable description	*PC1 Processing Speed*	*PC2 Working Memory*	*PC3 Inhibitory Control*
Digit vigilance RT (age 13)	**0.80**	0.20	−0.07
Choice RT (age 13)	**0.74**	−0.13	0.07
Simple RT (age 13)	**0.66**	−0.20	0.04
Stop Signal Go trials RT (age 10)	**0.49**	0.01	0.18
Selective attention speed (age 11)	**0.41**	−0.11	−0.09
2-back accuracy (age 17)	−0.08	**0.75**	0.00
Digit Vigilance accuracy (age 13)	0.12	**0.72**	0.01
Counting Span score (age 10)	−0.12	**0.60**	0.04
RT (3-back – 2-back)/(2-back) (age 17)	0.00	**0.55**	0.01
Dual task decrement score (age 11)	−0.09	**−0.42**	0.04
Stop Signal number of correct Stop trials (age 15)	−0.11	0.14	**0.83**
Stop Signal Go trials RT (age 15)	0.17	−0.04	**0.79**
Stop Signal number of correct Go trials (age 15)	0.02	0.18	**−0.66**
Eigenvalues	2.26	2.16	1.82
% of variance explained	16%	15%	13%
α	0.65	0.60	0.66

Factor scores for each individual were computed using the R psych package 'principal' which uses regression where the regression weights are $R^{-1}\lambda$ where λ is the matrix of component loadings. The regression weights are found from the inverse of the correlation matrix times the component loadings. This results in standardised component scores. Cronbach's alpha was computed for each scale and *Stop Signal number of correct Go trials* was removed from processing speed as it reduced the overall alpha.

3.3.1.2 Emotion Data

The 288 emotion items selected for imputation from the original 579 items (**Figure 3.1**) were then entered into a principal component analysis post-imputation. The Bartlett's test of sphericity indicated that correlations between items were sufficiently large for PCA, (χ^2 (41041) = 1100356, $p < .001$) with an overall Kaiser-Meyer-Olkin factor of 0.96. The scree plot indicated that a two factor solution explained the majority of the variance but that variance continued to be explained up to five factors. Therefore, a PCA was performed on a five-factor solution to allow for more types of emotion behaviour to be represented. Items loading below 0.3 or which double-loaded on two factors were removed, leaving 244 variables for a final five-component solution which explained 30% of the variance in the data and had a model fit of 0.93. **Supplementary Table 1** shows the final component loadings after rotation.

The first component (PC1) consisted of questions relating to aggressive and anti-social behaviours. Many of the questions came from the DAWBA looking at troublesome behaviours, the SDQ externalising behaviours and questions from SKUSE in relation to understanding others. Therefore, this factor was called *Externalising*. The next two components had similarities and differences. They both referred to worries: non-specific worries for component 3, and worries about health, what other people think, and the future, for component 2. They also both included items about negative feelings towards oneself. The third factor was more dominated by feelings of moodiness, sadness and loneliness as well as having low energy and feeling disinterested. The second component on the other hand referred more to catastrophizing, holding in one's feelings, feeling indecisive and not useful. Overall as items in component 2 referred more to worries about future problems this component was called *Anxiety*, while items in component 3 focused on a more present sense of worry, sadness and worthlessness and so we named this *Internalising*. Nolen-Hoeksema et al. (2008) pointed out that anxious rumination as opposed to depressive rumination as generally worry focused on future threats, or on the future implications of past threats. The final two factors were more positive. The fourth factor had items representing energy, being talkative, confident and having fun, it was therefore called *Extraversion*. Finally, the fifth factor had items reflecting diligence, helpfulness, focus and intelligence, and was consequently named *Conscientiousness*. **Table 3.5** gives an overview of the types of questions that were in each factor.

Table 3.5: Emotion PCA factor description

Factor	Question type
Externalising	Anger directed outwards: "Has severe tantrums" Poor relationships with others: "Often starts fights", "Is not generally liked by others" Lack of understanding: "Not aware of others feelings", "Cannot follow commands unless carefully worded" Deliberate behaviour: "Lies to get favours or get out of things", "Takes no notice of rules or refuses to do as told". Disruptive and antisocial behaviour: "Is involved with stealing on the streets" Difficulties in regulating emotion both in the short term "is difficult to reason with when upset" and long term "Does not bounce back quickly after setbacks".
Internalising	Moods and Feelings questionnaire questions: "I feel lonely", "I feel miserable or unhappy" PLIKS negative symptoms: "Has felt guilty", "Has cried about nothing", "is lacking in get up and go" IPIP, "Feels they have frequent moods swings", "feels others emotions" "feels they get upset easily"
Anxiety	Anxiety Sensitivity index: "Unusual feelings in YP's body scare them" and "YP does not like to let their feelings show" Cognitive Styles Questionnaire, "not being able to develop a close friendship with a specific person they like means there is something wrong with YP as a person", or "not being in an intimate relationship is YP's fault" Dysfunctional Attitudes scale, "if a person is not a success then his/her life is meaningless" showing a cognitive inflexibility with very rigid conclusions

	Mental wellbeing scale, "Frequency YP has not been feeling close to other people in the last 2 weeks" Self-esteem scale; "YP feels they cannot do anything right".
Extraversion	Orientated around being sociable, "Teenager talks to lots of different people at parties", "Teenager feels they make people feel at ease" active "Feels sporty"/" Feels active"/" Feels lively" and confident "Feels confident", Doesn't mind being centre of attention". Sensation seeking "When I listen to music, I like it to be loud" and "Enjoy playing sports and activities which could be dangerous".
Conscientiousness	Negatively loading sensation-seeking items "Don't worry about coming home late" and "Don't do homework until the last minute". Concentration "I can concentrate well", "feels focused" Planning "Teenager always follow a plan", Diligence "Feels hardworking", "They get the household tasks done straight away and Confident in their ability "Feels they have excellent ideas", "Feels they are quick to understand things".

Table 3.6 shows the Pearson's correlation matrix looking at the basic relationships between the cognitive and emotion factors. The three negative emotion factors (internalising, externalising and anxiety) are positively correlated and they are all negatively correlated with the positive factors (extraversion and conscientiousness) apart from extraversion and externalising. Their correlations with the cognitive factors go in the expected directions for working memory and processing speed but are more variable for inhibitory control which shared a negative relationship with internalising and no relationship with the other factors.

Table 3.6: Correlation matrix of cognitive and emotion factors

	1	2	3	4	5	6	7
1. Externalising							
2. Anxiety	.164[c]						
3. Internalising	.285[c]	.429[c]					
4. Extraversion	-.005	-.176[c]	-.110[c]				
5. Conscientiousness	-.131[c]	-.101[c]	-.087[b]	.036[a]			
6. Inhibitory Control	-.015	-.010	-.043[a]	.003	-.033		
7. Working Memory	-.190[c]	-.113[c]	-.074[b]	.004	.132[c]	-.024	
8. Processing Speed	.064[b]	.059[b]	.038[a]	-.104[b]	-.068[b]	.128[c]	-.207[c]

Pearson's correlation [a] $p<0.01$, [b] $p<.001$, [c] $p<1e^{-16}$.

3.3.2 Regression analyses

Tables 3.7 and **3.8** show the results of the regression analyses with the cognitive variables explaining the most variance in externalising and conscientiousness (4.4 and 4.5%) and considerably less in internalising, anxiety and extraversion (1.6 and 1.4%). WM explained the most variance in the maladaptive emotion traits (externalising,

internalising and anxiety), whereas processing speed explained the most variance in extraversion and verbal IQ in conscientiousness.

Table 3.7: Regression analysis showing the variance explained in the emotion PCA measures by the cognitive PCA and IQ measures

	Externalising		Internalising		Anxiety		Extraversion		Conscientiousnes s	
	β [95% CI]	*ΔR² (%)*	*β [95% CI]*	*ΔR² (%)*	*β [95% CI]*	*ΔR² (%)*	*β [95% CI]*	*ΔR² (%)*	*β [95% CI]*	*ΔR² (%)*
Verbal IQ	-.093 [-.122, -.065]	0.70[c]	.100 [.071, .130]	0.80[c]	-.022 [-.052, .007]	0.02	-.049 [-.079, -.020]	0.20[b]	.180 [.151, .209]	2.60[c]
Matrix IQ	-.001 [-.028, .025]	-0.02	.023 [003, .050]	0.03	.004 [-.031, .023]	-0.02	-.036 [-.063, -.009]	0.10[b]	-.008 [-.034, .019]	-0.01
Inhibitory Control	-.034 [-.059, -.008]	0.10[b]	-.036 [-.062, -.010]	0.10[b]	-.020 [-.046, .007]	0.02	.011 [-.016, .037]	-0.01	.004 [-.030, .022]	-0.02
Processing Speed	.025 [001, .051]	0.05	.032 [.005, .058]	0.10[a]	.038 [.012, .065]	0.10[b]	-.110 [-.137, -.083]	1.10[c]	-.034 [-.060, -.007]	0.10[a]
Working Memory	-.138 [-.168, -.109]	1.40[c]	-.120 [-.150, -.090]	1.10[c]	-.092 [-.123, -.062]	0.60[c]	.015 [-.016, .045]	-0.001	.043 [.014, .073]	0.10[b]
Total variance explained %	4.40%[c]		1.60%[c]		1.40%[c]		1.40%[c]		4.50%[c]	

[a]p<0.05, [b]p<.01, [c]p<.001

The PCA emotion measures explained the most variance in working memory and almost half of this was uniquely explained by externalising, with a further 1% uniquely explained by conscientiousness. Inhibitory Control had a very small amount of variance explained and it would seem mostly by internalising. Processing speed was mostly related to extraversion.

Table 3.8: Regression analysis showing the variance explained in the cognitive factors by the emotion traits

	Working Memory		Inhibitory Control		Processing Speed	
	β [CI]	*ΔR²*	*β [CI]*	*ΔR²*	*β [CI]*	*ΔR²*
Externalising	-.172[c] [-.199, -.144]	2.53%	-.009 [-.037, .020]	-0.01%	.054[c] [.026, .082]	0.20%
Anxiety	-.088[c] [-.117, -.059]	0.60%	.007 [-.023, .037]	-0.01%	.032 [a] [.002, .068]	0.10%
Internalising	.014	>-0.01%	-.048[b]	0.20%	-.005	-0.02%

	[-.015, .043]		[-.078, -.017]		[-.034, .025]	
Extraversion	-.014	>0.01%	.000	-0.02%	-.097[c]	0.90%
	[-.040, .012]		[-.036, .027]		[-.124, -.078]	
Conscientiousness	.105[c]	1.00%	-.038[b]	0.10%	-.055[c]	0.30%
	[.079, .131]		[-.065, -.011]		[-.082, -.029]	
Total variance explained %		5.3%[c]		0.2%[a]		1.8%[c]

[a]p<0.05, [b]p<.01, [c]p<.001

3.3.3 Linear vs quadratic relationships

We then went on to test the hypothesis that relationships between the cognitive and emotion factors could be quadratic rather than linear and found that nine of the associations had a significant quadratic effect, however mostly the quadratic term explained only a small amount of extra variance (< 1%, **Table 3.9**).

Table 3.9: Table of significant quadratic models of the relationship between cognitive and emotion measures

	Linear model (*df*=1,5560)	Quadratic model (*df*=2,5559)	Quadratic vs Linear
Working Memory ~ Externalising	F = 208.9, p<.001, R^2 = 3.60%	F = 106.6, p<.001, R^2 = 3.66%	ΔR^2 = 0.06%, p=.042
Working Memory ~ Internalising	F = 30.69, p<.001, R^2 = 0.53%	F = 24.98, p<.001, R^2 =0.86%	ΔR^2 = 0.32%, p<.001
Working Memory ~ Conscientiousness	F = 99.12, p<.001, R^2 = 1.73%	F = 61.19, p<.001, R^2 = 2.12%	ΔR^2 = 0.39%, p<.001
Processing Speed ~ Conscientiousness	F = 25.71, p=.004, R^2 < 0.00%	F = 16.48, p<.001, R^2 = 0.55%	ΔR^2 = 0.55%, p=.007
Externalising ~ Working Memory	F = 208.9, p<.001, R^2 = 3.60%	F = 110.5, p<.001, R^2 =3.79%	ΔR^2 = 0.19%, p<.001
Anxiety ~ Working Memory	F = 71.91, p<.001, R^2 = 1.26%	F = 39.14, p<.001, R^2 =1.35%	ΔR^2 = 0.09%, p=.012
Extraversion ~ Working Memory	F = 0.103 p=.748, R^2 = -0.02%	F = 3.141, p=.012, R^2 = 0.08%	ΔR^2 = 0.09%, p<.013
Extraversion ~ Inhibitory Control	F = 0.051, p=.821, R^2 = -0.02%	F = 3.404, p=.033, R^2 = 0.09%	ΔR^2 = 0.10%, p=.009
Extraversion ~ Processing Speed	F = 60.74, p<.001, R^2 = 1.06%	F = 32.88, p<.001, R^2 = 1.13%	ΔR^2 = 0.07%, p=.026

Figure 3.2 plots the quadratic models where $\Delta R^2 > 0.1\%$. Broadly, these plots show that the associations between the emotion and cognitive measures were mostly driven by individuals with lower cognitive skills (low working memory, slow processing speed) and higher levels of emotional problem behaviour (internalising, externalising) or low level of conscientiousness.

Figure 3.2: *Scatterplots and quadratic fits of the models where the quadratic term explained more than 0.1% unique variance.*

3.4 Discussion

The aim of this first study was to identify latent measures of cognitive abilities and emotional behaviours in the adolescent ALSPAC sample and investigate the associations between these measures. The PCA on the experimental cognitive measures identified

three components: working memory, inhibitory control and processing speed. The PCA on emotional behaviour questionnaires identified five factors: externalising, internalising, anxiety, extraversion and conscientiousness. Overall only small associations were observed between the cognitive and emotion measures, with some evidence of stronger associations between lower cognitive abilities and higher levels of problem behaviours.

3.4.1 Cognitive PCA

The PCA derived three cognitive components: working memory, inhibitory control and processing speed. Due to the fact that the measures had been taken at different time points, and the same tasks were not replicated (other than the Stop Signal task), there was a possibility that the variables would cluster based on age or task specific non-executive processes such as numerical processing. The three-factor solution however found that both working memory and the processing speed measures had variables from across the range of ages and tasks suggesting that they are measuring an underlying construct unrelated to age or task specific features. Conversely the inhibitory control measure only had measures from the age 15 stop signal task therefore loading both within task and age. It is possible that this task did not really successfully measure variance in inhibitory control due to task-specific limitations (parameter problems) or perhaps the age group tested. The Stop Signal task at age 15 was limited by the fact that different parameters had been set for different groups of participants. We corrected for this by regressing out the parameters from our scores, however this assumed a linear effect of delay time on accuracy. It has been suggested by Miyake and Friedman (2012) that inhibitory control does not explain any unique variance in executive functioning after the common variance between measures has been accounted for. Therefore, perhaps there is little unique inhibitory specific variance once working memory and processing speed have been accounted for and we are just picking up task specific variance.

The WM component was dominated by accuracy in the 2-back task and in the Digit Vigilance task. Both of these tasks require holding a number in working memory and updating this information when necessary. Additionally, they both require sustained attention. This is consistent with the view that WM and attention or executive attention are highly overlapping (Fougnie, 2008; Wendelken et al., 2011) or interchangeable constructs which involve the selection and maintenance of certain information in an active accessible state particularly in the presence of interference (Awh & Jonides, 2001; Kane, Bleckley, Conway, & Engle, 2001; Shimi & Scerif, 2017; Wendelken et al., 2011). The other updating measure present in the dataset (*Accuracy 3-back – 2-back*) was removed from the analysis due to a low KMO score which indicates little shared variance

between that and other measures. Perhaps the 3-back relies on more complex updating and manipulation skills or an alternative strategy than the 2-back and other working memory tasks. Three variables were removed from the PCA analysis for double loading and all of these variables double loaded with the WM component suggesting it could be representing a more general ability, rather than be specific to updating. The *Opposite World RT cost* was the only measure in the dataset representing shifting, and perhaps for this reason it failed to load on to any of the other factors.

Processing speed, not technically an executive function, has been modelled by many researchers interested in the unity and diversity of EFs as an important, but separate, factor (e.g. Huizinga et al., 2006; Kail, 2000; McAuley & White, 2011, see Lee et al., 2013 for discussion) due to its key role in cognition. Processing speed is highly correlated with white matter integrity (Kievit et al., 2016), has a strong developmental trajectory and appears to moderate fluid intelligence and working memory (Fry & Hale, 2002; Huizinga et al., 2006; Kievit et al., 2016; Lee et al., 2013; McAuley & White, 2011). Some have suggested that processing speed represents a constant underlying feature of our intelligence which explains individual differences within age, whereas executive functions explain the development of intelligence (Anderson, 2001). The processing speed measure contains reaction time variables from almost every measure across the different ages, other than the N-back and therefore seems to reflect a stable ability. In order to test the hypothesis that common variance in executive function could simply represent processing speed, Friedman and colleagues performed a confirmatory factor analysis and found it to be highly correlated with common EF (.67) and to a lesser amount with updating (.19) but also significantly different from all of them (Friedman et al., 2008). However, the Friedman et al. study shows how closely related processing speed and executive function are.

3.4.2 Emotion PCA

A five-factor solution in the PCA data allowed for the inclusion of positive as well as negative emotional behavioural regulation components. Although conscientiousness and extraversion would generally be considered more personality types rather than emotion-regulation measures, for the purposes of this thesis they are useful in representing a 'well-regulated' model to the extent that conscientiousness represents positive self-esteem and extraversion represents positive relationships with others which lie in contrast to the other three measures. This meant it was possible to test whether these more positive behavioural traits were associated with cognitive measures in a different way to the more negative behavioural traits. Conscientiousness was consistently related to higher cognitive ability, whereas extraversion showed more variable results (**Table 3.7**).

Extraversion has five items from the sensation seeking questionnaire positively loading which has been considered to be fundamental to extravert behaviour (Aluja, Garcia, & Garcia, 2003). However, sensation seeking has also been associated with risk-taking and addiction (Zuckerman, 2014) and therefore positive social relationships are not necessarily an indicator of 'adaptive' emotion regulation.

A two-factor solution would have found externalising and internalising solution as has been classically characterised (Achenbach, 1966). A five-factor solution found internalising to be split into anxiety and internalising with anxiety explaining the second largest amount of variance. Among the anxiety scale there are many self-blame and catastrophizing strategies, worry about the future and themselves in comparison to others. Internalising on the other hand, is more about general worry, moodiness, sadness and loneliness which are more associated with depression (Angold, Costello, Messer, & Pickles, 1995). It is possible that this higher proportion of variability explained by anxiety could be adolescence-specific due to the continued development of the social brain and increased importance of peers making them more vulnerable to peer evaluation (Blakemore, 2008; Sebastian et al., 2010).

In terms of the externalising factor, it is unclear whether the bad behaviour represented is due to a lack of understanding of others, or deliberate behaviour. This may reflect etiological differences in externalising behaviours as has been found within conduct disorder, where children show different levels of emotional processing in response to fear as a function of callous and unemotional traits (Sebastian et al., 2012).

Overall, the negative emotions (externalising, internalising and anxiety) are positively correlated with each other as are the positive emotions (extraversion and conscientiousness). The negative and positive emotions are negatively associated with each other with the exception of extraversion and externalising which are unrelated.

3.4.3 Relationship between EF and ER

The cognitive and emotion PCA measured explained a very small amount of variance in each other. The most being the variance explained in working memory by the other variables. On the other hand, working memory and externalising behaviour were fairly highly correlated considering the general nature of the measures (r = .19).

Little variance in internalising, anxiety or extraversion was explained by the cognitive variables (~2%). Almost all of the variance in internalising was explained uniquely by verbal IQ and working memory. Just under half of the variance in anxiety was uniquely

explained by working memory. Almost all the variance in extraversion explained by the cognitive variables was uniquely explained by processing speed. A slightly higher 4.4-4.5% of the variance in externalising and conscientiousness was explained by the cognitive variables with just over half of this was uniquely explained by verbal IQ for conscientiousness, and a third by working memory for externalising. A larger 5.3% of working memory was explained by the emotion measures, almost half of this was uniquely explained by externalising. Almost no variance in inhibitory control was explained (>1%), and only 1.8% variance in processing speed was explained, half of this uniquely by extraversion. Interestingly, pairwise correlations and the regressions showed that internalising was negatively associated with IC, and to a greater extent than externalising. This is the opposite of what would be predicted from the literature, where high IC predicts internalising and low IC predicts externalising (Carlson & Wang, 2007). However, these studies have generally been performed in young children; adult clinical studies find that depressed individuals make more errors and are slower in inhibitory control tasks (Gohier et al., 2009). Therefore, it is possible that the relationship found in childhood, is no longer relevant by adolescence.

To explore these relationships further analyses tested whether the pairwise associations were better fitted by linear or quadratic models. There were a number of relationships in which the quadratic term explained extra variance in the model, however, on the whole the quadratic term increased the variance explained by only a small amount (<1%). Cases where the quadratic fit explained > 0.1% of the variance were plotted. Above average levels of internalising were associated with lower levels of working memory, whereas lower levels of internalising were not associated with working memory. Similarly, lower levels of conscientiousness were associated with lower levels of working memory and slower processing speed and these relationships also disappeared with higher levels of conscientiousness. Finally, the association between working memory and externalising was consistently negative on both sides of the distribution, however, the correlation was stronger where levels of working memory were low and externalising was high. There were two instances where there was no linear relationship but a small but significant quadratic relationship: this was between extraversion and the two executive function measures. Both high and low levels of inhibitory control and working memory were associated with lower levels of extraversion.

Overall there was not a large relationship here between cognitive and emotional measures. They explained a small amount of variation in each other, but interestingly there was a suggestion that ER explained more variance in the cognitive data rather than the other way around. Analyses of the paired associations suggest that high levels of

negative emotion and low levels of positive emotion are associated with negative cognitive outcomes, but that the opposite pattern does not confer cognitive benefits.

IC predicts a very small amount of variance considering it seems to be the main driving factor in early childhood emotion regulation. One option is that it is important for early behavioural regulation such as not screaming when upset, however children master this and inhibitory control no longer becomes so important as children grow older. On the other hand, it may also be that in cases where inhibition has been found to be important in young children it has generally been measured within a context where a child has to inhibit a desire such as the gift delay task (Kochanska, Murray, & Harlan, 2000), the forbidden toy task (Lewis, Stanger, & Sullivan, 1989) and the disappointing gift task (Saarni, 1984). These might more helpfully be considered 'hot' inhibitory control tasks as emotion regulation is required. There is some evidence that 'hot' and 'cool' executive functions may function via different mechanisms (Zelazo & Carlson, 2012) and therefore it is plausible that inhibitory control as measured in a 'hot' context may be more relevant to emotion than 'cool' measures.

A limitation of the approach taken in this study is that principal component analysis is an inductive a-theoretic data driven method which seeks to find the best fit for the data. It is therefore possible that it may not have produced the best theoretical models of these constructs, which may have limited the possibility of addressing the relationships between cognitive and emotion measures. A further limitation is that averaging across ages may have hidden specific relationships between variables at specific points in adolescence.

3.4.4 Conclusion

This study identified three cognitive measures - working memory, processing speed and inhibitory control - and five emotion measures -internalising, externalising, anxiety, extraversion and conscientiousness- from the ALSPAC adolescent data. They were found to be related to a small but significant extent, with high levels of negative emotion and low levels of positive emotion showing stronger relationships with cognitive variables in general, but with a linear model explaining most of the variance in most of the relationships. Early studies looking at the relationship between emotional outcomes and cognition have often used more emotionally charged cognitive tasks, which may have inflated the observed association between for example inhibitory control and emotional regulation.

4. Associations between working memory, emotion and emotional regulation strategies in an adult sample

Poor executive function has been proposed as a risk factor for psychopathology via the mechanism of poor emotion regulation. This study looked at the relationship between the PCA emotion measures derived in Chapter 3, two validated emotion regulation questionnaires, the ERQ and CERQ, and an EF task involving emotional distraction, the Emotional Face N-back working memory task, which requires participants to update sequentially presented digits in the presence or absence emotional face distractors. Data were collected through an online experimental platform on a group of 82 adult participants. The aim was to investigate whether (1) the PCA emotion measures were related to emotion regulation strategies and (2) whether the PCA emotion measures were more related to working memory task performance in the emotional distractor condition (2-back Emotion) than in the standard condition (2-back blank). The results showed the PCA emotion measures were related to emotion regulation strategies and all showed unique patterns of association with different strategies. The association between working memory and externalising was replicated, but success in inhibiting emotional face distractors did not seem to relate to PCA emotion measures. Emotion regulation strategies were not more correlated with the working memory measures than the PCA emotion measures putting into question whether they really mediate the relationship between cognition and emotional outcomes.

4.1 Introduction

Cognitive emotional regulation strategies are a proposed mechanism by which emotion is regulated by conscious executive control (Zelazo & Cunningham, 2007). Emotion dysregulation is a key diagnostic criterion across all mental health disorders. This makes the link between executive function, emotion regulation strategies and emotional behaviour an important one to decipher.

4.1.1 Cognitive emotion regulation strategies

The strategies of reappraisal and suppression, measured using the Emotion Regulation Questionnaire (ERQ), have been used in a number of experimental studies investigating the down-regulation of emotion. In these studies participants who are asked to use reappraisal to down-regulate distressing images report experiencing less negative emotion than those using suppression or doing nothing (Gross & John, 2003). Neurally, reappraisal recruits PFC earlier than suppression and in doing so successfully down-regulates amygdala and insula activity in a sustained manner, where suppression does so only temporarily (Goldin et al., 2008). Habitual reappraisal use also predicts a decrease in amygdala and increase in PFC activation during ER tasks independently of an individual's emotional reactivity (as measured by a neuroticism and anxiety questionnaire) (Drabant et al., 2009).

4.1.2 Cognitive emotion regulation strategies are linked to mental well-being

Habitual use of reappraisal has been found to be negatively associated with depression, and positively associated with the number and closeness of relationships, as well as the amount one is liked by others (Gross & John, 2003). Suppression on the other hand is associated with reduced well-being, self-esteem and optimism (Gross & John, 2003). People who use suppression are also less likely to experience positive emotion (Balzarotti et al., 2010; Gross & John, 2003) and it is associated with increased rumination (Balzarotti et al., 2010), a major diagnostic factor in many psychopathologies (Aldao & Nolen-Hoeksema, 2010; Nolen-Hoeksema & Watkins, 2011).

Rumination is measured in the CERQ along with a handful of other cognitive ER strategies which have been identified in an attempt to characterise an individual's 'style' of responding to stressful situations. Strategies include catastrophizing, reappraisal, rumination, self-blame, other-blame and positive refocusing, refocus on planning and putting into perspective. Interestingly *all* of these strategies have been found to significantly positively associate with anxiety and depression, with rumination and self-

blame as the most significantly correlated (Garnefski, Kraaij, & Spinhoven, 2001; Garnefski & Kraaij, 2007). However, after controlling for other strategies, reappraisal, refocusing and catastrophizing were found to become significantly negatively associated with depression and anxiety, suggesting that strategies are used in combination with each other and are not clearly adaptive or maladaptive in themselves. Other researchers argue that regulation success depends on the ability to flexibly apply strategies (Gratz & Roemer, 2004). The CERQ has also been used to look at the relationship between strategies and internalising and externalising behaviours in adolescence. They find that internalising behaviours are positively associated with self-blame and rumination and negatively with reappraisal. Externalising interestingly was only positively associated with positive refocusing when controlling for all other strategies. Otherwise externalising also had positive correlations with catastrophizing and other blame (Garnefski, Kraaij, & van Etten, 2005).

4.1.3 Cognitive emotion regulation strategies are associated with executive functions

Rumination during adolescence is associated with difficulties inhibiting negative information when shifting from negative to positive blocks on an affective go-no-go task (Hilt et al., 2014). A similar result has been found in adults and it has been hypothesised that low cognitive control in people suffering from depression could be responsible for their trait-like rumination (Joormann et al., 2007). Poor IC has been associated with depression and rumination in adults and adolescents (Hilt et al., 2014; Whitmer & Banich, 2007). Depressed adult patients are generally slower and make more errors in IC tasks (Gohier et al., 2009) which is made worse when they are induced to ruminate (Philippot & Brutoux, 2008; Whitmer & Gotlib, 2012). Inducing rumination in the typical adult population also has a negative effect on WM (Curci, Lanciano, Soleti, & Rimé, 2013).

Greater use of reappraisal in adolescents has been associated with better executive functioning (Lantrip, Isquith, Koven, Welsh, & Roth, 2016) and neuroimaging studies suggest that greater prefrontal control facilitates better ER (Drabant et al., 2009; Goldin et al., 2008; Kim & Whalen, 2009), which has been linked to better WM (McRae, Jacobs, et al., 2012; Ochsner, Silvers, & Buhle, 2012; Pe et al., 2013). In **Chapter 3** limited relationships between PCA emotion measures and executive function measures were found. However, it is possible that emotional outcomes may be more related to EF tasks involving emotional content. Studies investigating emotion regulation using the ERQ and studies using EF tasks involving emotional distractors are generally associated with similar dorsolateral prefrontal cortex activation (Frank et al., 2014; Koch et al., 2007; Kohn et al., 2014). This is in contrast to those investigating 'hot' EF, tasks which are

emotionally or motivationally salient, which generally recruit more ventromedial regions (Zelazo & Carlson, 2012). Therefore, in this experiment, we look to see whether the PCA emotion traits may be more related to performance in an executive function task involving emotional distractors, compared to performance in a non-distractor condition.

Data were collected online in a new sample of adult participants. Adults were used due to ease of online recruitment. The main purpose of the study was to assess whether the PCA emotion measures correlated with emotion regulation measures, which were not available in ALSPAC, and assess whether PCA emotion measures are more related to EF performance during an emotional distractor condition than during a no distractor condition. Although we may expect higher levels of emotion in an adolescent group and therefore potentially more distractibility (Hare et al., 2008), relationships between ER strategies and EF in adolescents and adults have been previously found to be similar (Lantrip et al., 2016).

Here we tested (1) whether the emotion PCA measures were related to ER as defined by the ERQ and CERQ, (2) whether the emotion PCA measures had a stronger relationship with EF during an emotional distraction condition than that observed in a non-distraction condition and (3) whether ER strategies predicted working memory performance. We expected internalising would be positively associated with rumination and self-blame and negatively with reappraisal (Demeyer, De Lissnyder, Koster, & De Raedt, 2012; Garnefski et al., 2005; Nolen-Hoeksema, 2000) and that anxiety would be positively related to catastrophizing due to the types of questions relating to a lack of control over the world around them and future found in **Chapter 3,** and negatively with reappraisal. We also expected that externalising would be positively related to other-blame and catastrophizing (Garnefski et al., 2005) and that conscientiousness and extraversion to be positively related to reappraisal (Gross & John, 2003). Finally, we expected externalising to be negatively related to working memory (**Chapter 3**) and internalising and anxiety to show distractibility by fearful faces (Elliott, Rubinsztein, Sahakian, & Dolan, 2002; Ladouceur et al., 2009).

4.2 Methods

4.2.1 Sample

Data were collected by a BSc student and programmed using the Gorilla online platform (https://gorilla.sc). A total of 82 participants aged 16-40 (56 females) with English as a first language and no diagnosis of mental health or neurological disorders were recruited

using the online recruitment platform Prolific (https://www.prolific.ac/), opportunistically, and through the Birkbeck College participant recruitment system (Sona). The study was approved by Birkbeck's Department of Psychological Sciences ethics Board.

4.2.2 Measures

4.2.2.1 Emotional N-back task

The Emotional Face N-back (EFNBACK) paradigm (adapted from Ladouceur et al., 2009) assesses the effect of emotional distractors (happy faces and fearful faces) on working memory during an N-Back task. A numerical visual spatial N-Back (described in **Chapter 2.2.2.7**) is an updating task which requires participants to respond to a series of numbers presented in the centre of a screen and to judge whether each number is the same or different from the number shown on the previous screen (1-back), two screens back (2-back) or three screens back (3-back). The 0-back task asks participants to judge the number shown on the screen, e.g. to say whether is a zero or not. The 0-back task therefore does not have an updating working memory component, while 1-back, 2-back and 3-back conditions have increasing working memory loads. In the emotional variant of this task, used in the current study, 0-back and 2-back conditions were used and the numbers were flanked on either side by pairs of identical happy faces (happy distractor condition), fearful faces (fearful distractor condition) or nothing (no distractor condition) (**Figure 4.1**).

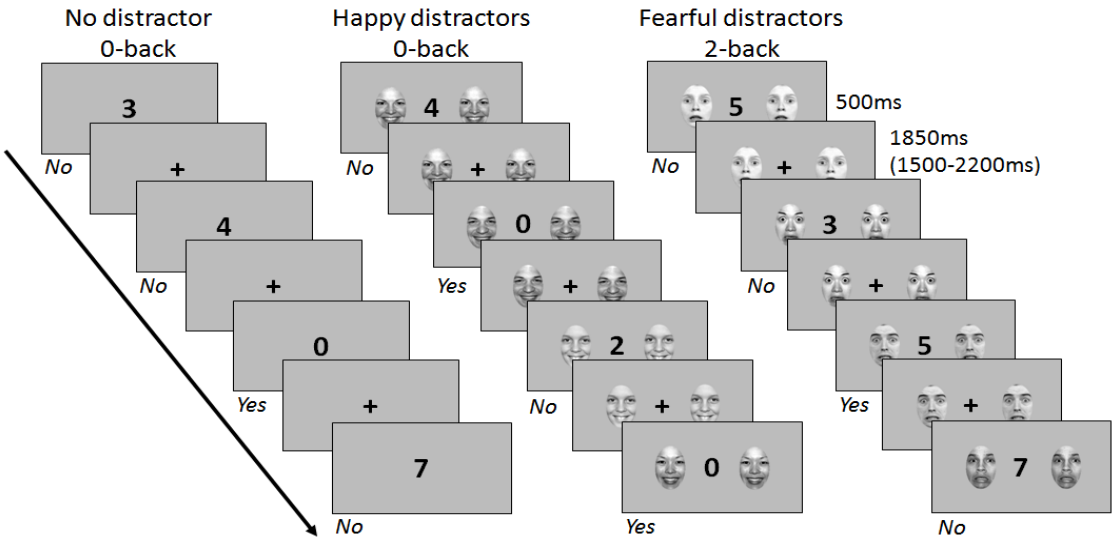


Figure 4.1: *Emotional Face N-Back demonstrating two examples of 0-back condition, in which participants must respond 'yes' to being presented with a zero, the left shows the 'no distractor' condition and the middle show the 'happy distractor' condition. The right-hand side shows the 2-back 'fearful distractor' condition in which participants must decide whether the number in the centre of the screen is the same or different to the one shown two screens previously.*

The effect of the emotional distractors in the 0-back condition provided a baseline measure of the ability to resist interference from emotional distractors, while the effect of the emotional distractors in the 2-back condition was a measure of emotional interference in WM. Each screen was presented for 500ms and then replaced by a fixation cross for a further 1500 – 2200ms (M = 1850ms, uniformly varying inter-stimulus interval). Participants were asked to respond to the task with a finger press for 'yes' (right index finger) or 'no' (middle index finger). During the emotional distractor conditions, the faces stayed on the screen alongside the fixation cross. The emotional face stimuli were taken from the NimStim database (Tottenham et al., 2009). They included 72 different individual faces (36 males) from different ethnicities which were cropped and standardised in terms of size and luminance. The trials were presented in blocks of the 0-back/2-back and emotional distractor conditions. Participants were informed at the beginning of each block whether it was a 0-back or 2-back condition. There were 6 conditions (0-back blank/happy/fearful and 2-back blank/happy/fearful) and 8 trials of a condition per block. Each session comprised three repeats of each block and every participant completed two sessions of the task with a short break in between. Although it is common to use RT measures in this task, particularly when looking at positive or negative bias (Ladouceur et al., 2009), we decided to use accuracy measures to make it more comparable with our WM factor from **Chapter 3.3.1.1** which comprised almost uniquely accuracy measures. Therefore, we had six accuracy scores, one for each condition, *0-back Blank, 0-back Happy* and *0-back Fearful* as well as *2-back Blank, 2-back Happy* and *2-back Fearful*. Furthermore, since our main question was about the effect of emotional distractors, we also created mean 'emotion' scores collapsing across happy and fearful faces *0-back Emotion* and *2-back Emotion*.

4.2.2.2 Emotion Regulation Questionnaire (ERQ)

The ERQ (**Supplementary Table 4.3**) is by far the most widely used questionnaire in the cognitive sciences, and is based on the process model of ER which asserts that there is a time-course over which emotions are generated and that the emotional outcome depends on the time point at which you begin to deploy a emotion regulation strategy (Gross, 1998). The questionnaire focuses around two strategies: reappraisal and suppression. Reappraisal is antecedent-focused and therefore changes the course of the emotion experience, and suppression is response-focused and therefore tries to stop the expression of the feeling once it has already arisen. The questionnaire asks participants to think about how they control their emotions by thinking about what they feel and how

they express their emotions. The questionnaire has a seven-point Likert scale ranging from 'strongly disagree' to 'strongly agree' and includes statements such as "When I want to feel more *positive* emotion (such as joy or amusement), I *change what I'm thinking about"* for reappraisal and "When I am feeling *positive* emotions, I am careful not to express them" for suppression (emphasis in original). There are ten questions overall, five for each construct. The scores for each construct are obtained by summing the Likert scores.

4.2.2.3 Cognitive Emotion Regulation Questionnaire (CERQ)

The CERQ (**Supplementary Table 4.4**) was also used as it encompasses a broader range of strategies which may allow for greater specificity than the simpler adaptive-maladaptive approach of the ERQ. The CERQ has eight sub-scales corresponding to four positive strategies and four negative strategies. We selected the negative strategy scales: rumination, e.g. "I dwell upon the feelings a situation has evoked in me", self-blame, e.g. "I feel that I am the one to blame for it", other-blame, e.g. "I feel that basically the cause lies in others" and catastrophizing, e.g. "I often think that what I have experienced is the worst that can happen to a person", as negative strategies tend to be more reliably associated with both executive deficits and mental health problems (Aldao & Nolen-Hoeksema, 2010). We also use the reappraisal scale, e.g. "I think that the situation also has its positive sides" in order to assess validity across the ERQ and CERQ. Participants are asked to think of situations that they have found threatening or stressful and the extent to which the statements reflect how they respond to such situations. There were 20 questions overall, four for each construct and questions were measured on a five-point Likert scale. The scores were calculated by summing the Likert scores.

4.2.2.4 Emotion PCA questionnaire

Also included were a subset of the questions making up each of the factors from the emotion-based PCA (**Chapter 3.2**). The original results included 244 questions, which would have led to a testing session lasting too long for participants, therefore a subset of 75 questions were chosen (**Supplementary Table 4.1 & 4.2**). The questions included in this study were the top loading questions of each construct; questions were skipped if they were similar to a question or questions already asked. For example, from the externalising principal component, "Does not notice effect of behaviour on family" was left out as "Behaviour disrupts family life", "Does not understand when they are offending people" and "Not aware of others feelings" were already included. The questionnaire used in the present study was divided into two sections. In the first section, participants were asked to think about the extent to which the statements described them from 'not at all

like me' to 'a lot like me'. The second section asked how often the statements below were true about them from 'never' to 'always'. In both sections participants responded along a five-point Likert scale. There were 16 questions for internalising and anxiety, 15 for externalising and extraversion and 13 for conscientiousness. Conscientiousness had slightly fewer questions as there were significantly fewer items from the PCA. Questions were presented in a random order. Which was the same for all participants, and scores on each component were calculated by summing the Likert scores.

4.2.2.5 State-Trait Anxiety Inventory (STAI)

Participants also completed the trait anxiety scale from the STAI (Spielberger & Gorsuch, 1966). The scale consists of 20 questions measuring general feelings of anxiety along a four-point Likert scale from "Almost never" to "Almost always". Items includes "An unimportant thought runs through my mind and bothers me", "I take disappointments so keenly that I can't put them out of my mind". The trait anxiety score was calculated by summing the Likert scores (reversing items when needed) with higher score indicating higher levels of anxiety. We included this in our analysis to test whether our measure of anxiety correlated well with a standardised measure.

4.2.2.6 Procedure

All participants completed the EFNBACK first to avoid priming effects from the questionnaires. Questionnaire and task order were counterbalanced to account for priming effects. Task order for the three blocks of the EFNBACK were randomly assigned

4.2.2.7 Statistical analysis

Pearson correlations were first performed to assess the associations between the measures included in the study and assess whether the ERQ or CERQ best associated with the emotion measures obtained from the ALSPAC data PCA. Three different path models were created in R using the lavaan package (Rosseel, 2012). The first tested whether there were any specific relationships between ER strategies and the emotion measures obtained in the ALSPAC data PCA, controlling for age and gender, and the second investigated whether the emotion measures were related to EFNBACK accuracy variables. The third assessed the relationship between the ER strategies and the EFNBACK. Finally, a repeated measures ANOVA was performed between the working memory and emotion condition for the EFNBACK to investigate possible interaction effects. The task order for the EFNBACK was included in all analyses but not found to be significant and so it has not been included in the results below.

4.3 Results

4.3.1 Partial Pearson correlations

Partial Pearson correlations controlling for age and gender were performed to test the associations between the different measures (**Table 4.1**). As predicted, the anxiety emotion PCA measure was strongly positively associated with trait anxiety as measured by the STAI (.826), but a similar association was observed with the internalising emotion PCA measure (.878). The reappraisal scores of the ERQ and CERQ were positively correlated with each other (.308), while the suppression score of the ERQ was positively correlated to the self-blame subscale of the CERQ. Accuracy on the EFNBACK task across conditions was negatively correlated with the emotion PCA externalising, internalising, and anxiety measures, as well as STAI trait anxiety. Associations with the CERQ were more limited, and there was no association with the emotion PCA extraversion and conscientiousness measures. No associations were found between EFNBACK and ERQ strategies. The repeated measures ANOVA found a significant main effect of the working memory condition ($F(1,289) = 21.61$, $p < .001$, $\eta_p^2 = .070$), but no significant effect of emotion ($F(1,289) = 0.23$, $p = .64$) and no interaction ($F(1,288) = 1.253$, $p = .26$).

Table 4.1: Partial correlation matrix of all the measures included in the study controlling for gender and sex

		STAI	CERQ					Emotions PCA measures					ERQ		EFNBACK Accuracy						
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
STAI	1. Trait anxiety																				
CERQ	2. Rumination	.614***																			
	3. Reappraisal	-.482***	-.043																		
	4. Self-blame	.671***	.615***	-.005																	
	5. Catastrophizing	.593***	.482***	-.376***	.380***																
	6. Other blame	.018	.018	.008	.028	.163															
Emotion PCA measures	7. Externalising	.512***	.199	-.402***	.240*	.445***	.257*														
	8. Internalising	.878***	.625***	-.375***	.636***	.561***	.004	.605***													
	9. Anxiety	.826***	.533***	-.437***	.599***	.585***	.065	.448***	.777***												
	10. Extroversion	-.400***	-.162	.344**	-.105	-.140	.219	-.118	-.333**	-.422***											
	11. Conscientiousness	-.528***	-.172	.454***	-.213	-.319**	.097	-.459***	-.513***	-.599***	.327**										
ERQ	12. Reappraisal	-.265**	-.024	.308**	-.036	-.031	.026	-.307**	-.261*	-.236	.216	.307**									
	13. Suppression	.282*	.211	-.002	.356***	.167	.216	.132	.194	.284*	.020	.081	.108								
EFNBACK Accuracy	14. 0-back Blank	-.280*	.032	.381***	.019	-.214	.051	-.228	-.218	-.355***	.102	.196	.117	-.098							
	15. 0-back Fearful	-.315**	-.114	.176	-.175	-.216	.105	-.132	-.338**	-.368***	.084	.059	.095	-.171	.714***						
	16. 0-back Happy	-.366***	-.164	.214	-.366***	-.107	.057	-.262*	-.412***	-.360***	.068	.100	.135	-.094	.661***	.643***					
	17. 2-back Blank	-.241*	-.074	.079	-.082	-.291*	-.094	-.331**	-.267*	-.214	.060	.074	.178	-.188	.208	.188	.292*				
	18. 2-back Fearful	-.179	.012	.116	.002	-.193	-.150	-.228	-.175	-.245*	.112	-.023	.069	-.065	.450***	.420***	.467***	.673***			
	19. 2-back Happy	-.236*	-.162	.091	-.098	-.088	-.151	-.281*	-.280*	-.251*	.117	.001	.087	-.191	.299*	.296*	.410***	.692***	.769***		
	20. 0-back Emotion	-.375***	-.153	.215	-.296*	-.180	.090	-.216	-.413***	-.401***	.084	.087	.127	-.147	.759***	.911***	.901***	.263*	.488***	.388***	
	21. 2-back Emotion	-.221	-.082	.110	-.052	-.148	-.160	-.271*	-.243*	-.264*	.122	-.012	.083	-.138	.397***	.379***	.466***	.726***	.938***	.943***	.465***

* $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$. They light grey sections highlight the correlations between the Emotion PCA measures and the ER strategies and the dark grey section highlights the correlations between the Emotion PCA measures and the EFNBACK WM task.

4.3.1 Model results

Model 1 tested associations between the emotion PCA measures and the emotional regulation subscales of the CERQ, controlling for age and gender. There was a positive association between rumination and internalising (**Figure 4.2**). Reappraisal was associated with all five emotion PCA measures: negatively with internalising, externalising and anxiety, and positively with extraversion and conscientiousness. Self-blame and catastrophizing were positively associated with internalising and anxiety and catastrophizing was also positively associated with externalising. Other blame was positively associated with externalising and extraversion. Finally, age was negatively associated with externalising and positively with conscientiousness. Gender and suppression were not found to have any association with emotion PCA measures.

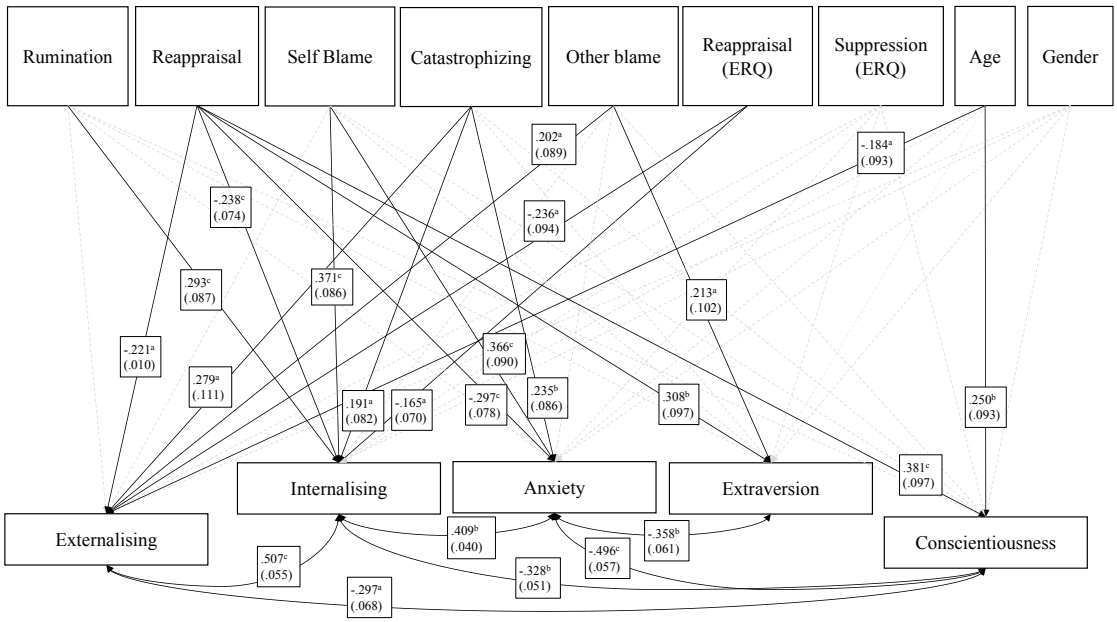


Figure 4.2: *Path diagram between the ER strategies measured by the ERQ and CERQ and the emotion PCA measures.*

Model 2 tested associations between EFNBACK accuracy and the emotion PCA measures, controlling for age and gender. Externalising was found to be related to WM as shown by its association with 2-back Blank. Internalising was associated with emotional distractor interference in the non-WM condition (0-back Emotion). Lastly, 0-back Blank accuracy was positively associated with conscientiousness (**Figure 4.3**).

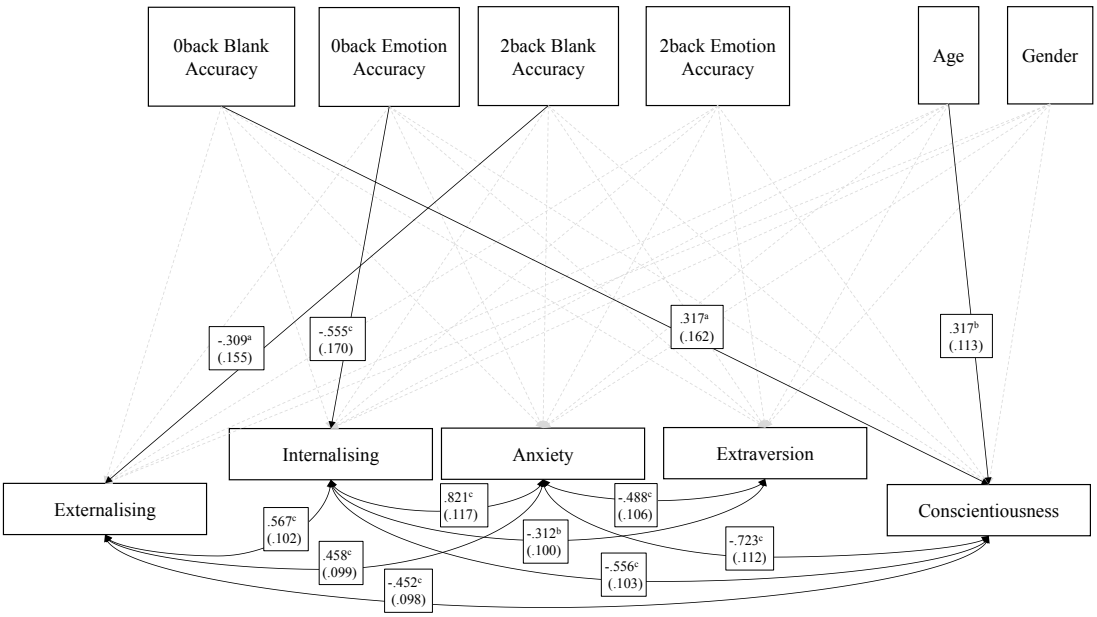


Figure 4.3: *Path diagram between the EFNBACK and the PCA emotion measures. Standardised betas (SE) are displayed in the boxes, [a] p ≤ .05, [b] p ≤ .01, [c] p ≤ .001 and dotted lines represent non-significant associations.*

Model 3 tested associations between cognitive ER strategies and EFNBACK accuracy controlling for age and gender. CERQ reappraisal was associated with 0-back Bank accuracy where ERQ reappraisal was associated with 2-back blank accuracy. These associations were smaller than those found in **Figure 4.3** between the EFNBACK and the PCA emotion measures. There were also significant associations between both 2-back measures and gender (**Figure 4.4**).

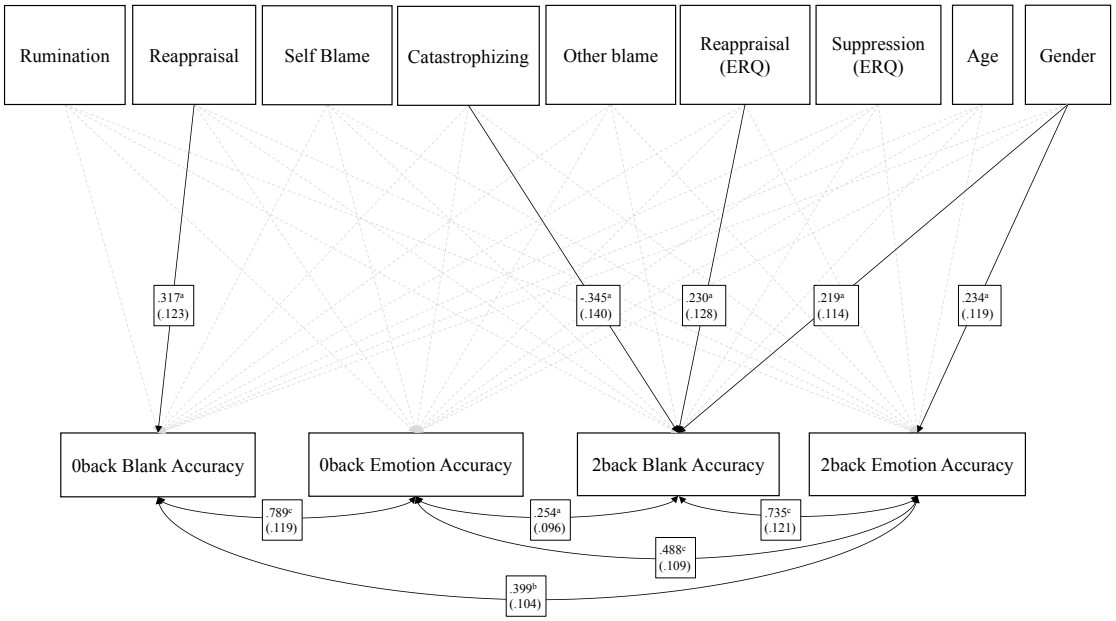


Figure 4.4: *Path diagram between cognitive ER strategies and the EFNBACK. Standardised betas (SE) are displayed in the boxes, [a] p ≤ .05, [b] p ≤ .01, [c] p ≤ .001 and dotted lines represent non-significant associations.*

4.4 Discussion

The aims of this study were three-fold. The first aim was to assess how much the measures derived from the emotion PCA on ALSPAC questionnaires may relate to standard anxiety and emotional regulation questionnaires. The results showed that the anxiety measure was indeed positively correlated with the STAI trait anxiety measure, although the internalising measure showed a similar correlation with trait anxiety. There were mostly no one-on-one relationships between emotion PCA measures and ER subscales. On one hand rumination associated with internalising and anxiety only, other-blame with externalising only and suppression with anxiety only, on the other CERQ-reappraisal associated with all emotion PCA measures. Self-blame and catastrophizing associated with a subset of the emotion PCA measures. The second aim was to investigate whether performance on an executive function task involving emotional distractors would show greater associations with emotion PCA measures than the small associations with EF tasks that did not involve emotional stimuli observed in **Chapter 3**. The results showed specific associations: conscientiousness was associated with overall task accuracy, externalising with the updating component of the task, and internalising with interference by emotional distractors. There was no specific association with emotional interference in the updating condition. The third aim was to investigate whether cognitive ER strategies predicted working memory performance. Only reappraisal was related to performance on the EFNBACK and the two different measures of reappraisal showed different associations. The ERQ measure was associated with working memory (2-back blank accuracy) where the CERQ measure was associated with 0-back blank accuracy, which was otherwise associated with conscientiousness.

4.4.1 Emotion PCA measures and emotion regulation

Model 1 found each emotion PCA measure to have a slightly different pattern of associations with the ER strategies. While both internalising and anxiety were associated with self-blame, catastrophizing and reappraisal, only internalising was associated with rumination. This positive association between rumination and internalising has been shown in the literature, which finds an association between rumination and depression (Hilt et al., 2014; Joormann et al., 2007; Whitmer & Banich, 2007) and between rumination and anxiety (McLaughlin & Nolen-Hoeksema, 2011). The correlation matrix did show rumination to be associated with anxiety, but not Model 1 where internalising was also accounted for in the model. It could be that the association between rumination and anxiety comes from the relationship between depression and anxiety, which are highly correlated (Nolen-Hoeksema, 2000). Externalising is predicted by reappraisal,

catastrophizing and other blame. This may be an indicator as to why there were high correlations between internalising and externalising behaviours – there is a tendency in both to catastrophize rather than reappraise, but where in one case individuals blame themselves, in the other individuals blame others. Internalising behaviours have previously been associated with self-blame (Gilbert & Miles, 2000). Extroversion and conscientiousness were both positively associated with reappraisal, but extraversion was also associated with other blame. Overall these findings showed a consistent pattern, whereby maladaptive strategies were associated with maladaptive behaviours and vice-versa.

Gender and suppression have no associations, which is surprising due to the literature finding associations between both gender and emotion (Brody & Hall, 2008) and suppression and negative outcomes (Gross & John, 2003). In this study with adults , we find the same pattern of a reduction in externalising with age as is found in development (Gilliom & Shaw, 2004; Mesman, Bongers, & Koot, 2001; Moilanen, Shaw, & Maxwell, 2010) suggesting that this may be a behaviour which continues to decrease beyond development and over the life course. Reappraisal was the only strategy associated with all outcomes, positively with positive outcomes and negatively with negative outcomes, reinforcing its widespread usage and replication in experimental studies (Drabant et al., 2009; Gross & John, 2003; Ochsner et al., 2012). Having said that reappraisal as measured by the ERQ and the CERQ were not very highly correlated (.308) and potentially measure slightly different things. The CERQ reappraisal was significantly positively correlated to 0-back blank in the correlation matrix and model 3, whereas the ERQ reappraisal measure was not significantly associated with any of the EFNACK measures in the correlation matrix but was with 2-back blank in model 3 replicating previous associations between ERQ reappraisal and working memory (McRae, Jacobs, et al., 2012; Pe et al., 2013). This suggests that the ERQ measure of reappraisal may be more related to working memory, but the CERQ measure perhaps conscientiousness as this was the only other association with 0-back blank accuracy. ERQ reappraisal did associate with both measures of anxiety, as well as internalising, externalising and anxiety. Whereas CERQ reappraisal related to all of these measures, the other PCA measures of extraversion and conscientiousness and CERQ catastrophizing. Future research could look at whether these are two aspects of reappraisal or if one of these measures is more successful than the other.

4.4.2 Emotion PCA measures and an emotional executive function task

In model 2 we replicated our previous finding (**Chapter 3.3.2**) that externalising is related to WM as shown by its association with 2-back Blank. This association has also

been found consistently in the literature (Hatoum et al., 2017). 0-back Blank accuracy, a condition which is neither emotionally salient nor taxing for WM was positively associated with conscientiousness (model 2) which is consistent with a desire to perform well.

The ANOVA showed there was no main effect of emotion or interaction between emotion and working memory. However, we found that internalising was associated with interference by emotional distractors, with a negative association with the non-WM emotion condition (0-back Emotion) (model 2). It is a common finding in studies of depression that individuals show preferential processing for negative stimuli (Elliott et al., 2002), however we find internalising to be associated with emotional distractibility in general and if anything the negative correlations between internalising and the emotional distractor conditions were higher for happy than fearful faces in both the 0-back and 2-back conditions.

Overall there did not seem to be a stronger relationship between emotion measures and EFNBACK than with the standard EF tasks used in **Chapter 3**. There were no specific association with 2-back emotion with any of our measures of emotion, suggesting that the association between emotion measures and the ability to resist emotional interference was independent of the working memory load. However, the emotional component in this study was non-focal, i.e. it was a distractor rather than an active part of the task. This may have reduced the need for ER and future studies could use a task where emotional faces are more central to the task (Berger, Richards, & Davelaar, 2018). Unlike other studies in this thesis, participants in this study were mostly adults and therefore these results can not necessarily be generalised back to adolescents where it has been proposed there is a temporary developmental mismatch in the development of 'hot' and 'cool' EF (Zelazo & Carlson, 2012). However, this study was still beneficial in demonstrating associations the emotion PCA measures used in the rest of this thesis and questionnaire and experimental measures of emotional regulation.

The correlations between the emotion PCA measures in this study and between those in the previous study (**Chapter 3**) went in the same direction but the size of the correlations in this study were substantially bigger, as were correlations with WM. Sum scores rather than factors scores were used in this study, there were fewer variables used for each measure, considerably more females than males and the population was adult rather than adolescent. However, it is probable that the difference in effect sizes was mainly influenced by the fact that all of the questionnaires were completed in the same sitting, whereas those in **Chapter 3** were taken at different time points across a period of ten

years. There is also a difference in sample size which may have contributed to a reduction in variance potentially inflating effect sizes. However, it remains the case that according to the correlation matrix and model 3, the emotion PCA measures were more highly associated with the EFNBACK than the cognitive ER strategies measures. This supports the continued use of the emotion PCA measures in further studies in this thesis but puts into question the proposal that ER strategies mediate or are the mechanism by which cognition influences trait emotion. Specifically, the relationship between externalising and working memory was stronger than reappraisal and working memory, however reappraisal was associated with internalising more than internalising was with working memory. Garnefski et al. (2005) find that the CERQ ER strategies are able to explain more variance in internalising than externalising and suggest that they are more strongly related to internalising than externalising problems. This is interesting as it is the opposite the what we have found with working memory suggesting that if this is the case, the association may not be facilitated by executive functions.

The EFNBACK task used in this study did not include a neutral face condition, which would have allowed to dissociate the influence of the presence of a distractor vs. the presence of an emotional distractor. The difficulty here is that neutral faces are ambiguous and can be interpreted as negative by some individuals with social anxiety (Yoon & Zinbarg, 2008) or depression (Bento de Souza, Barbosa, Lacerda, dos Santos, & Torro-Alves, 2014). Future work could look to develop a face-like distractor but which does not suffer from the same difficulties as a 'neutral' face. However, we did find that internalising and anxiety associated differently with happy and fearful faces indicating that the task was sensitive to more than just general distraction. A further limitation is that this study was performed in adults rather than adolescents and future work could investigate whether adolescents have the same associations between emotions, strategies and EF as adults.

For this study, an emotional distractor task was used as it was expected to be more related to emotion regulation. However, future studies may benefit from exploring whether trait emotion may be more related to 'hot' EF performance. 'Hot' performance involves decision-making under high motivationally or emotionally salient conditions and hence requires more of an integration between emotion and cognition which it has been argued is more ecologically valid (Tsermentseli & Poland, 2016). Furthermore, performance on 'hot' EF tasks may be particularly relevant to adolescent development due to the proposed differential developmental trajectory to 'cool' EF. The result of this is that 'hot' EF is less well developed in adolescents making them potentially poorer at making good cognitive

decisions under emotionally salient conditions (Gardner & Steinberg, 2005; Zelazo & Carlson, 2012).

4.4.3 Conclusion

Associations between cognitive measures and emotion PCA measures observed in the previous study (**Chapter 3**) were replicated but were found to be considerably larger in this smaller sample of adults. The emotion PCA measures were more highly correlated with the EFNBACK than the cognitive ER strategies measures, which supports the continued use of the emotion PCA measures in future studies. The ER strategies, other than reappraisal, did not predict working memory and reappraisal did not show a stronger relationship than externalising. This puts into question ER strategies as a mediator between trait emotion and cognition. We replicate our previous finding that externalising is related to WM and replicate the association observed in the literature between internalising and emotional distractibility and rumination. We also find reappraisal to be associated with all five measures in the expected directions.

5. Longitudinal executive function and emotion study

Poor executive functioning has been proposed as a risk factor for psychopathology. Executive function is a broad term which generally refers to a subset of cognitive processes necessary for the control of behaviour for the successful achievement of goals. Early in development a relationship has been found between children with low inhibitory control and externalising behaviour and high inhibitory control and poor cognitive flexibility with internalising behaviours and negative affect. Executive function deficits have been noted in many mental health disorders and correlate with levels of anxiety in the general population. However, little is known about the direction of this effect and how this may influence vulnerability during adolescence, a period which is marked by the onset of mental health issues and a time of great change in executive function and emotional reactivity. This study investigated the relationship between executive functions and internalising and externalising behaviours in adolescence. Uni and bi-directional effects between working memory and inhibitory control, and internalising and externalising were assessed in early and mid- to late adolescence using a cross-lag longitudinal design. Contrary to expectation executive functions did not predict emotional behaviour, but emotional behaviour did predict executive function longitudinally suggesting that emotional well-being is key for better executive functioning.

5.1 Introduction

Poor executive functioning has been proposed as a risk factor for psychopathology and evidence for associations between executive functioning and problem behaviour comes from studies in young children and adults. However, little is known about the direction of these associations and how they may influence vulnerability during adolescence, a period which is marked by the onset of mental health issues and a time of great change in executive function and emotional reactivity. This study aimed to investigate longitudinal associations between executive functioning and internalising and externalising behaviours between early and mid-adolescence.

5.1.2 Early developmental studies

Early in development a relationship has been found between executive function and the expression of feelings and emotional responses either as internalising behaviours, which are directed inwards and include fearfulness, social withdrawal and anxiety, or as externalising behaviours, which are directed towards the external environment and include physical aggression, disobeying rules, cheating, substance abuse and destruction of property (American Psychiatric Association, 2013). Rothbart and colleagues argue that high attentional control is key to low negative affect (Rothbart et al., 1994), attention being the mechanism by which perceived stimuli are selected from all sensory inputs, and orienting attention away from unpleasant or distressing stimuli allows for emotion regulation (Posner and Rothbart, 2000). Eisenberg et al. (2001) found that 4–8 year-old children with low attentional control were more likely to experience internalising difficulties, and those with low inhibitory regulation were more likely to experience externalising problems. This replicates their and others' research showing that children low in inhibitory control are impulsive, intense and prone to aggression (Eisenberg and Fabes, 1992), and although those with high inhibitory control are less likely to express negative affect (Eisenberg & Spinrad, 2004) they often have poor cognitive flexibility and are withdrawn, sad and anxious, which renders them more susceptible to internalising disorders (Fox, 1994; Nigg, 2000; Carlson & Wang, 2007) (**Figure 5.1**). Twin studies have also found significant phenotypic and genotypic correlations between differences in toddlers' emotion regulation ability and working memory (Wang and Saudino, 2013), an EF which is closely related to attentional control (Awh & Jonides, 2001; Fougnie, 2008; Kane et al., 2001).

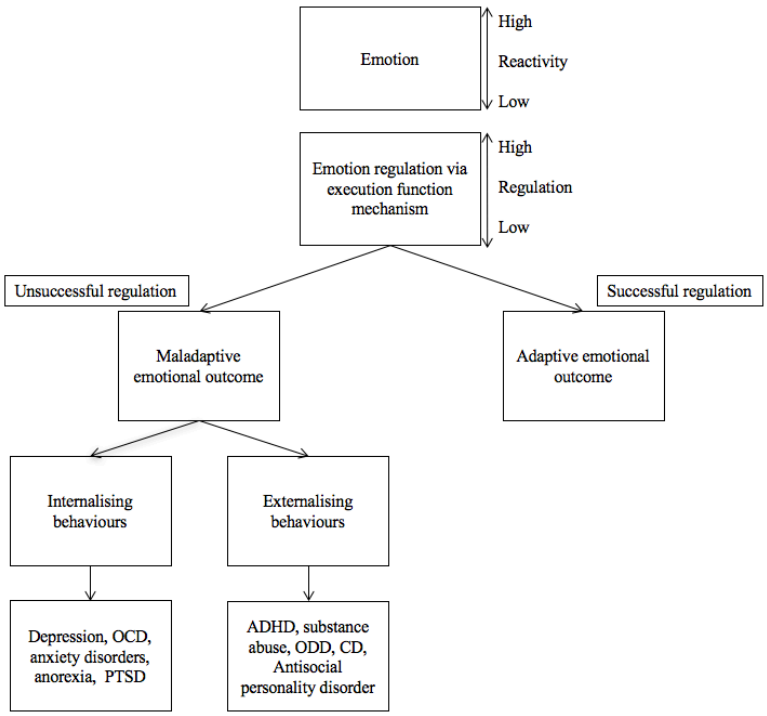


Figure 5.1: *Diagram representing the relationships between emotion regulation, internalising and externalising behaviours and psychopathology. An individual may have high or low emotional reactivity, but also high or low level of regulation any.* OCD: *Obsessive Compulsive Disorder*, PTSD: *Post Traumatic Stress Disorder*, ADHD: *Attention Deficit Hyperactivity Disorder*, ODD: *Oppositional Defiant Disorder*, CD: *Conduct Disorder*.

5.1.3 EF deficits in mental health disorders

Cross-sectional clinical and non-clinical studies of adults have found deficits across the spectrum of internalising and externalising disorders on almost all neuropsychological executive function tasks (Snyder, 2013). Internalising disorders such as depression, have shown impairments in shifting between items held in working memory (De Lissnyder et al., 2012); individuals are also likely to be slower and make more errors in inhibitory control tasks (Gohier et al., 2009) even once remitted (Aker et al., 2016). Poor inhibitory control has even been associated with depression and rumination in the general population (Hilt et al., 2014; Joormann et al., 2007; Whitmer & Banich, 2007). Externalising disorders have also been associated with small to medium sized deficits in shifting, inhibition and working memory (see Ogilvie et al., 2011 for meta-analysis).

Specifically the Stop Signal inhibitory control task and the n-back working memory task have previously been found to be impaired in those with psychopathologies (Harvey et al., 2004). Impairments in the Stop Signal task have been found in remitted Major Depressive Disorder (MDD) patients (Aker, Bo, et al, 2015), and have been associated

with substance abuse (Li, Milivojevic, Kemp, Hong, & Sinha, 2006), and ADHD (Dimoska et al., 2003).

FMRI studies have shown an association between better down-regulation of emotions, measured behaviourally, and a greater inverse functional connectivity between the amygdala and the PFC (Lee, Heller, van Reekum, Nelson, & Davidson, 2012; Ochsner, Silvers, & Buhle, 2012). Meta-analyses of neuroimaging studies looking at the down-regulation of emotion consistently show decreased activation in the amygdala alongside increased activation in the frontal gyri, interpreted to represent the cognitive regulation of emotion (Frank et al., 2014; Kohn et al., 2014). High levels of anxiety have also been associated with decreased structural connectivity between the prefrontal areas and limbic regions (Kim & Whalen, 2009; Kim et al., 2011) and reduced functional connectivity between these regions in adolescents at risk of psychosis (Gee et al., 2012). On the basis of developmental, neuropsychological and neuroimaging results it has been suggested that poor executive functions contribute to poor emotional regulation via poor top-down regulation of subcortical regions (Frank et al., 2014; Zelazo & Cunningham, 2007).

5.1.4 Executive functioning as 'transdiagnostic factor'

It has been suggested that executive function deficits may represent transdiagnostic risk factors explaining commonalities and comorbidities between emotional, behavioural, and psychotic disorders (Aldao & Nolen-Hoeksema, 2010; Benca et al., 2016; Huang-Pollock et al., 2017; Snyder et al., 2015). Some researchers have suggested that there is a common psychopathology latent factor (Caspi et al., 2014), which is related to executive functions (Martel et al., 2017). However, studies comparing whether executive functions show strongest associations with a general 'p' factor, internalising vs. externalising disorders, or with individual disorders have been inconsistent in their findings (Bloemen et al., 2018; Hatoum et al., 2017; Huang-Pollock et al., 2017)

5.1.5 Direction of this effect

Within this research there is still little evidence that poor executive functions have a causal impact on psychopathology or problem behaviour. Previous literature is mostly cross-sectional or fails to account for early correlations making it difficult to assess directionality. Bell and Wolfe (2004) suggest that there is a bi-directional relationship between emotion and cognition. They theorise, along similar lines to Posner and Rothbart (2000), that when early distress is regulated by parental use of attention distraction, this trains the infant in reorienting away from distress and establishes a foundation for the development of cognitive control. This foundation positively impacts

on working memory development which then supports better emotion-regulation (Posner and Rothbart, 2000; Bell & Wolfe, 2004). However, executive function training studies to improve anxiety symptoms by training executive functions remain inconclusive (Course-Choi, Saville, & Derakshan, 2017; Hotton, Derakshan, & Fox, 2018; Sari, Koster, Pourtois, & Derakshan, 2016). Others argue that the correlation between psychopathology and executive deficits are not causally related, but rather two separate symptoms caused by non-cortical dysfunction early in development (Halperin & Schulz, 2006).

5.1.6 Vulnerability during adolescence

Little research has investigated how these two constructs relate to each other and develop over adolescence. Cognitive and inhibitory control deficits have been related to depression and rumination in adolescents (Hilt, Leitzke, & Pollak, 2014). Friedman and colleagues also found that those who were high in self-restraint in childhood were also high in self-restraint as teenagers, and had lower cognitive flexibility, suggesting early EF differences may persist into adolescence (Friedman et al., 2011). A longitudinal structural neuroimaging study in adolescents looked at associations between levels of effortful control, cortical thinning in the anterior cingulate cortex and internalising and externalising psychopathological symptoms during adolescence. Reduced effortful control was found to predict less cortical thinning over time and greater psychopathological symptoms (Vijayakumar et al., 2014). Adolescence is a period which is marked by the onset of mental health issues and a time of great change in executive function and emotional reactivity (Crone & Dahl, 2012). A better understanding of how executive functions and emotion may interact during adolescence may help inform our understanding of adolescent specific behaviour. The present study investigated whether, as suggested by the literature, executive functions, measured using the Stop Signal inhibitory control task and the n-back working memory task, would longitudinally predict internalising and externalising tendencies over adolescence, or reversely whether internalising and externalising tendencies would predict executive functions, or yet whether the associations would be bi-directional.

5.2 Methods

5.2.1 Study cohort

The current study includes sample of 1,404 participants (703 males, 647 females, 54 unspecified) aged 10 yrs. 3m to 19 yrs. 6m from the ASLPAC cohort (**Chapter 2.1**). This

sample represents the total number of participants from the entire cohort who had a complete set of data for the measures used in this study.

5.2.2 Measures

5.2.2.1 Strengths and Difficulties Questionnaire

Internalising and externalising measures were collected using the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997), completed by a parent when the participant was 11 and 17 years old. The SDQ is a well validated measure of childhood behavioural and mental health problems (Ford, Collishaw, Meltzer, & Goodman, 2007). SDQ-externalising is made from the conduct problems and hyperactivity scales, and SDQ-internalising is made up from the emotional and peer problems scales of the SDQ. Scores range from 0 - 20 for both SDQ-internalising and SDQ-externalising. Each child had a sum score for early (age 11) and late (age 17) SDQ-internalising (e.g. "Often unhappy, downhearted" and "Often complains of headaches") and SDQ-externalising (e.g. "Often has temper tantrums or hot tempers", "Often fights with other children") which were age- and gender-regressed.

5.2.2.2 Early executive function measures

The **Counting Span task** (Case et al., 1982) is a WM task where at the end of each block of trials the participant is asked to recall in order the number of red dots presented on each trial of that block. A *Counting Span score* was calculated from the number of blocks where the information was correctly recalled (**Table 5.1**). The **Stop Signal task** (Logan & Cowan, 1984) is an IC task where the participant must respond to X's and O's on the screen by pressing the corresponding button as quickly as possible (Go trials). This establishes a mean baseline reaction time (RT). On Stop trials a beep played randomly 150ms or 250ms before the participant's baseline RT indicates the participant should refrain from responding. The task started with two practice blocks: first a block of 30 Go trials, then a block of 16 Go trials and eight Stop trials. There were then two experimental blocks of 48 trials, 16 of which were Stop trials (33%). As the number of correct Stop trials in the 150ms and 250ms delay conditions were highly correlated, an average *Stop Signal number of correct Stop trials* across delays was calculated for each individual (**Table 5.1**).

Table 5.1: Descriptive statistics of individual measures

Measure	Age	Mean (range)	Standard deviation
Early SDQ-internalising	11y8m – 13y3m	2.1 (0 – 15)	2.4
Early SDQ-externalising	11y8m – 13y3m	3.1 (0 – 19)	2.6
Late SDQ-internalising	16y6m – 18y4m	2.1 (0 – 17)	2.4
Late SDQ-externalising	16y6m – 18y4m	2.8 (0 – 18)	2.6
Early working memory [Counting Span score]	10y3m- 11y11m	19.9 (0 – 42)	7.7
Late working memory [2-back accuracy] (%)	16y3m – 19y6m	78.7 (15 – 100)	17.2
Early inhibitory control [Stop Signal number of correct Stop trials]	10y3m - 11y11m	13.1 (4 – 16)	2.3
Late inhibitory control [Stop Signal number of correct Stop trials]	14y3m – 17y1m	0.2 (-7.1 – 2.6)	1.8

5.2.2.3 Late executive function measures

An **N-back** task was used at 17 yrs. to test WM, more specifically updating. Participants were presented with numbers 0 – 9 for 500 ms and had 3000 ms to judge whether the current number was the same as the number shown either 2 or 3 trials before (2-back or 3-back). The practice block consisted of 12 trials with two targets, and there were single blocks of the 2-back and 3-back conditions each consisting of 48 trials with eight targets. The measure used from this task was the *2-back accuracy* as it was the highest loading variable on the working memory factor in study one (**Table 3.4**), it has also been used in other studies looking at the relationship between working memory and psychopathology (Snyder et al. 2015). The **Stop Signal task** from 10yrs. was repeated, with the same practice and test blocks but slightly different delay times between stimulus and stop signal presentations for different participants, hence a residual score covarying for delay duration was calculated for the purpose of this study. As at age 10, *Stop Signal number of correct Stop trials* across delays was computed.

5.2.3 Statistical Analysis

Change in internalising and externalising across adolescence will also be assessed using t-tests as this is something which has been found in previous studies (Gilliom & Shaw, 2004; Mesman et al., 2001). Change in both traits will be plotted to see how individuals change over time.

A cross-lag panel structural equation model was used to look at the longitudinal bi-directional associations between working memory and inhibitory control on one hand and

SDQ-externalising and SDQ-internalising on the other. A panel model postulates that there is a directional relationship between constructs using regression. We used the Lavaan version 0.5-23.1097 (Rosseel, 2012) structural equation modelling package in R (R Core Team, 2016) with Robust Maximum Likelihood estimator with Yuan-Bentler scaled statistic (MLR) to account for any violations of multivariate normality. Overall fit of the model was assessed using the Chi-square test, Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA) and the Standardised Root Mean Squared Residuals (SRMR). From the full sample outliers in the cognitive data more than 3.29 standard deviations from the mean were removed. This removed 105 participants from early IC, 70 from late IC and 22 from late WM. A data frame of complete case data was then created (N=1,404). The correlation between all constructs was controlled for at both time points to understand adolescence specific effects. The longitudinal path between the cognitive factors was not calculated to retain an over-identified model.

5.3 Results

Table 5.2 presents the correlations between the variables included in the cross-lag model. Early and late SDQ-internalising and SDQ-externalising behaviours were positively correlated [range: 0.230 - 0.603]. There were weaker correlations between early and late WM and IC [range: 0.088 - 0.244]. Parent-reported behaviours and EF cognitive measures were negatively correlated [range: -0.169 - -0.036].

Table 5.2: Correlations between variables where higher scores in SDQ-internalising and SDQ-externalising indicate more problem behaviours but higher scores in working memory and inhibitory control indicate better executive functioning.

	1	2	3	4	5	6	7
1. Early SDQ-internalising							
2. Early SDQ- externalising	.382[c]						
3. Late SDQ-internalising	.496[c]	.252 [c]					
4. Late SDQ-externalising	.230[c]	.603 [c]	.314[c]				
5. Early WM	-.078[b]	-.138 [c]	-.036	-.090[b]			
6. Early IC	-.053[a]	-.153 [c]	-.049	-.120[c]	.103[c]		
7. Late WM	-.133[c]	-.169 [c]	-.057[a]	-.167[c]	.244[c]	.113[c]	
8. Late IC	-.075[b]	-.069 [b]	-.069[a]	-.073[b]	.057[a]	.187[c]	.088[b]

[a] p<.05, [b] p<.01 [c] p<.001

Two t-tests were performed to see if mean levels of SDQ-externalising and SDQ-internalising at time one and time two were significantly different from each other. SDQ-externalising reduced significantly over the two time points t(2857.9) = 3.03, p=.003, whereas SDQ-internalising did not change t(2857.3)= 0.18, p=.859.

Figure 5.2 shows the relationship between change in SDQ-internalising and SDQ-externalising behaviours over time independently of cognitive factors. The plot shows a general positive correlation ($r = .24$, $p < .001$) so that an increase in externalising behaviours over time results in an increase in SDQ-internalising behaviours.

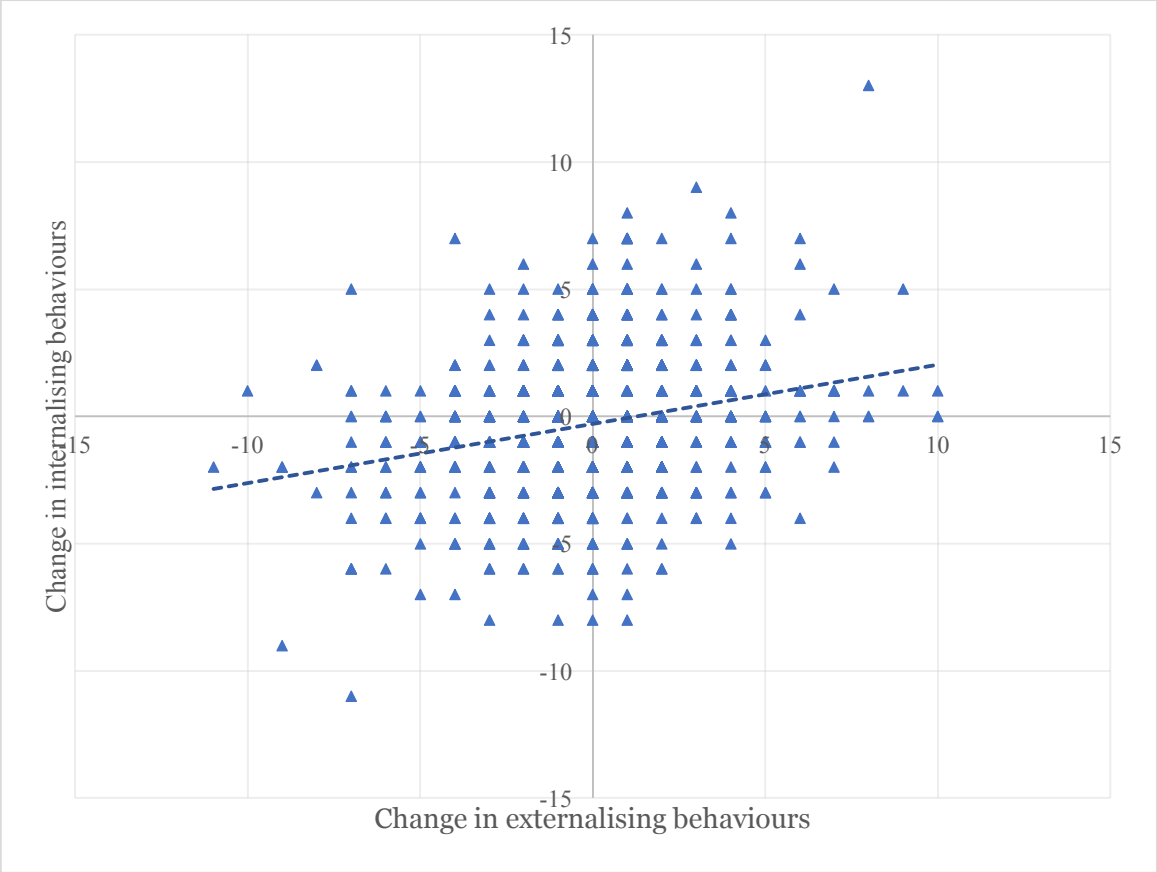


Figure 5.2: *Change in SDQ-externalizing behaviours plotted against change in SDQ-internalising behaviours*

The Cross-Lag model fit was $\chi^2(2) = 9.138$, $p = .01$; CFI = .996; RMSEA = .050 [.021 - .086]; SRMR = .012. The variance explained in the late measures was 8.2% for working memory, 3.8% for inhibitory control, 36.4% for SDQ-externalising and 25.1% for SDQ-internalising.

In early adolescence, all four measures were significantly correlated with each other, except SDQ-internalising and IC, while in late adolescence the only significant correlations were between SDQ-internalising and SDQ-externalising, and between SDQ-externalising and working memory (**Figure 5.3**).

Early SDQ-internalising longitudinally predicted variance in late SDQ-internalising and late WM. Similarly, early SDQ-externalising longitudinally predicted variance in late SDQ-externalising and late WM, and in addition predicted late SDQ-internalising. Early EF measures predicted variance in their equivalent late adolescence measure, but did not predict variance in problem behaviour tendencies in late adolescence (**Figure 5.3**).

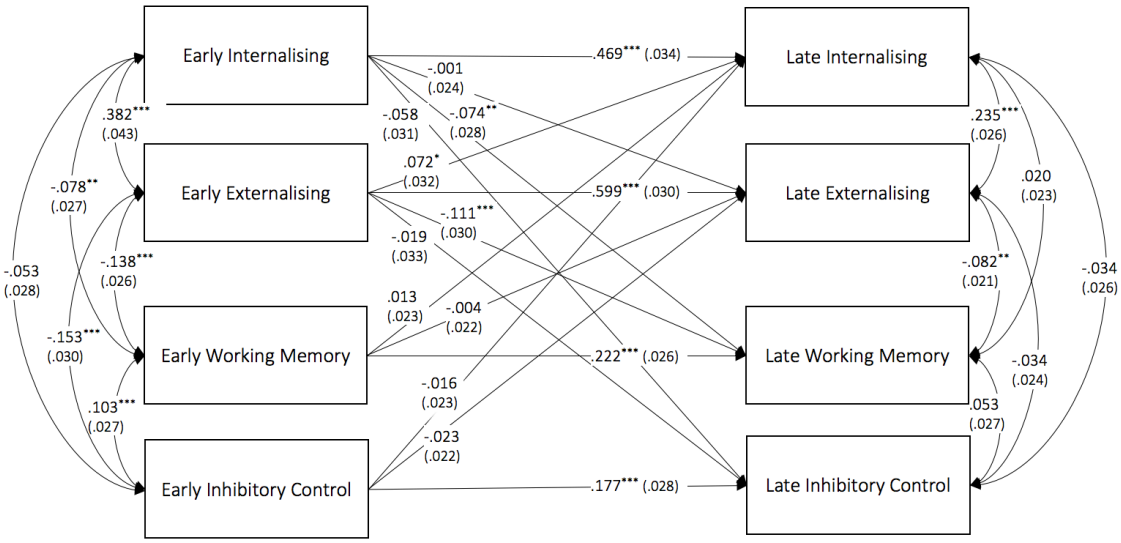


Figure 5.3: *Cross-lag model of the associations between working memory and inhibitory control and SDQ-externalising and SDQ-internalising behaviours in early and late adolescence. *p = <0.05, **p = < 0.01, ***p = < 0.001. Values represent standardised betas with standard errors in brackets. Early=10y3m-13y3m and Late = 14y3m -18y4m*

5.4 Discussion

The present study used a longitudinal cross-lag design to explore the directionality of cross-sectional correlations between executive functions and SDQ-internalising and SDQ-externalising behaviours during adolescence within the ALPSAC sample.

5.4.1 Emotional behaviours change over adolescence

As with previous studies, it was found that SDQ-internalising and SDQ-externalising behaviours were correlated with each other both early in adolescence and later on, although the strength of the correlations reduced over time. Early SDQ-externalising predicted later SDQ-internalising, suggesting a change in the expression of emotional-behavioural difficulties over adolescence, which has been found in a number of previous studies (Gilliom & Shaw, 2004; Mesman, Bongers, & Koot, 2001; Moilanen, Shaw, & Maxwell, 2010). Studies spanning from infancy to adolescence suggest that externalising

difficulties peak early in childhood whereas internalising difficulties continue to increase with age and these changes are attributed to cognitive development (Gilliom & Shaw, 2004). However, in the present study although SDQ-externalising decreased across adolescence, SDQ-internalising did not increase and is only correlated with early working memory and not later executive functions, suggesting EF development does not explain changes in SDQ-internalising behaviours during adolescence.

Another theory is that externalising behaviours may lead to social problems which in turn lead to internalising behaviours such as anxiety and depression, which has been observed in children (Patterson & Capaldi, 1990). There is evidence of this occurring over adolescence as well (Burke, Loeber, Lahey, & Rathouz, 2005). Adolescents may be particularly vulnerable to this type of social exclusion due to the salience of peer approval during this time (Steinberg & Morris, 2001). Young adolescent girls excluded from an online game of catch showed a greater decrease in mood and an increase in anxiety during the exclusion condition than adults (Sebastian et al., 2010). The model found that SDQ-externalising positively predicts later SDQ-internalising but the t-tests suggested a significant reduction in SDQ-externalising over time but a stable average SDQ-internalising. Therefore, it may be suspected that externalisers turn into internalisers and internalising with internalising reducing. However, the change in the raw scores over time did not show this pattern (**Figure 5.2**). Here if this was the case we would expect a clustering in the top left-hand corner of the graph but we see in fact a fairly evenly distributed graph with a positive correlation for an increase in one problem behaviour associated with the increase in the other. Studies in younger children also find that early internalising counts as 'protective' or is negatively associated with later externalising behaviours (Mesman et al., 2001), we did not find this association to continue into adolescence.

The present study showed SDQ-externalising behaviours are correlated with early and late working memory, but only early inhibitory control. These results replicate previous findings of associations between SDQ-externalising behaviours and visuospatial working memory capacity in a general population sample of 4-18 years olds (Ziermans et al., 2012) and between inhibitory control and SDQ-externalising in childhood (Eisenberg and Fabes, 1992) but goes against findings in adulthood (Gohier et al., 2009). Overall, correlations between executive functions and emotional behaviours reduced from the beginning to the end of adolescence. The Stop Signal task has been used successfully in adults not only in individual differences studies but also to highlight the exact associations investigated (Harvey et al., 2004; Kaiser et al., 2003), so it is unlikely that the EF tasks used here are too rudimentary to explain individual differences in late adolescence.

Another possibility is that a functional differentiation between 'cool' and 'hot' EF during adolescence could mean that 'cool' experimental tasks become less relevant for assessing cognitive influence on emotion (Gardner & Steinberg, 2005). Indeed, some researchers argue that 'hot' EF and 'cool' EF are separate processes supported by separate structures. 'Hot' EF is characterised by a task which is motivationally or emotionally salient and generally recruits ventral prefrontal systems (Zelazo & Carlson, 2012). The tasks used in this study could be classified as 'cool' EF as there is nothing emotionally salient about the tasks. These tasks generally recruit more dorsolateral aspects of the prefrontal cortex (Dolcos & McCarthy, 2006). Zelazo and Carlson (2012) argue that during adolescence 'hot' and 'cool' EF develop separately and that adult levels of 'cool' EF may be reached sooner than hot EF, however they also suggest that hot and cool EF are supported by the same underlying mechanisms, with 'hot' EF only becoming functionally specialised later in development. In a study with participants between the ages of 8 and 15, 'cool' EF measures were found to develop earlier than 'hot' EF measures, however they also loaded together onto one factor (Prencipe et al., 2011). Future studies could extend the present work by including measures of both 'hot' and 'cool' EF to understand more about how these mechanisms may relate.

5.4.2 Executive functions do not influence change in internalising or externalising over adolescence, but the other way around.

Neither of the early executive functions measures predicts later SDQ-externalising or SDQ-internalising behaviours, suggesting they do not have a causal influence on them over adolescence, which is evidence against the view that EF influences the emergence of internalising and externalising behaviours through emotional regulation. We find within time associations with working memory and inhibitory control but not across time predictions from the executive functions suggesting that they do not influence any change in emotional behaviours across adolescence. This may also be the case earlier in development. For example, in toddlers, Wang and Saudino (2013) found a significant genotypic correlation between emotion regulation as measured by Bayley's behavioural rating scale and a WM task. Although individual differences in both measures were significantly influenced by both genetic and non-shared environmental factors, only genetic factors contributed to covariation between the two traits (Wang & Saudino, 2013). This suggests that the nature of the correlation between WM and emotion regulation early in development is genetic in origin and environmental factors influencing change in one, will not influence change in the other.

A number of studies find cross-sectional associations between emotion regulation strategies, increased top-down control and reduced emotion (McRae et al., 2012;

Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner, Silvers, & Buhle, 2012) and links with executive function levels (McRae, Jacobs, et al., 2012; Pe et al., 2013; Schmeichel et al., 2008). The present study suggests that these correlations could be due to effects operating in the other direction. The results indicate that both early SDQ-internalising and SDQ-externalising predict later working memory, suggesting that it is emotional well-being that may influence changes working memory during adolescence and not the other way around. Unsuccessful top down control could be a consequence rather than a cause of increased emotionality. Large numbers of studies also document emotional interference in cognitive processing (De Houwer & Tibboel, 2010; Gray, 2001; Lavric, Rippon, & Gray, 2003; Zhou et al., 2011). These studies looking at emotion regulation and emotion interference generally refer to state interactions between emotion and cognition, whereas we have used more trait-like measures. A possible integration of previous research and the present study would suggest that top-down executive control is successful in regulating state emotion, but does not influence trait emotionality.

5.4.3 Limitations

Different WM tasks were administered to ALPSAC participants in early and late adolescence. In early adolescence, the span task requires maintenance of an increasing number of items in working memory, while in late adolescence the 2-back task requires maintenance of a more limited number of items (two) but also continuous updating and manipulation of the items in WM. One could therefore argue that the correlations between WM and SDQ-externalising and SDQ-internalising were not fully controlled for in early adolescence, which is why cross-time correlations are significant. However, a positive point is that the early and late WM measures are in fact more highly correlated with each other than the early and late IC measures, which were based on the same experimental task (Stop-Signal task). Note this could be to do with age-related changes in these constructs, or the reliability of the measures themselves.

The age at which participants completed the WM and IC task and at which their parents completed the SDQ was not exactly matched. For example, the late WM measure were collected at age 17, the late IC measure at age 15, and the early SDQ measures were collected at age 11-13 rather than 10-11 years old as the EF measures. This may have affected the results.

There are some outliers in the SDQ data which were not removed as their scores were normal for the scale, but because in general the sample had very low levels of internalising and externalising they fell outside of the 3.29 SD from the mean. In order to ensure that any effects seen were not being driven by these top scores, the analysis was re-run

removing those in the top quartile of internalising and externalising, results did not change.

Only a small amount of variance in late working memory and inhibitory control was explained by the model (8.2% for working memory, 3.8% for inhibitory control). This does fit with findings from **Chapter 3**, but also perhaps reflects the low level of test re-test reliability in executive functions measures (Hedge, Powell, & Sumner, 2018).

5.4.4 Conclusion

The present study used a longitudinal cross-lag design to explore the directionality of cross-sectional correlations between executive functions and internalising and externalising behaviours during adolescence within the ALPSAC sample. The results indicate that both early SDQ-internalising and SDQ-externalising predict later working memory, suggesting that it is emotional well-being that may influence changes working memory during adolescence and not the other way around. Neither of the early executive functions measures predicts later emotion behaviours, suggesting they do not have a causal influence on them over adolescence. Cross-sectional associations between emotion regulation, executive function level and emotion could be due to emotion effects on executive function or possibly that top-down executive control is successful in regulating state emotion, but does not influence trait emotion. Finally, future studies could look at the longitudinal relationship between attentional control to negative stimuli and emotional traits or other measures of 'hot' executive function alongside 'cool' measures to see whether these may have more influence on changes in internalising and externalising behaviours.

6. Cognition and emotion genome-wide association studies

Executive functions (EF) are the mechanisms by which we engage with the world in a goal-directed manner. Individual differences in EF are highly heritable and impaired EF is associated with poorer mental health and wellbeing. However, relatively little is known about the genetic architecture of EF traits or the emotional behaviours such as internalising and externalising that precede more severe mental-health disorders. In Chapter 3, three latent cognitive variables were characterised in an adolescent sample: two EF traits (working memory and inhibitory control) and processing speed, and three emotion measures related to psychopathology (internalising, externalising and anxiety). The goal of the present study was to add to the current understanding of the genetic contributions to variability in cognitive ability and emotion in adolescence, and examine the degree of shared genetic architecture between them. Moderate SNP heritabilities were estimated for working memory, processing speed, externalising and internalising and two gene associations were found with working memory and processing speed. The inhibitory control and anxiety phenotypes however were unable to provide stable estimates of heritability. Such insights will be important for furthering our understanding of pathways between specific cognitive functions and different psychological outcomes.

6.1 Introduction

Genetic methods used to study the origins of individual differences in higher level cognitive traits and behaviours traits have utilised twin studies, followed by molecular genetic strategies to identify specific genetic variants and/or candidate genes. With the advent of hypothesis-free genome-wide association strategies, it has been increasingly recognised that we lack sufficient knowledge of how genes affect behaviour to select candidate genes. The current paradigm of choice for detecting common variants that contribute to the heritability of a complex human traits therefore is genome-wide association.

6.1.2 Twin studies

Twin studies have demonstrated that executive functions (EF) are heritable with estimates of different latent factors ranging between 76 and 100% but with significantly lower estimates for individual EF measures (0-36%). Common EF, or shared variation in EF, has a heritability of ~99% (Engelhardt, Briley, Mann, Harden, & Tucker-Drob, 2015; Friedman et al., 2008), which has been replicated in older populations (OATS Research Team et al., 2012). Multivariate twin studies find evidence of both common and independent genetic effects (Friedman et al., 2011, 2008) with heritability increasing over childhood and then stabilising by late adolescence (Friedman et al., 2008; Polderman et al., 2007). In contrast, studies investigating internalising and externalising behaviours suggest that genes play a lesser role in explaining individual differences in internalising behaviours over time (59 – 40%), although externalising stays fairly stable (~51%) (Verhulst & Boomsma, 2003; van der Valk, Verhulst, Stroet, & Boomsma, 1998). Estimates of generalised anxiety disorder are lower still (32%) (Hettema et al., 2001).

6.1.3 Genome-Wide Associations Studies

6.1.3.1 Cognitive ability

To date, the majority of well-powered molecular genetic studies of cognitive ability have focused on 'g', or general intelligence - a common EF - due to its high heritability, and the fact that it explains a large amount of the variance in diverse cognitive tests (a fact that also facilitates easier integration and comparison across independent cohorts).

The first GWAS studies of 'g' (N<10,000) failed to uncover specific (and robustly) associated variants, but noted likely polygenic effects. For example, a GWAS of 'g' in 2013 using 7,100 unrelated participants reported a SNP heritability estimate of 35% but failed to find any genome-wide significant associations (Kirkpatrick et al., 2013). Subsequently,

larger GWA studies (N < 60,000) began to uncover specific variants, but often not necessarily in genes and not always obviously linked to cognitive function. The first meta-analysis of 'g' using 24 cohorts (N= 35,298) was performed by the COGENT consortium and successfully identified two SNP associations but reported a reduced SNP heritability estimate of 22% (Trampush et al., 2017). A larger-still meta-analysis of 31 GWA studies (N = 53, 949) found three significant associations with a SNP heritability of between 28-29% and a polygenic risk scores predicting ~1.2% of the variance in cognitive ability in an independent sample (Davies et al., 2015). More recent very large studies (N> 60,000) have found increasing numbers of SNP associations that replicate with related phenotypes (such as educational attainment) in independent samples, and show more consistent brain-related findings. For example the most recent meta-analysis of 78,308 individuals reported 18 independent SNP associations and 30 gene-based associations, and a SNP heritability of 20% (Sniekers et al., 2017). The authors of this study also found genetic associations between general cognitive ability and seemingly unrelated traits such as Body Mass Index and obesity, highlighting the likely pleiotropic nature of genetic effects (Hill et al., 2018).

The above-mentioned studies typically combined performance on various neurocognitive tasks including working memory, fluency, processing speed and declarative memory tasks. However, there were also a number of studies that examine specific cognitive function variables separately but as before, given the likely polygenic architecture studies initially used underpowered sample sizes and failed to identify specific genetic associations. For example, in 2011 Luciano et al. performed a GWAS using seven different measures of processing speed across four cohorts (N=305 – 1,659) and failed to identify any genome-wide significant SNPs (Luciano et al., 2011). With 32,070 participants, one SNP significantly associated with processing speed in adults was identified (Ibrahim-Verbaas et al., 2016). The largest reported GWAS of specific cognitive functions to date was performed using the UK Biobank (N=112, 151) and found only two significant associations with processing speed and estimated a SNP heritability of 11% and no reported associations with memory and a lower than expected SNP heritably of 5% (Davies et al., 2016). The comparative lack of success for the UK biobank study might in-part be due to impoverished phenotype measures used. Test-rest reliability on the Biobank measures ranged from 0.15 for the working memory measures, 0.54 for processing speed and 0.65 for the verbal-numerical reasoning tests, the latter two for which the associations were found. More reliable measures of working memory, such as the N-back, have found significantly higher SNP heritability estimates of between 24% (s.e=.14; 2back RT) to 41% (s.e=.14; 2back-0back accuracy) (Vogler et al., 2014). EF phenotypes such as working memory have used a GWAS approach in more complex study

designs that incorporate neuroimaging as an intermediary phenotype with some success (Blokland et al., 2016; Papassotiropoulos et al., 2011). However, suggestive findings, and in particular those from smaller studies require rigorous replication.

6.1.3.2 Emotion Traits

While no GWA studies for emotion regulation have been reported, there have been studies looking at related traits such as temperament (Verweij et al., 2010), proneness to anger (Mick et al., 2014), amygdala activation in bipolar disorder (Liu et al., 2010) and anxiety (Purves et al., 2017; Trzaskowski et al., 2013). The main findings from some of the key GWAS studies in these domains will now be briefly discussed.

The most recent GWAS analysis of anxiety (N = 157,366) using the UK Biobank sample of adults, found that clinical anxiety and population levels anxiety are significantly genetically correlated 20% - 30%, but that the SNP heritability estimate for clinical anxiety was much higher ~32% than anxiety in the normal range (4%) (Purves et al., 2017). This is in contrast to other studies that report lower estimates of clinical anxiety (h^2_{SNP} =10 - 14%) (Otowa et al., 2016). Internalising also varies widely in its SNP heritability estimates with one meta-analysis of preschool internalising (N = 4,596) reporting estimates ranging between 13 - 43% all using the same measure (Benke et al., 2014).

Larger studies of non-clinical emotion-related traits have identified significant SNP associations – three with subjective well-being (N=298,420), two with depressive symptoms (N=161,460) and 11 with neuroticism (N=170,911) (Okbay, Baselmans, et al., 2016). This relative success with a temperament measure has been found in other studies where trait-like questions relating to proneness to anger demonstrated more power in a moderate GWAS (N=8,747) than state-like questions (Mick et al., 2014). Cloninger's temperament scales (h^2_{TWIN} = . 30 - .60) are believed to represent the biological drives underlying variation in personality including: harm avoidance, novelty seeking, reward dependence and persistence. As expected, small studies (N=5,117) have not proved successful in finding significant SNP associations (Verweij et al., 2010) and larger studies have not yet been performed. Other attempts at using more biologically driven phenotypes such as amygdala activation to emotional faces reported a suggestive association in the gene *DOK5* ($p = 4.9 \times 10^{-7}$). Unusually, this study involved participants with and without bipolar disorder, but the association was found with the whole group supporting the idea of cumulative effects of common variation (Liu et al., 2010). What is clear from these studies is that SNP heritability estimates for emotion-based traits are

lower and effects sizes of associated variants are even smaller than those found in cognition. Exploring shared and distinct variation between cognition and emotion may be a fruitful way of understanding more about both traits.

6.1.3.3 The genetic relationship between cognition and emotion

There have only been a handful of genetically informed studies specifically looking at the possible relationship between emotion and cognition. A twin study investigating the relationship between emotion regulation and working memory found that covariation of emotion regulation and working memory in toddlerhood was largely due to genetic factors (.76 - .86) (Wang & Saudino, 2013). In 2016, Benca et al., (N=386) hypothesised that if EF deficits are a risk factor for psychiatric disorders then genetic risk for mental health disorders should predict experimental measures of EF in a non-clinical population. They created polygenic risk scores (PRS) for a number of psychiatric disorders and used these to predict the latent Miyake-Freidman (2000) measures of EF. Prior to correcting for multiple testing, they found a positive association between Major Depressive Disorder (MDD) and common EF, and ADHD and Schizophrenia with updating, and a negative association between schizophrenia and IQ. However, EFs were not more predictive of psychopathology than disease related predictors (i.e. depressive symptoms) suggesting, there is no evidence that they mediate associations between genes and psychopathology as has been proposed (Benca et al., 2016). A similar strategy was taken by Martin et al. (2014) who created an ADHD PRS to predict IQ, WM, IC and facial emotion recognition in 8.5 yr olds. The ADHD PRS was associated with lower IQ (beta=-.05, $p<.001$, $R^2=.003$), and WM (beta=-.034, $p<.013$, $R^2=.001$), partially supporting their hypothesis that ADHD is on the extreme end of the normal distribution for some traits, although not IC or emotion recognition (Martin et al., 2014).

In summary, EFs have been investigated as distinct cognitive traits, but not as well-characterised latent measures which contain less error-related variance and therefore should provide more power to detect genetic associations. There has been one study including IC, but heritability was not estimated and there were not SNP-based associations (Ibrahim-Verbaas et al., 2016) making the genetic basis of this trait particularly unknown. There hasn't been a comprehensive GWAS of externalising and internalising and anxiety have not been explored in terms of their genetic relationships with other traits which may be a useful way of understanding the genetics of these traits as increasing sample size hasn't been that successful. There have also been no genetic studies looking at how these traits relate during adolescence which may have developmentally specific associations.

6.1.4 The Present Study

The goal of the present study was to add to the current understanding of the genetic contributions to EF and emotion in adolescence, and examine the degree of shared genetic architecture between them. Such insights would be important for furthering our understanding of any relationships that exist between specific cognitive abilities and different emotional behaviours. This study aimed to identify common variants associated with cognitive and emotion measures in a population-based sample of adolescents. It then 1) investigated whether cognitive traits derived in **Chapter 3** were genetically distinguishable, 2) tested whether they are genetically associated with emotion measures and evaluated the extent of the shared genetic effects, and 3) tested whether study traits were differently associated with previous GWAS results of related to cognitive, educational and psychiatric phenotypes.

To address the aims, six univariate genome-wide association studies (GWAS) were performed on (1) working memory, (2) inhibitory control, (3) processing speed (N=4,611), and (4) internalising, (5) externalising and (6) anxiety behaviours (N = 5,485) in adolescents derived from the Avon Longitudinal Study for Parents and Children (ALSPAC). LD score regression was used to estimate the SNP heritability of each trait as well as to index genetic correlations between our traits and with measures of educational attainment, IQ and psychiatric disorders from publicly available GWAS summary statistics.

6.2 Methods

6.2.1 Study cohort

Participants for this study were selected from the 5,838 participants with cognitive phenotypic measures and the 6,876 participants with emotional phenotype measures created in **Chapter 3**. Of these, a sub-set of 4,611 (2,173 males) had both cognitive and genotype data and were unrelated, and 5,485 (2,602 males) had both emotional and genotype data and were unrelated.

6.2.2 Measures

Cognitive latent measures were created from a principal component analysis of 10 different cognitive tasks, which resulted in a 3-factor solution comprising of two EF measures: working memory and inhibitory control, and a processing speed measure (**see Chapter 3 for details**). The emotional and behavioural regulation measures were

created from a principal component analysis of 244 questionnaire items which resulted in a 5-factor solution. Factors were identified as externalising, internalising, anxiety, conscientiousness and extroversion. Only externalising, internalising and anxiety factors were chosen for genetic analyses as they explained the most variance in the PCA solution (**Chapter 3**). All phenotypes were age- and gender-regressed and quantile-normalised using SNPTEST (Marchini, Howie, Myers, McVean, & Donnelly, 2007).

6.2.3 Genotyping and quality control

Adolescents from the ALSPAC sample were genotyped using the Illumina HumanHap550 quad chip genotyping platforms by 23andme subcontracting the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory Corporation of America, Burlington, NC, US. Standard quality control (QC) was then performed on the raw genome-wide data. QC steps involve excluding both samples (individual participants in this case) and SNPs on the basis of unreliability.

Pre-Imputation sample QC was performed by ALPSAC: ALSPAC children were excluded on the basis of gender mismatches; minimal or excessive heterozygosity; disproportionate levels of individual missingness (>3%) and insufficient sample replication (Identity By Descent < 0.8). Population stratification was assessed by multidimensional scaling analysis and compared with Hapmap II (release 22) European descent (CEU), Han Chinese, Japanese and Yoruba reference populations; all individuals with non-European ancestry were removed and then after combining with maternal genotypes data any with potential ID mismatches were also removed. Cryptic relatedness was measured as proportion of identity by descent (IBD > 0.1). Related subjects that passed all other quality control thresholds were retained during subsequent phasing and imputation leaving a final sample of 8,941 children.

Pre-Imputation SNP QC was also performed by ALPSAC: SNPs with a minor allele frequency of < 1%, a call rate of < 95% or evidence for violations of Hardy-Weinberg equilibrium (HWE) ($p < 5E\text{-}7$) were removed. A total of 500,527 SNPs passed these quality control filters and these genotypes were then combined with maternal genotypes of which 477,482 matched. A further 11,742 SNPs with genotype missingness above 1%, or that were out of HWE, were removed.

Imputation performed by ALPSAC: Haplotypes were estimated using ShapeIT (v2.r644) (Delaneau, Marchini, & Zagury, 2012) which utilises relatedness during phasing. The phased haplotypes were then imputed to the Haplotype Reference Consortium (HRC)

panel of approximately 31,000 phased whole genomes. The HRC panel was phased using ShapeIt v2, and the imputation was performed using Impute V3 (Delaneau et al., 2012).

Further post-imputation sample QC was performed by the author for this thesis: Genetic data were available for 8,941 individuals (4580 males, 4361 females). Siblings were removed leaving 8,872 individuals (4,542 males, 4,330 females). Where one sibling had more phenotypic data than the other, that sibling was retained; where both siblings had equal phenotypic data, one sibling was removed at random allowing an equal number of older and younger siblings to be removed.

Ten principal components were created for the 8,872 unrelated individuals in order to control for population structure. Using only observed (i.e., non-imputed) SNPs, short and long-range LD pruning was performed (Price et al., 2008) and then ten principal components were created using the 'pca' function in PLINKv1.9 (Purcell et al., 2007). Principal components were plotted to check for outliers and subsequently four participants were removed to leave a final genetic sample of 8,868 individuals.

Post-Imputation SNP QC was performed by the author for this thesis: Summary statistics for each chromosome were created using QCtool and SNPs were then excluded on the basis of a MAF < 0.01, with an info score < 0.4, a call rate < 0.95 and HWE of p < 5E-7. A final 6,319,684 SNPs survived quality control. Following the sample and SNP QC steps described, phenotype and genotype data were retained for a) 4,611 unrelated individuals (2,173 males) for genome-wide analysis of the cognitive data and b) 5,485 individuals (2,602 males) and for the emotion traits.

Finally, GWAS and post-GWAS quality control was performed by including the 10 principal components in the analysis to account for any population structure. Results were also checked for inflation caused by population structure by interrogating the lambda, value which should be between 0.95 and 1.05. However, as lambda will inflate in the presence of real polygenic signal, it is also necessary to check the LD score intercept, which should be close to 1. Inflation of the LD score intercept represents the presence of population structure and complicates interpretation of results.

6.2.4 Statistical Analyses

All data preparation was performed using R (R Core Team, 2013). Univariate genotype-phenotype association analyses were performed using SNPTest v.2 (Marchini et al., 2007) which can be found at https://mathgen.stats.ox.ac.uk. For each of the six genome-wide analyses a normal linear regression additive model co-varying for ten principal

components was performed. Imputation probability scores rather than hard calls were used to increase statistical power. Gene-based association analyses were performed using MAGMA within the FUMA programme using the summary stats from each GWA analysis (Leeuw et al., 2015; Watanabe et al., 2017). LD score regression (LDSC) was performed using LD hub (http://ldsc.broadinstitute.org) to test for associations with previous GWAS and using ldsc in Python to estimate heritability and bivariate heritability estimates between the cognitive and emotion PCA measures.

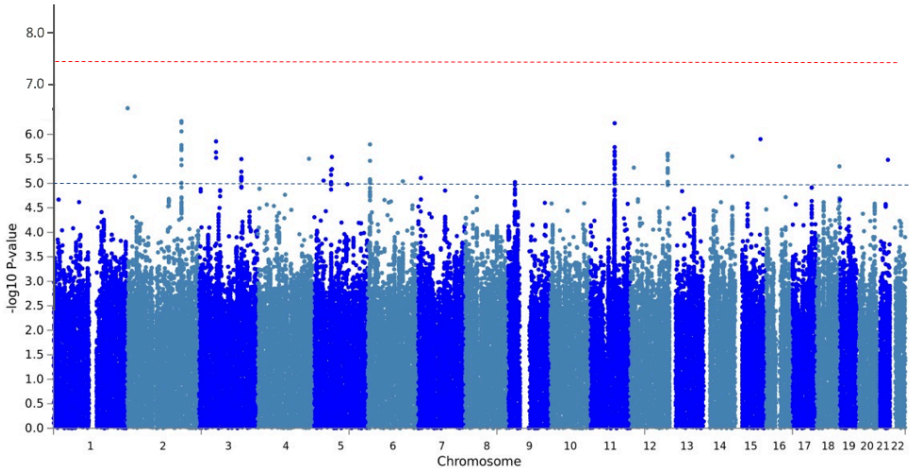
6.3 Results

Univariate analyses were performed for working memory, processing speed and inhibitory control as well as externalising, internalising and anxiety.

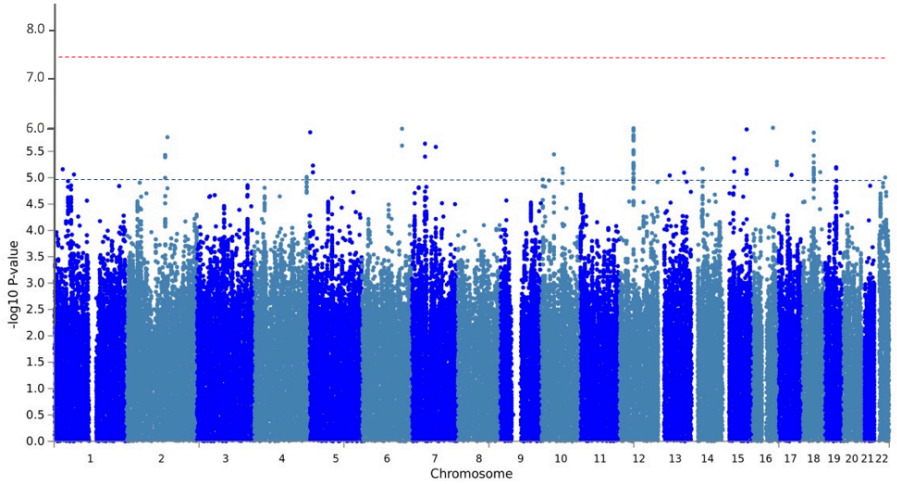
6.3.1 Genome-wide analyses

All six univariate genome-wide association analyses failed to identify any genome-wide significant SNP associations ($p<5x10^{-8}$; **Figures 6.1** and **6.2**), however many of the suggestive SNPs ($p<10^{-6}$) were located in or close to genes linked to neurocognitive decline, psychiatric disorders and/or educational attainment (**Supplementary Tables 6.1** and **6.2**).

A. Working memory (Lambda = 1.036, LD intercept = 1.001)



B. Processing speed (Lambda = 1.014, LD intercept = 1.007)



C. Inhibitory control (Lambda = 0.996, LD intercept = 1.004)

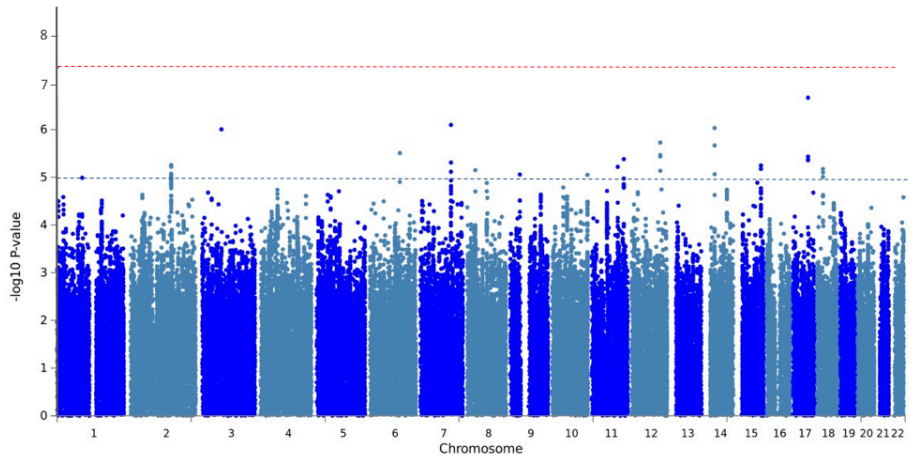
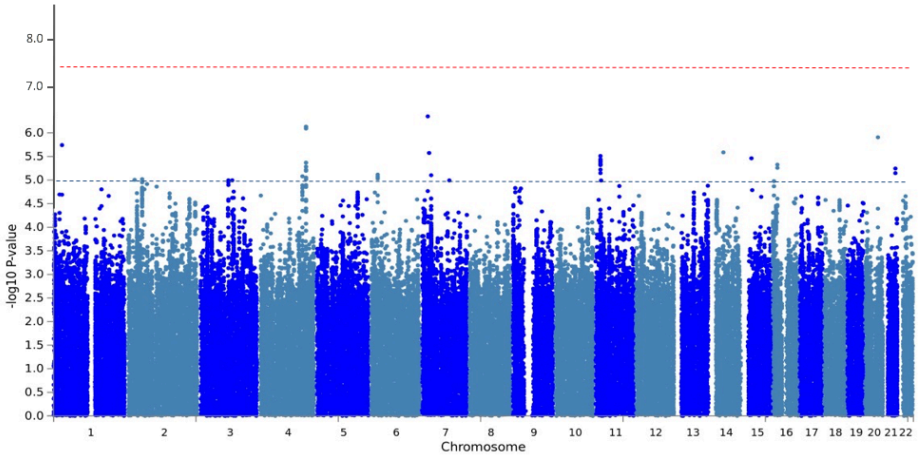
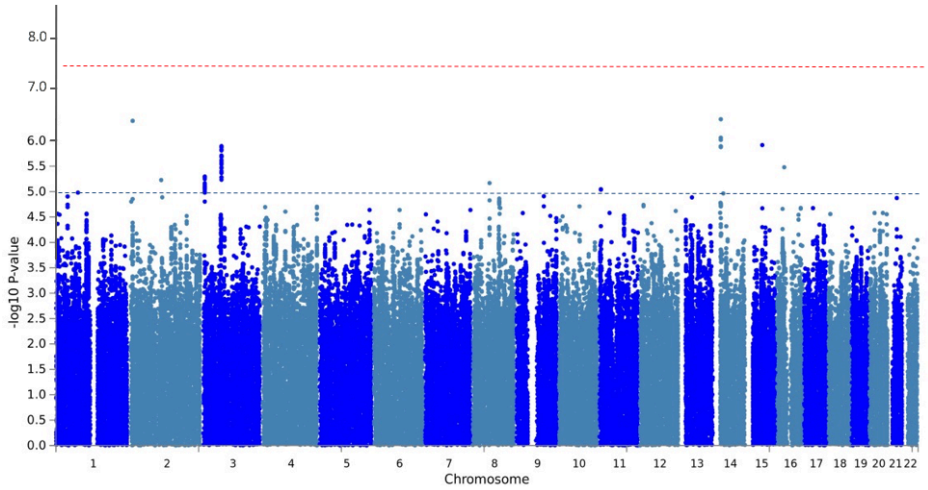


Figure 6.1: *Manhattan plot for univariate association analyses of the cognitive PCA measures*

A. Externalising (Lambda = 1.011, LD intercept = 1.008)



B. Internalising (Lambda = 1.026, LD intercept = 1.011)



C. Anxiety (Lambda = 1.005, LD intercept = 1.010)

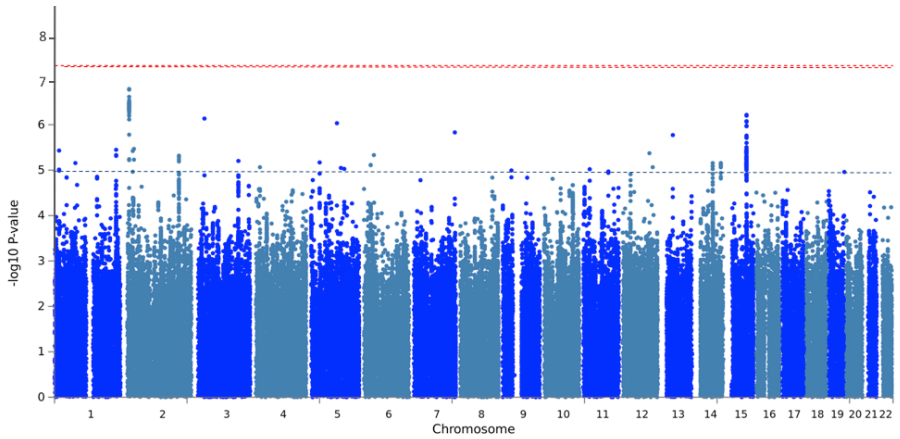


Figure 6.2: *Manhattan plot for univariate association analyses of the emotion PCA measures*

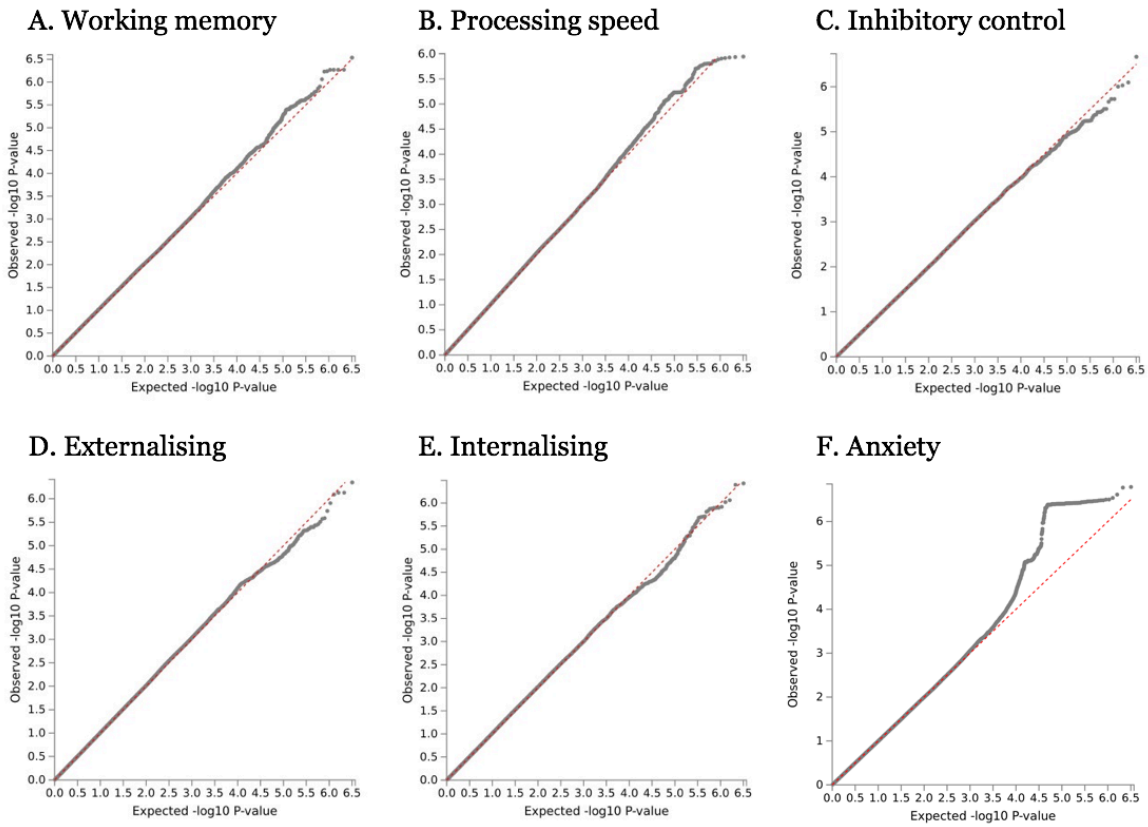


Figure 6.3: *Quantile-Quantile Plots for all six genome-wide association studies. Q-Q plots show the distribution of p-values against the expected p-values. We find a strangely inflated Anxiety QQ plot despite no heritability estimates.*

6.3.2 SNP heritability and genetic correlations for cognition and emotion

A SNP heritability estimate of 0.30 was obtained for working memory, 0.19 for processing speed, 0.13 for externalizing and 0.14 for internalizing. Both the inhibitory control and anxiety GWA analyses failed to detect any SNP heritability as shown by the negative estimates. For both traits, the mean $\chi^2<1$ meaning there is very little polygenic signal. They were therefore removed from further analysis. Bivariate SNP heritabilities were estimated for the remaining four traits, but none were significant due to the large standard errors (**Table 6.1**).

Table 6.1: SNP heritability estimates of the six GWAS traits along with phenotypic and genetic correlations

h^2_{SNP}	Phenotype Correlations (R)						
Genotype Correlations SNP rg (SE)		WM	IC	PS	EXT	INT	ANX
	WM	0.30 (0.07)	-0.03	-0.13***	-0.19***	-0.07**	-0.11***
	IC	NA	-0.01 (0.07)	-0.21***	-0.02	-0.04*	-0.01
	PS	-0.24 (0.32)	NA	0.19 (0.07)	0.06**	0.04*	0.06**
	EXT	-0.64 (0.35)	NA	0.36 (0.44)	0.13 (0.06)	0.29***	0.16***
	INT	0.60 (0.37)	NA	-0.26 (0.43)	0.42 (0.46)	0.14 (0.06)	0.43***
	ANX	NA	NA	NA	NA	NA	-0.11 (0.09)

****p<0.001. NA: genotypic correlations were not calculated for anxiety and inhibitory control as no SNP heritability was observed for these measures.*

6.3.3 Genetic Correlations between cognition and emotion and related phenotypes

In the ALSPAC sample working memory during adolescence was negatively correlated with slow processing rg_{SNP} = -.24, and externalising rg_{SNP} = -.64, and positively with internalising rg_{SNP} = .60. Slow processing is positively correlated with externalising rg_{SNP} =.36 and negatively with internalising rg_{SNP} = -.26. However internalising and externalising are positively correlated rg_{SNP} = .42 (**Table 6.1**). However, none of these associations reached significance and internalising and externalising both had too little power to find any associations with other traits due to the low ratio of heritability to standard error. SNP correlations were also estimated between the four cognitive and emotion measures with related phenotypes using the LDhub database (**Table 6.2**). The 28 traits selected for comparison include cognitive traits, psychiatric diseases, personality traits, education and brain volume (**Supplementary Table 6.3** and **6.4**). Working memory was significantly positively genetically correlated with Intelligence (rg_{SNP} = 1.15, p = 1.4 x 10^{-7}), Childhood IQ (rg_{SNP} = .80 p = 2.5 x 10^{-7}), and Yrs of schooling 2016 (rg_{SNP} = .70, p = 4.2 x 10^{-6}). There were further tentative positive correlations with thalamus volume (rg_{SNP} = .57, p = .03), openness to experience (rg_{SNP} = .49, p = .02) and Anorexia (rg_{SNP} = .20, p=.05) and negative correlations with ADHD (rg_{SNP} = -.67, p = .01), Depressive Symptoms (rg_{SNP} = -.41, p=.01) and Neuroticism (rg_{SNP} = -.26, p = .01). Furthermore, WM potentially had a trend shared genetic relationship with Autism (rg_{SNP} =. 30; p = .059), but not with other psychiatric traits such as bipolar disorder (rg_{SNP} = -.01), cross-disorder (rg_{SNP} = .05), major depressive disorder (rg_{SNP} = .03) or schizophrenia (rg =.05). Processing speed had one significant positive correlation with intelligence (rg_{SNP} = -.53, p=.05) and a high correlation – but also high standard error – with ADHD (rg_{SNP} = 1.17, SE = 0.63, p = .07.)

Table 6.2: Genetic correlations with independent GWAS of related traits estimated using LD Score Regression in LD Hub

Genotype Correlations

	Working Memory		Processing Speed		Externalising		Internalising	
	rg_{snp} (se)	p-value	rg_{snp} (se)	p-value	rg_{snp} (se)	p-value	rg_{snp} (se)	p-value
Intelligence	**1.15 (0.22)**	**1.36 x 10^{-7}**	**-0.53 (0.27)**	**0.05**	-0.95 (0.89)	0.283	0.30 (0.44)	0.501
Childhood IQ	**0.80 (0.16)**	**2.50 x 10^{-7}**	-0.45 (0.36)	0.211	NA	NA	NA	NA
Years of schooling 2016	**0.70 (0.15)**	**4.20 x 10^{-6}**	-0.16 (0.16)	0.293	-0.99 (1.21)	0.415	-0.08 (0.28)	0.786
Neuroticism	**-0.26 (0.10)**	**0.009**	0.08 (0.16)	0.614	0.90 (1.90)	0.635	1.18 (4.4)	0.787
Neo-openness to experience	**0.49 (0.22)**	**0.024**	0.20 (0.39)	0.592	-0.43 (1.21)	0.721	NA	NA
Anorexia Nervosa	**0.20 (0.10)**	**0.051**	0.04 (0.16)	0.782	0.02 (0.23)	0.926	NA	NA
Neo-conscientiousness	-0.23 (0.29)	0.432	0.63 (0.51)	0.216	-0.84 (1.86)	0.652	NA	NA
Subjective well being	0.05 (0.13)	0.709	0.11 (0.21)	0.602	-1.10 (1.58)	0.885	NA	NA
Depressive symptoms	**-0.41 (0.15)**	**0.006**	0.21 (0.21)	0.319	0.87 (1.58)	0.582	NA	NA
Major depressive disorder	0.03 (0.18)	0.855	-0.11 (0.25)	0.659	0.41 (0.39)	0.301	1.06 (1.1)	0.323
Attention deficit hyperactivity disorder	**-0.67 (0.27)**	**0.014**	1.17 (0.63)	0.066	0.45 (0.46)	0.327	0.54 (0.85)	0.523
Bipolar disorder	-0.01 (0.12)	0.967	0.17 (0.22)	0.425	-0.46 (1.28)	0.721	NA	NA
PGC cross-disorder analysis	0.05 (0.11)	0.662	0.26 (0.27)	0.340	0.87 (2.07)	0.675	NA	NA
Autism spectrum disorder	0.30 (0.16)	0.059	-0.25 (0.28)	0.390	0.62 (0.77)	0.419	1.07 (1.8)	0.551
Schizophrenia	0.05 (0.08)	0.503	0.18 (0.14)	0.200	NA	NA	NA	NA
Mean Thalamus	**0.57 (0.26)**	**0.029**	-0.01 (0.35)	0.975	-0.03 (0.51)	0.959	0.71 (2.1)	0.730
ICV	0.17 (0.22)	0.422	0.22 (0.34)	0.510	-0.71 (0.69)	0.304	0.05 (0.52)	0.930
Mean Accumbens	0.14 (0.30)	0.637	-0.28 (0.48)	0.556	-0.90 (1.11)	0.419	-0.36 (1.3)	0.780
Mean Caudate	0.06 (0.18)	0.751	0.09 (0.27)	0.730	-0.05 (0.42)	0.914	-0.16 (0.6)	0.788
Mean Hippocampus	0.11 (0.24)	0.663	-0.42 (0.42)	0.324	-0.50 (0.76)	0.513	-1.16 (3.3)	0.727
Mean Pallidum	0.21 (0.20)	0.283	0.11 (0.32)	0.723	0.22 (0.53)	0.681	-0.36 (1.1)	0.745
Mean Putamen	-0.01 (0.16)	0.932	-0.25 (0.28)	0.369	-0.50 (0.60)	0.405	-0.21 (0.70)	0.764

Bolded figures represent a significant (p<= .05) correlation. However, Bonferroni correction for multiple testing would require a p<.001. NA represents correlations that could not be estimated due to small heritabilities and large standard errors of both traits.

6.3.4 Gene-based analyses

Follow-up gene-based analyses were performed for each of the four traits with identified heritability. One gene was found to be significantly associated with working memory (*FAM181B*) and one with processing speed (*TNNI2)* (**Table 6.3**). Expression data from the GTEx portal for these two gene associations are also reported (**Supplementary Figures 6.3 and 6.4**).

Table 6.3 Significant Gene-based associations

Phenotype	Chromosome	Gene	Gene name	P	z-statistic
Working Memory	11	ENSG00000182103	FAM181B	1.99×10^{-6}	4.6124
Processing Speed	11	ENSG00000130598	TNNI2	2.74×10^{-6}	4.5453

6.4 Discussion

The goal of the present study was to further our current understanding of the genetic contributions to specific cognitive and emotion measures in adolescence, and examine the degree of shared genetic architecture between them. Six univariate genome-wide association studies for working memory, inhibitory control and processing speed as well as internalising, externalising and anxiety were performed. SNP heritability of each trait as well as the genetic correlations between the cognitive and emotion measures and measures of attainment, IQ and psychiatric disorders in independent samples was calculated. We found no significant SNP associations, but a moderate SNP heritability for working memory and processing speed, internalising and externalising and two gene-based associations. No estimates were achieved for inhibitory control or anxiety.

6.4.1 GWAS findings

We failed to identify any robust genetic associations at a genome-wide threshold with any of the six measures examined. However, for two of the cognitive measures (WM and PS) we report a number of suggestive hits in or near genes that have previously been associated with psychiatric disorders such as schizophrenia and major depression, sleep disorder and Alzheimer's disease. Interestingly, several of these SNPs have also been associated with neurological measures such as performance on the anti-saccade task, brain volume measures (cingulate and parietal cortex) as well as educational achievement (see **Supplementary Table 6.1**). Notably, we also found suggestive associations in regions previously associated with subjective well-being and Parkinson's disease. Turning to emotional behaviours, we found a suggestive association for externalising in a region associated with risky sexual behaviour (*FDSTL5*; chr 4). For internalising, we found three independent suggestive associations in the *SYNPR* gene, which has previously been linked to MDD (**Supplementary Table 6.2**). Finding associations with independent datasets for closely-related traits suggests that we are measuring related phenotypes and allows for more confidence in the measures.

6.4.2 SNP Heritability findings

LD score regression was used to estimate the SNP heritability of each trait. The highest heritability found was for working memory (h^2_{SNP} = .30), which is remarkably similar to other working memory SNP heritability estimates that use robust phenotypes (h^2_{SNP} = .24 - .41) (Vogler et al., 2014) but higher than others that use less well validated phenotypes (h^2_{SNP} = .05) (Davies et al., 2016) . In-line with other complex traits and behaviours, we note that our h^2_{SNP} estimate is lower than those obtained from twin estimates (h^2_{TWIN} =

.56 - 1) (Friedman et al., 2008). The 'missing heritability' between twin and SNP estimates has been extensively debated (e.g., see Manolio et al., 2009). There are several proposed reasons for this gap, including larger effects of rare variants not typically captured in a GWAS framework, interaction between genes and the environment, and epigenetic effects. Furthermore, LDSC has been found to derive lower heritability estimates than methods that use individual-level genetic data such as GCTA, particularly when applied to smaller samples (Otowa et al., 2016). The presence of SNP heritability suggests that larger GWAS are warranted if we want to identify specific variants which will be necessary to understand phenotype aetiology. In contrast, processing speed had a higher SNP heritability estimate (h^2_{SNP} = .19) than other studies (h^2_{SNP}=.11) (Davies et al., 2016) which may be due to the latent nature of the measure used in this study, which reduces error-related variability. Inhibitory control appeared to have no heritability (h^2_{SNP} = -.01). This may not be surprising as our measure consisted entirely of variables from the Stop Signal task which has been estimated in a twin study by Friedman and colleagues (2008) to be largely influenced by non-shared environmental factors (Friedman et al., 2008). There has only been one other GWAS (N=12,866) investigating inhibitory control, using the Stroop task, and whilst this study did not estimate SNP heritability it also failed to find any significant associations (Ibrahim-Verbaas et al., 2016). The Stroop task however has also been found to be mainly explained by both shared and nonshared environment (Friedman et al., 2008).

Externalising and internalising had similar heritability estimates at .13 and .14 respectively. These estimates are much larger than those previously found in related traits (h^2_{SNP}= ~.06; (Cheesman et al., 2017). In contrast, anxiety had too little heritability to estimate reliably (h^2_{SNP} = -.11). This is quite surprising from looking at the Manhattan plot which seems to show genetic signal and the QQ plot which has the highest inflation of all the phenotypes. Removing SNPs with a low info score did not change either the plots or the heritability estimate. However, all of the SNPs p <1 x 10^{-5}, had a MAF < .05. This reduced the mean χ^2 and means that LDSC cannot function properly. Although previous analyses have found SNP heritability estimates of between h^2_{SNP} = .19 and h^2_{SNP} = .32 for anxiety disorders, estimates for anxiety in the general population have been significantly lower h^2_{SNP} ~.04 in line with the present study (Otowa et al., 2016; Purves et al., 2017). During adolescence where anxiety is often higher due to social factors (Sebastian et al., 2010; Tillfors, Persson, Willén, & Burk, 2012), genetic effects may be further obscured.

6.4.3 Genetic correlations

LD score regression was also used to estimate genetic correlations. None of the genetic correlations between the ASLPAC cognitive and emotion measures were significant due to a lack of statistical power indicated by the large standard errors relative to the size of the heritability estimates. However, the directions of the correlations were all in line with the phenotypic correlations, with the exception of internalising. Here, the phenotypic data showed a slightly negative correlation between working memory and internalising (r = -.07), however the genetic correlation was estimated to be positive and large (rg_{SNP} =.60), implying that 60% of the variation in these measures that is explained by genetics is shared and operates in the same direction. Again, the phenotypic correlation between internalising and processing speed was positive (r = .04) but their genotype correlation was negative (rg_{SNP} = -.26). The opposite pattern was seen with externalising, (externalising-working memory rg_{SNP} = -.64, externalising-processing speed rg_{SNP} = .36) in line with the phenotype data, however internalising and externalising are positively correlated (rg_{SNP} = .42) suggesting that cognitive measures could be one of the elements that distinguishes between whether you are more susceptible to internalising or externalising behaviours. Why the relationship with internalising changes in the phenotypic data however is unclear but may be due to environmental influences on internalising behaviour.

As expected, WM was found to be highly significantly positively genetically correlated with other cognitive and academic traits. The correlation with intelligence is > 1 as LD score regression is not a bounded estimator and so can produce correlations larger than 1 or -1. This high correlation suggests that our WM GWAS is capturing largely the same genetic variance as the intelligence GWAS in independent adult samples using a latent factor ('g'). There were also significant positive correlations between WM and thalamus volume (rg_{SNP} = .57, p = .03), openness to experience (rg_{SNP} = .49, p = .02) and anorexia (rg_{SNP} = .20, p = .05) and negative correlations with ADHD (rg_{SNP} = -.67, p = .01), depressive symptoms (rg_{SNP} = -.41, p = .01) and neuroticism (rg_{SNP} = -.26, p = .01), although these would not survive correction for multiple testing (p < .002). It is interesting that WM was found to be negatively correlated with depressive symptoms, but has no relationship with major depressive disorder suggesting different aetiologies for differing experiences of depression, only some of which are related to working memory. There is a suggestive relationship with autism (rg_{SNP} =. 30, p = .059) but no association with other psychiatric traits such as bipolar disorder or schizophrenia.

Processing speed has one significant positive correlation with intelligence (rg_{SNP} = -.53, SE = .27; p = .05) and a high positive correlation but also high standard error with ADHD

(rg_{SNP} = 1.17, SE =.63; p = .07). Again, there were no significant associations with psychiatric disorders, but there are higher correlations were observed than with working memory, so it is possible that with more power these relationships could emerge. The present study's estimates were too unstable to make any strong predictions. The high standard error on a genetic correlation is a function of the heritability and sample size of the original studies. Genetic correlations are between the proportion of variance explained by genetic factors in each trait, not the total variance. The high standard errors therefore mean estimates are unlikely to be accurate. However, it would seem that our three cognitive measures are all quite different in terms of heritability estimates, as well at the traits they are related to. Working memory, as in previous chapters is most highly correlated with other variables.

6.4.4 Gene-based findings

Whilst we failed to detect SNP associations, a significant gene-wide association between working memory and *FAM181B* was found. Gene-based analyses potentially have more statistical power to detect causal variants as they aggregate correlated SNP effects across a gene, and reduce the multiple testing burden (Kang, Jiang, & Cui, 2013). *FAM181B* codes for an intracellular protein and is mostly expressed in the brain, showing enrichment in the caudate, cerebellum, cortex, hippocampus and hypothalamus. Expression of the gene is detected in endocrine tissue, the gastrointestinal tract and male (seminal vesicle) and female (fallopian tube, endometrium and ovary) tissues (**Supplementary Figure 6.3**). The *FAM181* gene family (of which there are *FAM181A* and *FAM181B*) is highly conserved among vertebrates. In mice, *FAM181B* transcripts have been detected early in embryonic brain development. The *FAM181B* loss-of-function mouse model found no obvious resulting phenotype (Marks et al., 2016), but differential expression has been reported in mouse models of tuberous sclerosis vs. wild type mice (Kong et al., 2014). SNP rs72952442-G which resides in the *FAM181B* gene reached suggestive significance (2×10^{-7}) in a previous GWAS of cerebral amyloid deposition in *APOEe4* non-carriers (Li, Parrado, Samtani, Narayan, & Alzheimer's Disease Neuroimaging Initiative, 2015). Finally, both *FAM181B* and *FAM181A* (thought to have overlapping function with *FAM181B;* Marks et al., 2016) have also been associated with Alzheimer's disease (Herold et al., 2016).

A gene-based association was also found between processing speed and *TNNI2*. *TNNI2*, a fast-skeletal muscle troponin 1 gene, is part of a collection of genes involved in governing muscle function (**Supplementary Figure 6.4**), and mutations in this gene are associated with muscle contractures (Sung et al., 2003; Toydemir & Bamshad, 2009). It has previously been associated with GWAS of inflammatory bowel disease (Jostins et al.,

2012). Speculatively there could be a plausible relationship between muscle function and physical speed of response, which would not necessarily reflect individual difference in cognition.

6.4.5 Conclusion

In conclusion, the cognitive measures identified in **Chapter 3** were all found to be quite different in their genetic characterisation. Heritability was estimated at 30% for our working memory measure and 19% for processing speed, while inhibitory control on the other hand appeared to have either very low levels of heritability or none at all. This was also the case for the emotion PCA anxiety measure and although heritability was estimated at 13% and 14% for externalising and internalising measures, there was too little power to be able to draw any strong conclusions about their genetic relationships with cognitive traits. However, we did note a surprising finding that although internalising is negatively correlated with working memory phenotypically, they are positively correlated genetically. We also found a contrary relationship between internalising and slow processing. This supports evidence from **Chapter 3** that internalising has a complex relationship with cognition. Future work could take advantage of new methods such as genomic SEM to untangle this relationship between internalising and cognition, working memory and depression and that between working memory and general intelligence (Grotzinger et al., 2018).

No SNP were significantly associated with any of the six cognitive and emotion measures but two genes were found to be associated with working memory and processing speed respectively. Replication of these gene-based hits should be performed and a GWAS of the anti-saccade task, the only inhibitory control task with significant twin heritability (Friedman et al., 2008) should be carried out to understand if inhibitory control has any genetic basis. If inhibitory control is entirely environmental this could have important implications for cognitive training studies.

7. How cognition and emotion predict academic achievement

Behavioural studies investigating EFs as predictors of academic achievement (AA) have tended to focus on preschool and primary school years but considering EFs continue to develop and differentiate during adolescence, as do schooling demands, this could potentially change the relationship between cognitive abilities and AA. Furthermore, few studies have sought to investigate the differential effects of specific cognitive abilities on different academic subjects. ER has been less widely studied in terms of its relationship to AA despite speculation about its importance. More studies have looked at individual emotional behaviours such as those established in Chapter 3.2 and their effects on AA in general, however again, few have assessed subject-specific associations either phenotypically or genetically. This study sought to investigate associations between different cognitive abilities and different academic outcomes during adolescence and to test whether the more parsimonious common models, or the more complex specific models for both cognitive and academic variables would better fit the data. It also assessed whether including emotional behaviours significantly added to our model of attainment. We found specific models fit better than common models, that both cognitive and emotion variables had specific effects but that the emotion variables added little extra variance explained.

7.1 Introduction

Executive functions (EFs) are predictive of early academic attainment. However, there is little research investigating whether academic outcomes are differentially associated with cognitive abilities during adolescence, when EFs are still developing. Furthermore, although there is research looking at how various aspects of how emotional behaviour interact with education, this study is unique in that it looks how different emotional behaviours relate to different subjects during adolescence, accounting for EF and IQ. This study sought to assess, using structural equation modelling, 1) whether there are specific relationships between cognitive factors and English, maths and science at age 16 controlling for attainment at age 11 and SES, 2) whether modelling cognitive factors and AA separately compared to modelling them as common factors resulted in a better model fit and 3) whether emotional and behavioural regulation measures significantly contributed to this model.

A number of cognitive abilities have been proposed to explain individual differences in academic attainment, including IQ, EFs and attention (Best et al., 2011; Cragg & Gilmore, 2014; St Clair-Thompson & Gathercole, 2006). IQ and AA have correlations ranging from 0.3 to 0.7 across the world across academic subjects and ages (Lynn & Mikk, 2007), with verbal IQ found to be a higher predictor than non-verbal IQ and with correlation found to be increasing over development (Laidra et al., 2007; Roth et al., 2015).

EFs have been shown to predict academic attainment independently of IQ both through individual task measures and latent factors (Alloway & Alloway, 2010; Cragg & Gilmore, 2014; Rhodes et al., 2016). A large number of cross-sectional studies have provided evidence that WM and inhibitory control account for unique variance in arithmetic, beyond variance explained by IQ, age, processing speed or reading, in a wide range of age groups (e.g. Monette, Bigras, & Guay, 2011; Bull & Scerif, 2001; see Cragg & Gilmore, 2014 for review). In general, associations between WM and maths and literacy have tended to be more consistent across ages, while IC may be a stronger predictor of pre-school (Blair & Razza, 2007; Espy et al., 2004), but not necessarily later primary school, maths and literacy (Bull & Scerif, 2001). Evidence is more limited regarding predictors of science attainment, however, using a large task battery including measures of both response and semantic inhibition, a cross-sectional study in 10 and 11 year-olds found a relationship between English, maths and science attainment and IC (St Clair-Thompson & Gathercole, 2006).

Most of these studies have tended to focus on preschool and primary school years (Brock et al., 2009; Bull & Scerif, 2001; Espy et al., 2004; Gilmore et al., 2013). There are few longitudinal studies of EFs as predictors of AA. The results support the cross-sectional data, with WM and IQ found to uniquely predict maths and reading outcome in primary and secondary school (Alloway & Alloway, 2010; Dumontheil & Klingberg, 2012; Mazzocco & Kover, 2007). However, as these studies have tended not to control for early AA, it is unclear whether EFs and IQ continue to uniquely influence academic outcomes beyond early effects. One study by Stipek and colleagues suggests that in fact, although working memory and attention are important in early attainment, there is a 'fade-out' by adolescence (Stipek & Valentino, 2015). This is an important issue, as a better understanding of the predictors of learning and AA throughout the school years could inform the potential of targeted interventions beyond the early years (Heckman, 2006).

While the studies reviewed above collected various measures of academic attainment, few systematically investigated the potential specific influences of IQ and EFs on different academic subjects. There is some evidence for similar effects from IQ and EF across academic subjects across time (Best et al., 2011; Roth et al., 2015), and some for different associations between cognitive abilities and different academic subjects in adolescents (Latzman et al., 2010).

Research looking at emotion and ER in AA is more mixed. It is unclear whether emotion or ER have direct effects on AA (Graziano et al., 2007) or whether their influence may operate via cognitive ability (Brock et al., 2009) or self-regulation (Howse et al., 2003). It is commonly found that externalising but not necessarily internalising behaviours uniquely predict under-achievement across school-age children (6-18 yrs) (Nelson et al., 2004; Risi et al., 2003) but there is debate as to whether this is due to co-occurring inattention difficulties (Frick et al., 1991). A large study using six population-based cohorts across the U.S., Britain and Canada found that in childhood, when controlling for prior attainment and attention, individual differences in internalising and externalising were not significantly associated with AA (Duncan et al., 2007). Anxiety is also thought to negatively influence attainment by decreasing attentional control (Eysenck et al., 2007; Rajchert et al., 2013). However others have argued that although inattention may be the main link between emotional behaviour and underachievement during childhood, by adolescence the relationship between emotional problems and underachievement becomes more direct (Hinshaw, 1992; Masten et al., 2005). Conscientiousness is consistently positively associated with achievement (Ivcevic & Brackett, 2014; Rimfeld et al., 2016) and extraversion is often negatively associated with attainment (Chamorro-

Premuzic & Furnham, 2003; O'Conner & Paunonen, 2007). But again, it is not clear whether these are also associated via cognitive mechanisms or independently.

Two main structural equation models were created. The first model investigated the relationship between cognitive variables and subject-specific academic achievement. Along-side model 1 two other models were also tested, one which tested whether the model fit improved if cognitive measures were treated as one common latent model, and the other which tested the model fit if English, maths and science were treated as one common AA latent measure. The second model incorporated emotion variables to assess whether they explained any additional variance and whether any specific relationships could be observed.

Included in all models alongside the cognitive factors were vocabulary (verbal) and matrix reasoning (non-verbal) measures of IQ, subject attainment at age 11 and social economic status (SES). SES is often found to be correlated with AA and is considered a major component influencing academic success (Hackman, Farah, & Meaney, 2010; Reardon, 2011; Sirin, 2005). It was expected that SES would have general effects whereas WM, processing speed, vocabulary and reasoning would show more specific associations. It was unclear whether IC would explain any variance in the different subjects due to the mixed evidence regarding its role in later AA. In model 2 it was expected that externalising, extraversion and anxiety would have a negative influence on all subjects and that conscientiousness would have a positive effect on all subjects. It was unclear whether internalising would be a positive or negative influence. The present study therefore sought to assess specific associations between cognitive abilities, emotional behaviours and academic attainment during adolescence.

7. 2 Methods

7.2.1 Study cohort

This study uses the ALSPAC cohort described in **Chapter 2.1**. The final sample for the current study includes 5,562 participants (2,624 males) aged 9 years 10 months to 20 years 0 months. This sample size represents the sample overlap between the cognitive and emotion PCA measures developed in **Chapter 3**.

7.2.2 Measures

Included in this study were the cognitive measures obtained in the principal component analysis in **Chapter 3.3.1.1**: working memory, inhibitory control and processing speed.

Also included were two measures of IQ, the vocabulary and matrix reasoning subtests of the WASI (**Chapter 2.2.6**), as well as the five emotion measures derived in **Chapter 3.3.1.2**: internalising, externalising, anxiety, conscientiousness and extraversion. SES was a measure of parental occupational social class (**Chapter 2.2.1**) scored from 1-6 (*M* = 4.0, range = 1.0 – 6.0). Academic attainment was assessed using national curriculum standardised tests at age 11 and 16 years old (**Chapter 2.2.4**).

7.2.3 Statistical analysis

Four structural equation models were fit. The first three assessed associations between the cognitive variables and the AA measures at age 16 controlling for AA at age 11. The first model includes a confirmatory factor analysis (CFA) using the factor structure derived in **Chapter 3.3.1.1** and English, maths and science as separate variables. The second CFA tested a common cognitive model with all variables loading onto one factor, and the third tested common AA model where English, maths and science were treated as one latent variable. The fourth model included the emotional factors derived in **Chapter 3.3.1.2** to see if the emotion behaviour variables contributed any additional variance explained.

The models were fit using the Lavaan version 0.5-23.1097 (Rosseel, 2012) package in R. The Robust Maximum Likelihood estimator with Yuan-Bentler scaled test statistic (MLR) was used to account for any violations of multivariate normality. We assessed the overall fit of the model with the chi-square test, the Root Mean Square Error of Approximation (RMSEA) and confidence interval, the Comparative Fit Index (CFI) and the Standardised Root Mean Squared Residuals (SRMR). A good model fit was defined as RMSEA and SRMR < .06 and < .08 respectively and CFI > .95 (Hu & Bentler, 1999).

7.3 Results

Analyses were performed using the cognitive and emotional and behavioural regulation measures created in **Chapter 3**. As the two sets of measures had slightly different samples, analyses were performed on participants which had both set of measures (N = 5,562). CFA was performed with the EF and processing speed variables based on the PCA model (**Chapter 3.3.1.1).** This model was compared against a simpler 'common EF model'. A CFA with all of the emotional variables was too complex to run and therefore emotion measures were included using their PCA factor scores (**Chapter 3. 3.1.2**). We performed the analyses keeping English, maths and science as separate subjects, but compared them with a model where they were treated as a common AA latent variable.

7.3.1 Correlation analyses

Supplementary Table 7.1 reports the Pearson's correlation coefficients between demographic, cognitive and academic attainment variables.

7.3.2 Structural Equation Models

Model 1 (**Figure 7.1**) had a decent model fit: $\chi^2(152) = 2418.21$, $p < .001$; CFI = .952; RMSEA = .052 [.050, .054]; SRMR = .046. Total variance explained by this model in English at age 16 was 65%, maths 71% and science 69%. The full covariance matrix and regression model can be found in **Supplementary Tables 7.2 & 7.3**. This model was compared against a common EF-processing speed factor model and the fit was significantly worse, (CFI=.833, RMSEA=.091, SRMR =.072, df=173, χ^2_{diff} = 5845.2, df_{diff} = 21, p <.001) as was a fit with a common AA factor (CFI=.925, RMSEA=.062, SRMR =.047, df = 170, χ^2_{diff} = 1111.8, df_{diff} = 18, p <.001).

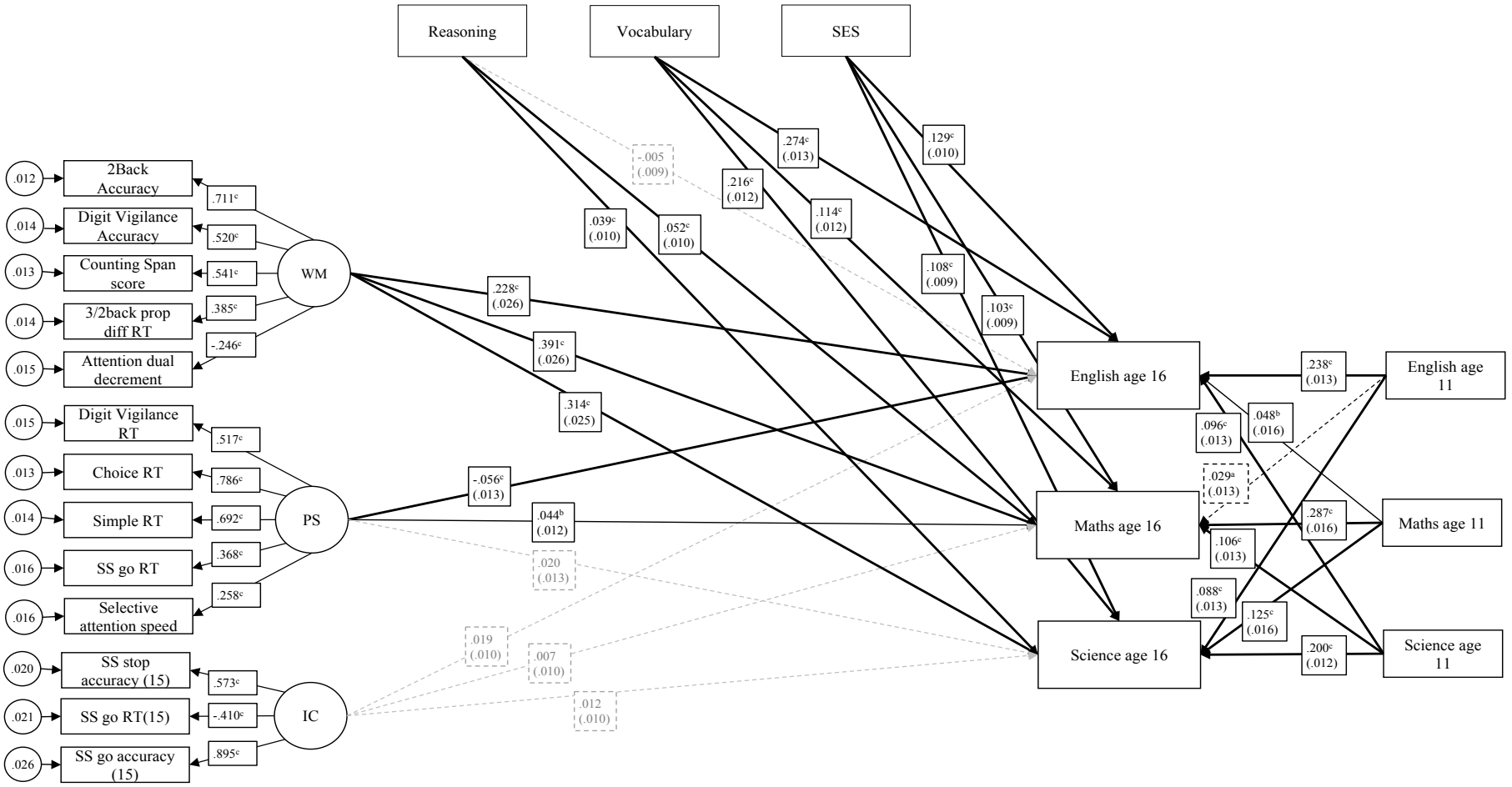


Figure 7.1: *Model 1 cognitive predictors of English, maths and science achievement at age 16 controlling for SES and attainment at age 11. Figures in boxes represent the beta values and the standard errors are in brackets.* [a] *p < .05 (black dashed lines),* [b] *p< .01 (thin full black lines),* [c] *p< .001 (thick full black lines), non-significant paths are shown with grey dashed lines.*

Model 2 with both the emotion and cognitive measures had a good fit: $\chi^2(202) = 2557.81$, $p < .001$; CFI=.953; RMSEA=.046 [.044, .048]; SRMR=.039. All the emotion measures, other than anxiety, significantly predicted all three subjects apart from internalising which failed to predict science (**Figure 7.2**). The associations between matrix reasoning, SES and AA were not affected by the addition of the ER measures. However, associations with working memory were reduced and to a lesser extent those with vocabulary and processing speed. Altogether 67%, 72% and 71% of variance in English, maths and science was explained respectively, meaning the ER data added 1-2% extra variance explained to each outcome measure (full covariance matrix and regression model in **Supplementary tables 7.4 and 7.5**). However, the model fit was not better than the EF-processing speed only model and so in this case the more parsimonious model is usually preferred.

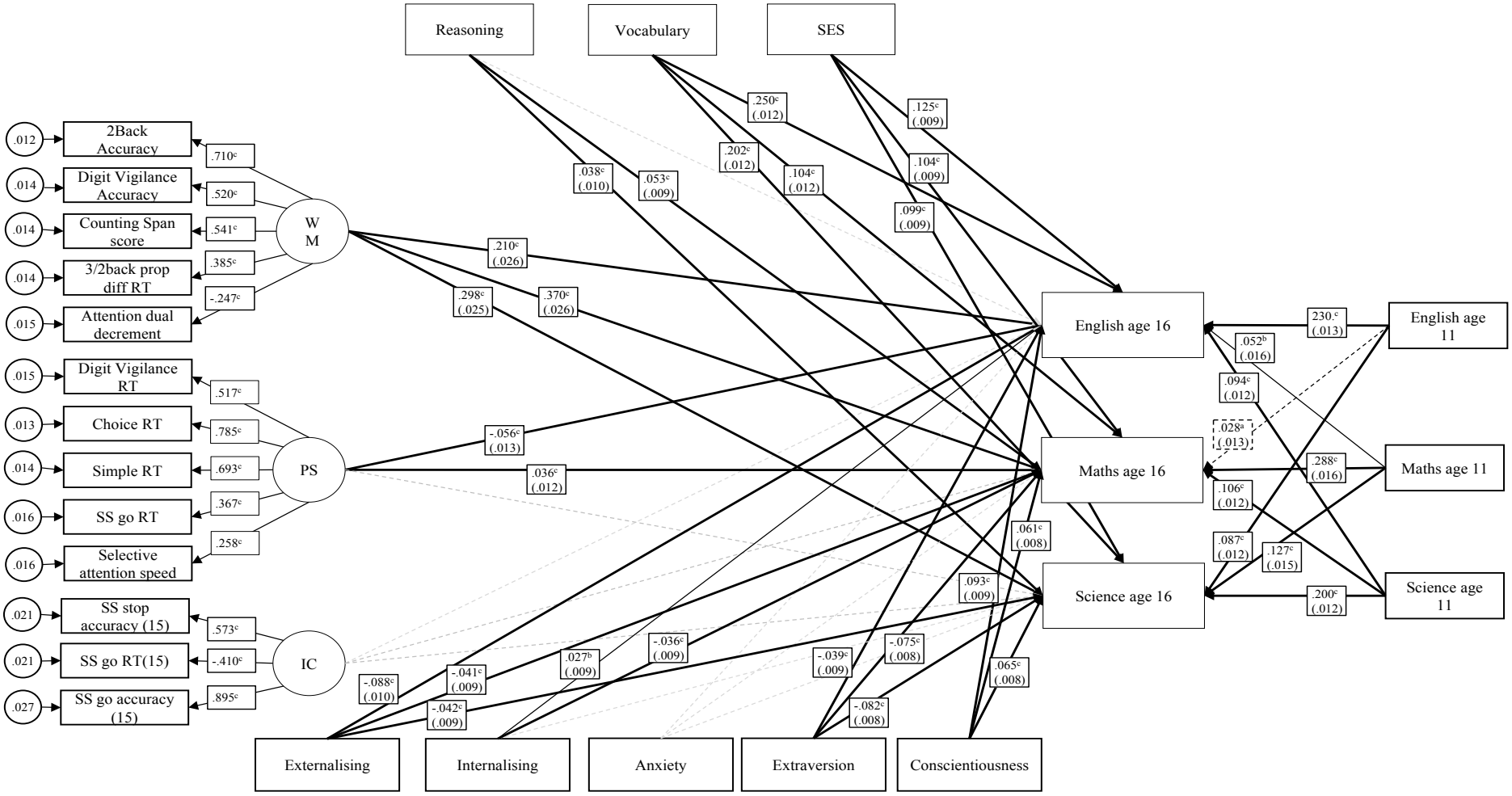


Figure 7.2: *Model 2 cognitive and affective predictors of English, maths and science achievement at age 16 controlling for SES and attainment at age 11. Note that this model was not found to be a significantly better fit to the data than Model 1. Figures in boxes represent the beta values and the standard errors are in brackets.* [a] *p < .05 (black dashed lines),* [b] *p< .01 (thin full black lines),* [c] *p< .001 (thick full black lines), non-significant paths are shown with grey dashed lines.*

7. 4 Discussion

The present study demonstrated that a range of cognitive abilities and emotional behaviours are uniquely and differentially associated with improvements in English, maths and science during adolescence. The study's strengths include the sample size, controlling for previous attainment to look at adolescence-specific effects and controlling for other subject attainment to assess subject-specific effects. In doing this we have shown that cognitive abilities and emotional behaviours are involved in influencing change in attainment over adolescence and that they do so with some subject specificity. We also tested against alternative models in which EF and AA were represented by the common variance explained but found the original model to be best.

The first part of this study tested the hypothesis that it is better to model both cognitive and AA as separate variables. In comparing a common EF and common AA model with a model with both factors distinct we found that the best model kept all of these variables separate. The correlation matrix (**Supplementary Table 7.1**) showed that attainment is highly correlated between academic subjects and becomes more correlated over time. It could be that as children get older discrete subject knowledge becomes less important to success than a more general ability to apply skills and knowledge appropriately. However, the model comparison suggests that despite large correlations between subjects it is preferable to keep academic subjects separate when investigating their relationship to cognitive measures and SES. Furthermore it was also shown that it is preferable to keep the cognitive factors as distinct components supporting studies that find a multi-factor solution for cognitive variables fits better than a one factor solution in adolescents and older (Lee et al., 2013; Lehto et al., 2003; Miyake et al., 2000).

WM explained significant unique variance in every subject over and above previous attainment and attainment in the other two subjects and explains the most unique variance in maths and science improvement across adolescence. This fits with previous research suggesting WM is the best predictor of maths attainment and does so over and above IQ (Alloway & Alloway, 2010; Dumontheil & Klingberg, 2012). WM is important for improvements in English possibly due to findings that it predicts reading (Lan et al., 2011) This could be by allowing pupils to keep in mind the context of a text and keep track of long sentences. The study by Stipek and colleagues found a 'fade-out' by adolescence – meaning WM and attention ceased to have a role in adolescent attainment (Stipek & Valentino, 2015). However, their EF measures did not increase in difficulty with age and ceiling effects were observed in adolescence, possibly explaining the lack of effect.

The IC measure failed to explain any significant unique variance in any of the academic subjects. If IC does reflect some general ability as suggested by Miyake and Friedman (2012), we would not expect it to represent any unique variance, but instead to correlate highly with AA overall. In fact, in the present study, IC correlated poorly with all cognitive measures (IQ, WM, PS and AA). Previous research is inconclusive about the role of IC in attainment. Some studies have found it to explain unique variance in attainment in young children (Blair & Razza, 2007; Espy et al., 2004; Lan et al., 2011) but studies with more complex tasks or older children have not found this association (Bull & Scerif, 2001; Monette, Bigras, & Guay, 2011). It could be that the Stop Signal task collected in the ALSPAC sample and which requires motor inhibition, is less relevant for later AA than semantic inhibition tasks, which have previously been associated with AA (Protopapas, Archonti, & Skaloumbakas, 2007; St Clair-Thompson & Gathercole, 2006). Note that the Stop Signal task at age 15 had a limitation in that different parameters had been set for different groups of participants. We corrected for this by regressing out the parameters from our scores, however this assumed a linear effect of delay time on accuracy.

Processing speed is highly correlated with white matter integrity (Kievit et al., 2016), has a strong developmental trajectory and appears to interact with the development of fluid intelligence and working memory (Fry & Hale, 2002; Huizinga et al., 2006; Kievit et al., 2016; Lee et al., 2013; McAuley & White, 2011). PS has a different association with each of the three subjects. Faster processing speed is beneficial for improvements in English, possibly due to its role in reading (Kail & Hall, 1994). With maths, it appears beneficial to have a slower processing speed, further work will need to replicate this finding, which may reflect an advantage of a slower more deliberative approach to complex maths problems. Science on the other hand is not associated with PS.

As with previous research correlations between academic attainment and verbal IQ were found to be between 0.47 – 0.60, lower correlations were observed for non-verbal IQ (0.23 – 0.36) and associations increased with age (Roth et al., 2015). Vocabulary was associated with significant unique variance in all three subjects and explained the most amount of variance in improvement in English across adolescence. It also explained more unique variance in science than previous science attainment. Reasoning did not however explain any unique variance in English improvement, but explained a small amount in maths and science which is different from findings observed by Deary and colleagues (2007).

As expected, SES was correlated with AA and these correlations increased with age from 0.30 – 0.33 at age 11 to 0.41 – 0.43 at age 16. SES explained a significant proportion of variance in AA, with 10% – 13% of unique variance explained across subjects between the ages of 11 and 16. This provides evidence that SES may influence progresses in academic attainment during early and mid-adolescence, beyond effects observed in the early years, which has been the main focus of research and policy (Hackman, Farah, & Meaney, 2010). Further work would be needed to identify what mediates these specific associations, but for example the presence of books in the house may mediate associations with English, while parents' numeracy may mediate associations with Maths. Although literature on school readiness predicts that self-regulation (including EF and emotion) is the main mechanism by which poverty influences attainment (Blair & Raver, 2015), we did not find SES to be more highly correlated with these factors than with AA itself, and associations with SES were observed even though two EF components were entered in the model. Correlations in other studies between SES and individual academic subjects tend to be higher than with overall attainment, suggesting again there may be specific routes through which SES affects individual subject attainment, and remains the same, or increases, over development (Sirin, 2005).

We found the direction of effects for externalising, extraversion and conscientiousness all were as expected. We found no effect of anxiety, and internalising was differentially associated with each subject. Externalising was most negatively associated with English achievement and to a lesser extent with maths and science (β = -.088, -.041, -.042, respectively). At the same time extraversion showed the exact opposite pattern and was least negatively associated with English and more so with maths and science (β = -.039, -.075, -.082 respectively). There is a belief that being more outgoing – or having more 'approach' like behaviours contributes to a positive social attitude which may be beneficial to education in that it is more likely to positively engage teachers obtaining more attention (Blair, 2002; Eisenberg et al., 2005). This assumption would predict that extraversion, would therefore have a positive influence on AA but consistent with much other research (Chamorro-Premuzic & Furnham, 2003; O'Conner & Paunonen, 2007) this does not seem to be the case. Conscientiousness is slightly more positively associated with English achievement than maths and science (β =.093, .061, .065 respectively). This suggests that English is the academic subject most negatively and positively influenced by behavioural factors.

Internalising was found to have a different relationship with each subject, a positive one with English (.027), negative with maths (-.036) and no relationship with science. This could perhaps explain previous mixed results in regard to the association with

internalising and overall academic achievement (Nelson et al., 2004; Risi et al., 2003). Variance explained by WM and vocabulary decreased slightly on the addition of the emotional variables as did the association between processing speed and maths. Including the emotion variables in the model slightly increased the variance explained in each subject (1-2%) but not the model fit. Anxiety and IC were not uniquely associated with any of the subjects. Matrix reasoning was not uniquely associated with English, and internalising and PS were not uniquely associated with Science.

7.4.1 Conclusion

The present study sought to characterise differential associations between cognitive abilities and emotional behaviours with attainment in English, maths and science during adolescence. We found that all the predictors apart from inhibitory control and anxiety had some specificity in terms of variance explained in different subjects and that they contributed to change in attainment over adolescence. These findings highlight the benefit of maintaining specificity when investigating adolescent predictors of academic attainment. The study also provides novel information regarding predictors of attainment in science, an under-studied academic subject which shares some features with English in the shared importance of vocabulary, and with maths in the role of working memory, reasoning and behavioural measures. Overall working memory and vocabulary explain the most variance in academic subjects in both models reinforcing previous findings. Some emotion measures such as externalising, conscientiousness and extraversion also play a smaller role, but one which may deserve attention.

This study looked broadly across adolescence from ages 11 to 16, however considerable changes happen at this time both in terms of cognitive and emotional development (Casey et al., 2008; Crone & Dahl, 2012; Steinberg, 2005). Future research could look in finer details at how specific developmental trajectories could be supported over this time period to facilitate better learning. For example, we know from **Chapter 5** that externalising reduces over this period, therefore at what point is it particularly harmful for education? There may also be gender differences driving relationships between certain subjects and emotional behaviours. In terms of cognitive ability, it would be useful to explore other types of inhibitory control such as semantic inhibition to try and understand whether these have any specific influences of academic improvement.

8: Genome-wide association study of English, maths and science and their genetic relationship with cognition and emotion

Both phenotypic and genetic studies examining the relationship between cognitive ability and academic achievement have modelled the two constructs either in terms of their common or domain-specific variance. For example, cognitive ability can be understood in terms of an individual's general ability across all domains conceptualised as IQ, 'g' or common EF. Alternatively, it can be modelled in terms of separable abilities such as WM and IC. Equally, academic achievement can be understood in general terms as a latent AA structure, or subject-specific performance – as achievement in English, maths and science. Findings from Chapter 7 indicate that there are specific associations between both cognitive and emotion measures and academic subjects during adolescence. Furthermore, model fit analyses suggest that a model that specifies academic subjects and cognitive variables as separate, provides a fit better than one that models them jointly. This study investigated the genetic relationships between individual differences in the latent cognitive and emotion factors identified in Chapter 3 and subject-specific academic achievement using DNA-based methods. In order to achieve these aims, it was first necessary to perform univariate GWA analyses of English, maths and science attainment. This represents the first GWAS of standardised national tests of English and Maths attainment, and the first ever GWAS of science attainment. The study then aimed to assess specificity of genetic associations across the three academic subjects, and examine the magnitude and pattern of genetic relationships with cognitive and emotional traits both within the ALPSAC sample in and in independent samples. Results show moderate heritability and significant SNP associations for all three subjects. A high proportion of shared genetic variance was observed between subjects and cognitive measures, however emotion-based measures shed light on areas of specificity.

8.1 Introduction

The molecular genetic study of AA and the overlap with cognitive and emotional variables is an area of research still very much in its infancy and (as discussed) GWASes of individual academic subjects are sparse. GWA studies focusing on maths ability began by comparing high vs low ability in small samples of between 602 to 2,365 individuals (Baron-Cohen et al., 2014; Docherty et al., 2010) but low sample sizes meant no genome-wide associations were found. Motivated by the large genetic correlation identified for maths and reading ability in multivariate twin studies (N=2,794) (Rimfeld et al., 2015; Tosto et al., 2013), Davis et al. (2014) (N=2,221) sought to replicate these findings using DNA-based approaches. They reported a significant genetic overlap between reading and maths when assessed at 12 years of age (i.e. significantly larger than 0), although the exact magnitude of effect was difficult to ascertain due to large standard errors but it was somewhere between 0.32 - 1.00. Individual differences in English ability have been studied less as an academic subject and more in terms of reading and language ability and disability (Gialluisi et al., 2014; Harlaar et al., 2014).

Overall robust subject-specific genetic associations have been hard to uncover and in the last few years there has been a move away from examining specific academic subjects, towards using a broader educational attainment phenotype. There are a number of reasons for this. Firstly, early GWA studies highlighted that individual effect sizes for educational and cognitive-associated loci were likely to be small, typically in the region of <0.5% explained per variant. Large sample sizes would therefore be required to detect robust associations that replicate (Davies et al., 2011). This necessitated the use of educationally-relevant variables that were widely available across cohorts – typically demographic variables such as number of years spent in education. Secondly twin studies showed that academic subjects and cognitive ability shared a large amount of common genetic variation dubbed 'generalist genes' (Kovas & Plomin, 2007).

The first large Educational Attainment (EA) GWAS (N=126,559) was a meta-analysis of 42 cohorts performed by the Social Science Genetic Association Consortium (SSGAC) and found three independent genome-wide significant SNPs, each with small effect sizes. The associations replicated and functional analyses revealed that the signal was located in (or close to) genes previously associated with health and cognition, supporting a more general approach to phenotyping (Rietveld et al., 2013; Trampush et al., 2015). A subsequent GWAS by the SSGAC (EA2; (N=293,723) found 74 associations that were mostly located in regions involved in regulating gene expression in foetal brain development (Okbay, Beauchamp, et al., 2016). The most recent GWAS by the same

consortium was published this year (EA3; N>1 million) and identified 1,271 significant loci. They found an enrichment of genes expressed postnatally in the central nervous system and involvement in cognitively-relevant biological functions such as neurotransmitter secretion and synaptic plasticity. Construction of a polygenic risk score (a score representing an individual's amalgamated genetic 'risk' derived from the GWAS results) was predictive of 7-10% of the variance in cognitive ability and 11-13% in educational achievement, making it one of the most predictive PGS currently available (Lee et al., 2018). Beyond cognitive performance, the specific genetic variants identified in the EA series of GWASes have been shown to be associated with affect-related traits including Strengths and Difficulties Questionnaire scores (SDQ; a measure of child problem behaviours), negative symptoms of affect (related to depression), callous and unemotional traits and ADHD (Krapohl et al., 2015; Zeeuw et al., 2014). These studies demonstrate the power of taking a broad phenotype to maximise discovery cohort GWAS samples sizes and thereby providing the statistical power required to uncover common genetic variants of small effect. However, despite these successes, there remains evidence for specificity in the genetic profile of individual academic subjects and cognitive ability. Questions remain as to what the underlying phenotypes – both cognitive and non-cognitive – contributing to EA are. We demonstrated in the previous study (**Chapter 7.3**) that not only does a SEM model treating AA as separate academic subjects fit the data better than a common AA model, but that there may be neurocognitive specificity to achievement in different subjects. Consistent with our findings, when controlling for IQ, bivariate twin estimates of English, maths and science, suggest that just over half of the remaining heritability is shared between subjects (Maths - English (0.54), Science - English (0.64), Science - Maths (0.69)), which leaves just under half of this remaining heritability not shared across subjects (Rimfeld et al., 2015). In another study, maths retained a heritability of 0.44 when controlling for general intelligence as well as reading ability (Tosto et al., 2013). Again, this suggests a significant amount of variance is not shared between subjects. Health, well-being, personality and home environment among other factors have all been shown to influence achievement over and above intelligence and may contribute to shared or specific variance between subjects (Krapohl et al., 2014).

To-date, there have been no genome-wide association studies reported for standardised school achievement scores in English and maths during adolescence, and no studies for science. In order to understand 1) whether there exist academic subject-specific genetic contributions to English, maths and science, and 2) the degree to which specific subjects are genetically related to discrete cognitive and emotional behaviours, we performed three univariate GWASes for English, maths and science, and used the GWAs summary statistics to estimate SNP heritability and genetic correlations with the cognitive and

emotion measures reported in **Chapter 6**. Using publicly available summary statistic GWAS datasets we also examined the genetic overlap with traits pertaining to academic achievement, cognitive ability, structural brain measures, psychopathologies and personality traits. We predicted that (i) there would be both differences and communality in the outcomes of the three GWAS, (ii) correlations between the three subjects and cognitive and emotional traits would vary.

8.2 Methods

8.2.1 Study cohort

The samples for this study are derived from the ALSPAC cohort (**Chapter 2.1**) and consists of samples for whom English (N= 5,983; 2,909 males), maths (N=6,017; 2,950 males), or science (N=6,089; 2,995 males) academic achievement data at ages 11 and 14 were available, along with genome-wide SNP genotyping data.

8.2.2 Measures

Sum scores of English, maths and science attainment were created using national curriculum scores taken at Key Stage 2 (KS2) and Key Stage 3 (KS3). Full details of the measures and how they were calculated are provided in **Chapter 2.2.4**. Briefly, KS2 tests are taken at the end of Year 6 (primary school) when children are aged 11, and KS3 tests are taken at the end of Year 9 (secondary school) when children are aged 14. These tests are national standardised exams, and summing over KS results provides a more representative and stable measure of academic ability than an individual measure. In our sample, individual attainment results were highly correlated, ranging between r = 0.67 - 0.81, justifying the use of an aggregate measure (**Table 8.1**). Participants without complete academic attainment data were removed and each measure was regressed on age at time of examination, sex and ten principal components to control for population stratification. Genome-wide analysis assumes traits are normally distributed and therefore the final sum-score phenotypes for English, maths and science were each quantile normalised using SNPTEST (Goh & Yap, 2009).

8.2.3 Quality control procedures

The procedures for the generation of genetic data and genotype and individual quality control steps are fully described in **Chapter 6.2.1**. Briefly, SNPs were filtered based on MAF < 0.01, with an info score < 0.4, a call rate < 0.95 and HWE of < 5E-7.

8.2.4 Statistical analyses

As above, individual SNP-trait association analyses, calculation of SNP heritability estimates and genetic correlation analyses are fully explained in section **6.2.1.** Briefly, genome-wide association analyses were performed using SNPTEST v.2 (https://mathgen.stats.ox.ac.uk/genetics_software/snptest/old/snptest_v2.2.0.html) with an additive model and probabilistic genotypes (see **Chapter 6.2.1**) for full description). Secondary gene-based analyses were conducted including tissue expression data of any significant gene associations using GTEx portal (https://gtexportal.org/home/). Genetic correlations between AA and the PCA cognitive and emotion measures (**Chapter 3 & 6**) were calculated using Linkage Disequilibrium score regression (LDsc) in python. Correlations with cognitive, educational and psychological traits in independent cohorts were calculated via the LD-hub test centre (http://ldsc.broadinstitute.org/login/).

8.3 Results

8.3.1 Genome-wide association analyses

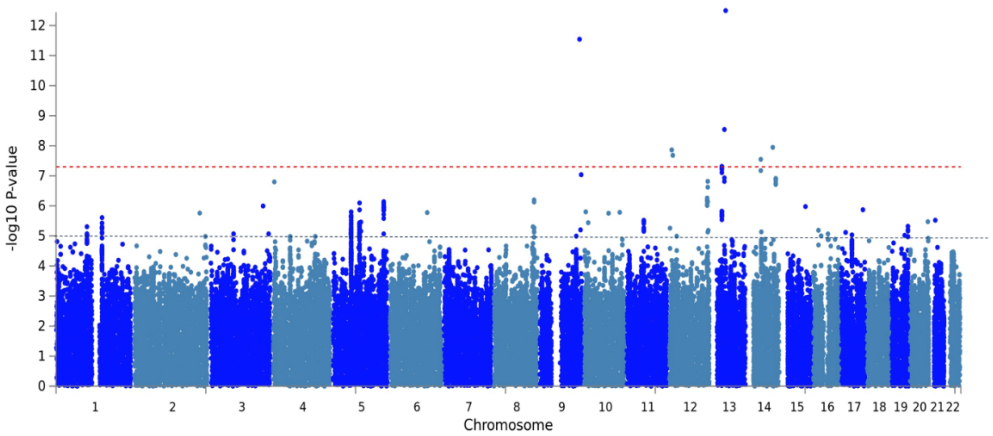
The overall pattern of results for the GWA analyses can be visualised in **Figure 8.1** and quantile-quantile plots demonstrate an inflation of lower p-values for all three traits (but most notably for science and maths; **Figure 8.2).** In total, eight independent SNPs passed the genome-wide significant threshold for science scores (**Table 8.1**), with a further 33 SNPS showing suggestive association ($p <= 1 \times 10^{-6}$) (**Supplementary table 8.1**). Five SNPs were also independently significantly associated with Maths scores, with a further 43 suggestive hits (**Supplementary table 8.2**). Finally, one SNP was significantly associated with English scores, with 19 suggestive associations (**Supplementary table 8.3**).

Table 8.1: Genome-wide significant associations with English, maths and science

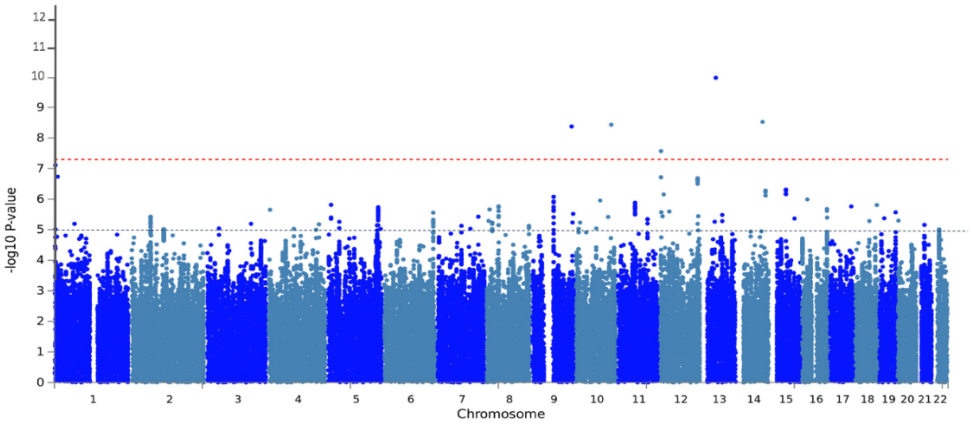
Subject	rsid	chr	position	Non-effect allele	Effect allele	MAF	p-value	beta	se	GENE
Science	rs758851[Obs]	9	132873970	A	C	0.227	$2.85x10^{-12}$	-0.201810	0.029	*GPR107*
Science	rs7399083*	12	8595531	A	G	0.069	$1.38x10^{-8}$	-0.249072	0.044	*OR7E149P*[a]
Science	rs5796485	12	12231733	G	T	0.306	$2.07x10^{-8}$	-0.131068	0.023	*BCL2L14*
Science	rs7321332	13	47999607	C	T	0.236	$3.18x10^{-13}$	-0.187585	0.026	*SUCLA2*[a]
Science	rs9533479	13	43987606	G	C	0.041	$2.88x10^{-09}$	-0.338247	0.057	*ENOX1*
Science	rs9529641	13	35319175	C	A	0.250	$4.86x10^{-08}$	0.115219	0.021	*NBEA*[a]
Science	rs2998300	14	84999158	T	C	0.230	$1.13x10^{-8}$	-0.171843	0.030	*FLRT2*[a]
Science	rs1959386	14	44990539	A	G	0.233	$2.83x10^{-8}$	-0.154329	0.028	*FSCB*[a]
Maths	rs758851	9	132873970	A	C	0.227	$4.21x10^{-9}$	-0.169596	0.029	*GPR107*
Maths	rs2254950	10	119036155	A	C	0.408	$3.69x10^{-9}$	-0.133242	0.023	*SLC18A2*
Maths	rs7139245	12	2955636	A	G	0.167	$2.69x10^{-8}$	-0.156821	0.028	*LOC100507424*
Maths	rs7321332	13	47999607	C	T	0.236	$1.08x10^{-10}$	-0.167575	0.026	*SUCLA2*[a]
Maths	rs2998300	14	84999158	T	C	0.230	$2.99x10^{-9}$	-0.179284	0.030	*FLRT2*[a]
English	rs7321332	13	47999607	C	T	0.236	$1.15x10^{-8}$	-0.148576	0.026	*SUCLA2*[a]

**Indicates the locus is an eQTL (i.e., a variant that influences gene expression) [a]Indicates it is near the gene not in it. [Obs]Indicates that this SNP was called rather than imputed*

A. Science attainment (λ = 1.06, LD intercept = 1.03)



B. Maths attainment (λ = 1.04, LD intercept = 1.02)



C. English attainment (λ = 1.04, LD intercept = 1.01)

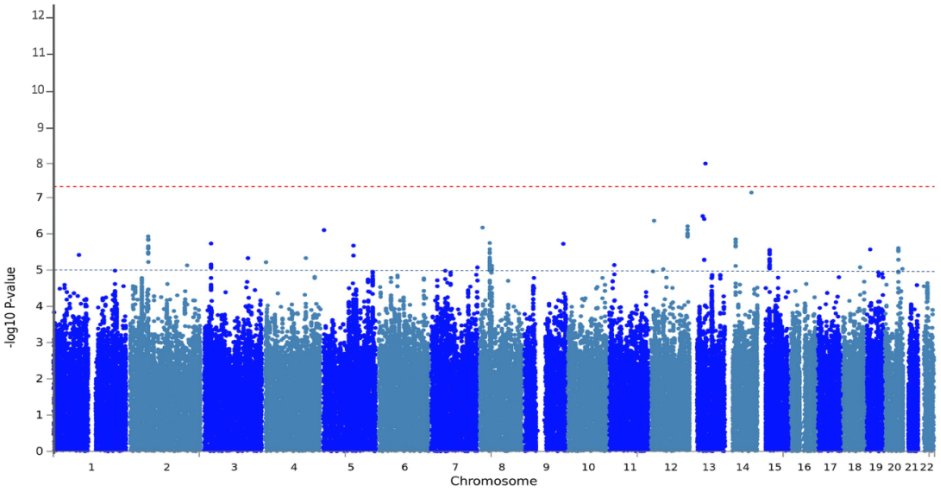


Figure 8.1 *Manhattan plots of genome-wide association analyses. Dashed red line represents the genome-wide significant line (p <5 x10^{-8}) and the blue dashed line is the suggestive line (p <1 x10^{-6})*

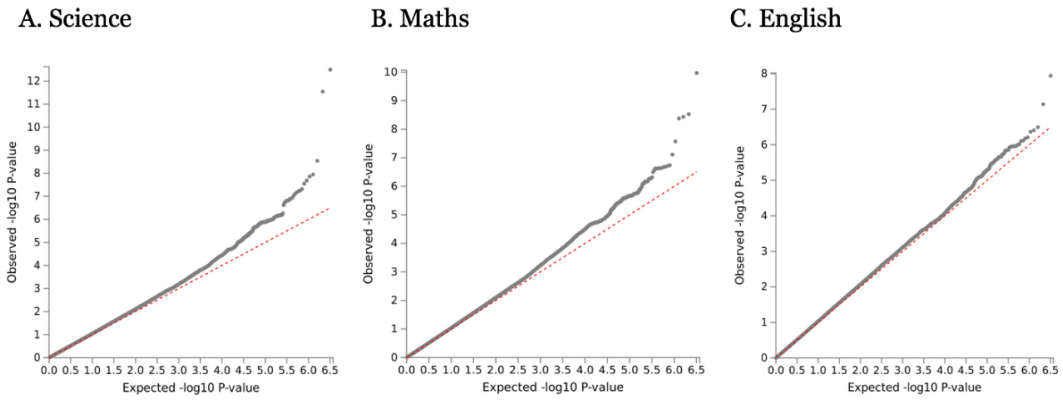


Figure 8.2: *Quantile-quantile plots for English, maths and science GWAS. Q-Q plots show deviation from the expected distribution of p-values. The red dotted line represents the expected p-values*

8.3.2 SNP based heritability estimates

SNP-based heritability estimates were considerable for all three subjects, but particularly maths and science (.47 and .54 respectively). Genetic correlations between academic subjects were also high (ranging between .62 and .75), illustrating a shared genetic influence, but also some genetic specificity as the values were less than 1.0 (**Table 8.2**).

Table 8.2: SNP heritability estimates, genotypic, and phenotypic correlations between academic subjects.

h^2	English	Maths	Science
English	0.360 (.058)	0.691***	0.732***
Maths	0.745 (.141) ***	0.473 (.058)	0.811***
Science	0.722 (.141) ***	0.620 (.121) ***	0.535 (.058)

**** p ≤ .001. Genetic correlations are presented below the diagonal (dark grey), SNP heritability on the diagonal (white) and phenotypic correlations above the diagonal (light grey). Intercept were constrained to 1 for heritability estimates.*

8.3.3 Genetic correlations

8.3.3.1 ALSPAC Cognitive and Emotion traits

Genetic correlations with cognitive and emotion traits were assessed using the cognitive and emotional PCA measures created in **Chapter 3** and the GWA summary statistics calculated in **Chapter 6**. WM was the only GWAS that significantly correlated with English, maths and science GWAS ($p \leq .05$). Genetic correlations with WM (**Table 8.3**) were highest for English ($rg_{SNP} = .75$), and similar between science ($rg_{SNP} = .52$) and maths ($rg_{SNP} = .53$)

8.3.3.2 Cognitive, educational, psychiatric and emotion-related traits in independent cohorts

Using LD hub, we assessed genetic relationships between subject-specific attainment and a range of cognitive, educational, psychiatric and emotion-related traits. Below we show those significantly ($p \leq .05$) correlated with at least one of the three academic subjects (**Table 8.3**). A full table of all associations performed can be found in **Supplementary tables 8.4, 8.5 and 8.6**. Genetic correlations with non-ALSPAC cognitive and academic attainment traits were found to be high (0.89 – 1.26) and fairly consistent across the academic subjects, with the lowest correlation between years of schooling and maths ability. Correlations with psychological measures were found to be more variable across academic subjects. For instance, English ($rg_{SNP} = .52$) and science ($rg_{SNP} = .41$) have significant correlations with openness to experience whereas maths ($rg_{SNP} = .30$) does not. On the other hand, maths ($rg_{SNP} = -.17$) and science ($rg_{SNP} = -.19$) are significantly negatively associated with neuroticism but not English ($rg_{SNP} = -.10$). Turning to psychiatric traits and disorders, Maths ($rg_{SNP} = .40$) and English ($rg_{SNP} = .39$) are most highly correlated with autism, and science ($rg_{SNP} = .25$) less so (although still significant). ADHD was highly negatively correlated across all three subjects, and interestingly the only significant correlation for anorexia was for English ($rg_{SNP} = .28$).

Table 8.3: Genetic correlations between English, maths and science and cognitive and emotional and behavioural regulation traits within the ALSPAC sample and with other psychological traits in independent GWAS.

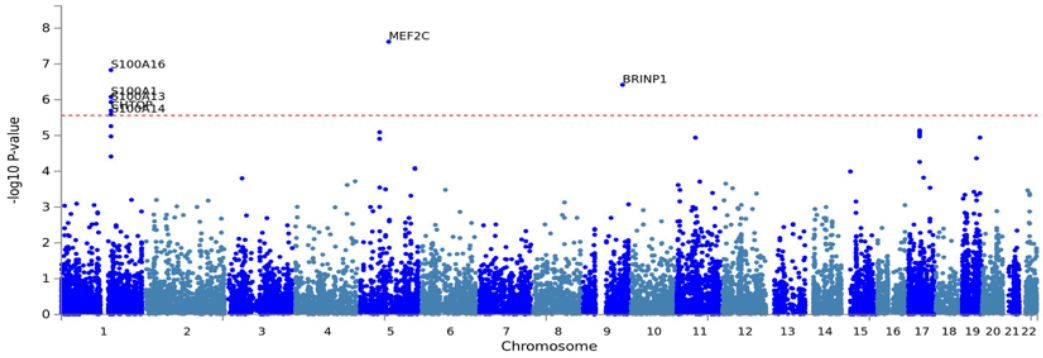
			English	Maths	Science
Within ALSPAC	EF traits	Working Memory	0.750 (0.212)***	0.524 (0.186)**	0.521 (0.176)**
		Processing Speed	-0.413 (0.263)	-0.295 (0.244)	-0.159 (0.232)
	Emotion traits	Internalising	0.054 (0.275)	0.060 (0.238)	0.224 (0.225)
		Externalising	-0.380 (0.294)	-0.314 (0.262)	-0.172 (0.262)
Independent GWAS	Cognitive traits	Intelligence	1.261 (0.188)***	1.197 (0.158)***	1.243 (0.173)***
		Childhood IQ	1.196 (0.240)***	1.020 (0.160)***	1.200 (0.205)***
	AA	Yrs of Schooling 2016	0.994 (0.150)***	0.894 (0.124)***	0.950 (0.132)***
	Personality	Neo-openness to experience	0.521 (0.234)*	0.299 (0.199)	0.407 (0.209)*
		Neuroticism	-0.102 (0.090)	-0.171 (0.085)*	-0.192 (0.091)*
	Psychopathology	ASD	0.394 (0.136)**	0.399 (0.120)***	0.246 (0.124)*
		ADHD	-0.721 (0.278)**	-0.615 (0.255)*	-0.770 (0.288)**
		Depressive symptoms	-0.267 (0.116)*	-0.365 (0.108)**	-0.387 (0.118)**
		Anorexia Nervosa	0.277 (0.099)**	0.079 (0.086)	0.040 (0.086)

**p<.05, **p<.01, ***p<.001. Note: LD score regression does not put bounds on its estimates and therefore it is possible to have correlations > 1 and < -1.*

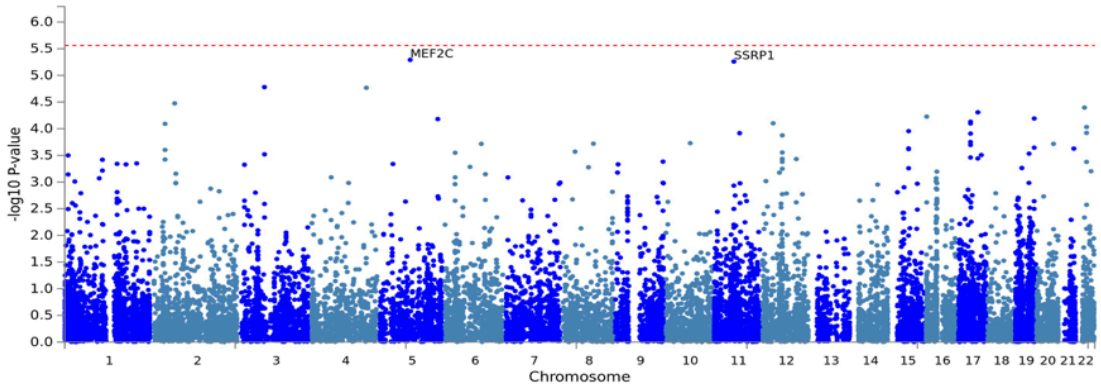
8.3.4 Gene-based association analyses

The results of the gene- based tests for association are shown in **Figure 8.3.** We find seven genome-wide significant gene-based associations with science, for the genes Myocyte Enhancer Factor 2C (*MEF2C*), Bone Morphogenetic Protein/Retinoic Acid Inducible Neural-Specific 1 (*BRINP1)*, Chromatin Target Of *PRMT1* (*CHTOP)*, *S100 Calcium Binding Proteins A1 (S100A1)*, A13 (*S100A13)*, A14 (*S100A14)* and A16 (*S100A16)* (**Table 8.4**). The strongest association signal was observed for *MEF2C* located on chromosome 5. No significant gene-based associations were detected for maths or English.

A. Science attainment



B. Maths attainment



C. English attainment

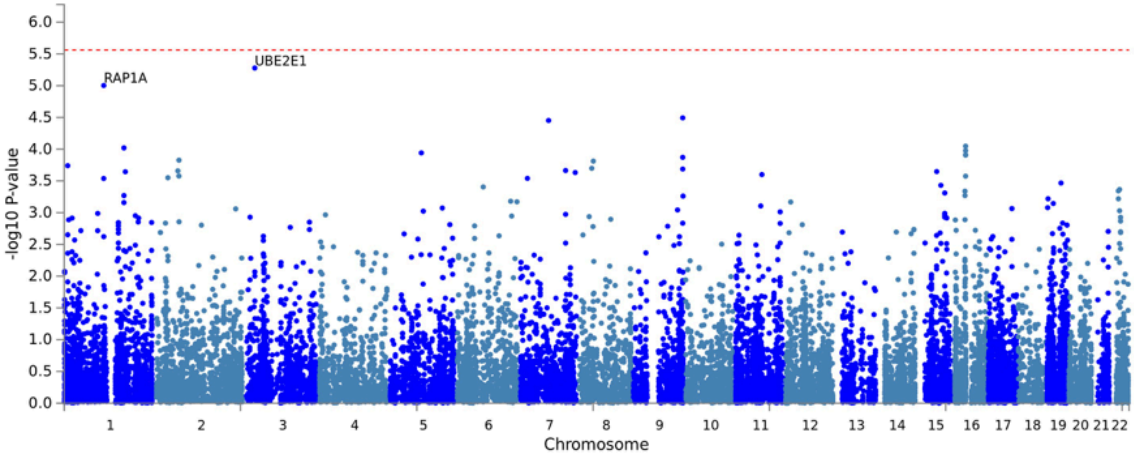


Figure 8.3: *Manhattan plots of the gene-based associations studies. Dashed line represents the genome-wide significant line ($p < 5 \times 10^{-6}$)*

Table 8.4: Table of significant gene-level associations for Science performance.

Chromosome	Ensembl Gene ID	Gene name	p-value	z-statistic
1	ENSG00000188643	S100A16	1.48×10^{-7}	5.126
1	ENSG00000160678	S100A1	8.32×10^{-7}	4.790
1	ENSG00000189171	S100A13	1.16×10^{-6}	4.723
1	ENSG00000189334	S100A14	2.56×10^{-6}	4.559
1	ENSG00000160679	CHTOP	2.02×10^{-6}	4.609
5	ENSG00000078725	MEF2C	2.39×10^{-8}	5.459
9	ENSG00000081189	BRINP1	3.82×10^{-7}	4.944

8.3.5 Gene Expression

Expression data was examined using the GTEx portal, which showed that *BRINP1* (**Figure 8.5**) is almost entirely expressed in the brain. Expression patterns for *MEF2C* are more variable, (**Figure 8.4**) but it is primarily expressed in the brain, lymphocytes and musculature. In contrast, *CHTOP* (**Figure 8.6**) is widely expressed throughout the body, suggesting a general house-keeping function. The four calcium binding proteins *S100A1*, *S100A13*, *S100A14* and *S100A16* have varying expression profiles, with *S100A1* mostly in the brain (**Supplementary Figure 8.2**), *S100A13* broadly throughout the body (**Supplementary Figure 8.3**), and *S100A14* and *S100A16* mainly in the oesophagus and vagina (**Supplementary Figure 8.4 & 8.5**).

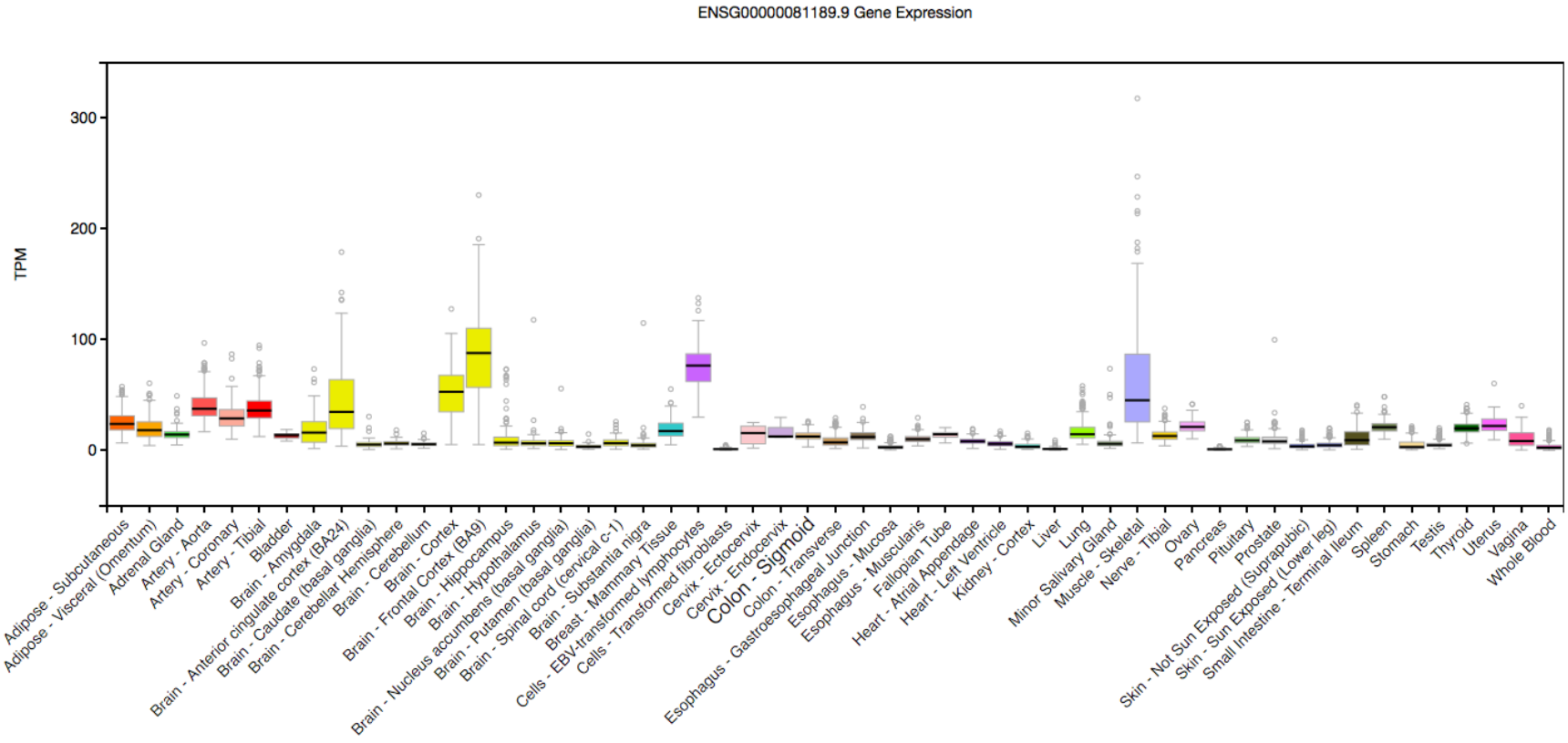


Figure 8.4: *MEF2C gene expression data from GTEx Portal*

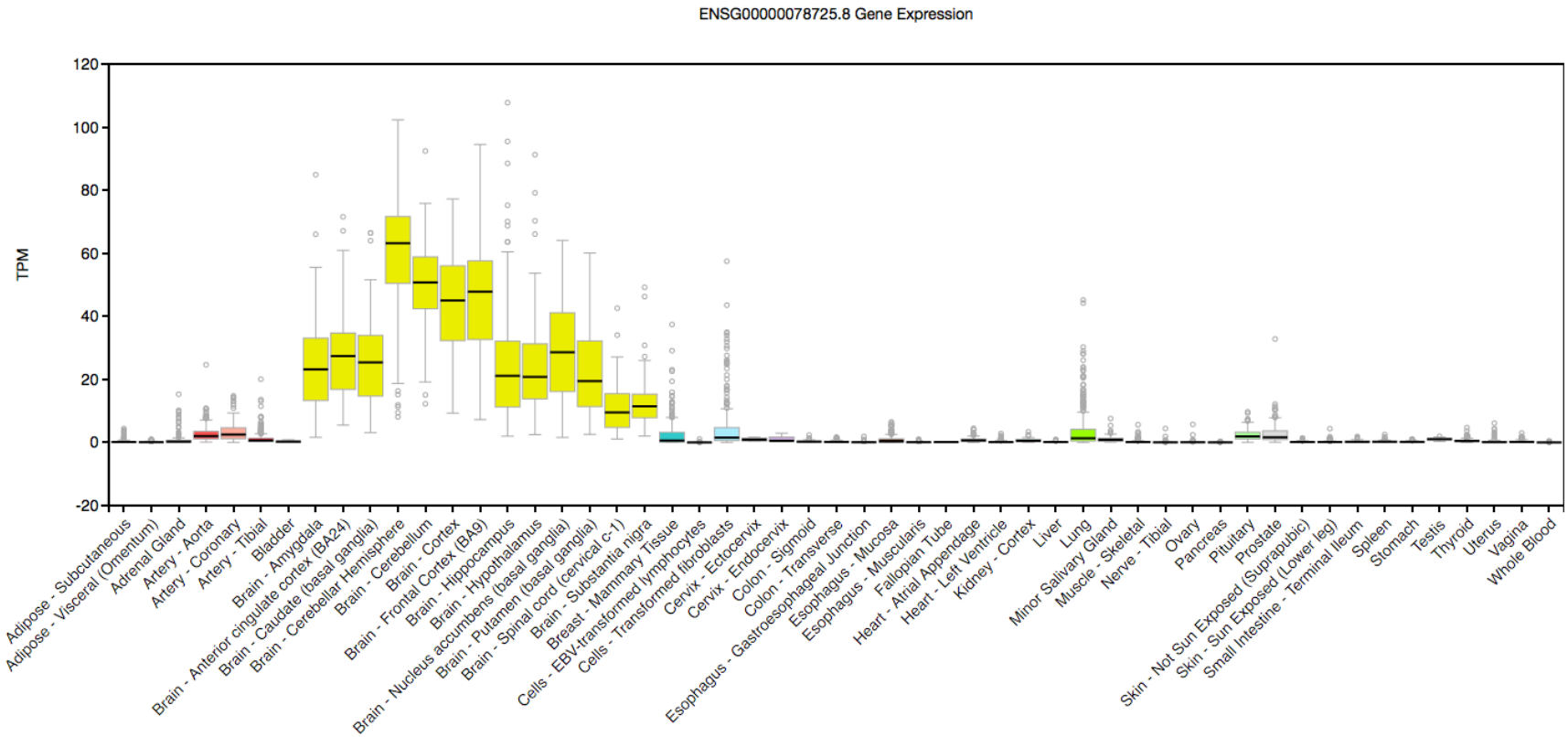


Figure 8.5: *BRINP1 gene expression data from the GTEx Portal*

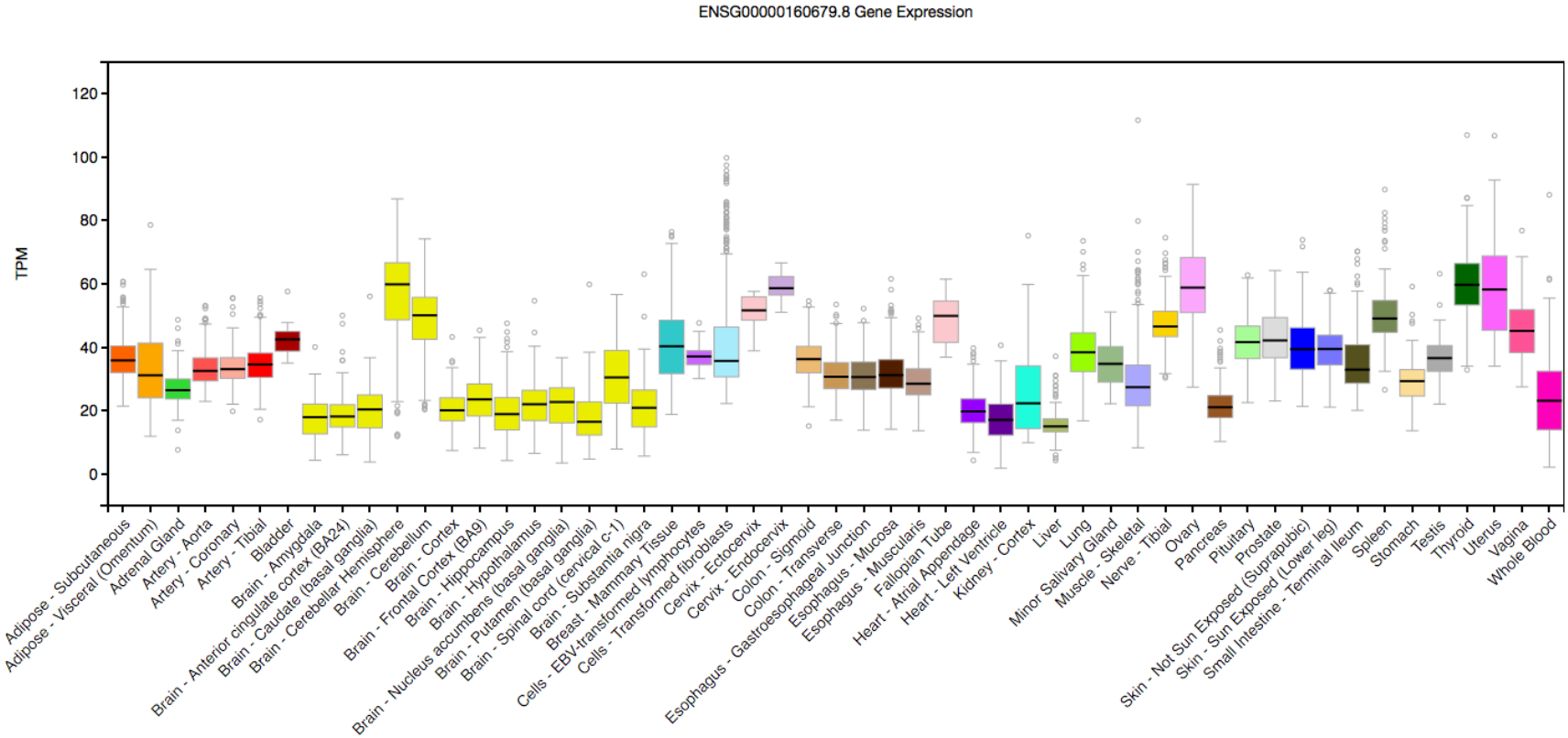


Figure 8.6: *CHTOP gene expression data from GTEx Portal*

8.4 Discussion

This study performed the first GWAS of science achievement and the largest GWAS of maths and English achievement using national standardised tests completed during early adolescence. Using GWAS summary statistics the study sought to assess whether genetic specificity existed that differentiated English, maths and science performance and to assess the degree of genetic overlap between AA and cognitive and emotional traits in the same sample (**Chapter 7**). We found a significant overlap of common genetic variants influencing variability in the three academic subjects, indicated by the large genetic correlations (rg_{SNP} = .62 - .75), but notably more than a quarter of genetic influence was specific to each academic subject indicating, as with the phenotypic data, a degree of specificity. Each subject showed different genetic correlations with other psychological phenotypes in independent samples highlighting possible sources of specific variance.

8.4.1. Heritability findings

SNP based heritability estimates were moderate for all three subjects, and largest for maths and science which had 47% and 54% SNP heritability respectively. This is substantially closer to the twin-based heritability estimates of 65% for maths and 54% for science (Rimfeld et al., 2015) than is often the case with DNA-based estimates (i.e maths ability h^2_{SNP} = .16; Lee el at., 2018). Phenotypically science was more highly correlated with English and maths than they were with each other (**Table 8.2**), suggesting academic performance in science might incorporate variance from both subjects. However, when we examined genetic correlations the opposite pattern was observed with science correlating the least with English and Maths. A possible explanation is that the factors contributing to the correlation in performance between science and maths, and science and English, is under greater environmental influence than factors contributing to the correlation between English and maths performance, that correlate more for genetic reasons.

8.4.2 Genetic Correlations

Within the ALSPAC sample, genetic overlap in individual differences in performance in AA and cognitive traits vary, but are highest for WM and AA with WM and English sharing 75% of genetic variance as compared to ~52% for both maths and science. None of the other comparisons were significant and high standard errors indicated that this is likely due to a lack of statistical power.

To complement comparisons with the cognitive and emotion GWAS performed in the ALSPAC sample, comparisons were also performed using the LD score regression online portal that makes available summary statistics from previously performed GWAS. With this resource, we were able to access larger, more powerful GWASes for traits known to be correlated with academic attainment and estimate the shared SNP heritability between cognitive, educational, psychiatric and emotion-related traits. Genetic correlations with cognitive and academic attainment in independent samples were found to be high and consistent across the academic subjects, with slightly higher correlations between years of schooling and English, than the other two subjects. The estimates with intelligence were > 1 even accounting for standard error, and although estimates greater than one are possible with the LD score regression method (see **Chapter 6**), it highlights the necessity to interpret these values with caution.

Correlations with personality traits were found to vary more across academic subjects. Openness to experience and neuroticism are both scales on the big five personality inventory (John & Srivastava, 1999). English and science, but not maths, were significantly positively correlated with openness to experience which is related to curiosity, imagination, deep thinking, reflection and artisticness. In contrast, maths (rg_{SNP} = -.17) and science (rg_{SNP} = -.19) were significantly negatively associated with neuroticism but English was not. Neuroticism is related to anxiety, irritability, discontent, shyness and impulsivity (John & Srivastava, 1999).

Correlations with psychopathology also differed between the subjects with maths and English significantly more positively associated with autism than science. Correlations with all three subjects and Autism fits with the current literature that consistently finds a genetic correlation between Autism and EA (Bulik-Sullivan, Finucane, et al., 2015). ADHD was most negatively correlated with science and English and significantly less with maths. Previously maths has been found to have higher twin-based genetic correlations with the inattentiveness (rg_{TWIN} = -.41) than the hyperactivity-impulsivity (rg_{TWIN} = -.22) scales of the ADHD assessment, but GWAS of these subscales were not available on LD hub (Greven, Kovas, Willcutt, Petrill, & Plomin, 2013). Maths (rg_{SNP} = -.37) and science (rg_{SNP} = -.39) were significantly more negatively associated with depression than English (rg_{SNP} = -.27). English is significantly positively associated with anorexia where the other two subjects are not. Anorexia been associated with higher intelligence phenotypically (Lopez, Stahl, & Tchanturia, 2010), with smaller effects seen genetically (David Hill, Davies, Liewald, McIntosh, & Deary, 2016) however the effect here seems to be more specific.

Although it is important not to over-interpret these results, broadly, it would seem that although there are underlying cognitive features which contribute to variance across all three academic subjects, there may be other (both genetic and non-genetic) factors which contribute to subject-specific variance. For example, both personality traits and psychopathological disorders showed more variability in the extent of genetic correlations across academic subjects. These results reflect both the findings and the conclusion of multivariate twin studies that examine genetic covariance between cognitive ability and subject attainment. For example, Kovas et al., (2005) investigated the genetic overlap between mathematics performance, reading and general intelligence in childhood. They reported considerable genetic correlations between mathematics and reading (rg_{TWIN} = .74) and between mathematics and g (rg_{TWIN} = .67), but noted that approximately a third of the genetic variance in mathematics was independent of both of these factors, suggesting some degree of genetic specificity (Kovas et al., 2005). A subsequent study using the same twin cohort study controlling for maths, English and 'g' investigated the extent to which there was genetic specificity in science attainment. Heritability was 49%; there were some shared environmental effects between the subjects that were not shared with g, but importantly, there were genetic effects beyond the other factors and specific to science (Haworth, Kovas, Dale, & Plomin, 2008). Finally, a multivariate twin study revealed that traits such as personality, wellbeing and behaviour problems explained 50% of the variance in GCSE scores independently of intelligence (Krapohl et al., 2014).

8.4.3 GWAS findings

Eight independent SNPs were significantly associated with Science achievement, five with maths and one with English. As predicted we observe a degree of overlap between the subjects. Specifically, the SNP rs7321332 located on chromosome 13 (nearest gene SUCLA2) was significant in all three GWAS, and the SNPs rs758851 (located in gene GPR107) and rs2998300 (nearest gene FLRT2) were significant for both maths and science. Encouragingly, the direction of effect seen for these three SNPs is consistent across subjects, with slightly larger effects sizes seen in science. However, these associations must be treated with caution until they have been replicated in an independent sample. Related to this, all but one GWAS significant SNPs were imputed and several have INFO scores < .7, which indicates a degree of uncertainty in the genotype calls. Finally, although many of the suggestive SNPs are located in (or near to) genes that have been previously associated with neurocognitive traits such as Alzheimer's, schizophrenia and depression, they are also associated with unrelated traits such as BMI and obesity, heart rate and stroke.

8.4.4 Gene-based associations with science

Gene-based association analyses also identified three genes associated with achievement in science, but none for maths or English. The strongest signal came from the *MEF2C* gene. *MEF2C*, located on chromosome 5 and has been linked to synaptic plasticity, memory and learning (Barbosa et al., 2008). It is primarily expressed in the brain and mutations or deletions in the gene are associated with severe cognitive impairment, stereotypic movements, epilepsy and cerebral malformation (Rocha, Sampaio, Rocha, Fernandes, & Leão, 2016). Evidence from animal models also suggests that it is involved in the development of memory and the consolidation of information. For example, Barbosa and colleagues (2008) found that deletion of the *MEF2C* transcription factor in mice impairs hippocampal-dependent learning and memory and results in an excess of excitatory synapses. The authors conclude that *MEF2c* facilitates learning by limiting the formation of synapses during activity dependent synaptic refinement (Barbosa et al., 2008). In humans, over-expression of *MEF2c* has also been implicated in poor developmental and cognitive outcomes (Cesaretti et al., 2016; Novara et al., 2013) and it has been associated with Alzheimer's disease (Tang et al., 2016). Studies looking at general cognitive ability seek *MEF2c* associations in hypothesis driven tests (Davies et al., 2015) and more recently it has been associated with a large meta-analysis of intelligence and years in education (Hill et al., 2018) and the largest depression GWAS to date (Wray et al., 2018).

The second most strongly associated gene was *BRINP1*, which is also primarily expressed in the brain and is involved in protein binding. *BRINP1* has been involved in a wide-range of processes related to cognition and behaviour: short-term memory, social behaviour, vocalization behaviour, exploration behaviour, maternal behaviour, fear response; cell physiology: cell cycle arrest, cellular response to retinoic acid, negative regulation of cell cycle, negative regulation of mitotic cell cycle; and neurogenesis: negative regulation of neurogenesis, positive regulation of neurogenesis, positive regulation of neuron differentiation (Uhlén et al., 2015; NCBI, 2018)

The third associated gene was *CHTOP*, which is more widely expressed but may play a key role in the regulation of foetal globin gene expression as well as the activation of oestrogen-responsive genes (NCBI, 2018). The final set of associated genes were *S100A1*, *S100A13*, *S100A14* and *S100A16*, which all encode calcium binding proteins and are involved in the regulation of cellular processes. These include cell cycle progression, differentiation and possibly stimulation of Ca2+ release (NCBI, 2018).

8.4.5 Limitations

The sample uses a relatively small N and therefore lacks statistical power. Those associations found should be interpreted with caution until replicated in an independent sample. The majority of the significant associations are imputed using the Haplotype Reference Consortium and include SNPs which are not otherwise imputed in 1000 genomes. Proxy SNPs will need to be assigned and the surrounding LD regions interrogated to ensure these are not spurious associations. The study is not fully multivariate but a new method of genomic SEM has also recently become available and may be helpful in trying to understand these different effects and locate specific variants involved in communality and difference between phenotypes.

8.4.6 Conclusion and next steps

In this study, we performed three univariate GWAS of English, maths and science standardised national achievement scores, calculated SNP heritability and assessed specificity and communality between genetic correlates of each subject. We found that the *MEFC2* gene was significantly associated with science and marginally with maths. We also found substantial differences in SNP heritability estimates and genetic correlations, with other neurocognitive traits indicating, as with the phenotypic data, a degree of overlap and specificity. This was the first GWAS of standardised tests in English and maths and the first ever GWAS of science. Future studies should include a replication of the *MEF2c* association and see whether this extends to all academic subjects. The subjects should be examined within a multivariate framework allowing the separation of general and specific genetic effects.

9. Discussion

9.1 Aims and findings

The aim of this thesis was to better understand the relationship between emotion and cognition during adolescence, whether there exists a genetic component to this relationship and how they influence academic achievement.

Chapter 3 broadly characterised cognition and emotion using a large number of experimental and questionnaire measures collected at different points across adolescence and assessed their relationship. Three cognitive measures: working memory, processing speed and inhibitory control, and five emotion measures: internalising, externalising, anxiety, extraversion and conscientiousness, were identified. Quadratic associations suggested by previous literature, in addition to linear relations were also tested. Relationships between cognitive and emotion measures were small, with the largest being between working memory and externalising. Although there were many instances where a quadratic term was significant, it explained very little extra variance in the model. The pattern however was consistent across associations: high levels of negative traits and low levels of positive traits were associated with negative cognitive outcomes, but in contrast low levels of negative traits, and high levels of positive traits were not associated with cognitive benefits.

Chapter 4 aimed to validate the emotion measures established in Chapter 3 against recognised emotion regulation questionnaires and an emotional variant of the N-back task in adults. Some specificity was found between the emotion PCA measures and certain emotion regulation strategies; however, we did not find a greater relationship between emotion regulation strategies and working memory performance than with the emotional outcomes, putting into question whether ER strategies are indeed a mediator or mechanism of influence. There was also no greater association with the 'hot' EF measures than with the 'cool' EF measures, if anything there were greater associations with the cool measures. There are limitations with considering this a measure of 'hot' EF, which are discussed later, and perhaps it is a task that has a minimal affective component. We replicated the finding from Chapter 3 (and other studies, e.g. (Hatoum et al., 2017)) that externalising and working memory were the most closely related measures. We also found internalising and anxiety to be associated with interference by emotional distractors.

Chapter 5 assessed the longitudinal relationship between executive function and internalising and externalising behaviours in order to test directional effects. A secondary aim was to test whether single measures of emotion and cognition may be more related than latent measures. Internalising and externalising in early adolescence (11yrs) negatively predicted later working memory (17yrs) but neither early working memory, nor early inhibitory control predicted later internalising or externalising. Although the effects were small, this is a novel finding which goes against the standard interpretation that executive functions are a key driver of emotional regulation (Zelazo & Cunningham, 2007) and shows that, during adolescence, the maturation of executive functions does not predict changes in emotional behaviours, and instead that early emotional behaviours may impact the maturation of working memory.

Chapter 6 used genome-wide genotype data to perform the first GWAS of latent executive function traits and the largest GWAS reported to-date of externalising and internalising behaviour. We sought to uncover genetic variation associated with adolescent cognition and emotion and evaluate genetic relationships. No genome-wide significant associations were identified. A moderate SNP heritability was found for working memory ($h^2_{SNP} = .30$), no heritability for inhibitory control and smaller estimates for processing speed, internalising and externalising, with larger standard errors. Internalising estimates (14%) are in line with previous estimates of 13-26% (Benke et al., 2014). GWAS of aggression performed in pre-schoolers in three different samples have widely varying estimates 10-54%; the lower estimate was derived from the ASLPAC sample at 4 yrs and was followed-up in adolescents (8%) (Pappa et al., 2016). The estimate from our study is slightly higher (13%) which is not surprising as externalising is a broader measure than aggression and potentially incorporates variance from other traits such as ADHD. Genetic correlations replicated Chapters 3 and 4's phenotypic findings regarding the association between working memory and externalising, but suggested a different genetic relationship between working memory and internalising.

Chapter 7 aimed to assess adolescent specific associations between cognitive and emotion measures with academic achievement in English, maths and science. A secondary aim was to test whether modelling cognitive measures together as one latent factor was better than modelling them separately, and similarly with academic achievement. Both cognitive and academic measures were found to be better modelled separately than as common factors, and most of the cognitive and emotion measures (other than anxiety and inhibitory control) contributed different patterns of unique variance in academic subject outcomes. However, the emotion measures contributed

considerably less variance, and working memory was one of the greatest contributors of variance, which is consistent with the suggestion that working memory is a key factor in academic success (Gathercole & Alloway, 2008).

Chapter 8 performed the first ever GWAS of science attainment and looked at the genetic relationship between cognitive and emotion measures (**Chapter 3**) with English, maths and science attainment in adolescence. All three academic subjects had high SNP-based heritability estimates, the highest coming from Science (h^2_{SNP} = .54), almost replicating twin estimates (Shakeshaft et al., 2013). In line with the phenotypic findings of Chapter 7, all three were genetically correlated with working memory, and significant genetic overlap with independent cognitive measures were also observed. Differential genetic correlations between individual academic subjects and personality traits and psychopathologies were identified. All three GWASs find significant SNP associations – some overlapping – and moderate to high genetic correlations between traits. A gene-based association between Science and *MEF2C*, a gene involved in memory and synaptic plasticity (Barbosa et al., 2008) was also found.

9.2 Emerging themes across chapters

9.2.1 Externalising and working memory

Chapters 3, 4, 5 and **6** all found that the strongest association between emotion and cognition was the negative association between externalising behaviour and working memory. It was also an association, unlike the others found in this thesis, which held for both low and high levels of externalising even though the association is stronger for high levels of externalising. **Chapter 6** suggests that this relationship may have a genetic basis as working memory was also negatively genetically correlated with externalising (rg_{SNP} = -.64). Literature investigating externalising behaviours argues that the relationship between externalising and cognition is driven by the inattentive symptoms of ADHD, and that conduct disorder (CD) or oppositional defiant disorder (ODD) do not show this association unless they are comorbid with ADHD (Clark, Prior, & Kinsella, 2000; Frick et al., 1991). Our studies are not able to pull apart the attentional and behavioural aspects of externalising, doing so may increase effect sizes within the attentional problem group. However, the PCA was unconstrained and we did not find a clear separation between these measures within the typical population. However, if it is the case that working memory deficits in externalising are being driven by attentional problems in ADHD, it puts into question the relationship between working memory and the emotional and behavioural problems seen in externalising behaviours.

9.2.2 Internalising and cognition

Findings from across the chapters in this thesis were less consistent in regard to the relationship between internalising and cognition. Variability was too high for significant genetic correlations between internalising and other traits to emerge and therefore all conclusions drawn from these associations are speculative and would require replication; however, contrary to the phenotypic correlations, genetically working memory was found to be positively correlated with internalising (rg_{SNP} = .60). Overall internalising had a mixed pattern of phenotypic relationships with the cognitive measures. **Chapter 3** showed that IQ was a positive predictor of internalising, while working memory was a negative predictor. Furthermore, the quadratic analysis suggested that only when internalising was above average did it become associated with reduced working memory, below this the relationship was quite flat. The positive genetic correlation suggests that the negative phenotypic correlation could be environmental in origin. Either environmental effects are influencing one trait and not the other, or they are influencing both traits differently. This could be why internalising decreases in heritability over development (Verhulst & Boomsma, 2003), while working memory increases (Friedman et al., 2016; Polderman et al., 2007). This interpretation also fits with findings from **Chapter 4,** which suggest that internalising may be less related to cognitive phenotypes (performance on the 0-back or 2-back), and more related to emotional processing (influence of the emotional distractors). The environmental influence on internalising could also have a subsequent effect on working memory as suggested by **Chapter 5** which found early internalising to negatively predict later working memory. On the other hand, **Chapter 6** also found working memory showed a negative genetic correlation with depressive symptoms in adults and no relationship with major depressive disorder in independent samples, neither of which fit with a clear interpretation of how working memory and internalising relate genetically. Future genetic research, with greater statistical power, could look to disentangle genetic relationships between working memory and internalising and how environments may influence change the direction of this relationship phenotypically.

9.2.3 Lack of an inhibitory control finding

Inhibitory control explained little meaningful variance in any of the studies. Although **Chapter 3** found IC explained nearly the same amount of variance in the cognitive data as working memory, it explained little to no variance in the emotion measures. We found the same in **Chapter 5**, where although there were small within time correlations with externalising and working memory in early adolescence, there were no significant

relationships in later adolescence. **Chapter 6** showed a lack of heritability for IC, and it failed to predict unique variance in English, maths or science in **Chapter 7**. Previous studies have found relationships between response inhibition and internalising (Joormann et al., 2007; Whitmer & Banich, 2007) and externalising (Young et al., 2009). The lack of similar findings in this thesis may be due to age-specific problems with this measure discussed below (section 9.3.1), but there is also literature arguing against inhibitory control as a general cognitive mechanism. The argument is that IC is the result of the re-activation of a goal-relevant processing which has the effect of inhibiting competing demands, however there is no inhibiting specific mechanism (Munakata et al., 2011). If this is the case, the IC measure may not be sufficiently distinct from the working memory measure used in this thesis to explain extra variance in other constructs. However, it is important to add that this interpretation differs from how others view the relationship between IC and working memory in general (Friedman & Miyake, 2017).

9.2.4 Emotion and emotion regulation – state vs trait?

Modest associations between emotion and cognition were found in **Chapters 3 – 6** and findings from **Chapter 5** suggest that it may be emotion influencing cognition rather than the other way around. The emotion PCA measures derived from the ALSPAC questionnaires were found to associate with emotion regulation strategies in **Chapter 4**. However, neither the correlation analyses nor the model predicting working memory from the ER strategies measures showed stronger associations between emotion regulation strategies and working memory than between emotion measures and working memory, which one would have expected if emotional regulation strategies reflected a cognitive process of executive function-led down-regulation of emotional responses. Although the ERQ measure of reappraisal was associated with working memory as has been previously reported (McRae, Jacobs, et al., 2012; Pe et al., 2013), the association was not stronger than that with the emotion measures. Therefore, it is possible that the correlations between emotion and cognitive measures reflect emotional reactivity and emotional responses in general rather than the cognitive aspects of emotional regulation.

Experimental ER studies which report associations between ER strategies and working memory (McRae, Jacobs, et al., 2012) and PFC activation (Ochsner et al., 2012) generally look at the down-regulation of affect on a trial-by-trial basis, independently of general emotional reactivity. While top-down control is influential in state-based emotions, it may have a more limited influence over trait-based emotions, as found in this thesis (**Chapters 3-5**), and in fact trait-based emotions could influence cognitive ability, as was observed in **Chapter 5**. There is evidence that instructing people to use reappraisal is sufficient to down-regulate state emotion, (Fabiansson, Denson, Moulds, Grisham, &

Schira, 2012) and that greater habitual use of reappraisal is associated with a decrease in amygdala and increase in PFC-parietal activity in spontaneous regulation, however it is not clear if habitual down-regulation influences trait emotion. Yurgelun-Todd and Killgore (2006) for example found increasing PFC activation in response to emotional faces across adolescence, but no age-related reductions in amygdala activity (Yurgelun-Todd & Killgore, 2006) suggesting increased cognitive control did not necessarily lead to reduced reactivity. Future studies could investigate whether formally instructed in-the-moment down-regulation of affect could lead to long-term changes in reactivity, as well as asses which aspect, state or trait, is a greater predictor of future mental health and well-being. This would also help establish the direction of causality between the fact that those who use reappraisal regulate better. Furthermore, more research is necessary to understand the cognitive mechanism by which emotion regulation functions if not via EF. Perhaps studies could assess whether 'hot' EF, associated with more ventral regions of the PFC (Zelazo & Cunningham, 2007), could be more related to emotion regulation ability. In fact, there is a suggestion that in older adults at least, there is not a direct relationship between lateral PFC activation and down-regulation of amygdala activity, but rather the relationship is mediated by the ventromedial PFC (Urry et al., 2006). This may be particularly relevant for emotion regulation in adolescents who typically underperform in tasks requiring this brain region (Crone & van der Molen, 2004; Hooper et al., 2004), but show better performance in cool cognitive tasks (Sebastian, Fontaine, et al., 2012).

Another possibility in regards to state-based emotion regulation relates to the above mentioned theory that inhibition is the result of increased competing activation (Munakata et al., 2011). Equally it could be argued that emotion regulation as such is not a mechanism in itself but rather the result of re-deployed attention or distraction. This could explain why suppression is not generally a very successful mechanism because it does not provide a competing focus of attention. It may also explain findings that engaging in a cognitively taxing task has a similar effect of reducing amygdala activity (Van Dillen, Heslenfeld, & Koole, 2009). However others have argued that although the same goal may be achieved, different neural mechanisms are activated in distraction to reappraisal (Kalisch, Wiech, Herrmann, & Dolan, 2006; McRae et al., 2010). Reappraisal is more associated with the medial PFC and anterior temporal cortices and distraction is more associated with prefrontal and parietal regions (McRae et al., 2010).

9.2.5 Executive Function, Emotion and Academic Achievement

Both **Chapters 7** and **8** showed contributions to academic achievement from both cognition and emotion. Although cognitive factors contributed significantly more variance to achievement in all subjects, emotional factors showed a more differential

pattern of association. However, these chapters find that overall emotional problems do not have large detrimental effects on AA. This may be because in general, the sample does not have particularly high levels of behavioural problems as measured by the SDQ in **Chapter 5,** and **Chapter 3** shows that it is mainly high levels of behavioural problems which impact on cognitive ability and therefore perhaps this is also the case for AA. There is some suggestion in the literature that during childhood emotions may impact attainment via cognitive ability (Brock et al., 2009; Rajchert et al., 2013) but that by adolescence there is a direct negative influence (Chamorro-Premuzic & Furnham, 2003a). **Chapter 7** shows that emotion and cognition contribute distinct variance to AA implying emotional associations are not mediated by cognition and that negative influence is small. This study controls for attainment at age 11 thereby looking at how emotion and cognition impact the change in attainment over adolescence. It could be that emotions do not change academic trajectories during this period, even if they are important in establishing them. Which is surprising given the literature regarding changes in adolescent emotional behaviour during this time (Crone & Dahl, 2012; Steinberg, 2005). It is possible that averaging emotion measures across time hides more specific relationships and this is discussed more in the limitations (9.3.1).

Chapters 7 and **8** replicate both genetically and phenotypically, the numerous previous findings on the important role of working memory in academic attainment. **Chapter 8** showed significant genetic effects influencing English, maths and science with a substantial amount of this variance being shared by working memory (52 – 72%). Correlations with cognitive traits such as IQ in independent samples were as high as 1, and consistent across subjects. In contrast, relationships with psychopathologies and personality traits in independent samples varied between academic subjects. Although, as before, emotion showed smaller genetic associations, they provide information about what factors differ between subjects other than large contributions from cognitive traits. It was somewhat surprising that the heritability for English, maths and science were considerably higher than those for the cognitive and emotion measures, which many people would argue are closer to biological measures of brain function. It could be that AA traits are broader in that they capture the genetic variance of many correlated cognitive (and non-cognitive) traits. However using a broader measure does not necessarily increase heritability as shown by heritability estimates of the latest educational attainment GWAS ($h^2_{SNP} = .12$) (Lee et al., 2018). On the other hand, this does replicate findings from studies that use endophenotype constructs – measures considered to be closer to biology – do not necessarily have higher SNP heritability, and the assumption that measuring something closer to biology increases the effect size of genetic associations has not held true. Flint and Munafo (2007) specifically assess the

example of the N-back working memory task as an endophenotype for schizophrenia and conclude that samples sizes necessary to detect an association would be equivalent to those needed to find association with schizophrenia (Flint & Munafò, 2007). It is possible that the national curriculum tests used are simply good at measuring learning ability and capturing performance-related skills and behaviours. In contrast to lab-based or even IQ tests, they incorporate a multitude of factors both cognitive and non-cognitive that are important to learning and have accumulated across the years in education. This means it may include gene environment correlations and heritability from 'non-inherited' alleles (Kong et al., 2018; Lee et al., 2018).

9.2.6 Models of adolescence

Changes to subcortical areas influencing arousal and motivation come about before the further development of regulatory elements in the PFC, potentially making adolescents more vulnerable to developing ER difficulties and subsequent mental health problems (Giedd et al., 2008; Mills et al., 2014; Prencipe et al., 2011; Steinberg, 2005). On this basis, it was predicted that adolescence may be a key time to understand associations between cognitive abilities and emotional experiences and behaviour. Furthermore, there is little research looking at emotion regulation during adolescence. We did not find particularly strong associations however, either averaging across time to look at trait-like behaviours (**Chapter 3**), looking at change over time (**Chapter 5**) or when predicting academic achievement (**Chapter 7**). This could be because perhaps our measures were not exactly capturing the most important changes in adolescence and that relations between emotion and 'hot' cognitive control could have shown greater associations than those with 'cool'. Although some consider that 'hot' and 'cool' EF are correlated and work together to bring about emotion regulation (Zelazo & Cunningham, 2007), there is also the possibility that this may not be so evident during adolescence. Even though self-report reappraisal use and 'cool' EF measures have been associated in adolescence using questionnaire data (Lantrip et al., 2015), performance on a 'hot' and 'cool' EF *tasks* are not necessarily correlated (Hooper et al., 2004). It may be that adolescence is precisely a time when 'hot' and 'cool' EF are less correlated due to different developmental trajectories (Zelazo & Carlson, 2012) meaning that adolescent emotion regulation becomes uncoupled from more decontextualized problem-solving. This also suggests that enhancing 'cool' EF would not necessarily be beneficial as is seen with the quadratic relationships in **Chapter 3**. Having said that, Prencipe et al., (2011) did find that during adolescence 'hot' and 'cool' EF do work better as a one-factor solution despite 'hot' EF being slower to develop than 'cool' EF. They conclude that 'hot' and 'cool' EF do work in concert and rely on the same mechanisms. More work will be required to understand the communalities and differences between ER, 'hot' and 'cool' EF in adolescents.

9.3 Limitations

9.3.1 Age, development and data collection

Most of the studies in this thesis have looked broadly across adolescence from 10 – 20yrs. and talked generally about this period, however considerable changes happen during this decade both in terms of cognitive and emotional development (Casey et al., 2008; Crone & Dahl, 2012; Steinberg, 2005). **Chapter 3** established measures of emotion and cognition which collapsed across the entire period of adolescence. The main reason that averaging was used was because of a shortage of repeated cognitive measures available in the ALSPAC sample. The Stop Signal Task was the only task collected at more than one time point and this second collection had its own limitations. The cognitive measures taken at 15yrs (the Stop Signal Task and the WASI IQ measures) were not entirely reliable. The mean scores on the IQ test collected at this time point were well below average (M=90), in contrast to the scores taken at 8yrs (M>100) (Chang et al., 2014; Horwood et al., 2008; Northstone, Joinson, Emmett, Ness, & Paus, 2012) and performance on the Stop Signal Task showed unusual patterns as performance in 'go' trials decreased across the blocks of the task even in the absence of stop signals. There has been a suggestion of a dip in cognitive ability during early adolescence (e.g. McGivern, Andersen, Byrd, Mutter, & Reilly, 2002), and transition from primary to secondary schools is often associated with academic underachievement (West, Sweeting, & Young, 2010). However, it is also likely that adolescents are less motivated to perform well on such tasks at this age (Duckworth, Quinn, Lynam, Loeber, & Stouthamer-Loeber, 2011). Although these measures may be less reliable in terms of representing cognitive ability, they could be informative if analysed in collaboration with time-congruent emotional measures which may have an influence on motivation. Instead in **Chapter 3** latent factors were created, but this does have the problem of hiding time specific-relationships which are important across development, but particularly in adolescence, where quadratic trajectories of cognitive and emotional development have been observed (Burnett, Bault, Coricelli, & Blakemore, 2010; Chein, Albert, O'Brien, Uckert, & Steinberg, 2011; McRae et al., 2012), and which would not be captured by averaging across years. Although in **Chapter 5**, we attempted to create more of a longitudinal model, which addressed some of the problems mentioned, there were also limitations with the use of early and late measures of both cognition and emotion. This misses out changes in this middle period of adolescence, potentially an important phase of development as shown by quadratic analyses (Burnett et al., 2010; Gardner & Steinberg, 2005; McRae, Gross, et al., 2012). Furthermore, the 'early' and 'late'

cognition and emotion measures were in fact collected over a range of years and therefore not fully matched, which may have reduced the strength of our analyses. **Chapter 7** used variables taken after age 16 (i.e. the N-back in the working memory trait) to predict attainment at age 16, and the emotion measures were averaged from 10 - 20 yrs., with some emotion measures representing the later years more than others. Although this is a limitation, particularly as this study is attempting to be more longitudinal in nature, the working memory measure was found in **Chapter 3** to form a latent trait together with measures taken at 10 and 13yrs, suggesting it reflects some relatively stable individual differences. **Chapter 4** used adult participants, so there are limitations in terms of the generality of these finding to adolescents. Although similar findings have be shown in an adolescent sample (Garnefski et al., 2005) in regards to questionnaire measures, we also found some differences and there is evidence that adolescents process fearful faces differently to adults (Guyer et al., 2008) possibly altering relationships with the EFNBACK.

At the same time, age is not the only factor influencing developmental changes at this time. Pubertal changes may be altering developmental trajectories differently to age and particularly effecting emotional development. Hormones have been shown to have both independent and interactive effects with age on subcortical regions of the brain (Goddings et al., 2014) and the re-wiring of dopamine projections to the pre-frontal cortex is presumed to influence emotional and cognitive processes (Luna et al., 2015; Wahlstrom et al., 2010). Tanner scores are available in ALSPAC and future studies could covary for pubertal development as this may influence cognition emotion interactions.

9.3.2 Emotion regulation, 'hot' EF, emotional focal or non-focal content

There is some cross-terminology in the literature where emotional behaviour, emotion regulation, 'hot' EF and emotional interference get used interchangeably causing a degree of confusion. Unfortunately, this thesis is limited by lacking a reliable measure of 'hot' EF or emotion regulation in adolescence which may have helped to pull apart some of the difficulties proposed in 9.2.4. and 9.2.6. ALSPAC did not have a questionnaire measure of Emotion Regulation (such as the ERQ or CERQ) or any 'hot' EF task, (i.e., one that was motivationally salient) and so it was difficult to compare and contrast associations between these constructs. The measure used in **Chapter 4**, is not strictly a 'hot' measure of EF, but has been used in the literature as an emotion regulation task (Ladouceur et al., 2013). However, the emotion in this task is non-focal meaning the emotional content is possible to ignore, and therefore may not necessarily require emotion regulation, furthermore it was performed in adults rather than adolescents.

9.3.3 Small effect sizes

Across the ALSPAC behavioural studies performed in this thesis we persistently found effects sizes that were small to very small, although there were some exceptions: **Chapter 3** working memory ~ externalising had a small-medium effect size (*d*=.39); and **Chapter 7** Maths, English, Science ~ WM had medium to large effect sizes (*d*=.85, *d*=.47, *d*=.66 respectively). In **Chapter 4**, using a smaller independent adult sample, slightly larger effects are found: WM (2-back blank) ~ externalising is medium to large (*d*=.70); WM (2-back blank) ~ internalising is medium (*d*=.55); emotion (0-back emotion) ~ internalising and anxiety is large (*d*=.91 and *d*=.88 respectively).

It is possible that we only find small effects sizes due to mixing experimental and questionnaire data. Previous studies have not always found very high correlations between measures of the same constructs using these two different types of data, including studies of ER (Carlson & Wang, 2007; Howse et al., 2003) and EF (Vriezen & Pigott, 2002). However, we also found that only a small amount of variance in the late EF measures (WM = 8.2%, IC = 3.8%) in **Chapter 5** was explained even though models included earlier measures of the same construct as predictors. This demonstrates the persistent problem of test-rest reliably of EF measures (Kuntsi, Stevenson, Oosterlaan, & Sonuga-Barke, 2001; Rabbitt, 2004). Although some suggest this can be remediated by using latent measures (Karalunas, Bierman, & Huang-Pollock, 2016), Hedge and colleagues argue that the problem stems from the fact that EF measures were derived for experimental paradigms which emphasise low between subject variability in search for general mechanisms. Therefore, they are not ideal for use in individual differences research which seeks to find measures that reliably rank individuals (Hedge et al., 2018). Therefore, even if our latent factors circumvent problems of reliability, it is possible they still fail to represent meaningful variation between people within the typical population. Furthermore, others argue that EF experimental tasks have little ecological validity and do not capture context-specific functioning (Chan, Shum, Toulopoulou, & Chen, 2008) which may be another reason they fail to correlate highly with questionnaire measures. Interestingly working memory and to a lesser extent processing speed did predict achievement in academic subjects which might be categorised as somewhere between questionnaire and experimental measures, they are taken under experimental conditions and participants generally answer objective informational questions rather than self-report introspective questions.

Larger effect sizes were found for **Chapter 4**, which had a significantly smaller sample size than the study using ALSPAC data. It is a consistent finding that there is a negative correlation between sample size and effect size (Slavin & Smith, 2009). These smaller

effect sizes are therefore potentially more realistic in terms of population level effects. For individuals, specific effects may be large, but this is not necessarily consistent across the population. **Chapter 4** also inevitably has larger effect sizes because of the temporal congruence between the measures taken. It may be that measures taken at the same time reflect both state and trait similarities rather than measures combined across long periods of time, which may more specifically reflect trait individual differences. However, our findings are comparable in terms of effects sizes with other studies looking at externalising and cognitive ability (see review by Ogilvie, Stewart, Chan, & Shum, 2011)

9.3.4 Genetic studies and interpretation of genetic findings

The aim of using more biological phenotypes, is not just the assumption that they are closer to gene function and therefore simpler in architecture, but it fits with the belief that it will enable us to map pathways from genes to behaviour via specific mechanisms like we are able to do in some types of disease (e.g., sickle cell disease) and developmental disorders (e.g. Fragile X). However, it is also widely accepted that there will be no direct mapping between genes and complex behaviours given widespread pleiotropy and polygenicity, therefore it is unlikely that genetic mechanisms of complex traits will function in this way. Some argue that genetic associations with complex traits are equally distributed across the genome and functional categories and that therefore there may be core genes which influence traits directly, but there is also a significantly larger background network of genes influencing the trait indirectly with even smaller effects (Boyle, Li, & Pritchard, 2017).

In terms of the core genes influencing cognitive abilities, it is likely, according to the generalist gene hypothesis, that it will be the same genes influencing the majority of cognitive functions (Kovas & Plomin, 2006). **Chapters 6** and **8** found that the majority of the cognitive traits measure (other than processing speed and inhibitory control) had a 100% genetic overlap with intelligence supporting this hypothesis. However, with each other, these traits were not so highly correlated. It is likely that intelligence is picking up the common genetic variance between the traits, so how do we explain the different genetic effects influencing English, maths, science and WM. This extra genetic variance is picking up subject specific variance not directly related to intelligence such as genetic factors influencing personality or affect. For this reason, future research could focus on the genetic overlap with other traits controlling for the shared effects of intelligence.

It is also possible that due to the homogenous nature of the sample, and the specific nature of the AA phenotypes, that we may be picking up on variance that wouldn't be generalizable outside of this context. The population dependency of these genetic effects

is a broader issue for genetics. The recent EA GWAS noted this recently in finding that although their polygenic risk score was able to predict up to 13% of the variance in white Western attainment, it only predicted 1.6% in African American attainment (Lee et al., 2018). Associations with maths in the Chinese population (Chen et al., 2017) raise some interesting questions about how population-specific variants may be, and how genetic variation may contribute differently to traits in different populations as well as different environmental contexts.

On a more practical level, LD score SNP heritability estimates are limited to variance contributed to a trait by common polygenic architecture, and is unable to account for all the heritability estimated by twin studies. Genetic correlations are proportional to these heritabilities, which makes it difficult to compare correlations across traits. For example, the fact that English is more highly genetically correlated with working memory than maths, could just be as a result of the lower heritability estimate for English. On the other hand, when genetic and phenotypic correlations between traits vary largely, this may give us some clue as to how environment may be influencing the relationships between traits, as with working memory and internalising. We must however, be careful in interpreting genetic correlations as they are not a true representation of genetic overlap. This is because it is calculated by multiplying the effect sizes of trait 1 by the effect sizes of trait 2, therefore if a trait shares some genetic variation positively and some negatively, this will be cancelled out. Therefore, it represents the proportion of variance that is shared in the same direction. Considering the complex nature of polygenic effects this is quite a limiting factor.

In terms of SNP associations, there are also difficulties in understanding functional significance. **Chapter 8** uncovered 10 independent SNP associations, some of these are in genes, others are not and there is one eQTL meaning it influences gene expression. However, it is still extremely difficult to relate this information to biological consequences, let alone behavioural consequences. For many, searching for associations between genes and behaviours suffers from theoretical problems of reductionism. It has been argued that because they operate on different levels of description, you cannot make causal inferences about one, based on the other. From a neuroconstructivist approach, mapping from genes to behaviour is limited by the fact that it does not account for the intricate developmental interactions that occur from genetic origins to the production of a behavioural phenotype. Higher order cognitive processes *develop*, and as such are influenced by the genetics and the development of a multitude of other factors. Genes therefore cannot be mapped directly to behaviour (Karmiloff-Smith, 2006; Westermann et al., 2007). In some ways, GWAS for behavioural traits reasserts the nature-nurture

dichotomy by looking for genes/variants associated with phenotypes which are inevitably a result of nature-nurture interactions.

There have been studies trying to address the issue of development by performing GWAS at different time points; indeed all the GWAS in this thesis have been performed in an adolescent sample. Some hypothesise that looking earlier in development may reduce environmental interference and boost genetic associations (Bradfield et al., 2012) others suggest there may be developmentally specific associations (Haworth & Davis, 2014). It may be possible to find developmentally specific genetic factors influencing phenotypes via GWAS, however it is not clear how one would pull apart developmental and non-developmental influences. This also does not quite address the point of development as an interactive process. A challenge to the field of behavioural genetics will be how to incorporate both environment and development.

9.4 Conclusion and future directions

The aim of this thesis was to understand the relationship between emotion and cognition during adolescence. In terms of stable cognitive and emotion measures, this relationship has proved to be small and correlations that do exist may be due the influences of emotion on cognition. This calls into question the mechanism by which cognition influences emotion, if indeed it does. There were suggestions that a link between externalising behaviour and working memory may originate genetically and continue to develop across adolescence. We find internalising may be more influenced by environmental experiences of emotion which potentially effect cognitive functioning. We found large associations between academic achievement and cognition phenotypically and genetically and smaller more specific associations with emotion. Future studies could seek to pull apart the relationships between state and trait cognitive and emotional individual differences and investigate whether ER strategies are a bi-product of, or a mediator between any of these relations. Future research could also investigate further the role of 'hot' EF in regulating emotion and in turn emotional outcomes. 'Hot' EF may be particularly relevant during adolescence, where motivational salience of reward and the social context, and sensation-seeking, are high (Steinberg, 2005). Finally, studies able to collect consistent longitudinal measures of both emotion and cognition during the second decade of life could start to unpack trajectories of interaction, possibly highlighting particular periods of change.

References

Achenbach, T. (1966). The Classification of Children's Psychiatric Symptoms: A Factor Analytic Study. *Psychological Monographs*, 7(80), 1–37.

Aker, M., Bø, R., Harmer, C., Stiles, T. C., & Landrø, N. I. (2016). Inhibition and response to error in remitted major depression. *Psychiatry Research,* 235, 116–122.

Aldao, A., Gee, D. G., De Los Reyes, A., & Seager, I. (2016). Emotion regulation as a transdiagnostic factor in the development of internalizing and externalizing psychopathology: Current and future directions. *Development and Psychopathology*, 28(4pt1), 927–946

Aldao, A., & Nolen-Hoeksema, S. (2010). Specificity of cognitive emotion regulation strategies: A transdiagnostic examination. *Behaviour Research and Therapy*, 48(10), 974–983.

Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. Clinical Psychology Review, 30(2), 217–237.

Aldao, A., & Tull, M. T. (2015). Putting emotion regulation in context. *Current Opinion in Psychology,* 3, 100–107.

Alloway, T. P., & Alloway, R. G. (2010). Investigating the predictive roles of working memory and IQ in academic attainment. *Journal of Experimental Child Psychology*, 106(1), 20–29.

Aluja, A., Garcia, Ó., & Garcia, L. F. (2003). Relationships among extraversion, openness to experience, and sensation seeking. *Personality and Individual Differences*, 35(3), 671–680.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub.

Anderson, C. A., Pettersson, F. H., Clarke, G. M., Cardon, L. R., Morris, A. P., & Zondervan, K. T. (2010). Data quality control in genetic case-control association studies. *Nature Protocols*, 5(9), 1564–1573.

Anderson, M. (2001). Annotation: Conceptions of Intelligence. *Journal of Child Psychology and Psychiatry*, 42(3), 287–298.

Angold, A., Costello, E. J., Messer, S. C., & Pickles, A. (1995). Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research*, 5(4), 237–249.

Angold, A., Costello, E., Messer, S., Pickles, A., Winder, F., & Silver, D. (1995). Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research*, 5, 237–249.

Arnett, J. (1994). Sensation seeking: A new conceptualization and a new scale. *Personality and Individual Differences*, 16(2), 289–296.

Arriaga, X. B., & Foshee, V. A. (2004). Adolescent Dating Violence: Do Adolescents Follow in Their Friends', Or Their Parents', Footsteps? *Journal of Interpersonal Violence*, 19(2), 162–184.

Awh, E., & Jonides, J. (2001). Overlapping mechanisms of attention and spatial working memory. *Trends in Cognitive Sciences*, 5(3), 119–126.

Azur, M. J., Stuart, E. A., Frangakis, C., & Leaf, P. J. (2011). Multiple Imputation by Chained Equations: What is it and how does it work? *International Journal of Methods in Psychiatric Research*, 20(1), 40–49.

Bachman, J. G. (1970). *The Impact of Family Background and Intelligence on Tenth-Grade Boys. Youth in Transition*. Volume II.

Balzarotti, S., John, O. P., & Gross, J. J. (2010). An Italian Adaptation of the Emotion Regulation Questionnaire. *European Journal of Psychological Assessment*, 26(1), 61–67.

Barbosa, A. C., Kim, M.-S., Ertunc, M., Adachi, M., Nelson, E. D., McAnally, J., … Olson, E. N. (2008). MEF2C, a transcription factor that facilitates learning and memory by negative regulation of synapse numbers and function. *Proceedings of the National Academy of Sciences*, 105(27), 9391–9396.

Barkley, R. A. (2001). The Executive Functions and Self-Regulation: An Evolutionary Neuropsychological Perspective. *Neuropsychological review,* 11(1), 1-29.

Baron-Cohen, S., Murphy, L., Chakrabarti, B., Craig, I., Mallya, U., Lakatošová, S., … Warrier, V. (2014). A Genome Wide Association Study of Mathematical Ability Reveals an Association at Chromosome 3q29, a Locus Associated with Autism and Learning Difficulties: A Preliminary Study. *PLOS ONE*, 9(5), e96374.

Beasley, T. M., Erickson, S., & Allison, D. B. (2009). Rank-Based Inverse Normal Transformations are Increasingly Used, But are They Merited? *Behavior Genetics*, 39(5), 580–595.

Beevers, C. G., Wells, T. T., & McGeary, J. E. (2009). The BDNF Val66Met polymorphism is associated with rumination in healthy adults. E*motion*, 9(4), 579–584.

Bell, M. A., & Wolfe, C. D. (2004). Emotion and Cognition: An Intricately Bound Developmental Process. *Child Development*, 75(2), 366–370.

Benca, C. E., Derringer, J. L., Corley, R. P., Young, S. E., Keller, M. C., Hewitt, J. K., & Friedman, N. P. (2016). Predicting Cognitive Executive Functioning with Polygenic Risk Scores for Psychiatric Disorders. *Behavior Genetics*, 47(1), 11-24.

Bender, P. K., Reinholdt-Dunne, M. L., Esbjørn, B. H., & Pons, F. (2012). Emotion dysregulation and anxiety in children and adolescents: Gender differences. *Personality and Individual Differences*, 53(3), 284–288.

Benke, K. S., Nivard, M. G., Velders, F. P., Walters, R. K., Pappa, I., Scheet, P. A., … Early Genetics and Lifecourse Epidemiology Consortium. (2014). A genome-wide association meta-analysis of preschool internalizing problems. *Journal of the American Academy of Child and Adolescent Psychiatry*, 53(6), 667-676.

Bento de Souza, I. B. M., Barbosa, F. F., Lacerda, A. M., dos Santos, N. A., & Torro-Alves, N. (2014). Evaluation of facial expressions in women with major depression: Is there a negative bias? *Psychology & Neuroscience*, 7(4), 513–519.

Berger, N., Richards, A., & Davelaar, E. J. (2018). Differential effects of angry faces on working memory updating in younger and older adults. Psychology and Aging, 33(4), 667–673.

Best, J. R., & Miller, P. H. (2010). A Developmental Perspective on Executive Function. *Child Development*, 81(6), 1641–1660.

Best, J. R., Miller, P. H., & Naglieri, J. A. (2011). Relations between executive function and academic achievement from ages 5 to 17 in a large, representative national sample. *Learning and Individual Differences*, 21(4), 327–336.

Bishara, A. J., & Hittner, J. B. (2012). Testing the significance of a correlation with non-normal data: Comparison of Pearson, Spearman, transformation, and resampling approaches. *Psychological Methods*, 17(3), 399–417.

Bishop, D. V. M. (1998). Development of the Children's Communication Checklist (CCC): A Method for Assessing Qualitative Aspects of Communicative Impairment in Children. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, 39(6), 879–891.

Blair, C. (2002). School readiness: Integrating cognition and emotion in a neurobiological conceptualization of children's functioning at school entry. *American Psychologist*, 57(2), 111–127.

Blair, C., & Raver, C. C. (2015). School Readiness and Self-Regulation: A Developmental Psychobiological Approach. *Annual Review of Psychology*, 66, 711–731.

Blair, C., & Razza, R. P. (2007). Relating effortful control, executive function, and false belief understanding to emerging math and literacy ability in kindergarten. *Child Development*, 78(2), 647–663.

Blakemore, S.-J. (2008). The social brain in adolescence. *Nature Reviews Neuroscience,* 9(4), 267–277.

Blakemore, S.-J., Burnett, S., & Dahl, R. E. (2010). The Role of Puberty in the Developing Adolescent Brain. *Human Brain Mapping*, 31(6), 926–933.

Bloemen, A. J. P., Oldehinkel, A. J., Laceulle, O. M., Ormel, J., Rommelse, N. N. J., & Hartman, C. A. (2018). The association between executive functioning and psychopathology: general or specific? *Psychological Medicine*, 1–8.

Blokland, G. A. M., Wallace, A. K., Hansell, N. K., Thompson, P. M., Hickie, I. B., Montgomery, G. W., … Wright, M. J. (2016). Genome-wide association study of working memory brain activation. *International Journal of Psychophysiology*, 115, 98-111.

Boldrini, M., Pace, L. D., Placidi, G. P. A., Keilp, J., Ellis, S. P., Signori, S., … Cappa, S. F. (2005). Selective cognitive deficits in obsessive-compulsive disorder compared to panic disorder with agoraphobia. *Acta Psychiatrica Scandinavica*, 111(2), 150–158.

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., … Davey Smith, G. (2013). Cohort Profile: The 'Children of the 90s'; the index offspring of The Avon Longitudinal Study of Parents and Children (ALSPAC). *International Journal of Epidemiology*, (42), 111–127.

Boyle, E. A., Li, Y. I., & Pritchard, J. K. (2017). An Expanded View of Complex Traits: From Polygenic to Omnigenic. *Cell,* 169(7), 1177–1186.

Bradfield, J. P., Taal, H. R., Timpson, N. J., Scherag, A., Lecoeur, C., Warrington, N. M., … Grant, S. F. A. (2012). A genome-wide association meta-analysis identifies new childhood obesity loci. *Nature Genetics*, 44(5), 526–531.

Brenhouse, H. C., & Andersen, S. L. (2011). Developmental trajectories during adolescence in males and females: A cross-species understanding of underlying brain changes. *Neuroscience & Biobehavioral Reviews*, 35(8), 1687–1703.

Brock, L. L., Rimm-Kaufman, S. E., Nathanson, L., & Grimm, K. J. (2009). The contributions of 'hot' and 'cool' executive function to children's academic achievement, learning-related behaviors, and engagement in kindergarten. *Early Childhood Research Quarterly,* 24(3), 337–349.

Brody, L. R., & Hall, J. A. (2008). Gender and emotion in context. In M. Lewis, J. M. Haviland-Jones, & L. F. Barrett (Eds.), *Handbook of emotions* (3rd ed., pp. 395–408). New York: Guilford Press.

Brown, B. B. (2004). Adolescents' Relationships with Peers. *Handbook of Adolescent Psychology* (363–394).

Buckholtz, J. W., Callicott, J. H., Kolachana, B., Hariri, A. R., Goldberg, T. E., Genderson, M., … Meyer-Lindenberg, A. (2007). Genetic variation in MAOA modulates ventromedial prefrontal circuitry mediating individual differences in human personality. *Molecular Psychiatry,* 13(3), 313–324.

Buckholtz, J. W., & Meyer-Lindenberg, A. (2008). MAOA and the neurogenetic architecture of human aggression. *Trends in Neurosciences*, 31(3), 120–129.

Bulik-Sullivan, B., Finucane, H. K., Anttila, V., Gusev, A., Day, F. R., Loh, P.-R., … Neale, B. M. (2015). An Atlas of Genetic Correlations across Human Diseases and Traits. *Nature Genetics*, 47(11), 1236–1241.

Bulik-Sullivan, B., Loh, P.-R., Finucane, H., Ripke, S., Yang, J., Patterson, N., … Neale, B. M. (2015). LD Score Regression Distinguishes Confounding from Polygenicity in Genome-Wide Association Studies. *Nature Genetics*, 47(3), 291–295.

Bull, R., & Scerif, G. (2001). Executive Functioning as a Predictor of Children's Mathematics Ability: Inhibition, Switching, and Working Memory. *Developmental Neuropsychology*, 19(3), 273–293.

Burke, J. D., Loeber, R., Lahey, B. B., & Rathouz, P. J. (2005). Developmental transitions among affective and behavioral disorders in adolescent boys. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 46(11), 1200–1210.

Burnett, S., Bault, N., Coricelli, G., & Blakemore, S.-J. (2010). Adolescents' heightened risk-seeking in a probabilistic gambling task. *Cognitive Development*, 25(2), 183–196.

Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice: Multivariate imputation by chained equations in R. *Journal of Statistical Software*, 45(3) 1-68.

Canli, T., & Lesch, K.-P. (2007). Long story short: the serotonin transporter in emotion regulation and social cognition. *Nature Neuroscience*, 10(9), 1103–1109.

Carlson, S. M., & Wang, T. S. (2007). Inhibitory control and emotion regulation in preschool children. *Cognitive Development*, 22(4), 489–510.

Case, R., Kurland, D. M., & Goldberg, J. (1982). Operational efficiency and the growth of short-term memory span. *Journal of Experimental Child Psychology,* 33(3), 386–404.

Casey, B. J., Getz, S., & Galvan, A. (2008). The adolescent brain. *Developmental Review*, 28(1), 62–77.

Casey, B. J., Somerville, L. H., Gotlib, I. H., Ayduk, O., Franklin, N. T., Askren, M. K., … Shoda, Y. (2011). Behavioral and neural correlates of delay of gratification 40 years later. *Proceedings of the National Academy of Sciences,* 108(36), 14998–15003.

Caspi, A, MacClay, J., Moffitt, T., Mill, J., Martin, J., Craig, I., … Poulton, R. (2002). Role of genotype in the cycle of violence in malteated children. *Science*, (297), 851–854.

Caspi, Avshalom, Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., … Moffitt, T. E. (2014). The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? *Clinical Psychological Science*, 2(2), 119–137.

Cesaretti, C., Spaccini, L., Righini, A., Parazzini, C., Conte, G., Crosti, F., … Rustico, M. (2016). Prenatal detection of 5q14.3 duplication including MEF2C and brain phenotype. *American Journal of Medical Genetics. Part A,* 170(5), 1352–1357.

Chamorro-Premuzic, T., & Furnham, A. (2003a). Personality predicts academic performance: Evidence from two longitudinal university samples. *Journal of Research in Personality*, 37(4), 319–338.

Chamorro-Premuzic, T., & Furnham, A. (2003b). Personality traits and academic examination performance. *European Journal of Personality*, 17(3), 237–250.

Chan, R. C. K., Shum, D., Toulopoulou, T., & Chen, E. Y. H. (2008). Assessment of executive functions: Review of instruments and identification of critical issues. *Archives of Clinical Neuropsychology,* 23(2), 201–216.

Chang, S.-S., Chen, Y.-Y., Heron, J., Kidger, J., Lewis, G., & Gunnell, D. (2014). IQ and adolescent self-harm behaviours in the ALSPAC birth cohort. *Journal of Affective Disorders*, 152–154, 175–182.

Cheesman, R., Selzam, S., Ronald, A., Dale, P. S., McAdams, T. A., Eley, T. C., & Plomin, R. (2017). Childhood behaviour problems show the greatest gap between DNA-based and twin heritability. *Translational Psychiatry*, 7(12), 1284.

Chein, J., Albert, D., O'Brien, L., Uckert, K., & Steinberg, L. (2011). Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry: Peer influence on risk taking. *Developmental Science*, 14(2), F1–F10.

Chen, H., Gu, X., Zhou, Y., Ge, Z., Wang, B., Siok, W. T., … Sun, Y. (2017). A Genome-Wide Association Study Identifies Genetic Variants Associated with Mathematics Ability. *Scientific Reports*, 7, 40365.

Clark, C., Prior, M., & Kinsella, G. J. (2000). Do executive function deficits differentiate between adolescents with ADHD and oppositional defiant/conduct disorder? A neuropsychological study using the Six Elements Test and Hayling Sentence Completion Test. *Journal of Abnormal Child Psychology*, 28(5), 403–414.

Cole, P. M., Martin, S. E., & Dennis, T. A. (2004). Emotion regulation as a scientific construct: Methodological challenges and directions for child development research. *Child Development*, 75(2), 317–333.

Conklin, H. M., Luciana, M., Hooper, C. J., & Yarger, R. S. (2007). Working Memory Performance in Typically Developing Children and Adolescents: Behavioral Evidence of Protracted Frontal Lobe Development. *Developmental Neuropsychology*, 31(1), 103–128.

Course-Choi, J., Saville, H., & Derakshan, N. (2017). The effects of adaptive working memory training and mindfulness meditation training on processing efficiency and worry in high worriers. *Behaviour Research and Therapy*, 89, 1–13.

Cragg, L., & Gilmore, C. (2014). Skills underlying mathematics: The role of executive function in the development of mathematics proficiency. *Trends in Neuroscience and Education*, 3(2), 63–68.

Crone, E. A., & Dahl, R. E. (2012). Understanding adolescence as a period of social–affective engagement and goal flexibility. Nature Reviews Neuroscience, 13(9), 636–650.

Crone, E. A., Donohue, S. E., Honomichl, R., Wendelken, C., & Bunge, S. A. (2006). Brain Regions Mediating Flexible Rule Use during Development. *Journal of Neuroscience, 26(43), 11239–11247.*

Crone, E. A., Richard Ridderinkhof, K., Worm, M., Somsen, R. J. M., & van der Molen, M. W. (2004). Switching between spatial stimulus-response mappings: a developmental study of cognitive flexibility. *Developmental Science,* 7(4), 443–455.

Crone, E. A., & van der Molen, M. W. (2004). Developmental changes in real life decision making: performance on a gambling task previously shown to depend on the ventromedial prefrontal cortex. *Developmental Neuropsychology*, 25(3), 251–279.

Curci, A., Lanciano, T., Soleti, E., & Rimé, B. (2013). Negative emotional experiences arouse rumination and affect working memory capacity. *Emotion*, 13(5), 867–880.

D'Alessandro, D. U., & Burton, K. D., (2006). Development and validation of the Dysfunctional Attitudes Scale for Children: Tests of Beck's cognitive diathesis-stress theory of depression, of its causal mediation component, and of developmental effects. *Cognitive Therapy and Research*, 30(3), 335-353.

Davies, G., Armstrong, N., Bis, J. C., Bressler, J., Chouraki, V., Giddaluru, S., … Deary, I. J. (2015). Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium (N=53 949). *Molecular Psychiatry*, 20(2), 183–192.

Davies, G., Marioni, R. E., Liewald, D. C., Hill, W. D., Hagenaars, S. P., Harris, S. E., … Deary, I. J. (2016). Genome-wide association study of cognitive functions and educational attainment in UK Biobank (N=112 151). *Molecular Psychiatry*, 21(6), 758–767.

Davies, G., Tenesa, A., Payton, A., Yang, J., Harris, S. E., Liewald, D., … Deary, I. J. (2011). Genome-wide association studies establish that human intelligence is highly heritable and polygenic. *Molecular Psychiatry*, 16(10), 996–1005.

Davis, O. S. P., Band, G., Pirinen, M., Haworth, C. M. A., Meaburn, E. L., Kovas, Y., … Spencer, C. C. A. (2014). The correlation between reading and mathematics ability at age twelve has a substantial genetic component. *Nature Communications*, 5, 4204.

De Houwer, J., & Tibboel, H. (2010). Stop what you are not doing! Emotional pictures interfere with the task not to respond. *Psychonomic Bulletin & Review*, 17(5), 699–703.

De Lissnyder, E., Koster, E. H. W., Everaert, J., Schacht, R., Van den Abeele, D., & De Raedt, R. (2012). Internal cognitive control in clinical depression: General but no emotion-specific impairments. *Psychiatry Research*, 199(2), 124–130.

Del Piero, L. B., Saxbe, D. E., & Margolin, G. (2016). Basic emotion processing and the adolescent brain: Task demands, analytic approaches, and trajectories of changes. *Developmental Cognitive Neuroscience*, 19, 174–189.

Delaneau, O., Marchini, J., & Zagury, J.-F. (2012). A linear complexity phasing method for thousands of genomes. *Nature Methods*, 9(2), 179–181.

Delis, D. C., Kaplan, E., & Kramer, J. (2001). Delis-Kaplan Executive Function System®(D-KEFS®): Examiner's Manual: Flexibility of Thinking, Concept Formation, Problem Solving, Planning, Creativity, Impluse Control, Inhibition. Pearson.

Demeyer, I., De Lissnyder, E., Koster, E. H. W., & De Raedt, R. (2012). Rumination mediates the relationship between impaired cognitive control for emotional information and depressive symptoms: A prospective study in remitted depressed adults. *Behaviour Research and Therapy*, 50(5), 292–297.

Dimoska, A., Johnstone, S. J., Barry, R. J., & Clarke, A. R. (2003). Inhibitory motor control in children with attention-deficit/hyperactivity disorder: event-related potentials in the stop-signal paradigm. *Biological Psychiatry*, 54(12), 1345–1354.

Docherty, S. J., Davis, O. S. P., Kovas, Y., Meaburn, E. L., Dale, P. S., Petrill, S. A., … Plomin, R. (2010). A genome-wide association study identifies multiple loci associated with mathematics ability and disability. *Genes, Brain, and Behavior*, 9(2), 234–247.

Dolcos, F., & McCarthy, G. (2006). Brain Systems Mediating Cognitive Interference by Emotional Distraction. *Journal of Neuroscience*, 26(7), 2072–2079.

Drabant, E. M., McRae, K., Manuck, S. B., Hariri, A. R., & Gross, J. J. (2009). Individual Differences in Typical Reappraisal Use Predict Amygdala and Prefrontal Responses. *Biological Psychiatry*, 65(5), 367–373.

Drabant, E. M., Ramel, W., Edge, M. D., Hyde, L. W., Kuo, J. R., Goldin, P. R., … Gross, J. J. (2012). Neural Mechanisms Underlying 5-HTTLPR-Related Sensitivity to Acute Stress. *American Journal of Psychiatry*, 169(4), 397–405.

Duckworth, A. L., Quinn, P. D., Lynam, D. R., Loeber, R., & Stouthamer-Loeber, M. (2011). Role of test motivation in intelligence testing. *Proceedings of the National Academy of Sciences of the United States of America*, 108(19), 7716–7720.

Dudbridge, F. (2013). Power and Predictive Accuracy of Polygenic Risk Scores. *PLoS Genet*, 9(3), e1003348.

Dudbridge, F. (2016). Polygenic Epidemiology. Genetic Epidemiology, 40(4), 268–272.

Dudbridge, F., & Gusnanto, A. (2008). Estimation of significance thresholds for genomewide association scans. *Genetic Epidemiology*, 32(3), 227–234.

Duell, N., Steinberg, L., Icenogle, G., Chein, J., Chaudhary, N., Di Giunta, L., … Chang, L. (2018). Age Patterns in Risk Taking Across the World. *Journal of Youth and Adolescence*, 47(5), 1052–1072.

Dumontheil, I., & Klingberg, T. (2012). Brain Activity during a Visuospatial Working Memory Task Predicts Arithmetical Performance 2 Years Later. *Cerebral Cortex*, 22(5), 1078–1085.

Dumontheil, I., Roggeman, C., Ziermans, T., Peyrard-Janvid, M., Matsson, H., Kere, J., & Klingberg, T. (2011). Influence of the COMT Genotype on Working Memory and Brain Activity Changes During Development. *Biological Psychiatry,* 70(3), 222–229.

Duncan, G. J., Dowsett, C. J., Claessens, A., Magnuson, K., Huston, A. C., Klebanov, P., … Japel, C. (2007). School readiness and later achievement. *Developmental Psychology, 43(6), 1428–1446*.

Egan, M. F., Goldberg, T. E., Kolachana, B. S., Callicott, J. H., Mazzanti, C. M., Straub, R. E., … Weinberger, D. R. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America,* 98(12), 6917–6922.

Eisenberg, N., & Fabes, R. A. (1992). Emotion, regulation, and the development of social competence. In *Emotion and social behavior* (pp. 119–150). Thousand Oaks, CA, US: Sage Publications, Inc.

Eisenberg, N., Sadovsky, A., & Spinrad, T. L. (2005). Associations of Emotion-Related Regulation with Language Skills, Emotion Knowledge, and Academic Outcomes. *New Directions for Child and Adolescent Development*, (109), 109–118.

Eisenberg, N., & Spinrad, T. L. (2004). Emotion-related regulation: Sharpening the definition. *Child Development*, 75(2), 334–339.

Elander, J., & Rutter, M. (1996). Use and development of the Rutter parents' and teachers' scales. *International Journal of Methods in Psychiatric Research,* 6(2), 63–78.

Elliott, R., Rubinsztein, J. S., Sahakian, B. J., & Dolan, R. J. (2002). The Neural Basis of Mood-Congruent Processing Biases in Depression. *Archives of General Psychiatry*, 59(7), 597–604.

Engelhardt, L. E., Briley, D. A., Mann, F. D., Harden, K. P., & Tucker-Drob, E. M. (2015). Genes Unite Executive Functions in Childhood. *Psychological Science,* 26(8), 1151–1163.

Erickson, K., Drevets, W. C., Clark, L., Cannon, D. M., Bain, E. E., Zarate Jr, C. A., … Sahakian, B. J. (2005). Mood-congruent bias in affective go/no-go performance

of unmedicated patients with major depressive disorder. *American Journal of Psychiatry*, 162(11), 2171–2173.

Espy, K. A., McDiarmid, M. M., Cwik, M. F., Stalets, M. M., Hamby, A., & Senn, T. E. (2004). The contribution of executive functions to emergent mathematic skills in preschool children. *Developmental Neuropsychology*, 26(1), 465–486.

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: Attentional control theory. *Emotion*, 7(2), 336–353.

Fabiansson, E. C., Denson, T. F., Moulds, M. L., Grisham, J. R., & Schira, M. M. (2012). Don't look back in anger: Neural correlates of reappraisal, analytical rumination, and angry rumination during recall of an anger-inducing autobiographical memory. *NeuroImage*, 59(3), 2974–2981.

Field, A., Miles, J., & Field, Z. (2012). *Discovering Statistics Using R*. Sage Publications.

Flint, J., & Munafò, M. R. (2007). The endophenotype concept in psychiatric genetics. *Psychological Medicine*, 37(02), 163-180.

Ford, T., Collishaw, S., Meltzer, H., & Goodman, R. (2007). A prospective study of childhood psychopathology: independent predictors of change over three years. *Social Psychiatry and Psychiatric Epidemiology*, 42(12), 953–961.

Fougnie, D. (2008). The Relationship between Attention and Working Memory. In N. B. Johansen (Ed.), *New research on short-term memory* (p. 45). New York: Nova Biomedical Books.

Fox, N. A. (1994). Dynamic Cerebral Processes Underlying Emotion Regulation. *Monographs of the Society for Research in Child Development,* 59(2/3), 152–166.

Frank, D. W., Dewitt, M., Hudgens-Haney, M., Schaeffer, D. J., Ball, B. H., Schwarz, N. F., … Sabatinelli, D. (2014). Emotion regulation: Quantitative meta-analysis of functional activation and deactivation. *Neuroscience & Biobehavioral Reviews*, 45, 202–211.

Frick, P. J., Kamphaus, R. W., Lahey, B. B., Anne, M., Christ, G., Hart, E. L., & Tannenbaum, L. E. (1991). Academic underachievement and the disruptive behavior disorders. *Journal of Consulting and Clinical Psychology*, 289–294.

Friedman, N. P., & Miyake, A. (2017). Unity and Diversity of Executive Functions: Individual Differences as a Window on Cognitive Structure. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, 86, 186–204.

Friedman, N. P., Miyake, A., Altamirano, L. J., Corley, R. P., Young, S. E., Rhea, S. A., & Hewitt, J. K. (2016). Stability and change in executive function abilities from late adolescence to early adulthood: A longitudinal twin study. *Developmental Psychology*, 52(2), 326–340.

Friedman, N. P., Miyake, A., Corley, R. P., Young, S. E., DeFries, J. C., & Hewitt, J. K. (2006). Not all executive functions are related to intelligence. *Psychological Science,* 17(2), 172–179.

Friedman, N. P., Miyake, A., Robinson, J. L., & Hewitt, J. K. (2011). Developmental Trajectories in Toddlers' Self-restraint Predict Individual Differences in Executive Functions 14 Years Later: A Behavioral Genetic Analysis. *Developmental Psychology*, 47(5), 1410–1430.

Friedman, N. P., Miyake, A., Young, S. E., DeFries, J. C., Corley, R. P., & Hewitt, J. K. (2008). Individual Differences in Executive Functions Are Almost Entirely Genetic in Origin. *Journal of Experimental Psychology. General,* 137(2), 201–225.

Fry, A., & Hale, S. (2002). Relationships among processing speed, working memory, and fluid intelligence in children. *Biological Psychology,* 54(1), 1–34.

Gadow, K. D., Pinsonneault, J. K., Perlman, G., & Sadee, W. (2014). Association of dopamine gene variants, emotion dysregulation and ADHD in autism spectrum disorder. *Research in Developmental Disabilities*, 35(7), 1658–1665.

Garcia-Andres, E., Huertas-Martínez, J. A., Ardura, A., & Fernández-Alcaraz, C. (2010). Emotional regulation and executive function profiles of functioning related to the social development of children. *Procedia - Social and Behavioral Sciences*, 5, 2077–

Gardner, M., & Steinberg, L. (2005). Peer Influence on Risk Taking, Risk Preference, and Risky Decision Making in Adolescence and Adulthood: An Experimental Study. *Developmental Psychology*, 41(4), 625–635.

Garnefski, N., Kraaij, V., & Spinhoven, P. (2001). Negative life events, cognitive emotion regulation and emotional problems. *Personality and Individual Differences*, 30(8), 1311–1327.

Garnefski, N., & Kraaij, V. (2007). The Cognitive Emotion Regulation Questionnaire. *European Journal of Psychological Assessment*, 23(3), 141–149.

Garnefski, N., Kraaij, V., & van Etten, M. (2005). Specificity of relations between adolescents' cognitive emotion regulation strategies and Internalizing and Externalizing psychopathology. *Journal of Adolescence*, 28(5), 619–631.

Gathercole, S., & Alloway, T. P. (2008). *Working Memory and Learning: A Practical Guide for Teachers*. SAGE.

Genotype imputation and genetic association studies of UK biobank. (2015, May). Retrieved 10 September 2018, from http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/imputation_documentation_May2015.pdf

Gialluisi, A., Newbury, D. F., Wilcutt, E. G., Olson, R. K., DeFries, J. C., Brandler, W. M., … Fisher, S. E. (2014). Genome-wide screening for DNA variants associated with reading and language traits. *Genes, Brain and Behavior,* 13(7), 686–701.

Giedd, J. N., Keshavan, M., & Paus, T. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews. Neuroscience,* 9(12), 947–957.

Gilbert, P., & Miles, J. N. V. (2000). Sensitivity to Social Put-Down: it's relationship to perceptions of social rank, shame, social anxiety, depression, anger and self-other blame. *Personality and Individual Differences,* 29(4), 757–774.

Gilliom, M., & Shaw, D. S. (2004). Codevelopment of externalizing and internalizing problems in early childhood. *Development and Psychopathology,* 16(2) 313-333.

Gilmore, C., Attridge, N., Clayton, S., Cragg, L., Johnson, S., Marlow, N., … Inglis, M. (2013). Individual Differences in Inhibitory Control, Not Non-Verbal Number Acuity, Correlate with Mathematics Achievement. *PLOS ONE*, 8(6), e67374.

Goddings, A.-L., Mills, K. L., Clasen, L. S., Giedd, J. N., Viner, R. M., & Blakemore, S.-J. (2014). The influence of puberty on subcortical brain development. *NeuroImage*, 88, 242–251.

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., … Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America,* 101(21), 8174–8179.

Goh, L., & Yap, V. B. (2009). Effects of normalization on quantitative traits in association test. *BMC Bioinformatics*, 10(1), 415.

Gohier, B., Senior, C., Radua, J., El-Hage, W., Reichenberg, A., Proitsi, P., … Surguladze, S. A. (2014). Genetic modulation of the response bias towards facial displays of anger and happiness. *European Psychiatry*, 29(4), 197–202.

Gohier, B, Ferracci, L., Surguladze, S. A., Lawrence, E., El Hage, W., Kefi, M. Z., … Le Gall, D. (2009). Cognitive inhibition and working memory in unipolar depression. *Journal of Affective Disorders*, 116(1), 100–105.

Goldberg, L. R. (1992). The development of markers for the Big-Five factor structure. *Psychological Assessment,* 4(1), 26–42.

Goldberg, L. R. (1999). A broad-bandwidth, public domain, personality inventory measuring the lower-level facets of several five-factor models. In I. Mervielde, I. Deary, F. De Fruyt, & F. Ostendorf (Eds.), *Personality Psychology in Europe* (Vol. 7, pp. 7–28). Tilburg, The Netherlands: Tilburg University Press.

Goldin, P. R., McRae, K., Ramel, W., & Gross, J. J. (2008). The Neural Bases of Emotion Regulation: Reappraisal and Suppression of Negative Emotion. *Biological Psychiatry*, 63(6), 577–586.

Goodman, A., Lamping, D. L., & Ploubidis, G. B. (2010). When to Use Broader Internalising and Externalising Subscales Instead of the Hypothesised Five Subscales on the Strengths and Difficulties Questionnaire (SDQ): Data from British Parents, Teachers and Children. *Journal of Abnormal Child Psychology,* 38(8), 1179–1191.

Goodman, R. (1997). The Strengths and Difficulties Questionnaire: a research note. *Journal of Child Psychology and Psychiatry*, 38(5), 581–586.

Goodman, R., Ford, T., Richards, H., Gatward, R., & Meltzer, H. (2000). The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *Journal of Child Psychology and Psychiatry,* 41(05), 645–655.

Gratz, K. L., & Roemer, L. (2004). Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the difficulties in emotion regulation scale. *Journal of Psychopathology and Behavioral Assessment*, 26(1), 41–54.

Gray, J. R. (2001). Emotional Modulation of Cognitive Control: Approach-Withdrawal States Double-Dissociate Spatial From Verbal Two-Back Task Performance. *Journal of Experimental Psychology: General*, 130(3), 436–452.

Graziano, P. A., Reavis, R. D., Keane, S. P., & Calkins, S. D. (2007). The Role of Emotion Regulation and Children's Early Academic Success. *Journal of School Psychology*, 45(1), 3–19.

Greven, C. U., Kovas, Y., Willcutt, E. G., Petrill, S. A., & Plomin, R. (2013). Evidence for shared genetic risk between ADHD symptoms and reduced mathematics ability: a twin study. *Journal of Child Psychology and Psychiatry*, 55(1), 39–48.

Gross, J. J. (1998). Antecedent-and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. *Journal of Personality and Social Psychology*, 74(1), 224.

Gross, J. J. (2002). Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology*, 39(03), 281–291.

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology*, 85(2), 348–362.

Gross, J.J, & Munoz, R. (1995). Emotion Regulation and Mental Health. *Clinical psychology: Science and practise*, 2(2). 151-164.

Grotzinger, A. D., Rhemtulla, M., de Vlaming, R., Ritchie, S. J., Mallard, T. T., Hill, W. D., … Tucker-Drob, E. M. (2018). Genomic SEM Provides Insights into the Multivariate Genetic Architecture of Complex Traits. *bioRxiv*, 305029.

Gullone, E., Hughes, E. K., King, N. J., & Tonge, B. (2010). The normative development of emotion regulation strategy use in children and adolescents: a 2-year follow-up study: A longitudinal study of two specific emotion regulation strategies. *Journal of Child Psychology and Psychiatry*, 51(5), 567–574.

Guy, S. C., Gioia, G. ., & Isquith, P. K. (2004). *BRIEF-SR: Behavior Rating Inventory of Executive Function--self-report Version*: Professional Manual. Psychological Assessment Resources.

Guyer, A. E., Monk, C. S., McClure-Tone, E. B., Nelson, E. E., Roberson-Nay, R., Adler, A. D., … Ernst, M. (2008). A Developmental Examination of Amygdala Response to Facial Expressions. *Journal of Cognitive Neuroscience*, 20(9), 1565–1582.

Hackman, D. A., Farah, M. J., & Meaney, M. J. (2010). Socioeconomic status and the brain: mechanistic insights from human and animal research. *Nature Reviews Neuroscience*, 11(9), 651–659.

Haeffel, G. J., Gibb, B. E., Metalsky, G. I., Alloy, L. B., Abramson, L. Y., Hankin, B. L., … Swendsen, J. D. (2008). Measuring cognitive vulnerability to depression: Development and validation of the cognitive style questionnaire. *Clinical Psychology Review*, 28(5), 824–836.

Halperin, J. M., & Schulz, K. P. (2006). Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. *Psychological Bulletin*, 132(4), 560–581.

Hankin, B. L., Snyder, H. R., & Gulley, L. D. (2016). Cognitive risks in developmental psychopathology. In D. Cicchetti (Ed.), *Developmental Psychopathology, maladaption and psychopathology* (3), p. 312. Wiley.

Haplotype Reference Consortium, McCarthy, S., Das, S., Kretzschmar, W., Delaneau, O., Wood, A. R., … Marchini, J. (2016). A reference panel of 64,976 haplotypes for genotype imputation. *Nature Genetics*, 48(10), 1279–1283.

Hare, T. A., Tottenham, N., Galvan, A., Voss, H. U., Glover, G. H., & Casey, B. J. (2008). Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biological Psychiatry*, 63(10), 927–934.

Hariri, A. R., & Holmes, A. (2006). Genetics of emotional regulation: the role of the serotonin transporter in neural function. *Trends in Cognitive Sciences,* 10(4), 182–191.

Harlaar, N., Meaburn, E. L., Hayiou-Thomas, M. E., Davis, O. S. P., Docherty, S., Hanscombe, K. B., … Plomin, R. (2014). Genome-Wide Association Study of Receptive Language Ability of 12-Year-Olds. *Journal of Speech Language and Hearing Research*, 57(1), 96.

Harvey, P. O., Le Bastard, G., Pochon, J. B., Levy, R., Allilaire, J. F., Dubois, B., & Fossati, P. (2004). Executive functions and updating of the contents of working memory in unipolar depression. *Journal of Psychiatric Research*, 38(6), 567–576.

Hatoum, A. S., Rhee, S. H., Corley, R. P., Hewitt, J. K., & Friedman, N. P. (2017). Do executive functions explain the covariance between internalizing and externalizing behaviors? *Development and Psychopathology*, 1–17.

Hawn, S. E., Overstreet, C., Stewart, K. E., & Amstadter, A. B. (2015). Recent advances in the genetics of emotion regulation: a review. Current Opinion in Psychology, 3, 108–116.

Haworth, C. M. A., & Davis, O. S. P. (2014). From observational to dynamic genetics. *Frontiers in Genetics*, 5(6).

Haworth, C. M. A., Kovas, Y., Dale, P. S., & Plomin, R. (2008). Science in elementary school: Generalist genes and school environments. Intelligence, 36(6), 694–701.

Heckman, J. J. (2006). *Skill Formation and the Economics of Investing in Disadvantaged Children*. *Science,* 312(5782), 1900–1902.

Hedge, C., Powell, G., & Sumner, P. (2018). The reliability paradox: Why robust cognitive tasks do not produce reliable individual differences. *Behavior Research Methods,* 50(3), 1166–1186.

Heinz, A., Smolka, M. N., Braus, D. F., Wrase, J., Beck, A., Flor, H., … Weinberger, D. R. (2007). Serotonin Transporter Genotype (5-HTTLPR): Effects of Neutral and Undefined Conditions on Amygdala Activation. *Biological Psychiatry*, 61(8), 1011–1014.

Herold, C., Hooli, B. V., Mullin, K., Liu, T., Roehr, J. T., Mattheisen, M., … Tanzi, R. E. (2016). Family-based association analyses of imputed genotypes reveal genome-wide significant association of Alzheimer's disease with OSBPL6, PTPRG, and PDCL3. *Molecular Psychiatry*, 21(11), 1608–1612.

Hettema, J. M., Neale, M. C., & Kendler, K. S. (2001). A Review and Meta-Analysis of the Genetic Epidemiology of Anxiety Disorders. *American Journal of Psychiatry*, 158(10), 1568–1578.

Hill, W. D., Marioni, R. E., Maghzian, O., Ritchie, S. J., Hagenaars, S. P., McIntosh, A. M., … Deary, I. J. (2018). A combined analysis of genetically correlated traits identifies 187 loci and a role for neurogenesis and myelination in intelligence. *Molecular Psychiatry*, 1 .

Hill, W. David, Davies, G., Liewald, D. C., McIntosh, A. M., & Deary, I. J. (2016). Age-Dependent Pleiotropy Between General Cognitive Function and Major Psychiatric Disorders. *Biological Psychiatry*, 80(4), 266–273.

Hilt, L. M., Leitzke, B. T., & Pollak, S. D. (2014). Cognitive Control and Rumination in Youth: The Importance of Emotion. *Journal of Experimental Psychopathology,* 5(3), 302–313.

Hinshaw, S. P. (1992). Externalizing Behavior Problems and Academic Underachievement in Childhood and Adolescence: Causal Relationships and Underlying Mechanisms. *Psychological Bulletin*, 111(1), 127–155.

Hirschhorn, J. N., & Daly, M. J. (2005). Genome-wide association studies for common diseases and complex traits. *Nature Reviews Genetics*, 6(2), 95–108.

Hirschhorn, J. N., Lohmueller, K., Byrne, E., & Hirschhorn, K. (2002). A comprehensive review of genetic association studies. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, 4(2), 45–61.

Hofmann, W., Schmeichel, B. J., & Baddeley, A. D. (2012). Executive functions and self-regulation. *Trends in Cognitive Sciences*, 16(3), 174–180.

Hooper, C. J., Luciana, M., Conklin, H. M., & Yarger, R. S. (2004). Adolescents' performance on the Iowa Gambling Task: implications for the development of decision making and ventromedial prefrontal cortex. *Developmental Psychology*, 40(6), 1148–1158.

Horwood, J., Salvi, G., Thomas, K., Duffy, L., Gunnell, D., Hollis, C., … Harrison, G. (2008). IQ and non-clinical psychotic symptoms in 12-year-olds: results from the ALSPAC birth cohort. *British Journal of Psychiatry*, 193(03), 185–191.

Hotton, M., Derakshan, N., & Fox, E. (2018). A randomised controlled trial investigating the benefits of adaptive working memory training for working memory capacity and attentional control in high worriers. *Behaviour Research and Therapy*, 100, 67–77.

Howse, R. B., Calkins, S. D., Anastopoulos, A. D., Keane, S. P., & Shelton, T. L. (2003). Regulatory contributors to children's kindergarten achievement. *Early Education and Development*, 14(1), 101–119.

Hu, L., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal*, 6(1), 1–55.

Huang-Pollock, C. L., Nigg, J. T., & Carr, T. H. (2005). Deficient attention is hard to find: applying the perceptual load model of selective attention to attention deficit hyperactivity disorder subtypes. *Journal of Child Psychology and Psychiatry*, 46(11), 1211–1218.

Huang-Pollock, C., Shapiro, Z., Galloway-Long, H., & Weigard, A. (2017). Is Poor Working Memory a Transdiagnostic Risk Factor for Psychopathology? *Journal of Abnormal Child Psychology,* 45(8), 1477–1490.

Huizinga, M., Dolan, C. V., & van der Molen, M. W. (2006). Age-related change in executive function: Developmental trends and a latent variable analysis. *Neuropsychologia*, 44(11), 2017–2036.

Huttenlocher, P. (2002). *Neural plasticity: The effects of environment on the development of the cerebral cortex*. London: Harvard University Press.

Ibrahim-Verbaas, C. A., Bressler, J., Debette, S., Schuur, M., Smith, A. V., Bis, J. C., … Mosley, T. H. (2016). GWAS for executive function and processing speed suggests involvement of the CADM2 gene. *Molecular Psychiatry*, 21(2), 189–197.

Ivcevic, Z., & Brackett, M. (2014). Predicting school success: Comparing Conscientiousness, Grit, and Emotion Regulation Ability. *Journal of Research in Personality,* 52, 29–36.

John, O. P., & Srivastava, S. (1999). The Big Five trait taxonomy: History, measurement, and theoretical perspectives. In L. A. Pervin (Ed.), *Handbook of Personality, Second Edition: Theory and Research* (Vol. 2, pp. 102–138). Elsevier.

Johnson, D. P., Whisman, M. A., Corley, R. P., Hewitt, J. K., & Friedman, N. P. (2014). Genetic and Environmental Influences on Rumination and its Covariation with Depression. *Cognition & Emotion*, 28(7), 1270–1286.

Jones, L. B., Rothbart, M. K., & Posner, M. I. (2003). Development of executive attention in preschool children. *Developmental Science*, 6(5), 498–504.

Joormann, J., Yoon, K. L., & Zetsche, U. (2007). Cognitive inhibition in depression. *Applied and Preventive Psychology*, 12(3), 128–139.

Joseph, J. E., Liu, X., Jiang, Y., Lynam, D., & Kelly, T. H. (2009). Neural Correlates of Emotional Reactivity in Sensation Seeking. *Psychological Science*, 20(2), 215–223.

Jostins, L., Ripke, S., Weersma, R. K., Duerr, R. H., McGovern, D. P., Hui, K. Y., … Cho, J. H. (2012). Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*, 491(7422), 119–124.

Kail, R. (2000). Speed of Information Processing: Developmental Change and Links to Intelligence. *Journal of School Psychology*, 38(1), 51–61.

Kail, R., & Hall, L. K. (1994). Processing speed, naming speed, and reading. *Developmental Psychology*, 30(6), 949–954.

Kaiser, S., Unger, J., Kiefer, M., Markela, J., Mundt, C., & Weisbrod, M. (2003). Executive control deficit in depression: event-related potentials in a Go/Nogo task. *Psychiatry Research: Neuroimaging*, 122(3), 169–184.

Kalisch, R., Wiech, K., Herrmann, K., & Dolan, R. J. (2006). Neural Correlates of Self-distraction from Anxiety and a Process Model of Cognitive Emotion Regulation. *Journal of Cognitive Neuroscience*, 18(8), 1266–1276.

Kane, M. J., Bleckley, M. K., Conway, A. R. A., & Engle, R. W. (2001). A controlled-attention view of working-memory capacity. *Journal of Experimental Psychology: General*, 130(2), 169–183.

Kang, G., Jiang, B., & Cui, Y. (2013). Gene-based Genomewide Association Analysis: A Comparison Study. *Current Genomics*, 14(4), 250–255.

Karalunas, S. L., Bierman, K. L., & Huang-Pollock, C. L. (2016). Test-Retest Reliability and Measurement Invariance of Executive Function Tasks in Young Children With and Without ADHD. *Journal of Attention Disorders*, 1087054715627488. Advance online publication.

Karmiloff-Smith, A. (2006). The tortuous route from genes to behavior: A neuroconstructivist approach. *Cognitive, Affective, & Behavioral Neuroscience*, 6(1), 9–17.

Kievit, R. A., Davis, S. W., Griffiths, J., Correia, M. M., Cam-CAN, & Henson, R. N. (2016). A watershed model of individual differences in fluid intelligence. *Neuropsychologia*, 91, 186–198.

Kim, M. J., & Whalen, P. J. (2009). The Structural Integrity of an Amygdala-Prefrontal Pathway Predicts Trait Anxiety. *Journal of Neuroscience*, 29(37), 11614–11618.

Kim, M. J, Loucks, R. A., Palmer, A. L., Brown, A. C., Solomon, K. M., Marchante, A. N., & Whalen, P. J. (2011). The structural and functional connectivity of the amygdala: From normal emotion to pathological anxiety. *Behavioural Brain Research*, 223(2), 403–410.

Kirkpatrick, McGue, Iacono, Miller, & Basu. (2013). Results of a 'GWAS plus:' general cognitive ability is substantially heritable and massively polygenic. *PloS One*, 9(11), e112390–e112390.

Koch, K., Pauly, K., Kellermann, T., Seiferth, N. Y., Reske, M., Backes, V., … Habel, U. (2007). Gender differences in the cognitive control of emotion: An fMRI study. *Neuropsychologia*, 45(12), 2744–2754.

Kochanska, G., Murray, K. T., & Harlan, E. T. (2000). Effortful control in early childhood: Continuity and change, antecedents, and implications for social development. *Developmental Psychology*, 36(2), 220–232.

Kochanska, G., Philibert, R. A., & Barry, R. A. (2009). Interplay of genes and early mother–child relationship in the development of self-regulation from toddler to preschool age. *Journal of Child Psychology and Psychiatry*, 50(11), 1331–1338.

Kohn, N., Eickhoff, S. B., Scheller, M., Laird, A. R., Fox, P. T., & Habel, U. (2014). Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. *NeuroImage*, 87, 345–355.

Kong, A., Thorleifsson, G., Frigge, M. L., Vilhjalmsson, B. J., Young, A. I., Thorgeirsson, T. E., … Stefansson, K. (2018). The nature of nurture: Effects of parental genotypes. *Science*, 359(6374), 424–428.

Kong, S. W., Sahin, M., Collins, C. D., Wertz, M. H., Campbell, M. G., Leech, J. D., … Kohane, I. S. (2014). Divergent dysregulation of gene expression in murine models of fragile X syndrome and tuberous sclerosis. *Molecular Autism*, 5, 16.

Kovas, Y., Harlaar, N., Petrill, S. A., & Plomin, R. (2005). 'Generalist genes' and mathematics in 7-year-old twins. *Intelligence*, 33(5), 473–489.

Kovas, Y., & Plomin, R. (2006). Generalist genes: implications for the cognitive sciences. *Trends in Cognitive Sciences*, 10(5), 198–203.

Kovas, Y., & Plomin, R. (2007). Learning Abilities and Disabilities: Generalist Genes, Specialist Environments. Current Directions in Psychological Science, 16(5), 284–288.

Krapohl, E., Euesden, J., Zabaneh, D., Pingault, J.-B., Rimfeld, K., von Stumm, S., … Plomin, R. (2015). Phenome-wide analysis of genome-wide polygenic scores. *Molecular Psychiatry*, 21(9), 1188-1193.

Krapohl, E., Rimfeld, K., Shakeshaft, N. G., Trzaskowski, M., McMillan, A., Pingault, J.-B., … Plomin, R. (2014). The high heritability of educational achievement reflects many genetically influenced traits, not just intelligence. *Proceedings of the National Academy of Sciences,* 111(42), 15273–15278.

Kuntsi, J., Stevenson, J., Oosterlaan, J., & Sonuga-Barke, E. J. S. (2001). Test-retest reliability of a new delay aversion task and executive function measures. *British Journal of Developmental* Psychology, 19(3), 339–348.

Ladouceur, C. D., Diwadkar, V. A., White, R., Bass, J., Birmaher, B., Axelson, D. A., & Phillips, M. L. (2013). Fronto-limbic Function in Unaffected Offspring at Familial Risk for Bipolar Disorder during an Emotional Working Memory Paradigm. *Developmental Cognitive Neuroscience*, 5, 185–196.

Ladouceur, C. D., Silk, J. S., Dahl, R. E., Ostapenko, L., Kronhaus, D. M., & Phillips, M. L. (2009). Fearful faces influence attentional control processes in anxious youth and adults. *Emotion*, 9(6), 855–864.

Laidra, K., Pullmann, H., & Allik, J. (2007). Personality and intelligence as predictors of academic achievement: A cross-sectional study from elementary to secondary school. *Personality and Individual Differences*, 42(3), 441–451.

Lan, X., Legare, C. H., Ponitz, C. C., Li, S., & Morrison, F. J. (2011). Investigating the links between the subcomponents of executive function and academic achievement: A cross-cultural analysis of Chinese and American preschoolers. *Journal of Experimental Child Psychology*, 108(3), 677–692.

Lander, E. S., & Schork, N. J. (1994). Genetic Dissection of Complex Traits, *Science,* 265(5185), 2037-2048.

Lantrip, C., Isquith, P. K., Koven, N. S., Welsh, K., & Roth, R. M. (2016). Executive Function and Emotion Regulation Strategy Use in Adolescents. *Applied Neuropsychology: Child*, 5(1), 50–55.

Latzman, R. D., Elkovitch, N., Young, J., & Clark, L. A. (2010). The contribution of executive functioning to academic achievement among male adolescents. *Journal of Clinical and Experimental Neuropsychology*, 32(5), 455–462.

Laviola, G., Macrı`, S., Morley-Fletcher, S., & Adriani, W. (2003). Risk-taking behavior in adolescent mice: psychobiological determinants and early epigenetic influence. *Neuroscience & Biobehavioral Reviews*, 27(1–2), 19–31.

Lavric, A., Rippon, G., & Gray, J. R. (2003). Threat-Evoked Anxiety Disrupts Spatial Working Memory Performance: An Attentional Account. *Cognitive Therapy and Research*, 27, 5, 489-504.

Lee, H., Heller, A. S., van Reekum, C. M., Nelson, B., & Davidson, R. J. (2012). Amygdala–prefrontal coupling underlies individual differences in emotion regulation. *NeuroImage*, 62(3), 1575–1581.

Lee, J. J., Wedow, R., Okbay, A., Kong, E., Maghzian, O., Zacher, M., … Cesarini, D. (2018). Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nature Genetics*, 50(8), 1112-1121.

Lee, K., Bull, R., & Ho, R. M. H. (2013). Developmental Changes in Executive Functioning. *Child Development*, 84(6), 1933–1953.

Leeuw, C. A. de, Mooij, J. M., Heskes, T., & Posthuma, D. (2015). MAGMA: Generalized Gene-Set Analysis of GWAS Data. *PLOS Computational Biology*, 11(4), e1004219.

Lehto, J. E., Juujärvi, P., Kooistra, L., & Pulkkinen, L. (2003). Dimensions of executive functioning: Evidence from children. *British Journal of Developmental Psychology*, 21(1), 59–80.

Lesch, K.-P., Bengal, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., … Murphy, D. L. (1996). Association of Anxiety-Related Traits with a Polymorphism in the Serotonin Transporter Gene Regulatory Region. *Science*, 274(5292), 1527–1531.

Lewis, M., Stanger, C., & Sullivan, M. W. (1989). Deception in 3-year-olds. *Developmental Psychology*, 25(3), 439.

Li, C. R., Huang, C., Yan, P., Bhagwagar, Z., Milivojevic, V., & Sinha, R. (2008). Neural Correlates of Impulse Control During Stop Signal Inhibition in Cocaine-Dependent Men. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, 33(8), 1798–1806.

Li, C. R., Milivojevic, V., Kemp, K., Hong, K., & Sinha, R. (2006). Performance monitoring and stop signal inhibition in abstinent patients with cocaine dependence. *Drug and Alcohol Dependence,* 85(3), 205–212.

Li, Q. S., Parrado, A. R., Samtani, M. N., Narayan, V. A., & Alzheimer's Disease Neuroimaging Initiative. (2015). Variations in the FRA10AC1 Fragile Site and 15q21 Are Associated with Cerebrospinal Fluid Aβ1-42 Level. *PloS One*, 10(8), e0134000.

Lijffijt, M., Kenemans, J. L., Verbaten, M. N., & van Engeland, H. (2005). A meta-analytic review of stopping performance in attention-deficit/hyperactivity disorder: deficient inhibitory motor control? *Journal of Abnormal Psychology*, 114(2), 216–222.

Liu, X., Akula, N., Skup, M., Brotman, M. A., Leibenluft, E., & McMahon, F. J. (2010). A Genome-Wide Association Study of Amygdala Activation in Youths With and Without Bipolar Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 49(1), 33–41.

Logan, G. D., & Cowan, W. B. (1984). On the ability to inhibit thought and action: A theory of an act of control. *Psychological Review*, 91(3), 295.

Lopez, C., Stahl, D., & Tchanturia, K. (2010). Estimated intelligence quotient in anorexia nervosa: a systematic review and meta-analysis of the literature. *Annals of General Psychiatry*, 9, 40.

Luciano, H., Davies, Medland, Räikkönen, Tenesa, Widen, … Deary. (2011). Whole genome association scan for genetic polymorphisms influencing information processing speed. *Biological Psychology*, 86(3), 193–202.

Luna, B., Marek, S., Larsen, B., Tervo-Clemmens, B., & Chahal, R. (2015). An Integrative Model of the Maturation of Cognitive Control. *Annual Review of Neuroscience*, 38(1), 151–170.

Lynn, R., & Mikk, J. (2007). National differences in intelligence and educational attainment. *Intelligence*, 35(2), 115–121.

Manolio, T. A., Collins, F. S., Cox, N. J., Goldstein, D. B., Hindorff, L. A., Hunter, D. J., … Visscher, P. M. (2009). Finding the missing heritability of complex diseases. *Nature, 461(7265), 747–753.*

Mantella, R. C., Butters, M. A., Dew, M. A., Mulsant, B. H., Begley, A. E., Tracey, B., … Lenze, E. J. (2007). Cognitive Impairment in Late-Life Generalized Anxiety Disorder. *The American Journal of Geriatric Psychiatry,* 15(8), 673–679.

Marchini, J., Howie, B., Myers, S., McVean, G., & Donnelly, P. (2007). A new multipoint method for genome-wide association studies by imputation of genotypes. *Nature Genetics*, 39(7), 906–913.

Marks, M., Pennimpede, T., Lange, L., Grote, P., Herrmann, B. G., & Wittler, L. (2016). Analysis of the Fam181 gene family during mouse development reveals distinct strain-specific expression patterns, suggesting a role in nervous system development and function. *Gene*, 575(2), 438–451.

Martel, M. M., Pan, P. M., Hoffmann, M. S., Gadelha, A., do Rosário, M. C., Mari, J. J., … Salum, G. A. (2017). A general psychopathology factor (P factor) in children: Structural model analysis and external validation through familial risk and child global executive function. *Journal of Abnormal Psychology,* 126(1), 137–148.

Martin, J., Hamshere, M. L., Stergiakouli, E., O'Donovan, M. C., & Thapar, A. (2014). Neurocognitive abilities in the general population and composite genetic risk scores for attention-deficit hyperactivity disorder. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 56(6), 648-656.

Masten, A. S., Roisman, G. I., Long, J. D., Burt, K. B., Obradović, J., Riley, J. R., … Tellegen, A. (2005). Developmental Cascades: Linking Academic Achievement and Externalizing and Internalizing Symptoms Over 20 Years. *Developmental Psychology*, 41(5), 733–746.

Mazzocco, M. M. M., & Kover, S. T. (2007). A Longitudinal Assessment of Executive Function Skills and Their Association with Math Performance. *Child Neuropsychology*, 13(1), 18–45.

McAuley, T., & White, D. (2011). A Latent Variables Examination of Processing Speed, Response Inhibition, and Working Memory during Typical Development. *Journal of Experimental Child Psychology*, 108(3), 453–468.

McGivern, R. F., Andersen, J., Byrd, D., Mutter, K. L., & Reilly, J. (2002). Cognitive efficiency on a match to sample task decreases at the onset of puberty in children. *Brain and Cognition*, 50(1), 73–89.

McLaughlin, K. A., & Nolen-Hoeksema, S. (2011). Rumination as a transdiagnostic factor in depression and anxiety. *Behaviour Research and Therapy*, 49(3), 186–193.

McRae, K., Gross, J. J., Weber, J., Robertson, E. R., Sokol-Hessner, P., Ray, R. D., … Ochsner, K. N. (2012). The development of emotion regulation: an fMRI study of cognitive reappraisal in children, adolescents and young adults. *Social Cognitive and Affective Neuroscience*, 7(1), 11–22.

McRae, K., Hughes, B., Chopra, S., Gabrieli, J. D. E., Gross, J. J., & Ochsner, K. N. (2010). The Neural Bases of Distraction and Reappraisal. *Journal of Cognitive Neuroscience*, 22(2), 248–262.

McRae, K., Jacobs, S. E., Ray, R. D., John, O. P., & Gross, J. J. (2012). Individual differences in reappraisal ability: Links to reappraisal frequency, well-being, and cognitive control. *Journal of Research in Personality*, 46(1), 2–7.

Mesman, J., Bongers, I. L., & Koot, H. M. (2001). Preschool developmental pathways to preadolescent internalizing and externalizing problems. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, 42(5), 679-689.

Messer, S. C., Angold, A., Costello, E. J., Loeber, R., & et al. (1995). Development of a short questionnaire for use in epidemiological studies of depression in children and

adolescents: Factor composition and structure across development. International *Journal of Methods in Psychiatric Research*, 5(4), 251–262.

Mick, E., McGough, J., Deutsch, C. K., Frazier, J. A., Kennedy, D., & Goldberg, R. J. (2014). Genome-Wide Association Study of Proneness to Anger. *PLoS ONE*, 9(1), e87257.

Mills, K. L., Goddings, A.-L., Clasen, L. S., Giedd, J. N., & Blakemore, S.-J. (2014). The developmental mismatch in structural brain maturation during adolescence. *Developmental Neuroscience*, 36(3–4), 147–160.

Mills, K. L., Goddings, A.-L., Herting, M. M., Meuwese, R., Blakemore, S.-J., Crone, E. A., … Tamnes, C. K. (2016). Structural brain development between childhood and adulthood: Convergence across four longitudinal samples. *NeuroImag*e, 141, 273–281.

Miyake, A., & Friedman, N. P. (2012). The Nature and Organization of Individual Differences in Executive Functions: Four General Conclusions. *Current Directions in Psychological Science*, 21(1), 8–14.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. *Cognitive Psychology*, 41(1), 49–100.

Moilanen, K. L., Shaw, D. S., & Maxwell, K. L. (2010). Developmental cascades: Externalizing, internalizing, and academic competence from middle childhood to early adolescence. *Development and Psychopathology*, 22(3), 635–653.

Monette, S., Bigras, M., & Guay, M.-C. (2011). The role of the executive functions in school achievement at the end of Grade 1. *Journal of Experimental Child Psychology*, 109(2), 158–173.

Munakata, Y., Herd, S. A., Chatham, C. H., Depue, B. E., Banich, M. T., & O'Reilly, R. C. (2011). A unified framework for inhibitory control. *Trends in Cognitive Sciences*, 15(10), 453–459.

NCBI, (2018, June), Retrieved from https://www.ncbi.nlm.nih.gov/gene

Nelson, J. R., Benner, G. J., Lane, K., & Smith, B. W. (2004). Academic Achievement of K-12 Students with Emotional and Behavioral Disorders. *Exceptional Children*, 71(1), 59–73.

Neumann, A. (2010). Affect dysregulation and adolescent psychopathology in the family context. Amsterdam: Vrije Universiteit.

Nigg, J. T. (2000). On inhibition/disinhibition in developmental psychopathology: Views from cognitive and personality psychology and a working inhibition taxonomy. *Psychological Bulletin*, 126(2), 220–246.

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of Abnormal Psychology*, 109(3), 504–511.

Nolen-Hoeksema, S., & Watkins, E. R. (2011). A Heuristic for Developing Transdiagnostic Models of Psychopathology: Explaining Multifinality and Divergent Trajectories. *Perspectives on Psychological Science*, 6(6), 589–609.

Northstone, K., Joinson, C., Emmett, P., Ness, A., & Paus, T. (2012). Are dietary patterns in childhood associated with IQ at 8 years of age? A population-based cohort study. *Journal of Epidemiology and Community Health*, 66(7), 624–628.

Novara, F., Rizzo, A., Bedini, G., Girgenti, V., Esposito, S., Pantaleoni, C., … Estienne, M. (2013). MEF2C deletions and mutations versus duplications: a clinical comparison. *European Journal of Medical Genetics*, 56(5), 260–265.

Novembre, J., Johnson, T., Bryc, K., Kutalik, Z., Boyko, A. R., Auton, A., … & Stephens, M. (2008). Genes mirror geography within Europe. *Nature*, *456*(7218), 98.

Nowicki, S., Strickand, J., & Bonnie, R. (1971). A Locus of Control Scale for Children. *Presented at the 79th Annual Convention of the American Psychological Association,* Washington D.C.

OATS Research Team, Lee, T., Mosing, M. A., Henry, J. D., Trollor, J. N., Ames, D., … Sachdev, P. S. (2012). Genetic Influences on Four Measures of Executive Functions and Their Covariation with General Cognitive Ability: The Older Australian Twins Study. *Behavior Genetics*, 42(4), 528–538.

Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. E. (2002). Rethinking Feelings: An fMRI Study of the Cognitive Regulation of Emotion. *Journal of Cognitive Neuroscience,* 14(8), 1215–1229.

Ochsner, K N., Silvers, J. A., & Buhle, J. T. (2012). Functional imaging studies of emotion regulation: A synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences*, 1251, E1-24.

O'Conner, M., & Paunonen, S. (2007). Big Five personality predictors of post-secondary academic performance. *Personality and Individual Differences*, 43(5), 971–990.

Ogilvie, J. M., Stewart, A. L., Chan, R. C. K., & Shum, D. H. K. (2011). Neuropsychological Measures of Executive Function and Antisocial Behavior: A Meta-Analysis. *Criminology*, 49(4), 1063–1107.

Okbay, A., Baselmans, B. M. L., De Neve, J.-E., Turley, P., Nivard, M. G., Fontana, M. A., … Cesarini, D. (2016). Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nature Genetics,* 48(6), 624–633.

Okbay, A., Beauchamp, J. P., Fontana, M. A., Lee, J. J., Pers, T. H., Rietveld, C. A., … Benjamin, D. J. (2016). Genome-wide association study identifies 74 loci associated with educational attainment. *Nature*, 533(7604), 539–542.

OPCS. (1990). Standard Occupational Classification. London: Her Majesty's Stationary Office.

Otowa, T., Hek, K., Lee, M., Byrne, E. M., Mirza, S. S., Nivard, M. G., … Hettema, J. M. (2016). Meta-analysis of genome-wide association studies of anxiety disorders. *Molecular Psychiatry*, 21(10), 1391–1399.

Papassotiropoulos, H., Stefanova, A., Müller, A., Demougin, P., … de Quervain. (2011). A genome-wide survey of human short-term memory. *Molecular Psychiatry*, 16(2), 184–192.

Pappa, I., St Pourcain, B., Benke, K., Cavadino, A., Hakulinen, C., Nivard, M. G., … Tiemeier, H. (2016). A genome-wide approach to children's aggressive behavior: The EAGLE consortium. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*, 171(5), 562–572.

Parihar, R., & Ganesh, S. (2013). The SCN1A gene variants and epileptic encephalopathies. *Journal of Human Genetics*, 58(9), 573–580.

Patterson, G. R., & Capaldi, D. . (1990). A mediational model for boys' depressed mood. In J. Rolf & A. S. Masten (Eds.), *Risk and protective factors in the development of psychopathology* (pp. 141–163). New York: Cambridge University Press.

Pe, M. L., Raes, F., & Kuppens, P. (2013). The Cognitive Building Blocks of Emotion Regulation: Ability to Update Working Memory Moderates the Efficacy of Rumination and Reappraisal on Emotion. *PLOS ONE*, 8(7), e69071.

Petanjek, Z., Judas, M., Simic, G., Rasin, M. R., Uylings, H. B. M., Rakic, P., & Kostovic, I. (2011). Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proceedings of the National Academy of Sciences*, 108(32), 13281–13286.

Pfeifer, J. H., & Allen, N. B. (2012). Arrested development? Reconsidering dual-systems models of brain function in adolescence and disorders. *Trends in Cognitive Sciences*, 16(6), 322–329.

Philippot, P., & Brutoux, F. (2008). Induced rumination dampens executive processes in dysphoric young adults. *Journal of Behavior Therapy and Experimental Psychiatry*, 39(3), 219–227.

Plomin, R., DeFries, J. C., McClearn, G. E., & Rutter, M. (1997). Behavioral genetics. *Behavioral Genetics*., (Ed. 3). WH Freeman and Co..

Plomin, R., DeFries, J. C., Knopik, V. S., & Neiderhiser, J. M. (2016). Top 10 Replicated Findings From Behavioral Genetics. *Perspectives on Psychological Science*, 11(1), 3–23.

Polderman, T. J. C., Posthuma, D., De Sonneville, L. M. J., Stins, J. F., Verhulst, F. C., & Boomsma, D. I. (2007). Genetic analyses of the stability of executive functioning during childhood. *Biological Psychology*, 76(1–2), 11–20.

Posner, M. I., & Rothbart, M. (2000). Developing mechanisms of self-regulation. *Development and Psychopathology*, 12(3), 427–441.

Prencipe, A., Kesek, A., Cohen, J., Lamm, C., Lewis, M. D., & Zelazo, P. D. (2011). Development of hot and cool executive function during the transition to adolescence. *Journal of Experimental Child Psychology*, 108(3), 621–637.

Price, A. L., Patterson, N. J., Plenge, R. M., Weinblatt, M. E., Shadick, N. A., & Reich, D. (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics,* 38(8), 904–909.

Price, A. L., Weale, M. E., Patterson, N., Myers, S. R., Need, A. C., Shianna, K. V., … Reich, D. (2008). Long-Range LD Can Confound Genome Scans in Admixed Populations. *American Journal of Human Genetics*, 83(1), 132–135.

Protopapas, A., Archonti, A., & Skaloumbakas, C. (2007). Reading ability is negatively related to Stroop interference. *Cognitive Psychology*, 54(3), 251–282.

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A. R., Bender, D., … Sham, P. C. (2007). PLINK: a tool set for whole-genome association and population-based linkage analyses. *American Journal of Human Genetics*, 81(3), 559–575.

Purves, K. L., Coleman, J. R. I., Rayner, C., Hettema, J. M., Deckert, J., McIntosh, A. M., … Eley, T. C. (2017). The Common Genetic Architecture of Anxiety Disorders. *BioRxiv*, 203844.

R Core Team. (2013). R: A language and environment for statistical computing. *R Foundation for Statistical Computing*. Vienna, Austria.

Rabbitt, P. (2004). Introduction: Methodologies and models in the study of executive function. In *Methodology of Frontal and Executive Function* (pp. 9-45). Routledge.

Rajchert, J., Zoltak, T., & Smulczyk, M. (2013). Trait-anxiety's moderating role in predicting academic performance improvement in PISA. *Polish Journal of Applied Psychology*, 11(3), 73–92.

Reardon, S. F. (2011). The widening academic achievement gap between the rich and the poor: New evidence and possible explanations. *Whither Opportunity*, 91–116.

Reed, E., Nunez, S., Kulp, D., Qian, J., Reilly, M. P., & Foulkes, A. S. (2015). A guide to genome-wide association analysis and post-analytic interrogation. *Statistics in Medicine*, 34(28), 3769–3792.

Reiss, S., Peterson, R. A., Gursky, D. M., & McNally, R. J. (1986). Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behaviour Research and Therapy*, 24(1), 1–8.

Revelle, W. (2018). psych: Procedures for Personality and Psychological Research. Northwestern University, Evanston, Illinois, USA.

Rhodes, S. M., Booth, J. N., Palmer, L. E., Blythe, R. A., Delibegovic, M., & Wheate, N. J. (2016). Executive functions predict conceptual learning of science. *British Journal of Developmental Psychology,* 34(2), 261–275.

Rietveld, C. A., Medland, S. E., Derringer, J., Yang, J., Esko, T., Martin, N. W., … Koellinger, P. D. (2013). GWAS of 126,559 Individuals Identifies Genetic Variants Associated with Educational Attainment. *Science*, 340(6139), 1467–1471.

Rimfeld, K., Kovas, Y., Dale, P. S., & Plomin, R. (2015). Pleiotropy across academic subjects at the end of compulsory education. *Scientific Reports*, 5, 111713.

Rimfeld, K., Kovas, Y., Dale, P. S., & Plomin, R. (2016). True grit and genetics: Predicting academic achievement from personality. *Journal of Personality and Social Psychology*, 111(5), 780–789.

Risi, S., Gerhardstein, R., & Kistner, J. (2003). Children's classroom peer relationships and subsequent educational outcomes. *Journal of Clinical Child and Adolescent Psychology: The Official Journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association*, Division 53, 32(3), 351–361.

Robbins, T. W., & Arnsten, A. F. T. (2009). The Neuropsychopharmacology of Fronto-Executive Function: Monoaminergic Modulation. *Annual Review of Neuroscience*, 32(1), 267–287.

Robertson, I., Ward, T., Ridgeway, V., & Nimmo-Smith, I. (1996). The structure of normal human attention: The Test of Everyday Attention. *Journal of the International Neuropsychological Society*, 2(6), 525–534.

Rocha, H., Sampaio, M., Rocha, R., Fernandes, S., & Leão, M. (2016). MEF2C haploinsufficiency syndrome: Report of a new MEF2C mutation and review. European *Journal of Medical Genetics,* 59(9), 478–482.

Rosenberg, M. (1965). The measurement of self-esteem. Society and the Adolescent Self Image, 307, 297.

Rosenberg, M. (2015). Society and the Adolescent Self-Image. Princeton University Press.

Rosseel, Y. (2012). lavaan: An R Package for Structural Equation Modelling. *Journal of Statistical Software,* 2(48), 1–36.

Roth, B., Becker, N., Romeyke, S., Schäfer, S., Domnick, F., & Spinath, F. M. (2015). Intelligence and school grades: A meta-analysis. *Intelligence*, 53, 118–137.

Rothbart, M. K., Derryberry, D., Posner, M. I., & others. (1994). A psychobiological approach to the development of temperament. *Temperament: Individual Differences at the Interface of Biology and Behavior*, 83–116.

Saarni, C. (1984). An Observational Study of Children's Attempts to Monitor Their Expressive Behavior. *Child Development*, 55(4), 1504–1513.

Salvatore, J. E., Aliev, F., Bucholz, K., Agrawal, A., Hesselbrock, V., Hesselbrock, M., … Dick, D. M. (2015). Polygenic risk for externalizing disorders: Gene-by-development and gene-by-environment effects in adolescents and young adults. *Clinical Psychological Science: A Journal of the Association for Psychological Science*, 3(2), 189–201.

Sari, B. A., Koster, E. H. W., Pourtois, G., & Derakshan, N. (2016). Training working memory to improve attentional control in anxiety: A proof-of-principle study

using behavioral and electrophysiological measures. *Biological Psychology*, 121, 203–212.
Schafer, J. L., & Graham, J. W. (2002). Missing data: Our view of the state of the art. *Psychological Methods*, 7(2), 147–177.
Schmeichel, B. J., Volokhov, R. N., & Demaree, H. A. (2008). Working memory capacity and the self-regulation of emotional expression and experience. *Journal of Personality and Social Psychology*, 95(6), 1526–1540.
Sebastian, C. L., Burnett, S., & Blakemore, S.-J. (2008). Development of the self-concept during adolescence. *Trends in Cognitive Sciences*, 12(11), 441–446.
Sebastian, C. L., Fontaine, N. M. G., Bird, G., Blakemore, S.-J., De Brito, S. A., McCrory, E. J. P., & Viding, E. (2012). Neural processing associated with cognitive and affective Theory of Mind in adolescents and adults. *Social Cognitive and Affective Neuroscience*, 7(1), 53–63.
Sebastian, C. L., McCrory, E. J., Cecil, C. A., Lockwood, P. L., De Brito, S. A., Fontaine, N. M., & Viding, E. (2012). Neural responses to affective and cognitive theory of mind in children with conduct problems and varying levels of callous-unemotional traits. *Archives of General Psychiatry*, 69(8), 814–822.
Sebastian, C. L., Tan, G. C. Y., Roiser, J. P., Viding, E., Dumontheil, I., & Blakemore, S.-J. (2011). Developmental influences on the neural bases of responses to social rejection: Implications of social neuroscience for education. *NeuroImage*, 57(3), 686–694.
Sebastian, C. L., Viding, E., Williams, K. D., & Blakemore, S.-J. (2010). Social brain development and the affective consequences of ostracism in adolescence. *Brain and Cognition*, 72(1), 134–145.
Shaffer, D., Fisher, P., Lucas, C. P., Dulcan, M. K., & Schwab-stone, M. E. (2000). NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): Description, Differences From Previous Versions, and Reliability of Some Common Diagnoses. *Journal of the American Academy of Child & Adolescent Psychiatry*, 39(1), 28–38.
Shakeshaft, N. G., Trzaskowski, M., McMillan, A., Rimfeld, K., Krapohl, E., Haworth, C. M. A., … Plomin, R. (2013). Strong Genetic Influence on a UK Nationwide Test of Educational Achievement at the End of Compulsory Education at Age 16. *PLoS ONE*, 8(12), e80341.
Shakespeare, W. (2001). *The Winter's Tale*. Classic Books Company.
Shields, A., & Cicchetti, D. (1997). Emotion regulation among school-age children: The development and validation of a new criterion Q-sort scale. *Developmental Psychology*, 33(6), 906–916.
Shimi, A., & Scerif, G. (2017). Towards an integrative model of visual short-term memory maintenance: Evidence from the effects of attentional control, load, decay, and their interactions in childhood. *Cognition*, 169, 61–83.
Simpson, P. M., Surmon, D. J., Wesnes, K. A., & Wilcock, G. K. (1991). The cognitive drug research computerized assessment system for demented patients: A validation study. *International Journal of Geriatric Psychiatry*, 6(2), 95–102.
Sirin, S. R. (2005). Socioeconomic Status and Academic Achievement: A Meta-Analytic Review of Research. *Review of Educational Research*, 75(3), 417–453.
Skuse, D. H., James, R. S., Bishop, D. V. M., Coppin, B., Dalton, P., Aamodt-Leeper, G., … Jacobs, P. A. (1997). Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature,* 387(6634), 705–708.

Slavin, R., & Smith, D. (2009). The Relationship between Sample Sizes and Effect Sizes in Systematic Reviews in Education. *Educational Evaluation and Policy Analysis*, 31(4), 500–506.

Smith, D. J., McVie, S., Woodward, R., Shute, J., & McAra, L. (2001). The Edinburgh Study of Youth Transitions and Crime: Key Findings at Ages 12 and 13. *British Journal of Criminology*, 43, 169-195.

Sniekers, S., Stringer, S., Watanabe, K., Jansen, P. R., Coleman, J. R. I., Krapohl, E., … Posthuma, D. (2017). Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. *Nature Genetics*, 49(7), 1107–1112.

Snyder, H. R. (2013). Major Depressive Disorder is Associated with Broad Impairments on Neuropsychological Measures of Executive Function: A Meta-Analysis and Review. *Psychological Bulletin*, 139(1), 81–132.

Snyder, H. R., Hutchison, N., Nyhus, E., Curran, T., Banich, M. T., O'Reilly, R. C., & Munakata, Y. (2010). Neural inhibition enables selection during language processing. *Proceedings of the National Academy of Sciences*, 201002291.

Snyder, H. R., Miyake, A., & Hankin, B. L. (2015). Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. *Frontiers in Psychology*, 6, 328.

Solomon, S. R., & Sawilowsky, S. S. (2009). Impact of rank-based normalizing transformations on the accuracy of test scores. *Journal of Modern Applied Statistical Methods*, 8(2), 9.

Sowell, E. R., Trauner, D. A., Gamst, A., & Jernigan, T. L. (2002). Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. *Developmental Medicine and Child Neurology*, 44(1), 4–16.

Spear, L. P., & Varlinskaya, E. I. (2010). Sensitivity to ethanol and other hedonic stimuli in an animal model of adolescence: implications for prevention science? *Developmental Psychobiology*, 52(3), 236–243.

Spielberger, C. D., & Gorsuch, R. L. (1966). The development of the state-trait anxiety inventory. *Mediating Processes in Verbal Conditioning*, 8–43.

St Clair-Thompson, H. L., & Gathercole, S. E. (2006). Executive functions and achievements in school: Shifting, updating, inhibition, and working memory. *The Quarterly Journal of Experimental Psychology*, 59(4), 745–759.

Steinberg, L. & Morris, A. S., (2001). Adolescent development. *Annual review of psychology*, 52(1),83-110.

Steinberg, L. (2005). Cognitive and affective development in adolescence. *Trends in Cognitive Sciences*, 9(2), 69–74.

Steinberg, L. (2008). A social neuroscience perspective on adolescent risk-taking. *Developmental Review*, 28(1), 78–106.

Stipek, D., & Valentino, R. (2015). Early childhood memory and attention as predictors of academic growth trajectories. *Journal of Educational Psychology*, 107(3), 71.

Straus, M. A. (1979). Measuring Intrafamily Conflict and Violence: The Conflict Tactics (CT) Scales. *Journal of Marriage and Family*, 41(1), 75–88.

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Oxford University Press.

Sturman, D. A., & Moghaddam, B. (2011). The neurobiology of adolescence: Changes in brain architecture, functional dynamics, and behavioral tendencies. *Neuroscience & Biobehavioral Reviews*, 35(8), 1704–1712.

Sung, S. S., Brassington, A.-M. E., Grannatt, K., Rutherford, A., Whitby, F. G., Krakowiak, P. A., … Bamshad, M. (2003). Mutations in genes encoding fast-twitch contractile proteins cause distal arthrogryposis syndromes. *American Journal of Human Genetics*, 72(3), 681–690.

Swart, M., Bruggeman, R., Larøi, F., Alizadeh, B. Z., Kema, I., Kortekaas, R., … Aleman, A. (2011). COMT Val158Met polymorphism, verbalizing of emotion and activation of affective brain systems. *NeuroImage*, 55(1), 338–344.

Tang, S.-S., Wang, H.-F., Zhang, W., Kong, L.-L., Zheng, Z.-J., Tan, M.-S., … Tan, L. (2016). MEF2C rs190982 polymorphism with late-onset Alzheimer's disease in Han Chinese: A replication study and meta-analyses. *Oncotarget*, 7(26), 39136–39142.

Tennant, R., Hiller, L., Fishwick, R., Platt, S., Joseph, S., Weich, S., … Stewart-Brown, S. (2007). The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation. *Health and Quality of Life Outcomes*, 5(63).

Tillfors, M., Persson, S., Willén, M., & Burk, W. J. (2012). Prospective links between social anxiety and adolescent peer relations. *Journal of Adolescence*, 35(5), 1255–1263.

Tosto, M. G., Malykh, S., Voronin, I., Plomin, R., & Kovas, Y. (2013). The Etiology of Individual Differences in Maths beyond IQ: Insights from 12-year Old Twins. Procedia - Social and *Behavioral Sciences*, 86, 429–434.

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., … Nelson, C. (2009). The NimStim set of facial expressions: Judgments from untrained research participants. *Psychiatry Research*, 168(3), 242–249.

Toydemir, R. M., & Bamshad, M. J. (2009). Sheldon-Hall syndrome. *Orphanet Journal of Rare Diseases,* 4(1), 11.

Trampush, J. W., Yang, M. L. Z., Yu, J., Knowles, E., Davies, G., Liewald, D. C., … Lencz, T. (2017). GWAS meta-analysis reveals novel loci and genetic correlates for general cognitive function: a report from the COGENT consortium. *Molecular Psychiatry*, 22(3), 336–345.

Trampush, J. W., Lencz, T., Knowles, E., Davies, G., Guha, S., Pe'er, I., … Malhotra, A. K. (2015). Independent evidence for an association between general cognitive ability and a genetic locus for educational attainment: Genetic Overlap Between Cognition and Education. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 168(5), 363–373.

Trzaskowski, M., Eley, T. C., Davis, O. S. P., Doherty, S. J., Hanscombe, K. B., Meaburn, E. L., … Plomin, R. (2013). First Genome-Wide Association Study on Anxiety-Related Behaviours in Childhood. *PLOS ONE*, 8(4), e58676.

Tsermentseli, S., & Poland, S. (2016). Cool versus hot executive function: A new approach to executive function. *Encephalos*, 53(1), 11-14.

Uhlén, M., Fagerberg, L., Hallström, B. M., Lindskog, C., Oksvold, P., Mardinoglu, A., … Pontén, F. (2015). Tissue-based map of the human proteome. *Science*, 347(6220), 1260419.

Urry, H. L., Reekum, C. M. van, Johnstone, T., Kalin, N. H., Thurow, M. E., Schaefer, H. S., … Davidson, R. J. (2006). Amygdala and Ventromedial Prefrontal Cortex Are Inversely Coupled during Regulation of Negative Affect and Predict the Diurnal Pattern of Cortisol Secretion among Older Adults. *Journal of Neuroscience,* 26(16), 4415–4425.

van der Valk, J. C., Verhulst, F. C., Stroet, T. M., & Boomsma, D. I. (1998). Quantitative genetic analysis of internalising and externalising problems in a large sample of 3-

year-old twins. *Twin Research: The Official Journal of the International Society for Twin Studies*, 1(1), 25–33.

Van Dillen, L. F., Heslenfeld, D. J., & Koole, S. L. (2009). Tuning down the emotional brain: an fMRI study of the effects of cognitive load on the processing of affective images. *NeuroImage*, 45(4), 1212–1219.

Verbruggen, F., & Logan, G. D. (2009). Proactive adjustments of response strategies in the stop-signal paradigm. *Journal of Experimental Psychology. Human Perception and Performance,* 35(3), 835–854.

Verhulst, F.C., & Boomsma, D. I. (2003). Genetic and environmental contributions to stability and change in children's internalizing and externalizing problems. *Journal of the American Academy of Child and Adolescent Psychiatry,* 42(10) (pp. 1212–1220).

Verma, S. S., de Andrade, M., Tromp, G., Kuivaniemi, H., Pugh, E., Namjou-Khales, B., … Ritchie, M. D. (2014). Imputation and quality control steps for combining multiple genome-wide datasets. *Frontiers in Genetics*, 5, 370.

Verweij, K. J. H., Zietsch, B. P., Medland, S. E., Gordon, S. D., Benyamin, B., Nyholt, D. R., … Wray, N. R. (2010). A genome-wide association study of Cloninger's Temperament scales: Implications for the evolutionary genetics of personality. *Biological Psychology*, 85(2), 306–317.

Viding, E., Sebastian, C. L., Dadds, M. R., Lockwood, P. L., Cecil, C. A. M., De Brito, S. A., & McCrory, E. J. (2012). Amygdala Response to Preattentive Masked Fear in Children With Conduct Problems: The Role of Callous-Unemotional Traits. *American Journal of Psychiatry,* 169(10), 1109-1116.

Vijayakumar, N., Whittle, S., Dennison, M., Yücel, M., Simmons, J., & Allen, N. B. (2014). Development of temperamental effortful control mediates the relationship between maturation of the prefrontal cortex and psychopathology during adolescence: A 4-year longitudinal study. *Developmental Cognitive Neuroscience*, 9, 30–43.

Visscher, P. M., Brown, M. A., McCarthy, M. I., & Yang, J. (2012). Five Years of GWAS Discovery. *The American Journal of Human Genetics*, 90(1), 7–24.

Vogel, A. C., Power, J. D., Petersen, S. E., & Schlaggar, B. L. (2010). Development of the Brain's Functional Network Architecture. *Neuropsychology Review*, 20(4) 362-375.

Vogler, C., Gschwind, L., Coynel, D., Freytag, V., Milnik, A., Egli, T., … Papassotiropoulos, A. (2014). Substantial SNP-based heritability estimates for working memory performance. *Translational Psychiatry, 4(*9), e438.

Vriezen, E. R., & Pigott, S. E. (2002). The Relationship Between Parental Report on the BRIEF and Performance-Based Measures of Executive Faction in Children with Moderate to Severe Traumatic Brain Injury. *Child Neuropsychology*, *8*(4), 296.

Wahlstrom, D., Collins, P., White, T., & Luciana, M. (2010). Developmental changes in dopamine neurotransmission in adolescence: Behavioral implications and issues in assessment. *Brain and Cognition*, *72(*1), 146–159.

Wang, M., & Saudino, K. J. (2013). Genetic and environmental influences on individual differences in emotion regulation and its relation to working memory in toddlerhood. *Emotion*, *13*(6), 1055–1067.

Wang, Z., Hart, S. A., Kovas, Y., Lukowski, S., Soden, B., Thompson, L. A., … Petrill, S. A. (2014). Who is afraid of math? Two sources of genetic variance for mathematical anxiety. *Journal of Child Psychology and Psychiatry, 55*(9), 1056–1064.

Wang, Z., Lukowski, S. L., Hart, S. A., Lyons, I. M., Thompson, L. A., Kovas, Y., … Petrill, S. A. (2015). Is Math Anxiety Always Bad for Math Learning? The Role of Math Motivation. *Psychological Science, 26*(12), 1863–1876.

Watanabe, K., Taskesen, E., Bochoven, A. van, & Posthuma, D. (2017). Functional mapping and annotation of genetic associations with FUMA. *Nature Communications*, *8*(1), 1826.

Watts, T. W., Duncan, G. J., & Quan, H. (2018). Revisiting the Marshmallow Test: A Conceptual Replication Investigating Links Between Early Delay of Gratification and Later Outcomes. *Psychological Science*, *29*(7), 1159–1177.

Wechsler, D. (1999). Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation: Harcourt Brace & Company. New York, NY.

Weissman, A. N. (1979). The Dysfunctional Attitude Scale: A Validation Study. Publicly Accessible Penn Dissertations. Retrieved from https://repository.upenn.edu/edissertations/1182

Wendelken, C., Baym, C. L., Gazzaley, A., & Bunge, S. A. (2011). Neural indices of improved attentional modulation over middle childhood. *Developmental Cognitive Neuroscience*, *1*(2), 175–186.

West, P., Sweeting, H., & Young, R. (2010). Transition matters: pupils' experiences of the primary–secondary school transition in the West of Scotland and consequences for well-being and attainment. *Research Papers in Education*, *25*(1), 21–50.

Westermann, G., Mareschal, D., Johnson, M. H., Sirois, S., Spratling, M. W., & Thomas, M. S. C. (2007). Neuroconstructivism. *Developmental Science*, *10*(1), 75–83.

Whalen, P. J., & Davis, M. (2001). The amygdala: vigilance and emotion. *Molecular Psychiatry*, *6*, 13–34.

White, I. R., Royston, P., & Wood, A. M. (2011). Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in Medicine, 30*(4), 377–399.

Whitmer, A. J., & Banich, M. T. (2007). Inhibition versus switching deficits in different forms of rumination. *Psychological Science, 18*(6), 546–553.

Whitmer, A. J., & Gotlib, I. H. (2012). Switching and backward inhibition in major depressive disorder: the role of rumination. Journal of Abnormal Psychology, *121*(3), 570–578.

Wiebe, S. A., Espy, K. A., & Charak, D. (2008). Using confirmatory factor analysis to understand executive control in preschool children: I. Latent structure. *Developmental Psychology, 44*(2), 575.

Wiebe, S. A., Sheffield, T., Nelson, J. M., Clark, C. A. C., Chevalier, N., & Espy, K. A. (2011). The structure of executive function in 3-year-old children. *Journal of Experimental Child Psychology*, 108(3), 436–452.

Wolke, D., Woods, S., Stanford, K., & Schulz, H. (2001). Bullying and victimization of primary school children in England and Germany: prevalence and school factors. *British Journal of Psychology*, *92*(4), 673–696.

Wray, N. R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E. M., Abdellaoui, A., … Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics*, *50*(5), 668–681.

Yang, J., Lee, S. H., Goddard, M. E., & Visscher, P. M. (2011). GCTA: A Tool for Genome-wide Complex Trait Analysis. *American Journal of Human Genetics*, *88*(1), 76–82.

Yang, T. T., Simmons, A. N., Matthews, S. C., Tapert, S. F., Frank, G. K., Max, J. E., … Paulus, M. P. (2010). Adolescents With Major Depression Demonstrate Increased Amygdala Activation. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(1), 42–51.

Yap, M. B. H., Allen, N. B., & Sheeber, L. (2007). Using an Emotion Regulation Framework to Understand the Role of Temperament and Family Processes in Risk for Adolescent Depressive Disorders. *Clinical Child and Family Psychology Review*, *10*(2), 180–196.

Yoon, K. L., & Zinbarg, R. E. (2008). Interpreting neutral faces as threatening is a default mode for socially anxious individuals. *Journal of Abnormal Psychology*, *117*(3), 680–685.

Young, S. E., Friedman, N. P., Miyake, A., Willcutt, E. G., Corley, R. P., Haberstick, B. C., & Hewitt, J. K. (2009). Behavioral Disinhibition: Liability for Externalizing Spectrum Disorders and Its Genetic and Environmental Relation to Response Inhibition Across Adolescence. *Journal of Abnormal Psychology*, *118*(1), 117–130.

Yurgelun-Todd, D. A., & Killgore, W. D. S. (2006). Fear-related activity in the prefrontal cortex increases with age during adolescence: A preliminary fMRI study. *Neuroscience Letters*, *406*(3), 194–199.

Zanarini, M. C. (2003). The Childhood Interview for DSM-IV Borderline Personality Disorder (CI-BPD). Belmont, MA: McLean Hospital and Harvard Medical School.

Zeeuw, E. L. de, Beijsterveldt, C. E. M. van, Glasner, T. J., Bartels, M., Ehli, E. A., Davies, G. E., … Boomsma, D. I. (2014). Polygenic scores associated with educational attainment in adults predict educational achievement and ADHD symptoms in *children*. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 165(6), 510–520.

Zelazo, P. D., & Carlson, S. M. (2012). Hot and Cool Executive Function in Childhood and Adolescence: Development and Plasticity. *Child Development Perspectives*, 6(4), 354–360.

Zelazo, P. D., & Cunningham, W. (2007). Executive function: Mechanisms underlying emotion regulation. In James J. Gross (Ed.), *Handbook of Emotion Regulation* (pp. 135–158). New York: Guilford.

Zheng, J., Erzurumluoglu, A. M., Elsworth, B. L., Kemp, J. P., Howe, L., Haycock, P. C., … Wren, J. (2017). LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. *Bioinformatics*, *33*(2), 272–279.

Zhou, D., Lebel, C., Treit, S., Evans, A., & Beaulieu, C. (2015). Accelerated longitudinal cortical thinning in adolescence. *NeuroImage*, *104,* 138–145.

Zhou, J., Gao, T., Zhang, Y., Liang, J., Shui, R., & Shen, M. (2011). Losing control in front of a fearful face: The effect of emotional information on cognitive control. *The Quarterly Journal of Experimental Psychology*, *64*(6), 1187–1199.

Ziermans, T., Dumontheil, I., Roggeman, C., Peyrard-Janvid, M., Matsson, H., Kere, J., & Klingberg, T. (2012). Working memory brain activity and capacity link MAOA polymorphism to aggressive behavior during development. *Translational Psychiatry*, *2*(2), e85.

Zuckerman, M., & Neeb, M. (1979). Sensation seeking and psychopathology. *Psychiatry Research, 1*(3), 255–264.

Zuckerman, Marvin. (2014). Sensation seeking (psychology revivals): beyond the optimal level of arousal. Psychology Press.

Supplementary Data

Chapter 2

Supplementary Table 2.1: ALSPAC version of Arnett's Inventory of Sensation Seeking

	Very like me	Quite like me	Not much like me	Not at all like me
1. I can see how it would be interesting to marry someone from a different country				
2. When the water is very cold I prefer not to swim even on a hot day				
3. When I have to wait in a long line I am usually patient about it				
4. When I listen to music I like it to be loud				
5. When I take a trip it's best to make as few plans as possible and take what comes				
6. I avoid movies that are frightening/highly suspenseful				
7. I think it's fun/exciting to perform/speak in front of a group				
8. When I visit an amusement park I prefer to ride the rollercoaster or other fast rides				
9. I would like to travel to places that are strange/far away				
10. I would never like to gamble with money even if I could afford it				
11. I would have enjoyed being one of the first explorers of an unknown land				
12. I likes movies where there are a lot of explosions/car chases				
13. I do not like extremely hot and spicy food				
14. In general I work better when under pressure				
15. I often like to have TV/radio on while I am doing something else				
16. I think it would be interesting to see a car accident happen				
17. I think it's best to order something familiar when eating in a restaurant				
18. I like the feeling of standing next to the edge of a high place and looking down				
19. I would be first in line to sign up for a free trip to the moon/another planet				
20. I can see how it must be exciting to be in a battle during war				

Supplementary Table 2.2: Table of questions developed by ALSPAC regarding social skills, behaviour, eating habits and self-image

Social Skills	Age asked (months)
Teenager's ability to laugh around with others, in comparison to others the same age	160
Teenager's ability to chat easily, even if topic isn't of interest, in comparison to others the same age	160
Teenager's ability to compromise and be flexible, in comparison to others the same age	160
Teenager's ability to say/do right thing to defuse tense/embarrassing situation, in comparison to others the same age	160
Teenager's ability to be graceful/good loser when things don't go their way, in comparison to others the same age	160
Teenager's ability to make other people feel at ease, in comparison to others the same age	160

Teenager's ability to read between lines to work out what people think/feel, in comparison to others the same age	160
Teenager's ability to say sorry/sort things out without bad feeling, in comparison to others the same age	160

Behaviour	
Teenager goes to extremes to prevent those they love from leaving	160
Teenager either loves someone or hates them, nothing in between	160
Teenager often wonders who they really are	160
Teenager has tried to hurt or kill themselves	160
Teenager is very moody	160
Teenager feels life is dull and meaningless	160
Teenager has difficulty controlling anger/temper	160
When teenager stressed out, things happen, feels paranoid, detached from self or things	160
Teenager gone on eating binges	160
Teenager drunk too much alcohol	160
Teenager taken drugs	160
Teenager spent more money than has	160
Teenager yelled at people	160
Teenager broken things	160
Teenager hit people	160
Teenager stolen things	160

Eating habits	
Teenager spends a lot of time thinking about food	160, 166, 198
Teenager has such a strong desire of food, it feels like an addiction	160, 166
Teenager loses control of what eaten and eats lots in short time	160, 166
When this happens, teenager has a sense of losing control over eating	160, 166
Worries about eating really interfere in his/her life	160, 166, 198
When teenager eats too much, he/she blames themselves	160, 166, 198
Teenager upset or distressed about weight/body shape	160, 166, 198
Teenager's concern about weight/eating has effected how well they gets on with rest of family/ they makes/keeps friends/ their learning or class work/ their hobbies, sport, leisure activities/ has put a burden on the whole family	160, 198
Degree to which child avoids food that thinks will make them fat	166
Frequency child avoids fattening foods	166
Degree to which child ate less at meal times to avoid putting on weight over last 3 months	166
Degree to which child skipped meals to avoid putting on weight over last 3 months	166
Degree to which child went without food for long periods e.g. all/most of day to avoid putting on weight over last 3 months	166
Degree to which child hid/threw away food others gave them to avoid putting on weight over last 3 months	166
Degree to which child exercised more to avoid putting on weight over last 3 months	166
Degree to which child made them self sick to avoid putting on weight over last 3 months	166
Degree to which child took pills/medicines in order to lose weight over last 3 months	166
Degree to which child did other things in order to lose weight over last 3 months	166
Child has ever thought they were fat even when others said they were very thin	166
Child would be ashamed if other people knew how much they eat	166
Child has ever deliberately made them self sick	166
Teenager is afraid of gaining weight or getting fat	198
Teenager has had any months when her period didn't happen at all	166, 198

Self-Image	
Frequency child feels they are generous	166
Frequency child feels they are lively	166
Frequency child feels they are keen to learn	166
Frequency child feels they are affectionate	166
Frequency child feels they are reliable & responsible	166
Frequency child feels they are easy going	166
Frequency child feels they are good fun & good sense of humour	166

Frequency child feels they are interested in many things	166
Frequency child feels they are caring/kind-hearted	166
Frequency child feels they are bounces back quickly after setbacks	166
Frequency child feels they are grateful/appreciative of what they get	166
Frequency child feels they are independent	166
Frequency child feels they are help's around home	166
Frequency child feels they are gets on well with rest of family	166
Frequency child feels they are does homework without reminding	166
Frequency child feels they are does creative activities: art/acting/music/making things	166
Frequency child feels they are likes involvement in family activities	166
Frequency child feels they are takes care of appearance	166
Frequency child feels they are keeps bedroom tidy	166
Frequency child feels they are good at school work	166
Frequency child feels they are polite	166
Frequency child feels they are good at sport	166
Frequency child feels they are good with friends	166
Frequency child feels they are well behaved	166
Frequency child feels they are kind	166
Frequency child feels they are happy	166
Frequency child feels they are friendly	166
Frequency child feels they are funny	166
Frequency child feels they are helpful	166
Frequency child feels they are hard working	166
Frequency child feels they are talkative	166
Frequency child feels they are confident	166
Frequency child feels they are sporty	166
Frequency child feels they are intelligent	166
Frequency child feels they are fun to be with	166
Frequency child feels they are good looking	166
Frequency child feels they are lazy	166
Frequency child feels they are annoying	166
Frequency child feels they are moody	166
Frequency child feels they are shy	166
Frequency child feels they are cheeky	166
Frequency child feels they are loud	166
Frequency child feels they are sarcastic/bitchy	166
Frequency child feels they are bossy	166
Frequency child feels they are short tempered	166
Frequency child feels they are easily bored	166
Frequency child feels different from others	166
Frequency child messes about	166
Frequency child worries a lot	166

Supplementary Table 2.3: Questions from the ALSPAC adapted version of the Friends and Peers interview

Questions + follow up response/reason
Friends wouldn't hang around with teenager to upset teenager + told teacher/told someone at home
Friends have tried to get teenager to do things didn't want to do + told teacher/told someone at home
Friends have told lies about teenager + told teacher/told someone at home
Friends have spoilt games to upset teenager + told teacher/told someone at home
Friends have done other things to upset teenager + told teacher/told someone at home
Teenager especially affected/unaffected by events mentioned above

Teenager has not hung around with friend to upset them

Teenager has tried to get friend to do something they didn't want to do

Teenager has told lies about friend

Teenager has spoilt games to upset friend

Teenager has done other things to upset friend

Reasons teenager does bad things to others – ethnic/gender/appearance/character trait/ family/SES/fun/ felt like it/ retaliation/ don't know/ name/ they don't like me/ happens to everyone/ other

Teenager especially affected/unaffected by events mentioned above

Chapter 3

Supplementary Table 3.1: Component loadings in the final emotional measures PCA. PC: principal component

Variable description	*Externalising*	*Anxiety*	*Internalising*	*Extraversion*	*Conscientiousness*
Child has been angry or resentful	**0.71**	-0.03	0.14	0.07	0.06
Child has done things to annoy others	**0.71**	-0.01	0.04	0.1	0.05
Child has taken no notice of rules or refused to do as told	**0.71**	-0.01	0.04	0.12	0.03
Child has blamed others for own mistakes	**0.71**	-0.02	0.06	0.11	0.06
Child has argued with grown-ups	**0.69**	-0.03	0.07	0.14	0.04
Child has been touchy or easily annoyed	**0.69**	-0.03	0.14	0.05	0.08
Childs behaviour has disrupted family life	**0.67**	-0.02	0.09	0.06	0.1
Child has had severe tantrums	**0.67**	-0.02	0.07	0.07	0.09
Teenager is considerate of other people's feelings	**-0.64**	-0.04	0.08	0.02	0.13
Child did not understand when child was offending people	**0.63**	0.02	0.02	0.03	0.11
Child did not seem to understand social skills	**0.63**	0.03	0.03	-0.04	0.15
Child did not notice the effect of behaviour on family members	**0.62**	0.04	0.02	0.02	0.07
Child has tried to get own back on others	**0.62**	0	0.04	0.07	0.1
Frequency child easy going	**-0.62**	0.04	-0.05	0.14	0.03
Frequency child caring/kind-hearted	**-0.62**	-0.05	0.14	0.08	0.18
Child has been spiteful	**0.62**	-0.01	0.03	0.06	0.07
Frequency child well behaved	**-0.62**	-0.04	0.03	-0.11	0.22
Mothers assessment of how child's awkward behaviour compares with other children	**0.61**	0.01	0.01	0.13	-0.15
Child was difficult to reason with when upset	**0.61**	-0.02	0.11	0.02	0.06
Child did not pick up on body language	**0.61**	0.04	0	-0.08	0.13
Child did not respond when told to do something	**0.6**	-0.02	0.04	0.04	0.01
Child was not aware of others feelings	**0.6**	0.06	-0.05	-0.04	0.06

Variable description	*Externalising*	*Anxiety*	*Internalising*	*Extraversion*	*Conscientiousness*
Teenager is generally obedient, usually does what adults request	**-0.59**	0	-0.02	-0.09	0.12
Frequency child grateful/appreciative of what they get	**-0.58**	0	0.05	0.04	0.2
Frequency child reliable & responsible	**-0.58**	-0.06	0.04	-0.02	0.23
Frequency child gets on well with rest of family	**-0.57**	-0.02	-0.02	0.05	0.1
Frequency child polite	**-0.57**	-0.04	0.07	-0.04	0.22
Child has been very demanding of other time	**0.56**	0	0.11	0.07	0.15
Teenager's ability to compromise and be flexible	**-0.56**	0	0.04	0.14	0.12
Teenager has often had temper tantrums or hot tempers	**0.55**	-0.06	0.2	0.06	0
Teenager has difficulty controlling anger/temper	**0.54**	-0.08	0.22	0.02	-0.01
Teacher has complained of this type of behaviour	**0.54**	0.05	0.01	0.2	-0.05
Child did not realise when others were upset	**0.54**	0.06	-0.04	-0.02	0.11
Frequency child good fun & good sense of humour	**-0.53**	-0.02	0.05	0.24	0.09
Teenager's ability to say/do right thing to defuse tense/embarrassing situation	**-0.52**	-0.04	0.12	0.25	0.1
Teenager's ability to say sorry/sort things out without bad feeling	**-0.52**	-0.02	0.11	0.12	0.13
Teenager has shared readily with other children/teenagers	**-0.52**	-0.02	0.05	0.12	0.03
Teenager's awareness of what is/isn't appropriate in social situations	**-0.51**	-0.07	0.09	0.17	0.12
Child has bullied or threatened people	**0.5**	0	0.03	0.09	0.02
Teenager's ability to be graceful/good loser when things don't go their way	**-0.5**	0.02	-0.01	0.06	0.11
Teenager is helpful if someone is hurt, upset or ill	**-0.5**	-0.06	0.17	0.14	0.08
Child has told lies to get favours or to get out of things	**0.5**	0	0.07	0.14	-0.08
Frequency child good with friends	**-0.49**	-0.02	-0.02	0.29	0
Degree to which child often fought with or bullied children	**0.48**	-0.01	0.06	0.05	0.07
Frequency child generous	**-0.47**	-0.04	0.16	0.09	0.18
Child has often started fights	**0.47**	0	0.07	0.08	0.01
Frequency child bounces back quickly after setbacks	**-0.47**	0	-0.03	0.28	0.06
Child could not follow commands unless carefully worded	**0.46**	0.07	0.03	-0.04	0.15
Frequency child affectionate	**-0.46**	-0.07	0.15	0.08	0.19
Degree to which child was generally liked by peers	**-0.46**	0.02	-0.1	0.26	-0.1
Child did not understand how to behave in public	**0.45**	0.02	-0.05	-0.04	0.11
Study teenager is kind to younger children	**-0.45**	-0.02	0.06	0.13	0.05

Variable description	*Externalising*	*Anxiety*	*Internalising*	*Extraversion*	*Conscientiousness*
Teenager's ability to read between lines to work out what people think/feel	**-0.44**	-0.04	0.14	0.23	0.08
Study teenager often volunteers to help others (parents, teachers, other teenagers)	**-0.4**	-0.07	0.13	0.16	0.21
Frequency child likes involvement in family activities	**-0.4**	-0.04	0.01	0.07	0.27
Teenager either loves someone or hates them	**0.38**	-0.05	0.17	0.01	0.02
Frequency child independent	**-0.35**	-0.04	0.04	0.3	0
Study teenager has at least one good friend	**-0.34**	0	-0.07	0.22	-0.09
Adult knowledge of whether YP has been involved in stealing on the streets	**0.33**	0.02	-0.01	0.02	0.08
When teenager stressed out things happen, feels paranoid, detached from self or things	**0.32**	-0.05	0.27	-0.06	0.08
YP feels they are able to do things as well as most other people	0	**-0.66**	-0.04	0.07	0.26
Agree/disagree: not being able to develop a close friendship with a specific person they like means there is something wrong with YP as a person	0.04	**0.63**	-0.04	-0.04	0.15
Frequency YP has been feeling good about self	0.06	**-0.62**	-0.13	-0.04	0.23
Agree/disagree: reason for not being able to develop a close friendship with a specific person they like leads to problems in all areas of YP's life	0.08	**0.62**	-0.07	-0.03	0.1
Agree/disagree: people not being interested in YP at a party means there is something wrong with YP as a person	0.03	**0.62**	-0.08	-0.06	0.17
Agree/disagree: reason for people not being interested in YP at a party will cause problems in all areas of YP's life	0.05	**0.6**	-0.1	-0.1	0.13
Frequency YP has been feeling cheerful	0.03	**-0.6**	-0.09	0	0.23
YP feels that they have a number of good qualities	-0.02	**-0.6**	-0.02	0.07	0.24
Agree/disagree: not being in an intimate relationship means there is something wrong with YP as a person	0.01	**0.59**	-0.03	-0.09	0.14
Agree/disagree: reason for not being in an intimate relationship leads to problems in all areas of YP's life	0.02	**0.59**	0.03	-0.04	0.12
Frequency YP has been thinking clearly	0.02	**-0.59**	-0.1	-0.11	0.27
Frequency YP has been dealing with problems well	0.05	**-0.59**	-0.07	-0.04	0.22
Agree/disagree: class reacting badly to YP's talk means there is something wrong with YP as a person	0.02	**0.58**	-0.03	-0.06	0.14
Frequency YP has been able to make up own mind about things	0.01	**-0.58**	-0.02	0.03	0.21

Variable description	*Externalising*	*Anxiety*	*Internalising*	*Extraversion*	*Conscientiousness*
Agree/disagree: negative evaluation in the first year of YP's chosen career would mean there was something wrong with YP as a person	-0.04	**0.57**	0.01	-0.04	0.14
YP feels that they are a person of worth, at least on an equal plane with others	-0.01	**-0.57**	-0.06	0.05	0.2
YP feels they cannot do anything right	0	**0.57**	0.19	0.02	-0.09
YP feels that their life is not very useful	0.03	**0.56**	0.19	-0.02	-0.13
Frequency YP has been feeling loved	-0.01	**-0.56**	-0.02	-0.01	0.21
YP thinks they are no good at all	0.02	**0.56**	0.15	0.01	-0.1
Frequency YP has been feeling close to other people	0	**-0.56**	-0.04	0.05	0.22
YP agrees/disagrees that when YP is afraid they worry that they might be crazy	0.05	**0.55**	0.09	0.06	0.18
YP takes a positive attitude towards themselves	0	**-0.55**	-0.09	0.09	0.19
Agree/disagree: people not being interested in YP at a party says a lot about YP as a person	0.02	**0.54**	-0.05	-0.12	0.16
YP agrees/disagrees that: if YP does well it is probably due to chance, if they do badly it is probably their own fault	0.02	**0.54**	0.06	0.02	0.02
Agree/disagree: reason for not being in an intimate relationship means YP will not have intimate relationship in the future	0.05	**0.54**	-0.04	-0.08	0.12
Frequency YP has been interested in new things	0.05	**-0.53**	0	0.01	0.28
Agree/disagree: reason for people not being interested in YP at a party will cause people at future parties to be same	-0.01	**0.52**	-0.06	-0.15	0.12
Frequency YP has been feeling relaxed	0.07	**-0.51**	-0.11	-0.04	0.14
YP agrees/disagrees that: turning to someone else for advice or help is an admission of weakness	0.06	**0.51**	0.01	0.09	0.05
YP agrees/disagrees that: if a person is not a success then his/her life is meaningless	0.09	**0.5**	0.04	0.11	0.12
Agree/disagree: getting along badly with parents means there is something wrong with YP as a person	0.06	**0.5**	-0.01	-0.01	0.13
YP agrees/disagrees that: when YP cannot keep their mind on their task they worry they might be going crazy	0.03	**0.5**	0.14	0.05	0.14
Agree/disagree: unhappiness does not mean there is something wrong with YP as a person	-0.01	**-0.47**	0	-0.02	-0.1
Agree/disagree: reason for negative evaluation in the first year of YP's chosen career would not cause failures in all areas of YP's life	-0.03	**-0.46**	0.06	0.01	-0.03
YP agrees/disagrees that: funny feelings in YP's body scare them	0	**0.46**	0.08	0.01	0.25

Variable description	*Externalising*	*Anxiety*	*Internalising*	*Extraversion*	*Conscientiousness*
Frequency YP has been feeling interested in other people	-0.04	**-0.45**	0.05	0.01	0.28
Agree/disagree: reason for unhappiness causes problems in all areas of YP's life	-0.04	**0.45**	0.16	0.08	0.09
Agree/disagree: not being able to develop a close friendship with a specific person they like says nothing about YP as a person	0	**-0.45**	0.09	0.03	-0.12
Agree/disagree: not being able to complete all the given work in an important class says a lot about YP as a person	-0.03	**0.45**	0.05	0.07	0.08
Frequency YP has been feeling optimistic about the future	-0.04	**-0.44**	0.01	0.01	0.27
YP feels that they do not have much to be proud of	0.05	**0.44**	0.09	0.02	-0.13
YP agrees/disagrees that: YP's value as a person depends greatly on what others think of them	-0.05	**0.43**	0.1	0.09	0.19
YP agrees/disagrees that: YP is scared when they can't keep their mind on their work	0	**0.43**	0.13	0.03	0.21
YP agrees/disagrees that: YP's life is wasted unless they are a success	0	**0.43**	0.14	0.13	0.19
YP agrees/disagrees that: YP is scared when they feel nervous	0.01	**0.42**	0.18	-0.01	0.19
Frequency YP has had energy to spare	0.07	**-0.42**	-0.09	-0.02	0.23
Agree/disagree: not being able to complete all the given work in an important class does not mean there is something wrong with YP as a person	-0.07	**-0.42**	0.1	0.01	-0.07
Agree/disagree: reason for not being able to complete all the given work in an important class will cause problems in all areas of YP's life	0.01	**0.42**	0.08	0.05	0.06
Agree/disagree: not being able to develop a close friendship with a specific person they like is YP's fault	0.02	**0.41**	-0.01	-0.01	0.06
YP agrees/disagrees that: if a person has to be alone for a long period of time it follows that he/she has to feel lonely	0.03	**0.41**	0.09	0.07	0.09
YP has felt they have had a good time	0.02	**-0.4**		-0.16	0.06
Agree/disagree: reason for class reacting badly to YP's talk will not cause failures in all areas of YP's life	-0.05	**-0.4**	0.09	0.09	-0.05
YP agrees/disagrees that: unusual feelings in YP's body scare them	0	**0.39**	0.11	0.03	0.25
Agree/disagree: reason for unhappiness will always make YP unhappy	0.01	**0.39**	0.07	0.07	0.06

Variable description	*Externalising*	*Anxiety*	*Internalising*	*Extraversion*	*Conscientiousness*
YP agrees/disagrees that: when YP notices that their heart is beating fast, they worry there might be something wrong with them	0.02	**0.39**	0.1	0.02	0.22
Agree/disagree: not being in an intimate relationship is YP's fault	0	**0.38**	0.05	-0.03	0.11
Agree/disagree: reason for getting along badly with parents will stop them getting along well in future	0.1	**0.37**	0	-0.02	0.02
YP agrees/disagrees that: YP is scared when their heart beats fast	0.04	**0.37**	0.1	0.02	0.18
Agree/disagree: not being in an intimate relationship says nothing about YP as person	-0.02	**-0.36**	0.05	0.05	-0.15
Agree/disagree: reason for negative evaluation in the first year of YP's chosen career would not impact future job evaluations	0.05	**-0.36**	0.02	0.09	-0.07
Agree/disagree: reason for negative evaluation in the first year of YP's chosen career would effect future job evaluations	-0.01	**0.36**	0.01	-0.02	0.03
YP agrees/disagrees that: when YP's stomach hurts, they worry that they might be really sick	0.06	**0.35**	0.12	0.01	0.21
Agree/disagree: unhappiness says a lot about YP's strengths/weaknesses	0.02	**0.35**	0.04	0.02	0.1
Agree/disagree: class reacting badly to YP's talk says nothing about YP's strengths/weaknesses	0.03	**-0.35**	0.05	0.16	-0.12
YP agrees/disagrees that: YP is scared when they feel shaky	-0.02	**0.34**	0.19	-0.01	0.18
YP agrees/disagrees that: if someone performs a selfish act, this means he/she is a selfish person	0.07	**0.34**	-0.02	0.03	0.09
Agree/disagree: reason for not being able to complete all the given work in an important class will cause similar failures in completing future work	-0.01	**0.33**	0.08	0.03	0.04
Agree/disagree: reason for getting along badly with parents causes problems in all areas of life	0.05	**0.33**	0.09	0.05	0.01
Agree/disagree: reason for not being in an intimate relationship will have no effect on future relationships	0.05	**-0.33**	-0.02	0.05	-0.1
YP agrees/disagrees that: YP does not like to let their feelings show	-0.01	**0.31**	0.11	0	0.03
Study teenager felt lonely	0.07	0.13	**0.64**	-0.12	0.07
YP has had spell of feeling sad/miserable/depressed	-0.06	0.02	**0.63**	-0.15	-0.03
Study teenager has felt miserable or unhappy	0.11	0.1	**0.63**	-0.02	0
Study teenager felt they were no good anymore	0.12	0.19	**0.6**	-0.03	0.03

Variable description	*Externalising*	*Anxiety*	*Internalising*	*Extraversion*	*Conscientiousness*
Study teenager hated themselves	0.13	0.18	**0.59**	-0.01	0.05
Teenager often feels sad	-0.05	0	**0.58**	-0.21	-0.05
Study teenager cried a lot	0.06	0.08	**0.57**	0.03	0.05
Teenager feels they get upset easily	-0.09	-0.04	**0.56**	-0.18	-0.01
Teenager is very moody	0.25	-0.11	**0.55**	0.01	-0.15
Study teenager thought they could never be as good as others	0.11	0.21	**0.55**	-0.09	0.04
Teenager feels they get stressed out easily	0.02	-0.05	**0.55**	-0.03	-0.1
Study teenager felt they did everything wrong	0.17	0.22	**0.54**	0	0.01
Study teenager thought nobody really loved them	0.19	0.16	**0.54**	0.01	0.03
Teenager worries about things	-0.12	-0.06	**0.54**	-0.2	0.05
Teenager feels they have frequent mood swings	0.02	-0.05	**0.53**	0.05	-0.21
Teenager feels they change their mood a lot	-0.02	-0.07	**0.52**	-0.03	-0.15
Study teenager found it hard to think properly or concentrate	0.15	0.15	**0.51**	0.05	-0.08
Frequency child feels different from others	-0.05	-0.04	**0.51**	-0.13	0.01
YP has felt sad	-0.04	0.22	**0.51**	0.05	0
Teenager feels they get irritated easily	0.02	-0.05	**0.5**	-0.03	-0.15
YP has felt pessimistic about everything	-0.05	0.22	**0.49**	0.01	0.05
Study teenager felt they were a bad person	0.19	0.18	**0.48**	0.07	0.02
Been told moody person	0.04	-0.1	**0.47**	0.09	-0.04
YP has felt lacking in get up and go	-0.04	0.22	**0.47**	0.03	-0.1
Study teenager was very restless	0.19	0.03	**0.47**	0.13	-0.03
Mood changes - Angry/Panicked/Hopeless	0.02	-0.14	**0.47**	0.06	0
YP has cried about nothing	-0.04	0.16	**0.46**	0.09	-0.01
YP has felt they can never get things done	-0.01	0.25	**0.46**	0.03	-0.05
YP lacked energy and felt tired all the time, in period when sad/irritable/lost interest	-0.06	0.17	**0.45**	0.06	0
worries about behaviour, school, disasters, health, bad things, future	0.07	0.02	**0.45**	-0.07	0.16
Frequency child feels they are moody	0.03	-0.09	**0.45**	0	-0.19
YP has felt lacking in motivation	-0.04	0.2	**0.45**	0	-0.08
Mood changes - Sad/Cross/Nervous/Scared	-0.03	-0.14	**0.45**	0.08	0
Study teenager felt so tired that they just sat around and did nothing	0.03	0.08	**0.44**	-0.01	-0.09
YP has felt that they are spending their days doing nothing	0	0.21	**0.43**	-0.02	-0.06
Frequency child worries a lot	-0.07	0.22	**0.42**	-0.13	0.2
YP has felt guilty	-0.03	0.16	**0.42**	0.07	0.06
Affective instability symptom present	0.08	-0.12	**0.42**	0.06	-0.03
Emptiness symptom present	0.03	-0.05	**0.41**	0.03	0.04
Length of time period of being miserable has lasted	0.16	-0.06	**0.41**	-0.03	0.06
YP has felt they only have a few hobbies or interests	0	0.18	**0.4**	-0.06	-0.1

Variable description	*Externalising*	*Anxiety*	*Internalising*	*Extraversion*	*Conscientiousness*
Degree to which child dreaded having to do things	-0.03	-0.03	**0.4**	-0.14	-0.2
Study teenager has many worries, often seems worried	0.22	-0.04	**0.4**	-0.19	0.18
Study teenager has many worries, often seems worried	0.19	0.2	**0.39**	-0.06	-0.04
Child's school is a place where they get upset	0.08	0.02	**0.39**	-0.15	0.01
YP has felt they have no interest in being with other people	-0.01	0.23	**0.38**	-0.1	0.03
YP has hurt themselves on purpose	0.02	0.13	**0.38**	0.06	-0.09
YP has felt they are not a very lively person	-0.04	0.25	**0.37**	-0.21	-0.01
Frequency child feels they are short tempered	0.12	-0.03	**0.37**	0.1	-0.24
Child's school is a place where they feel worried	0.01	0.02	**0.36**	-0.2	0.04
Compared to others of their age, amount YP has worried about own appearance or weight	0.02	0	**0.36**	0	0.05
Lost temper and really shouted	0.16	-0.1	**0.36**	0.1	-0.06
YP has felt they experience few or no emotions at important events	0.05	0.17	**0.35**	-0.02	0.01
Felt angry - Managed to hide it	0.02	-0.06	**0.35**	0.01	0.03
YP is worried in general	0.02	-0.02	**0.35**	-0.17	0.17
Teenager upset or distressed about weight/body shape	0.11	-0.04	**0.34**	-0.02	0.05
wonders who they really are	0.23	-0.06	**0.33**	-0.09	0.07
Teenager feels others emotions:	-0.12	-0.1	**0.3**	0.16	0.21
Teenager talks to a lot of different people at parties:	0.02	-0.02	0	**0.66**	0.01
Teenager feels they are the life of the party	0.04	0.04	-0.01	**0.65**	-0.08
Teenager starts conversations	0	-0.05	0.01	**0.63**	0.05
Teenager does not talk a lot	-0.04	0.02	0.08	**-0.62**	0.02
Frequency child feels they are talkative	0.07	-0.04	0.05	**0.62**	-0.01
Frequency child feels they are confident	0.07	-0.04	-0.15	**0.61**	0.14
Teenager feels they have little to say	-0.01	0.08	0.05	**-0.58**	-0.04
Teenager does not mind being the centre of attention	0.01	-0.02	0.11	**0.57**	-0.01
Frequency child feels they are loud	0.13	0.01	0.13	**0.56**	-0.2
Frequency child feels they are shy	-0.09	0.01	0.15	**-0.56**	0.02
Teenager keeps in the background	-0.03	0.02	0.18	**-0.56**	0.03
Teenager feels they are quiet around strangers:	-0.06	-0.03	0.14	**-0.49**	0.07
Frequency child feels they are funny	0.03	-0.05	-0.09	**0.48**	0.18
Teenager thinks it's fun and exciting to perform or speak before a group	-0.03	-0.04	0.12	**0.44**	0.22
Frequency child feels they are sporty	-0.05	0.06	-0.25	**0.44**	0.07
Teenager feels comfortable around people	-0.01	-0.09	-0.11	**0.43**	0.09
Frequency child feels they are sporty	0.06	0.07	-0.27	**0.43**	0.08

Variable description	*Externalising*	*Anxiety*	*Internalising*	*Extraversion*	*Conscientiousness*
Enjoy playing sports and activities which could be dangerous	0.06	0.02	0.01	**0.43**	-0.16
Teenager does not like to draw attention to themselves	-0.08	0	0.06	**-0.42**	0.07
Degree to which child was very active	0.07	0.01	-0.23	**0.42**	0.18
Frequency child feels they are funny	0.05	-0.04	-0.02	**0.42**	0.12
YP has felt they are not a very lively person	-0.15	0	0.03	**0.41**	0.1
YP fears/avoids situations that involve a lot of people or meeting new people	0.16	0.04	0.08	**-0.4**	0.07
Like using the diving boards when swimming:	0.04	0.01	-0.05	**0.4**	-0.03
YP has been afraid of speaking in class	0.17	0	0.02	**-0.4**	-0.04
Teenager is rather solitary, tends to play alone	0.23	-0.03	0.17	**-0.4**	0.11
YP has been afraid of situations involving meeting a lot of people (e.g. at a party)	0.19	0	0.06	**-0.38**	0.1
YP has been afraid of meeting new people	0.19	0	0.05	**-0.38**	0.08
Frequency child feels they are cheeky	0.09	-0.03	0.21	**0.37**	-0.23
When listen to music, like it to be loud	0.08	0	0.14	**0.37**	-0.26
Study teenager is nervous or clingy in new situations, easily loses confidence	0.25	0.04	0.1	**-0.36**	0.09
YP has felt like they are not much of a talker	-0.05	0.19	0.27	**-0.35**	0.02
YP has been afraid of reading out loud in front of others,	0.19	0.02	-0.03	**-0.34**	-0.05
Frequency child feels they are good looking	0.09	-0.03	-0.2	**0.33**	0.13
Likes to ride on roller coasters/other fast rides	0.03	-0.01	-0.05	**0.33**	-0.12
Teenager feels they make people feel at ease	-0.11	-0.06	0.15	**0.33**	0.21
Frequency child feels they are hard working	-0.09	0.01	-0.1	-0.02	**0.55**
Degree to which child could concentrate well	-0.05	-0.05	-0.18	0.06	**0.51**
Frequency child feels they are helpful	-0.11	-0.02	-0.05	0.04	**0.46**
Teenager feels they pay attention to details	-0.05	-0.07	-0.02	-0.05	**0.46**
Teenager feels they are always prepared	-0.04	-0.03	-0.14	-0.06	**0.46**
Frequency child feels they are intelligent	-0.07	-0.09	-0.03	0.11	**0.44**
Teenager feels they are exacting in their work	-0.05	-0.03	0.07	0.03	**0.43**
Teenager feels they get household tasks done right away	-0.03	0.04	-0.15	-0.03	**0.43**
Teenager feels they avoid their duties	0.05	0.01	0.21	0.08	**-0.4**
Don't do homework until last minute	0.09	0.02	0.16	0.14	**-0.4**
Degree to which child could keep thoughts on what they were doing	-0.06	0	-0.15	0.09	**0.39**
Teenager feels they have a wide vocabulary	-0.08	-0.09	0.14	0.07	**0.38**
Teenager feels they have excellent ideas	0	-0.05	0.1	0.28	**0.37**
Frequency child feels they are easily bored	0.08	0	0.26	0.08	**-0.36**
Teenager feels they are quick to understand things	-0.07	-0.1	0.05	0.11	**0.36**
Teenager follows a plan	-0.02	0.01	0.03	0.02	**0.36**

Frequency child feels they are kind	-0.14	-0.07	-0.11	0.08	**0.34**
Frequency child feels they are lazy	-0.01	-0.03	0.23	0.02	**-0.33**
Don't worry about coming home late	0.12	0.02	0.05	0.2	**-0.32**
Eigenvalues	20.30	19.51	16.68	10.23	7.10
% variance explained	8%	8%	7%	4%	3%
Cronbach's α	.96	.96	.95	.91	.85

YP= Young Person

Supplementary Table 3.2: Correlation matrix between all imputed EF variable

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. Counting Span task: *Score*																		
2. Stop Signal task: *Stop trials*	-.085																	
3. Stop Signal task*: Go trials*	.134	.399																
4. Stop Signal task: *Go RT*	.139	-.199	.080															
5. Sky Search task: *Speed*	-.151	.174	-.086	-.135														
6. Dual task: *Decrement score*	-.154	.063	-.060	-.077	-.018													
7. Opposite Worlds task: *RT cost*	-.075	.064	-.075	-.042	.097	.093												
8. Digit Vigilance task: *Accuracy*	-.220	.175	-.071	-.150	.133	.112	.045											
9. Digit Vigilance task: *RT*	.232	-.051	.122	.111	-.109	-.142	-.093	-.194										
10. Simple RT task: *Simple RT*	-.067	.230	-.123	-.149	.184	.023	.008	.337	.090									
11. Choice RT task: *Choice RT*	.046	.027	.175	.084	-.047	-.063	-.046	.160	.200	.002								
12. Choice RT task: *correct trials*	-.217	.286	-.078	-.148	.174	.090	.066	.532	-.138	.407	.259							
13. Stop Signal task: *Stop trials*	.045	-.068	.018	.066	-.004	-.043	-.009	-.093	.066	-.072	-.037	-.112						
14. Stop Signal task: *Go trials*	-.066	.247	.052	-.084	.077	.042	.035	.184	-.037	.145	.085	.222	-.335					
15. Stop Signal task: *Go RT*	.051	.087	.259	.093	-.038	-.053	-.079	.012	.070	-.075	.209	.043	-.288	.471				
16. N-back task: *2-back Acc*	.199	-.077	.080	.090	-.103	-.083	-.080	-.099	.213	-.049	.057	-.120	.057	-.062	.073			
17. N-back task: *2-back RT*	.365	-.082	.165	.165	-.181	-.214	-.175	-.293	.416	-.050	.132	-.264	.111	-.090	.089	.250		
18. N-back task: *3-back - 2-back Acc*	.068	.164	.101	.016	.070	-.054	.016	-.043	.152	.131	.066	.086	.009	.120	.093	-.137	.312	
19. N-back task: *RT (3-back – 2back)/2-back)*	-.079	.004	-.011	-.071	.020	.035	.047	.100	-.108	-.052	-.015	.064	-.039	.000	.004	.122	-.587	-.150

Blue cells p< .001, grey cells p< .01 pale blue cells p<.05

Supplementary Table 4.1: Emotion PCA measures questions Section 1

	1 Not like me at all	2	3	4	5 A lot like me	Measure
1. I don't take any notice of rules or do what I am told						Externalising
2. I am the life of the party						Extroversion
3. I am able to do things as well as most others						Anxiety
4. I talk to lots of different people at parties						Extroversion
5. I do things to deliberately to annoy people						Externalising
6. I pay attention to detail						Conscientiousness
7. I am quiet around strangers*						Extroversion
8. I am confident						Extroversion
9. I get touchy or easily annoyed						Externalising
10. I feel like I am a person of worth, at least on an equal place with others*						Anxiety
11. I keep in the background*						Extroversion
12. I am always prepared						Conscientiousness
13. My behaviour disrupts family life						Externalising
14. I do not realise when I am offending people						Externalising
15. I have a number of good qualities*						Anxiety
16. I do not understand social skills						Externalising
17. I feel shy*						Extroversion
18. It is difficult to reason with me when I am upset						Externalising
19. I don't mind being centre of attention						Extroversion
20. I am easy going*						Externalising
21. I am not very aware of other people's feelings						Externalising
22. I do not like to draw attention to myself*						Extroversion
23. If I am successful I feel like it's luck, but if I fail then it's my fault						Anxiety
24. I find it fun/exciting to perform or speak in front of a group						Extroversion
25. I get upset easily						Internalising
26. I feel comfortable around people						Extroversion
27. I think that not being in an intimate relationship means there is something wrong with me as a person						Anxiety
28. I enjoy playing sports and activities which could be dangerous						Extroversion
29. I am exacting in my work						Conscientiousness
30. If people are not being interested in me at a party I feel there must be something wrong with me as a person						Anxiety

31. I am funny						Extroversion
32. I am intelligent						Conscientiousness
33. I get household tasks done right away						Conscientiousness
34. I am quite solitary and tend to hang out alone						Extroversion
35. I am hard working						Conscientiousness
36. If I can't develop a close friendship with a specific person I like, I feel like there is something wrong with me as a person						Anxiety
37. I feel stressed out easily						Internalising

Supplementary Table 4.2: Emotion PCA measures questions Section 2

	1 Never	2 Hardly ever	3 Sometimes	4 Often	5 Always	Measure
38. I get angry or resentful						Externalising
39. I feel like I cannot do anything right						Anxiety
40. I blame others when things go wrong						Externalising
41. I am fun to be with						Extroversion
42. I have excellent ideas						Conscientiousness
43. I worry about things						Internalising
44. I feel my life is useful*						Anxiety
45. I can make my mind up*						Anxiety
46. I am focused						Conscientiousness
47. I feel close to others*						Anxiety
48. I am lacking in energy						Internalising
49. I can be spiteful						Externalising
50. I feel good about myself*						Anxiety
51. I think nobody really loves me						Internalising
52. I have been thinking clearly*						Anxiety
53. I feel sad						Internalising
54. I avoid my duties*						Conscientiousness
55. I deal with problems well*						Anxiety
56. I feel lonely						Internalising
57. I get bored						Conscientiousness
58. I have strong emotional outbursts						Externalising
59. I feel miserable						Internalising
60. I am interested in new things *						Anxiety
61. I feel like I am no good						Anxiety
62. I have mood swings						Internalising
63. I do not pick up on body language						Externalising
64. I can concentrate well						Conscientiousness
65. I am lack get up and go						Internalising

66. I spend my days doing nothing		Internalising
67. I feel I am helpful		Conscientiousness
68. I don't do work until the last minute*		Conscientiousness
69. I try to get my own back on people		Externalising
70. I think I could never be as good as other people		Internalising
71. I feel like I can never get things done		Internalising
72. I cry		Internalising
73. I feel pessimistic about everything		Internalising
74. I am afraid to read/speak out loud in front of people		Extroversion
75. I feel lacking in motivation		Internalising

Supplementary Table 4.3: Emotion Regulation Questionnaire (ERQ)

We would like to ask you some questions about your emotional life, in particular, how you control (that is, regulate and manage) your emotions. The questions below involve two distinct aspects of your emotional life. One is your emotional experience, or what you feel like inside. The other is your emotional expression, or how you show your emotions in the way you talk, gesture, or behave. Although some of the following questions may seem similar to one another, they differ in important ways. For each item, please answer using the scale:

	1 Strongly disagree	2	3	4 Neutral	5	6	7 Strongly Agree	Scale
1. When I want to feel more *positive* emotion (such as joy or amusement), I *change what I'm thinking about*								Reappraisal
2. I keep my emotions to myself								Suppression
3. When I want to feel less *negative* emotion (such as sadness or anger), I *change what I'm thinking about*								Reappraisal
4. When I am feeling *positive* emotions, I am careful not to express them								Suppression
5. When I'm faced with a stressful situation, I make myself *think about it* in a way that helps me stay calm								Reappraisal
6. I control my emotions by *not expressing them*								Suppression

7. When I want to feel more *positive* emotion, I *change the way I'm thinking* about the situation		Reappraisal
8. I control my emotions by *changing the way I think* about the situation I'm in		Reappraisal
9. When I am feeling *negative* emotions, I make sure not to express them		Suppression
10. When I want to feel less *negative* emotion, I *change the way I'm thinking* about the situation		Reappraisal

Supplementary Table 4.4: Cognitive Emotion Regulation Questionnaire (CERQ)

Think of situations that you have found threatening or stressful in your life. To what extent do the following statements reflect you response to these situations.

	1 Almost never 2 3 Sometimes 4 5 Almost always	scale
1. I dwell upon the feelings a situation has evoked in me		Rumination
2. I look for the positive sides to the matter		Reappraisal
3. I feel that I am the one to blame for it		Self-blame
4. I often think that what I have experienced is the worst that can happen to a person		Catastrophizing
5. I think that the situation also has its positive sides		Reappraisal
6. I want to understand why I feel the way I do about what I have experienced		Rumination
7. I feel that basically the cause lies in others		Other blame
8. I think about the mistakes I have made in this matter		Self-blame
9. I think about the mistakes others have made in this matter		Other blame
10. I often think that what I have experienced is much worse than what others have experienced		Catastrophizing
11. I feel that I am the one who is responsible for what has happened		Self-blame
12. I often think about how I feel about what I have experienced		Rumination
13. I think I can learn something from the situation		Reappraisal
14. I continually think about how horrible the situation has been		Catastrophizing
15. I feel that others are responsible for what has happened		Other blame

16. I think that I can become a stronger person as a result of what has happened		Reappraisal
17. I think that basically the cause must lie within myself		Self-blame
18. I keep thinking about how terrible it is what I have experienced		Catastrophizing
19. I feel that others are to blame for it		Other blame
20. I am often preoccupied with what I think and feel about what I have experienced		Rumination

Supplementary Table 4.5: Full regression table for Model 1 between the ER strategies measured by the ERQ and CERQ and the emotion PCA measures.

	Externalising			Internalising			Anxiety			Extraversion			Conscientiousness		
	Beta	SE	p	Beta	SE	p	Beta	SE	p	Beta	SE	P	Beta	SE	p
Rumination	-.037	.118	.755	.289	.087	.001	.158	.091	.084	-.154	.134	.252	.013	.118	.916
Reappraisal	-.221	.100	.027	-.238	.074	.001	-.297	.078	.000	.308	.114	.007	.322	.100	.001
Self-Blame	.124	.116	.288	.371	.086	.000	.366	.090	.000	-.014	.133	.914	-.193	.117	.099
Other Blame	.202	.089	.024	-.038	.066	.565	-.003	.069	.961	.213	.102	.037	.087	.090	.335
Catastrophizing	.279	.111	.012	.191	.082	.020	.235	.086	.006	.022	.127	.865	-.144	.111	.195
Suppression ERQ	.030	.098	.762	-.006	.072	.936	.097	.076	.200	-.007	.112	.950	.132	.098	.180
Reappraisal ERQ	-.236	.094	.012	-.165	.070	.018	-.134	.073	.068	.118	.108	.276	.168	.095	.076
age	-.130	.093	.163	-.039	.069	.567	-.046	.072	.521	.058	.106	.585	.250	.093	.007
gender	.006	.092	.950	-.112	.068	.100	-.044	.071	.537	.108	.105	.302	-.162	.092	.080

Supplementary Table 4.6: Full regression table for Model 2 between the EFNBACK measures and emotion PCA measures.

	Externalising			Internalising			Anxiety			Extraversion			Conscientiousness		
	Beta	SE	p	Beta	SE	p	Beta	SE	p	Beta	SE	P	Beta	SE	p
0-back Emotion	-.021	.170	.903	-.555	.170	.001	-.269	.172	.112	-.038	.181	.842	-.111	.171	.517
2-back Emotion	.026	.170	.88	.102	.171	.544	-.011	.173	.947	.142	.182	.454	-.235	.172	.173
0-back Blank	-.151	.161	.356	.213	.161	.182	-.111	.163	.490	.081	.172	.651	.317	.162	.052
2-back Blank	-.309	.155	.05	-.238	.155	.121	-.086	.157	.579	-.053	.165	.758	.203	.156	.197
age	-.206	.112	.077	-.098	.113	.385	-.198	.114	.084	.128	.120	.315	.317	.113	.006
gender	.079	.113	.491	-.072	.113	.518	-.067	.115	.557	.139	.121	.270	-.126	.114	.273

Supplementary Table 4.7: Full regression table for Model 3 between the ER strategies measured by the ERQ and CERQ and the EFNBACK measures

	0-back Blank			2-back Blank			0-back Emotion			2-back Emotion		
	Beta	SE	p	Beta	SE	p	Beta	SE	p	Beta	SE	p
Rumination	.090	.142	.544	.091	.142	.538	.047	.143	.754	-.065	.149	.675
Reappraisal	.317	.123	.012	-.146	.123	.246	.174	.124	.170	.039	.129	.768
Self-Blame	.080	.142	.577	.092	.142	.518	-.255	.143	.076	.078	.150	.602
Other Blame	.103	.116	.346	000	.116	.998	.113	.116	.302	-.112	.122	.330
Catastrophizing	-.133	.14	.329	-.345	.140	.012	-.018	.141	.897	-.063	.147	.662
Suppression ERQ	-.133	.124	.266	-.209	.124	.081	-.073	.125	.546	-.107	.130	.395
Reappraisal ERQ	.025	.128	.829	.230	.128	.051	.051	.129	.665	.085	.134	.491
age	.128	.117	.282	.099	.117	.405	.194	.118	.106	.127	.123	.310
gender	.105	.113	.353	.219	.114	.054	.102	.114	.373	.234	.119	.050

Supplementary Table 6.1: Suggestive SNPs associated with working memory and processing speed

Phenotype	Chr	allele	rsid	Base position	MAF	Beta (SE)	p-value	No. SNPs	No. of SNPs p<1e-5	Gene	Previous GWAS
Working memory	2	A:C	rs181853190	25900633	0.013	0.471 (0.11)	7.2×10^{-6}	1	1	DTNB*	Schizophrenia, parietal cortex measurement, cingulate cortex measurement
Working memory	2	A:G	rs7566497	183724622	0.039	0.269 (0.05)	5.37×10^{-7}	183	155	FRZB**	Major Depressive disorder, Night sleep phenotypes
Working memory	3	C:T	rs114144395	57395019	0.012	-0.483 (0.10)	1.39×10^{-6}	5	3	DNAH12**	
Working memory	3	A:T	rs838625	143191553	0.318	0.10 (0.02)	3.20×10^{-6}	39	34	SLC9A9**	Night sleep phenotypes, cognitive impairment
Working memory	4	C:T	rs78890674	173886129	0.012	-0.570 (0.12)	3.15×10^{-6}	3	2	GALNTL6**	Night sleep phenotypes (Neuritic plaques)
Working memory	5	A:G	rs2089199	31910627	0.390	-0.098 (0.02)	8.8×10^{-6}	3	2	PDZD2**	Anti-saccade error rate in psychotic disorders
Working memory	5	A:G	rs10079220	57453718	0.024	-0.307 (0.07)	6.7×10^{-6}	6	5	PGAM1P1*	
Working memory	5	A:C	rs10042036	57649291	0.219	-0.115 (0.03)	5.3×10^{-6}	51	36	PLK2*	Alzheimer's
Working memory	5	C:T	rs60258111	60079231	0.025	0.360 (0.08)	2.9×10^{-6}	5	3	ELOVL7**	Schizophrenia, parietal cortex measurement, cingulate cortex measurement, Educational attainment, Anti-saccade error rate in psychotic disorders
Working memory	6	A:T	rs551980	8282533	0.497	-0.102 (0.02)	1.6×10^{-6}	31	27	SLC35B3*	
Working memory	6	C:T	rs143248626	119256466	0.034	-0.275 (0.06)	9.1×10^{-6}	3	2	MCM9**	
Working memory	7	C:T	rs117555423	9133779	0.023	-0.331 (0.07)	7.8×10^{-6}	1	1	NXPH1*	Schizophrenia, parietal cortex measurement, cingulate cortex measurement
Working memory	9	C:G	rs1333039	22065657	0.412	-0.094 (0.02)	9.5×10^{-6}	65	44	CDKN2B-AS1**	

Phenotype	Chr	allele	rsid	Base position	MAF	Beta (SE)	p-value	No. SNPs	No. of SNPs p<1e-5	Gene	Previous GWAS
Working memory	11	A:G	rs474357	82437118	0.216	0.127 (0.03)	5.9×10^{-7}	71	58	FAM181B*	Cerebral amyloid deposition in APOEe4 non-carriers
Working memory	11	A:G	rs523867	82479873	0.160	-0.132 (0.03)	3.4×10^{-6}	14	11	FAM181B*	
Working memory	12	A:G	rs10744264	126967956	0.105	-0.164 (0.04)	5.0×10^{-6}	1	1	RP5-944M2.3*	
Working memory	12	A:C	rs10773290	126985979	0.172	-0.135 (0.03)	2.6×10^{-6}	25	18	NDUFA5P6*	
Working memory	14	A:G	rs28576539	96306550	0.107	-0.156 (0.03)	2.8×10^{-6}	53	40	LINC00617*	
Working memory	15	C:G	rs75024542	84192118	0.033	-0.308 (0.06)	1.3×10^{-6}	2	1	SH3GL3**	Schizophrenia, height
Working memory	18	A:G	rs652730	77162525	0.096	-0.163 (0.04)	4.5×10^{-6}	16	10	NFATC1**	
Working memory	21	A:G	rs4816642	41110282	0.210	-0.133 (0.03)	3.3×10^{-6}	1	1	IGSF5*	Suicide risk
Processing Speed	1	A:G	rs79914264	29685027	0.012	-0.479 (0.11)	6.9×10^{-6}	1	1	RP3-437I16.1*	
Processing Speed	1	A:G	rs80032087	68548953	0.051	0.219 (0.05)	8.7×10^{-6}	1	1	GNG12-AS1*	
Processing Speed	2	A:G	rs117204046	134023319	0.046	-0.236 (0.05)	3.7×10^{-6}	4	4	NCKAP5**	Cognitive decline
Processing Speed	2	A:C	rs75924665	141786613	0.110	0.165 (0.04)	1.7×10^{-6}	1	1	LRP1B**	Educational attainment, night sleep phenotypes, Schizophrenia, parietal cortex measurement, cingulate cortex measurement
Processing Speed	4	A:G	rs77612362	180688931	0.131	-0.138 (0.03)	9.7×10^{-6}	12	11	SNORD65*	
Processing Speed	5	C:T	rs2353010	1912480	0.255	0.118 (0.03)	1.4×10^{-6}	1	1	LOC101929081*	
Processing Speed	5	A:C	rs61749834	11387815	0.036	-0.253 (0.06)	5.9×10^{-6}	2	2	CTNND2**	Alzheimer's, cannabis dependencies, bipolar disorder, schizophrenia
Processing Speed	6	A:C	rs117328143	137654309	0.030	-0.321 (0.07)	1.2×10^{-6}	2	2	IFNGR1*	Cognitive decline rate in cognitive impairment, BMI
Processing Speed	7	A:G	rs1880318	46028167	0.208	-0.122 (0.03)	2.3×10^{-6}	4	3	FTLP15*	

Phenotype	Chr	allele	rsid	Base position	MAF	Beta (SE)	p-value	No. SNPs	No. of SNPs p<1e-5	Gene	Previous GWAS
Processing Speed	7	A:C	rs56957961	83255557	0.063	0.205 (0.04)	2.6×10^{-6}	20	16	SEMA3E**	
Processing Speed	10	C:T	rs11238581	44026005	0.221	0.119 (0.03)	3.6×10^{-6}	4	4	ZNF487*	
Processing Speed	10	G:T	rs10999869	73292871	0.085	-0.169 (0.04)	6.7×10^{-6}	8	2	CDH23**	
Processing Speed	10	C:T	rs72812273	74872426	0.027	-0.420 (0.09)	8.1×10^{-6}	7	1	NUDT13**	
Processing Speed	12	C:T	rs58366817	47934532	0.071	-0.200 (0.04)	1.2×10^{-6}	97	84	RPAP3*	
Processing Speed	13	C:T	rs73176740	38996158	0.023	-0.361 (0.08)	9.1×10^{-6}	3	3	UFM1* LINC00437*	Aggressiveness in ADHD, Schizophrenia, anti-saccade error rate in psychotic disorders
Processing Speed	13	A:T	rs72632563	88930653	0.067	0.187 (0.04)	8.0×10^{-6}	20	13	RPL29P29*	
Processing Speed	14	G:T	rs7144325	37038310	0.420	-0.095 (0.02)	6.7×10^{-6}	67	50	RPL29P3* Other snps (NKX2-1-AS1**, PHKBP2**, RPL29P3**, NKX2-8**)	Intelligence, Cognitive ability, Educational attainment, general cognitive ability.
Processing Speed	15	C:T	rs79896452	38589654	0.037	0.260 (0.06)	4.3×10^{-6}	3	3	SPRED1**	Psychosis
Processing Speed	15	A:G	rs117831562	38684951	0.019	-0.346 (0.08)	7.7×10^{-6}	3	1	SPRED1*	
Processing Speed	15	C:T	rs187701342	81911145	0.057	-0.229 (0.05)	1.2×10^{-6}	9	7	LOC101929655*	PTSD, Parkinson's
Processing Speed	16	C:T	rs71399907	70032959	0.021	0.377 (0.08)	1.1×10^{-6}	4	2	PDXDC2P**	
Processing Speed	17	A:G	rs138181598	43997525	0.013	-0.463 (0.10)	8.9×10^{-6}	1	1	MAPT**	Educational attainment, Alzheimer's, Cognitive decline rate.
Processing Speed	18	G:T	rs3752060	39145147	0.031	0.296 (0.06)	1.4×10^{-6}	33	31	KC6*	
Processing Speed	18	A:G	rs78392342	39153288	0.017	0.367 (0.08)	7.9×10^{-6}	55	47	KC6*	

Processing Speed	18	C:T	rs117911120	61581325	0.012	-0.468 (0.11)	7.9×10^{-6}	2	1	SERPINB10**	
Processing Speed	19	C:T	rs12982734	38593151	0.335	0.099 (0.02)	6.4×10^{-6}	72	57	SIPA1L3**	Subjective well-being, Life satisfaction
Processing Speed	22	A:G	rs228912	37503668	0.249	0.107 (0.02)	9.9×10^{-6}	2	2	TMPRSS6**	

*nearest gene ** in gene

Supplementary Table 6.2: Suggestive SNPs associated with externalising and internalising

Phenotype	Chr	allele	rsid	Base position	MAF	Beta (SE)	p-value	No. SNPs	No. of SNPs p<1e-5	Gene	Previous GWAS
Externalising	1	A:G	rs114661498	29685657	0.027	0.323 (0.07)	1.8×10^{-6}	1	1	PTPRU*	
Externalising	2	C:T	rs1446869	23166973	0.365	0.090 (0.02)	9.9×10^{-6}	7	6	KLHL29*	
Externalising	2	A:C	rs817036	49624772	0.151	0.120 (0.03)	9.6×10^{-6}	27	17	FSHR*	
Externalising	4	C:T	rs13143096	149720635	0.499	-0.085 (0.02)	8.3×10^{-6}	11	10	NR3C2*	
Externalising	4	A:G	rs17040956	162286482	0.375	-0.098 (0.02)	7.4×10^{-7}	37	23	FSTL5*	Risky sexual behaviours
Externalising	6	A:C	rs62400307	24114249	0.153	-0.118 (0.03)	7.7×10^{-6}	10	8	NRSN1*	
Externalising	7	A:C	rs148970512	20433949	0.012	0.469 (0.09)	4.5×10^{-7}	3	3	ITGB8**	
Externalising	7	C:T	rs73094018	25297464	0.025	0.290 (0.06)	2.7×10^{-6}	4	1	NPVF*	
Externalising	7	A:G	rs11760568	32446058	0.197	0.109 (0.02)	7.9×10^{-6}	1	1	LSM5*	
Externalising	11	A:C	rs7928810	17372443	0.379	0.091 (0.02)	3.1×10^{-6}	29	18	NCR3LG1*	
Externalising	14	A:G	rs60499279	46315839	0.283	0.102 (0.02)	2.6×10^{-6}	8	6	LINC00871*	
Externalising	15	C:G	rs1039394	32407729	0.063	0.201 (0.04)	3.5×10^{-6}	2	1	CHRNA7**	
Externalising	16	C:T	rs4781695	15968150	0.139	0.132 (0.03)	4.7×10^{-6}	5	5	FOPNL**	
Externalising	20	A:G	rs16992404	45803273	0.033	0.280 (0.06)	1.2×10^{-6}	1	1	EYA2**	
Externalising	21	C:T	rs113290387	40908306	0.030	0.255 (0.06)	5.7×10^{-6}	2	2	LOC729056*	
Internalising	2	A:G	rs56026054	7171020	0.102	-0.160 (0.03)	4.0×10^{-7}	11	9	RNF144A**	
Internalising	2	A:T	rs78844122	107175314	0.026	-0.272 (0.06)	5.9×10^{-6}	1	1	RGPD3*	
Internalising	3	C:G	rs7621548	4943554	0.436	-0.087 (0.02)	5.1×10^{-6}	22	17	BHLHE40-AS1**	
Internalising	3	C:T	rs35693695	63347260	0.189	-0.112 (0.02)	4.0×10^{-6}	1	1	SYNPR**	MDD
Internalising	3	A:C	rs71298649	63348310	0.153	-0.128 (0.03)	1.3×10^{-6}	26	19	SYNPR**	MDD
Internalising	3	C:T	rs12638347	63385023	0.129	-0.138 (0.03)	1.3×10^{-6}	15	13	SYNPR**	MDD
Internalising	8	A:G	rs73605763	58741053	0.068	-0.171 (0.04)	6.8×10^{-6}	3	2	CTD-2339F6.1*	
Internalising	11	C:T	rs7925958	5138247	0.105	-0.138 (0.03)	9.0×10^{-6}	9	8	OR52A4*	
Internalising	14	C:T	rs2331490	22522345	0.248	0.114 (0.02)	3.8×10^{-7}	11	9	TRAVE21*	
Internalising	15	C:T	rs149713297	55216079	0.015	0.428 (0.09)	1.2×10^{-6}	3	3	RP11-548M13.1*	
Internalising	16	A:T	rs79832641	24650652	0.069	0.179 (0.04)	3.3×10^{-6}	3	1	AC012317.1	

*nearest gene ** in gene

Supplementary Table 6.3: Genetic Correlations with working memory and independent GWAS from LD Hub

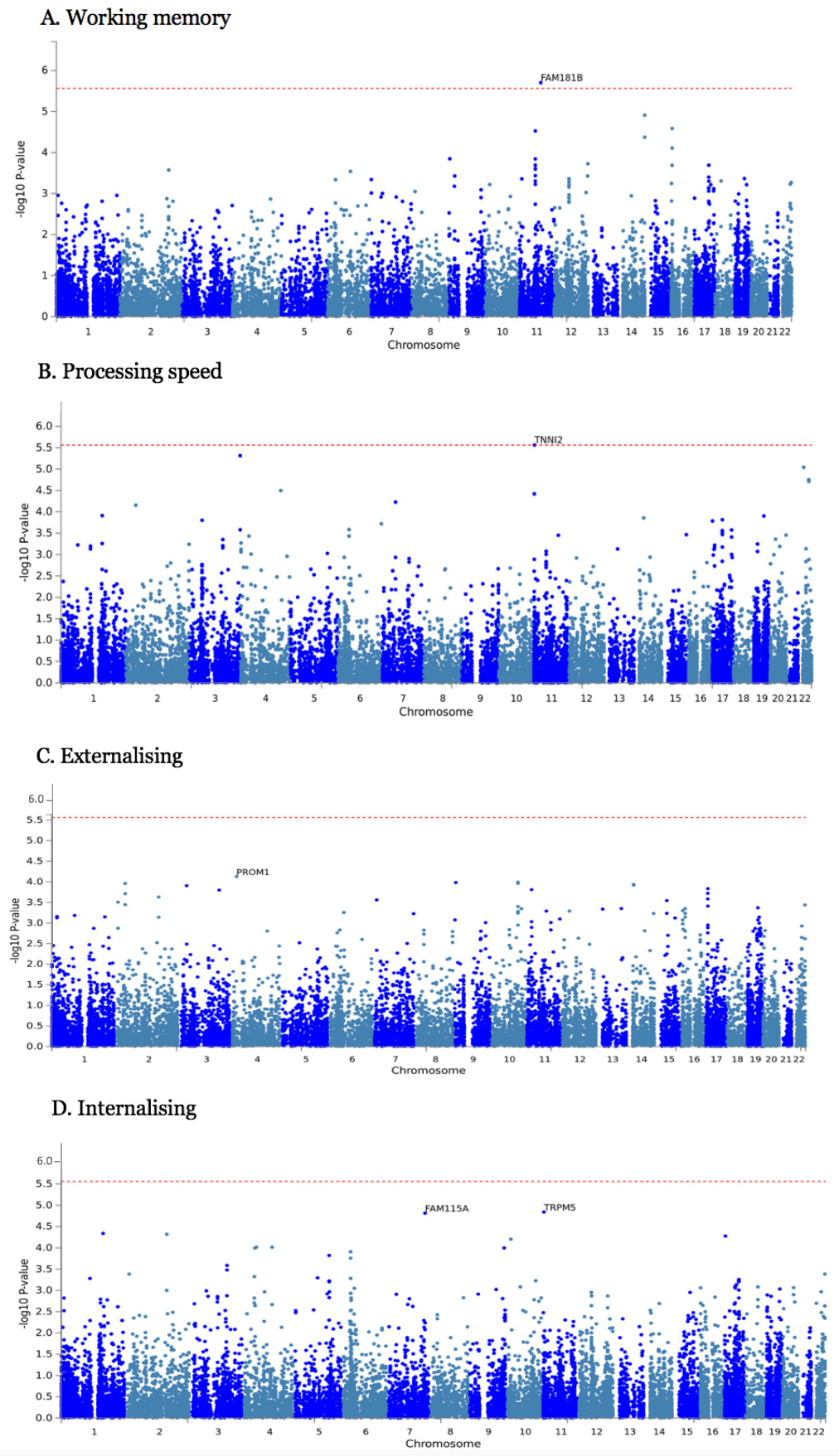
trait1	trait2	PMID	rg	se	z	p	h2_obs	h2_obs_se	h2_int	h2_int_se	gcov_int	gcov_int_se	Category	ethnicity
Working Memory	Intelligence	28530673	1.1539	0.219	5.27	1.36×10^{-7}	0.1873	0.0105	1.0053	0.01	0.0364	0.0057	cognitive	European
Working Memory	Childhood IQ	23358156	0.8017	0.1554	5.1575	2.50×10^{-7}	0.305	0.0502	0.9929	0.0113	0.2552	0.0068	education	European
Working Memory	Years of schooling 2016	27225129	0.6972	0.1515	4.6013	4.20×10^{-6}	0.1248	0.0048	0.9378	0.0128	0.0139	0.0063	education	European
Working Memory	Years of schooling (proxy cognitive performance)	25201988	0.6716	0.145	4.6323	3.62×10^{-6}	0.1074	0.0077	1.0246	0.0107	0.0002	0.0061	education	European
Working Memory	Years of schooling 2013	23722424	0.6629	0.1386	4.7813	1.74×10^{-6}	0.0833	0.0063	1.02	0.0103	-0.016	0.0059	education	European
Working Memory	College completion	23722424	0.6509	0.1304	4.9926	5.96×10^{-7}	0.0783	0.0063	1.0223	0.0103	0.0189	0.0055	education	European
Working Memory	Mean Thalamus	25607358	0.5733	0.2617	2.1905	0.0285	0.1402	0.0386	0.9773	0.0074	-0.0072	0.0049	brain volume	European
Working Memory	Neo-openness to experience	21173776	0.4929	0.2179	2.2625	0.0237	0.1028	0.0308	0.9936	0.0083	-0.0077	0.0055	personality	European
Working Memory	Anorexia Nervosa	24514567	0.1983	0.1014	1.9554	0.0505	0.6089	0.0333	0.8605	0.0089	-0.0036	0.0059	psychiatric	European
Working Memory	Attention deficit hyperactivity disorder	20732625	-0.6701	0.2717	-2.4662	0.0137	0.2708	0.1019	1.0012	0.008	-0.0044	0.0053	psychiatric	European
Working Memory	Depressive symptoms	27089181	-0.4052	0.1481	-2.7366	0.0062	0.0466	0.0041	1.0008	0.0089	0.0074	0.0058	psychiatric	European
Working Memory	Neuroticism	27089181	-0.2561	0.0976	-2.6228	0.0087	0.0887	0.0074	0.9874	0.0136	0.0118	0.006	personality	European
Working Memory	ICV	25607358	0.1732	0.2158	0.8025	0.4223	0.1957	0.0476	0.9985	0.0078	-0.0016	0.0055	brain volume	European
Working Memory	Mean Accumbens	25607358	0.139	0.2947	0.4717	0.6371	0.0859	0.0369	0.9791	0.007	0.0013	0.0052	brain volume	European
Working Memory	Mean Caudate	25607358	0.0562	0.177	0.3175	0.7509	0.2381	0.0432	0.9755	0.0081	-0.0008	0.0055	brain volume	European
Working Memory	Mean Hippocampus	25607358	0.1057	0.2429	0.4353	0.6633	0.14	0.0442	0.9906	0.0081	0.0045	0.0057	brain volume	European

trait1	trait2	PMID	rg	se	z	p	h2_obs	h2_obs_se	h2_int	h2_int_se	gcov_int	gcov_int_se	Category	ethnicity
Working Memory	Mean Pallidum	25607358	0.2109	0.1966	1.0732	0.2832	0.177	0.0474	0.9746	0.0086	3.79E-05	0.0058	brain volume	European
Working Memory	Mean Putamen	25607358	-0.0139	0.1631	-0.0854	0.9319	0.2621	0.0499	0.9601	0.0087	0.0041	0.0053	brain volume	European
Working Memory	Neo-conscientiousness	21173776	-0.2252	0.2865	-0.7859	0.4319	0.0708	0.0332	1.0005	0.0085	0.004	0.0056	personality	European
Working Memory	Bipolar disorder	21926972	-0.0049	0.1207	-0.0409	0.9674	0.4459	0.041	1.0175	0.0084	-0.0004	0.0058	psychiatric	European
Working Memory	PGC cross-disorder analysis	23453885	0.0493	0.1129	0.4366	0.6624	0.1716	0.014	1.0158	0.0129	-0.0116	0.0072	psychiatric	European
Working Memory	Major depressive disorder	22472876	0.0328	0.1799	0.1826	0.8551	0.1781	0.0309	1.0027	0.008	-0.0072	0.0055	psychiatric	European
Working Memory	Autism spectrum disorder	0	0.3011	0.1591	1.8927	0.0584	0.4481	0.0542	0.9662	0.0083	-0.0009	0.0055	psychiatric	European
Working Memory	Schizophrenia	25056061	0.05	0.0747	0.6697	0.5031	0.4701	0.0192	1.0383	0.0141	-0.0056	0.0076	psychiatric	Mixed
Working Memory	Subjective well being	27089181	0.0502	0.1343	0.3735	0.7088	0.0243	0.0022	1.0062	0.0088	-0.0054	0.0063	psychiatric	European
Working Memory	Neuroticism	24828478	-0.1412	0.2015	-0.7008	0.4834	0.0156	0.0035	1.0011	0.0078	0.0107	0.0057	personality	European
Working Memory	Attention deficit hyperactivity disorder (GC)	27663945	0.1338	0.2843	0.4708	0.6378	0.0791	0.0311	0.9924	0.0091	-0.1067	0.0062	psychiatric	European
Working Memory	Attention deficit hyperactivity disorder (No GC)	27663945	0.1328	0.285	0.4658	0.6413	0.0799	0.0315	1.0072	0.0093	-0.1071	0.0063	psychiatric	European

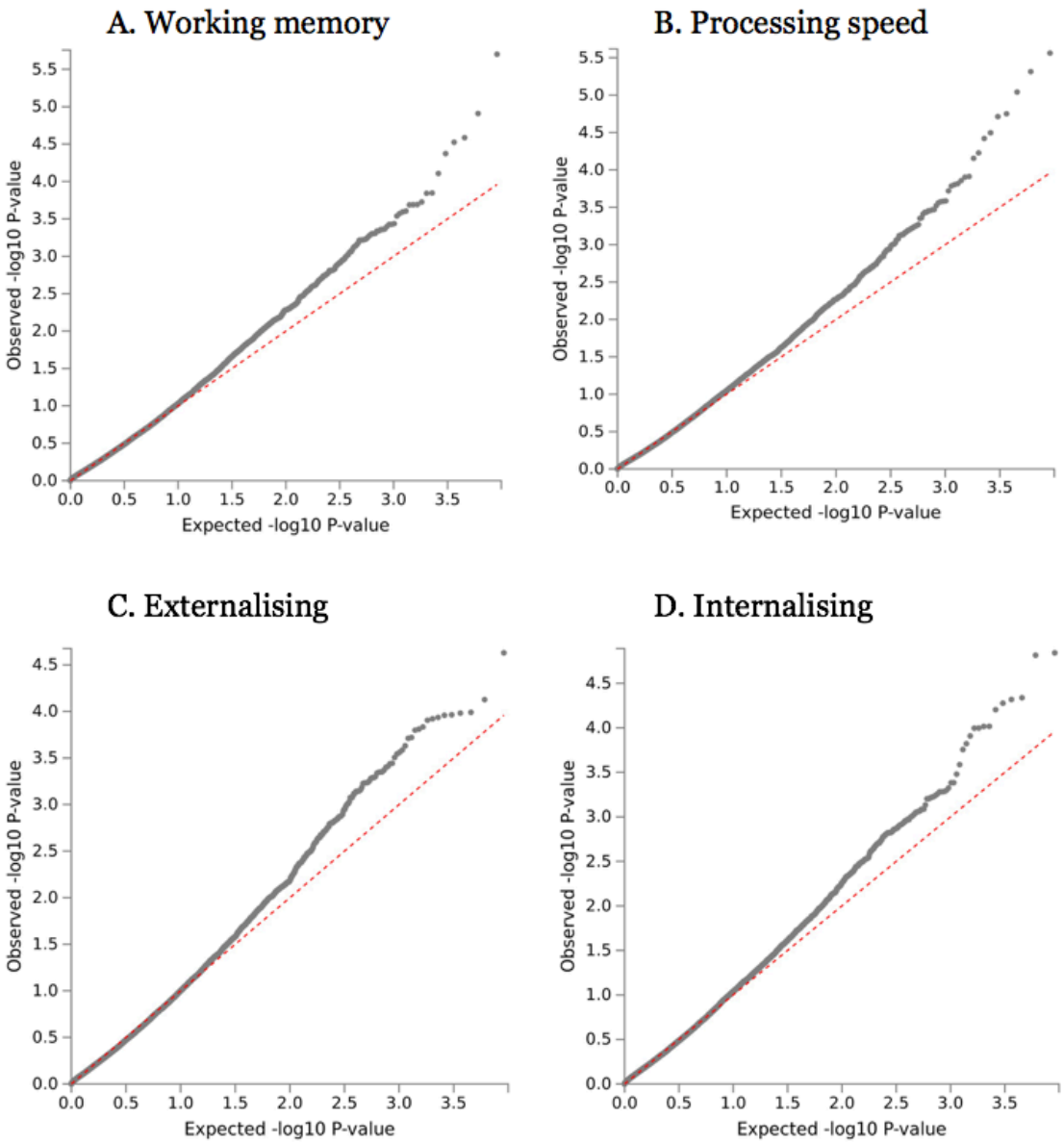
Supplementary Table 6.4: Genetic Correlations with Processing Speed and independent GWAS from LD Hub

trait1	trait2	PMID	rg	se	z	p	h2_obs	h2_obs_se	h2_int	h2_int_se	gcov_int	gcov_int_se	Category	ethnicity
Processing Speed	Intelligence	28530673	-0.5258	0.2683	-1.9598	0.05	0.1873	0.0105	1.0053	0.01	-0.0132	0.0063	cognitive	European
Processing Speed	Childhood IQ	23358156	-0.4454	0.3563	-1.2503	0.2112	0.305	0.0502	0.9929	0.0113	-0.1036	0.0075	education	European
Processing Speed	Years of schooling 2016	27225129	-0.1634	0.1553	-1.052	0.2928	0.1248	0.0048	0.9378	0.0128	-0.003	0.0063	education	European
Processing Speed	Mean Thalamus	25607358	-0.011	0.3537	-0.0312	0.9751	0.1402	0.0386	0.9773	0.0074	-0.0009	0.0054	brain volume	European
Processing Speed	Neo-openness to experience	21173776	0.1976	0.3686	0.5361	0.5919	0.1028	0.0308	0.9936	0.0083	-0.0066	0.0057	personality	European
Processing Speed	Anorexia Nervosa	24514567	0.0428	0.1546	0.2767	0.782	0.6089	0.0333	0.8605	0.0089	-0.0065	0.0058	psychiatric	European
Processing Speed	Attention deficit hyperactivity disorder	20732625	1.1653	0.6334	1.8397	0.0658	0.2708	0.1019	1.0012	0.008	-0.006	0.0057	psychiatric	European
Processing Speed	Depressive symptoms	27089181	0.2108	0.2115	0.9967	0.3189	0.0466	0.0041	1.0008	0.0089	-0.0028	0.0058	psychiatric	European
Processing Speed	Neuroticism	27089181	0.0801	0.159	0.5039	0.6144	0.0887	0.0074	0.9874	0.0136	0.0007	0.0059	personality	European
Processing Speed	ICV	25607358	0.2227	0.3382	0.6585	0.5102	0.1957	0.0476	0.9985	0.0078	-0.0012	0.0055	brain volume	European
Processing Speed	Mean Accumbens	25607358	-0.2838	0.482	-0.5889	0.5559	0.0859	0.0369	0.9791	0.007	0.0013	0.0049	brain volume	European
Processing Speed	Mean Caudate	25607358	0.0933	0.2702	0.3453	0.7299	0.2381	0.0432	0.9755	0.0081	-0.0092	0.0051	brain volume	European
Processing Speed	Mean Hippocampus	25607358	-0.4151	0.4211	-0.9857	0.3243	0.14	0.0442	0.9906	0.0081	0.003	0.0053	brain volume	European
Processing Speed	Mean Pallidum	25607358	0.1141	0.3218	0.3547	0.7229	0.177	0.0474	0.9746	0.0086	-0.0057	0.0053	brain volume	European
Processing Speed	Mean Putamen	25607358	-0.2512	0.2798	-0.8977	0.3693	0.2621	0.0499	0.9601	0.0087	-0.0019	0.0058	brain volume	European
Processing Speed	Neo-conscientiousness	21173776	0.6293	0.5082	1.2382	0.2157	0.0708	0.0332	1.0005	0.0085	-0.0007	0.0058	personality	European
Processing Speed	Bipolar disorder	21926972	0.1733	0.2172	0.7978	0.425	0.4459	0.041	1.0175	0.0084	-0.0021	0.0061	psychiatric	European
Processing Speed	PGC cross-disorder analysis	23453885	0.26	0.2726	0.9538	0.3402	0.1716	0.014	1.0158	0.0129	-0.0051	0.0081	psychiatric	European

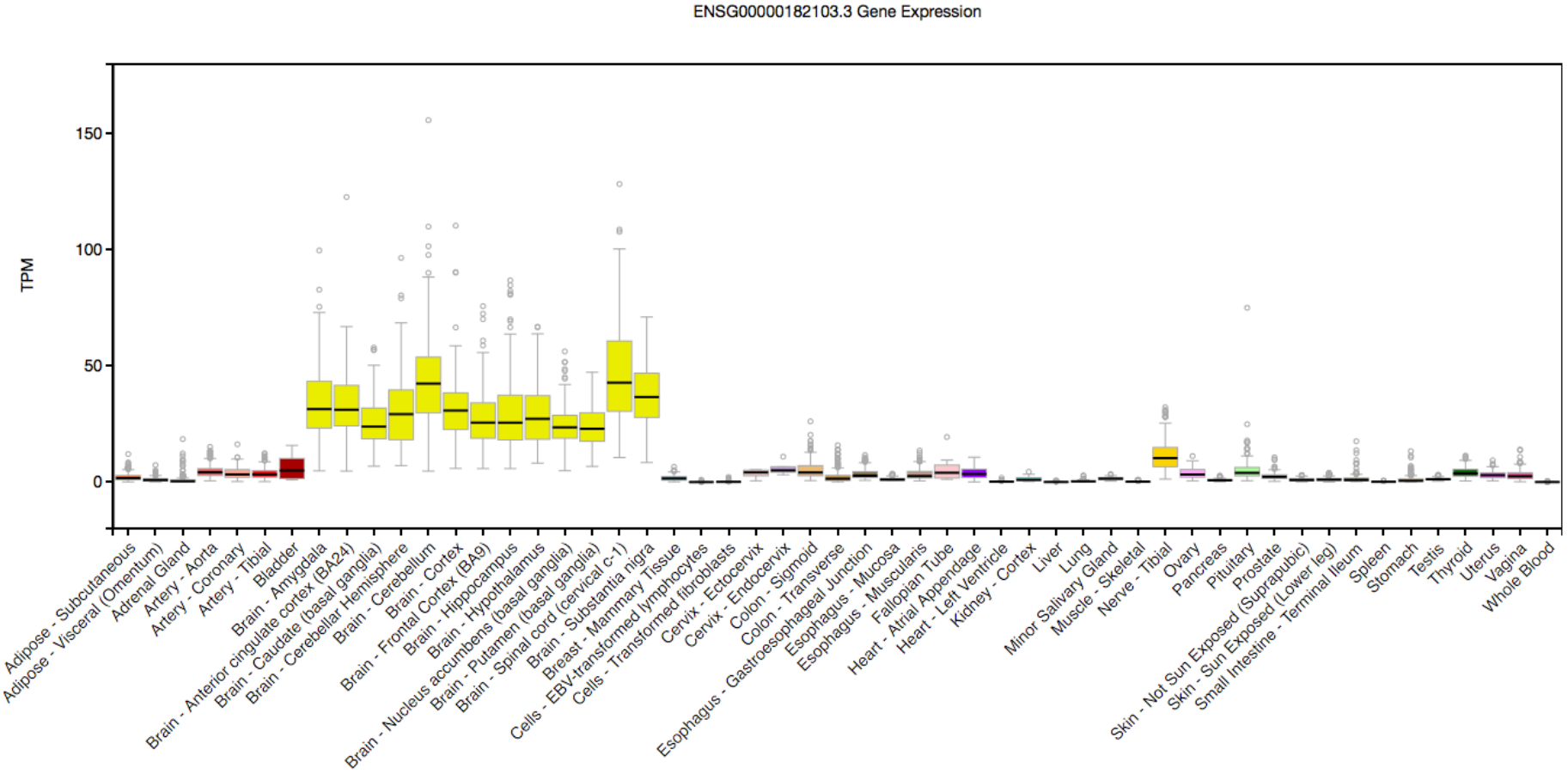
trait1	trait2	PMID	rg	se	z	p	h2_obs	h2_obs_se	h2_int	h2_int_se	gcov_int	gcov_int_se	Category	ethnicity
Processing Speed	Major depressive disorder	22472876	-0.1085	0.2456	-0.4417	0.6587	0.1781	0.0309	1.0027	0.008	-0.0015	0.0057	psychiatric	European
Processing Speed	Autism spectrum disorder	0	-0.2467	0.2843	-0.8678	0.3855	0.4481	0.0542	0.9662	0.0083	0.0048	0.0049	psychiatric	European
Processing Speed	Schizophrenia	25056061	0.1842	0.1437	1.282	0.1998	0.4701	0.0192	1.0383	0.0141	-0.0047	0.0079	psychiatric	Mixed
Processing Speed	Subjective well being	27089181	0.1114	0.2136	0.5216	0.602	0.0243	0.0022	1.0062	0.0088	-0.0062	0.0064	psychiatric	European
Processing Speed	Attention deficit hyperactivity disorder (GC)	27663945	0.2266	0.3754	0.6037	0.546	0.0791	0.0311	0.9924	0.0091	0.0511	0.0058	psychiatric	European
Processing Speed	College completion	23722424	-0.1884	0.2171	-0.868	0.3854	0.0783	0.0063	1.0223	0.0103	-0.0019	0.0068	education	European
Processing Speed	Years of schooling (proxy cognitive performance)	25201988	-0.1545	0.1939	-0.7969	0.4255	0.1074	0.0077	1.0246	0.0107	0.0018	0.007	education	European
Processing Speed	Years of schooling 2013	23722424	-0.0926	0.1875	-0.4939	0.6214	0.0833	0.0063	1.02	0.0103	0.0027	0.0067	education	European
Processing Speed	Neuroticism	24828478	-0.1382	0.2985	-0.4629	0.6435	0.0156	0.0035	1.0011	0.0078	-0.005	0.0054	personality	European
Processing Speed	Attention deficit hyperactivity disorder (No GC)	27663945	0.2328	0.3768	0.6178	0.5367	0.0799	0.0315	1.0072	0.0093	0.0512	0.0059	psychiatric	European



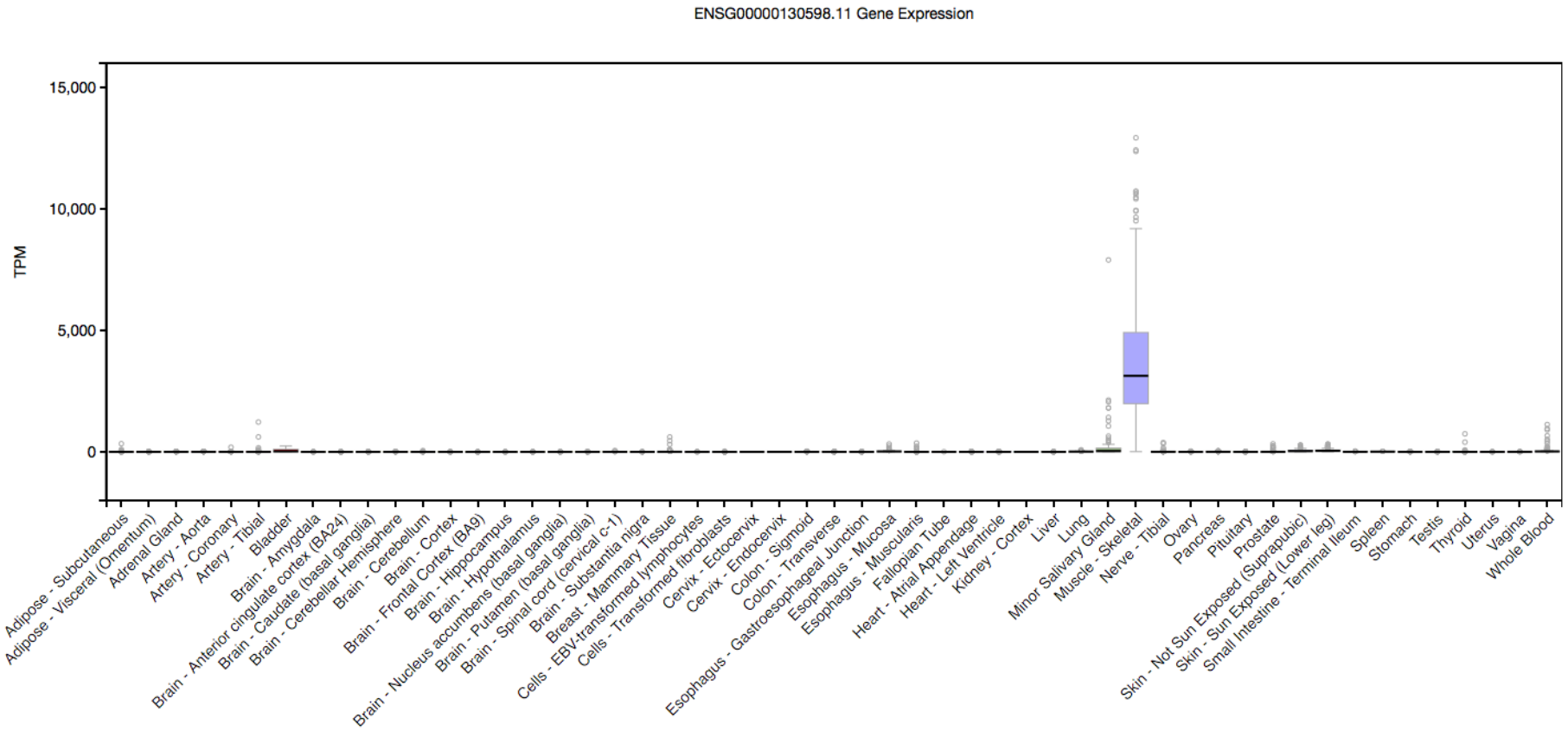
Supplementary Figure 6.1 *Manhattan plots for PCA cognitive and emotion measure gene-based association analyses*



Supplementary Figure 6.2: *Quantile-Quantile Plots for gene-based association analyses*



Supplementary Figure 6.3: *Expression data of gene FAM181B*



Supplementary Figure 6.4: *Expression data of gene TNNI2*

Supplementary Table 7.1: Pearson's correlation matrix between the demographic, cognitive, emotion and academic attainment variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. Externalising																			
2. Anxiety	.148																		
3. Internalising	.277	.401																	
4. Extrovert	-.005	-.174	-.112																
5. Conscientious	-.135	-.092	-.081	.038															
6. SES	-.078	-.053	-.017	-.017	.123														
7. Verbal IQ	-.160	-.069	.052	-.036	.206	.355													
8. Matrix Reasoning IQ	-.063	-.038	.007	-.036	.043	.142	.199												
9. Inhibitory Control	-.015	-.010	-.043	.003	-.033	-.066	-.130	-.011											
10. Working Memory	-.190	-.113	-.074	.004	.132	.286	.457	.296	-.024										
11. Processing Speed	.064	.059	.038	-.104	-.068	-.047	-.135	-.051	.128	-.207									
12. EngAGE11	-.184	-.090	.000	.023	.147	.324	.525	.222	-.030	.499	-.240								
13. MathsAGE11	-.178	-.098	-.064	.010	.119	.298	.466	.286	-.020	.576	-.217	.589							
14. SciAGE11	-.173	-.086	-.017	.005	.123	.296	.517	.245	-.026	.465	-.167	.588	.630						
15. EngAGE14	-.220	-.083	.011	-.007	.230	.371	.616	.239	-.081	.529	-.238	.667	.559	.557					
16. MathsAGE14	-.226	-.114	-.074	-.042	.176	.378	.582	.355	-.030	.655	-.224	.627	.805	.664	.666				
17. SciAGE14	-.214	-.097	-.034	-.056	.198	.391	.653	.318	-.052	.582	-.186	.644	.694	.714	.702	.823			
18. EngAGE16	-.267	-.113	-.022	-.033	.260	.429	.653	.246	-.064	.557	-.230	.667	.591	.592	.773	.719	.745		
19. MathsAGE16	-.244	-.121	-.093	-.075	.209	.406	.575	.343	-.029	.629	-.186	.596	.736	.625	.649	.881	.799	.759	
20. SciAGE16	-.238	-.105	-.049	-.085	.223	.420	.642	.314	-.050	.600	-.185	.627	.665	.663	.700	.816	.848	.807	.847

Supplementary table 7.2: Covariance matrix of SEM model 1 including EF data

	Eng16	Mat16	Sci16	Mat11	Eng11	Sci11	SES	WM	PS	IC	VIQ	MIQ
English 16	1	0.386	0.461	X	X	X	X	X	X	X	X	X
Maths 16		1	0.532	X	X	X	X	X	X	X	X	X
Science 16			1	X	X	X	X	X	X	X	X	X
Maths 11				1	0.589	0.630	0.298	0.717	-0.283	-0.078	0.466	0.286
English 11					1	0.588	0.324	0.632	-0.315	-0.093	0.525	0.222
Science 11						1	0.296	0.591	-0.243	-0.063	0.517	0.245
SES							1	0.345	-0.106	-0.058	0.355	0.142
Working Memory								1	-0.425	-0.096	0.569	0.366
Processing Speed										0.307	-0.212	-0.084
Inhibitory Control										1	-0.184	-0.020
Verbal IQ											1	0.199
Matrix Reasoning IQ												

Greyed cells indicated non-significant associations

Supplementary table 7.3: Full results from SEM model 1 including EF data

	English age 16				Maths age 16				Science age 16		
	β	SE	p		β	SE	p		β	SE	p
English age 11	.238	.013	>.001	Maths age 11	.287	.016	>.001	Science age 11	.200	.012	>.001
Maths age 11	.048	.016	.003	English age 11	.027	.013	.039	English age 11	.088	.013	>.001
Science age 11	.096	.013	>.001	Science age 11	.106	.013	>.001	Maths age 11	.125	.016	>.001
SES	.129	.010	>.001	SES	.103	.009	>.001	SES	.108	.009	>.001
Working Memory	.228	.026	>.001	Working Memory	.391	.026	>.001	Working Memory	.314	.025	>.001
Processing Speed	-.056	.013	>.001	Processing Speed	.044	.012	>.001	Processing Speed	.020	.013	.119
Inhibitory Control	.019	.010	.063	Inhibitory Control	.007	.010	.448	Inhibitory Control	.012	.010	.230
Verbal IQ	.274	.013	>.001	Verbal IQ	.114	.012	>.001	Verbal IQ	.216	.012	>.001
Matrix IQ	-.005	.009	.624	Matrix IQ	.052	.010	>.001	Matrix IQ	.039	.010	>.001
Total variance explained		.650				.710				.693	

Supplementary table 7.4: Covariance matrix of model 2 including EF and emotion variables

	Eng16	Mat16	Sci 16	Mat11	Eng11	Sci11	Exter	Anx	Inter	Extro	Consc	SES	WM	PS	IC	VIQ	MIQ
English 16	1	.365	.442	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Maths 16		1	.513	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Science 16			1	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Maths 11				1	.589	.630	-.178	-.098	-.064	.010	.119	.298	.717	-.283	-.078	.466	.286
English 11					1	.588	-.184	-.090	0	.023	.147	.324	.632	-.315	-.093	.525	.222
Science 11						1	-.173	-.086	-.017	.005	.123	.296	.591	-.244	-.063	.517	.245
Externalising							1	.148	.277	-.005	-.135	-.078	-.230	.093	.004	-.160	-.063
Anxiety								1	.401	-.174	-.092	-.053	-.140	.08	-.001	-.069	-.038
Internalising									1	-.112	-.081	-.017	-.087	.041	-.029	.052	.007
Extraversion										1	.038	-.017	.001	-.119	.006	-.036	-.036
Conscientiousness											1	.123	.159	-.107	-.039	.206	.043
SES												1	.345	-.106	-.058	.355	.142
Working Memory													1	-.425	-.096	.569	.366
Processing Speed														1	.307	-.212	-.084
Inhibitory Control															1	-.184	-.020
Verbal IQ																1	.199
Matrix Reasoning IQ																	1

Greyed cells indicate non-significant associations

Supplementary table 7.5: Full regression results from SEM model 2

	English age 16				Maths age 16				Science age 16		
	β	SE	p		β	SE	p		β	SE	p
English age 11	.230	.013	>.001	Maths age 11	.288	.016	>.001	Science age 11	.200	.012	>.001
Maths age 11	.052	.016	.001	English age 11	.028	.013	.028	English age 11	.087	.012	>.001
Science age 11	.094	.012	>.001	Science age 11	.106	.012	>.001	Maths age 11	.127	.015	>.001
Externalising	-.088	.010	>.001	Externalising	-.041	.009	>.001	Externalising	-.042	.009	>.001
Anxiety	-.018	.009	.053	Anxiety	-.005	.009	.564	Anxiety	-.004	.009	.685
Internalising	.027	.009	.003	Internalising	-.036	.009	>.001	Internalising	-.012	.009	.203
Extrovert	-.039	.009	>.001	Extrovert	-.075	.008	>.001	Extrovert	-.082	.008	>.001
Conscientious	.093	.009	>.001	Conscientious	.061	.008	>.001	Conscientious	.065	.008	>.001
SES	.125	.009	>.001	SES	.099	.009	>.001	SES	.104	.009	>.001
Working Memory	.210	.026	>.001	Working Memory	.370	.026	>.001	Working Memory	.298	.025	>.001
Processing Speed	-.056	.013	>.001	Processing Speed	.036	.012	.003	Processing Speed	.011	.012	.371
Inhibitory Control	.017	.010	.084	Inhibitory Control	.008	.009	.418	Inhibitory Control	.013	.010	.181
Verbal IQ	.250	.012	>.001	Verbal IQ	.104	.012	>.001	Verbal IQ	.202	.012	>.001
Matrix IQ	-.004	.009	.685	Matrix IQ	.053	.009	>.001	Matrix IQ	.038	.010	>.001
Total variance explained		.668				.723				.706	

Supplementary table 8.1: Top genetic associations with science attainment

Chr	allele	rsid	Base position	MAF	Beta	SE	p-value	No. SNPs	No. of SNPs p<1e-5	Gene
1	A:G	rs6688495	103204647	0.152	-0.117	0.026	4.92573e-06	78	58	COL11A1*
1	G:A	rs10797090	153624791	0.461	-0.083	0.018	4.97466e-06	118	72	CHTOP*
1	G:A	rs11264236	153658480	0.291	0.099	0.021	2.46138e-06	4	3	NPR1**
3	C:T	rs7625242	75512272	0.039	-0.294	0.066	8.51386e-06	21	3	ENPP7P2**
3	C:T	rs78393327	174079287	0.019	-0.325	0.066	1.00812e-06	5	1	NLGN1*
3	C:G	rs180928518	192643866	0.013	0.418	0.094	8.55345e-06	6	4	MB21D2*
5	C:T	rs27565	59837591	0.476	0.084	0.019	7.08646e-06	2	1	PART1**
5	C:T	rs13158665	60069057	0.457	-0.085	0.018	3.71483e-06	4	3	ELOVL7**
5	A:G	rs1444240	60069934	0.439	-0.089	0.019	1.59222e-06	207	148	ELOVL7**
5	A:G	rs10462335	88088204	0.479	-0.089	0.018	7.98498e-07	91	72	MEF2C**
5	C:T	rs13171212	92674287	0.324	-0.097	0.021	3.46263e-06	1	1	NR2F1-AS1*
5	C:T	rs4869194	92675000	0.201	-0.104	0.023	6.93104e-06	5	3	NR2F1-AS1*
5	A:G	rs264864	169061462	0.312	0.097	0.020	7.21213e-07	143	99	DOCK2**
8	A:G	rs10100356	130626164	0.226	-0.099	0.022	4.94552e-06	16	12	CCDC26**
8	A:G	rs4736679	134499912	0.057	0.177	0.039	5.3081e-06	14	14	ST3GAL1**
8	C:T	rs1554968	134507904	0.106	0.147	0.029	6.36532e-07	3	2	ST3GAL1**
9	A:C	rs758851	132873970	0.222	-0.202	0.029	2.85439e-12	2	1	GPR107**
9	C:T	rs608292	136207302	0.092	-0.191	0.042	6.30582e-06	3	1	MED22**
10	C:T	rs10905791	5688085	0.394	0.091	0.019	1.58036e-06	1	1	ASB13**
11	A:G	rs11603691	57107617	0.115	-0.133	0.028	3.02285e-06	48	41	P2RX3**
12	A:G	rs7139245	2955636	0.169	-0.128	0.028	5.51535e-06	1	1	ITFG2**
12	A:T	rs6486622	128909299	0.092	-0.211	0.040	1.52437e-07	2	2	TMEM132C**
12	A:C	rs4882758	128909655	0.225	-0.116	0.026	7.43571e-06	1	1	TMEM132C**
13	A:C	rs9529641	35319175	0.248	0.115	0.021	4.86118e-08	36	29	LINC00457*
14	C:T	rs2415955	46803675	0.435	-0.081	0.018	7.34628e-06	264	198	LINC00871**
14	A:G	rs7141746	94993936	0.420	-0.102	0.019	1.22133e-07	7	5	SERPINA12*
16	A:T	rs9939366	17434019	0.154	-0.142	0.031	6.50062e-06	7	1	XYLT1**

Chr	allele	rsid	Base position	MAF	Beta	SE	p-value	No. SNPs	No. of SNPs p<1e-5	Gene
16	A:G	rs237149	26649640	0.401	-0.082	0.018	9.9374e-06	6	3	HS3ST4*
17	C:T	rs2529909	13928634	0.164	0.127	0.028	7.65824e-06	1	1	COX10-AS1**
17	A:G	rs35751000	34913528	0.419	0.082	0.018	9.24825e-06	94	62	GGNBP2**
19	A:G	rs35681564	43959388	0.188	-0.104	0.024	9.53603e-06	49	33	LYPD3*
19	C:T	rs62133140	54773032	0.498	-0.087	0.019	4.79579e-06	36	21	LILRB2*
20	C:T	rs28579792	59937459	0.395	-0.091	0.020	3.36566e-06	1	1	CDH4**
21	C:T	rs35739539	18803733	0.110	0.145	0.031	3.00694e-06	1	1	RNU6-113P*

*Nearest gene, ** In gene

Supplementary table 8.2: Top genetic associations with maths attainment

Chr	allele	rsid	Base position	MAF	Beta	SE	p-value	No. SNPs	No. of SNPs p<1e-5	Gene
1	A:G	rs1572040	3337543	0.119	-0.157	0.029	7.77192e-08	2	1	PRDM16**
1	C:T	rs148442247	67984971	0.018	0.325	0.072	6.41266e-06	1	1	SERBP1*
2	C:T	rs72815377	63599530	0.208	0.104	0.022	3.7796e-06	199	146	WDPCP**
2	A:T	rs138004766	107911721	0.050	0.190	0.043	9.55642e-06	225	184	AC006227.1**
3	G:T	rs145032667	39361044	0.018	0.310	0.070	9.03065e-06	9	8	CX3CR1*
4	A:T	rs11099631	84901818	0.019	-0.322	0.072	9.36458e-06	4	3	RP11-8L2.1**
4	A:C	rs72699806	169552640	0.222	-0.098	0.022	6.66452e-06	2	2	PALLD**
5	A:T	rs55962375	10084607	0.019	-0.323	0.067	1.53876e-06	7	6	FAM173B*
5	A:G	rs138210978	37748954	0.311	0.094	0.020	5.53979e-06	52	34	WDR70**
5	A:G	rs2961857	165947835	0.270	0.093	0.021	7.06092e-06	91	66	CTB-7E3.1*
5	A:G	rs264864	169061462	0.220	-0.100	0.022	1.84691e-06	143	99	DOCK2*, SPDL1* (with other r2 snps)
6	C:G	rs227479	165445123	0.382	0.088	0.019	2.78877e-06	31	20	C5orf118*
7	A:G	rs78700728	81501789	0.329	0.090	0.020	7.51124e-06	23	20	CACNA2D1*
7	C:T	rs75215979	111308302	0.038	0.216	0.048	9.30675e-06	3	2	DOCK4 or IMMP2L*
7	A:C	rs4732313	138091839	0.033	0.256	0.058	3.77484e-06	10	10	TRIM24*
8	C:T	rs60626139	6503455	0.331	-0.093	0.020	5.16734e-06	1	1	MCPH1*

Chr	allele	rsid	Base position	MAF	Beta	SE	p-value	No. SNPs	No. of SNPs p<1e-5	Gene
8	C:T	rs66477371	18313717	0.067	-0.170	0.037	5.84668e-06	8	8	NAT2*
8	C:G	rs55780284	39989212	0.033	0.236	0.052	1.72448e-06	10	8	C8orf4*
8	A:G	rs4961372	142358865	0.183	-0.128	0.029	8.70503e-06	1	1	GPR20*
9	C:T	rs10780702	72537085	0.222	-0.170	0.029	8.37177e-07	24	19	C9orf135*
9	C:T	rs10780705	72539240	0.287	0.100	0.020	6.21318e-06	6	4	C9orf135*
9	A:C	rs758851	132873970	0.092	-0.192	0.042	4.20884e-09	2	1	GPR107**
9	C:T	rs608292	136207302	0.189	0.106	0.023	5.83103e-06	3	1	MED22**
10	C:G	rs10795666	8686904	0.099	-0.189	0.041	9.3395e-06	4	3	CHCHD3P1*
10	A:G	rs10822834	68224205	0.029	-0.251	0.056	9.08227e-06	3	3	CTNNA3**
10	A:G	rs2418818	108497211	0.243	-0.096	0.022	3.84278e-06	102	80	SORCS1**
11	C:G	rs7129491	57095082	0.114	-0.138	0.028	1.30961e-06	48	41	SSRP1**
11	C:G	rs1504712	99240470	0.497	-0.084	0.018	4.49509e-06	13	8	CNTN5**
12	A:G	rs7139245	2955636	0.170	-0.157	0.028	2.68581e-08	1	1	ITFG2**
12	A:G	rs74398913	4027686	0.266	0.098	0.021	2.6852e-06	2	2	PARP11*
12	A:G	rs11545332	31256995	0.031	0.270	0.057	2.54929e-06	1	1	DDX11**
12	A:G	rs10744264	126967956	0.100	-0.145	0.032	6.43614e-06	1	1	RP5-944M2.3*
13	C:T	rs9541641	69524675	0.451	-0.087	0.019	3.29871e-06	60	44	ZDHHC20P4*
14	A:G	rs7141746	94993936	0.420	-0.097	0.019	5.28688e-07	7	5	SERPINA12*
15	A:C	rs7182195	53027917	0.019	-0.344	0.068	4.86817e-07	10	8	ONECUT1*
16	A:T	rs9939366	17434019	0.154	-0.156	0.032	1.02708e-06	8	2	XYLT1**
16	A:G	rs72797219	83715276	0.178	0.114	0.024	2.10121e-06	45	31	CDH13**
16	C:T	rs118158969	84404400	0.106	-0.138	0.030	4.03818e-06	10	10	ATP2C2**
18	C:T	rs12967053	47635907	0.160	-0.156	0.033	5.22751e-06	13	7	MYO5B**
18	A:C	rs56357213	73005870	0.279	-0.093	0.020	1.55605e-06	2	1	THHZ1*
20	A:T	rs146283583	2736559	0.019	0.326	0.071	5.06341e-06	1	1	EBF4**
21	C:T	rs66795148	24356507	0.366	0.086	0.019	6.95792e-06	48	38	ZNF299P*
22	C:T	rs62219796	23631823	0.277	0.090	0.020	9.79888e-06	79	65	BCR**

*Nearest gene, ** In gene

Supplementary table 8.3: Top genetic associations with English attainment

Chr	allele	rsid	Base position	MAF	Beta	SE	p-value	No. SNPs	No. of SNPs p<1e-5	Gene
1	A:G	rs77176926	88142569	0.021	-0.324	0.070	3.8215e-06	1	1	LMO4*
2	A:G	rs145957568	63454007	0.016	-0.371	0.076	1.17187e-06	31	21	WDPCP**
2	A:C	rs75001760	196825238	0.039	0.262	0.058	7.40141e-06	3	2	DNAH7**
3	C:T	rs6767406	23862463	0.443	-0.088	0.019	7.00263e-06	12	8	UBE2E1**
3	A:T	rs6779537	23901028	0.258	-0.096	0.021	1.85256e-06	21	15	UBE2E1**
3	A:G	rs35576002	150212583	0.486	-0.083	0.018	4.67294e-06	7	5	SERP1*
4	G:T	rs75596547	140729403	0.030	-0.259	0.057	4.65246e-06	1	1	MAML3**
5	C:T	rs13188649	103467631	0.016	0.356	0.075	2.10573e-06	3	3	NUDT12*
7	C:T	rs118066386	158839899	0.024	0.289	0.065	8.44708e-06	1	1	VIPR2**
8	C:T	rs35112066	34289939	0.097	0.149	0.031	1.78723e-06	180	136	Rp11-258J101*
8	C:G	rs147918758	41167562	0.390	-0.084	0.019	7.58707e-06	42	31	SFRP1*
9	A:C	rs758851	132873970	0.222	-0.138	0.029	1.8886e-06	2	1	GPR107**
11	C:T	rs36234212	17499694	0.045	-0.206	0.046	7.26659e-06	1	1	ABCC8*
12	G:T	rs7305366	43577713	0.459	-0.081	0.018	9.45549e-06	23	18	ADAMTS20*
13	A:T	rs2485296	38559319	0.374	-0.134	0.026	3.2292e-07	2	1	LOC101929077*
14	A:T	rs9707389	30535726	0.018	0.332	0.069	1.41658e-06	15	8	PRKD1**
15	C:G	rs12441039	36326018	0.131	-0.127	0.027	2.77558e-06	39	28	MIR450*
19	C:T	rs117322896	11979669	0.013	0.384	0.082	2.69438e-06	82	1	ZNF439**
20	C:T	rs115416341	46471358	0.025	0.276	0.059	2.47858e-06	16	15	SULF2*

*Nearest gene, ** In gene

Supplementary table 8.4: LD score genetic correlations results for science

trait1	trait2	PMID	rg	se	z	p	h2_obs	h2_obs_se	h2_int	h2_int_se	gcov_int	gcov_int_se	Category	ethnicity
Science	Intelligence	28530673	1.2426	0.1727	7.194	6.29E-13	0.1875	0.0105	1.0051	0.01	0.0277	0.0062	cognitive	European
Science	Childhood IQ	23358156	1.2003	0.2052	5.8499	4.92E-09	0.3045	0.0504	0.993	0.0114	0.2657	0.0077	education	European
Science	Years of schooling 2016	27225129	0.95	0.1322	7.1847	6.73E-13	0.1248	0.0048	0.9381	0.0129	-0.0045	0.0064	education	European
Science	Years of schooling (proxy cognitive performance)	25201988	0.9024	0.183	4.9299	8.23E-07	0.1075	0.0077	1.0243	0.0107	-0.0035	0.0065	education	European
Science	College completion	23722424	0.8829	0.1658	5.3256	1.01E-07	0.0782	0.0063	1.0226	0.0103	0.0146	0.0066	education	European
Science	Years of schooling 2013	23722424	0.8717	0.1729	5.0418	4.61E-07	0.0837	0.0064	1.0188	0.0105	-0.0222	0.0061	education	European
Science	Neo-openness to experience	21173776	0.4069	0.2087	1.9497	0.0512	0.105	0.0305	0.9927	0.0083	0.0008	0.0059	personality	European
Science	Autism spectrum disorder	0	0.2456	0.1244	1.9742	0.0484	0.4542	0.0539	0.9649	0.0082	0.0042	0.0053	psychiatric	European
Science	Attention deficit hyperactivity disorder (No GC)*	27663945	-0.7697	0.2883	-2.6703	0.0076	0.0802	0.0315	1.0071	0.0093	-0.1028	0.0065	psychiatric	European
Science	Attention deficit hyperactivity disorder (GC)*	27663945	-0.7664	0.2872	-2.6681	0.0076	0.0795	0.031	0.9923	0.0092	-0.1025	0.0064	psychiatric	European
Science	Depressive symptoms	27089181	-0.3869	0.1183	-3.271	0.0011	0.0464	0.0041	1.0016	0.0091	-0.0012	0.0062	psychiatric	European
Science	Neuroticism	27089181	-0.1919	0.0914	-2.1006	0.0357	0.0889	0.0074	0.9868	0.0135	0.0003	0.007	personality	European
Science	Attention deficit hyperactivity disorder*	20732625	-0.3321	0.2498	-1.3293	0.1837	0.2692	0.1017	1.0015	0.0079	-0.009	0.0053	psychiatric	European
Science	Bipolar disorder	21926972	0.1947	0.1313	1.4824	0.1382	0.445	0.0405	1.0178	0.0086	-0.0081	0.0059	psychiatric	European
Science	PGC cross-disorder analysis	23453885	0.0087	0.1254	0.0692	0.9448	0.1719	0.0138	1.0152	0.0128	-0.0138	0.0081	psychiatric	European
Science	Major depressive disorder	22472876	-0.1337	0.148	-0.9036	0.3662	0.1746	0.0309	1.004	0.0081	-0.0076	0.0056	psychiatric	European
Science	Schizophrenia**	25056061	-0.0356	0.0641	-0.5553	0.5787	0.4701	0.019	1.0382	0.0141	-0.015	0.0077	psychiatric	Mixed
Science	Subjective well being	27089181	0.0828	0.1267	0.6536	0.5134	0.0243	0.0023	1.0057	0.0093	-0.0007	0.0057	psychiatric	European
Science	Neuroticism	24828478	-0.2208	0.1831	-1.2058	0.2279	0.0152	0.0035	1.0026	0.0079	0.0085	0.0057	personality	European
Science	ICV	25607358	0.3173	0.1878	1.6895	0.0911	0.1955	0.0476	0.9985	0.0078	-0.0033	0.0056	Brain volume	European

trait1	trait2	PMID	rg	se	z	p	h2_obs	h2_obs_se	h2_int	h2_int_se	gcov_int	gcov_int_se	Category	ethnicity
Science	Mean Accumbens*	25607358	0.1354	0.2563	0.5282	0.5974	0.0833	0.0377	0.9799	0.0073	-0.0044	0.0055	Brain volume	European
Science	Mean Caudate	25607358	0.0208	0.1516	0.137	0.8911	0.2359	0.043	0.9761	0.0081	-0.0023	0.0054	Brain volume	European
Science	Mean Hippocampus	25607358	0.0628	0.2079	0.3022	0.7625	0.1414	0.0438	0.9902	0.0081	0.0041	0.0057	Brain volume	European
Science	Mean Pallidum	25607358	0.1536	0.1849	0.831	0.406	0.1788	0.0475	0.9742	0.0086	-0.0119	0.0058	Brain volume	European
Science	Mean Putamen	25607358	-0.0382	0.1531	-0.2493	0.8031	0.2619	0.0507	0.9602	0.0088	0.0008	0.0059	Brain volume	European
Science	Mean Thalamus	25607358	0.1094	0.1863	0.5875	0.5569	0.139	0.0392	0.9776	0.0076	-0.0064	0.0053	Brain volume	European
Science	Anorexia Nervosa	24514567	0.04	0.0864	0.4632	0.6432	0.5896	0.0319	0.8675	0.0089	-0.0021	0.0059	psychiatric	European
Science	Neo-conscientiousness*	21173776	-0.2446	0.2821	-0.8671	0.3859	0.0703	0.0332	1.0007	0.0085	0.0006	0.0058	personality	European

* These data may yield results <.0 or >1 due to relative low Z score of the SNP heritability of the trait
** These data may yield less robust results due to minor departure of the LD structure

Supplementary table 8.5: LD score genetic correlations results for maths

trait1	trait2	PMID	rg	se	z	p	h2_obs	h2_obs_se	h2_int	h2_int_se	Gcov int	Gcov int se	Category	ethnicity
Maths	Intelligence	28530673	1.1973	0.1576	7.5974	3.02E-14	0.1878	0.0105	1.0046	0.01	0.0348	0.0061	cognitive	European
Maths	Childhood IQ	23358156	1.0198	0.1597	6.3839	1.73E-10	0.3045	0.0504	0.993	0.0114	0.2701	0.0072	education	European
Maths	Years of schooling 2016	27225129	0.894	0.1239	7.2161	5.35E-13	0.1249	0.0048	0.9378	0.0128	0.0046	0.0066	education	European
Maths	Years of schooling (proxy cognitive performance)	25201988	0.8964	0.1565	5.7269	1.02E-08	0.1075	0.0077	1.0243	0.0107	-0.0018	0.0067	education	European
Maths	Years of schooling 2013	23722424	0.8543	0.1453	5.881	4.08E-09	0.0838	0.0064	1.0187	0.0105	-0.0197	0.0063	education	European
Maths	College completion	23722424	0.8544	0.1481	5.7694	7.96E-09	0.0783	0.0063	1.0225	0.0102	0.0192	0.0061	education	European
Maths	Autism spectrum disorder	0	0.3986	0.1201	3.3181	0.0009	0.4562	0.0538	0.9644	0.0081	0.001	0.0053	psychiatric	European

trait1	trait2	PMID	rg	se	z	p	h2_obs	h2_obs_se	h2_int	h2_int_se	gcov_int	gcov_int_se	Category	ethnicity
Maths	Attention deficit hyperactivity disorder (GC)*	27663945	-0.6147	0.2551	-2.4096	0.016	0.0794	0.031	0.9923	0.0091	-0.121	0.0063	psychiatric	European
Maths	Attention deficit hyperactivity disorder (No GC)*	27663945	-0.6165	0.2562	-2.4059	0.0161	0.0801	0.0315	1.0071	0.0093	-0.1214	0.0064	psychiatric	European
Maths	Depressive symptoms	27089181	-0.3646	0.1084	-3.3645	0.0008	0.0464	0.0041	1.0016	0.0091	-0.0017	0.0059	psychiatric	European
Maths	Neuroticism	27089181	-0.1708	0.0845	-2.0221	0.0432	0.089	0.0074	0.9867	0.0134	-0.0008	0.0067	personality	European
Maths	ICV	25607358	0.188	0.1742	1.0793	0.2804	0.195	0.0477	0.9986	0.0078	0.0013	0.0057	Brain volume	European
Maths	Mean Accumbens*	25607358	0.2937	0.2435	1.2059	0.2278	0.0834	0.0377	0.9799	0.0073	-0.0078	0.0053	Brain volume	European
Maths	Mean Caudate	25607358	-0.0511	0.1326	-0.3853	0.7	0.2361	0.043	0.976	0.0081	-0.0007	0.0051	Brain volume	European
Maths	Mean Hippocampus	25607358	0.0305	0.1942	0.1568	0.8754	0.1418	0.0438	0.9901	0.008	0.0049	0.0058	Brain volume	European
Maths	Mean Pallidum	25607358	0.1536	0.163	0.9426	0.3459	0.1789	0.0476	0.9742	0.0086	-0.011	0.0061	Brain volume	European
Maths	Mean Putamen	25607358	0.0448	0.138	0.3248	0.7453	0.2619	0.0507	0.9602	0.0088	-0.0006	0.006	Brain volume	European
Maths	Mean Thalamus	25607358	0.1746	0.1778	0.9821	0.3261	0.1394	0.0393	0.9775	0.0076	-0.0083	0.0051	Brain volume	European
Maths	Anorexia Nervosa	24514567	0.0789	0.0863	0.9141	0.3607	0.59	0.032	0.8674	0.0089	-0.0089	0.0057	psychiatric	European
Maths	Neo-conscientiousness	21173776	-0.0235	0.2463	-0.0953	0.924	0.0706	0.0332	1.0006	0.0085	-0.005	0.0056	personality	European
Maths	Neo-openness to experience	21173776	0.2994	0.199	1.5046	0.1324	0.1049	0.0304	0.9928	0.0083	-0.0015	0.0059	personality	European
Maths	Attention deficit hyperactivity disorder*	20732625	-0.2353	0.2262	-1.0404	0.2982	0.2691	0.1018	1.0016	0.0079	-0.0121	0.0053	psychiatric	European
Maths	Bipolar disorder	21926972	0.2075	0.1135	1.828	0.0676	0.4454	0.0405	1.0176	0.0086	-0.009	0.0057	psychiatric	European
Maths	PGC cross-disorder analysis	23453885	0.0117	0.1177	0.0993	0.9209	0.172	0.0139	1.0152	0.0128	-0.0106	0.0078	psychiatric	European
Maths	Major depressive disorder	22472876	-0.168	0.148	-1.1348	0.2565	0.1738	0.0309	1.0044	0.0081	-0.0076	0.0058	psychiatric	European
Maths	Schizophrenia**	25056061	-0.0326	0.064	-0.5084	0.6112	0.4701	0.019	1.0383	0.0141	-0.0082	0.0073	psychiatric	Mixed
Maths	Subjective well being	27089181	0.1032	0.1092	0.9449	0.3447	0.0244	0.0023	1.0053	0.0093	0.0026	0.0055	psychiatric	European
Maths	Neuroticism*	24828478	-0.2547	0.1764	-1.4437	0.1488	0.0154	0.0035	1.0022	0.0079	0.0113	0.0057	personality	European

* These data may yield results <.0 or >1 due to relative low Z score of the SNP heritability of the trait

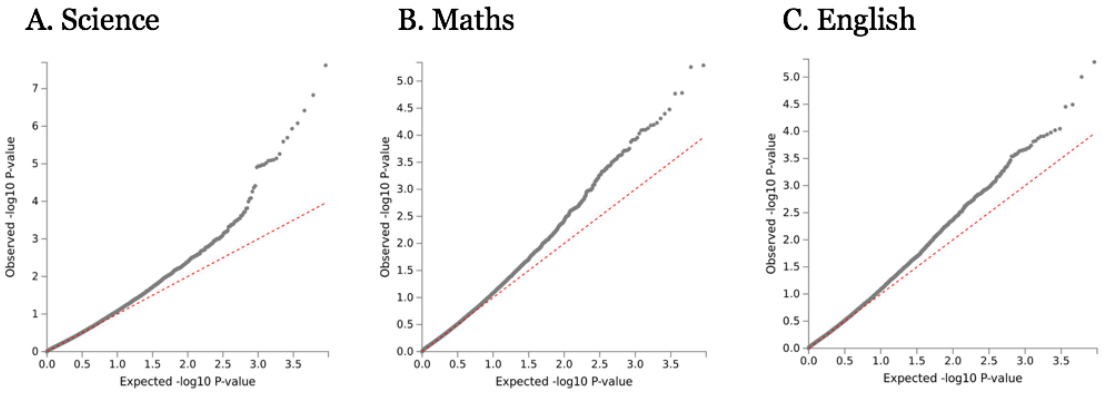
** These data may yield less robust results due to minor departure of the LD structure

Supplementary table 8.6 LD score genetic correlations results for English

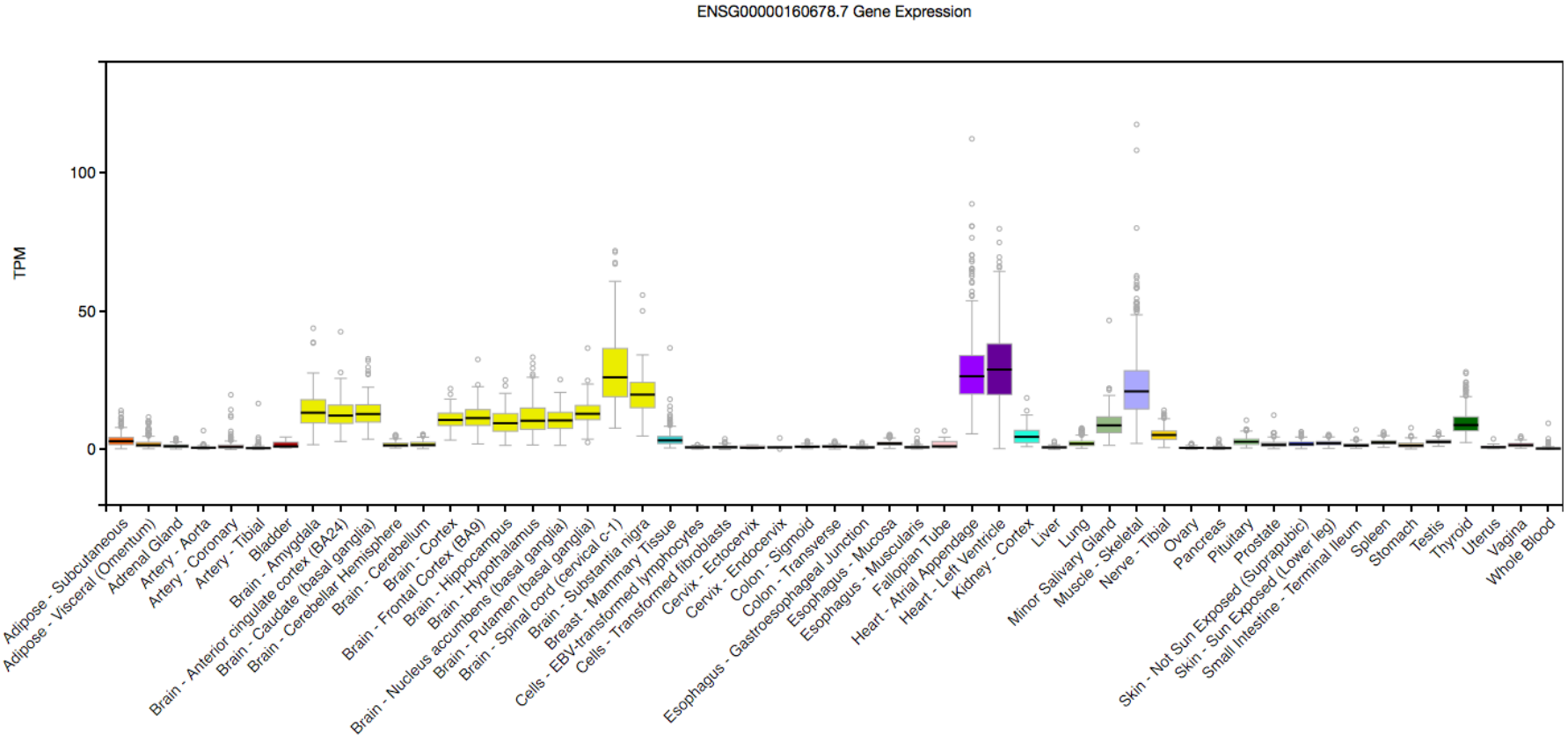
trait1	trait2	PMID	rg	se	z	p	h2_obs	h2_obs_se	h2_int	h2_int_se	gcov_int	gcov_int_se	Category	ethnicity
English	Intelligence	28530673	1.2608	0.1877	6.718	1.84E-11	0.1876	0.0105	1.0049	0.0101	0.0203	0.0061	cognitive	European
English	Childhood IQ	23358156	1.1959	0.2397	4.9882	6.09E-07	0.3044	0.0504	0.9931	0.0114	0.2217	0.0078	education	European
English	Years of schooling 2016	27225129	0.994	0.15	6.6259	3.45E-11	0.1249	0.0048	0.9375	0.0128	-0.0032	0.0061	education	European
English	College completion	23722424	0.9127	0.1723	5.2979	1.17E-07	0.0783	0.0063	1.0225	0.0102	0.0089	0.0063	education	European
English	Years of schooling (proxy cognitive performance)	25201988	0.8793	0.1684	5.2225	1.76E-07	0.1075	0.0077	1.0243	0.0107	-0.0064	0.0066	education	European
English	Years of schooling 2013	23722424	0.8779	0.1734	5.062	4.15E-07	0.0838	0.0064	1.0187	0.0105	-0.0241	0.0063	education	European
English	Neo-openness to experience	21173776	0.521	0.2338	2.2285	0.0258	0.1044	0.0305	0.9929	0.0083	-0.0029	0.0057	personality	European
English	Autism spectrum disorder	0	0.3942	0.136	2.8981	0.0038	0.4573	0.0531	0.9642	0.008	-0.0011	0.0056	psychiatric	European
English	Anorexia Nervosa	24514567	0.277	0.0986	2.8081	0.005	0.5911	0.032	0.867	0.0089	-0.012	0.0058	psychiatric	European
English	Attention deficit hyperactivity disorder (GC)*	27663945	-0.7208	0.2777	-2.5959	0.0094	0.0795	0.031	0.9922	0.0091	-0.1176	0.0062	psychiatric	European
English	Attention deficit hyperactivity disorder (No GC)*	27663945	-0.7239	0.2784	-2.6007	0.0093	0.0803	0.0315	1.007	0.0092	-0.118	0.0063	psychiatric	European
English	Depressive symptoms	27089181	-0.2672	0.1159	-2.3051	0.0212	0.0464	0.0041	1.0018	0.0091	0.0006	0.0057	psychiatric	European
English	Neo-conscientiousness	21173776	-0.1414	0.2706	-0.5226	0.6012	0.0703	0.0332	1.0007	0.0085	-0.0057	0.0056	personality	European
English	Neuroticism	27089181	-0.1016	0.0902	-1.1272	0.2597	0.089	0.0074	0.9867	0.0134	-0.003	0.007	personality	European
English	Attention deficit hyperactivity disorder*	20732625	-0.4499	0.248	-1.8141	0.0697	0.2682	0.102	1.0017	0.0079	-0.0078	0.0056	psychiatric	European
English	Bipolar disorder	21926972	0.1962	0.1383	1.4191	0.1559	0.4454	0.0405	1.0176	0.0086	-0.0058	0.0062	psychiatric	European
English	PGC cross-disorder analysis	23453885	0.0851	0.1161	0.7332	0.4634	0.172	0.0139	1.0152	0.0128	-0.0022	0.0084	psychiatric	European
English	Major depressive disorder	22472876	0.0353	0.1562	0.226	0.8212	0.1745	0.0309	1.0041	0.008	-0.0034	0.006	psychiatric	European
English	Schizophrenia**	25056061	0.0652	0.0672	0.97	0.3321	0.4702	0.019	1.0381	0.0141	-0.0046	0.0072	psychiatric	Mixed
English	Subjective well being	27089181	-0.1243	0.1224	-1.0158	0.3097	0.0243	0.0023	1.0057	0.0093	0.0089	0.0058	psychiatric	European
English	Neuroticism*	24828478	-0.0993	0.1915	-0.5188	0.6039	0.0153	0.0035	1.0025	0.0079	0.0042	0.0062	personality	European

trait1	trait2	PMID	rg	se	z	p	h2_obs	h2_obs_se	h2_int	h2_int_se	gcov_int	gcov_int_se	Category	ethnicity
English	ICV	25607358	0.0622	0.1838	0.3384	0.7351	0.1959	0.0478	0.9984	0.0078	0.0062	0.0057	brain volume	European
English	Mean Accumbens*	25607358	0.3856	0.2739	1.4077	0.1592	0.0837	0.0377	0.9798	0.0073	-0.0069	0.0056	Brain Volume	European
English	Mean Caudate	25607358	-0.0022	0.1599	-0.0136	0.9891	0.2362	0.0429	0.976	0.0081	-0.0015	0.0055	Brain Volume	European
English	Mean Hippocampus	25607358	0.0977	0.2117	0.4617	0.6443	0.1427	0.0437	0.9898	0.0081	-0.0023	0.0056	Brain Volume	European
English	Mean Pallidum	25607358	0.2943	0.209	1.4078	0.1592	0.1794	0.0474	0.974	0.0086	-0.0134	0.006	Brain Volume	European
English	Mean Putamen	25607358	0.1787	0.1789	0.999	0.3178	0.2627	0.0507	0.9599	0.0088	-0.0034	0.0067	Brain Volume	European
English	Mean Thalamus	25607358	0.2905	0.2118	1.3716	0.1702	0.139	0.0392	0.9776	0.0076	-0.0118	0.0051	Brain Volume	European

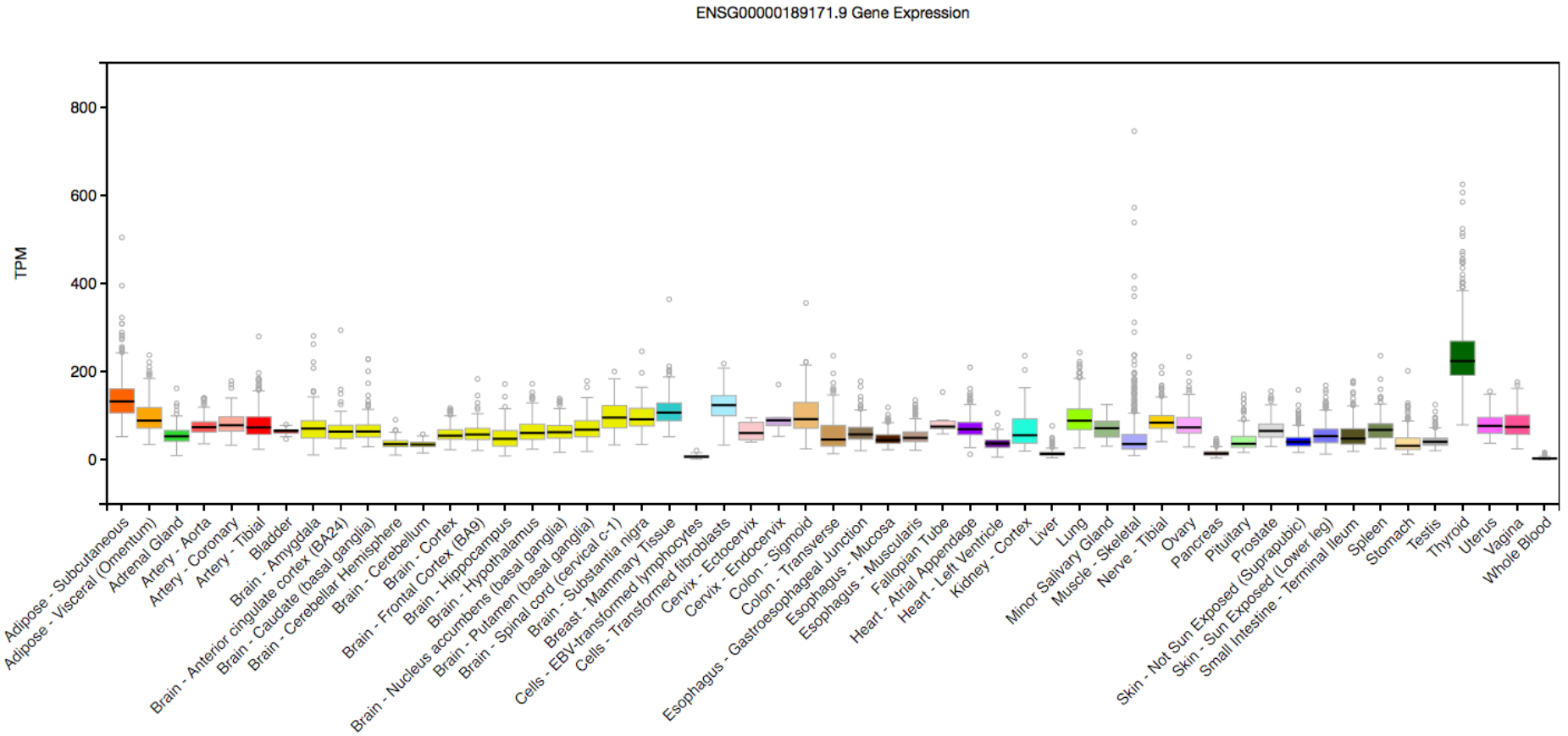
* These data may yield results <.0 or >1 due to relative low Z score of the SNP heritability of the trait
** These data may yield less robust results due to minor departure of the LD structure



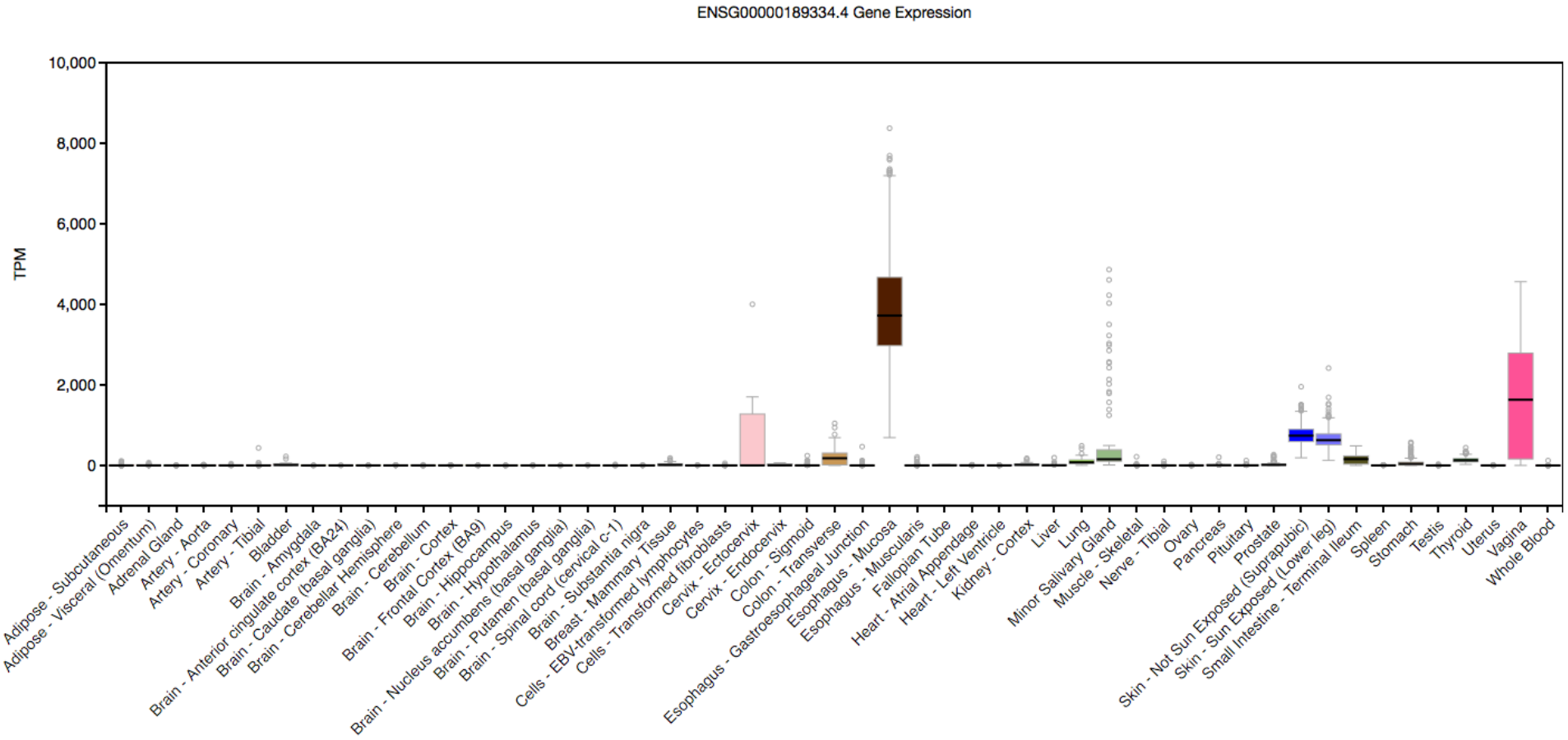
Supplementary Figure 8.1: *Gene-based Q-Q plots for English, maths and Science*



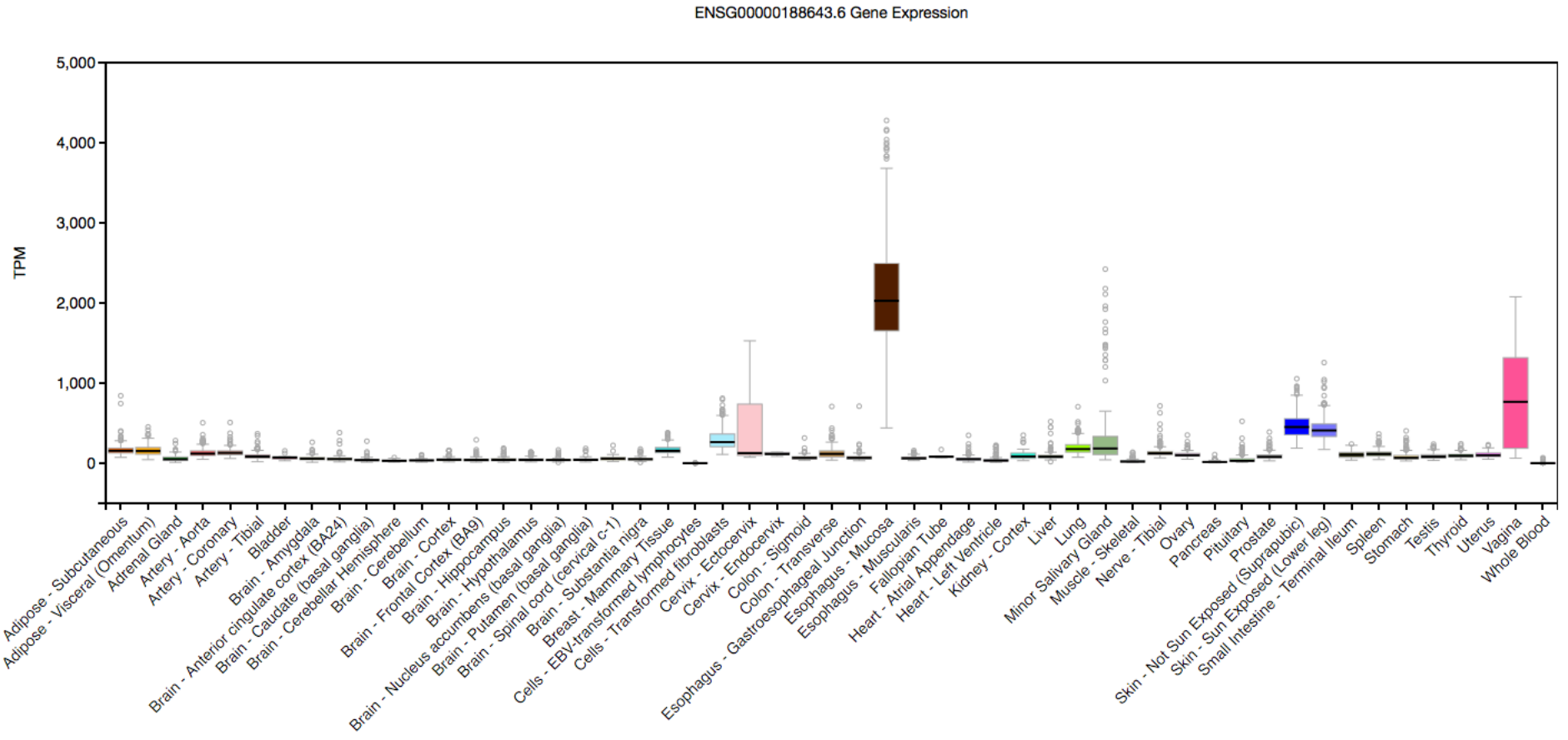
Supplementary Figure 8.2: *S100A1 gene expression data from GTEx Portal*



Supplementary Figure 8.3: *S100A13 gene expression data from GTEx Portal*



Supplementary Figure 8.4: *S100A14 gene expression data from GTEx Portal*



Supplementary Figure 8.5: *S100A16 gene expression data from GTEx Portal*