Neurobiological Mechanisms of Externalising in Adolescence

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Submitted to fulfil the requirements of the Doctorate in Clinical Psychology (D.Clin.Psy.)

Thesis Volume 1

June 2023

University College London

Thesis declaration form

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

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Overview

This thesis explores externalising behaviour and possible developmentally sensitive reward-processing mechanisms in early adolescence. Initially, Part One provides a conceptual introduction to this topic. It discusses the conception and definition of adolescence and externalising, followed by a discussion of the association between externalising, reward processing and neurological findings in adolescents. Here the focus is on theoretical understandings and empirical evidence.

Part Two describes a research study of secondary data derived from the Adolescent Brain Cognitive Development (ABCD)[SM] Study. The ABCD Study is a comprehensive longitudinal project which is ongoing. The data employed in this study are from two time points: baseline (when participants are aged 9-10) and follow-up (when participants are 11-12). The study examines the relationship between externalising and the performance of two experimental paradigms – the Monetary Incentive Delay and Stop Signal Task – which elicit anticipatory and receipt components of reward-processing, impulsivity and error monitoring. Region of Interest (ROI) analysis of functional magnetic resonance imaging blood-oxygen-level-dependent signal has been used to examine the relationship between externalising and brain activation in response to different task conditions. Regression analyses assess these associations cross-sectionally at both time points and longitudinally. Findings provide evidence of a causal link between brain activation and externalising. However, factors of sex, socioeconomic status, puberty and IQ may be more useful in identifying those at risk of developing externalising. The implications and limitations of this study are discussed.

The final part of this thesis, Part 3, critically appraises this work and the research process.

Impact statement

This research has some key implications for academic research and clinical practice relating to adolescent behaviour and neurobiological understanding of reward processes.

This thesis includes an empirical study of secondary data derived from The ABCD Study®. The ABCD Study captures a broad variety of multifaceted information relating to the biological, environmental, neurological, familial, psychological and social development of approximately 11,000 9-10-year olds, the largest of its kind. Therefore, analysis of this study data has implications for understanding adolescent development. Mental health research examining the critical developmental period of adolescence lags behind that of adult research. This thesis provides evidence implicating neurobiological reward processing networks in the development of externalising during adolescence, meeting a gap within research.

Most previous task-fMRI research is underpowered due to small sample sizes, which can result in the inflation of effect sizes and reduced reproducibility. This thesis is sufficiently powered to detect small effects due to relying upon a large sample. It so has significant implications given that it has reproduced findings from smaller-scale samples and may provide more accurate information regarding effect sizes.

The findings of this study suggest that externalising is associated with specific neural activations in contexts of reward. This supports a growing body of research which implicates neurobiological systems in the development of externalising. As this study assesses relationships longitudinally it can draw conclusions about the nature of relationships over time, which has implications for

identifying the roles of neural mechanisms in behaviour. This addresses current limitations in the literature of a lack of high-quality longitudinal studies. Findings suggest that brain activations in response to reward processing stimuli at age 9-10 can predict externalising at age 11-12. This study also provides recommendations for future research.

This research suggests that externalising is partly explained by differences in neurological functioning in response to anticipation and receipt of reward and loss, as well as impulsivity and error monitoring. This may provide some rationale for research into developing behavioural interventions which aim to modify these processes.

Understanding that there could be a neurobiological basis for externalising behaviour may also impact how individuals who present with externalising behaviour are viewed by clinicians and society, which may result in increased compassion towards individuals who may be highly stigmatised and excluded. This could substantially benefit these individuals' social functioning and psychological wellbeing.

While this study has found evidence of neurobiological relevance to externalising, it has also highlighted the relationships between externalising and sex, pubertal development, socioeconomic status and intelligence. These factors may be more amenable to targeted interventions to mitigate their negative effects compared to targeting neurobiological networks. Understanding these factors and improving the quality of life for those from low socioeconomic status would likely reduce the prevalence of externalising behaviours generally.

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Acknowledgements

I would like to thank my research supervisor and course tutor Christina Carlisi for her support throughout my time on the DClinPsy course. I am extremely grateful for your support during some tough moments and for supporting my foray into the world of fMRI. Alice – I'm so glad we could work alongside each other during this research process.

Completing yet another university qualification was an easy decision because I know I have the love and support of my friends and family. In particular, Tala and Sakshi have been my key motivators during the writing of this thesis. Alison, Ewan, Lewis, Rachel, Jenny, Alex, and Blythe - thank you for being my people.

Part One: A conceptual introduction to the neurobiological role of reward processing and impulsivity in adolescent externalising.

Introduction

The purpose of this conceptual review is to explore the literature base related to reward processing and impulsivity in adolescence. Initially, definitions and understanding of what period 'adolescence' refers to will be addressed. This area has changed over recent years due to research findings informed by neurocognitive methods and understanding pubertal markers. Then externalising disorders will be defined and discussed in the context of the adolescent period alongside theoretical explanations for the development and risk of developmental disorders. Finally, empirical research will be discussed examining the role of the brain and cognitive factors in the relationship between adolescence and reward processing and impulsivity. Literature on these topics has been searched in a structured manner. For example: ("adolesc*" OR teen* OR youth* OR young (person* OR people*) AND (externalising OR risky OR risk-taking OR impulsiv* OR (substance AND (use* OR disorder*) OR devien* OR disrupti* OR conduct) AND fMRI. Searches were conducted via Ovid hosted databases including psychINFO, MEDLINE and EMBASE, between September 2022 and April 2023. From here, key papers, including reviews and empirical papers, were identified and used to inform the conceptual introduction.

Defining Adolescence

Adolescence, a term used interchangeably with young people, teenagers etc., refers to the period between childhood and adulthood. Often adolescence is considered to begin with the biological developmental marker puberty and ends with a social marker of independence or a temporal marker, such as reaching the age of 18. At this

point, a person is legally considered to be an adult. Due to the contextual dependence of this concept, definitions are arguably vague and variable. Precise definitions vary within the literature as a result.

The conceptualisation of adolescence has also been expanding. Puberty is considered a stage of reproductive life rather than a single event and is marked by biological and sexual maturation (Styne & Grumbach, 2011). Pubertal changes depend upon pre-existing patterns of endocrine secretion; however, its onset is a complex process that is not fully understood by researchers (Lee & Styne, 2013).

In girls, the onset of puberty is the development of breast tissue, although menstruation is often used as a proxy for the onset of puberty. Menstruation occurs around three years after the onset of puberty (Lee & Styne, 2013). In males, the most accurate method of determining the onset of puberty is an increase of testicular volume, which typically occurs 6-12 months before other signs of male puberty (Lee & Styne, 2013; Tanner & Whitehouse, 1976).

Researchers have noted that the age of onset of puberty appears to be decreasing over time (Lee & Styne, 2013). For example, within a sample of 2095 Danish girls, the mean age of thelarche (breast tissue development) decreased from 10.88 years to 9.86 years after adjusting for BMI (Aksgleade et al., 2009). Male puberty has exhibited similar decreases in onset compared to previous studies. For example, Sorensen et al., (2010) reported a decrease of onset age from 11.92 to 11.66 years. One caveat of research is that the majority of these studies draw from populations in the US or Western Europe and thus cannot necessarily be generalised globally. However, Eckert-Lind et al.,'s (2020) meta-analysis drawing on literature from global samples, found that in girls, the age of thelarche decreased at a rate of approximately three months per decade between the years 1977 to 2013. However,

there is geographical variation in the age of onset. In Africa, the onset age was 10.1-13.2 years, while the US has an onset age of 8.8-10.3 years. Authors propose that the age of puberty onset may be a sensitive marker of human health, given that correlates of onset include nutrition, socioeconomic status, and stress (Eckert-Lind et al., 2020).

Herting et al., (2021) analysed Pubertal Development Scale (PDS, Petersen et al., 1988) scores, perceived physical maturation and hormone levels to replicate the finding that females were at a more advanced stage of pubertal development compared to boys at age 9-10 years. Indeed, they found that around two-thirds of females aged 9-10 were at the early pubertal stage or later compared to only one-third of boys. They also demonstrated that more advanced puberty was related to weight, ethnicity (more advanced among Black youth) and sociodemographic factors.

The age of pubertal onset is important to understand given that pubertal onset is the beginning of the cascade of physiological, neurological and social changes associated with this developmental phase. Research has suggested that puberty may be implicated in various psychological outcomes. As well as physiological changes, such as hormone levels, puberty is related to changes in sexual interest, motivation, psychology and social factors. Blakemore et al., (2010) argue that puberty plays an important role in brain and cognitive development. Thus, puberty and chronological age should be measured within studies of adolescents.

Blakemore et al., (2010) propose that gonadarche (growth of ovaries in females and testes in males resulting in increased production of sex hormones) typically begins between the ages of 8 and 14 in females (mean age 11) and between ages 9 and 15 in males (mean age 12), while adrenarche (activation of the hypothalamic-pituitary-adrenal axis) often begins earlier, between 6 and 9 in females and 7 and 10 in males (Dorn, 2006; Grumbach & Styne, 2003). Steroid and adrenal hormonal changes in

puberty also influence the brain and behaviour through organisational and activating processes. Blakemore et al., (2010) explain that gonadal hormones (testosterone and oestrogen) act upon dormant neural circuits to activate adult reproductive behaviours and also result in structural reorganisation and plasticity in the brain (see Blakemore et al., 2010, for further detail).

As this process of structural reorganisation and plasticity is not well understood in humans, we can look to animal studies demonstrating reorganisation in sensory, motivational and attentional processes. The evolutionary interpretation of these changes is that they facilitate sexual behaviour. For example, in the rodent nucleus accumbens, pubertal increases in testosterone remodel neural circuits increasing motivation to reward seeking-behaviours such as sexual behaviours (Braams et al., 2016). Alongside the neurological changes related to puberty, Dahl (2004) cites that evidence supports puberty-specific maturation within the domains of romantic motivation, sexual interest, emotional intensity, sleep and arousal regulation, appetite, risk for affective disorders in females and increase in risk, novelty and sensation-seeking.

Why is adolescence relevant to emotional and behavioural disorders?

Dahl (2004) describes adolescence as a paradox in that adolescents are strong and resilient from a physiological and developmental perspective, yet they experience difficulties in the control of behaviour and emotion. For example, adolescents have improved decision-making capacity. However, they simultaneously demonstrate high rates of reckless behaviour. Although this is a simplified example, understanding the vulnerable period of adolescence is complex. It requires an approach to consider multiple mechanisms that interact, including biology, neurobiology, emotion,

cognition and social factors. Research indicates that adolescence is a critical period for the onset of emotional and behavioural psychopathology; the onset of internalising and externalising disorders sharply increases during adolescence. The median age of onset for anxiety and impulse control disorders is 11 years. Furthermore, half of all lifetime cases of DSM-IV disorders occur before age 14, with 75% occurring before age 24 (Kessler et al., (2005).

While adolescence may represent a period of vulnerability to emotional and behavioural difficulties, there is also the capacity for this to be a period of opportunity to positively influence development, provided that we have a good understanding of vulnerability mechanisms. The current focus is externalising behaviour and understanding mechanisms that contribute to developing and maintaining externalising behaviour in young people. The remainder of this chapter will discuss externalising and potential contributary mechanisms.

Externalising Behaviour

Definition and Conceptualisation

Mental health disorders are frequently considered to comprise two dimensions: internalising and externalising (Plenty et al., 2021). Internalising problems relate to problems and symptoms that are internally focused, such as depression or anxiety. Conversely, externalising problems are those or symptoms that impact the external environment and others within it, for example, risk-taking, impulsivity, sensation-seeking, aggressiveness and conduct problems. Externalising difficulties have generally been conceptualised as psychiatric disorders, non-clinical behaviours and/or personality traits (Barr & Dick, 2020).

Diagnostic frameworks would consider that externalising disorders are characterised by problematic behaviours related to poor impulse control, rule-breaking, aggression, impulsivity and inattention. Child and adolescent-specific diagnoses include conduct disorder, oppositional defiant disorder and attention-deficit-hyperactivity disorder (ADHD; Samek & Hicks, 2014). Other relevant categories include those with problematic alcohol or substance use or delinquent or offending behaviour. It may also be that some externalising behaviours are present but may not breach a threshold of a diagnostic category (e.g. risky sexual behaviour or alcohol or drug use that may not have been identified as problematic or come to the attention of services).

Externalising behaviour is also important in frameworks of personality and personality disorder. For example, antisocial behaviour and personality traits often overlap with externalising behaviours and disorders. We know that childhood externalising disorders predict personality disorder diagnosis in adulthood. For example, a ten-year longitudinal follow-up study found that oppositional defiant disorder significantly increased the risk for conduct disorder and antisocial personality disorder (Biedermam et al., 2008).

Some have proposed an alternative to the internalising and externalising dimensional models of psychopathology. P-factor is a means of understanding psychiatric disorders by three factors: internalising, externalising and thought disorder (Capsi et al., 2014). P is a superordinate factor that captures the shared variance between internalising and externalising disorders. Some research has found P to be a stronger predictor over traditional categorical diagnoses of neurocognition, impulsivity, fear, distress and social adversity than internalising or externalising factors alone (Brislin et al., 2021). Given high comorbidities between internalising and

externalising and shared risk factors, P may be helpful in conceptualising psychological difficulties.

Prevalence

Epidemiological research has often employed a categorical interpretation of externalising and estimates of lifetime prevalence vary between categories. For example, Hamdi and Iacono (2014) examined the Minnesota Twin Family Study and estimated the lifetime prevalence of alcohol dependence to be 14.1% (8.2% females; 20.1% males); cannabis dependence to be 7.5% (5.9% females; 9.2% males); and antisocial personality disorder to be 3.5% (1.2% females and 5.8% males). A longitudinal study of Swedish Children (part of the Children of Immigrants Longitudinal Survey in Four European Countries (CILS4EU, www.cils4.eu) found that 25.16% of adolescents (mean age 14.02, SD=0.26) exhibited externalising behaviour, with 14.42% reporting one behaviour and 10.74% reporting more than one behaviour considered a marker of externalising problems (such as damaging property, stealing from a shop or a person, truanting from school, receiving punishment at school, arguing with teachers). UK-based cohort studies have provided varying estimates of externalising prevalence in children and young people. Data from the ALSPAC cohort indicate that 15.3% of adolescents presented with externalising problems (Huisman et al., 2010); the eRISK study found that externalising problems affected 8.5% of children (Jaffee et al., 2002); and the Millennium Cohort Study demonstrates that up to 11% of children had clinically significant internalising and externalising difficulties (Hope et al., 2021). Based on the National Comorbidity Survey Replication, the lifetime prevalence of ADHD in the USA is estimated to be 8.1% (Hamdi & Iacono, 2013).

Sex differences

One of the most studied factors influencing externalising disorder is sex. Literature indicates that in childhood, girls tend to show greater levels of depression and anxiety (internalising characteristics), while boys show more aggression and non-compliance (externalising characteristics; Chaplin & Aldao, 2013). Using the Adolescent Brain Cognitive Development (ABCD) study data, Loso et al., (2021) found that males demonstrated higher levels of clinically significant psychopathology across all syndromes – internalising and externalising. One limitation of research of externalising behaviours is that males and females may present differently to each other. In recent years research has identified that girls may be under-diagnosed with ADHD, for example, due to socialisation differences and alternative presentation compared with symptomology in males (Stibbe et al., 2020).

Recent research has highlighted nuanced sex differences of externalising disorders. Murray et al., (2022) examined the trajectories of mental health issues in adolescence to find that although there are sex/gender differences in mental health symptoms and course, in both males and females, there is a strong tendency for multiple issues to co-occur. Of note is that they could not model a trajectory of females being 'severely affected' by externalising disorders, nor could they model a trajectory of males 'severely affected' by internalising disorders. This suggests that the number of females severely affected by externalising disorders (and males severely affected by internalising disorders) was insufficient. What we may take from this is that females are unlikely to present with severe symptoms associated with externalising disorders. Murray et al., (2021) found that ADHD and conduct symptoms were more prominent for males and that males were more likely to begin adolescence with symptoms of ADHD and that these symptoms more quickly escalated to clinical

ranges. In contrast, females were more likely to begin adolescence with symptoms below a borderline range and show a later escalation (around age 13) to clinical ranges of ADHD.

Regarding conduct problems, Murray et al., (2021) found antisocial adolescent behaviour to be driven mainly by a small group (6.1% of the sample) of males. The group representing the males severely affected showed elevated symptoms when entering adolescence and a steady increase until age 15. In contrast, the two less severely affected groups showed similarity across gender, and those groups demonstrated low or moderate symptoms that were relatively stable across adolescence. From this research, attention should be paid to males before adolescence or early adolescence to identify and prevent the onset or escalation of severe externalising symptom trajectories.

Moffitt's (1993) developmental taxonomy proposes two main categories of antisocial offenders. Firstly, some persistently offend over their lives, beginning in early childhood (Moffitt, 1993). This group show pervasive, persistent antisocial behaviour from early childhood to adulthood. These individuals are responsible for various offences, from traffic to violence (Moffitt, 2018). Secondly, some exhibit similar levels of antisocial behaviour as the life-course-persistent offenders, but this occurs during adolescence only. This group is considered normative, as those who never offend are rare. Data from the Dunedin Study, a population-representative longitudinal cohort study based in New Zealand, identifies that 12% of individuals present with life-course-persistent antisocial behaviour and 23% present with adolescence-limited antisocial behaviour (Carlisi et al., 2020). Moffitt posits that our understanding of male offending is more complete than female offending, where there are mixed findings regarding childhood-limited offending (Moffitt, 2018). Research

indicates various individual and environmental risk factors for both kinds of antisocial behaviour, including personality, learning problems, social problems, attachment disruption, harsh discipline, and engagement with antisocial peers (Moffitt 2018). Given that life-course-persistent antisocial behaviour is thought to develop earlier than adolescent-limited antisocial behaviour (in childhood and adolescence, respectively), research must consider potential vulnerability factors in both childhood and adolescence.

Heritability

A recent systematic review strongly supports a genetic component of externalising behaviour (Jami et al., 2021). Larger studies found correlations between birth parents and offspring externalising, antisocial and callous-unemotional behaviours. However, they note that oppositional and ADHD behaviours in offspring were unrelated to birth parent antisocial measures. This review also identified the role of genes in the transmission of general risk for several mental health difficulties. For example, they found reliable evidence that parental phenotypes of depression, criminal behaviour, educational attainment, and substance abuse were all associated with externalising behaviours in offspring via genetic pathways (Jami et al., 2021). However, they also stress that there is a need for further research in this area to more fully disentangle genetic transmission and genetic-nurture transmission (Jami et al., 2021).

Socioeconomic Influence

Research consistently finds that social and environmental factors increase the risk of mental health difficulties, and estimates of the magnitude of this effect vary.

Recent research finds that children and adults living in the lowest 20% of household income for the UK were two to three times more likely to develop mental health difficulties compared to those in the highest 20% (Mental Health Foundation: https://www.mentalhealth.org.uk/explore-mental-health/mental-health-statistics/poverty-statistics). Furthermore, longitudinal studies have indicated that those from lower socioeconomic backgrounds have an increased lifetime risk of depression and reduced functioning in adulthood (Gilman et al., 2023; Goodman et al., 2011). Within the ABCD dataset, Maxwell et al., (2022) found that neighbourhood poverty was positively related to externalising symptoms. Thus, research and practice must consider the role of socioeconomic factors in the development of externalising behaviour and prevention interventions.

It is also essential to consider that within the UK, rates of child poverty for the year 2020-2021 were estimated at between 27% (Child Poverty Action Group, n.d.) and 31% (Joseph Rowntree Foundation, UK Poverty 2022); and, the Joseph Rowntree Foundation predicts that this increasing trend will continue due to the economic and political climate (JRF, UK Poverty 2022). Given these high levels of child poverty, it seems likely that externalising behaviour and mental health difficulties, in general, will increase in this group.

Development of externalising problems

Compared to adults, it has been observed that adolescence is associated with increased approach behaviours, including risk-taking and sensation-seeking (Galvan, 2013) and poorer inhibition (Ferguson et al., 2021). Indeed, risk-taking and reward responsiveness peak during adolescence (Galvan 2010; Galvan 2013; Braams et al.,

2015; Carver & White, 1994). This is normative to adolescence and may be evolutionarily adaptive.

Murray et al., (2021) demonstrated pre-adolescence and early adolescence as critical periods for the development of externalising symptoms and that these symptoms increase or maintain across adolescence. Of course, some externalising behaviour in adolescents is normative and may be necessary for developing independence, where adolescents typically begin to engage less with family influences and take more risks (Felson & Haynie, 2002). Social and evolutionary theorists posit that risk-taking behaviour is advantageous at this age and is related to social acceptance. We know that adolescents are particularly attuned to social factors and that social acceptance is processed similarly to other (non-social) rewards in this age group (Nelson et al., 2016). It has been hypothesised that risk-taking may facilitate social reward. For example, risk-taking may be advantageous in seeking sexual partners and successfully reproducing and thus may have been a trait that has been sexually selected. Risk-taking may also be crucial to intrasexual selection, such as through dominance displays in males which are vital to social hierarchies, obtaining sexual partners and resources and preventing other males from obtaining these resources. Dominance in adolescent boys was desirable for adolescent females (Pellegrini and Long, 2003). Social and evolutionary theories may account for the gender differences in risk-taking behaviour.

However, this behaviour goes beyond typical adolescent rebellion for some. Early puberty is related to increased psychopathology across adolescence in both sexes (see Ullsperger & Nikolas, 2017 for review). Still, there does not seem to be an interaction between sex and puberty (Loso et al., 2021).

In a keynote address, Dahl (2004) posits that adolescence is a paradoxical period whereby adolescents' physical and mental capabilities increase compared to children, and they have not suffered the effects of ageing. Yet, mortality rates increase by 200% over the same period. Critically, this increased mortality rate is not attributable to disease or other organic causes but is related to emotional and behavioural factors. In the UK, there has been an increase in adolescent mortality between 2014 and 2020, and two of the leading causes of death of 10-19-year-olds in England and Wales were accidental injury and intentional self-harm or suicide (RCPCH state of the child, 2020). A report from the CDC (2006) highlights that while progress in preventing other causes of mortality, such as disease or illness, in this age group has been made, there has not been a similar decline in mortality related to risk-taking.

Externalising behaviour has also been associated with an increased risk of suicide. It is understood that externalising disorders, such as oppositional defiant disorder, ADHD, and conduct disorder, are associated with an increased risk of suicide. Shoval et al., 2021 found that 27.4% of those with an externalising diagnosis (based on KSADS-5) presented with suicidality and that 41.1% of those with suicidality also met criteria for an externalising disorder. Of note, those prescribed ADHD medications were less likely to report suicidality compared to those without medications. Furthermore, higher externalising symptoms at baseline were associated with greater odds of suicidality at follow-up (OR, 1.33; 95% CI, 1.14-1.55; $p<0.001$), and this association was not present for those who received ADHD medications. Thus, it may be that medication to manage externalising difficulties or active treatment may protect against suicidality.

Using the ABCD dataset, Chan et al., (2022) used a machine learning approach to prospectively predict conduct disorder from initial baseline data (ages 9-10) two years (ages 11-12) later with 91.18% accuracy. They describe that risk for the development of conduct disorder was prospectively predicted, with 91.18% accuracy and an area under the curve of 0.96 (sensitivity of 89.03% and specificity of 93.44%), by "unpredictable, impulsive, deprived, and emotional external and internal contexts". The social factors of lower parental monitoring, more aggression in the household, and lower-income; psychological factors of greater ADHD, and oppositional defiant disorder symptoms, lower crystallised cognition and poorer card sorting performance; and the disrupted topology of subcortical and frontoparietal networks all contributed to the computational model to predict conduct disorder.

One hypothesis is that different environmental experiences shape common risk for externalising behaviours; protective environments result in ADHD, whereas in high-risk environments, conduct disorder and ADHD emerges (Beauchine et al., 2007; Beauchaine & Neuhaus, 2008). Data supporting this hypothesis indicates that there may be a common neural alteration for both ADHD and conduct disorder, and once antisocial behaviours become established, long-term patterns of neural processing are altered for those that progress to conduct disorder and ADHD (Beauchaine & Neuhaus, 2008; Biederman et al., 2008).

Neurobiological Mechanisms Implicated in Externalising Behaviour in Adolescents

Neurobiological research has developed various theories that attempt to at least partially account for externalising behaviour. The theoretical model known as the dual systems model (Steinberg 2008) or maturational imbalance model (Casey, 2008) is

prominent within the literature and accounts for empirical findings of risk-taking and sensation-seeking in adolescence. Fundamentally, these models attribute this behaviour to a developmental mismatch whereby the socioemotional system is at its peak, but the cognitive control system lags behind (Steinberg, 2008, Casey et al., 2008). The models differ in their predictions of the development of socioemotional and cognitive control systems in later adolescence and early adulthood. The Dual Systems Model predicts that the socieoemotional system follows an inverted-u shaped trajectory, while the cognitive control system increases steadily in strength. This means that initially the socieoemotional system is stronger and that after peaking during adolescence, the socioemotional system declines in strength. By adulthood, this theory predicts the cognitive control system to be will be more highly developed than socioemotional system (Steinberg, 2008). Whereas, Casey's (2008) model predicts that the socioemotional system peaks around mid-adolescence and then plateaus into adulthood, and the cognitive control system follows a similar trajectory but lags behind that of the socioemotional system. Casey's (2008) proposes that by adulthood the socieoemotional system and cognitive control system are equally developed.

Maturational imbalance models (e.g. Steinberg, 2008, Casey et al., 2008, Luna et al., 2015) identify the role of reward and motivational systems in response to socioemotional stimuli. Key brain areas implicated are the amygdala, nucleus accumbens, orbitofrontal cortex, medial prefrontal cortex, medial prefrontal cortex, and superior temporal sulcus (see Nelson et al., 2005).

Empirical findings support these theories and indicate that adolescence is critical for developing reward and loss processing systems (Galavan, 2010). For example, research finds that amongst the company of peers, adolescents demonstrate increased reward-seeking behaviour (Chein et al., 2011; Reniers et al., 2016; Smith et

al., 2018). Steinberg (2008) relates this to changes in the socio-emotional system. Risk-taking in the presence of peers decreases in adulthood, and Steinberg (2008) connects this to the development of the cognitive control system.

Alternatively, Erst et al., (2006) propose a triadic model emphasising the amygdala's role. They suggest that reward/novelty seeking in the face of uncertainty or potential harm is explained by 1. A strong reward system (implicating the nucleus accumbens); 2. A weak harm-avoidant system (amygdala); 3. An inefficient supervisory system (medial/ventral prefrontal cortex).

Studies have used MRI to assess brain structure and function of the developing brain (see Rosenberg et al., 2018). Such studies have implicated late childhood to adolescence as a critical period of development and support the above theories. Previous research has found that different parts of the brain develop at different stages and rates. For example, it is suggested that the prefrontal cortex, related to the top-down regulation of emotions and behaviour, undergoes the most pronounced and protracted development during adolescence (Sawyer et al., 2012; Choudhury et al., 2006; Giedd et al., 1999; Casey et al., 2010). Consequently, there may be a mismatch between the maturation of different brain areas. This may mean that the PFC (associated with cognitive processing) is relatively underdeveloped compared with other neural areas, including the limbic system (associated with emotional processing; Casey et al., 2008). These developmental mismatches have been related to externalising behaviours such as compulsive drinking (Sicilano et al., 2019) and early alcohol use (Zhao et al., 2021). This may go some way to account for the increased emotional reactivity and the development of externalising behaviours observed in adolescence (Casey et al., 2008).

Externalising and reward: the dopaminergic system

Externalising behaviours are hypothesised to be related to reward sensitivity and associated neurobiological mechanisms. Research indicates that the dopaminergic system and regions (including striatal areas) are critical for learning and reward processing across domains (including monetary, novel and social rewards; Galvan, 2010 & 2013). In response to reward, dopamine neurons fire in specific regions (dopamine is projected along the mesolimbic pathway: from the ventral tegmental area to the nucleus accumbens, within the ventral striatum and the prefrontal cortex; Valenzuela & Morton, 2014), thus reinforcing behaviour. Thus, dopamine response is critical for positive reinforcement. A classic example is animals (often rats) learning to press a lever for rewards such as food, water, cocaine or sexual contact. It has been thoroughly demonstrated that such learning fails to occur if dopaminergic systems are blocked by neuroleptic drugs or lesions (see Wise, 2004 for review). It is also thought that dopamine serves a 'drive' or priming function in that it is essential for reinforcing behaviour and is also involved in motivating it due to the anticipation of reward. Stimuli that were previously associated with reward are thought to cause motivational arousal due to a memory trace of the behaviour, thereby increasing the likelihood of the behaviour occurring. Furthermore, if dopamine systems are blocked, previously rewarding behaviours become extinguished over time (see Wise, 2004, for review). The reinforcing and motivating roles of dopamine are well established within research.

Dopamine and Externalising in Adolescents

Given that the dopaminergic system is critical to reward and learning, it is considered likely that these systems are implicated in both adaptive and maladaptive externalising behaviours. For example, substantial literature discusses the links

between the dopaminergic system and addictions. We know that experimental paradigms which elicit reward and impulsivity processes are associated with activation in frontoparietal and striatal regions (see Frost & McNaughton, 2017, Water et al., 2017, Hamilton, et al., 2020), and evidence supports that externalising symptomology is related to reward and impulsivity systems. Thus, further understanding the functionality and connectivity of these neural regions is of interest in improving the understanding of externalising.

Research also indicates that externalising behaviour is related to reward sensitivity and impulsivity and that individuals who engage in externalising behaviours may be more likely to learn from rewarding feedback and less sensitive to punishing feedback (Poulton & Hester, 2020). This could mean that externalising behaviours are causally linked to reward processing systems, and individuals may be predisposed to engage in externalising behaviour due to alterations in these processes.

One interpretation is that the mismatch in development between the socioemotional system (including striatal regions) and the cognitive control systems (including prefrontal cortex) reflects an imbalance of dopamine receptors in the prefrontal cortex relative to the striatum and that this may result in 'reward deficiency syndrome'. Blum et al., (1996) describe 'reward deficiency syndrome' as a form of sensory deprivation of the neural pleasure mechanisms resulting in a neurobiological inability to derive reward from everyday stimuli, thus resulting in greater levels of sensation-seeking, such as addictive behaviour and risk-taking (externalising behaviours).

Alternatively, there may be increased sensation-seeking due to reduced dopamine in the prefrontal cortex. The prefrontal cortex is the 'cognitive control centre' and provides top-down regulation of behaviour (see Ridderinkhof, 2006).

Theoretically, the dopamine in this region promotes negative regulatory feedback in childhood, allowing for the inhibition of behaviour. Therefore, the relative decline in adolescence is hypothesised to result in a reduced capacity for inhibitory control, thereby increasing risk-taking/sensation-seeking/externalising behaviour. This suggests a relative increase in the sensitivity of dopamine which may make sensation-seeking more rewarding and thus reinforcing. As dopamine levels redistribute with increasing age, this capacity increases in adulthood, thereby accounting for a reduction of such behaviour.

Neurobiological Changes During Adolescence

Studies have used magnetic resonance imaging (MRI) to assess brain structure and function across development (see Rosenberg et al., 2018). Normative adolescence involves profound and protracted structural neurological changes, and large longitudinal samples have consistently demonstrated changes in grey (cell bodies, synapses and neuropil) and white (myelinated axons) matter. Such studies have implicated late childhood to adolescence as a critical period of development and support dual processing and maturational imbalance theories. Structural findings indicate that there are maturational differences between cortical regions (primarily the PFC, including the ventromedial prefrontal cortex and the orbitofrontal cortex) and subcortical regions, e.g. the amygdala and ventral striatum (Casey et al., 2008; Somerville et al., 2010).

Casey et al., (2005) describe three key neurological processes occurring around adolescence. Firstly, grey-matter volume decreases in several cortical areas across adolescence. Grey matter loss occurs initially in the primary sensorimotor areas and then spreads over the prefrontal cortex, the parietal and occipital cortices and

finally, the temporal cortices. Alternatively, other findings indicate an inverted u-shaped pattern of brain development whereby grey-matter volume peaks at approximately 16 years of age, followed by a decline through late adolescence and early twenties (Giedd et al., 1999). It is thought that this decrease in volume reflects synaptic eliminations or 'pruning', resulting in the elimination of inactive and weakened synapses and the resulting strengthening of active synapses (Foulkes & Blakemore, 2018). This synaptic pruning is considered a mechanism of 'fine tuning' function (Giedd et al., 1999). Synaptic pruning is a process of 'fine-tuning' where unused neuronal connections are eliminated. Casey et al., (2005) suggest that this process begins in pre-adolescence and is largely complete by mid-adolescence.

Secondly, there is also an increase in white matter within the prefrontal cortex due to myelination, the sheathing of nerve fibres with myelin which provides insulation of the neural circuitry. Gotgay et al., (2004)'s research indicates that white matter volume increases linearly during the first two decades of life. This is attributed to axons becoming more insulated by myelin and the growth of dendrite branches which increase connectivity. Casey et al., (2005) describe this process as ongoing into the 20s and 30s. This improved connectivity accounts for the improvements observed in higher-order cognitive functions (e.g. response inhibition, planning). Thirdly, the proliferation of projections of white matter tracts across brain regions results in greater connectivity between regions and systems, such as cortical and subcortical regions. The increased connectivity between the prefrontal and limbic regions (for example, amygdala, nucleus accumbens and hippocampus) is of particular relevance. This is thought to account for improved regulation of emotion. Poorer connectivity between these regions is thought to explain impulsive and reactive behaviour observed in adolescence (Reyna & Farley 2006).

Dopaminergic system changes

Given that the brain regions that undergo dramatic reorganisation and development during adolescence are regions that are implicated in the processing of reward, it is important to consider how the dopaminergic system is functioning during this period. During adolescence, the mesolimbic dopamine system undergoes substantial changes (see Wahlstron et al., 2010, for in-depth review). These changes are challenging to examine within human adolescence; thus, theories often rely on animal samples. Animal studies show that the density of dopamine receptors (D1 and D2) in the ventral striatum, nucleus accumbens and prefrontal cortex increases from pre-adolescence in animals (rats and non-human primates) and peaks during adolescence. However, this timing differed between brain regions (Andersen et al., 1997; Wahlstron et al., 2010). Wahlstron et al., (2010) also propose that the synaptic pruning which occurs during adolescence does not prune all synapses equally. Pruning processes preferentially target glutamate receptors which results in enhanced dopamine signalling. They suggest that this pruning process may increase dopamine neurotransmission within the prefrontal cortex, where development occurs later, thereby causing excitatory-inhibitory imbalance resulting in the prefrontal cortex being 'overdosed' with dopamine (Wahlstron et al., 2010). Wahlstron et al., (2010) consider that the dopamine system is in relative over-drive during this period. This is relatively unregulated due to the structural immaturity of the prefrontal cortex, and thus behavioural inhibition is weaker. These high dopamine levels during adolescence may have the behavioural impact of increased exploration and novelty seeking, which could drive and reward externalising behaviours.

Neuroimaging studies examining mechanisms of externalising in adolescence

Structural findings

Literature fairly consistently implicates abnormal structure (e.g., cortical volume, thickness, or surface area) of grey matter regions, including the amygdala, medial prefrontal cortex and cingulate cortex in externalising behaviour (Siever, 2008; Jarvers et al., 2022; Ducharme et al., 2014; Whittle et al., 2020; Bos et al., 2018; Dennis et al., 2019; Muetzel et al., 2018). However, findings differ in terms of increases or decreases in cortical volume or thickness association with externalising. For example, Jarvers et al., (2022) found that reduced subcortical grey matter volume predicted externalising in younger adolescents, but larger subcortical grey matter predicted more externalising in older adolescents. Longitudinal neurological studies have provided insight into the relationship between brain structure and the development of externalising behaviours and identified specific regions of interest. For example, Whittle et al., (2020) found that at age eight, higher cortical thickness in the medial occipitofrontal cortex and the left post-central gyrus was predictive of externalising symptoms at age ten.

Connective structures between regions have also been considered to be of importance. White matter fibre tracts connecting the limbic system (hippocampus and amygdala) and the prefrontal cortex are some of the latest structures to develop in the adolescent brain (Andre et al., 2020). Andre et al., (2020) demonstrated that alterations in white matter fractional anisotropy and mean diffusivity linking the prefrontal cortex and limbic system was related to externalising behaviour at subclinical levels. This advanced previous literature which identified similar findings in diagnostic groups related to externalising behaviour, including conduct disorder, antisocial traits and

ADHD (Castellanos et al., 2014; Filipek et al., 1997; Gau et al., 2015; Hoogman et al., 2017).

Functional findings

Atypical brain activation can be seen via the functional magnetic resonance imaging (fMRI) BOLD (blood oxygen level dependent) signal. Changes in blood flow occur when neural activity increases in a particular brain region, which may be attributed to specific cognitive or behavioural processes. Experimental paradigms, in combination with brain imaging techniques, have been used to examine the possible role of brain functioning in externalising in adolescents. Experimental paradigms that have been designed to activate reward processing, motivation, impulsivity and impulse control networks are of particular interest and will be discussed here. One frequently used example of such tasks is the Monetary Incentive Delay task (MID; Knutson et al., 2000; Yau et al., 2012) and the Stop Signal Task (SST; Logan, 1994). Frontostriatal regions have been specifically identified as involved in reward processing and impulsivity and implicated in theories which identify development of these regions as possible factors important in externalising (Heitzeg et al., 2014; Andrews et al., 2011; Balodis & Potenza, 2015; Beck et al., 2009; Villafuerte et al., 2012; Wrase et al., 2007; Yau et al., 2012; Whelan et al., 2012; Hart et al., 2012; Smith & Cyders 2016).

Abnormal activation responses in the ventral striatum may be considered a biomarker for externalising (specifically impulsivity and addictions; Balodis & Potenza, 2015). For example, Liston et al., (2006) demonstrate that the maturity of the ventral frontostriatal pathway predicts better impulse control. Thus, frontostriatal regions have been of interest in relevant functional imaging studies.

Tasks of reward processing have often found that there are no behavioural differences in performance relating to externalising behaviour, including conduct disorder and ADHD, in adolescents (Rodriguez-Thompson et al., 2020; Crowley et al., 2010; Finger et al., 2012; Bjork et al., 2010; Geurts, van den Bergh et al., 2014). Thus, although these tasks activate the reward-processing network, these activation patterns cannot be explained purely by behavioural performance. Further tasks may lack ecological validity, as differences are not robustly seen between those with externalising presentations compared to controls.

The literature indicates some relationships between brain functioning in response to tasks eliciting reward processing and externalising in this group. In particular, the ventrolateral prefrontal cortex and striatum have been associated with externalising and disruption in activation in these regions may contribute to altered decision-making and impulse control, thereby resulting in externalising behaviour (e.g. Rubia et al., 2009).

Direction of Effects

In studies examining reward processing, there is discrepancy in findings relating to the direction of effects or patterns of activation that may be disorder-specific (for review, see Sonuga-Barke et al., 2016). For example, Rubia et al., (2009) demonstrated that a non-comorbid ADHD group had reduced activation in the bilateral ventrolateral prefrontal cortex combined with increased activation in the cerebellum. In contrast, a non-comorbid conduct disorder group had decreased activation in the cerebellum and paralimbic regions of the insula, hippocampus and anterior cingulate. Similarly, some research findings support the proposition that activation in the ventral striatum is blunted in relation to reward anticipation in those identified as at risk for

externalising (Sonuga-Barke et al., 2016; Everitt & Robbins, 2013; Konzok et al., 2021; Buckholtz et al., 2010; Salimpoor et al., 2011; Castellanos-Ryan et al., 2014). For example, Foell et al. (2016) found that high externalising predicted reduced nucleus accumbens activation.

Some propose that dopamine structures (such as the accumbens) are overactive, resulting in increased responding or perseverating behaviour (e.g. addictions; Gatzke-Kopp et al., 2009; O'Brien & Gardner 2005). This picture becomes further complicated by the use of substances as some (e.g. nicotine) increase activation in the ventral striatum and the anterior insula, both of which are implicated in the dopaminergic reward processing system). For example, Van Hoorn et al., (2020) differentiated adolescents with conduct problems from typically developing youth by differential activation during risky decision-making. They found that those with conduct problems showed greater ventral striatum activity during safe compared to risky decisions, while typically developing youth showed the opposite pattern (greater ventral striatum activity during risky decision-making). Their analysis indicated that ventral striatum activity (when responding to an experimental risk-taking paradigm) mediated the association between group (conduct problems or typically developing) and real-life risk-taking.

Differences have been identified across different aspects of reward processing. In response to reward anticipation, research finds associations between reduced activation in frontostriatal regions. A recent systematic review found that there is evidence for both heightened and blunted activation of striatal regions in response to monetary reward anticipation associated with substance use in adolescents (Goncalves et al., 2022). Authors conclude that findings often associated increased frontoparietal (striatal) activity with monetary reward in substance use but that heavy substance use

was related to decreased activation (Goncalves et al., 2022). Thus, it may be the case that increased activity in these regions is initially a vulnerability factor and that reward responsiveness may change over time due to exposure. It may also be that activation patterns are dependent upon various factors such as the perceived reward value, level of uncertainty, temporal proximity, mechanism of learning or associated risk making disentangling these factors particularly complex given the high levels of individual differences associated with such factors. Further research is needed to understand this more fully.

Similarly, altered activation has been found in other externalising groups. Increased striatal response in reward anticipation conditions has been associated with callous-unemotional traits (Huang et al., 2019). Further, reduced activation in the medial frontal cortex and thalamus in response to reward anticipation was found to be related to ADHD symptoms and polygenic risk for ADHD (Chen et al., 2021). In response to reward anticipation, hyper or hypoactivation in these regions may mean individuals have difficulties processing or responding to anticipated rewards. The implication of this may be that they have altered motivation or impulsivity (hyper-activation) or decreased self-regulation or decision-making capacity (hypo-activation). This may contribute to externalising behaviour and maintenance of impulsive or sensation-seeking. As altered activation has been found across phenotypes of externalising, it could be that activation in frontostriatal regions in response to reward anticipation is a key marker for externalising generally.

In response to reward feedback task conditions (when participants receive feedback about whether they have received a reward), research has found externalising behaviour in adolescents to be associated with altered neural activation patterns. In particular, differences are often found in the ventromedial prefrontal cortex (often, the

medial orbitofrontal cortex, the anterior cingulate cortex, caudate) and the ventral striatum (often the caudate nucleus; White et al., 2016; Finger et al., 2011; Geurts et al., 2014). This altered activation may reflect that individuals could have difficulty in processing and responding to rewards. If an individual has difficulties with this, this could disrupt the learning processes, which may facilitate or maintain externalising behaviours and sensation-seeking. Such difficulties, for example, in linking outcomes with antecedent events, could result in an impaired ability to learn how to respond to the environment. This also may result in the inflexible use of different strategies (i.e. difficulties in adapting behavioural strategies depending on the environmental cues or context). This may explain why those with externalising show perseverative behaviours, and prefer larger rewards, immediate rewards, and higher levels of aggression in response to lack of reward (Hawes et al., 2020).

Impulsivity

Delay discounting refers to the idea that the perceived value of a reward is reduced if there is a delay in its receipt, meaning that smaller immediate rewards are preferred to larger later rewards. Delay discounting, particularly the propensity to prefer smaller, sooner rewards, has frequently been related to externalising behaviours, especially impulsivity. Impulsivity (indexed by delay discounting) is often used as a measure of risk-taking behaviour. There is evidence of this being a transdiagnostic process altered across psychiatric disorders as well as a function of basic demographics such as socioeconomic status and parental education (Amlung et al., 2019). The correlation between cash-choice task performance and externalising was better modelled by shared environment rather than heritable influences (Isen et

al., 2014). This indicates that cash-choice tasks may index environmental risk for externalising in late adolescents.

Differences in behavioural responses and neurobiological patterns have been implicated in reward prediction processes and externalising behaviours. Enhanced sensation-seeking, reward sensitivity, poor response inhibition and impulsive choices (delay discounting) have been associated with particular patterns of behavioural and neurological responses (Castellanos-Ryan et al., 2014). Of importance is that personality, cognitive and neural predictors of externalising problems at 16 were stable over time. In particular, externalising was related to high levels of impulsivity and delay discounting as well as reduced activation in the substantia nigra, subthalamic nucleus and increased activation in the pre-supplementary motor area and precentral gyrus in response to successful inhibition (Castellanos-Ryan et al., 2014). Thus, these regions are implicated in inhibitory control, motivation and choice evaluation. These regions are thereby related to vulnerability to externalising problems. Some evidence suggests that increased activation in the left middle frontal gyrus, parietal cortex and posterior cingulate, related to delayed discounting, is a finding specific to externalising rather than being a transdiagnostic marker (Rodriguez-Thompson et al., 2020).

Rodriguez-Thompson et al., (2020) also demonstrated that the relationship between externalising and impaired cognitive control was strongest in the inhibition of responses to stimuli that have been previously rewarding. These findings indicate that differences in inhibition were unrelated to bottom-up regions of reward processing. Authors thereby propose that this implicates domain-general impairments of executive function, which impact cognitive control. However, this study examined

a relatively small sample of adolescents across a relatively wide age range and thus may not be able to capture developmentally nuanced changes in functioning.

When comparing high and low-sensation groups, adolescents with low sensation-seeking had stronger right inferior frontal gyrus activation associated with reward prediction error than those with higher sensation-seeking (Cao et al., 2019). Cao et al., (2019) suggest that this may indicate that high sensation seekers allocate fewer attentional resources to the discrepancy between anticipated and received outcome. In turn, this may impact future behaviour as the feedback/reinforcement stage of learning is disrupted. During reward receipt, the ventromedial prefrontal cortex was reliably activated, but the ventral striatum was reliably activated following a reward prediction error. This may indicate that the amount of reward associated with the value is specifically encoded in the ventromedial prefrontal cortex. In contrast, the reward prediction errors are coded in the ventral striatum (Cao et al., 2019).

Gender

Some gender differences in brain function in response to reward-processing tasks have also been found. This may indicate that reward processing networks are largely similar but have some specific differences between males and females. For example, previous findings indicate that adolescent males engage in more risk-taking behaviour than females (Steinberg, 2004). This research indicates that the gender differences observed in the study of adults are present during adolescence and supports theoretical and other empirical findings of gender influences on adolescent brain function. Another potential explanation may be that sex hormones play a role. Pubertal development involves changing sex hormones, and these have been implicated in neurological responses in males and females. For example, Op de Macks et al., (2011)

demonstrated a positive correlation between testosterone and striatal activation in response to monetary reward in males and females.

Studies of Diagnostic Categories and Brain Activation

Research has linked particular patterns of neurological activation in response to reward processing paradigms to specific diagnoses or risk groups, which will be summarised.

Drug/substance risk/use

Risk for substance or alcohol abuse disorders has been related to alterations in activation in response to rewards even when externalising symptoms are absent (Gottlieb et al., 2012, 2010; Heitzeg al., 2010). Similarly, differences in inhibitory activation and reward activation in reward processing paradigms (e.g. Monetary Incentive Delay, Go/No-Go) have been used to differentiate high and low-risk groups, with deactivation in the caudate being highlighted as related to reduced externalising symptoms and being considered low-risk for alcohol use problems (Martz et al., 2021).

Research findings may suggest that those who are at risk of alcohol use difficulties are less able to deactivate the frontoparietal regions during successful inhibition (Heitzeg et al., 2010). This may account for behavioural findings and supports other research findings indicating that successful inhibition relies on activating task-related brain regions and deactivating irrelevant brain regions (Greicius et al., 2003).

A general consensus within the literature identifies striatal and prefrontal area involvement in risk for and presence of alcohol and/or drug use. Thus, pre-existing abnormality in striatal and prefrontal functioning in those at risk for externalising

behaviours may impact motivation and reward systems. Additionally, findings indicate that prefrontal areas, which down-regulate behaviour, may become less efficient with substance use. Combined, these alterations may dysregulate this circuitry. One discrepancy within the literature is the direction of relationships, with some studies reporting externalising behaviour being associated with activation (e.g. Durston et al., 2002) and others reporting associations with deactivation (e.g. Hester et al., 2004); Stevens et al., 2007).

ADHD

Differences in the function of the ventral striatum have been causally linked to the development of substance use disorders, particularly in those at increased risk for ADHD (Carey et al., 2017) observed increased response in the ventral striatum to mediate a causal pathway between polygenic risk for ADHD and problematic alcohol use in young adults.

However, this finding is not universally supported; others have not found these differences in ADHD versus control groups (including other externalising groups, e.g. Paraskevopoulou et al., 2022). Discrepancies in findings may be related to ADHD treatments, such as medications, or may be due to specific facets of externalising more generally rather than diagnostic categories.

Oppositional defiance, Conduct disorder and Callous-unemotional traits

Meta-analysis findings indicate that the best and most consistent evidence associates disruptive behaviour disorders (e.g. oppositional/conduct disorders) with dysfunction of dorsomedial, frontal and striatal regions in response to reward-based decision-making (Alegria et al., 2016). This meta-analysis also indicated that

adolescents with disruptive behavioural disorders may have altered motivation experiences, as indicated by altered decision-making in response to reward or punishment.

Reward anticipation in those with callous-unemotional traits has been associated with activation in the ventral striatum (Huang et al., 2020). However, measures of externalising generally, but not callous-unemotional traits specifically, have been significantly negatively associated with amygdala activation during punishment receipt. This may indicate that callous-unemotional traits may have specific neurobiological associations that are distinct from the more general construct of externalising. Authors argue that such findings contribute to the literature demonstrating hyper-responsivity to reward and hypo-responsivity to punishment. Within the literature, researchers have suggested that abnormal anticipatory responses in the ventral striatum may be considered a biomarker for impulsivity and addictions linked to conduct disorders (e.g. Balodis & Potenza, 2015; Hawes et al., 2021). While psychopathic traits particularly have been related to dysfunction in the ventromedial prefrontal cortex, the limbic system and hyperfunctioning of the frontostriatal region (Alegria et al., 2016). This is thought to reflect poor affect reactivity and empathy alongside hyperactive executive control, which may explain the phenotype of callous-unemotional propose to which psychopathic traits were related.

Summary

Overall, the literature indicates alterations in functional brain networks associated with various externalising presentations. Most often, the neural regions implicated are the striatal and prefrontal regions. Researchers propose that dopamine-related reward processes in these regions are critical to adolescents' normative and non-normative externalising behaviour. Some problems with the evidence base so far is inconsistency in findings. This may be for a variety of reasons. There are inconsistencies across various domains, for example, the methods used to identify brain regions of interest; experimental tasks used to activate the reward-processing network; definitions of adolescents; conceptualisation of externalising.

Furthermore, fMRI studies are frequently cross-sectional and often rely on smaller samples due to practicalities and expense. These factors make overall conclusions challenging to draw and hard to generalise to the population. Larger multisite cohort studies which collect data at regular intervals are becoming more valuable means of examining brain functioning and provide large samples of representative, rich and robustly gathered data which can mitigate limitations of previous research. The study described in Part Two aims to capitalise on the comprehensive data gathered by one such study - ABCD Study. Using this data will allow for questions to be answered relating to the nature of the relationship between reward-processing networks and externalising over the adolescent period.

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Part Two: Reward processing and impulsivity: externalising behaviour in adolescence –analysis of data from the Adolescent Brain Cognitive Development (ABCD)℠ Study

Abstract

Aims

This study aims to investigate cross-sectional and longitudinal associations between externalising and performance measures of neurobiological responses to experimental reward processing paradigms (the Monetary Incentive Delay and Stop Signal Task).

Methods

Secondary data from the ABCD Study was used in mixed effects linear regression models. At baseline, participants were aged 9-10 years old, and at follow-up, participants were 11-12 years old (n=4558, 47.13% female, 60.55% White). The externalising subscale of the Child Behavioural Checklist measured externalising. Based on prior research, regions of interest were selected, and beta-weights from contrasts of different task conditions (e.g. anticipation of reward vs no reward) were employed as measures of brain activation. Behavioural outcomes were calculated based on task response. Measures of socioeconomic status, sex, pubertal development and intelligence were also included in analyses.

Results

Findings indicate that there are neurobiological associations between ROI activation in response to reward processing tasks and current and future externalising. Externalising was associated with faster and less accurate behavioural responses; distinct patterns of activation in response to the anticipation of and loss of reward, and error processing and response inhibition.

Conclusion

This study provides evidence of the role of neurobiological mechanisms in the development of externalising behaviour. These relationships are complex and further study is required. Other mechanisms (socioeconomic status, sex, pubertal development and intelligence) were also found to significantly affect future externalising. There are clear implications for the understanding of externalising, including for future research and implications for possible interventions in the future.

Introduction

Externalising behaviour is a broad term encompassing risk-taking, impulsivity, sensation-seeking and conduct problems. They can also include diagnostic categories such as attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder, alcohol/substance use disorder, conduct disorder and antisocial personality disorder. As such, externalising behaviours encompass a wide range of behaviours and severities.

The presence of externalising behaviours in childhood and adolescence have been related to poor outcomes in adulthood, including addictions, criminal behaviour, mental health difficulties, personality disorders and mortality (Petersen et al., 2014; Biederman et al., 2008; Dahl, 2004; Shoval et al., 2021; Arslan et al., 2021). Prevalence estimates vary between 8% to 25% for children and adolescents (Huisman et al., 2010; Jaffee et al., 2002; Hope et al., 2021; Hamdi & Iacono, 2013). Indeed, the median onset age for impulse control disorder is 11 years and half of all lifetime cases of psychological disorders onset before age 14 (Kessler et al., 2005).

Externalising problems are highly comorbid (Murray et al., 2022) and demonstrate nuanced sex differences. Females are unlikely to present with severe externalising symptoms, and when symptoms are present, they progress to clinical ranges of severity more slowly (Murray et al., 2021; Chaplin & Aldao, 2013). Pubertal development has been implicated in the onset of psychological difficulties, including externalising problems. Puberty marks the onset of physiological, neurological and social changes related to adolescence, and plays a vital role in brain and cognitive development and is associated with structural reorganisation and plasticity in the

brain, including neural circuitry relating to reward processing (Blakemore et al., 2010; Stato et al., 2008).

Given the potentially high clinical, personal and social costs of externalising behaviour, substantial research has focused on understanding its development. Pre and early adolescence are acknowledged to be critical periods for the development of externalising symptoms (Murray et al., 2021; Galavan, 2010). Typically, externalising behaviours persist from childhood, increasing into early adolescence before decreasing in later adolescence through adulthood (Reef et al., 2011; Petersen et al., 2014). Studies modelling developmental trajectories of externalising indicate that any externalising behaviour during childhood or adolescence is associated with internalising and externalising in adulthood and disruptive behaviour in adulthood (Reef et al., 2011). The current understanding of life course trajectories of antisocial behaviour suggests that life-course-persistent antisocial behaviour presents earlier than adolescent-limited antisocial behaviour (Moffit, 2018). Considering examining pre-adolescents over time will provide insights into this distinction.

Brain regions involved in reward processing and impulsivity systems have been examined as potential neurobiological mechanisms related to the development of externalising behaviours. Maturational imbalance models attribute risk-taking and sensation-seeking in adolescence to a developmental mismatch between socioemotional systems (involving motivational and reward systems) and cognitive control systems (Casey et al., 2008). Empirical research has connected this theory to particular brain regions – the amygdala, nucleus accumbens, orbitofrontal cortex, medial prefrontal cortex and superior temporal sulcus (Nelson et al., 2005). The prefrontal cortex has been related to the top-down regulation of emotions and behaviour and undergoes pronounced and protracted development during adolescence

(Sawyer et al., 2012; Choudhury et al., 2006; Giedd et al., 1999; Casey et al., 2010; Cao et al., 2019). This longer developmental process leaves the prefrontal cortex relatively underdeveloped compared to other neural areas, such as the limbic system (related to emotional processing; Casey et al., 2008; Somerville et al., 2010; Giedd et al., 1999; Foulkes & Blakemore, 2018). To some extent, these findings account for increased emotional reactivity and externalising behaviours observed in adolescence.

Research indicates that externalising behaviour is related to reward sensitivity and impulsivity. Individuals who engage in externalising behaviours may be more likely to learn from rewarding feedback and less sensitive to punishing feedback (Poulton & Hester, 2020). This could mean that externalising behaviours are causally linked to reward processing systems, and individuals may be predisposed to engage in externalising behaviour due to alterations in these processes. Consequently, functional activity in the brain has been a target for research.

Functional Magnetic Resonance Imaging (fMRI) studies have indicated that alterations in response of the ventral striatum may be considered a biomarker for externalising behaviours (Balodis & Potenza, 2015; Liston et al., 2006; Rubia et al., 2009). Altered activation in this region has been demonstrated in groups of substance use, ADHD, and callous-unemotional traits (Sonuga-Barke et al., 2016; Everitt & Robbins, 2013; Konzok et al., 2021; Buckholtz et al., 2010; Salimpoor et al., 2011; Castellanos-Ryan et al., 2014; Goncalves et al., 2022). However, research conflicts regarding the nature or direction of such activation alterations (Goncalves et al., 2022).

Research indicates that the differences seen may be a more nuanced picture than increased or reduced activation. For example, differences may be seen in response to different contexts, such as anticipation, perceived reward value, uncertainty of

reward, temporal proximity or reward receipt. In particular, the medial frontal cortex has been implicated in anticipatory conditions (Huang et al., 2019; Chen et al., 2021; White et al., 2016; Finger et al., 2011; Geurts et al., 2014). This altered activation may reflect difficulties in processing and responding to rewards resulting in disrupted learning processes, thereby facilitating externalising behaviours. For example, difficulties in linking an outcome with a previous cue could result in difficulties in motivation to work for long-term rewards, thereby predisposing someone to impulsive behaviour. Impaired learning of the relationship between cue and reward may also result in frustration (possibly aggressive responses) in response to changing demands or lack of reward receipt.

Impulsivity has been used to measure risk-taking. The ability to inhibit responses and related brain activations (e.g. in the frontal gyrus, parietal cortex and cingulate regions) difficulties in inhibiting responses may be considered a marker of externalising (Castellanos-Ryan et al., 2014; Rodriguez-Thompson et al., 2020). Although, risk-taking can also be partially explained by demographic characteristics such as socioeconomic status and parental education (Amlung et al., 2019).

Behavioural tasks assessing higher-order dimensions of cognitive function have been shown to have region-specific neural correlates. In combination with experimental paradigms, fMRI has been used within research to shed light on these complex interactions and improve understanding of reward systems and impulsivity and their neurobiological contribution to behaviours. The Monetary Incentive Delay (MID) and Stop Signal Task (SST) are two experimental paradigms that have been developed to assess different elements of the reward processing systems and are the tasks employed within this study. These tasks have been identified as activating

overlapping but distinct neurological regions the relevance of each is briefly outlined below.

The MID measures two key functional domains: reward processing and motivation. Neurological responses, primarily in the ventral striatum, orbitofrontal and medial prefrontal cortex, are measured to assess the anticipation of reward as well as response to receiving reward and loss. Furthermore, motivation to respond to wins or avoiding loss can be measured in trial by trial comparisons of activity in the ventral striatum and ventromedial prefrontal cortex (Bjork et al., 2004; Heitzeg et al., 2014; Andrews et al., 2011; Balodis and Potenza, 2015, Beck et al., 2009, Villafuerte et al., 2012, Wrase et al., 2007, Yau et al., 2012). Distinct patterns of activation and connectivity during reward processing during MID have been found. For instance, Cao et al. (2019) found distinct activation patterns related to specific stages of reward processing (reward anticipation vs reward receipt) in 1,510 adolescents. They found that the bilateral ventral striatum, pallium, insula, thalamus, hippocampus, cingulate cortex, midbrain, motor area and occipital areas were reliably activated during reward anticipation while during reward receipt the bilateral ventromedial prefrontal cortex was observed to be positively activated and the bilateral thalamus was negatively activated. Furthermore, the ventral striatum was reliably active following prediction errors.

Abnormal activation responses in the ventral striatum may be considered a biomarker for externalising (specifically impulsivity and addictions; Balodis & Potenza, 2015). Differences in the function of the ventral striatum have been linked to the development of substance use disorders, particularly in those at increased genetic risk for ASD. For example, Carey et al., (2017) observed increased response in the

ventral striatum to be mediate a causal pathway between polygenic risk for ADHD and problematic alcohol use in adolescents.

Whereas, the SST (Logan, 1994) was developed to assess impulsivity and impulse control. Activity in the dorsal striatum and anterior cingulate cortex is assessed in response to failed stops to provide information about impulsivity and error monitoring while activity in the ventrolateral prefrontal cortex and the anterior cingulate cortex in response to correct stops provides information about impulse control, conflict monitoring and resolution. The dorsal striatum, anterior cingulate cortex, and prefrontal cortex areas are known to be activated during the SST as well as being implicated in impulsive phenotypes (Cieslik et al., 2015; Casey et al., 2018; Whelan et al., 2012; Hart et al., 2012, Smith et al., 2014).

Previous research has used this task to demonstrate neurological components implicated in impulsivity and impulse control difficulties. For example, Lees et al., (2020) demonstrated that within the Adolescent Brain and Cognitive Development Study, children with parental history of alcohol use disorder showed greater activation in fronto-basal ganglia and cerebellar networks (particularly the right medial frontal gyrus, left paracentral lobule, left superior parietal lobule, prefrontal cortex, supplementary motor area) during response inhibition compared to those with no parental alcohol use disorder. This may indicate a neurobiological vulnerability to risk or impulsivity related behaviours (Lees et al., 2020). Korucuoglu et al., (2021) demonstrated good test retest reliability of the SST in relation to response inhibition and error monitoring and identified activations clustering in: the inferior to middle frontal gyrus, bilateral insula, superior frontal gyrus, rostral anterior cingulate cortex, right superior temporal lobe, right dorsolateral prefrontal cortex. This study makes

recommendations regarding the use of particular ROI's in future studies (these recommendations will be employed within this study, see methods for more detail).

Given the high cost and complexity of fMRI research, research often relies on cross-sectional samples. However, large-scale longitudinal cohort studies offer the opportunity for insight into the development of externalising behaviour across the lifespan. A longitudinal examination of externalising behaviours and cognitive functioning may help further knowledge relating to relationships over time, which is crucial for the development of interventions which may prevent or treat psychopathology. Understanding this within the adolescent period is critical as this period is where interventions may be the most beneficial due to age and ongoing brain development.

The Adolescent Brain Cognitive Development (ABCD) Study is a large ongoing ten-year prospective project which has recruited 11,875 socioeconomically diverse children (52.4% male) when they were aged 9-10 years across 21 locations in the USA (Garavan et al., 2018; Casey et al., 2018). The ABCD protocol collects functional and resting state neuroimaging data, psychological, behavioural and cognitive measures across several developmental time points, alongside other biopsychosocial measures. Data is collected at six-month intervals, with brain scans at two-yearly intervals, and is curated for release to researchers.

This database may help distinguish relationships between externalising behaviours and reward processing and impulsivity and enhance understanding of the role of specific neural regions. This may provide important information to detect psychopathology and direct intervention. Moreover, mechanisms of adverse mental health outcomes, are likely to be more subtle in childhood when any mental health difficulties are in their early stages (Smith & Nichols, 2018). Therefore, analyses of

ABCD data that explore these early markers and mechanisms are anticipated to yield small effects (Karcher & Barch, 2021).

This study investigates the relationship between reward processing, impulsivity and externalising behaviours within adolescence. Analysis of the ABCD data has been chosen as this study encompasses the most comprehensive longitudinal study of neurobiological information and development from late childhood through to early adulthood (Hagler et al., 2019).

Aims

This study aims to investigate the relationship between reward processing, impulsivity and externalising behaviours within early adolescence. Performance on well-established cognitive tasks (Monetary Incentive Delay and Stop Signal Task) and associated neural activity will assess reward processing and impulsivity. Longitudinal analysis will allow for the examination of the directionality of relationships and relevance of over time. Socioeconomic status, sex, IQ and pubertal timing will be included as covariates, as these factors are frequently associated with mental health outcomes in this age group.

Hypotheses

Hypothesis One

a (cross-sectional):

Increased externalising behaviour will be associated with differences in anticipatory reward processing and sensitivity to reward receipt in the Monetary Incentive Delay Task (MID).

b (cross-sectional):

Externalising behaviour will be associated with altered impulsive responding and error monitoring in the Stop Signal Task (SST)

Hypothesis Two

a (cross-sectional):

Externalising behaviours will be associated with patterns of neural activity within the ventral striatum and anterior cingulate cortex during the MID.

b (cross-sectional):

Externalising behaviours will be associated with patterns of neural activity within the prefrontal cortex and the ventral striatum during the SST.

Hypothesis Three (longitudinal):

Performance on cognitive tasks (MID, SST) and associated brain activity at time points one will predict externalising profile at time point two.

Methods

Participants

Baseline data for the ABCD study are reported to be a sample of 11,875 individuals aged 9-10 years (Karcher & Barch, 2020). Of this group, 47.8% are female, 52.1% are white, 15.0% are Black, 20.3% are Hispanic, 2.1% are Asian and 10.5% identified as other (Karcher & Barch, 2020).

Participants were recruited through public and private schools and probability sampling was used to capture the demographic diversity of the USA. Schools within 50 miles of each of the 21 research sites were targeted. Each area was coded for demographic composition (including factors such as race, sex, ethnicity and socioeconomic status). From this, a subset of schools was targeted for recruitment, and the caregivers of eligible children were approached. In addition to this approach, 860 twin pairs were included, and research sites employed existing recruitment approaches to enrol twins. See Karcher and Barch (2021) for more information about recruitment and sampling.

The ABCD study had several exclusion criteria including:

1. Children not fluent in English
2. Children without a parent fluent in either English or Spanish
3. Gestational age <28 weeks or birth weight <1200g
4. Presence of a major medical or neurological condition that would impact the child's ability to comply with the study protocol
5. Contraindications to MRI scanning (such as metal implants)
6. History of traumatic brain injury
7. Current diagnosis of schizophrenia, moderate/severe Autism Spectrum Disorder, intellectual disability or alcohol/substance use disorder

Procedure

Data Acquisition

Data collection began in September 2016 and recruited approximately 12,000 participants (including 800 pairs of twins) aged 9-10 years old across 21 sites in the USA, with the aim of following up this cohort for ten years.

Data was collected relating to brain, social, emotional and cognitive development, mental health, gender identity, addiction, family histories and environmental, biological and physiological parameters. Self-report, behavioural and biospecimen data are collected yearly at an in-person follow-up session, with some measures gathered at six monthly intervals via a remote session. MRI scans are conducted biennially.

Data from the ABCD study has been made available for public sharing in raw and processed forms through the NIMH Data Archive (see https://data-archive.nimh.nih.gov/abcd). Data is released annually in the form of curated datasets and released data has been anonymised and quality assured. At the time of the present study, Annual Release 4.0 is the most up-to-date released data and includes 11,877 participants (sample size varies between collected measures).

Permission was sought from and approved by the NIMH to access the dataset. Application to access was conducted in collaboration with Alice Zacharia, a fellow Clinical Psychology Trainee at UCL (Zacharia, 2023; see Appendix for Joint Working Statement). All other aspects of this study were completed independently. Following UCL guidelines, data was downloaded and accessed within Data Safe Haven, UCL's walled garden. The Data Safe Haven has been certified to the ISO27001 information security standard, and data is stored, processed and managed within the security system to protect data.

fMRI Data

Participants participate in multimodal magnetic resonance imaging (MRI) biennially. T1-weighted and T2-weighted structural (sMRI), diffusion MRI (dMRI), and fMRI, including resting-state (rs-fMRI) and task (task-fMRI (see Casey, Cannonier, Conley, Cohen, Barch, Heitzeg et al., 2018; Hagler, Hatton, Cornejo, Makowski, Fair, Dick et al., 2019, for full details) are collected.

Task-fMRI is the focus of this thesis, and relevant tasks will be described here. The modified monetary incentive delay task (MID, Knutson et al., 2000) and stop signal task (SST; Logan, 1994) were used in conjunction with fMRI to elicit reward processing and executive control networks (Casey et al., 2018).

The imaging protocol for the ABCD data collection involved multiple scanner systems at multiple sites. Study designers worked alongside MRI manufacturers to establish appropriate motion correction and image distortion approaches (see Hagler et al., 2019, for details).

Measures

Demographic Information

Within the ABCD study a form completed by parents at baseline provides information about sex, racial identity and socioeconomic status, three variables of which are being used in the present study. Sex has been recorded as male or female based on parental report of sex assigned at birth. Race and ethnicity have been recorded as White, Black, Hispanic, Asian or 'Other'. A measure of combined parental income from baseline data collection is used as a proxy for socio-economic status. Combined parental income has been recorded by parental report as in one of ten

income brackets: <$5,000, $5,000-11,999, $12,000-15,999, $16,000-24,999, $25,000-34,999, $35,000-49,999, $50,000-74,999, $75,000-99,000, $100,000-199,999, >$200,000. This information is only available for the baseline time point and thus, when included in analysis refers only to combined parental income at baseline.

IQ

The matrix reasoning task of the Wechsler Intelligence Scale for Children (Fifth Version; WISC-V, Wechsler, 2014), which assesses fluid reasoning has been used as a proxy for intelligence in its total scaled score form. Matrix reasoning measures visual processing and abstract, spatial perception. This results in participants receiving a score of 1-19 with higher values indicating higher scores on the matrix reasoning task. Participants completed this assessment at baseline only thus, in analyses of later time points the baseline measure of IQ has been used.

Pubertal Development

Puberty is theorised to impact neurological development. To account for individual differences in pubertal development, summary scores from the Pubertal development scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988) have been used here. The PDS is a brief self-report measure which assesses secondary sexual characteristics and is a frequently used measures within the research literature. The PDS has previously demonstrated a high correlation with physician ratings of puberty indicating the validity of this measure (Petersen et al., 1987). Participants and their parents are asked to respond to five questions, specific to their/their child's self-identified gender, relating to physical development on a four-point scale (1=no development; 2= beginning development; 3=additional development; and

4=development completed). Females are asked to indicate their physical development in relation to body hair, breast change, skin change, growth spurt and menarche. Males are asked to indicate their physical development in relation to body hair, voice change, skin change, growth spurt and facial hair. For the current purposes, parental report has been used, similar to other studies using ABCD data (e.g. Thijssen et al., 2020; 2022). Previous research has found that parental reports may be more valid than child report in relation to measures of puberty as younger children may overestimate their development (Schlossberger et al., 1992). A summary variable based on parental report was extracted from the ABCD database for the present study whereby individuals were assigned to one of five categories: pre-puberty, early puberty, mid-puberty, late puberty or post-puberty at baseline and follow-up.

Externalising

For the current purposes a summary score of externalising based on the parent rating of the Child Behavioural Checklist (CBCL; Achenbach & Ruffle, 2000) has been employed. The CBCL is a questionnaire which measures (on a three-point Likert scale) emotional and behavioural difficulties over the prior six-month period and has been frequently used in relation individuals aged 4-18. The measure comprises eight subscales four of which relate to externalising: social problems, aggressive behaviour, rule-breaking behaviour and attention problems. The CBCL (parent report version) has demonstrated high test-retest reliability (.87-.99, Achenbach & Edelbrock, 1979; Achenbach & Edelbrock, 1981), internal consistency (alpha=.63-.79), criterion validity ($p<.01$ discrimination between referred and non-referred children; Achenbach & Rescorla, 2019), and good agreement between maternal and paternal ratings (.67-

.99; Achenbach & Edelbrock, 1979; Achenbach & Edelbrock, 1981). The summary score of externalising subscales has been extracted from the ABCD data for this study.

Behavioural tasks

Monetary Incentive Delay (MID; Knutson et al., 2000).

The MID measures two key functional domains: reward processing and motivation. Previous research has associated the MID with activation of the ventral striatum, orbitofrontal and medial prefrontal cortex (Casey et al., 2018).

During the MID, participants are presented with an incentive cue of five possible trial types: small win, big win, small loss, big loss or neutral (no money is at stake). Win trials are displayed as a circle which contains text of either: "win $.20" or "win $5". Loss trials are squares containing text of either: "lose $.20" or "lose $5". Neutral trials are triangles which say "no money at stake".

Incentive cue trials are followed by an anticipation event consisting of a fixation cross varying between 1500-4000ms. Next a target appears, and the participant has to respond as quickly as possible (i.e. during the target duration) by a button press to either win or avoid losing money (depending on the trial type displayed previously) which is followed by feedback which informs them of the outcome of the trial (i.e. if they were successful in winning or avoiding losing money). Task difficulty is adjusted by increasing or decreasing target duration over the course of the task to reach an accuracy rate of 60%. Performance in a practice session dictates the response target duration.

Figure 1 summarises this procedure, displaying each of the five trial types and the order of presentation (trial, fixation cross, target, response, feedback). For example: a participant is initially presented with an incentive cue trial. They see a

circle containing the text “win $5” for 2000ms. They are then presented with a fixation cross (the anticipation event) for between 1500 and 4000ms. The corresponding target is then displayed (a circle, square or triangle depending on the cue) for between 150 and 500ms. Within this time, they must respond by a button press. They are then shown the outcome. In this example would be “you won $5” if they responded quickly enough.

Each participant is presented with 40 reward and loss anticipation trials and 20 no money anticipation trials. For the feedback component, the adaptive algorithm results in approximately 24 positive feedback trials for each reward and loss trials and 16 negative feedback trials for both reward and loss. See Casey et al., (2018) for more details regarding the accuracy rates and adaptive algorithm.

Behavioural Measures derived from the MID

Behavioural analysis is based on performance calculations of correct hits, response time and monetary pay-out and outcomes for each of the following conditions are considered: reward vs no money anticipation, loss vs no money anticipation, reward positive feedback vs. Reward negative feedback, loss positive feedback vs loss negative feedback. Behavioural analysis has also distinguished between small and large rewards and losses. Therefore, the following measures were included in behavioural analysis:

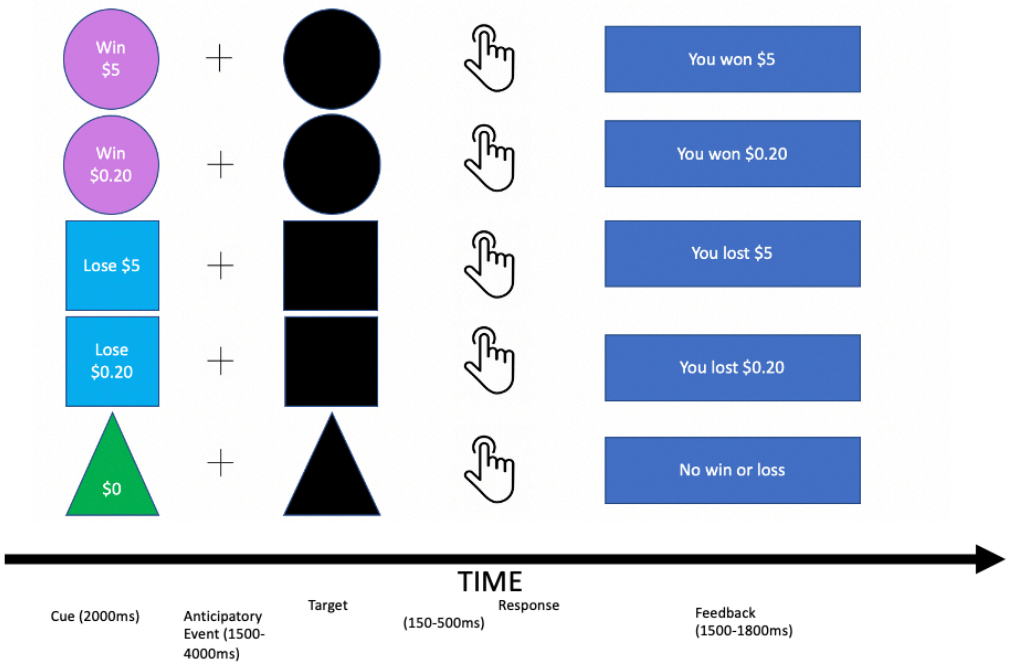
- Mean reaction time for:
    - small reward trials
        - with positive feedback
        - with negative feedback
    - large reward trials
        - with positive feedback
        - with negative feedback
    - small loss trials
        - with positive feedback
        - with negative feedback
    - large loss trials
        - with positive feedback

        - with negative feedback
    - neutral trials
        - with positive feedback
        - with negative feedback

- Number of incorrectly answered:
    - large reward trials
    - small reward trials
    - large loss
    - small loss

Contrasts of the MID task Selected for ROI Analysis

Figure 1: Monetary Incentive Delay Task, adapted from Knutson et al., 2000

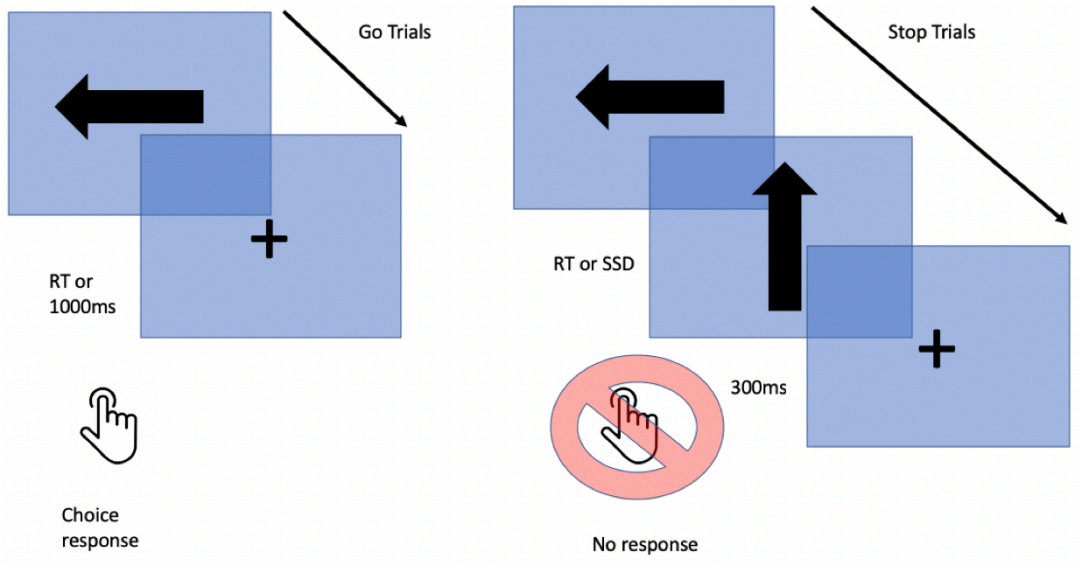


Stop Signal Task (SST; Logan, 1994).

The SST measures impulse control and comprises two runs of 180 trials of images of a black arrow pointing either right or left. Participants are instructed to press the button (right or left) corresponding to the direction of the arrow as quickly as possible using their dominant hand ('go' trials). On 30 of the 180 trials, an upward facing arrow is displayed. During this trial type participants are required to not respond. This is known as a 'stop trial'. See Figure 2.

The stop trials are presented unpredictably for 300ms. As the 'go trials' are more frequent, participants learn a strong prepotent 'go response'. To ensure that approximately 50% of the stop trials are successful and 50% are unsuccessful, the time of cue presentation for 'go trials' varies automatically based on a tracking algorithm. This is referred to the Stop Signal Delay (SSD) and makes the task easier or harder depending on previous performance and thus individually varies. Previous research implicates activation of the ventral striatum and prefrontal cortex (see Part One and Korucuoglu et al., 2021; Casey et al., 2018).

Figure 2: Stop Signal Task (adapted from Bissett et al., 2021)



This figure depicts the SST. The left-hand side demonstrates a 'go trial'. Here the participant is presented with a cue requiring pressing the left arrow button. They are then presented with a fixation cross for either the duration time taken for them to respond to the cue (the RT) or 1000ms if no response has been made. There is then an inter-trial interval (not displayed in the image) for 700-2000ms.
The right-hand side demonstrates a 'go trial'. The participant is presented with a cue (for the duration of the stop signal delay) followed by an upwards arrow which indicates they must not respond ('stop signal'). The stop signal is displayed for 300ms. There is then the fixation cross which is displayed for to 1000ms. Again, there is the inter-trial interval (700-2000ms) prior to the next trial starting.

Behavioural Measures from the SST:

Various outcome measures can be computed from the SST. For the current purposes, in line with previous research (e.g. Zhu et al., 2022) six outcome measures have been calculated and used within analysis.

1. Correct Go Response Time
2. Failed Stop Response Time
3. ‘Go’ Accuracy: measured by the rate of correct go trials.
4. Inhibitory Accuracy (‘stop’ accuracy): accuracy of correct stopping is considered to be a measure of the ability to inhibit the ‘go’ motor response. The stop signal is less frequent and unpredictable
5. Stop signal reaction time (SSRT): SSRT is considered to be a measure of inhibitory control, lower values indicate better control and reflects the time required to complete the inhibition process. It is calculated based on the distribution of response times to go trials, the success rate of stop trials and the man stop-signal delay. (Chen & Muggleton, 2020). The SSRT was calculated using the integration method, which is the method frequently employed in the literature (e.g. Hall et al., 2022).
6. Mean Stop Signal Delay (SSD): this is the mean of the time which the cue is presented in stop trials and varies individually to ensure that approximately 50% of tasks are successful

Contrasts selected for ROI analysis

This successful response inhibition of responding represents a successful trial while impulsively responding with either answer is considered unsuccessful inhibition. Consequently, response inhibition is measured as the rate of correct ‘stop’ trials. Thus, mean beta weights of the contrast of correct stop contrasted with correct go was selected for comparing neural responses relating to response inhibition.

Error monitoring is the second component captured by the SST. Error monitoring is calculated based on the rate of incorrect ‘stop’ vs correct ‘go’ trials.

Therefore, mean beta weights for contrasts of incorrect stops with correct go were used to assess neural activity relating to error processing.

These contrasts have been used previously in analysing this task (e.g. Lees et al., 2020).

fMRI Regions of Interest (ROIs)

Resulting images are available in pre-processed and processed forms, including brain segmentation from the ABCD pipeline (see Hagler et al., 2019 for more detail). ROIs were based on FreeSurfer's anatomically defined parcellations for cortical surface regions of interest (ROIs; Desikan et al., 2006; Destrieux et al., 2010) and subcortical ROIs (Fischl, 2012) FreeSurfer has been validated for use in child populations (Hagler et al., 2019). In line with previous research in this area and using the ABCD sample.

Regions of interest have been selected *a priori* based on previous research examining reward processing and impulsivity in relation to the MID task and the SST (e.g. McNeilly et al., 2022; Kennedy et al., 2022; Knutson et al., 2000; Knutson et al., 2001; Korucuoglu et al., 2021; Lee et al., 2022).

The current study extracted the beta weights from contrasts between trial types of processed ROI data from task-fMRI.

ROIs selected for MID:

Ventral Striatum Areas selected ("aseg" segmentations; Fischl et al., 2012)

- Left and Right Accumbens Area
- Left and Right Caudate
- Left and Right Putamen

Prefrontal Cortex Areas Selected ("aparc' segmentations; Desikan et al., 2006; Destrieux et al., 2010)

- Left and Right Lateral Orbitofrontal Cortex
- Left and Right Medial Orbitofrontal Cortex

ROIs selected for the SST

Based on previous research, the following ROIs have been selected for analysing activation relating to response inhibition and error monitoring (see Korucuoglu et al., 2021; Lee et al., 2022). Measures included in the analysis are based on the beta weights of the contrast between different trial types in each of the ROIs (see previous section).

Areas relating to Response Inhibition ("aparc" segmentations; Desikan et al., 2006; Destrieux et al., 2010)

- Left Supramarginal Gyrus
- Left Inferior Parietal Cortex
- Left Lateral Occipital Cortex
- Left Pars Triangularis
- Left Pars Orbitalis
- Left Lateral Orbital Frontal Cortex
- Right Superior Frontal Gyrus

Areas relating to Error Processing ("aparc" segmentations; Desikan et al., 2006; Destrieux et al., 2010)

- Right Rostal Middle Frontal Gyrus
- Right Inferior Parietal Cortex
- Right Supramarginal Gyrus
- Right Pars Triangularis
- Right Pars Opercularis
- Right Lateral Orbital Frontal Cortex
- Left Superior Frontal Gyrus

- Left Rostal Anterior Cingulate
- Right Superior Temporal Gyrus
- Right Bank Superior Temporal Sulcus
- Left Pars Triangularis
- Left Pars Orbitalis
- Left Lateral Orbital Frontal Cortex
- Right Caudal Middle Frontal Gyrus
- Right Precentral Gyrus
- Left Superior Parietal Cortex
- Left Lateral Occipital Cortex
- Left Supramarginal Gyrus
- Left Inferior Parietal Cortex
- Right Superior Parietal Cortex
- Right Precuneus Cortex
- Left Bank Superior Temporal Sulcus

Statistical Analysis

Outliers

As extreme values do not always reflect errors in a dataset and may be values of interest, outliers were not removed (Aguinis et al., 2013; Bjork et al., 2017; Volkow et al., 2018; Osborn & Overbay, 2014; Tong, 2019). However, extreme and influential outliers were examined for each model in turn. In these analyses, stringent criteria for inclusion (such as removing participants that have been coded with 'unacceptable' performance flags in the SST) have been used, and thus outliers have not been excluded.

Treatment of Missing Values

Analysis of the MID and the SST has resulted in using different subsets of participants based on performance and missing data to maximise the sample size for analyses.

Participants were removed where data is missing for the measures of externalising (derived from the CBCL), demographic information (combined parental income, sex and race), information regarding relatedness to other participants, IQ, puberty, site of collection, ranked propensity scores (used to weight data to account for representativeness of the sample distribution and selection biases based on demographic and socio-economic factors).

In analyses of the MID, complete case analysis was used. Thus, the sample size for baseline and follow-up are the same (n=4558). In the analysis of the behavioural component of this task, the sample sizes are smaller and vary due to missing behavioural data within the fMRI sample. As such, the behavioural sample comprises a subset of the MID fMRI sample, and participants with missing data were removed within individual analyses. Of note is that at baseline, the sample size for the analysis of behavioural responses to the MID is 976, and follow-up is 4012. Previous studies have reported similar sample sizes using this data (e.g. Casey et al., 2018).

The sample was treated differently for the SST due to a larger amount of missing data. After removing participants with missing data for externalising, puberty, demographic information, relatedness, collection site, and ranked propensity scores, data were removed if they had been recorded with a 'performance flag'. This means that their trials were coded as 'unacceptable' due to responding issues (less than 4 responses in any trial type). It was decided that removing participants that had missing data for behavioural responses and fMRI was a poor strategy as this left an extremely

small sample. Consequently, only those with performance flag issues were removed, and then participants with missing data were excluded within each analysis automatically. As a result, the sample size for the SST task varies depending on the analysis performed.

Given the large sample size, no imputation methods have been employed.

Power

As this is a secondary analysis of an existing dataset, the sample size has already been established, with 11,875 children included the ABCD study in total. Very large datasets such as this have been deemed necessary to explore early markers and mechanisms of negative mental health outcomes, as these markers are likely to be more subtle in childhood when any mental health difficulties are in their early stages (Smith & Nichols, 2018). Therefore, analyses of ABCD data that explore these early markers and mechanisms are anticipated to yield small effects (Karcher & Barch, 2021).

A sample of this size will be able to detect an effect size of $\rho=0.033$ or larger if the alpha is 0.05 and the power is 0.95. Given that an effect size of $\rho=0.1$ is conventionally considered a 'small' effect, this suggests that the ABCD study sample is sufficiently powered to detect very small effect sizes (calculated using G*Power; Faul et al., 2007). Post-hoc power analysis for a two-tiled multiple regression model with 45 predictors (the maximum number of predictors used in this study) with a sample size of 976 participants (the smallest sample size used in this study) indicates this study is sufficiently powered to detect small ($\rho=0.1$) effects (power> .95).

Sample Demographics

Demographic statistics presented are based on the sample used within the analysis of the MID task. Comparisons of sample demographics in relation to externalising scores have been conducted and reported below.

Analysis indicates no significant differences between this sample and the samples used for analyses of SST (see Appendix).

Hypothesis Testing

Mixed effects linear regression models (with "*bobyqua*" optimisation) have been created for both cross-sectional and longitudinal analysis within R's package "*lmer*" (Burt et al., 2001; Bates et al., 2014). In each model, externalising was the dependent variable, and predictors include behavioural or beta weight values of ROI variables for each MID and SST task (see above). Each model also includes covariates of sex, puberty, IQ, and SES as fixed factors.

As ABCD data includes a subset of twins and data that has been collected from 21 separate sites. Saragos-Harris et al. (2022) recommend that when analysing data from the ABCD dataset that nesting factors for relatedness and study sight should be considered. Consequently, regression models include random factors to account for study site and relatedness to provide unbiased effects estimates.

Due to the study and analysis design the estimation method used was residual (or restricted) maximum likelihood (REML; Patterson & Thompson, 1971) rather than maximum likelihood methods with R function "*lmer*" (within "*lme4*"). REML is a method for estimating variance when variation may arise from multiple sources within the model and takes account of the number of fixed effects parameters (O'Neill, 2010). REML has been employed in analysis of large data sets and in clinical trials where

there may be multiple centres. For analysis of fixed and random factors, REML is an appropriate procedure as it automatically adjusts the degrees of freedom for different effects and is considered to minimise the effects of bias from missing data and imbalanced samples. In this case, Brown and Kempton (1994) consider REML to be preferable to other maximum likelihood methods in repeated measures studies as the bias within covariance estimates is reduced.

Consequently, REML criterion at convergence (lower scores indicate better fit) will be reported as a measure of model fit within tables alongside, R values, R^2 values and fixed effects estimates and their standard errors.

Within the text, regression standardised beta coefficients and confidence intervals [2.5%, 97.5%] for significant measures are reported.

P-values are not reported as standard within R's "*lmer*" function as this would require the estimation of degrees of freedom which is considered non trivial (Bates et al., 2015). So, *p*-values of beta coefficients were calculated using "*lmerTest*" (Kuznetsova et al., 2017) which uses Scatterthwaite's approximation for degrees of freedom (Wald, 1943).

Separate regression models have been created using behavioural measures from the MID and SST to predict cross-sectionally (baseline model and follow-up model) and longitudinally (baseline behavioural measures predicting follow-up externalising). Thus, three regressions have been used to analyse the behavioural responses to both the MID and SST task.

The MID evaluates different aspects of reward processing: anticipation phase (reward vs. no money contrasts and loss vs. no money contrasts); and, feedback phase (reward positive vs. reward negative feedback contrasts and loss positive vs. loss negative feedback contrasts) ROI activation in response to both aspects have been

included in the same models. Similarly, the SST assesses error processing and response inhibition, ROI activation in response to both aspects are included within the same models. Regression models have been created for cross-sectional predictions of externalising (at baseline and follow-up) and longitudinal predictions of externalising (baseline measures predicting follow-up externalising). Thus, three regression models analyse ROI activation for each task.

In total here are 12 models evaluating performance and neurological activation as predictors of externalising.

Assumption Testing

Linear mixed-effects models make several assumptions relating to the distribution of residual and random effects (Bolker et al., 2009). Assumptions were checked visually using the "*check_model"* function from the '*Performance'* package in R. This creates plots of Posterior Predictive Model Checks (evaluating how well the model fits the observed data); linearity; homogeneity of variance, normality of random effects; and, normality of residuals. In testing assumptions for the regression models described in this chapter, it was found that there were some violations (see Appendices). The assumptions of normality of random effects were upheld and posterior predictive checks indicate that the model approximates the data. However, there were some deviations in terms of homogeneity of variance and a small number of variables showed high levels of collinearity (Variance Inflation Factor) within models (see Appendices).

In research violations of assumptions are common (Schielzeth et al., 2020). However, statisticians argue that linear mixed-effects models are robust to violations of assumptions; as has been demonstrated by Schielzeth et al. (2020) who found that

biases and violations did not affect model parameters. This suggests that it is acceptable to employ this methodology even when assumptions are violated (Lee & Nelder, 2004). Research indicates that violations of random effects have minimal impact on models due to the robust nature of testing (Arnau, Bendayan, Blanca, & Bono, 2013; Jacqmin-Gadda, Sibillot, Proust, Molina, & Thiebaut, 2007; Maas & Hox, 2004; McCulloch & Neuhaus, 2011; Sinharay & Stern, 2003; Verbeke & Lesaffre, 1997; Warrington et al., 2014) and that consequences for random effects are minor (Schielzeth et al., 2020). Sometime violations of normality of data speak to real differences in the data and transforming this would occlude important findings. Due to these arguments, there have not been any methods of data transformation applied. However, this does have potential implications for the results, which should be interpreted with caution given there are some violations of model assumptions.

Weights and Scaling

ABCD summary data provides a measure of 'ranked propensity score'. This score measures the representativeness of the sample distribution and selection biases based on demographic and socio-economic factors. Within each analysis the sample weights are adjusted by the ranked propensity score which represents the proportion of group size divided by the sum of sampling weights within each group has been weighted based on the ranked propensity score using "*rescale_weights*" function within *R*. This implements an algorithm proposed by Asparouhov (2006) and Carle (2009). Here, weights are scaled based on the ranked propensity score that so that the new weights sum to the cluster sample size (Carle, 2009). Carle (2009) recommends this method for nested data.

Corrections

False discovery rate (FDR) correction for multiple comparisons, calculated using "*p.adjust*'' in *R* Version 2023.03.0+386, was applied to significance values of outputs to control for multiple comparisons (Benjamini & Hochberg, 1995)

Results

Descriptive statistics

Demographic Information

Following removal of missing data based on demographic information, and participants with baseline and follow-up data for the MID task, the sample comprised of 4558 participants, 47.13% female and 60.55% white, see Table 1. Combined parental income, indicative of socio-economic status, and IQ were measured at baseline. The modal combined parental income was $100,000-$199,999 and median IQ score was 10 (range 1-19).

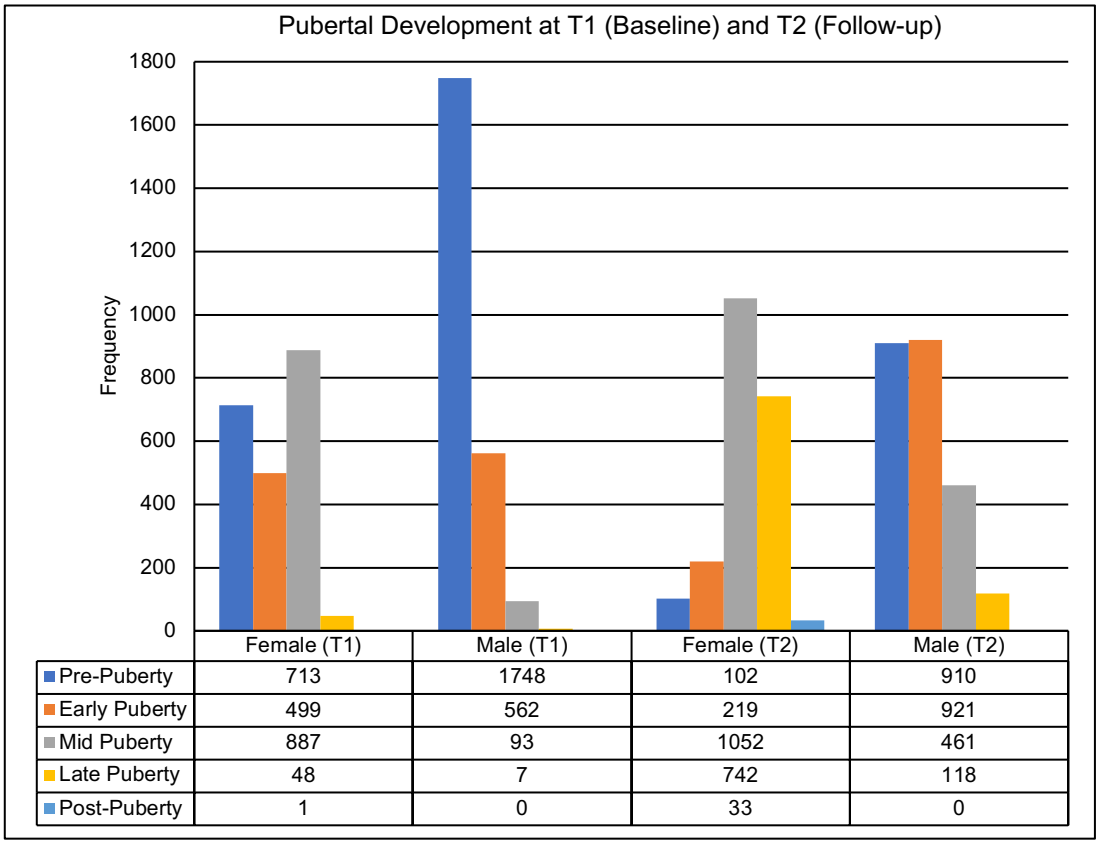
Table 1: Demographic Information (MID sample, n=4558)

		n	%
Gender	Female	2148	47.13
	Male	2410	52.87
Ethnicity	White	2760	60.55
	Black	445	9.76
	Hispanic	814	17.86
	Asian	77	1.69
	Other	462	10.14
Parental Income	<$5000	94	2.06
	$5000-11,999	111	2.44
	$12,000-15,999	90	1.97
	16,000-24,999	190	4.17
	$25,000-34,999	274	6.01
	$35,000-49,999,	401	8.80
	$50,000-74,999	651	14.28
	$75,000-99,999	721	15.82
	$100,000-199,999	1509	33.11
	>$200,000	517	11.34

Pubertal Development

Chi-Squared test indicates significant differences between pubertal development between males and females across time points ($X^2_{(13)}$ =4638, p<0.001), females demonstrate more advanced pubertal development at T1 and T2, see Figure 3.

Figure 3: Pubertal Development (based on sample used for analysis of MID tasks, n=4558)



	Female (T1)	Male (T1)	Female (T2)	Male (T2)
Pre-Puberty	713	1748	102	910
Early Puberty	499	562	219	921
Mid Puberty	887	93	1052	461
Late Puberty	48	7	742	118
Post-Puberty	1	0	33	0

Chi-Squared test indicates significant differences between ethnicity and combined parental income ($X^2_{(36)}$=1033.90, p<0.001). Overall, all racial identities were underrepresented at lower income brackets, but this was particularly the case for white participants (see supplementary materials).

Ordinary least squares regression modelling indicates that race, sex and income significantly predicted IQ ($F_{(6,4551)}$=68.71, p<0.001, R^2=0.08; see supplementary materials). Black, Hispanic and Other racial identities was associated

with lower IQ, while Asian and White ethnicities predicted higher IQ. Combined parental income and being female were positively associated with IQ.

Hypothesis Testing

Prior to presenting full results, a summary of key findings is presented in Table 2. Tables 3-6 present information and results from regression analyses and Figures 4-6 relate to behavioural and neurological regression models of each task and provide a visual representation of strength and direction of effects and their theoretical distributions based on the normal curve.

Table 2:Summary of Key Findings

Hypothesis	Hypothesis Supported?	Key Points
Increased externalising behaviour will be associated with differences in anticipatory reward processing and sensitivity to reward receipt in the Monetary Incentive Delay Task.	Partially	• Mean reaction time to small reward trials associated with externalising • Higher rates of small reward trials with incorrect responses associated with externalising • Significant effects shown cross-sectionally at follow-up only • Small sample for baseline timepoint
Externalising behaviour will be associated with increased impulsive responding (i.e. errors of commission) and error monitoring (correct vs incorrect responses to 'go' trials) in the Stop Signal Task	Partially	• No association between response inhibition and externalising. • Reduced accuracy to 'go' trials associated with higher externalising cross-sectionally
Externalising behaviours will be associated with patterns of neural activity within the ventral striatum and arterial cingulate cortex during the MID.	Partially	• Activation of the left putamen (increased) and right putamen (decreased) in loss anticipation associated with externalising over time • Externalising associated in response to reward receipt with left lateral orbitofrontal cortex (increased), right lateral orbitofrontal cortex (increased), right medial orbitofrontal cortex (decreased) • Effects inconsistent between time-points
Externalising behaviours will be associated with patterns of neural activity within the prefrontal cortex and the ventral striatum during the Stop Signal Task.	Partially	• Activation related to response inhibition not associated cross-sectionally to externalising • Activations of left superior parietal cortex (decreased), precuneus cortex (increased), right superior temporal gyrus (decreased), right caudal middle frontal gyrus (increased) and left bank superior temporal sulcus (increased) due to error processing was associated with cross-sectional relationships with externalising
Performance on cognitive tasks (MID, SST) and associated brain activity at time points one will predict externalising profile at time point two	Partially	• No longitudinal associations between SST or MID performance and externalising • Externalising predicted by activations related to anticipation of loss important (MID): (decreased right putamen and increased right accumbens area) • Externalising was predicted by activations related to reward receipt: left putamen (increased), Right putamen (decreased), right accumbens area (decreased) • Activations related to loss receipt left caudate (decreased), left accumbens area (increased), left medial orbitofrontal cortex. (increased) • Response inhibition related activations: left pars orbitalis (increased) • Activations due to error processing responses (SST) in the left superior frontal gyrus are associated with longitudinal decreased externalising. • activation in the left pars orbitalis related to response inhibition was positively associated with externalising over time.

Hypothesis One:

a) Increased externalising behaviour will be associated with differences in anticipatory reward processing and sensitivity to reward receipt in the Monetary Incentive Delay Task

Cross-sectional mixed effects linear regressions indicate that models with predictors of behavioural outcomes in response to the MID as well as covariates of sex, pubertal development, SES and IQ with fixed factors of study site and participant relatedness were able to predict externalising at baseline (T1) and follow-up (T2): R^2=.61 (for both). Fixed effects demonstrated R^2=.04 (baseline and follow-up). See Table 3.

Baseline

As shown in Table 3, at baseline, three significant predictors were present: sex (B=1.02, CI [0.20, 12.69], $t_{(948.82)}$=2.36, p=0.02); SES (B=-0.28, CI [-0.28, -0.09], $t_{(698.58)}$=-2.92, p<0.001) and the mean response time for neutral trials with positive feedback (B=0.03, CI [0.01, 0.05], $t_{(896.88)}$=2.81, p=0.01). All other beta-coefficients demonstrated non-significant effects.

Table 3: MID Behavioural Performance Regression Models

	T1 Externalising Predicted by MID Behavioural Performance	T2 Externalising Predicted by MID T2 Behavioural Performance	T2 Externalising Predicted by MID T1 Behavioural Performance
Sex (Male)	1.02 *	1.42 ***	0.77
	[0.20, 1.84]	[1.01, 1.84]	[-0.13, 1.68]
Puberty (T1)	-0.14	-	-0.38
	[-0.63, 0.35]	-	[-0.89, 0.14]
Puberty (T2)	-	0.30 **	0.38
	-	[0.11, 0.50]	[-0.07, 0.83]
SES	-0.28 **	-0.23 ***	-0.20 *
	[-0.46, -0.09]	[-0.31, -0.14]	[-0.38, -0.02]
IQ	-0.02	-0.07 *	-0.04
	[-0.15, 0.11]	[-0.13, -0.02]	[-0.16, 0.09]
Mean RT for small reward trials	-0.01	-0.03 ***	-0.00
	[-0.04, 0.01]	[-0.04, -0.01]	[-0.03, 0.02]
Mean RT for small rewards with positive feedback	-0.00	0.02 *	0.01
	[-0.03, 0.03]	[0.00, 0.04]	[-0.02, 0.04]
Mean RT for small rewards with negative feedback	0.00	0.01 ***	0.01
	[-0.01, 0.01]	[0.01, 0.01]	[-0.00, 0.02]
Mean RT for large reward trials	-0.00	-0.00	0.01
	[-0.02, 0.02]	[-0.02, 0.01]	[-0.02, 0.03]
Total number of large reward trials answered incorrectly	-0.07	0.04	-0.08
	[-0.31, 0.17]	[-0.07, 0.15]	[-0.30, 0.14]
Total number of small reward trials answered incorrectly	0.07	0.14 *	0.02
	[-0.18, 0.32]	[0.03, 0.25]	[-0.21, 0.24]
Mean RT for large reward trials with negative feedback	0.00	-0.00	-0.00
	[-0.00, 0.01]	[-0.01, 0.00]	[-0.01, 0.00]
Mean RT for small loss trials	-0.00	0.01	0.01
	[-0.02, 0.02]	[0.00, 0.03]	[-0.01, 0.03]
Mean RT for small loss trials with positive feedback	-0.01	0.01	-0.01
	[-0.04, 0.01]	[-0.01, 0.02]	[-0.04, 0.02]
Mean RT for small loss trials with negative feedback	-0.00	-0.00	-0.00
	[-0.01, 0.01]	[-0.01, 0.00]	[-0.01, 0.01]
Mean RT for large loss trials	-0.01	0.00	-0.01
	[-0.03, 0.02]	[-0.01, 0.01]	[-0.03, 0.01]
Total number of large loss trials answered incorrectly	0.01	0.02	0.05
	[-0.22, 0.24]	[-0.09, 0.13]	[-0.16, 0.26]
Total number of small loss trials answered incorrectly	0.03	-0.06	0.02
	[-0.21, 0.27]	[-0.17, 0.05]	[-0.19, 0.23]
Mean RT for large loss trials with negative feedback	0.01	-0.00	0.00
	[-0.00, 0.01]	[-0.01, 0.00]	[-0.01, 0.01]
Mean RT for neutral trials	-0.01	-0.00	-0.01
	[-0.03, 0.00]	[-0.01, 0.01]	[-0.02, 0.01]
Mean RT for neutral trials with positive feedback	0.03 **	-0.00	-0.00
	[0.01, 0.05]	[-0.02, 0.01]	[-0.02, 0.02]
Mean RT for neutral trials with negative feedback	-0.00	0.00	-0.00
	[-0.01, 0.01]	[0.00, 0.01]	[-0.01, 0.00]
Mean RT for large reward trials with positive feedback	-0.02	-0.01	-0.03
	[-0.05, 0.01]	[-0.02, 0.01]	[-0.06, -0.00]
N	976	4012	984
N(relatedness)	876	3535	883
N (Study Site)	21	21	21
REML Criterion at Convergence	6272.20	24790.10	6262.50
R2 (fixed)	0.04	0.04	0.04
R2 (total)	0.61	0.61	0.66

All continuous predictors are mean-centered and scaled by 1 standard deviation. Standard errors are heteroskedasticity robust. *** p < 0.001; ** p < 0.01; * p < 0.05.

Follow-up

At follow-up (T2), eight significant predictors were present: sex (B=1.42, CI [1.01, 1.84], $t_{(3945)}$=6.70, p<0.001); pubertal development (B=0.30, CI [0.11, 0.50],

$t_{(3906)}$=3.07, p<0.001); SES (B=-0.23, CI [-0.31, -0.14], $t_{(2212)}$=-5.30, p<0.001), IQ (B=-0.74, CI [-0.13, -0.02], $t_{(3855)}$=-2.52, p=0.01); mean reaction time to small reward trials (B=-0.03, CI [-0.04, -0.01], $t_{(3935)}$=-3.73, p<0.001); mean reaction time to small reward trials with positive feedback (B=0.02, CI [0.00, 0.04], $t_{(3756)}$=2.36, p=0.02); mean reaction time to small reward trials with negative feedback (B=0.01, CI [0.01, 0.01], $t_{(3951)}$=4.65, p<0.001); total number of small reward trials answered incorrectly (B=0.14, CI [0.03, 0.25], $t_{(3816)=}$2.52, p=0.01). Two predictors became non-significant following FDR correction (mean response time to small loss trials and mean reaction time for neutral trials with negative feedback). All other beta-coefficients demonstrated non-significant effects.

b) Externalising behaviour will be associated with increased impulsive responding (i.e. errors of commission) and error monitoring (correct vs incorrect responses to 'go' trials) in the Stop Signal Task

Cross-sectional mixed effects linear regressions indicate that models with predictors of behavioural performance in the SST with covariates of sex, pubertal development, SES and IQ with fixed factors of study site and participant relatedness were able to predict externalising at baseline (T1) and follow-up (T2): R^2=.55 and R^2=.59, respectively. Fixed effects demonstrated R^2=0.04 (baseline) and R^2=0.03 (follow-up). See Table 4.

Baseline

In terms of fixed effects, 'Go Accuracy' was associated with reduced externalising: B=-4.33, CI [-6.38, -2.28], $t_{(4895.08)}$=-4.13, p<0.001). No other performance measures demonstrated effects. However, measures of: Sex (B=1.28, CI [0.95, 1.61], $t_{(5064.61)}$=7.50, p<0.001); pubertal development (B=0.21, CI [0.02, 0.41],

$t_{(5012.04)}$=2.12, p=0.03; SES (B=-0.28, CI [-0.36, -0.21], $t_{(3206.42)}$=-7.40, p<0.001) and IQ (B=-0.07, CI [-0.12, -0.02], $t_{(5027.18)}$=-2.57, p=0.01), were significant predictors of externalising at baseline.

Table 4: SST Behavioural Performance Regression Models

	T1 Externalising Predicted by SST T1 Behavioural Performance	T2 Externalising Predicted by SST T2 Behavioural Performance	T2 Externalising Predicted by SST T1 Behavioural Performance
Sex (Male)	1.28 ***	1.11 ***	1.36 ***
	[0.95, 1.61]	[0.72, 1.50]	[0.95, 1.78]
Puberty (T1)	0.21 *	-	0.41 **
	[0.02, 0.41]	-	[0.16, 0.66]
Puberty (T2)	-	0.15	0.07
	-	[-0.03, 0.33]	[-0.15, 0.28]
SES	-0.28 ***	-0.23 ***	-0.19 ***
	[-0.36, -0.21]	[-0.31, -0.15]	[-0.27, -0.10]
IQ	-0.07 *	-0.05	-0.06 *
	[-0.12, -0.02]	[-0.10, 0.01]	[-0.11, -0.00]
Correct Go Response Time	0.00	0.01	0.00
	[-0.01, 0.01]	[-0.00, 0.02]	[-0.01, 0.01]
Failed Stop Response Time	-0.01	0.00	-0.00
	[-0.01, 0.00]	[-0.01, 0.01]	[-0.01, 0.01]
Go Accuracy	-4.33 ***	-4.37 ***	-1.81
	[-6.38, -2.28]	[-6.92, -1.81]	[-4.24, 0.62]
Inhibitory Accuracy	-0.35	3.15	-2.37
	[-4.95, 4.26]	[-1.94, 8.24]	[-7.87, 3.13]
Stop Signal Reaction Time	-0.00	-0.00	0.00
	[-0.01, 0.01]	[-0.01, 0.01]	[-0.01, 0.01]
Mean Stop Signal Delay	-0.00	-0.01	-0.00
	[-0.01, 0.00]	[-0.02, 0.00]	[-0.01, 0.01]
N	5079	3946	3778
N (relatedness)	4432	3527	3386
N (site)	21	21	21
REML	31092.73	23732.13	22805.94
R2 (fixed)	0.04	0.03	0.03
R2 (total)	0.55	0.59	0.58

All continuous predictors are mean-centered and scaled by 1 standard deviation. Standard errors are heteroskedasticity robust. *** p < 0.001; ** p < 0.01; * p < 0.05. FDR correction applied

Follow-up

In terms of fixed effects, predictors of: sex (B=1.11, CI [0.72, 1.50], $t_{(3906.47)}$=5.60, p<0.001); SES (B=-0.23, CI [-0.31, -0.15], $t_{(1688.75)}$=-5.64, p<0.001) and Go Accuracy (B=-4.37, CI [-6.92, -1.81], $t_{(3281.34)}$=-3.35, p<0.01), were significant predictors of externalising at follow-up.

Hypothesis Two

a) Externalising behaviours will be associated with patterns of neural activity within the ventral striatum and arterial cingulate cortex during the MID.

Cross-sectional mixed effects linear regressions with predictors of ROI activation in response to four trial contrast types of the MID: a) anticipation of reward vs. neutral; b) anticipation of loss vs. neutral; c) reward positive vs. reward negative feedback; d) loss positive vs. neutral feedback as well as covariates of sex, pubertal development, SES and IQ with fixed factors of study site and participant relatedness were able to predict externalising at baseline (T1) and follow-up (T2): R^2=.55 and R^2=.59, respectively. Fixed effects demonstrated R^2=.05 (baseline) and R^2=.04 (follow-up). See Table 5.

Baseline

As shown in Table 5, at baseline, eight significant predictors were present: sex (B=1.51, CI [1.15, 1.87], $t_{(4491.61)}$=8.13, p<0.001); pubertal development (B=0.20, CI [0.02, 0.39], $t_{(4406.61)}$=2.13, p=0.03); SES (B=-0.77, CI [-0.95, -0.59], $t_{(2683.92)}$=-8.43, p<0.001), IQ (B=-0.28, CI [-0.44, -0.12], $t_{(4426.35)}$=-3.38, p<0.001); activation of the left and right putamen in response to anticipation of loss vs. neutral contrast (B=0.43, CI [0.02, 0.84], $t_{(4342.37)}$=2.04, p=0.04; and, B=-0.45, CI [-0.86, -0.04], $t_{(4420.57)}$=-2.13, p=0.03, respectively); and, activation of the left lateral orbitofrontal cortex in response to reward positive vs negative feedback (B=0.30, CI [0.05, 0.55], $t_{(4226.91)}$=2.35, p=0.02); All other beta-coefficients demonstrated non-significant effects.

These results indicate that higher externalising scores were significantly predicted by being male, more advanced pubertal development, lower SES, lower IQ, increased activation of the left putamen and decreased activation of the right putamen

during anticipation of loss vs. neutral contrast conditions, increased activation of the left medial orbitofrontal cortex during loss positive vs negative feedback conditions and increased activation of the left lateral orbitofrontal cortex during reward positive vs. negative feedback conditions. However, the size of these effects is small, as indicated by fixed effects R^2=.05.

Follow-up

At follow-up (T2) six significant predictors were present: sex (B=1.38, CI [1.00, 1.76], $t_{(4494.92)}$=7.08, p<0.001); pubertal development (B=0.30, CI [0.10, 0.49], $t_{(4406.31)}$=3.02, p<0.001); SES (B=-0.57, CI [-0.75, -0.40], $t_{(2326.24)}$=-6.62, p<0.001), IQ (B=-0.25, CI [-0.41, -0.10], $t_{(4389.15)}$=-3.25, p<0.001); activation of the right lateral orbitofrontal cortex in response to reward positive vs. negative feedback (B=0.35, CI [0.12, 0.58], $t_{(4243.50)}$=3.02, p<0.001); and, activation of the right medial orbitofrontal cortex in response to reward positive vs. negative feedback (B=-0.35, CI [-0.57, -0.12], $t_{(4294.55)}$=-3.05, p<0.001). All other beta-coefficients demonstrated non-significant effects.

These results indicate that higher externalising scores were significantly predicted by being male, more advanced pubertal development, lower SES, lower IQ, increased activation of the of the lateral orbitofrontal cortex in response to reward positive vs. negative feedback conditions and reduced activation of the right medial orbitofrontal cortex in response to reward positive vs. negative feedback conditions.

Table 5: MID fMRI regression models

		T1 Externalising Predicted by ROI Activation at T1	T2 Externalising Predicted by ROI Activation at T2	T2 Externalising Predicted by ROI Activation at T1
	Sex (Male)	1.51 ***	1.38 ***	1.42 ***
		[1.15, 1.87]	[1.00, 1.76]	[1.03, 1.81]
	Puberty (T1)	0.20 *	-	0.24 *
		[0.02, 0.39]	-	[0.04, 0.44]
	Puberty (T2)	-	0.30 **	0.17
		-	[0.10, 0.49]	[-0.04, 0.38]
	SES	-0.77 ***	-0.57 ***	-0.56 ***
		[-0.95, -0.59]	[-0.75, -0.40]	[-0.74, -0.39]
	IQ	-0.28 ***	-0.25 **	-0.27 ***
		[-0.44, -0.12]	[-0.41, -0.10]	[-0.42, -0.12]
Reward Anticipation: Reward vs. Neutral Contrast	L Caudate	-0.10	-0.14	-0.34
		[-0.59, 0.39]	[-0.65, 0.36]	[-0.81, 0.13]
	L Putamen	-0.37	-0.20	-0.29
		[-0.77, 0.04]	[-0.62, 0.22]	[-0.67, 0.09]
	L Accumbens-Area	0.08	0.14	-0.05
		[-0.19, 0.35]	[-0.13, 0.41]	[-0.31, 0.21]
	R Caudate	0.20	0.03	0.41
		[-0.29, 0.70]	[-0.48, 0.55]	[-0.06, 0.88]
	R Putamen	0.35	0.22	0.34
		[-0.07, 0.78]	[-0.20, 0.64]	[-0.07, 0.74]
	R Accumbens-Area	0.07	0.02	-0.07
		[-0.22, 0.35]	[-0.24, 0.29]	[-0.34, 0.21]
	L Lateral Orbitofrontal Cortex	-0.04	-0.13	0.09
		[-0.38, 0.30]	[-0.42, 0.16]	[-0.23, 0.41]
	R Lateral Orbitofrontal Cortex	-0.20	-0.06	0.07
		[-0.54, 0.15]	[-0.36, 0.24]	[-0.26, 0.39]
	L Medial Orbitofrontal Cortex	0.07	0.00	-0.01
		[-0.26, 0.40]	[-0.28, 0.28]	[-0.32, 0.31]
	R Medial Orbitofrontal Cortex	-0.05	0.06	-0.31
		[-0.39, 0.29]	[-0.23, 0.34]	[-0.63, 0.01]
Reward Anticipation: Loss vs. Neutral Contrast	L Caudate	0.12	0.25	0.39
		[-0.38, 0.62]	[-0.24, 0.75]	[-0.09, 0.87]
	L Putamen	0.43 *	0.15	0.32
		[0.02, 0.84]	[-0.25, 0.56]	[-0.08, 0.71]
	L Accumbens-Area	0.01	-0.12	-0.09
		[-0.29, 0.32]	[-0.39, 0.14]	[-0.38, 0.20]
	R Caudate	-0.26	-0.35	-0.26
		[-0.76, 0.24]	[-0.86, 0.15]	[-0.74, 0.21]
	R Putamen	-0.45 *	-0.25	-0.47 *
		[-0.86, -0.04]	[-0.67, 0.16]	[-0.86, -0.08]
	R Accumbens-Area	0.03	-0.02	0.32 *
		[-0.28, 0.33]	[-0.28, 0.25]	[0.02, 0.61]
	L Lateral Orbitofrontal Cortex	0.11	0.24	-0.15
		[-0.23, 0.44]	[-0.04, 0.53]	[-0.47, 0.17]
	R Lateral Orbitofrontal Cortex	0.01	0.10	-0.18
		[-0.33, 0.36]	[-0.19, 0.38]	[-0.51, 0.14]
	L Medial Orbitalfrontal Cortex	0.11	-0.02	0.17
		[-0.24, 0.47]	[-0.30, 0.26]	[-0.17, 0.50]
	R Medial Orbitofrontal Cortex	-0.10	-0.09	0.22
		[-0.50, 0.29]	[-0.38, 0.20]	[-0.15, 0.59]
Feedback: Reward Positive vs. Negative Feedback	L Caudate	0.06	-0.06	0.07
		[-0.32, 0.44]	[-0.45, 0.33]	[-0.29, 0.43]
	L Putamen	0.12	0.13	0.28 *
		[-0.17, 0.41]	[-0.20, 0.45]	[0.00, 0.56]
	L Accumbens-Area	0.07	0.12	-0.06
		[-0.14, 0.27]	[-0.10, 0.34]	[-0.26, 0.13]
	R Caudate	-0.11	0.10	-0.05
		[-0.51, 0.28]	[-0.29, 0.49]	[-0.42, 0.33]
	R Putamen	-0.16	-0.11	-0.31 *
		[-0.45, 0.12]	[-0.44, 0.23]	[-0.58, -0.04]
	R Accumbens-Area	-0.13	-0.16	-0.22 *
		[-0.34, 0.07]	[-0.38, 0.07]	[-0.41, -0.02]
	L Lateral Orbitofrontal Cortex	0.30 *	-0.02	0.15
		[0.05, 0.55]	[-0.24, 0.20]	[-0.08, 0.39]
	R Lateral Orbitofrontal Cortex	-0.04	0.35 **	-0.08
		[-0.30, 0.22]	[0.12, 0.58]	[-0.33, 0.17]
	L Medial Orbitalfrontal Cortex	-0.04	0.02	0.06
		[-0.29, 0.21]	[-0.19, 0.23]	[-0.18, 0.29]
	R Medial Orbitofrontal Cortex	-0.03	-0.35 **	-0.00

			[-0.30, 0.24]	[-0.57, -0.12]	[-0.26, 0.25]
Feedback: Positive Negative Feedback	Loss vs.	L Caudate	-0.20	-0.05	-0.41 *
			[-0.61, 0.22]	[-0.43, 0.34]	[-0.80, -0.02]
		L Putamen	-0.01	0.07	0.15
			[-0.35, 0.33]	[-0.25, 0.39]	[-0.17, 0.48]
		L Accumbens-Area	0.13	-0.05	0.24 *
			[-0.12, 0.38]	[-0.27, 0.17]	[0.01, 0.48]
		R Caudate	0.32	0.12	0.32
			[-0.12, 0.75]	[-0.24, 0.48]	[-0.10, 0.73]
		R Putamen	-0.13	-0.28	-0.16
			[-0.48, 0.21]	[-0.60, 0.04]	[-0.48, 0.17]
		R Accumbens-Area	-0.15	0.08	-0.08
			[-0.41, 0.10]	[-0.14, 0.30]	[-0.32, 0.16]
		L Lateral Orbitofrontal Cortex	-0.06	0.10	-0.29
			[-0.39, 0.27]	[-0.12, 0.32]	[-0.60, 0.03]
		R Lateral Orbitofrontal Cortex	-0.09	-0.10	0.11
			[-0.43, 0.26]	[-0.33, 0.14]	[-0.21, 0.44]
		L Medial Orbitofrontal Cortex	0.32 *	0.03	0.28 *
			[0.05, 0.58]	[-0.20, 0.26]	[0.03, 0.54]
		R Medial Orbitofrontal Cortex	-0.13	0.01	-0.20
			[-0.44, 0.18]	[-0.22, 0.25]	[-0.49, 0.10]
Model Summary		N	4539	4543	4539
		N (Relatedness)	3995	3999	3995
		N (Study Site)	21	21	21
		REML Criterion at Convergence	28239.95	27855.92	27821.28
		R2 (fixed)	0.05	0.04	0.04
		R2 (total)	0.55	0.59	0.59

All continuous predictors are mean-centred and scaled by 1 standard deviation. Standard errors are heteroskedasticity robust.
*** p < 0.001; ** p < 0.01; * p < 0.05.

b) Externalising behaviours will be associated with patterns of neural activity within the prefrontal cortex and the ventral striatum during the Stop Signal Task.

Cross-sectional mixed effects linear regressions indicate that models with predictors of ROI activation in response to two trial contrast types of the SST: correct stop vs. correct go (measuring response inhibition) and incorrect stop vs correct go (measuring error processing) as well as covariates of sex, pubertal development, SES and IQ with fixed factors of study site and participant relatedness were able to predict externalising at baseline (T1) and follow-up (T2): R^2=.55 and R^2=.59, respectively. Fixed effects demonstrated R^2=.04 (baseline) and R^2=.03 (follow-up). See Table 6.

Baseline

As shown in Table 6, at baseline, six significant predictors were present: sex (B=1.26, CI [0.92, 1.59] $t_{(4893.32)}$=7.35, p<0.001); pubertal development (B=0.22, CI

[0.02, 0.42], $t_{(4868.95)}$=2.17,*p*=0.03); SES (B=-0.32, CI [-0.32, -0.24], $t_{(2928.45)}$=-8.15, *p*<0.001), IQ (B=-0.08, CI [-0.14, 0.03], $t_{(4868.82)}$=-3.19, *p*<0.001); activation of the left superior parietal cortex (B=-4.00, CI [-6.82, -1.17], $t_{(4715.33)}$=-2.78, *p*=0.01) and the right precuneus (B=2.52, CI [0.42, 4.62], $t_{(4787.25)}$=2.36, *p*=0.02) in the error processing condition (incorrect stop vs. correct go contrast).

Follow-up

At follow-up, five significant predictors were present: sex (B=1.05, CI [0.66, 1.44], $t_{(3780.32)}$=5.23, *p*<0.001); SES (B=-0.21, CI [-0.29, -0.13], $t_{(1358.54)}$=-5.24, *p*<0.001); activation of the right superior temporal gyrus (B=-2.77, CI [-5.20, -0.35], $t_{(3399.77)}$=-2.24, *p*=0.03), the right caudal middle frontal gyrus (B=4.56, CI [1.86, 7.26], $t_{(3576.01)}$=3.31, *p*<0.001) and left bank superior temporal sulcus (B=3.09, CI [1.45, 4.74], $t_{(3489.19)}$=3.68 *p*<0.001) in the error processing condition (incorrect stop vs. correct go contrast). IQ (T1) and pubertal development (T2) were not significant predictors at follow-up (T2).

Table 6: SST fMRI Regression Models

		T1 Externalising Predicted by ROI Activation at T1	T2 Externalising Predicted by ROI Activation at T2	T2 Externalising Predicted by ROI Activation at T1
	Sex (Male)	1.26 ***	1.05 ***	1.28 ***
		[0.92, 1.59]	[0.66, 1.44]	[0.87, 1.69]
	Puberty (T1)	0.22 *	-	0.37 **
		[0.02, 0.42]	-	[0.13, 0.62]
	Puberty (T2)	-	0.12	0.04
		-	[-0.07, 0.30]	[-0.18, 0.25]
	SES	-0.32 ***	-0.21 ***	-0.21 ***
		[-0.39, -0.24]	[-0.29, -0.13]	[-0.29, -0.12]
	IQ	-0.08 **	-0.05	-0.07 *
		[-0.14, -0.03]	[-0.11, 0.00]	[-0.13, -0.01]
Response Inhibition (Correct Stop vs Correct Go Contrasts)	L Supramarginal gyrus	0.44	-0.51	0.33
		[-1.47, 2.36]	[-2.80, 1.77]	[-1.83, 2.48]
	L Inferior parietal cortex	-0.86	0.19	-0.04
		[-2.72, 1.00]	[-1.92, 2.30]	[-2.11, 2.04]
	L Pars triangularis	-0.37	0.21	-0.94
		[-1.58, 0.84]	[-1.26, 1.68]	[-2.33, 0.45]
	L Pars orbitalis	0.24	-0.12	0.83 *
		[-0.43, 0.90]	[-0.77, 0.53]	[0.05, 1.61]
	L Lateral orbital frontal cortex	-0.47	0.60	-0.28
		[-1.31, 0.37]	[-0.36, 1.55]	[-1.22, 0.66]
Error Processing (Incorrect Stop vs Correct Go Contrasts)	R Superior frontal gyrus	0.06	-1.68	2.61
		[-3.51, 3.64]	[-6.13, 2.77]	[-1.39, 6.61]
	R Rostal middle frontal gyrus	0.30	0.99	-0.26
		[-1.04, 1.65]	[-0.77, 2.76]	[-1.81, 1.29]
	R Inferior parietal cortex	-0.01	-1.72	-0.89
		[-2.18, 2.17]	[-5.06, 1.63]	[-3.61, 1.84]
	R Supramarginal gyrus	-0.02	1.57	1.18
		[-2.50, 2.46]	[-1.60, 4.73]	[-1.56, 3.92]
	R Pars triangularis	-0.03	-1.44	-0.09
		[-1.40, 1.34]	[-3.17, 0.29]	[-1.65, 1.47]
	R Pars opercularis	-0.39	-1.24	-0.37
		[-2.13, 1.34]	[-3.45, 0.98]	[-2.32, 1.58]
	R Lateral orbital frontal cortex	0.02	-0.68	-0.35
		[-0.84, 0.88]	[-1.67, 0.31]	[-1.29, 0.60]
	L Superior frontal gyrus	-1.22	-2.67	-3.71 *
		[-4.36, 1.92]	[-6.80, 1.47]	[-7.30, -0.13]
	L Rostal anterior cingulate	-0.13	0.65	0.07
		[-1.11, 0.86]	[-0.49, 1.79]	[-1.07, 1.21]
	R Superior temporal gyrus	-0.25	-2.77 *	0.42
		[-2.31, 1.81]	[-5.20, -0.35]	[-1.92, 2.76]
	R Bank superior temporal sulcus	0.54	0.57	0.58
		[-0.89, 1.96]	[-1.17, 2.32]	[-0.98, 2.14]
	R Caudal middle frontal gyrus	-1.50	4.56 ***	-0.67
		[-3.60, 0.60]	[1.86, 7.26]	[-2.97, 1.63]
	R Precentral gyrus	-0.03	0.96	-0.16
		[-2.47, 2.42]	[-2.30, 4.22]	[-2.90, 2.58]
	L Superior parietal cortex	-4.00 **	-1.85	-3.28
		[-6.82, -1.17]	[-5.56, 1.86]	[-6.64, 0.09]
	L Lateral occipital cortex	0.41	0.05	-0.07
		[-0.58, 1.39]	[-1.06, 1.15]	[-1.19, 1.05]
	L supramarginal gyrus	1.00	0.60	-1.09
		[-1.59, 3.59]	[-2.60, 3.81]	[-3.99, 1.81]
	R superior parietal cortex	0.62	-0.40	1.92
		[-2.09, 3.32]	[-4.01, 3.21]	[-1.20, 5.05]
	R Precuneus cortex	2.52 *	0.96	2.29
		[0.42, 4.62]	[-1.47, 3.39]	[-0.05, 4.63]
	L Bank superior temporal sulcus	1.09	3.09 ***	0.02
		[-0.27, 2.45]	[1.45, 4.74]	[-1.46, 1.51]
Model Summary	N	4942	3821	3670
	N (Relatedness)	4329	3424	3303
	N (Study Site)	21	21	21
	REML Criterion at Convergence	30184.21	22807.34	22010.14
	R2 (fixed)	0.04	0.03	0.04
	R2 (total)	0.55	0.59	0.59

All continuous predictors are mean-centered and scaled by 1 standard deviation. Standard errors are heteroskedasticity robust. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

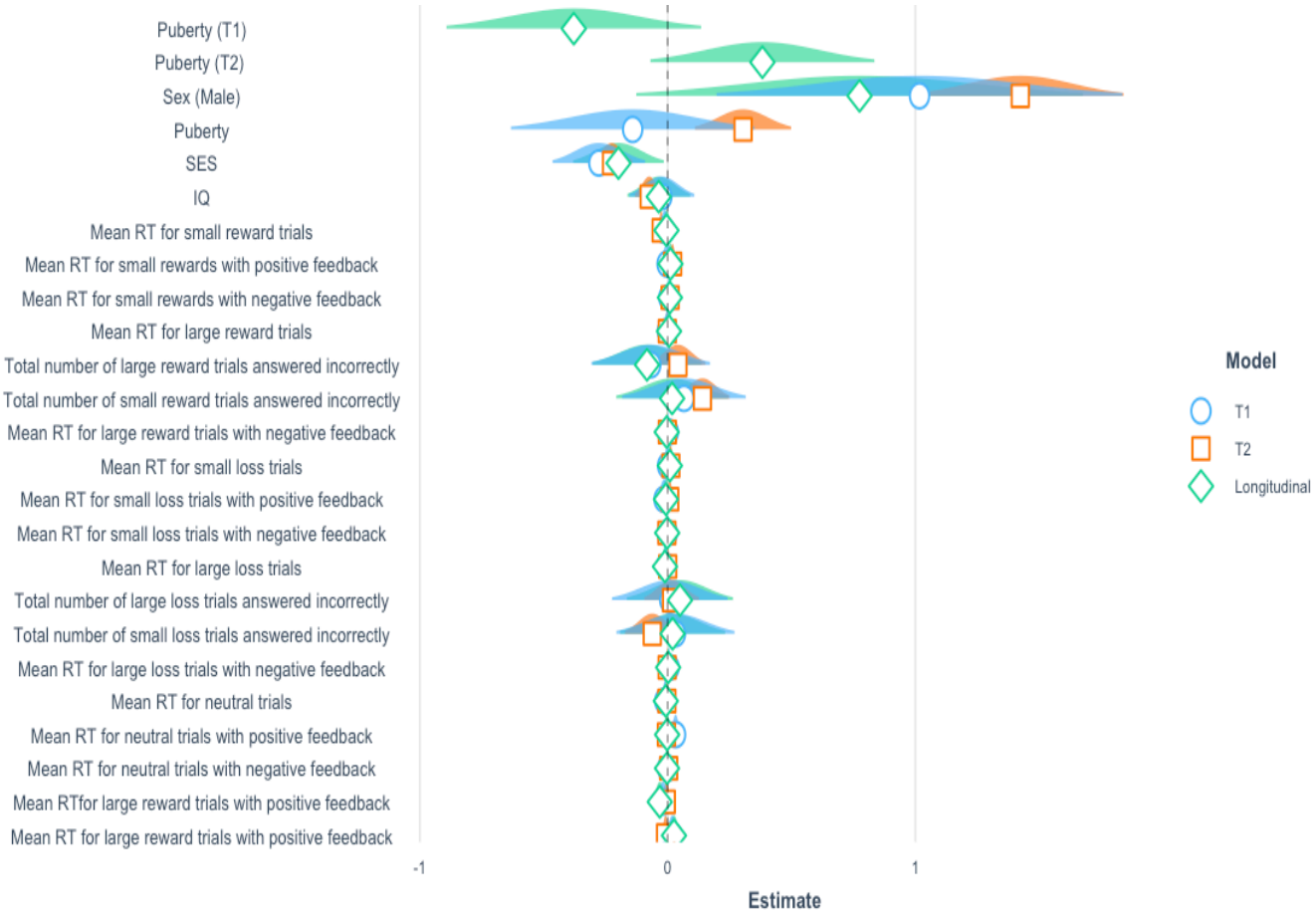
Hypothesis Three:

Performance on cognitive tasks (MID, SST) and associated brain activity at time point one will predict externalising profile at time point two.

i) Baseline MID Behavioural Performance Predicting Follow-up Externalising

Longitudinal analysis (mixed-effects regression modelling) predicted externalising at follow-up (T2) by baseline measures (pubertal development at follow-up was also included in this model; R^2=.66 and for fixed effects only R^2=.04). See Table 3.

Figure 4: Effect sizes and theoretical distributions of measures included in regression models of the MID (behavioural measures)



Estimates are based on standardized beta coefficients. RT = reaction time. T1 refers to the regression model analyzing cross-sectional associations at baseline. T2 refers to the regression model analyzing cross-sectional associations at follow up.

Regarding fixed effects, only one measure demonstrated significant effects: SES (B=-0.20, CI [-0.38, -0.02], $t_{(680.19)}$=7.19, p=0.03). Mean RT for large reward trials with positive feedback was initially a significant predictor but did not survive FDR correction. No other behavioural predictors from baseline showed significance in predicting externalising at follow-up.

ii) Baseline MID ROI Activations Predicting Follow-up Externalising

Longitudinal analysis (mixed-effects regression modelling) predicted externalising at follow-up (T2) by baseline measures (pubertal development at follow-up was also included in this model; R^2=.59 and for fixed effects only R^2=.04. See Table 5.

In terms of fixed effects, 13 measures demonstrated significant effects: sex (B=1.42, CI [1.03, 1.81], $t_{(4483.32)}$=7.19, p<0.001; pubertal development (baseline; B=0.24, CI[0.04, 0.44], $t_{(4443.67)}$=2.36, p=0.02); SES (B=-0.56, CI [-0.74, -0.39], $t_{(2350.32)}$=-6.48, p<0.001); baseline IQ(B=-0.27, CI [-0.42, -0.12], $t_{(4368.77)}$=-3.44, p<0.001); activation of the right putamen (B=-0.47, CI [0.86, -0.08], $t_{(4367.48)}$=-2.37, p=0.02) and right accumbens area (B=0.32, CI [0.02, 0.61], $t_{(4225.07)}$=2.11, p=0.03) in response to anticipation of loss vs. neutral contrast; activation of the right putamen (B=-0.31, CI [-0.58, 0.04], $t_{(3861.50)}$=-2.26, p=0.02) and right accumbens-area (B=-0.22, CI [-0.41, -0.02], $t_{(4304.77)}$=-2.17, p=0.03) in response to reward positive vs. negative feedback contrast (activation of the left putamen became non-significant following FDR correction of p-values in response to the reward positive vs. negative feedback condition); activation of the left caudate (B=-0.41, $t_{(4258.46)}$=-2.04, p=0.04), left accumbens-area (B=-0.41, CI [-0.80, -0.02], $t_{(4258.46)}$=-2.04, p=0.04) and left

medial orbitofrontal cortex (B=0.28, CI [0.03, 0.54], $t_{(4488.45)}$=2.20, p=0.03) in response to loss positive vs. negative feedback contrast.

Figure 5: Effect sizes and theoretical distribution of ROI activation in response to the MID Task

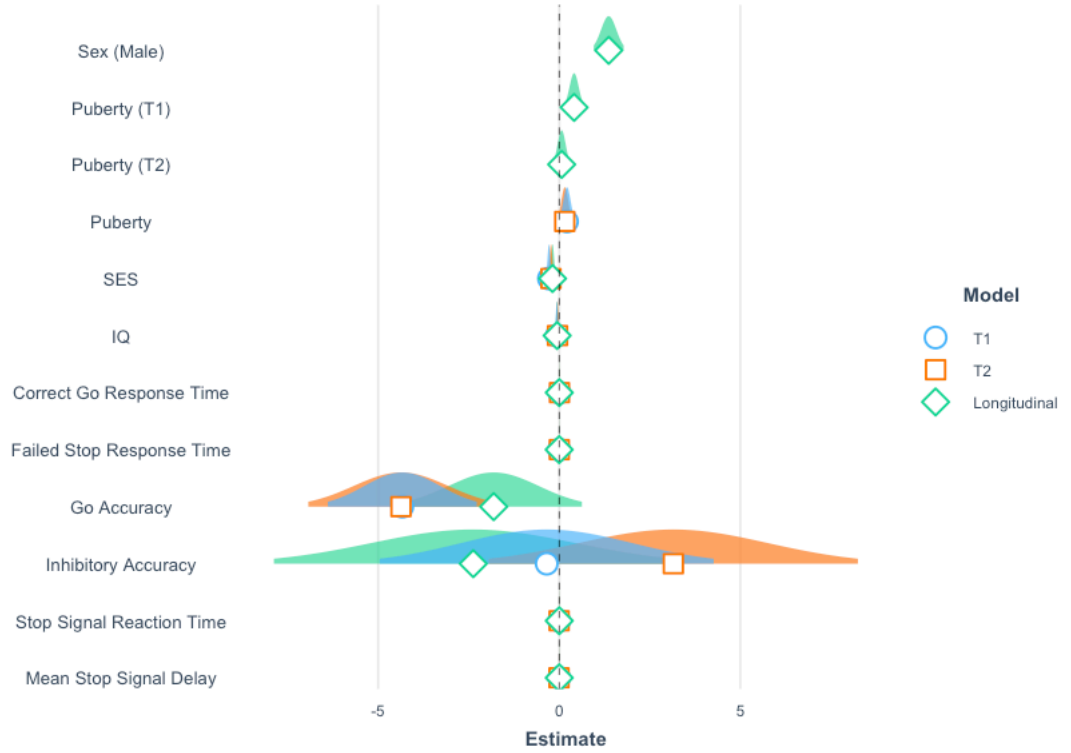
Estimates are based on standardized beta coefficients. RT = reaction time. T1 refers to the regression model analyzing cross-sectional associations at baseline. T2 refers to the regression model analyzing cross-sectional associations at follow up. 'ARVN' = anticipation of reward vs. neutral contrast; 'ALVN'= anticipation of loss vs. neutral contrast; 'FPVN'=feedback of reward positive vs. negative; 'FLPVN'= feedback of loss positive vs. negative. L= left; R= Right

iii) Baseline SST Behavioural Performance Predicting Follow-up Externalising

Longitudinal analysis (mixed-effects regression modelling) predicted externalising at follow-up (T2) by baseline measures of performance on the SST (pubertal development at follow-up was also included in this model; R^2=.58 and for fixed effects only R^2=.03. See Table 4.

In terms of fixed effects sex (B=1.36, CI [0.95, 1.78], $t_{(3730.63)}$=6.49, p<0.001; pubertal development at baseline (B=0.41, CI [0.16,0.66], $t_{(3736.12)}$=3.28, p<0.001); SES (B=-0.19, CI [-0.27, -0.10], $t_{(1953.91)}$=-4.36, p<0.001) predicted follow-up externalising. However, no performance measures demonstrated effects.

Figure 6: Effect sizes and theoretical distribution of behavioural performance measures in response to the SST



Estimates are based on standardized beta coefficients. RT = reaction time. T1 refers to the regression model analyzing cross-sectional associations at baseline. T2 refers to the regression model analyzing cross-sectional associations at follow up.

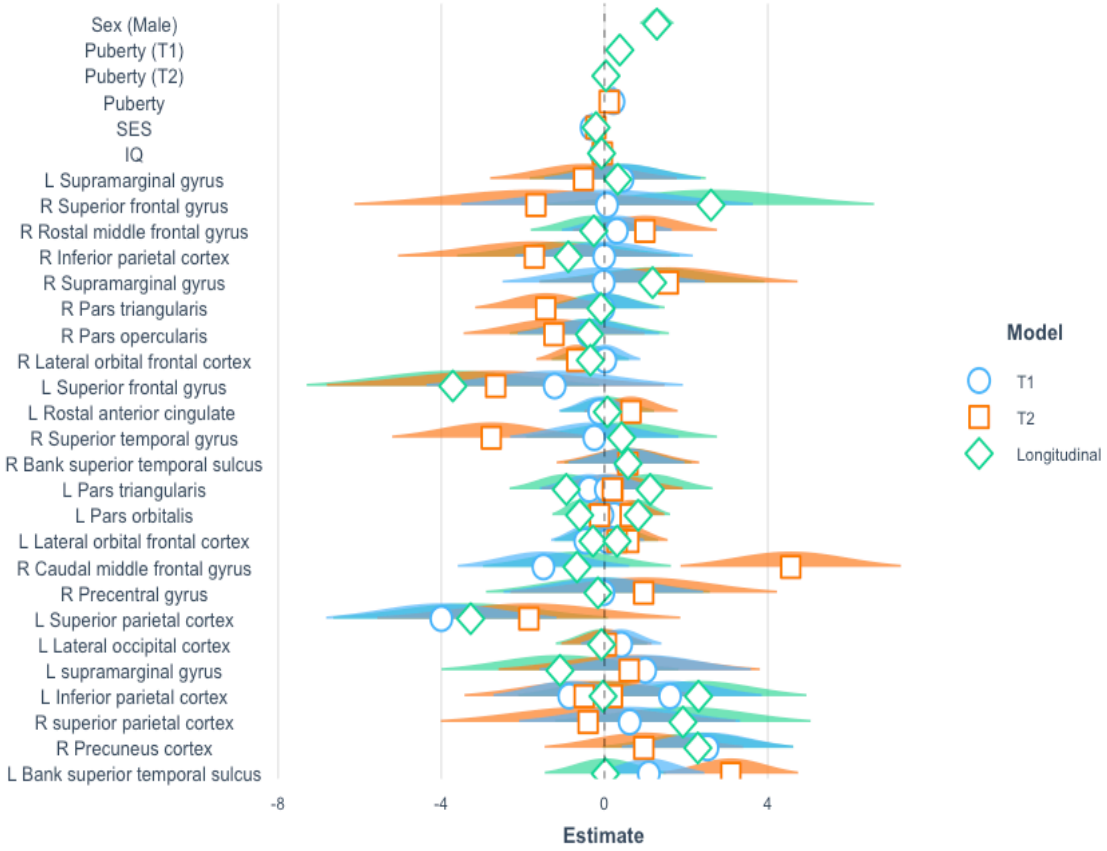
iv) Baseline SST ROI Activation Predicting Follow-up Externalising

Longitudinal analysis (mixed-effects regression modelling) predicted externalising at follow-up (T2) by baseline measures (pubertal development at follow-up was also included in this model; R^2=.59 and for fixed effects only R^2=.04. See Table 6.

In terms of fixed effects, 13 measures demonstrated significant effects: sex (B=1.28, CI [0.87, 1.69], $t_{(3633.32)}$=6.13, p<0.001; pubertal development (baseline; B=0.37, [0.13, 0.62], $t_{(3613.91)}$=2.96, p<0.001); SES (B=-0.21 CI [-0.29, -0.12], $t_{(1830.80)}$=-4.81, p<0.001); baseline IQ(B=-0.07 CI [-0.13, -0.01], $t_{(3582.97)}$=-2.46, p<0.001); and, activation of the left pars orbitalis (B=0.83, CI [0.05, 1.61], $t_{(3598.13)}$=2.08, p=0.04) in response to the response inhibition condition (correct stop vs. correct go contrast); following FDR correction no other predictors were significant

(left superior frontal gyrus previously was marginally significant prior to FDR correction).

Figure 7: Effect sizes and theoretical distribution of ROI activation measures in response to the SST



Estimates are based on standardised beta coefficients. RT = reaction time. T1 refers to the regression model analyzing cross-sectional associations at baseline. T2 refers to the regression model analyzing cross-sectional associations at follow-up. L=left, R=right.

Discussion

Overall, this study has provided mixed findings, which partially support each of the three hypotheses; a summary of key findings is provided in Table Two. Generally, the effect sizes observed are in line with magnitudes seen in previous ABCD studies attempting to explain the variance of psychological constructs, including externalising (e.g. Qu et al., 2023; Xie et al., 2023). The interpretation and implication of key findings will now be discussed, followed by a discussion of the limitations of this study.

Key findings

As anticipated, being male, more advanced pubertal development, lower SES, and lower IQ were stable predictors of externalising across most models. These were the most robust predictors of externalising scores cross-sectionally and longitudinally examined within these analyses. This highlights the importance of prevention and early intervention approaches to support those at increased risk of externalising behaviours. Although work is ongoing, future research is essential to understand the specific mechanisms of the relationships between these factors. Given that SES and IQ measures used here were taken from time point one only and that these were predictors of future externalising, individuals are sensitive to the negative impact of these factors even at young ages (age 9-10). This suggests that interventions should be targeted to children before adolescence to mitigate the effects of risk factors in hopes of preventing the development of externalising. Addressing unmet needs in these areas may also be important targets for individuals that have already developed problematic externalising behaviours to improve pro-social behaviour. This would be particularly

important to achieve during adolescence to reduce the likelihood that an individual may follow the trajectory of a persistent life-course offender (Moffit 1993, 2018).

That SES is linked to externalising is well established within research (Schneider et al., 2003; Najman et al., 2004; Vásquez-Echeverría et al., 2020; Tort-Carrera et al., 2023), and the relationship holds across various measures of externalising. This study found that each SES standard deviation increase was associated with a .19 and .77 standard deviation decrease in externalising. Multiple layers of disadvantage may be captured by 'low socioeconomic status'. Lower family income, poor housing quality, and indexes of deprivation based on geographical location are measures of SES that are frequently used but may also partly capture the effect of marginalisation or stigma, which could be distinct from a financial aspect of low SES. Thus, SES is multifaceted, and a more nuanced understanding of how these interact with other risk factors and how this relates to externalising are essential targets for further study. This is necessary to improve interventions for those at risk.

Furthermore, how these factors interact with the kind of externalising may also differ. For example, lack of financial resources may be tied explicitly to offending behaviour such as theft or fraud as an attempt to meet financial needs. At the same time, the experience of marginalisation could be related to different forms of externalising, which are more related to gaining power, status or control. Understanding needs in various parts of an individual's life and supporting those needs being met by adaptive and prosocial means constitutes the underpinning of some offending risk reduction interventions, such as the Good Lives Model (Ward & Gannon, 2006; Ward & Stewart, 2003). This has implications for the type of interventions that may be appropriate for individuals and for how society conceptualises those who offend.

It could also be that the best intervention to prevent externalising behaviour lies at the feet of social and welfare policy and not psychological intervention. Suppose low SES families can be supported financially or through improved housing conditions and improvements in public environments and resources. In that case, this may substantially mitigate this risk factor and prevent externalising behaviours from developing for most adolescents.

Being male is not a modifiable risk factor. However, a greater understanding of why males are more at risk than females of externalising is essential. This study found that being male was associated with a substantial increase in externalising behaviour (between .77 and 1.58 standard deviation increase in CBCL scores). This finding replicates a body of cross-cultural evidence which has established this finding (e.g. Lau et al., 2021). Environmental factors have been explored as factors interacting with gender. For example, Shoenberger and Rocheleau (2017) discuss that males were more likely to receive physical punishment from parents, and the effects of discipline differed between males and females. They also found that self-control, theorised by Gottfredson and Hirschi's theory of crime as key to offending behaviour, was related to gendered differences in parenting practices (such as monitoring, supervision and active, positive engagement, e.g. reading together).

Early puberty has an established relationship with externalising and may be related to associating with deviant peers (Lynne et al., 2007; Felson & Haynie, 2002). The current findings replicate this finding and puberty at baseline, but not at follow-up, was associated with externalising cross-sectionally and longitudinally. This may mean that the deleterious effect of earlier pubertal development is established at age 9-10. Alternatively, puberty two years later may not differ substantially in terms of distribution across participants to account for any additional variance on top of that

explained by the baseline measure. Within this study, standardised beta values indicate that each standard deviation increase of pubertal development was associated with between .24 and .41 increase in externalising. This may be an area whereby supporting individuals who have undergone early puberty or are at a more advanced stage of pubertal development to have age-appropriate social relationships and a comprehensive understanding of their physical development may be beneficial (Laube & Fuhrmann, 2020). Ensuring that those who are closely involved in looking after children and adolescents (parents, teachers etc.) are aware of the potentially negative associations of early pubertal development (e.g. Senia et al., 2018; Copeland et al., 2011) could facilitate enhanced support for those who may require it.

The association between low IQ and externalising behaviour is a robust cross-cultural finding within the literature and is found in children and adolescents (Koenen et al., 2008; Lahey et al., 1995). This finding was partially replicated by this study. But the effect of IQ was inconsistent between models. The relationship between IQ and externalising may be due to difficulties in understanding rules and social norms, frustrations and difficulties in social interactions. Environmental and genetic mechanisms (e.g. maltreatment, deprivation, parental conflict., executive function, ADHD; Burt et al., 2001; Lynam & Henry, 2001) have been proposed to mediate the relationship between low IQ and externalising. Such findings support the need for addressing environmental factors (e.g. low socioeconomic status) that interact with genetic risk to reduce the development or extent of externalising.

While these factors are clearly important for understanding externalising behaviour and identifying the risk of future externalising, the main focus of this thesis is the contribution of possible neurobiological mechanisms. These will now be discussed in relation to the analysis of each task in turn.

MID

Anticipation Phase

These current results provide weak support for Hypothesis One (an increased externalising behaviour will be associated with differences in anticipatory reward processing and sensitivity to reward receipt in the MID) and Hypothesis Three (performance on cognitive tasks (MID, SST) and associated brain activity at time points one will predict externalising profile at time point two). Some effects related to anticipatory and feedback processes via the MID task were demonstrated, supporting previous research (e.g. Cao et al., 2019). However, these small effects are inconsistent across models, indicating no robust support for this hypothesis.

Cross-sectionally at follow-up, the increased number of incorrect responses to small rewards and faster reaction times on small reward trials were associated with externalising. Effect sizes (standardised beta) indicate that each standard deviation increase of the number of incorrect small reward trials is associated with a .14 standard deviation increase in externalising score. Similarly, for every standard deviation decrease in reaction time to small reward trials (i.e. faster responding), there is a .03 increase in externalising score on the CBCL. Together this may indicate that in the anticipation phase of reward processing, those with higher externalising may respond faster and less accurately to small reward trials. The same effect was not seen for large rewards, and this may be due to greater consideration or more caution when the reward is higher. As this is a cross-sectional association, no inference can be drawn about the direction of effect. This finding supports previous research (e.g. Hawes et al., 2021) and implies that early adolescents may assess that when the reward is low, it is worth the risk to act quickly and less accurately, but if the reward is of greater value, more caution is taken.

Contrary to our second hypothesis, there were no regions where the anticipation of reward (relative to no reward/no loss, i.e. 'reward anticipation: reward vs neutral contrast') was associated with externalising cross-sectionally or longitudinally. Demidenko et al., (2021) found that reward anticipation contrasts did not show the expected activations, and these were not similar to other contrasts and hypothesised that this might be related to the involvement of other cognitive processes which co-occur during anticipation. They suggest that when effortful engagement is higher (e.g. when processing reward anticipation), these other cognitive processes are highly activated, which may result in violations of assumptions when contrasting signals.

No significant behavioural effects were seen in loss trials across all models. This contradicts some previous findings that have associated higher externalising characteristics with reduced accuracy to the MID across all trial types (Gu et al., 2017). However, like the present findings, Gatzke-Kopp et al., (2009) also demonstrated null results of behavioural effects of a MID task in associations with externalising.

Previous research also indicates that anticipation and receipt of reward (rather than loss) is the component of reward processing more reliably related to externalising. For example, it has been hypothesised that those with higher levels of externalising are less likely to respond to extinction or punishment cues once they have engaged in a behaviour (e.g. Iaboni et al., 1997; Fonseca & Yule,1995; Milich et al., 1994; Newman & Wallace, 1993). This is supported by the current finding that associations between ROI activation were related to the anticipation of reward loss in this task. When anticipating loss (relative to no loss/no reward; i.e. 'reward anticipation: loss vs neutral contrast'), decreased activation of the right putamen at baseline predicted higher externalising at baseline (B=-.45) and follow-up (B=-.47). Increased baseline

activation of the left putamen was also cross-sectionally associated with externalising (B=.43). This means that each standard deviation increase of activation in the right putamen at baseline is associated with .45 of a standard deviation reduction in the externalising score at baseline and .47 of a standard deviation reduction at follow-up. This finding provides evidence partially supporting Hypothesis Two and Three. That this effect was not seen in relation to larger losses, may suggest that externalising is more prominent when the risk is lower. When the risk is higher, then individuals are less likely to engage in externalising processes.

Feedback Phase

In the feedback conditions, various regions had activation patterns in response to contrasts of reward positive vs negative feedback (i.e. reward receipt) and loss positive vs negative feedback (i.e. loss receipt), which predicted externalising across time points. This provides further support for Hypotheses Two and Three.

When receiving a monetary reward (in contrast to no reward), baseline measures of increased activation of the left putamen and decreased activation of the right putamen and right accumbens area significantly predicted externalising at follow-up. Increased activation of the left lateral orbitofrontal cortex during reward receipt was also associated with externalising cross-sectionally at baseline but not at other time points. While at follow-up, the cross-sectional analysis indicated reduced activation of the right medial orbitofrontal cortex and increased activation of the right lateral orbitofrontal cortex, predicted externalising. This supports findings from the anticipation phase of this task, indicating the importance of reward in the development of externalising. This finding suggests that reinforcement of rewards may be particularly salient in those with externalising and that this may help us understand why those who are high externalises perseverate in learned actions, finding it difficult

to inhibit previously rewarded behaviours and are less likely to respond to punishments (e.g. Milich et al., 1993).

Regarding the feedback component of the MID task, significant reaction time effects were demonstrated in response to small reward with positive feedback and negative feedback trials (both positive in direction) at follow-up. However, given that the response time was increased for all small reward trials, this result may not add anything additional but indicates that reaction time increases when there is positive and negative feedback to small reward trials. This suggests that slower responses to positive and negative feedback trials were associated with increased externalising (B=.02 and .01, respectively).

Decreased baseline activation of the left caudate and increased activation of the left accumbens area and the left medial orbitofrontal cortex in response to monetary loss (contrast to no loss) predicted externalising at follow-up. Cross-sectionally, activation of the left medial orbitofrontal cortex was also associated with externalising in response to monetary loss. That decreased activation in some regions (right putamen, left caudate) and increased activation in other regions (left putamen, left accumbens area, left medial orbitofrontal cortex) may support suggestions (e.g. Greicius et al., 2003) regarding the importance of being able to effectively and flexibly activate and deactivate appropriate brain regions as required for the activity demands to act or inhibit actions appropriately.

No behavioural effects predicted externalising over time. Thus, behavioural responses to the MID may not be helpful or reliable indicators of future externalising. In analyses of behavioural responses to the MID, there are few significant effects with analysis using baseline data (n=976-984). It could be that the smaller sample size limits the power to detect minor effects here, given that there is a greater number of

effects present in the analysis of follow-up behavioural data where the sample size is 4,012 participants. Alternatively, although neurological relationships related to loss of reward are associated with current and future externalising, this has not resulted in behavioural differences. It could be that this shows the beginning of a cumulative effect of neurological activation patterns that, over more extended periods, will affect future behaviour. Repeating this analysis with future waves of the ABCD Study will help to examine this proposal more fully. Another possible interpretation is that blunted activation in response to loss may only be seen in groups with exceptionally high levels of externalising rather than a cohort sample which is likely to represent a broader spectrum of severity of externalising.

SST

Response Inhibition

The results indicate partial support of this Hypothesis 1b (externalising behaviour will be associated with impulsive responding (i.e. errors of commission) and error monitoring in the SST). Response inhibition is frequently measured by the rate of correct stop trials (labelled as inhibitory accuracy in tables and figures). Previous research indicates that an increased rate of correct stops is associated with improved impulse control (e.g. Hall et al., 2022). This finding was not replicated in the current data set.

In cross-sectional models, there were no activation measures concerning the response inhibition trials that predicted externalising. However, higher externalising two years later was positively predicted by activation of the left pars orbitalis in the response inhibition component. The inferior frontal gyrus (which includes the pars orbitalis) is a region previously implicated in inhibiting behavioural responses. For example, damage to this region impairs response inhibition in the SST (Aron et al.,

2003). Simmonds et al., (2008) argue that when attentional or memory resources are in higher use then frontal areas (e.g. anterior cingulate, striatum and temporal regions) are also associated with performance in the stop signal task in children with externalising-related diagnoses (ADHD; Batty et al., 2010). Findings are heterogenous, suggesting a wide variety of neurological changes associated with externalising behaviour that cannot be easily categorised. The current findings support the involvement of the inferior frontal gyrus regions in the presentation and development of externalising behaviour. Still, it is unclear if this is part of broader neurological alterations. Frontal gyrus areas (including pars orbitalis have also been associated with differences in emotional processing and regulation (Vigilis et al., 2019). As such, further research may explore potential interactions between externalising and emotional regulation capacities and activation in this region.

The results also showed reduced 'go' accuracy was associated with higher externalising cross-sectionally. Effect sizes (standardised beta) indicate that each standard deviation decrease in inhibitory accuracy increased externalising scores by 4.33, a relatively large effect. This may suggest that those with higher externalising scores are allocated fewer attentional resources to error monitoring. However, like the MID task, SST performance measures could not predict future externalising. They thus may be more relevant to current externalising than they are to a causal mechanism of future externalising.

Error Monitoring

Neurological associations with error monitoring found that specific regions and activation directions differed between cross-sectional and longitudinal models. In cross-sectional models at baseline, decreased activation of the left superior parietal cortex (B-4.00) and increased right precuneus (B=2.52) activation. At follow-up,

increased right caudal middle frontal gyrus, increased left bank superior temporal sulcus and reduced right superior temporal gyrus activation predicted externalising. Furthermore, decreased left superior frontal gyrus activation at baseline predicted higher externalising scores at follow-up. This effect was mirrored in directionality at cross-sectional time points but was not significant in predicting externalising cross-sectionally. In particular, the superior temporal sulcus has previously been implicated in prosocial behaviour, social cues, and autism spectrum disorders (Sturm et al., 2016). As such, these findings may provide further support for the shared neurobiological substrates of social and non-social (e.g. financial, drug) rewards.

Summary

Faster and less accurate responses predicted externalising when anticipating a small reward. Anticipation of loss was associated with increased activation of the right putamen, and this predicted externalising over time. Reduced activation of the left caudate and increased activation of the left accumbens and left medial orbitofrontal cortex in response to monetary loss also predicted externalising over time. Finally, response inhibition was related to activation of the left pars orbitalis, which longitudinally was associated with externalising. Decreased left superior frontal gyrus activation related to error monitoring predicted externalising over time and may indicate that externalising develops partly due to insufficient allocation of resources to error monitoring. Together these findings suggest that alterations in neurobiological processes are implicated in the development of externalising behaviour. Results also highlight that the appropriate activation and deactivation of relevant neural regions may be necessary to adapt flexibly to changing demands, and impairment in this may be a marker of externalising. While this study indicates the relevance of neurobiological processes in the development of externalising, it is also important to

emphasise that sex, SES, IQ and pubertal development were strong predictors of externalising and may be more easily targeted by interventions to reduce the risk of externalising in adolescents.

Limitations

There are several important limitations of this study worthy of discussion. Firstly, a single measure, the CBCL, has measured externalising behaviour. Importantly, this questionnaire measure of behaviour is subject to various forms of bias, such as responder bias. As this is not a direct measure of behaviour, it may not be a true reflection of actual behaviour, limiting this study's ecological validity. Future research using this dataset may consider using multiple measures in combination with the CBCL to obtain a more valid estimate of externalising. Furthermore, the CBCL measure used here is based on parent-report of their child's behaviour. We know that there are differences when comparing parental and child reporting of emotional and behavioural problems (Van Roy et al., 2010). As such there are advantages and disadvantages to using each. Previous research has found that on the externalising scale of the CBCL, parent and child reports have high agreement (Rey et al., 1992). However, interpretations of the results must caution that predictions relating to the parental reporting of externalising rather than self-report of externalising.

Further, the CBCL externalising subscale combines various components of externalising. So, this study has not explored relationships between neurobiological factors and specific forms of externalising behaviour (e.g. rule-breaking vs aggression). The CBCL also provides a score for each item, and thus each item is weighted equally. We may consider, for example, that items relating to ADHD symptomology may require different clinical approaches than items relating to

conduct disorder and that, as such, they could be weighted differently or examined separately in future research.

An important limitation of the research conducted in Chapter Two is that many variables or confounding may be related to externalising that have not been accounted for within analyses (for example, parental behaviour, parenting style, attachment, and parental psychological histories).

Analysis has not included any measures of other factors related to externalising and reward processing. For example, internalising is highly associated with externalising and thus may be a confounding factor in the current analysis. Including internalising within research could provide information about activation patterns and performance that are independently attributable to the externalising construct. It was decided that as externalising and internalising are highly comorbid, controlling for internalising within analysis could result in losing essential components shared between the two constructs. Similarly, multiple other factors may interact with externalising and impact brain structure and function, such as early attachment relationships and personality, which have not been included in this analysis due to the current scope. This is an avenue for future study using this dataset.

This study took an ROI approach to the analysis of brain activation. An alternative method would be to use a whole-brain approach. The ROI approach involves identifying *a priori* regions for analysis based on theoretical hypotheses or prior research findings. This method requires anatomical atlases, which provide maps to identify specific regions. One issue is that maps may differ in mapping brain regions. The mapping methods employed here are based on frequently used atlas methods, thus minimising this issue as results can be easily contrasted to other studies. A whole-brain approach is typically more exploratory and involves analysing

activation across the brain to identify clusters of activity. A whole-brain approach may identify other regions not included in the current analysis. ROI was considered the most appropriate approach for this study as areas were selected based on multiple previous studies that have found associations between the tasks used and externalising in other samples.

The outcome measures from each task did not include looking at performance or BOLD activation on trials directly following reward/loss or correct/incorrect responses. How individuals respond to and recover from wins or losses may be of importance for this area of study. For example, if it takes a long time for individuals to return to baseline activation or performance following a failed trial, they may be more likely to take greater risks in subsequent tasks.

Implications

This study adds to the growing body of literature indicating that neurobiological processes are developmentally sensitive and are a possible mechanism for developing externalising behaviours. Patterns of neural activations associated with externalising are nuanced and involve increased activations in some regions and simultaneously decreased activations in others. The direction of effects are related to task conditions, indicating that neurological responses may be specifically tied to conditions such as reward vs loss, anticipation, task complexity, size of the reward, perceived size of the loss and the anticipated kind of reward. These findings have clear implications for understanding the neurobiological substrate of externalising behaviours. This research must continue across the entire adolescent period to identify if there are neurological markers of those at risk for developing chronic externalising behaviour (such as life-course persistent offending) or comorbidities from those who

may have time-limited or transient displays of externalising behaviour. If this is established, it may be possible to develop interventions targeting those with particular risk factors.

Future research should consider replicating this analysis as future waves of data from the ABCD Study are released, also including alternative measures of externalising, such as observations of externalising behaviours rather than solely relying on self/parental report questionnaire measures to examine how these findings relate to observable behaviours outwith lab conditions. Another possibility would be to consider the effect of change in neural activations over time on externalising and relationships with diagnostic categories related to externalising. Research could also address whether similar results are observed in other types of reward, such as social reward, which may be particularly relevant for adolescents.

From a prevention or intervention perspective, one possible avenue worth exploring would be to investigate if individuals with high externalising can improve their capacity to inhibit previously rewarding behaviours. Designing paradigms to train this ability may establish if this is possible within a laboratory context, the ecological validity of which could be tested.

One ‘big-picture’ implication relates to how we understand behaviour, particularly behaviour which does not conform to social norms. Increasing understanding of neurobiological underpinnings of externalising behaviour alongside effective public engagement and knowledge sharing may help people respond more compassionately to those who display externalising behaviours, which can result in stigma and marginalisation. Such alternative approaches may be beneficial in supporting and managing externalising, particularly given externalisers' difficulties in inhibiting behaviour.

Conclusion

Neurobiological activations at baseline are more able to predict future externalising than behavioural performance at baseline in relation to reward-processing paradigms, the MID and SST. Results indicate that nuanced increased and decreased activation patterns are associated with externalising behaviour in reward-processing brain regions and effects may be cumulative. This provides evidence that flexibly activating and deactivating relevant brain regions is key to developing externalising behaviours. Patterns of activation that predict externalising over time may suggest that externalising networks come online when the risks are lower, as when anticipating greater financial loss, externalising-related activations were not seen. Externalising was also predicted by differential activation relating to reinforcement reward processes, suggesting that externalising is related to difficulties in inhibiting previously rewarded behaviours. The current results suggest that fewer attentional resources are allocated to error monitoring when externalising is high, but the direction of this effect is unclear. However, demographic, pubertal and social factors were stronger predictors of future externalising, and thus psychosocial interventions may currently be the most appropriate for preventing or reducing externalising behaviour.

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Chapter Three: Critical Appraisal

This chapter will consider the processes involved in conducting this research project. Three key areas will be explored: the advantages of large cohort studies, reflections on particular difficulties encountered, and 'big picture' issues related to this research.

Advantages of cohort studies

A frequently cited issue within the literature relating to developmental research within psychology is that there is a lack of longitudinal data and that many studies are limited in their scope to conclude due to small sample sizes. Cross-sectional studies, or indeed studies which examine a phenomenon retrospectively, are limited in their ability to conclude causality. Small sample sizes typically mean that studies may be underpowered to detect true effects, and research which uses lots of statistical tests amplifies the risk of false-positive results (Ranganathan et al., 2016). Longitudinal cohort studies, which collect data at regular specified time points over a long duration, provide an ideal solution to these issues. Prospective cohort studies, of which the ABCD Study is one example, typically recruit participants from the community or population rather than targeting individuals based on the presence of particular symptoms to observe the development of the subject of interest (in this case, externalising behaviour). Thus, this can provide a temporal framework for examining causal mechanisms. In this way, cohort designs can draw strong conclusions about the direction of effects as cohort studies involve large sample populations. For example, some cohort studies sample entire populations (e.g. Dunedin Longitudinal Study, Lothian Birth Cohort). Large cohort studies (e.g. ABCD Study participants

n=~11,000) are sufficiently powered to examine many outcomes and factors within the same study (Song & Chung, 2010). Consequently, this maximises the ability of researchers to draw conclusions that are generalisable to broader populations.

These designs allow for the direct comparison of individuals within the sample, who are in theory similar, who have (in this case) developed a behavioural outcome, to those who have not. Research can then explore what other factors may be associated with risk for or development of the outcome (such as behaviour, symptom, illness, disease). Measures are recorded at regular intervals over time, allowing the opportunity to map the development and trajectory of the examined outcome and earlier measures of risk factors. This means that usually (see discussion below regarding COVID-19), data is gathered regardless of life events which means causality can be assessed.

Like the ABCD Study, prospective designs are beneficial as they are less subject to participant recall biases. The way cohort designs are established usually means that participants are enrolled at an early age, sometimes from birth (e.g. Millennium Cohort Study). This allows researchers to maximise the potential to capture relevant information as early as possible to track relationships over time with an ability to identify causal mechanisms. This is particularly important if we are interested in developmental processes and improving our understanding of factors affecting children and adolescents.

However, these studies have some disadvantages. They are labour-intensive and expensive to run due to the large-scale nature of the design and comprehensive assessment protocols involved. This also means that the participant burden is high. For example, the ABCD Study reports that data-collection protocol involves 6-7 hours of participation every two years with 2-3-hour sessions on the alternate year and 3 and

6 monthly follow-up sessions conducted online or over the phone. A high participant burden is associated with increased dropout rates, so cohort studies will likely be subject to high attrition (Booker et al., 2011). However, ABCD Study reports that 87% of participants completed data-collection at the two-year follow-up time point (ABCDStudy.org). Difficulties of attrition is further increases researchers' cost and time commitment to maintain contact with participants and motivate their ongoing involvement in research. My previous post-doctoral experience of working on a longitudinal cohort study (The Tees Valley Baby Study) gave me insight (albeit on a far smaller scale) into the time-consuming nature of this as well as the balance of trying to encourage participants' engagement while balancing the ethical responsibility of not pressuring individuals and the right of participants to withdraw from research involvement.

Difficulties Encountered

Using cohort study data that has already been collected and is accessible provides a highly ethical means to answer important research questions as it requires no further participant burden. As such, the ABCD Study was identified as a dataset that could answer the questions of this research project. The ABCD Study data is freely available to access and involves a relatively straightforward application to the National Institute of Mental Health (NIMH). So, data access was initially thought to be a relatively simple process. However, this was a more complex and time-consuming process than anticipated. Legal teams affiliated with University College London (UCL) required significant amounts of time to examine the application before signing off on our NIMH application. This resulted in several months of back-and-forth between the researchers, UCL Contracts Team, and NIMH Data Access Team debating if the ABCD Study data constituted anonymised or pseudo-anonymised data

and frequent chasing of this process. This resulted in substantial delays in accessing the data and, thus, in beginning data cleaning and analysis.

Ultimately this delay resulted in one part of the planned analysis being dropped from the project. Initial plans involved using factor analysis techniques to identify underlying constructs to represent externalising from multiple measures of externalising – including observed behaviours and diagnostic measures. This was unfortunate given that a key limitation of the current study is using a single subscale measure of externalising (the CBCL).

Upon receiving access to the data, there was then the experience of a vast overwhelm. Although the variables of interest had been determined *a priori*, understanding the naming conventions and identifying the relevant data within the ABCD database was challenging.

The biggest hurdle to overcome was the fMRI data itself. Without prior experience or confidence with fMRI data, I was naive to the complexity of this data and the plethora of options available for analysis. The literature review identified key brain regions that would be important for research, but I was left to decide how to identify and segment these regions. This introduced me to the world of brain atlases and the differences between different methods of brain parcellations. All methods had pros and cons. While it was initially considered potentially preferable to have smaller regions, it became clear that previous research, including research from well-established laboratories, used larger regions within ROI analyses in similar studies. As this was an entirely novel area to me, I followed the methodological approaches that well-established groups published. However, this has resulted in analyses including several large brain regions which could mean less specific and less nuanced results.

I had anticipated that the most time-consuming aspect of data analysis would be data-cleaning and preparation. Given the complexity of the ABCD Study data, this was indeed a challenging process. While published research provides information regarding statistical methodology and sometimes includes access to scripts for coding, it rarely provides important information relating to the data preparation processes. This task was fairly daunting and sometimes seemed to be trial and error. Consulting with others that have previously used this data was valuable. In particular, the sharing of part of a script which included a function of how to read in a file whilst removing the second line of the data (as this was a description of each variable), was invaluable.

From a personal, although unlikely to be unique, perspective, switching between analysing complex data and clinical practice was particularly challenging. This resulted in much time spent refamiliarising myself with what I had done, and it felt like a very inefficient use of time. Similarly, having not used R for approximately three years felt like a steep (and frustrating) learning curve.

Within the ABCD Study data, there were also some important elements to consider. Firstly, participants were enrolled in this study at age nine. The ABCD Study aims to examine developmental processes associated with adolescence. While this is likely a sufficiently young age to capture relevant factors, it is known that pubertal development occurs at an increasingly young age and often begins around age 9-10. Thus, there may be important factors that relate to the outcomes of interest (for example, externalising) that have occurred before the first wave of data collection, which is therefore not accounted for, such as developmental factors in early or middle childhood. This is particularly relevant to externalising as we know this behaviour can often present in childhood, earlier than internalising disorders (Donati et al., 2021).

However, the study protocol also includes retrospective measures provided by parents that substantially mitigate this limitation.

Data collection began in 2018 with yearly in-person sessions and 3-6 monthly online or telephone sessions scheduled for follow-up. Like many other research projects, this was impacted by the COVID-19 pandemic. It is rare for such a large study with participants from multiple areas of a country to be affected in this way. Consequently, face-to-face assessment sessions became virtual. One potential issue here is that there may be differences attributable to the difference between online vs face-to-face that need to be accounted for. Pandemic-related stressors may also have impacted participation, and we know that the pandemic had greater adverse effects on those from disadvantaged or marginalised groups, which may bias participation or data. While cohort studies are generally a methodology which is optimal for developmental research, it is very difficult to separate developmental effects from cohort effects, including historical or cultural events that occur alongside development. The COVID-19 pandemic is one such event, the effects of which will be difficult to disentangle from other developmental factors.

As well as the COVID-19 pandemic, other events would have affected this cohort. The Black Lives Matter (BLM) movement, although originating in 2013, rose within the social consciousness following the highly publicised murder of George Floyd in America in 2020. This event and the subsequent BLM movement profoundly affected society and, in particular, affected Black communities. Political unrest (resulting in protests and violence), public discussion of systemic racism and fear for personal safety at this time had a profound personal and global impact. Again, this is likely to constitute a cohort effect and, further, occurred alongside the COVID-19 pandemic and is likely to have distinct effects for disadvantaged and marginalised

groups. From a research perspective, accounting for this impact is likely to be extremely complex. The ABCD Study has also been used to examine the impact of the BLM movement. For example, Baskin-Sommers et al., (2019) published research exploring the emotional experiences of Black adolescents when exposed to the BLM movement, highlighting the benefit of civic engagement for this group while also acknowledging the complexity of this experience.

'Big-Picture' Issues

Prioritising Mental Health Research

Childhood and adolescence represent a critical period of vulnerability for developing psychological disorders, including externalising. We know that mental health difficulties are the largest cause of global disability and account for nearly 15% of years of life lost, resulting in significant personal and economic costs (Arias et al., 2022). However, UK institutions receive only 5.5% of the UK's health research budget for all mental health research. In contrast, cancer research receives 19.6% of spending (MQ Landscape Analysis, 2015). While clearly, there is also a need to research physical health conditions; this demonstrates the significant underfunding of mental health research in the UK. The prioritisation of physical health at the detriment of mental health is also exhibited in funding by Clinical Commissioning Groups; Rocks et al., (2019) showed that spending £100 more on physical health services was associated with a 9% lower spend in CAMHS services. Without appropriate investment in research and services driven by policy and political decision-making, understanding and developing interventions for mental health difficulties across the board will likely lag behind physical health with destructive personal and societal consequences.

Legal Ramifications of Neuroscientific Research

Neuroscience has the potential to radically shift our understanding of behaviour. At the extreme end of the externalising spectrum lies criminal offending such as drug use, violence and antisocial behaviour. Neuroscientific, psychological and psychiatric research of externalising, therefore, has the potential to alter our understanding of such offences and could have legal implications for personal responsibility for offending. There is already a long-standing precedent for exempting or reducing criminal accountability based on mental illness. For example, in the UK, established defences may include the 'Not Guilty by Reason of Insanity' or 'Diminished Responsibility' arguments.

A review of case law by Catley and Claydon (2015) found that the use of neuroscientific evidence, such as brain imaging (most frequently MRI or CAT scan), has been increasing in defence appeal cases (appealing a sentence or conviction) between the years of 2005 and 2012 (total of 204 cases where neuroscientific evidence has been presented as part of the defence for criminal charges). Of these cases, 28% were accused of homicide (Catley & Claydon, 2015), and 26.2% of the 204 cases resulted in a successful appeal based on neuroscientific evidence. While there are currently robust systems in place to interrogate such evidence, it is not outwith the realms of possibility that advances in understanding the brain's function and how this impacts behaviour could have legal ramifications for offenders. This could also change how society views and holds those who commit such offences accountable. This could also identify those who are at risk of violent behaviours by virtue of neurological structure or functioning and may result in premature punitive or restrictive approaches to individuals who have not yet (or who may not) behaved violently. This would be an oversimplification of understanding the causes of

offending. Consequently, neuroscientific evidence should always be considered along with a comprehensive assessment of other important factors (e.g. social factors), including protective factors, when considering someone's offending risk.

fMRI Research Methodology

One criticism of imaging research is the potential disconnect between findings and implications for clinical practice. In some cases, implications are clear; for example, studies of structural abnormalities and associated behaviours have clear implications for treatment. However, frequently findings have less direct relevance to clinical practice. The current study arguably falls into this category. Substantial amounts of ongoing research using imaging techniques are likely required for clear relationships between brain activity and behaviour to be established prior to the development of interventions. In this way, such research may be seen as fulfilling an academic curiosity more than a clinical need. However, the aim of this kind of research is to improve our understanding of the brain, thereby addressing clinical needs.

On the other hand, understanding particular functional differences could result in individuals being more likely to demonstrate externalising behaviour does provide scope for intervention. For example, interventions to support the development of strategies to mitigate the impact of altered reward-processing networks (such as supporting an individual to take steps to reduce impulsivity) could be of substantial benefit. Similarly, an awareness of one's increased neurobiological risk for externalising related behaviours, such as addiction, could result in individuals taking additional precautions to avoid engaging in substance use. The more we learn about neurobiological risk, the more we can establish ways to modify, mitigate or manage such risk factors.

Conclusion

Overall, this research increased my knowledge and skills in data analysis and neuroscientific approaches to developmental research. Writing this chapter has also allowed me to reflect upon specific and broader contextual factors and processes related to this research, enhancing my appreciation for theory-practice links and continuing my ongoing interest in participating in clinically relevant research.

References

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Catley, P., & Claydon, L. (2015). The use of neuroscientific evidence in the courtroom by those accused of criminal offenses in England and Wales. Journal of law and the biosciences, 2(3), 510–549. https://doi.org/10.1093/jlb/lsv025

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Ranganathan, P., Pramesh, C. S., & Buyse, M. (2016). Common pitfalls in statistical analysis: The perils of multiple testing. Perspectives in clinical research, 7(2), 106–107. https://doi.org/10.4103/2229-3485.179436

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Webpages:

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Appendices

A. Pre-Registration Info

Pre-registration of this study was created with OSF:
https://doi.org/10.17605/OSF.IO/PAGT3

B. Details of Joint Working

Alice Zacharia and I both completed research studies using data from the ABCD Study. As such we applied to the NIMH for data access together, for approval purposes these projects were considered two branches of the same project. This also resulted in us working in Data Safe Haven under the same project folder and so we worked together to download the data and import this into Data Safe Haven.

Design, analysis, interpretation and write up of each study was conducted independently.

C. Supplementary Analsysis

Chi Squared Test – independence of race, income and sex

Call: xtabs(formula = ~race_ethnicity + demo_comb_income_v2, data =
T1completeNumber of cases in table: 4558
Number of factors: 2
Test for independence of all factors:
    Chisq = 1033.9, df = 36, p-value = 1.186e-193
    Chi-squared approximation may be incorrect
Call: xtabs(formula = ~Pubertal_merged + eventname + sex, data = data)
Number of cases in table: 9116
Number of factors: 3
Test for independence of all factors:
    Chisq = 4638, df = 13, p-value = 0
MODEL INFO:
Observations: 4558
Dependent Variable: pea_wiscv_tss
Type: OLS linear regression

MODEL FIT:
F(6,4551) = 68.71, p = 0.00
R^2 = 0.08
Adj. R^2 = 0.08

Standard errors: OLS

	Est.	S.E.	t val.	p
(Intercept)	8.54	0.19	45.81	0.00
demo_comb_income_v2	0.27	0.02	12.73	0.00

sexM	-0.32	0.08	-3.98	0.00
race_ethnicity2	-1.20	0.15	-7.87	0.00
race_ethnicity3	-0.52	0.12	-4.43	0.00
race_ethnicity4	0.07	0.32	0.21	0.84
race_ethnicity5	-0.07	0.14	-0.47	0.64

Chi Squared Test of Independence – Pubertal Development, Sex, Time

3-Way Frequency Table
> mytablepuberty <- xtabs(~Pubertal_merged+eventname+sex, data=data)
> ftable(mytablepuberty) # print table

		sex	F	M
Pubertal_merged	eventname			
1	2_year_follow_up_y_arm_1		102	910
	baseline_year_1_arm_1		713	1748
2	2_year_follow_up_y_arm_1		219	921
	baseline_year_1_arm_1		499	562
3	2_year_follow_up_y_arm_1		1052	461
	baseline_year_1_arm_1		887	93
4	2_year_follow_up_y_arm_1		742	118
	baseline_year_1_arm_1		48	7
5	2_year_follow_up_y_arm_1		33	0
	baseline_year_1_arm_1		1	0

> summary(mytablepuberty) # chi-square test of indepedence
Call: xtabs(formula = ~Pubertal_merged + eventname + sex, data = data)
Number of cases in table: 9116
Number of factors: 3
Test for independence of all factors:
Chisq = 4638, df = 13, p-value = 0

Linear Model of Intelligence (IV- sex, race, SES)

<-lm(pea_wiscv_tss~demo_comb_income_v2+sex+race_ethnicity, data=T1complete)
> summ(z)
MODEL INFO:
Observations: 4558
Dependent Variable: pea_wiscv_tss
Type: OLS linear regression

MODEL FIT:
F(6,4551) = 68.71, p = 0.00
R^2 = 0.08
Adj. R^2 = 0.08

Standard errors: OLS

	Est.	S.E.	t val.	p
(Intercept)	8.54	0.19	45.81	0.00
demo_comb_income_v2	0.27	0.02	12.73	0.00
sexM	-0.32	0.08	-3.98	0.00
race_ethnicity2	-1.20	0.15	-7.87	0.00
race_ethnicity3	-0.52	0.12	-4.43	0.00
race_ethnicity4	0.07	0.32	0.21	0.84
race_ethnicity5	-0.07	0.14	-0.47	0.64

>

D. Tests of Assumptions

Figure 8: Assumption Checks - MID Behavioural Model at T1

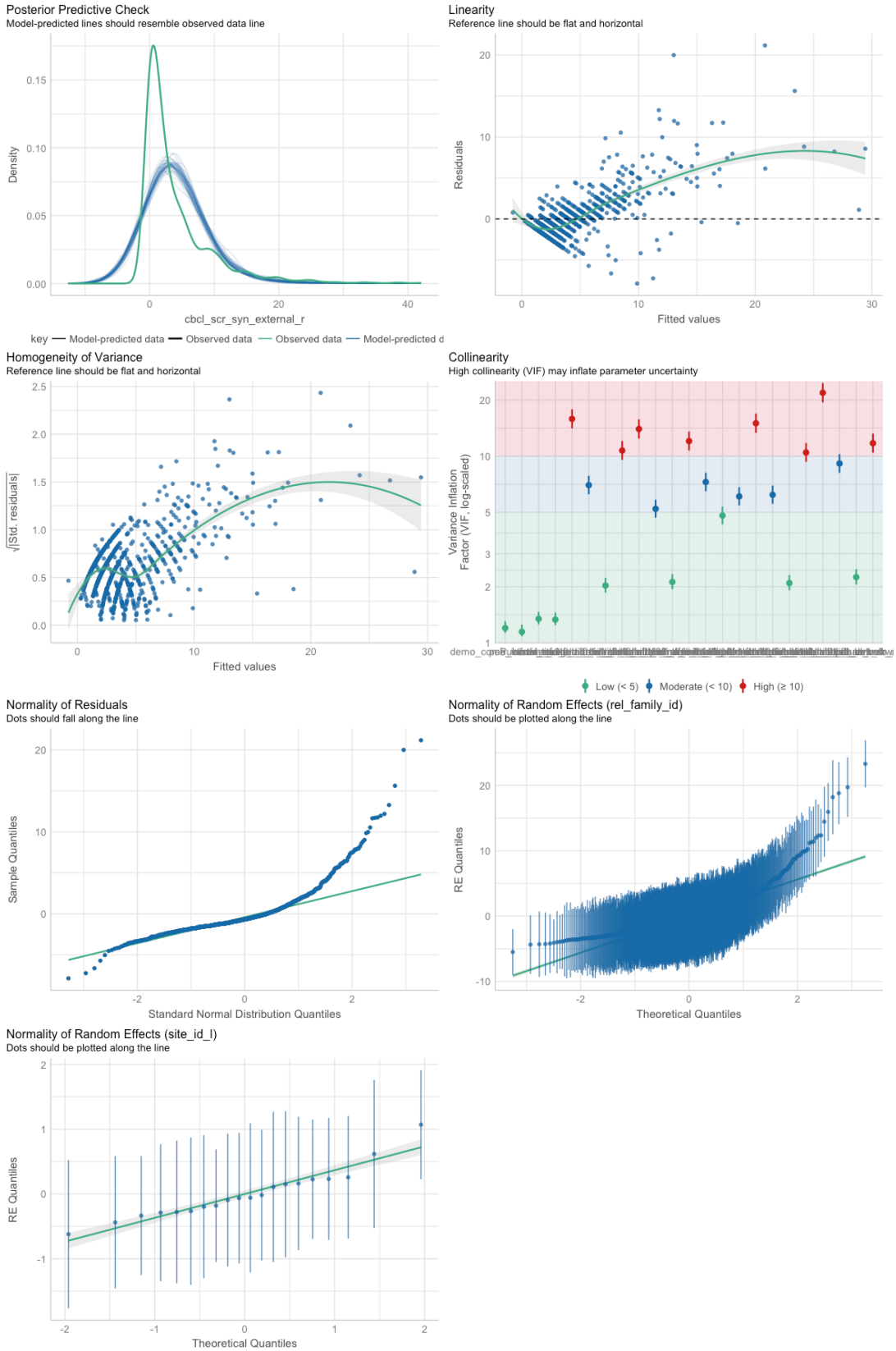


Figure 9: Assumption Checks MID Behavioural Model at T2

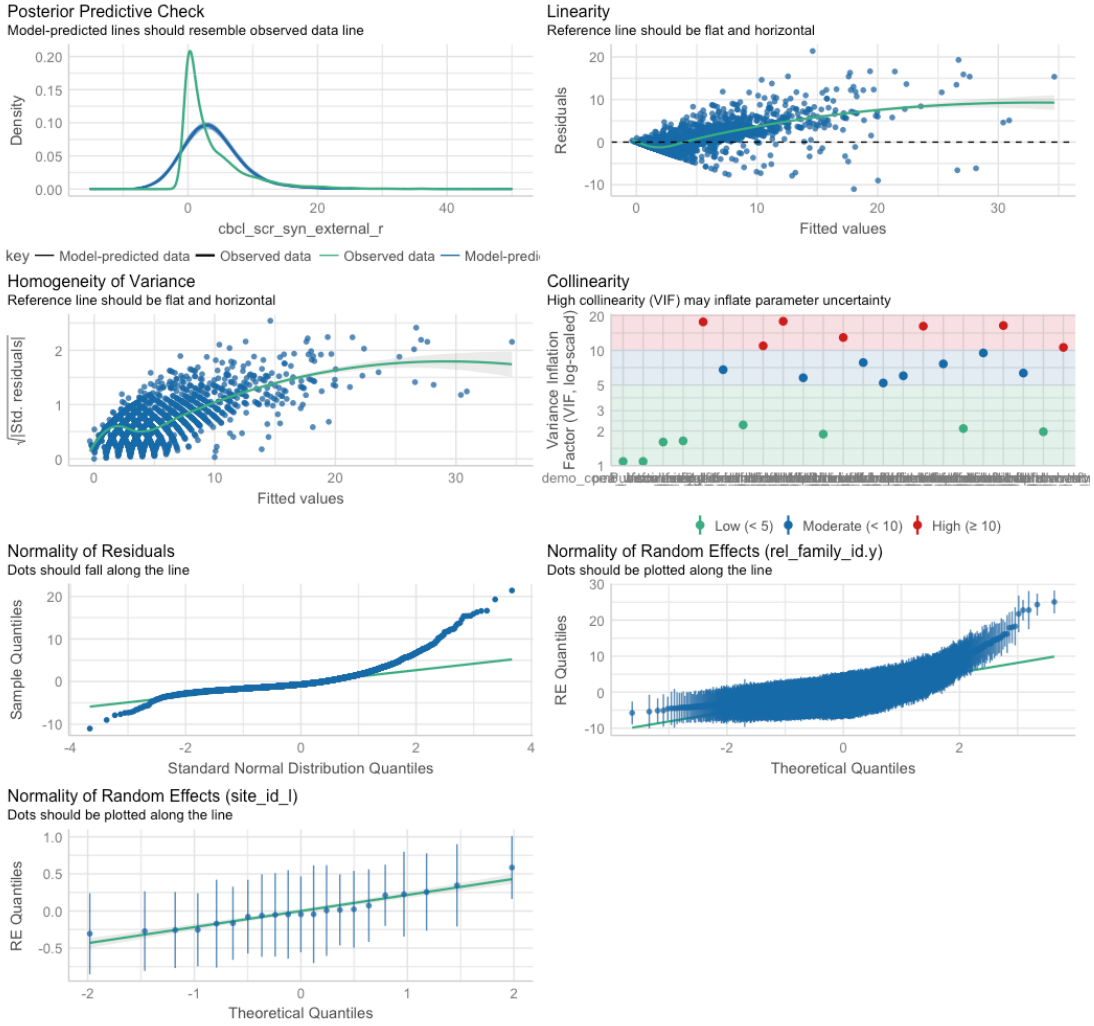


Figure 10: Assumption Checks MID Behavioural Model - Longitudinal

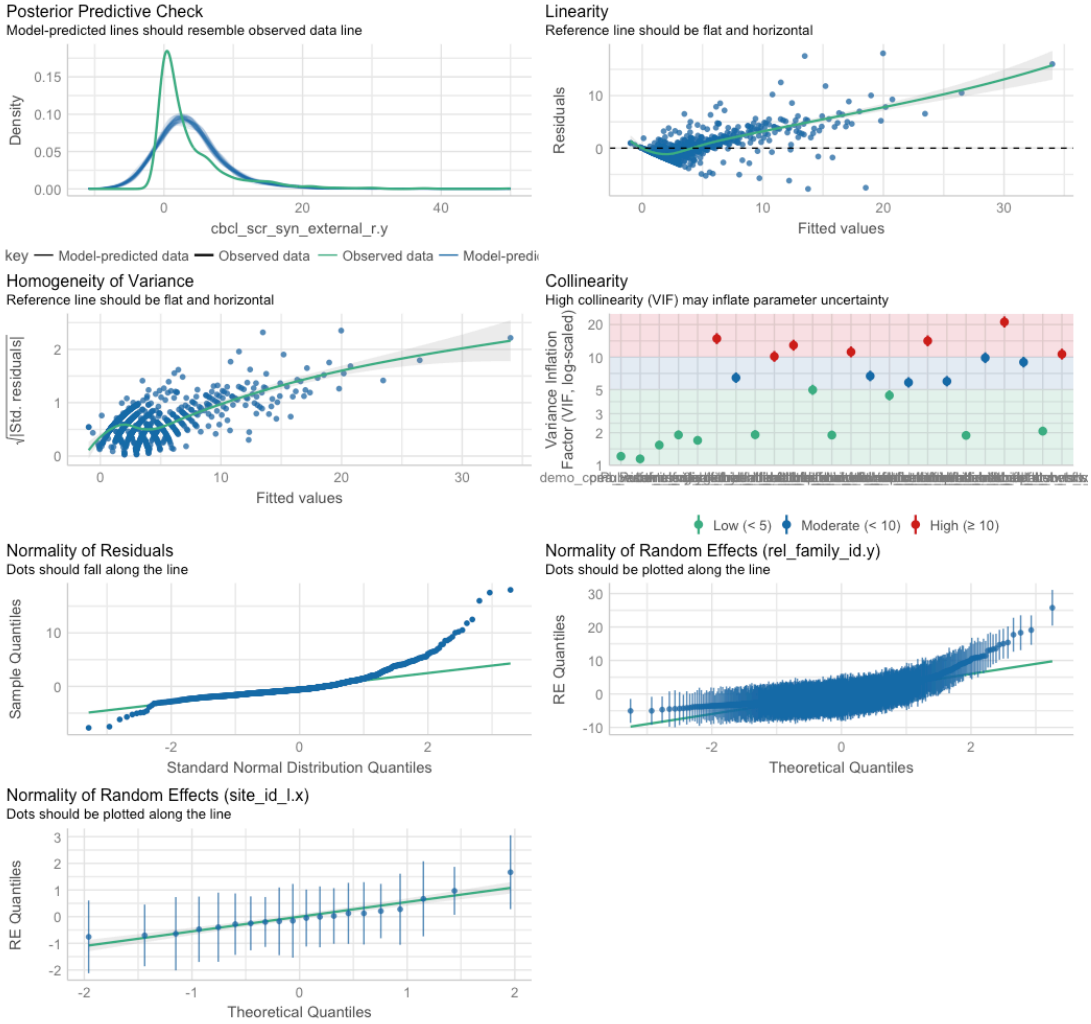


Figure 11: Assumption Checks MID ROI Model at T1

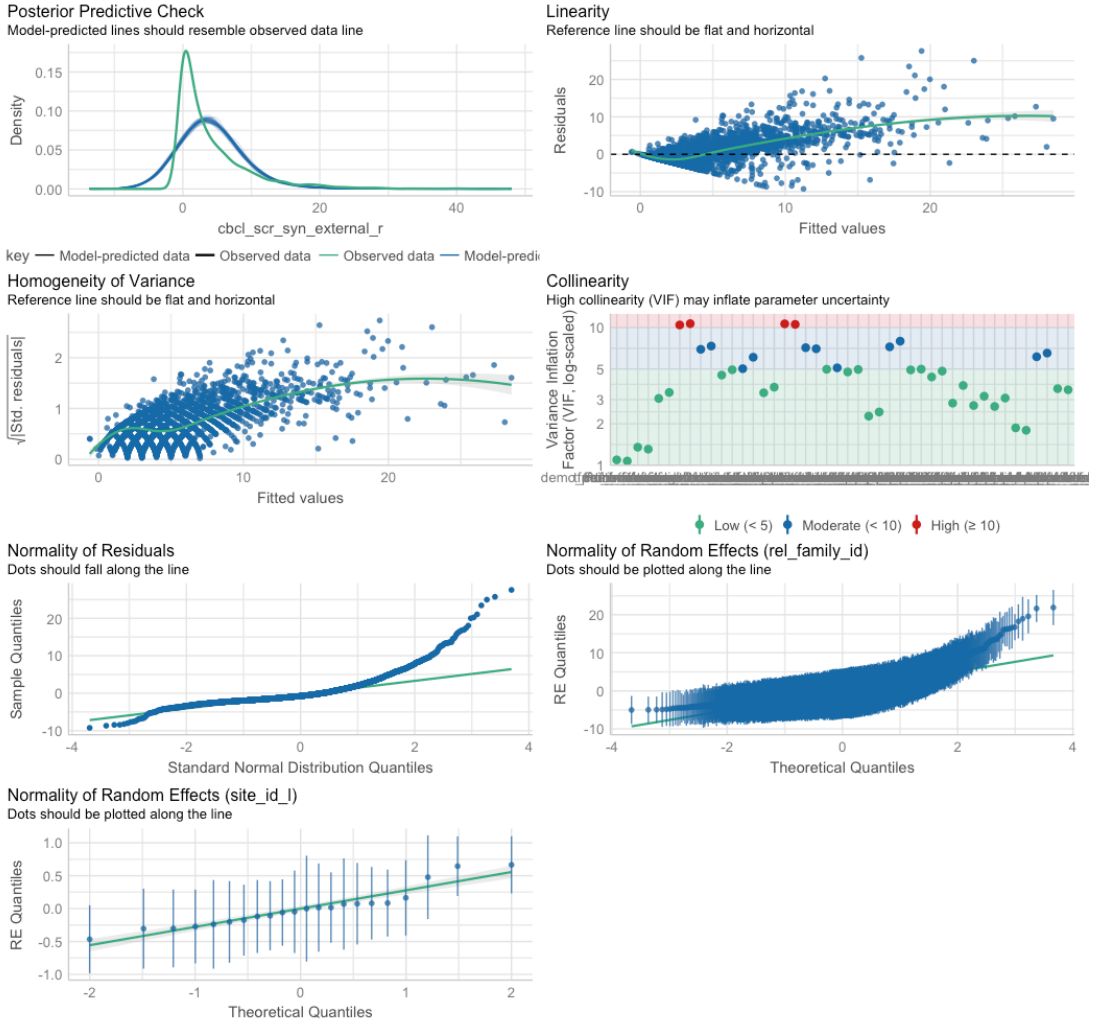


Figure 12: Assumption Checks MID ROI Model at T2

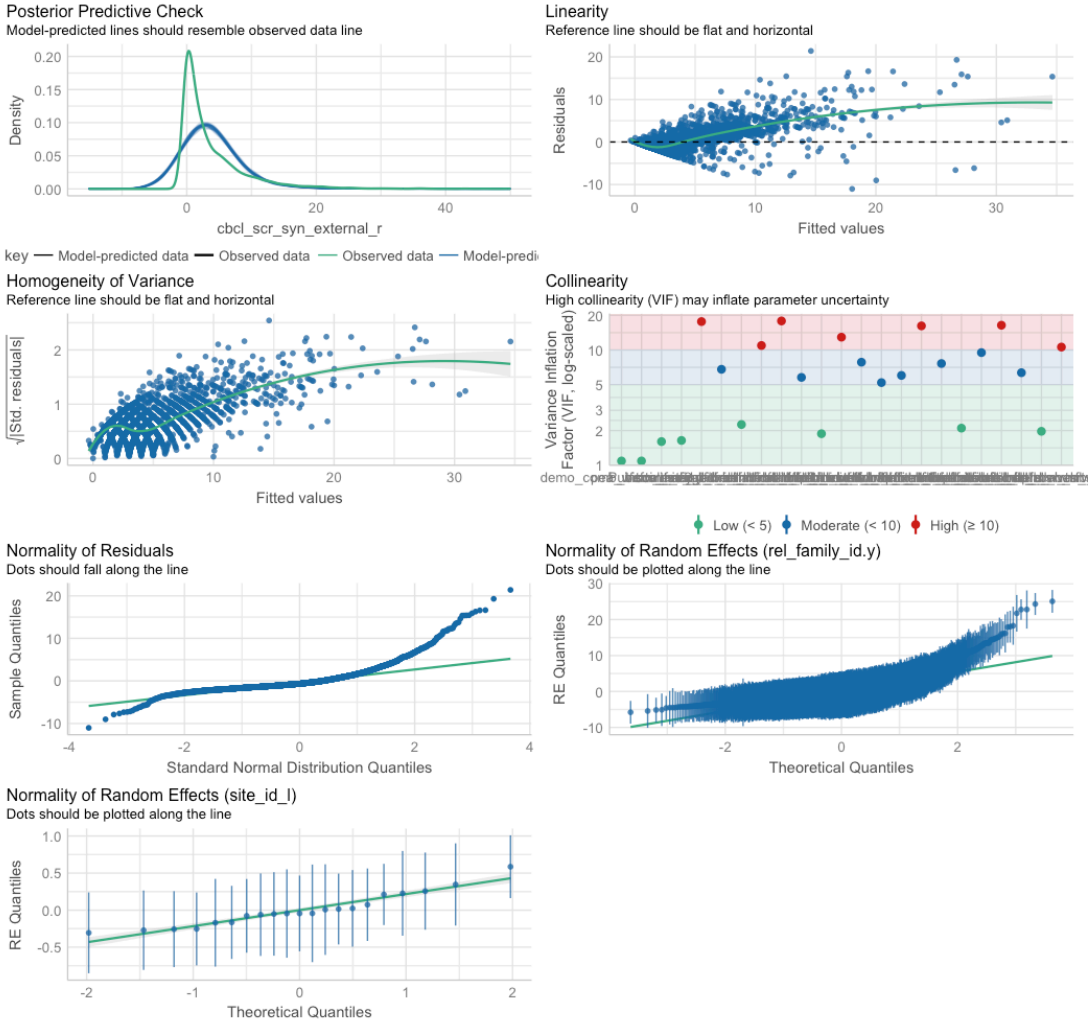
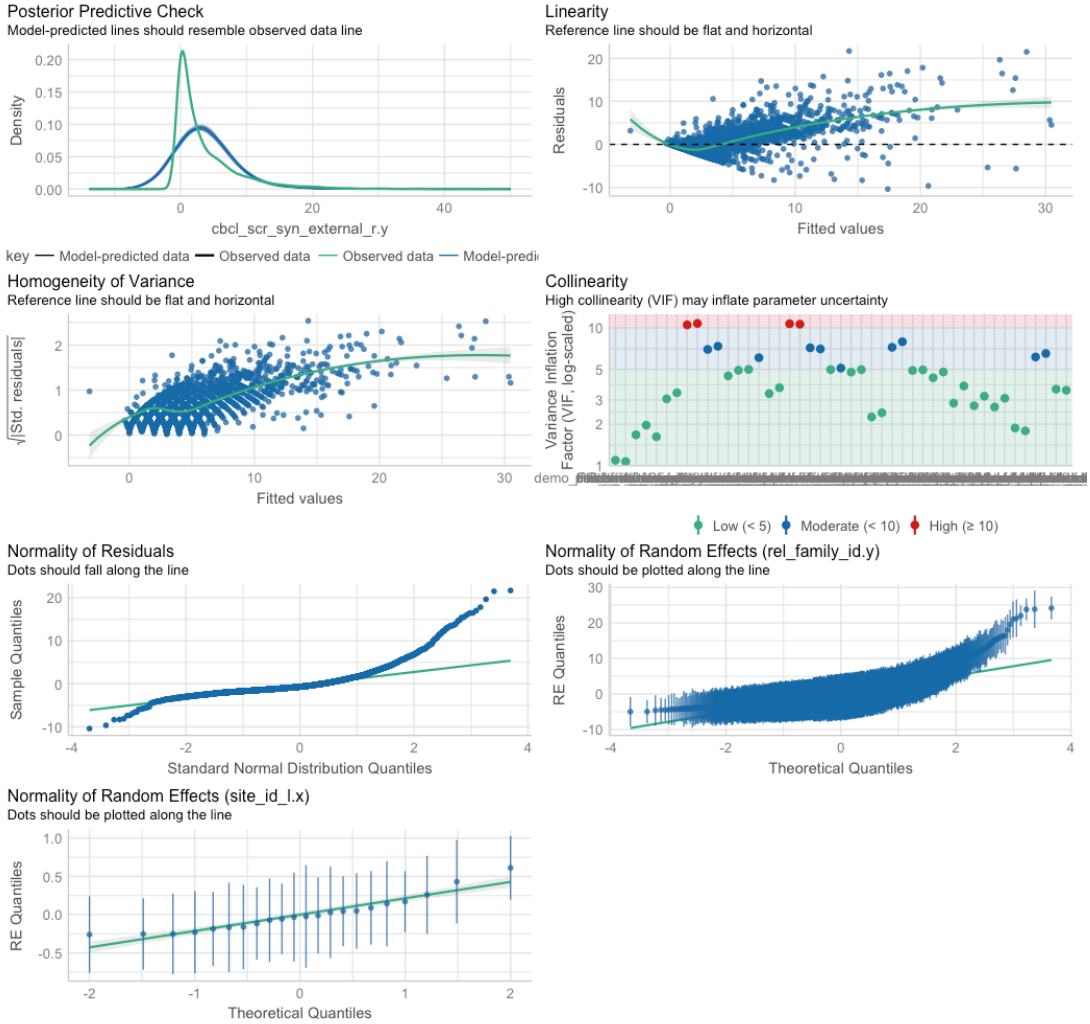


Figure 13: Assumption Checks MID ROI Models - Longitudinal



E. R-Script (Regression Analysis)

```
setwd("~/Desktop/Eilidh/ABCD_DATA/ABCD_Analysis")
data_dir <- ("~/Desktop/Eilidh/ABCD_DATA")
output_dir <- "Results"

#install.packages("dplyr")
#install.packages("readr")
#install.packages("tidyr")
#install.packages("knitr")

library(dplyr)
library(readr)
library(tidyr)
library(psych)
library(knitr)

# Note ABCD files needed and create full pathnames

mhy02_filename <- "abcd_mhy02.txt"
mhy02_filename <- paste(data_dir, mhy02_filename, sep="/")

mid02_filename <- "abcd_mid02.txt"
mid02_filename <- paste(data_dir, mid02_filename, sep="/")
```

```
midtlb01_filename <- "abcd_midtlb01.txt"
midtlb01_filename <- paste(data_dir, midtlb01_filename, sep="/")

sst02_filename <- "abcd_sst02.txt"
sst02_filename <- paste(data_dir, sst02_filename, sep="/")

ypdms01_filename <- "abcd_ypdms01.txt"
ypdms01_filename <- paste(data_dir, ypdms01_filename, sep="/")

cbcls01_filename <- "cbcls01_id.txt"
cbcls01_filename <- paste(data_dir, cbcls01_filename, sep="/")

lpds01_filename <- "lpds01_id.txt"
lpds01_filename <- paste(data_dir, lpds01_filename, sep="/")

midaparc03_filename <- "midaparc03_id.txt"
midaparc03_filename <- paste(data_dir, midaparc03_filename, sep="/")

midaparcp203_filename <- "midaparcp203_id.txt"
midaparcp203_filename <- paste(data_dir, midaparcp203_filename, sep="/")

mrisst02_filename <- "mrisst02.txt"
mrisst02_filename <- paste(data_dir, mrisst02_filename, sep="/")

abcd_midabwdp01_filename<- "abcd_midabwdp01.txt"
abcd_midabwdp01_filename <- paste(data_dir, abcd_midabwdp01_filename, sep="/")

abcd_midabwdp202_filename<- "abcd_midabwdp202.txt"
abcd_midabwdp202_filename <- paste(data_dir, abcd_midabwdp202_filename, sep="/")

abcd_ppdms01_filename <- "abcd_ppdms01.txt"
abcd_ppdms01_filename <- paste(data_dir, abcd_ppdms01_filename, sep = "/")

pdem02_filename <- "pdem02.txt"
pdem02_filename <- paste(data_dir, pdem02_filename, sep = "/" )

abcd_ssphp01_filename <- "abcd_ssphp01.txt"
abcd_ssphp01_filename <- paste(data_dir, abcd_ssphp01_filename, sep="/")

abcd_lt01_filename <- "abcd_lt01.txt"
abcd_lt01_filename <- paste(data_dir, abcd_lt01_filename, sep="/")

acspsw03_filename <- "acspsw03.txt"
acspsw03_filename <- paste(data_dir, acspsw03_filename, sep = "/" )

abcd_ps01_filename <- "abcd_ps01.txt"
abcd_ps01_filename <- paste(data_dir, abcd_ps01_filename, sep = "/")

# The following function reads in an ABCD datafile using readr to get around some formatting issues, namely
# that the file is tab delimited and the first row is the variable description name which tends
# set the variable type wrongly. This code reads in the column names, then reads in the datafile
# skipping the first two rows, then uses column names already read in. This means read_delim
# correctly identifies the data type when it reads in the data

read_abcd_file <- function(abcd_filename) {
  col_names <- names(read_delim(abcd_filename, delim="\t", n_max = 0))
  abcd_df <- read_delim(abcd_filename, delim="\t", na = "", col_names = col_names, skip = 3)
  return(abcd_df)
}

# Read mhy02 file, remove collection_title variable for each variable/data source
mhy02 <- read_abcd_file(mhy02_filename)
mhy02$collection_title <- NULL

mid02 <- read_abcd_file(mid02_filename)
mid02$collection_title <- NULL
```

```
midtlb01 <- read_abcd_file(midtlb01_filename)
midtlb01$collection_title <- NULL

sst02 <- read_abcd_file(sst02_filename)
sst02$collection_title <- NULL

ypdms01 <- read_abcd_file(ypdms01_filename)
ypdms01$collection_title <- NULL

cbcls01 <- read_abcd_file(cbcls01_filename)
cbcls01$collection_title <- NULL

lpds01 <- read_abcd_file(lpds01_filename)
lpds01$collection_title <- NULL

midaparc03 <- read_abcd_file(midaparc03_filename)
midaparc03$collection_title <- NULL

midaparcp203 <- read_abcd_file(midaparcp203_filename)
midaparcp203$collection_title <- NULL

mrisst02 <- read_abcd_file(mrisst02_filename)
mrisst02$collection_title <- NULL

mrisst02 <- read_abcd_file(mrisst02_filename)
mrisst02$collection_title <- NULL

abcd_midabwdp01<- read_abcd_file(abcd_midabwdp01_filename)
abcd_midabwdp01$collection_title <- NULL

abcd_midabwdp202_filename<- read_abcd_file(abcd_midabwdp202_filename)
abcd_midabwdp202_filename$collection_title <- NULL

ppdms01 <- read_abcd_file(abcd_ppdms01_filename)
ppdms01$collection_title <- NULL

pdem02 <- read_abcd_file(pdem02_filename)
pdem02$collection_title <- NULL

ssphp01 <- read_abcd_file(abcd_ssphp01_filename)
ssphp01$collection_title <- NULL

lt01 <- read_abcd_file(abcd_lt01_filename)
lt01$collection_title <- NULL

acspsw03 <- read_abcd_file(acspsw03_filename)
acspsw03$collection_title <- NULL

ps01 <- read_abcd_file(abcd_ps01_filename)
ps01$collection_title <- NULL
#Create a subset of cbcls01 with only columns I want (subjectkey, eventname, sex, internalising)

CBCL_data <- cbcls01[, c("subjectkey","eventname", "sex", "cbcl_scr_syn_external_r")]

#Create a subset of mid behavioural data with only columns I want (subjectkey, eventname, ...)

midbehaviour_data <- mid02 [, c("subjectkey", "eventname",
                        "tfmri_mid_all_beh_srw_mrt","tfmri_mid_all_beh_srw_stdrt",
                        "tfmri_mid_all_beh_srwpfb_mrt", "tfmri_mid_all_beh_srwpfb_stdrt",
                        "tfmri_mid_all_beh_srwnfb_mrt", "tfmri_mid_all_beh_srwnfb_stdrt",
                        "tfmri_mid_all_beh_lrw_mrt", "tfmri_mid_all_beh_lrw_stdrt",
                        "tfmri_mid_all_beh_lrwnfb_nt",  "tfmri_mid_all_beh_srwnfb_nt",
                        "tfmri_mid_all_beh_lrwnfb_mrt", "tfmri_mid_all_beh_lrwnfb_stdrt",
                        "tfmri_mid_all_beh_sl_mrt", "tfmri_mid_all_beh_sl_stdrt",
                        "tfmri_mid_all_beh_slpfb_mrt", "tfmri_mid_all_beh_slpfb_stdrt",
                        "tfmri_mid_all_beh_slnfb_mrt","tfmri_mid_all_beh_slnfb_stdrt",
```

```
                    "tfmri_mid_all_beh_ll_mrt","tfmri_mid_all_beh_ll_stdrt",
                    "tfmri_mid_all_beh_llnfb_nt", "tfmri_mid_all_beh_slnfb_nt",
                    "tfmri_mid_all_beh_llnfb_mrt", "tfmri_mid_all_beh_llnfb_stdrt",
                    "tfmri_mid_all_beh_nt_mrt","tfmri_mid_all_beh_nt_stdrt",
                    "tfmri_mid_all_beh_ntpfb_mrt", "tfmri_mid_all_beh_ntpfb_stdrt",
                    "tfmri_mid_all_beh_ntnfb_mrt","tfmri_mid_all_beh_ntnfb_stdrt",
                    "tfmri_mid_r1_beh_t_earnings",  "tfmri_mid_r2_beh_t_earnings",
                    "tfmri_mid_all_beh_lrwpfb_mrt", "tfmri_mid_all_beh_llpfb_mrt",
                    "tfmri_mid_all_beh_lrwpfb_stdrt", "tfmri_mid_all_beh_llpfb_stdrt")]

#Create a subset of mid (neuroimaging data) with only the columns I want
#Columns relate to negative vs. neutral activation in my ROIs
#Include subjectkey and eventname in every subset as this is what you are joining them by.

neuroimaging_data <- midaparc03[,c("subjectkey","eventname",
                          "tfmri_ma_acdn_b_scs_cdlh", "tfmri_ma_acdn_b_scs_ptlh",
                          "tfmri_ma_acdn_b_scs_aalh", "tfmri_ma_acdn_b_scs_cdrh",
                          "tfmri_ma_acdn_b_scs_ptrh", "tfmri_ma_acdn_b_scs_aarh",
                          "tfmri_ma_acvn_b_scs_cdlh", "tfmri_ma_acvn_b_scs_ptlh",
                          "tfmri_ma_acvn_b_scs_aalh", "tfmri_ma_acvn_b_scs_cdrh",
                          "tfmri_ma_acvn_b_scs_ptrh", "tfmri_ma_acvn_b_scs_aarh",
                          "tfmri_ma_rpvnfb_b_scs_cdlh", "tfmri_ma_rpvnfb_b_scs_ptlh",
                          "tfmri_ma_rpvnfb_b_scs_aalh", "tfmri_ma_rpvnfb_b_scs_cdrh",
                          "tfmri_ma_rpvnfb_b_scs_ptrh", "tfmri_ma_rpvnfb_b_scs_aarh",
                          "tfmri_ma_lpvnfb_b_scs_cdlh", "tfmri_ma_lpvnfb_b_scs_ptlh",
                          "tfmri_ma_lpvnfb_b_scs_aalh", "tfmri_ma_lpvnfb_b_scs_cdrh",
                          "tfmri_ma_lpvnfb_b_scs_ptrh", "tfmri_ma_lpvnfb_b_scs_aarh",
                          "tfmri_ma_alrvn_b_scs_cdlh", "tfmri_ma_alrvn_b_scs_ptlh",
                          "tfmri_ma_alrvn_b_scs_aalh", "tfmri_ma_alrvn_b_scs_cdrh",
                          "tfmri_ma_alrvn_b_scs_ptrh", "tfmri_ma_alrvn_b_scs_aarh",
                          "tfmri_ma_asrvn_b_scs_cdlh", "tfmri_ma_asrvn_b_scs_ptlh",
                          "tfmri_ma_asrvn_b_scs_aalh", "tfmri_ma_asrvn_b_scs_cdrh",
                          "tfmri_ma_asrvn_b_scs_ptrh", "tfmri_ma_asrvn_b_scs_aarh",
                          "tfmri_ma_alvcr_b_scs_cdlh", "tfmri_ma_alvcr_b_scs_ptlh",
                          "tfmri_ma_alvcr_b_scs_aalh", "tfmri_ma_alvcr_b_scs_cdrh",
                          "tfmri_ma_alvcr_b_scs_ptrh", "tfmri_ma_alvcr_b_scs_aarh",
                          "tfmri_ma_aclvn_b_scs_cdlh", "tfmri_ma_aclvn_b_scs_ptlh",
                          "tfmri_ma_aclvn_b_scs_aalh", "tfmri_ma_aclvn_b_scs_cdrh",
                          "tfmri_ma_aclvn_b_scs_ptrh", "tfmri_ma_aclvn_b_scs_aarh",
                          "tfmri_ma_acmvn_b_scs_cdlh", "tfmri_ma_acmvn_b_scs_ptlh",
                          "tfmri_ma_acmvn_b_scs_aalh", "tfmri_ma_acmvn_b_scs_cdrh",
                          "tfmri_ma_acmvn_b_scs_ptrh", "tfmri_ma_acmvn_b_scs_aarh",
                          "tfmri_ma_acgml_b_scs_cdlh", "tfmri_ma_acgml_b_scs_ptlh",
                          "tfmri_ma_acgml_b_scs_aalh", "tfmri_ma_acgml_b_scs_cdrh",
                          "tfmri_ma_acgml_b_scs_ptrh", "tfmri_ma_acgml_b_scs_aarh")]

neuroimaging_dataPFC <- midaparcp203[,c("subjectkey","eventname",
                            "tfmri_ma_arvn_b_cds_lobofrlh", "tfmri_ma_arvn_b_cds_mobofrlh",
                            "tfmri_ma_arvn_b_cds_lobofrrh", "tfmri_ma_arvn_b_cds_mobofrrh",
                            "tfmri_ma_acvn_b_cds_lobofrlh", "tfmri_ma_acvn_b_cds_mobofrlh",
                            "tfmri_ma_acvn_b_cds_lobofrrh", "tfmri_ma_acvn_b_cds_mobofrrh",
                            "tfmri_ma_rpvnfb_b_cds_lobofrlh", "tfmri_ma_rpvnfb_b_cds_mobofrlh",
                            "tfmri_ma_rpvnfb_b_cds_lobofrrh", "tfmri_ma_rpvnfb_b_cds_mobofrrh",
                            "tfmri_ma_lvnfb_b_cds_lobofrlh", "tfmri_ma_lvnfb_b_cds_mobofrlh",
                            "tfmri_ma_lvnfb_b_cds_lobofrrh", "tfmri_ma_lvnfb_b_cds_mobofrrh",
                            "tfmri_ma_alrvn_b_cds_lobofrlh", "tfmri_ma_alrvn_b_cds_mobofrlh",
                            "tfmri_ma_alrvn_b_cds_lobofrrh", "tfmri_ma_alrvn_b_cds_mobofrrh",
                            "tfmri_ma_asrvn_b_cds_lobofrlh", "tfmri_ma_asrvn_b_cds_mobofrlh",
                            "tfmri_ma_asrvn_b_cds_lobofrrh", "tfmri_ma_asrvn_b_cds_mobofrrh",
                            "tfmri_ma_alvsr_b_cds_lobofrlh", "tfmri_ma_alvsr_b_cds_mobofrlh",
                            "tfmri_ma_alvsr_b_cds_lobofrrh", "tfmri_ma_alvsr_b_cds_mobofrrh",
                            "tfmri_ma_allvn_b_cds_lobofrlh", "tfmri_ma_allvn_b_cds_mobofrlh",
                            "tfmri_ma_allvn_b_cds_lobofrrh", "tfmri_ma_allvn_b_cds_mobofrrh",
                            "tfmri_ma_asvn_b_cds_lobofrlh", "tfmri_ma_asvn_b_cds_mobofrlh",
                            "tfmri_ma_asvn_b_cds_lobofrrh", "tfmri_ma_asvn_b_cds_mobofrrh",
                            "tfmri_ma_alvsl_b_cds_lobofrlh", "tfmri_ma_alvsl_b_cds_mobofrlh",
                            "tfmri_ma_alvsl_b_cds_lobofrrh", "tfmri_ma_alvsl_b_cds_mobofrrh")]
```

```
#Create an overarching data frame with just the variables I am interested in.
#MERGE by subjectkey and eventname.
#Start off with core variables: CBCL_data, neuroimaging_data, neuroimaging_dataPFC, midbehaviour_data.
#Do not separate out by timepoint for now. Can use the  $ function later to pull this out.

#Join CBCL data and neuroimaging data into overarching df 'data'.
#Use inner_join to only return rows with values in both data frames.

data <- CBCL_data %>% inner_join(neuroimaging_data, by= c("subjectkey"="subjectkey",
"eventname"="eventname"))

data <- neuroimaging_dataPFC %>% inner_join(data, by= c("subjectkey"="subjectkey",
"eventname"="eventname"))

data <- midbehaviour_data %>% inner_join(data, by= c("subjectkey"="subjectkey", "eventname"="eventname"))
#Next step is to join covariates to the 'data' df. Need to create subsets of these first.

#Create a subset for SES with only columns I want (combined family income, subjectkey, eventname)

SES_data <- pdem02[, c("subjectkey","eventname", "demo_comb_income_v2")]

#Create a subset for pubertal data. Some data cleaning is required first.
#Pubertal data is split into two columns - for females and males.
#Combine the two male/female columns so that an answer in either one goes into a new column,
Pubertal_merged.

ssphp01$Pubertal_merged <- coalesce(ssphp01$pds_p_ss_female_category_2,
ssphp01$pds_p_ss_male_category_2)
Pubertal_data <- ssphp01[, c("subjectkey","eventname", "Pubertal_merged")]
#Join covariates to 'data' df.
#Use left_join to add any matching data in covariates to the existing 'data' df.

data <- data %>% left_join(SES_data, by= c("subjectkey"="subjectkey", "eventname"="eventname"))
data <- data %>% left_join(Pubertal_data, by= c("subjectkey"="subjectkey", "eventname"="eventname"))
#Repeat same process to join covariates of no interest
#First create subsets for Study site, Demographics, IQ.
#Demographics includes relatedness, ethnicity and weight propensity scores.

Study_site <- lt01[, c("subjectkey", "eventname", "site_id_l")]
Demographics <- acspsw03[,c("subjectkey", "eventname", "race_ethnicity", "rel_family_id",
"acs_raked_propensity_score")]
IQ <- ps01[,c("subjectkey", "eventname", "pea_wiscv_tss")]

#join covariates of no interest to 'data' df.
#Use left_join to add any matching data to the existing 'data' df.

data <- data %>% left_join(Study_site, by= c("subjectkey"="subjectkey", "eventname"="eventname"))
data <- data %>% left_join(Demographics, by= c("subjectkey"="subjectkey", "eventname"="eventname"))
data <- data %>% left_join(IQ, by= c("subjectkey"="subjectkey", "eventname"="eventname"))

#Remove missing data
#I tried to remove missing data from all columns: data <- na.omit(data)
#This removed all 2-year FU data due to missing FU data from some covariates.
#There is no 2-yr FU data for 4 covariates: SES, parental MH, IQ, relatedness.
#(Conceptually this is fine)

#New approach is to first remove missing data from columns with FU data available.

#Remove missing data from CBCL internalising column.
#NB missing data is already removed from neuroimaging and nback behavioural data from using inner_join
function.

data <- data[!is.na(data$cbcl_scr_syn_external_r),]

#Check numbers remaining by time point
table(data$eventname)
```

```
#Remove missing data from sex
data <- data[!is.na(data$sex),]
table(data$sex)
#Check numbers remaining by time point
table(data$eventname)

#Remove missing data from Pubertal_merged
data <- data[!is.na(data$Pubertal_merged),]

#Check numbers remaining by time point
table(data$eventname)

#Remove missing data from site
data <- data[!is.na(data$site_id_l),]

#Check numbers remaining by time point
table(data$eventname)

#Check numbers remaining by time point
table(data$eventname)
table(data$sex)
#For covariates where there is no 2-year FU data (SES, PMH, IQ, relatedness, ethnicity, propensity scores):
#Remove missing data only for baseline data rows
data <- data[!is.na(data$demo_comb_income_v2 & data$eventname=="baseline_year_1_arm_1"),]
data <- data[!is.na(data$pea_wiscv_tss & data$eventname=="baseline_year_1_arm_1"),]
data <- data[!is.na(data$rel_family_id & data$eventname=="baseline_year_1_arm_1"),]
data <- data[!is.na(data$race_ethnicity & data$eventname=="baseline_year_1_arm_1"),]
data <- data[!is.na(data$acs_raked_propensity_score & data$eventname=="baseline_year_1_arm_1"),]

#Remove SES data where values are 999 (=don't know) and 777 (=refuse to answer).

data <- data[!data$demo_comb_income_v2 %in% c("999", "777"),]

#Check numbers remaining by time point
table(data$eventname)

table(data$sex)

#Remove rows that don't have both baseline and FU data.
#Want an equal number of baseline and FU - i.e. the same ppts.

data <- subset(data, ave(subjectkey, subjectkey, FUN=length) >=2)
table(data$eventname)

#Need to change some variable types (sex, PMH, pubertal data).
#Do this both in data_total and T2complete.

#change sex so that M=2 and F=1.
#Then change from integer to categorical (factor).

data$sex <-factor(data$sex)
table(data$sex)
str(data$sex)
#change Pubertal_merged from integer to categorical (factor)
#data$Pubertal_merged <-factor(data$Pubertal_merged, levels=c("1", "2", "3", "4", "5"), ordered=TRUE)
#Change SES from numerical to categorical (factor)
#data$demo_comb_income_v2 <-factor(data$demo_comb_income_v2, levels=c("1", "2", "3", "4", "5", "6", "7",
"8", "9", "10"), ordered=TRUE)
#Change race_ethnicity from numerical to categorical (factor)

data$race_ethnicity <-factor(data$race_ethnicity, levels=c("1", "2", "3", "4", "5"), ordered=FALSE)
#Create T1 and T2 data frames
T1<-subset(data,eventname=="baseline_year_1_arm_1")
T2<-subset(data,eventname=="2_year_follow_up_y_arm_1")

#copy SES, PMH, IQ and Demographics data from baseline to 2yr FU by matching based on subject key.
```

```
T2_merge_SESIQ<-T2
test<-T2_merge_SESIQ[,c("subjectkey","sex")]
test2<-T1[,c("subjectkey", "demo_comb_income_v2")]
jointest<-left_join(test, test2,by="subjectkey")
test3<-T1[,c("subjectkey", "demo_comb_income_v2", "pea_wiscv_tss")]
jointest2<-left_join(T2_merge_SESIQ, test3,by="subjectkey")
test4<-T1[,c("subjectkey", "demo_comb_income_v2", "pea_wiscv_tss",  "rel_family_id",
"acs_raked_propensity_score", "race_ethnicity")]
jointest3 <-left_join(T2_merge_SESIQ, test4, by="subjectkey")

#Tidy up. Rename data frames for clarity

T2complete <- jointest3
T1complete <- T1

#Merge into one big new data frame called 'data_total'.

data_total <- merge(T1complete, T2complete, by="subjectkey")

#neuro analysis MID
allinone2aT1fit<-lmer(cbcl_scr_syn_external_r~sex+Pubertal_merged + demo_comb_income_v2 +
pea_wiscv_tss
                + tfmri_ma_acdn_b_scs_cdlh + tfmri_ma_acdn_b_scs_ptlh + tfmri_ma_acdn_b_scs_aalh
                + tfmri_ma_acdn_b_scs_cdrh + tfmri_ma_acdn_b_scs_ptrh + tfmri_ma_acdn_b_scs_aarh
                +tfmri_ma_arvn_b_cds_lobofrlh +tfmri_ma_arvn_b_cds_lobofrrh +
tfmri_ma_arvn_b_cds_mobofrlh +tfmri_ma_arvn_b_cds_mobofrrh
                 + tfmri_ma_acvn_b_scs_cdlh + tfmri_ma_acvn_b_scs_ptlh + tfmri_ma_acvn_b_scs_aalh
                + tfmri_ma_acvn_b_scs_cdrh + tfmri_ma_acvn_b_scs_ptrh + tfmri_ma_acvn_b_scs_aarh
                +tfmri_ma_acvn_b_cds_lobofrlh +tfmri_ma_acvn_b_cds_lobofrrh +
tfmri_ma_acvn_b_cds_mobofrlh +tfmri_ma_acvn_b_cds_mobofrrh
                 + tfmri_ma_rpvnfb_b_scs_cdlh + tfmri_ma_rpvnfb_b_scs_ptlh + tfmri_ma_rpvnfb_b_scs_aalh
                + tfmri_ma_rpvnfb_b_scs_cdrh + tfmri_ma_rpvnfb_b_scs_ptrh + tfmri_ma_rpvnfb_b_scs_aarh
                +tfmri_ma_rpvnfb_b_cds_lobofrlh +tfmri_ma_rpvnfb_b_cds_lobofrrh +
tfmri_ma_rpvnfb_b_cds_mobofrlh +tfmri_ma_rpvnfb_b_cds_mobofrrh
                 + tfmri_ma_lpvnfb_b_scs_cdlh + tfmri_ma_lpvnfb_b_scs_ptlh + tfmri_ma_lpvnfb_b_scs_aalh
                + tfmri_ma_lpvnfb_b_scs_cdrh + tfmri_ma_lpvnfb_b_scs_ptrh + tfmri_ma_lpvnfb_b_scs_aarh
                +tfmri_ma_lvnfb_b_cds_lobofrlh +tfmri_ma_lvnfb_b_cds_lobofrrh +
tfmri_ma_lvnfb_b_cds_mobofrlh +tfmri_ma_lvnfb_b_cds_mobofrrh+
                 (1|site_id_l) + (1|rel_family_id),
                data=T1complete, control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5)),
weights = pweights_a)
b<-anova(allinone2aT1fit)
b
p_value(b, ci=0.95, adjust="fdr")

allinone2aT2fit<-lmer(cbcl_scr_syn_external_r~sex+Pubertal_merged + demo_comb_income_v2.y +
pea_wiscv_tss.y
                + tfmri_ma_acdn_b_scs_cdlh + tfmri_ma_acdn_b_scs_ptlh + tfmri_ma_acdn_b_scs_aalh
                + tfmri_ma_acdn_b_scs_cdrh + tfmri_ma_acdn_b_scs_ptrh + tfmri_ma_acdn_b_scs_aarh
                +tfmri_ma_arvn_b_cds_lobofrlh +tfmri_ma_arvn_b_cds_lobofrrh +
tfmri_ma_arvn_b_cds_mobofrlh +tfmri_ma_arvn_b_cds_mobofrrh +
                 + tfmri_ma_acvn_b_scs_cdlh + tfmri_ma_acvn_b_scs_ptlh + tfmri_ma_acvn_b_scs_aalh
                + tfmri_ma_acvn_b_scs_cdrh + tfmri_ma_acvn_b_scs_ptrh + tfmri_ma_acvn_b_scs_aarh
                +tfmri_ma_acvn_b_cds_lobofrlh +tfmri_ma_acvn_b_cds_lobofrrh +
tfmri_ma_acvn_b_cds_mobofrlh +tfmri_ma_acvn_b_cds_mobofrrh +
                 + tfmri_ma_rpvnfb_b_scs_cdlh + tfmri_ma_rpvnfb_b_scs_ptlh + tfmri_ma_rpvnfb_b_scs_aalh
                + tfmri_ma_rpvnfb_b_scs_cdrh + tfmri_ma_rpvnfb_b_scs_ptrh + tfmri_ma_rpvnfb_b_scs_aarh
                +tfmri_ma_rpvnfb_b_cds_lobofrlh +tfmri_ma_rpvnfb_b_cds_lobofrrh +
tfmri_ma_rpvnfb_b_cds_mobofrlh +tfmri_ma_rpvnfb_b_cds_mobofrrh +
                 + tfmri_ma_lpvnfb_b_scs_cdlh + tfmri_ma_lpvnfb_b_scs_ptlh + tfmri_ma_lpvnfb_b_scs_aalh
                + tfmri_ma_lpvnfb_b_scs_cdrh + tfmri_ma_lpvnfb_b_scs_ptrh + tfmri_ma_lpvnfb_b_scs_aarh
                +tfmri_ma_lvnfb_b_cds_lobofrlh +tfmri_ma_lvnfb_b_cds_lobofrrh +
tfmri_ma_lvnfb_b_cds_mobofrlh +tfmri_ma_lvnfb_b_cds_mobofrrh+
                 (1|site_id_l) + (1|rel_family_id.y),
                data=T2complete, control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5)),
weights = pweights_a)
```

```
library(parameters)
c<-anova(allinone2aT2fit)
p_value(c, ci=0.95, adjust="fdr")

fitH3<-lmer(cbcl_scr_syn_external_r.y~sex.x+Pubertal_merged.y + Pubertal_merged.x +
demo_comb_income_v2.y + pea_wiscv_tss.y
        + tfmri_ma_acdn_b_scs_cdlh.x + tfmri_ma_acdn_b_scs_ptlh.x + tfmri_ma_acdn_b_scs_aalh.x
        + tfmri_ma_acdn_b_scs_cdrh.x + tfmri_ma_acdn_b_scs_ptrh.x + tfmri_ma_acdn_b_scs_aarh.x
        +tfmri_ma_arvn_b_cds_lobofrlh.x +tfmri_ma_arvn_b_cds_lobofrrh.x +
tfmri_ma_arvn_b_cds_mobofrlh.x +tfmri_ma_arvn_b_cds_mobofrrh.x +
         + tfmri_ma_acvn_b_scs_cdlh.x + tfmri_ma_acvn_b_scs_ptlh.x + tfmri_ma_acvn_b_scs_aalh.x
        + tfmri_ma_acvn_b_scs_cdrh.x + tfmri_ma_acvn_b_scs_ptrh.x + tfmri_ma_acvn_b_scs_aarh.x
        +tfmri_ma_acvn_b_cds_lobofrlh.x +tfmri_ma_acvn_b_cds_lobofrrh.x +
tfmri_ma_acvn_b_cds_mobofrlh.x +tfmri_ma_acvn_b_cds_mobofrrh.x +
         + tfmri_ma_rpvnfb_b_scs_cdlh.x + tfmri_ma_rpvnfb_b_scs_ptlh.x + tfmri_ma_rpvnfb_b_scs_aalh.x
        + tfmri_ma_rpvnfb_b_scs_cdrh.x + tfmri_ma_rpvnfb_b_scs_ptrh.x + tfmri_ma_rpvnfb_b_scs_aarh.x
        +tfmri_ma_rpvnfb_b_cds_lobofrlh.x +tfmri_ma_rpvnfb_b_cds_lobofrrh.x +
tfmri_ma_rpvnfb_b_cds_mobofrlh.x +tfmri_ma_rpvnfb_b_cds_mobofrrh.x +
         + tfmri_ma_lpvnfb_b_scs_cdlh.x + tfmri_ma_lpvnfb_b_scs_ptlh.x + tfmri_ma_lpvnfb_b_scs_aalh.x
        + tfmri_ma_lpvnfb_b_scs_cdrh.x + tfmri_ma_lpvnfb_b_scs_ptrh.x + tfmri_ma_lpvnfb_b_scs_aarh.x
        +tfmri_ma_lvnfb_b_cds_lobofrlh.x +tfmri_ma_lvnfb_b_cds_lobofrrh.x +
tfmri_ma_lvnfb_b_cds_mobofrlh.x +tfmri_ma_lvnfb_b_cds_mobofrrh.x+
         (1|site_id_l.x) + (1|rel_family_id.y),
        data=data_total, control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5)), weights =
pweights_a)
d<-anova(fitH3)
p_value(d, ci=0.95, adjust="fdr")

#mid behavioural analysis
fitH1behaviouralallmrt<-lmer(cbcl_scr_syn_external_r~sex+Pubertal_merged + demo_comb_income_v2 +
pea_wiscv_tss
                    +tfmri_mid_all_beh_srw_mrt
                    +tfmri_mid_all_beh_srwpfb_mrt
                    +tfmri_mid_all_beh_srwnfb_mrt
                    +tfmri_mid_all_beh_lrw_mrt
                    +tfmri_mid_all_beh_lrwnfb_nt+tfmri_mid_all_beh_srwnfb_nt
                    +tfmri_mid_all_beh_lrwnfb_mrt
                    +tfmri_mid_all_beh_sl_mrt
                    +tfmri_mid_all_beh_slpfb_mrt
                    +tfmri_mid_all_beh_slnfb_mrt
                    +tfmri_mid_all_beh_ll_mrt
                    +tfmri_mid_all_beh_llnfb_nt+tfmri_mid_all_beh_slnfb_nt
                    +tfmri_mid_all_beh_llnfb_mrt
                    +tfmri_mid_all_beh_nt_mrt
                    +tfmri_mid_all_beh_ntpfb_mrt
                    +tfmri_mid_all_beh_ntnfb_mrt
                    +mean_tfmri_mid_beh_earnings
                    +tfmri_mid_all_beh_lrwpfb_mrt+tfmri_mid_all_beh_llpfb_mrt
                    + (1|site_id_l) + (1|rel_family_id),
                    data=T1complete, control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5)),
weights = pweights_a)
h<-anova(fitH1behaviouralallmrt)
p_value(h, ci=0.95, adjust="fdr")

fitH1behaviouralallmrtT2<-lmer(cbcl_scr_syn_external_r~sex+Pubertal_merged + demo_comb_income_v2.y +
pea_wiscv_tss.y
                     +tfmri_mid_all_beh_srw_mrt
                     +tfmri_mid_all_beh_srwpfb_mrt
                     +tfmri_mid_all_beh_srwnfb_mrt
                     +tfmri_mid_all_beh_lrw_mrt
                     +tfmri_mid_all_beh_lrwnfb_nt+tfmri_mid_all_beh_srwnfb_nt
                     +tfmri_mid_all_beh_lrwnfb_mrt
                     +tfmri_mid_all_beh_sl_mrt
                     +tfmri_mid_all_beh_slpfb_mrt
                     +tfmri_mid_all_beh_slnfb_mrt
                     +tfmri_mid_all_beh_ll_mrt
                     +tfmri_mid_all_beh_llnfb_nt+tfmri_mid_all_beh_slnfb_nt
```

```
                        +tfmri_mid_all_beh_llnfb_mrt
                        +tfmri_mid_all_beh_nt_mrt
                        +tfmri_mid_all_beh_ntpfb_mrt
                        +tfmri_mid_all_beh_ntnfb_mrt
                        +mean_tfmri_mid_earnings
                        +tfmri_mid_all_beh_lrwpfb_mrt+tfmri_mid_all_beh_llpfb_mrt
                        + (1|site_id_l) + (1|rel_family_id.y),
                        data=T2complete, control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5)),
weights = pweights_a)
y<-anova(fitH1behaviouralallmrtT2)
p_value(y, ci=0.95, adjust="fdr")

fitH3behaviouralallmrtT3<-lmer(cbcl_scr_syn_external_r.y~sex.x+Pubertal_merged.x + Pubertal_merged.y +
demo_comb_income_v2.y + pea_wiscv_tss.y
                        +tfmri_mid_all_beh_srw_mrt.x
                        +tfmri_mid_all_beh_srwpfb_mrt.x
                        +tfmri_mid_all_beh_srwnfb_mrt.x
                        +tfmri_mid_all_beh_lrw_mrt.x
                        +tfmri_mid_all_beh_lrwnfb_nt.x+tfmri_mid_all_beh_srwnfb_nt.x
                        +tfmri_mid_all_beh_lrwnfb_mrt.x
                        +tfmri_mid_all_beh_sl_mrt.x
                        +tfmri_mid_all_beh_slpfb_mrt.x
                        +tfmri_mid_all_beh_slnfb_mrt.x
                        +tfmri_mid_all_beh_ll_mrt.x
                        +tfmri_mid_all_beh_llnfb_nt.x+tfmri_mid_all_beh_slnfb_nt.x
                        +tfmri_mid_all_beh_llnfb_mrt.x
                        +tfmri_mid_all_beh_nt_mrt.x
                        +tfmri_mid_all_beh_ntpfb_mrt.x
                        +tfmri_mid_all_beh_ntnfb_mrt.x
                        +tfmri_mid_all_beh_lrwpfb_mrt.x+tfmri_mid_all_beh_llpfb_mrt.x
                        + (1|site_id_l.x) + (1|rel_family_id.y),
                        data=data_total, control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5)),
weights = T1complete$pweights_a)
k<-anova(fitH3behaviouralallmrtT3)
p_value(k, ci=0.95, adjust="fdr")

#clear console and environment

setwd("~/Desktop/Eilidh/ABCD_DATA/ABCD_Analysis")
data_dir <- ("~/Desktop/Eilidh/ABCD_DATA")
output_dir <- "Results"

#install.packages("dplyr")
#install.packages("readr")
#install.packages("tidyr")
#install.packages("knitr")

library(dplyr)
library(readr)
library(tidyr)
library(psych)
library(knitr)
library(jtools)
library(lme4)

# Note ABCD files needed and create full pathnames

mhy02_filename <- "abcd_mhy02.txt"
mhy02_filename <- paste(data_dir, mhy02_filename, sep="/")

mid02_filename <- "abcd_mid02.txt"
mid02_filename <- paste(data_dir, mid02_filename, sep="/")

midtlb01_filename <- "abcd_midtlb01.txt"
midtlb01_filename <- paste(data_dir, midtlb01_filename, sep="/")

sst02_filename <- "abcd_sst02.txt"
```

```
sst02_filename <- paste(data_dir, sst02_filename, sep="/")

ypdms01_filename <- "abcd_ypdms01.txt"
ypdms01_filename <- paste(data_dir, ypdms01_filename, sep="/")

cbcls01_filename <- "cbcls01_id.txt"
cbcls01_filename <- paste(data_dir, cbcls01_filename, sep="/")

lpds01_filename <- "lpds01_id.txt"
lpds01_filename <- paste(data_dir, lpds01_filename, sep="/")

midaparc03_filename <- "midaparc03_id.txt"
midaparc03_filename <- paste(data_dir, midaparc03_filename, sep="/")

midaparcp203_filename <- "midaparcp203_id.txt"
midaparcp203_filename <- paste(data_dir, midaparcp203_filename, sep="/")

mrisst02_filename <- "mrisst02.txt"
mrisst02_filename <- paste(data_dir, mrisst02_filename, sep="/")

abcd_midabwdp01_filename<- "abcd_midabwdp01.txt"
abcd_midabwdp01_filename <- paste(data_dir, abcd_midabwdp01_filename, sep="/")

abcd_midabwdp202_filename<- "abcd_midabwdp202.txt"
abcd_midabwdp202_filename <- paste(data_dir, abcd_midabwdp202_filename, sep="/")

abcd_ppdms01_filename <- "abcd_ppdms01.txt"
abcd_ppdms01_filename <- paste(data_dir, abcd_ppdms01_filename, sep = "/")

pdem02_filename <- "pdem02.txt"
pdem02_filename <- paste(data_dir, pdem02_filename, sep = "/" )

abcd_ssphp01_filename <- "abcd_ssphp01.txt"
abcd_ssphp01_filename <- paste(data_dir, abcd_ssphp01_filename, sep="/")

abcd_lt01_filename <- "abcd_lt01.txt"
abcd_lt01_filename <- paste(data_dir, abcd_lt01_filename, sep="/")

acspsw03_filename <- "acspsw03.txt"
acspsw03_filename <- paste(data_dir, acspsw03_filename, sep = "/" )

abcd_ps01_filename <- "abcd_ps01.txt"
abcd_ps01_filename <- paste(data_dir, abcd_ps01_filename, sep = "/")

# The following function reads in an ABCD datafile using readr to get around some formatting issues, namely
# that the file is tab delimited and the first row is the variable description name which tends
# set the variable type wrongly. This code reads in the column names, then reads in the datafile
# skipping the first two rows, then uses column names already read in. This means read_delim
# correctly identifies the data type when it reads in the data

read_abcd_file <- function(abcd_filename) {
  col_names <- names(read_delim(abcd_filename, delim="\t", n_max = 0))
  abcd_df <- read_delim(abcd_filename, delim="\t", na = "", col_names = col_names, skip = 3)
  return(abcd_df)
}

# Read mhy02 file, remove collection_title variable for each variable/data source
mhy02 <- read_abcd_file(mhy02_filename)
mhy02$collection_title <- NULL

mid02 <- read_abcd_file(mid02_filename)
mid02$collection_title <- NULL

midtlb01 <- read_abcd_file(midtlb01_filename)
midtlb01$collection_title <- NULL

sst02 <- read_abcd_file(sst02_filename)
```

```
sst02$collection_title <- NULL

ypdms01 <- read_abcd_file(ypdms01_filename)
ypdms01$collection_title <- NULL

cbcls01 <- read_abcd_file(cbcls01_filename)
cbcls01$collection_title <- NULL

lpds01 <- read_abcd_file(lpds01_filename)
lpds01$collection_title <- NULL

midaparc03 <- read_abcd_file(midaparc03_filename)
midaparc03$collection_title <- NULL

midaparcp203 <- read_abcd_file(midaparcp203_filename)
midaparcp203$collection_title <- NULL

mrisst02 <- read_abcd_file(mrisst02_filename)
mrisst02$collection_title <- NULL

mrisst02 <- read_abcd_file(mrisst02_filename)
mrisst02$collection_title <- NULL

abcd_midabwdp01<- read_abcd_file(abcd_midabwdp01_filename)
abcd_midabwdp01$collection_title <- NULL

abcd_midabwdp202_filename<- read_abcd_file(abcd_midabwdp202_filename)
abcd_midabwdp202_filename$collection_title <- NULL

ppdms01 <- read_abcd_file(abcd_ppdms01_filename)
ppdms01$collection_title <- NULL

pdem02 <- read_abcd_file(pdem02_filename)
pdem02$collection_title <- NULL

ssphp01 <- read_abcd_file(abcd_ssphp01_filename)
ssphp01$collection_title <- NULL

lt01 <- read_abcd_file(abcd_lt01_filename)
lt01$collection_title <- NULL

acspsw03 <- read_abcd_file(acspsw03_filename)
acspsw03$collection_title <- NULL

ps01 <- read_abcd_file(abcd_ps01_filename)
ps01$collection_title <- NULL

#Create a  of cbcls01 with only columns I want (subjectkey, eventname, sex, internalising)
CBCL_data<- cbcls01[, c("subjectkey","eventname", "sex", "cbcl_scr_syn_external_r")]

CBCL_data2 <- cbcls01[, c("subjectkey","eventname", "cbcl_scr_syn_external_r", "cbcl_scr_syn_internal_r")]

sst_behaviour_data <- sst02

SST_Bdata <- CBCL_data2 %>% inner_join(sst_behaviour_data, by= c("subjectkey"="subjectkey",
"eventname"="eventname"))

#Create a subset for SES with only columns I want (combined family income, subjectkey, eventname)

SES_data <- pdem02[, c("subjectkey","eventname", "demo_comb_income_v2")]

#Create a subset for pubertal data. Some data cleaning is required first.
#Pubertal data is split into two columns - for females and males.
#Combine the two male/female columns so that an answer in either one goes into a new column,
Pubertal_merged.
```

```
ssphp01$Pubertal_merged <- coalesce(ssphp01$pds_p_ss_female_category_2,
ssphp01$pds_p_ss_male_category_2)
Pubertal_data <- ssphp01[, c("subjectkey","eventname", "Pubertal_merged")]
#Join covariates to 'data' df.
#Use left_join to add any matching data in covariates to the existing 'data' df.

SST_Bdata <- SST_Bdata %>% left_join(SES_data, by= c("subjectkey"="subjectkey",
"eventname"="eventname"))
SST_Bdata  <- SST_Bdata  %>% left_join(Pubertal_data, by= c("subjectkey"="subjectkey",
"eventname"="eventname"))

sst_fmri<-mrisst02[, c("subjectkey", "eventname", "tfmri_sacsvcg_bcdk_smlh", "tfmri_sacsvcg_bcdk_ifpalh",
"tfmri_sacsvcg_bcdk_laoclh", "tfmri_sacsvcg_bcdk_pstglh","tfmri_sacsvcg_bcdk_psobslh",
"tfmri_sacsvcg_bcdk_laobofrlh",
                'tfmri_saisvcg_bcdk_sufrrh', "tfmri_saisvcg_bcdk_rmdfrrh", "tfmri_saisvcg_bcdk_ifparh",
                "tfmri_saisvcg_bcdk_smrh", "tfmri_saisvcg_bcdk_pstgrh", "tfmri_saisvcg_bcdk_psoperh",
                "tfmri_saisvcg_bcdk_laobofrrh", "tfmri_saisvcg_bcdk_sufrlh", "tfmri_saisvcg_bcdk_racgelh",
                "tfmri_saisvcg_bcdk_sutprh", "tfmri_saisvcg_bcdk_bktsrh", "tfmri_saisvcg_bcdk_pstglh",
"tfmri_saisvcg_bcdk_psobslh",
                "tfmri_saisvcg_bcdk_laobofrlh", "tfmri_saisvcg_bcdk_cdmdfrrh", "tfmri_saisvcg_bcdk_precnrh",
"tfmri_saisvcg_bcdk_supalh",
                "tfmri_saisvcg_bcdk_laoclh", "tfmri_saisvcg_bcdk_smlh", "tfmri_saisvcg_bcdk_ifpalh",
"tfmri_saisvcg_bcdk_suparh", "tfmri_saisvcg_bcdk_pcurh", "tfmri_saisvcg_bcdk_bktslh")]

SST_Bdata <- SST_Bdata %>% left_join(sst_fmri, by= c("subjectkey"="subjectkey",
"eventname"="eventname"))

#Repeat same process to join covariates of no interest
#First create subsets for Study site, Demographics, IQ.
#Demographics includes relatedness, ethnicity and weight propensity scores.

Study_site <- lt01[, c("subjectkey", "eventname", "site_id_l")]
Demographics <- acspsw03[,c("subjectkey", "eventname", "race_ethnicity", "rel_family_id",
"acs_raked_propensity_score")]
IQ <- ps01[,c("subjectkey", "eventname", "pea_wiscv_tss")]

#join covariates of no interest to 'data' df.
#Use left_join to add any matching data to the existing 'data' df.

SST_Bdata  <- SST_Bdata  %>% left_join(Study_site, by= c("subjectkey"="subjectkey",
"eventname"="eventname"))
SST_Bdata  <- SST_Bdata  %>% left_join(Demographics, by= c("subjectkey"="subjectkey",
"eventname"="eventname"))
SST_Bdata  <- SST_Bdata  %>% left_join(IQ, by= c("subjectkey"="subjectkey", "eventname"="eventname"))
SST_Bdata <- SST_Bdata[!is.na(SST_Bdata$cbcl_scr_syn_external_r),]

#Check numbers remaining by time point
table(SST_Bdata$eventname)

#Remove missing data from sex
SST_Bdata <- SST_Bdata[!is.na(SST_Bdata$sex),]
table(SST_Bdata$sex)
#Check numbers remaining by time point
table(SST_Bdata$eventname)

#Remove missing data from Pubertal_merged
SST_Bdata <- SST_Bdata[!is.na(SST_Bdata$Pubertal_merged),]

#Check numbers remaining by time point
table(SST_Bdata$eventname)

#Remove missing data from site
SST_Bdata <-SST_Bdata[!is.na(SST_Bdata$site_id_l),]

#Remove missing data only for baseline data rows
SST_Bdata <- SST_Bdata[!is.na(SST_Bdata$demo_comb_income_v2 &
SST_Bdata$eventname=="baseline_year_1_arm_1"),]
```

```
SST_Bdata <- SST_Bdata[!is.na(SST_Bdata$pea_wiscv_tss &
SST_Bdata$eventname=="baseline_year_1_arm_1"),]
SST_Bdata <- SST_Bdata[!is.na(SST_Bdata$rel_family_id &
SST_Bdata$eventname=="baseline_year_1_arm_1"),]
SST_Bdata <- SST_Bdata[!is.na(SST_Bdata$race_ethnicity &
SST_Bdata$eventname=="baseline_year_1_arm_1"),]
SST_Bdata <- SST_Bdata[!is.na(SST_Bdata$acs_raked_propensity_score &
SST_Bdata$eventname=="baseline_year_1_arm_1"),]

#Remove SES data where values are 999 (=don't know) and 777 (=refuse to answer).

SST_Bdata <- SST_Bdata[!SST_Bdata$demo_comb_income_v2 %in% c("999", "777"),]

#Check numbers remaining by time point
table(SST_Bdata$eventname)

table(SST_Bdata$sex)

#Remove rows that don't have both baseline and FU data.
#Want an equal number of baseline and FU - i.e. the same ppts.

SST_Bdata <- subset(SST_Bdata, ave(subjectkey, subjectkey, FUN=length) >=2)
table(SST_Bdata$eventname)

#Need to change some variable types (sex, PMH, pubertal data).
#Do this both in data_total and T2complete.

#change sex so that M=2 and F=1.
#Then change from integer to categorical (factor).

SST_Bdata$sex <-factor(SST_Bdata$sex)
table(SST_Bdata$sex)
str(SST_Bdata$sex)
#change Pubertal_merged from integer to categorical (factor)
#data$Pubertal_merged <-factor(data$Pubertal_merged, levels=c("1", "2", "3", "4", "5"), ordered=TRUE)
#Change SES from numerical to categorical (factor)
#data$demo_comb_income_v2 <-factor(data$demo_comb_income_v2, levels=c("1", "2", "3", "4", "5", "6", "7",
"8", "9", "10"), ordered=TRUE)
#Change race_ethnicity from numerical to categorical (factor)

SST_Bdata$race_ethnicity <-factor(SST_Bdata$race_ethnicity, levels=c("1", "2", "3", "4", "5"),
ordered=FALSE)
summary(SST_Bdata$tfmri_sst_beh_performflag)
#1=acceptable performance' 0=unacceptable - fewer than three events for positive and negative feedback
#want to remove all 0 scores and missing
SST_Bdata <- SST_Bdata[!SST_Bdata$tfmri_sst_beh_performflag %in% c("0", "NA"),]
SST_Bdata <-SST_Bdata[!is.na(SST_Bdata$tfmri_sst_beh_performflag),]
summary(SST_Bdata$tfmri_sst_beh_performflag)
SST_BTdata<-filter(SST_Bdata, SST_Bdata$tfmri_sst_nbeh_nruns=="2")
SST_Bdata <- SST_Bdata[!SST_Bdata$tfmri_sst_beh_violatorflag %in% c("1"),]

library(dplyr)
T2_merge_SESIQ<-T2
test<-T2_merge_SESIQ[,c("subjectkey","sex")]
test2<-T1[,c("subjectkey", "demo_comb_income_v2")]
jointest<-left_join(test, test2,by="subjectkey")
test3<-T1[,c("subjectkey", "demo_comb_income_v2", "pea_wiscv_tss")]
jointest2<-left_join(T2_merge_SESIQ, test3,by="subjectkey")
test4<-T1[,c("subjectkey", "demo_comb_income_v2", "pea_wiscv_tss",  "rel_family_id",
"acs_raked_propensity_score", "race_ethnicity")]
jointest3 <-left_join(T2_merge_SESIQ, test4, by="subjectkey")

T2complete <- jointest3
T1complete <- T1

#Merge into one big new data frame called 'data_total'.
data_total <- merge(T1complete, T2complete, by="subjectkey")
```

```
library(lme4)
library(jtools)
library (broom)
library(parameters)
T2complete <- rescale_weights(data=T2complete, "site_id_l", "acs_raked_propensity_score.y")
data_total <- rescale_weights(data=data_total, "site_id_l.x", "acs_raked_propensity_score")
T1complete <- rescale_weights(data=T1complete, "site_id_l", "acs_raked_propensity_score")

#neuro analysis SST

m1<- lmer(cbcl_scr_syn_external_r ~ sex + Pubertal_merged + demo_comb_income_v2 + pea_wiscv_tss +
          tfmri_sacsvcg_bcdk_smlh + tfmri_sacsvcg_bcdk_ifpalh + tfmri_sacsvcg_bcdk_laoclh+
tfmri_sacsvcg_bcdk_pstglh + tfmri_sacsvcg_bcdk_psobslh + tfmri_sacsvcg_bcdk_laobofrlh +
          tfmri_saisvcg_bcdk_sufrrh + tfmri_saisvcg_bcdk_rmdfrrh+tfmri_saisvcg_bcdk_ifparh +
          tfmri_saisvcg_bcdk_smrh + tfmri_saisvcg_bcdk_pstgrh+tfmri_saisvcg_bcdk_psoperh +
          tfmri_saisvcg_bcdk_laobofrrh+ tfmri_saisvcg_bcdk_sufrlh+tfmri_saisvcg_bcdk_racgelh +

tfmri_saisvcg_bcdk_sutprh+tfmri_saisvcg_bcdk_bktsrh+tfmri_saisvcg_bcdk_pstglh+tfmri_saisvcg_bcdk_psobsl
h +

tfmri_saisvcg_bcdk_laobofrlh+tfmri_saisvcg_bcdk_cdmdfrrh+tfmri_saisvcg_bcdk_precnrh+tfmri_saisvcg_bcdk
_supalh +

tfmri_saisvcg_bcdk_laoclh+tfmri_saisvcg_bcdk_smlh+tfmri_saisvcg_bcdk_ifpalh+tfmri_saisvcg_bcdk_suparh+t
fmri_saisvcg_bcdk_pcurh+tfmri_saisvcg_bcdk_bktslh
        +(1|site_id_l) + (1|rel_family_id),
        data=T1complete ,control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun = 2e5)), weights =
pweights_a)
p<-anova(m1)

p_value(p, ci=0.95, adjust="fdr")
m2<- lmer(cbcl_scr_syn_external_r ~ sex + Pubertal_merged + demo_comb_income_v2.y + pea_wiscv_tss.y
+tfmri_sacsvcg_bcdk_smlh + tfmri_sacsvcg_bcdk_ifpalh + tfmri_sacsvcg_bcdk_laoclh+
tfmri_sacsvcg_bcdk_pstglh + tfmri_sacsvcg_bcdk_psobslh + tfmri_sacsvcg_bcdk_laobofrlh +
          tfmri_saisvcg_bcdk_sufrrh + tfmri_saisvcg_bcdk_rmdfrrh+tfmri_saisvcg_bcdk_ifparh +
          tfmri_saisvcg_bcdk_smrh + tfmri_saisvcg_bcdk_pstgrh+tfmri_saisvcg_bcdk_psoperh +
          tfmri_saisvcg_bcdk_laobofrrh+ tfmri_saisvcg_bcdk_sufrlh+tfmri_saisvcg_bcdk_racgelh +

tfmri_saisvcg_bcdk_sutprh+tfmri_saisvcg_bcdk_bktsrh+tfmri_saisvcg_bcdk_pstglh+tfmri_saisvcg_bcdk_psobsl
h +

tfmri_saisvcg_bcdk_laobofrlh+tfmri_saisvcg_bcdk_cdmdfrrh+tfmri_saisvcg_bcdk_precnrh+tfmri_saisvcg_bcdk
_supalh +

tfmri_saisvcg_bcdk_laoclh+tfmri_saisvcg_bcdk_smlh+tfmri_saisvcg_bcdk_ifpalh+tfmri_saisvcg_bcdk_suparh+t
fmri_saisvcg_bcdk_pcurh+tfmri_saisvcg_bcdk_bktslh
        +(1|site_id_l) + (1|rel_family_id.y),
        data=T2complete, REML=TRUE, control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun =
2e5)), weights = pweights_a)
q<-anova(m2)
p_value(q, ci=0.95, adjust="fdr")

fitH3<-m3<- lmer(cbcl_scr_syn_external_r.y ~ sex.x + Pubertal_merged.x +Pubertal_merged.y +
demo_comb_income_v2.y + pea_wiscv_tss.y +
                tfmri_sacsvcg_bcdk_smlh.x + tfmri_sacsvcg_bcdk_ifpalh.x + tfmri_sacsvcg_bcdk_laoclh.x+
tfmri_sacsvcg_bcdk_pstglh.x + tfmri_sacsvcg_bcdk_psobslh.x + tfmri_sacsvcg_bcdk_laobofrlh.x +
                tfmri_saisvcg_bcdk_sufrrh.x + tfmri_saisvcg_bcdk_rmdfrrh.x+tfmri_saisvcg_bcdk_ifparh.x +
                tfmri_saisvcg_bcdk_smrh.x + tfmri_saisvcg_bcdk_pstgrh.x+tfmri_saisvcg_bcdk_psoperh.x +
                tfmri_saisvcg_bcdk_laobofrrh.x+ tfmri_saisvcg_bcdk_sufrlh.x+tfmri_saisvcg_bcdk_racgelh.x +

tfmri_saisvcg_bcdk_sutprh.x+tfmri_saisvcg_bcdk_bktsrh.x+tfmri_saisvcg_bcdk_pstglh.x+tfmri_saisvcg_bcdk_p
sobslh.x +

tfmri_saisvcg_bcdk_laobofrlh.x+tfmri_saisvcg_bcdk_cdmdfrrh.x+tfmri_saisvcg_bcdk_precnrh.x+tfmri_saisvcg_
bcdk_supalh.x +
```

```
tfmri_saisvcg_bcdk_laoclh.x+tfmri_saisvcg_bcdk_smlh.x+tfmri_saisvcg_bcdk_ifpalh.x+tfmri_saisvcg_bcdk_su
parh.x+tfmri_saisvcg_bcdk_pcurh.x+tfmri_saisvcg_bcdk_bktslh.x
              +(1|site_id_l.x) + (1|rel_family_id.y),
              data=data_total , REML=TRUE, control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun =
2e5)), weights = pweights_a)

r<-anova(fitH3)
p_value(R, ci=0.95, adjust="fdr")

#behavioural sst

aa<-lmer (cbcl_scr_syn_external_r ~   + sex + Pubertal_merged + demo_comb_income_v2 + pea_wiscv_tss+
           + tfmri_sst_all_beh_crgo_rt + tfmri_sst_all_beh_crgo_mrt
          + tfmri_sst_all_beh_incrgo_rt + tfmri_sst_all_beh_incrgo_mrt
          + tfmri_sst_all_beh_crs_rt + tfmri_sst_all_beh_incrs_rt+tfmri_sst_all_beh_incrs_mrt
          + tfmri_sst_all_beh_total_issrt
          +(1|site_id_l) + (1|rel_family_id),
          data=T1complete ,REML=TRUE, control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun =
2e5)), weights = pweights_a)
aar<-anova(aa)
p_value(aar, ci=0.95, adjust="fdr")

a2<-lmer(cbcl_scr_syn_external_r ~   sex+  Pubertal_merged + demo_comb_income_v2.y + pea_wiscv_tss.y+
           + tfmri_sst_all_beh_crgo_rt + tfmri_sst_all_beh_crgo_mrt
          + tfmri_sst_all_beh_incrgo_rt + tfmri_sst_all_beh_incrgo_mrt
          + tfmri_sst_all_beh_crs_rt + tfmri_sst_all_beh_incrs_rt+tfmri_sst_all_beh_incrs_mrt
          + tfmri_sst_all_beh_total_issrt +(1|site_id_l) + (1|rel_family_id.y),
          data=T2complete ,REML=TRUE, control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun =
2e5)), weights = pweights_a)
a2r<-anova(a2)
p_value(a2r, ci=0.95, adjust="fdr")

fitH3sstrt<-lmer(cbcl_scr_syn_external_r.y ~ + sex.x + Pubertal_merged.x + Pubertal_merged.y +
demo_comb_income_v2.y + pea_wiscv_tss.y +
               + tfmri_sst_all_beh_crgo_rt.x + tfmri_sst_all_beh_crgo_mrt.x
              + tfmri_sst_all_beh_incrgo_rt.x + tfmri_sst_all_beh_incrgo_mrt.x
              + tfmri_sst_all_beh_crs_rt.x + tfmri_sst_all_beh_incrs_rt.x +tfmri_sst_all_beh_incrs_mrt.x
+tfmri_sst_all_beh_total_issrt.x
              +(1|site_id_l.x) + (1|rel_family_id.y),
              data=data_total , REML=TRUE, control = lmerControl(optimizer = "bobyqa", optCtrl = list(maxfun =
2e5)), weights = pweights_a)
fh3r<-anova(fitH3sstrt)
p_value(fh3r, ci=0.95, adjust="fdr")
```