Neural Correlates of Impulsivity, Sensation-Seeking and Weight In Healthy Children and Young Adolescents.

Rachel J. Sharkey

Integrated Program in Neuroscience,
McGill University, Montreal

May 2019

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of a Doctor of Philosophy

Table of Contents

Abstract

Body weight is, ultimately, a reflection of eating behaviour, which is, in turn, governed by multiple aspects of personality and decision-making which are themselves governed by multiple aspects of brain structure and function. The traits which put people at increased risk for weight gain later in life begin developing very early during childhood and adolescence (Casey et al., 2011). Impulsivity and sensation-seeking, and the neural networks associated with them, have been previously associated with increased weight and increased risk of future weight gain over time (Duckworth et al., 2010; Schlam et al., 2012; Vainik et al., 2013). Impulsivity typically increases during adolescence (Collado et al., 2014). While this is a normal feature of brain development, possibly arising from an asymmetrical development of sub-cortical and cortical regions, adolescents who score more highly on tests of impulsivity and sensation-seeking are still at increased risk of multiple poor outcomes, including greater weight gain and risk for overweight and obesity (Batterink et al., 2010; Delgado-Rico et al., 2012).

This thesis examined the relationship between body weight, impulsivity and sensation-seeking and several aspects of brain structure and function in two developing populations, to develop our understanding of which systems are involved with both impulsivity and sensation-seeking and body weight during childhood and early adolescence.

Our initial research found that cortical thickness, which is commonly found to be reduced in overweight and obese adults, was not correlated with weight in children (Sharkey et al., 2015). This finding guided the development of our next two studies which both measured correlates of resting state connectivity in a sample of young adolescents. Firstly, we used a multivariate analysis to examine the relationship between the connectivity of the striatum and midbrain, and body weight, impulsivity and sensation-seeking. This analysis identified the connectivity of the limbic system to the striatum and midbrain, rather than the expected regions in the prefrontal cortex as a system involved with all three behavioural factors (Sharkey et al., 2019). Secondly, we used independent component analysis to define the large scale intrinsic resting state networks in our sample and identify relationships between internetwork connectivity and body weight (Allen et al., 2011; Smith et al., 2009). This study identified a set of network interactions involved in weight which were only weakly associated with impulsivity and sensation-seeking.

These studies add support to the idea of body weight control as a multi-network phenomenon, and emphasizes the role of subcortical networks, specifically the limbic system, in both weight and impulsivity.

Résumé

Le poids est ultimement une réflexion des habitudes alimentaires, lesquelles sont gouvernées par de multiples aspects de la personnalité et de la prise de décision qui sont eux-mêmes régis par différentes fonctions et structures du cerveau. Les traits qui augmentent les risques de prise de poids plus tard dans la vie commencent à se développer très tôt pendant l'enfance et l'adolescence (Casey et al., 2011). L'impulsivité et la recherche de sensations ainsi que les réseaux neuronaux associés à ces traits ont étés précédemment associés à un gain de poids et à un risque plus élevé de prise de poids avec le temps (Duckworth et al., 2010; Schlam et al., 2012; Vainik et al., 2013). L'impulsivité augmente généralement pendant l'adolescence (Collado et al., 2014). Bien que ce soit normal lors du développement du cerveau, cette augmentation est possiblement causée par une asymétrie du développement des régions corticales et sous-corticales. Les adolescents qui ont des résultats plus élevés aux tests d'impulsivité et de recherche de sensations ont également un risque plus important de développer différents maux, notamment d'avoir une prise de poids plus importante ainsi que de souffrir d'embonpoint et d'obésité (Batterink et al., 2010; Delgado-Rico et al., 2012).

Cette thèse a examiné les relations entre la prise de poids, l'impulsivité et la recherche de sensations ainsi que plusieurs aspects de la structure et des fonctions du cerveau dans deux populations en développement afin de développer notre compréhension des systèmes impliqués à la fois dans l'impulsivité, la recherche de sensations et le gain de poids pendant l'enfance et au début de l'adolescence.

Notre première étude a démontré que l'épaisseur corticale, communément reportée comment étant réduite chez les adultes obèses ou avec de l'embonpoint, n'était pas significativement corrélée avec le poids des enfants (Sharkey et al., 2015). Ce résultat a guidé la réalisation de nos deux études subséquentes démontrant que ces deux mesures sont corrélées significativement avec la connectivité cérébrale au repos dans un groupe de jeunes adolescents. Premièrement, nous avons utilisé une analyse multivariée pour examiner la relation entre la connectivité du striatum et du mésencéphale avec le gain de poids, l'impulsivité et la recherche de sensations. Cette analyse a identifié le réseau impliquant le système limbique et ses connections avec le striatum et le mésencéphale, plutôt que les régions attendues du cortex préfrontal, en tant que système impliqué dans ces trois facteurs comportementaux (Sharkey et al., 2019). Deuxièmement, nous avons utilisé une analyse en composantes indépendantes

(independent component analysis) afin de définir le réseau intrinsèque à grande échelle au repos dans notre échantillon et d'identifier les relations entre la connectivité inter-réseau et le gain de poids (Allen et al., 2011; Smith et al., 2009). Cette étude a identifié un ensemble d'interactions entre les réseaux impliqués dans le gain de poids, lesquels étaient seulement faiblement associés à l'impulsivité et à la recherche de sensations.

Ces études supportent l'idée que le contrôle du poids corporel serait un phénomène impliquant plusieurs réseaux et elles mettent l'emphase sur le rôle des réseaux sous-corticaux, spécifiquement du système limbique, dans l'impulsivité et le poids.

Acknowledgements

I would firstly like to thank my supervisor, Dr. Alain Dagher who has been a tremendously supportive supervisor throughout my doctoral studies. I would also like to thank the other members of my advisory committee; Dr. Lesley Fellows and Dr. Sherif Karama, who have likewise been very generous with their time and expertise. My program mentor Dr. Heather Durham has also been incredibly generous and supportive.

I would also like to thank Dr. Bratislav Mišić, who very generously took the time to teach me the use of partial least squares correlation and to answer my follow-up questions about the technique, and Dr. Abbas Sadikot and Dr. Ayca Altınkaya, who generously allowed me to use their data on the ventral tegmental area. Professors Rhonda Amsel and Hsiu-Ting Yu for their extensive and timely help with statistical methods and tools, and the differences between the two.

All the other members of the Dagher lab have all been amazingly supportive throughout my tenure here. I would most especially like to thank Kevin Larcher who both contributed a huge amount to all three of these manuscripts and taught me how to write code of my own. He has been a remarkably patient and generous teacher. Dr. Selin Neseliler, Claire Han, and Stephanie Scala for their ongoing encouragement. Dr. Yashar Zeighami and Dr. Mahsa Dadar for sharing both their technical and methodological expertise. Dr. Travis Baker for helping us set up Neuroventure, Dr. Mayte Prada for a last minute rescue. Dr. Uku Vainik, Dr. Andreanne Michaud, Dr. Isabelle Garcia-Garcia, Dr. Mathias Kirschner and Yvonne Yau for taking the time to hear me talk through my experiments, you are the best bunch of rubber ducks I could have hoped for. And thank you to Christina Tremblay for translating my abstract into French.

And my two, excellent undergraduate honour students Anton Plavski and Brianna Barsati-Innes who both had the hard job of assisting on projects which were just getting off the ground, and who both rose to the occasion marvellously.

I would also like to thank Dr. Patricia Conrod, Josiane Bourque, Vincent Migneron-Foisy and the rest of the Neuroventure team who organized, recruited and tested our volunteers, and the Neuroventure participants themselves, for volunteering their time and brains for our research.

Lastly I would like to thank my parents, Keith and Sandra and my sister Sarah who have given me not only emotional but also financial support and endless good advice, and been remarkably willing to hear more about the ins and outs of imaging methodology and statistics

than I’m sure they ever planned to. I love you, and I would say that I’ll stop telling you these things, but I’d be lying.

Contributions to Original Knowledge

This thesis is composed of three original manuscripts which add novel contributions to the literature on the neural correlates of body weight and impulsivity and sensation-seeking during development including childhood and early adolescence and two separate neuroimaging measures, cortical thickness and resting state functional magnetic resonance imaging.

Study 1 (Chapter 2):
Sharkey, R.J., Karama, S., Dagher, A., 2015. Overweight is not associated with cortical thickness alterations in children. Front. Neurosci. 9, https://doi.org/10.3389/fnins.2015.00024.

Study 2 (Chapter 3):
Sharkey, R.J., Bourque, J., Larcher, K., Mišić, B., Zhang, Y., Altınkaya, A., Sadikot, A., Conrod, P., Evans, A.C., Garavan, H., Leyton, M., Seguin, J.R., Pihl, R., Dagher, A., 2018. Mesolimbic connectivity signatures of impulsivity and BMI in early adolescence. Appetite, Sept 29;132:25-36. doi: 10.1016/j.appet.2018.09.019.

Study 3 (Chapter 4):
Sharkey, R.J., Bourque, J., Mišić, B., Conrod P., Evans, A.C., Garavan, H., Leyton, M., Séguin, J.R., Pihl, R., Dagher, A. 2018. Global internetwork connectivity correlates of body weight in healthy young adolescents. In preparation.

Contributions of Authors

In study one Rachel Sharkey conducted the statistical analysis and wrote the manuscript. Dr. Sherif Karama provided the data and some of the code, and advised on the code and edited the manuscript, Dr. Alain Dagher designed the experiment and edited the manuscript.

In study two Rachel Sharkey organized and preprocessed the data, designed and conducted the experiment, and wrote the manuscript. Josiane Bourque collected the data. Kevin Larcher provided advice on preprocessing and help write code to preprocess the data. Dr. Bratislav Misic provided advise and help with coding in conducting the partial least squares correlations along with the basis of the code. Dr. Yu Zhang provided the region of interest masks for the substantia nigra and sub-thalamic nucleus. Dr. Ayca Altinkaya and Dr. Abbas Sadikot provided the region of interest mask for the ventral tegmental area and advice on its use. Dr. Patricia Conrod, Dr. Alan C Evans, Dr. Hugh Garavan, Dr. Marco Leyton, Dr. Jean R. Seguin, and Dr. Robert Pihl designed, wrote and submitted the original Neuroventure study and grant. Dr. Alain Dagher designed and wrote the original Neuroventure study and grant, advised on the experimental design and edited the manuscript.

In study three Rachel Sharkey designed the experiment wrote the code and preprocessed the data and drafted the manuscript. Josiane Bourque Collected the Neuroventure data, Dr. Bratislav Misic provided advice about the statistics, specifically and coding, and the basis for the code. Dr. Patricia Conrod, Dr. Alan C. Evans, Dr. Hugh Garavan, Dr. Marco Leyton, Dr. Jean R Seguin, and Dr. Robert Pihl, contributed to writing the original Neuroventure study and grant. Dr. Alain Dagher advised on the experimental design and results, and edited the manuscript.

Introduction and Literature Review

Literature Review

Impulsivity, the tendency to favour short-term goals, or to act quickly without thinking is a facet of normal personality variation. However, people who demonstrate greater impulsivity are known to be at risk of a range of poor outcomes including greater weight gain and greater risk for overweight and obesity (Appelhans et al., 2012; Jokela et al., 2013; Vainik et al., 2013).

In addition to variation between individuals in the adult population, trait impulsivity is also known to vary over the lifespan within individuals. This variation typically demonstrates an inverse U-shaped time course. Impulsivity increases as children enter adolescence, peaks in middle adolescence and then decreases into adulthood. This increase in impulsivity is generally understood to be a typical feature of normal adolescent development (Casey et al., 2016; Collado et al., 2014).

Impulsivity is a complex, multifactorial trait which relates to the function of multiple neural systems, including the limbic and temporoparietal regions and the dopaminergic midbrain-striato-cortical system. The developmental increases in impulsivity which occur during adolescence are believed to arise from differences in the developmental trajectories of those regions (Buckholtz et al., 2010; Casey, 2014; Christakou et al., 2011, 2009; Moreno-Lopez et al., 2016; Tomasi and Volkow, 2014, 2013).

However, increased impulsivity also predisposes adolescents to engage in more risky behaviours than adults. Additionally, like adults, adolescents who demonstrate higher levels of impulsivity relative to their peers are at greater risk for poor outcomes including greater weight gain, and higher risk of obesity (Appelhans et al., 2012; Duckworth et al., 2010; Moreno-López et al., 2012; Schlam et al., 2012).

Impulsivity and weight regulation are behaviourally related. More impulsive individuals make more food choices which put them at risk for weight gain, for example, but they also share neural underpinnings. The same circuits which are known to be related to impulsive decision-making in general are also known to affect decisions about food and eating behaviour, which affects body mass index (BMI) and weight gain across the lifespan (Horstmann et al., 2011; Moreno-López et al., 2012; Stevenson and Francis, 2017).

Brain Development During Childhood and Adolescence

Structural Development of the Cortex during Childhood and Adolescence

Synaptogenesis in the brain peaks near age two and most increases in brain volume are complete after age five. In general, after twelve, there is a decrease in grey matter/increase in white matter but the rates, timeframes and trajectory are region dependent and subject to modulation by sex hormones during puberty (Casey et al., 2000).

Overall, cortical thickness, a measure of the total amount of cortical grey matter, follows an inverse U-shaped trajectory during development, but the exact timing and peaks varies regionally. The exact shape of this curve is at least partly dependent on the type of measurement. Measures of grey matter based on surface area tend to demonstrate more linear decreases over the same period of time, while grey matter density has been found to increase during adolescence (Gennatas et al., 2017; Sowell et al., 2004; Tamnes et al., 2017). Alterations to this trajectory may be involved in a range of neuropsychiatric disorders including attention-deficit disorder (Giedd and Rapoport, 2010). Overall, the cortex matures in a caudal to rostral pattern (Giedd and Rapoport, 2010). The prefrontal cortex is one of the latest developing areas of the brain and is associated with three major groups of cognitive functions: response inhibition, working memory and selective attention (Casey et al., 2000).

Changes in the brain during puberty and adolescence result in the development of adult cognitive abilities, including overall reductions in cortical thickness and strengthened prefrontal cortico-limbic connections. These changes are believed to be affected by sex hormones, which can exert an immediate activational effect or a longer-term organizational effect on the brain (Vigil et al., 2011).

There is some degree of sexual dimorphism in human brain development and performance on cognitive tasks, which emerge during puberty when physical sexual dimorphism develops (Giedd et al., 1997; Raznahan et al., 2010). Ventricular volume increases more in males with age than females. Males show a decrease in the size of the globus pallidus, which females do not. Males show an increase in amygdala volume which females do not, but females show an increase in the size of the hippocampus, which males do not. Males also have an average overall larger cerebral volume (Giedd et al., 1997). Sex differences in the amygdala and hippocampus may be related to the concentration of androgen and estrogen receptors in those structures (Giedd et al., 1997). Frontal and parietal grey matter peaks in width earlier in girls, and temporal cortex peaks very

slightly earlier in boys and girls tend to have higher overall grey matter density (Gennatas et al., 2017; Giedd et al., 2006).

Cortical thinning during development is driven by multiple mechanisms, including synaptic pruning in the grey matter, but also increased myelination and increases in white matter volume (Østby et al., 2009; Paus, 2010; Petanjek et al., 2011; Sowell et al., 2004, 2002). During adolescence white matter gets more organized and bigger and both axons and myelin get thicker (Paus, 2010). These changes are widespread between 6-19, especially in the corpus callosum, basal ganglia and the striatothalamic and ventral visual and prefrontal areas. The white matter gain and associated grey matter loss spreads from the sensorimotor areas (Barnea-Goraly et al., 2005). Increases in white matter are steeper in boys than girls during adolescence. This is thought to be due to the effects of testosterone and is modulated by receptor types that affect testosterone availability. Differences in white matter volume could be explained by increases in g-ratio/axon calibre as well as increases in myelin and it is possible that g-ratio might increase in males but not females which would explain the differences in volume and density (Paus, 2010; Perrin et al., 2008). White matter density also increases (measured from 4 to 17) but it is denser in females. Changes in density are reflected in fractional anisotropy and mean diffusivity, measures of white matter density and integrity which are usually (Paus, 2010).

Structural Development of the Subcortical Regions during Childhood and Adolescence

The subcortical grey matter in the subcortical structures in the basal ganglia, hippocampus and amygdala have their own developmental trajectories, which are regionally heterogeneous and distinct from the cortical grey matter (Gogtay et al., 2006; Murty et al., 2016; Østby et al., 2009; Sowell et al., 2002; Sussman et al., 2016). Studies of the developmental trajectory of the hippocampus and amygdala in general have mixed findings about the overall trajectory of hippocampal volume. Most studies find an upside-down U trajectory, with some resulting in a slight increase in volume and others a slight decrease (Gogtay et al., 2006; Murty et al., 2016; Østby et al., 2009; Sussman et al., 2016). This may simply reflect slightly different study end-points, but the same set of studies also find that the anterior and posterior segments of the hippocampus have distinct trajectories, generally with posterior increases and inverse U development resulting in an overall decrease in the anterior segments which complicates measurements of overall hippocampal development (Gogtay et al., 2006; Sussman et al., 2016). At the same time, the major white matter tract connecting the hippocampal regions to the

prefrontal cortex, the uncinate fasciculus also develops along the same upward trajectory as most cortical white matter, and this is accompanied by increased prefrontal-hippocampal functional connectivity over the same time frame (Murty et al., 2016).

The different nuclei in the basal ganglia also have distinct developmental trajectories, but they all generally show a decrease in size, relative to the rest of the brain over the course of adolescence, while the thalamus stays proportionally a similar size or increases slightly (Østby et al., 2009; Sowell et al., 2002; Sussman et al., 2016).

Functional Development of the Brain

The structural development of the adolescent brain is accompanied by changes in functional connectivity and activity during specific tasks and notable differences from both adults and children in task performance.

Studies of the overall connectivity of the large-scale connections of the brain have found that children have similar reliably identifiable brain networks as adults. However, as children age the networks become more clearly spatial defined, and internetwork connectivity between task and default mode networks decrease, while connectivity between motor and executive networks increase (Krafft et al., 2014; Muetzel et al., 2016; Stevens et al., 2009; Thomason et al., 2011).

Studies of alterations in network connectivity in adults have found that internetwork connectivity more generally increases during aging while efficiency decreases and multistep networks become more common (Allen et al., 2011; Betzel et al., 2014; La et al., 2015). This suggest an overall inverted U shape to network efficiency over time, peaking in young adulthood.

Impulsivity and the Adolescent Brain

One of the most notable behavioural features of adolescence is an increase in impulsive and risk-taking behaviour. Adolescence is a complex phenomenon, with physical, cognitive and social components. Adolescence is generally understood to begin at the onset of puberty and end once adulthood has been reached. But while the onset of puberty is a relatively well-defined, the exact boundary between the end of late adolescence, and the true start of adulthood is more complex. The attainment of the legal status of adulthood, the social standing and privileges associated with adulthood, the physical, and the neurological developmental markers of adulthood may all be attained at different times (Cohen et al., 2016).

Neurological development extends from birth past adolescence, into the mid-twenties, and contribute to the specific neurology and behaviour characteristic of adolescence (Petanjek et al., 2011).

Definition of Impulsivity

The five-factor model of personality is one of the most frequently used personality instruments in neuroscience research. The five-factor personality inventory was originally developed based on a linguistic inventory of personality description, subjected to factor analysis, revealing the five factors termed Neuroticism, Extroversion, Conscientiousness, Openness to Experience and Agreeableness (Costa and McCrae, 1997; McCrae and John, 1992). This five factor structure has been replicated across age, gender and culture (Costa et al., 2001). Each of the five broad factors has been subdivided into six sub-categories, called facets. The facets are not mathematically derived but are widely used (Costa and McCrae, 1995).

Neuroticism, is generally understood to relate to a person's overall vulnerability, or sensitivity to negative stimuli, while Extraversion relates to a person's reactivity to positive stimuli. Conscientiousness is an overall measurement of a person's ability to work towards long term goals, and suppress impulses. Openness to Experience measures a willingness to investigate and experience new things, and the different facets of Openness to Experience assess openness to multiple different types or domains or experience. Agreeableness measures an individual's overall tendency towards pro-social, cooperative behaviour (Costa and McCrae, 1995, 1997; Deyoung and Gray, 2009; McCrae and John, 1992).

Impulsivity is a facet of the Neuroticism factor of the five factor model but it can also be approached as the opposite of, or the low-scoring end of the Conscientiousness scale (Costa and McCrae, 1995; Whiteside and Lynam, 2001). However, impulsivity is, itself, also a complex, multifactorial trait which can be assessed in multiple ways (Duckworth and Kern, 2012). Typically, impulsivity is most broadly defined as a tendency to favor short-term goals and rewards. However, more specific forms of impulsivity are defined, including motor impulsivity, struggling to repress motor actions, delay discounting, over-valuing small short-term rewards as compared to more distant, larger rewards or cognitive impulsivity, acting without considering longer-term consequences (Duckworth and Kern, 2012; Whiteside and Lynam, 2001).

Impulsivity is generally measured through either laboratory tasks assessing a specific type of impulsivity, or through questionnaires aimed at assessing overall trait impulsivity. Commonly

used impulsivity tasks include the delay discounting task or the marshmallow task, which assess how much an individual will devalue a larger delayed reward as compared to a smaller, immediate one (Duckworth and Kern, 2012; Mischel et al., 1989, 1972; Myerson et al., 2001). The stop signal task, which assesses the ability to suppress an already initiated motor response, the balloon analogue risk task, which assesses risk tolerance for a reward (Bar, 2010; Duckworth and Kern, 2012; Mischel et al., 1989, 1972). More general measures of cognitive control, like the Stroop task are also often included along with more specific tests of impulsivity (Duckworth and Kern, 2012).

Commonly used impulsivity scales including the Impulsive Behaviour Scale, the Behavioural Activation and Behavioural Inhibition Questionnaire, and the Substance Use Risk Profile Scale (SURPS) among others aim to assess multiple aspects of impulsive thought and behaviour to create what is, in essence, a combined score (Carver and White, 1994; Krank et al., 2011; Whiteside and Lynam, 2001; Woicik et al., 2009). Questionnaire-based assessment of impulsivity may or may not break impulsivity into finer sub-scales.

While impulsivity is coherently constructed as a single trait, overall, an individual's score on multiple impulsivity questionnaires will correlate, but intra-subject correlations between tasks and questionnaires are much lower, as are the correlations between scores on specific tasks (Braams et al., 2015; Duckworth and Kern, 2012; Whiteside and Lynam, 2001).

A related but somewhat different construct is sensation-seeking. An individual's propensity for sensation-seeking is usually defined as their degree of desire for novel or intense sensations, or their willingness to take risks, to get them. Within the framework of the five factor model, sensation-seeking is considered to be a facet of Extraversion. Large-scale meta-analysis of concordance between measures of self-control and impulsivity have found that sensation-seeking could be distinguished from impulsivity, although the two were correlated (Duckworth and Kern, 2012). However, while sensation-seeking can coherently be approached as an independent trait, or an aspect of Extraversion, it is most often considered a sub-trait of impulsivity. As a result the literature on the effects and neural correlates on sensation-seeking specifically is relatively sparse.

Studies dissociating impulsivity and sensation-seeking have found that increased sensation-seeking, specifically, is related to increased bingeing behaviour, but not to the other externalizing

behaviours like conduct problems, aggression, or drug use, which have been associated with increased impulsivity (Castellanos-Ryan et al., 2011).

The SURPS, which is the personality instrument used in this thesis, is a more focused test of personality. While the five-factor model aims to capture as complete a picture of personality as possible, the SURPS focuses on four traits specifically linked to increased risk for substance abuse (Jurk et al., 2015; Krank et al., 2011; Woicik et al., 2009). The SURPS is comprised of four subscales capturing overall measures of four separate personality traits: impulsivity, sensation-seeking, negative-thinking and anxiety sensitivity. Each of the four subscales is made of a combination of items from earlier tests, including the NEO-five factor inventory, a short form measure of the five-factor model personality traits (Jurk et al., 2015; Krank et al., 2011; Woicik et al., 2009). The SURPS has been adapted for both adult and adolescent populations, specifically (Jurk et al., 2015).

Trajectory of Impulsivity in Adolescence

Although impulsivity, like most personality traits is generally considered to be fixed in adulthood, impulsivity and sensation-seeking, along with related measures of risk-taking change over the course of adolescence, with an inverted-U trajectory, typically peaking between early and mid-adolescence (ages 13-16) (Collado et al., 2014; Crone et al., 2016; Defoe et al., 2015; Steinberg, 2010). Adolescent impulsivity, in most studies, peaks at around 14 years of age, but impulsivity measured in laboratory studies peaks earlier than ecological measurements, like rates of accidents, which peak later, around 16 – 18 years (Chick, 2015). Interventions to reduce impulsivity and sensation-seeking traits have been found to reduce subsequent problematic drug use (Conrod et al., 2011, 2010, 2008).

Sensation-seeking and impulsivity are correlated across the age range, with $r = 0.34$-0.41, suggesting that these personality traits share a common neural substrate. Sensation-seeking and impulsivity are related to the Extraversion and the Conscientiousness and Neuroticism factors respectively of the Five-Factor Model (Collado et al., 2014; MacPherson et al., 2010).

Neural Correlates of Impulsivity

Impulsivity and sensation-seeking are linked to the function of multiple systems within the brain, and different aspects of impulsivity are correlated with different regions.

Variation in activity in the ventral striatum has been associated with impulsivity and reward responsiveness in prior studies, using a variety of impulsivity measures (Braams et al., 2015;

Buckholtz et al., 2010). Despite being a comparatively small brain region, the striatum is densely connected to other regions throughout the brain and fulfills a wide range of functions. The striatum can be broadly divided into dorsal and ventral regions. The ventral region is more heavily involved in emotion and reward processing, and the dorsal region in cognitive and motor functions (Di Martino et al., 2008; Postuma and Dagher, 2006).

Based on anatomical tracing studies in animals, the striatum is connected to the frontal cortex through a series of reciprocal cortico-striatal loops (Haber, 2003; Haber et al., 2000; Postuma and Dagher, 2006). A 2006 meta-analysis found that the ventral striatum was functionally connected predominantly to the amygdala and hippocampus and to the ventral midbrain structures (Postuma and Dagher, 2006). A resting state functional magnetic resonance imaging (fMRI) study in 2008, however, found that activity in the ventral striatum also covaried with the orbitofrontal cortex, as well as the dorsolateral and inferior frontal cortex, the anterior and posterior cingulate cortex and the parahippocampal gyrus (Di Martino et al., 2008). Another study in 2012 based on cerebral seed regions found that the ventral striatum activity covaried with the fMRI signal in orbitofrontal and temporal poles (Choi et al., 2012). This may be the result of differing techniques, or of different parcellation schemes.

Motivated, goal-directed behaviour, in general, is generated through the function of the corticostriatal system, innervated by the dopaminergic midbrain. This system progresses in a rostral to caudal direction (in the cortex) and a ventral to dorsal direction (in the striatum), which corresponds functionally to a progression from motivation, to decision-making, to specific motor behaviour (Haber et al., 2000). Different aspects of impulsivity can be mapped to the function of different anatomical regions of the corticostriatal system. The more cognitive and emotional aspects of impulsivity relate to the reward circuits between the ventral striatum, especially the nucleus accumbens, and the orbitofrontal and ventromedial prefrontal cortex. These regions are involved in the calculation of the reward value of various stimuli in the environment, using information from a larger network involved in the calculation of value including the prefrontal cortex, anterior cingulate cortex, the dopaminergic midbrain and the limbic system (Bar, 2010). These value calculations are also influenced by the more dorsal/caudal loops connecting to the lateral and dorsolateral prefrontal cortex which modulates value and exerts top-down control in favour of longer-term goals with less immediate reward (Christakou et al., 2011; Haber et al., 2000; van den Bos et al., 2015).

Connectivity within the corticostriatal reward system, including the ventral striatum, and ventromedial prefrontal cortex and orbitofrontal cortex is generally associated with increased delay discounting (i.e. greater impulsivity), while greater connectivity to more lateral parts of the prefrontal cortex is associated with reduced delay discounting (Kishinevsky et al., 2012; Lawyer et al., 2015; Li et al., 2013; Sripada et al., 2011; Weygandt et al., 2013).

The motivational and motor functions of the corticostriatal system are heavily dopaminergic, and innervated by two midbrain dopaminergic nuclei, the ventral tegmental area, and the substantia nigra pars compacta. The motivational and emotional (i.e. ventral) regions of the corticostriatal system are more heavily innervated by the ventral tegmental area, while the substantia nigra pars compacta primarily innervates the associative and motor elements of the striatum (Murty et al., 2014).

Dopamine plays a variety of roles in the corticostriatal system during tests of impulsivity. The dopaminergic midbrain, along with the ventral striatum, also exhibits a reward signal response and its connections to both the ventral striatum and orbitofrontal cortex relates to reinforcement and learning (Aron et al., 2004; Braams et al., 2015). Performance on the stop signal task has been found to be correlated with levels of dopaminergic release in the orbitofrontal and prefrontal cortex, and negatively correlated with its release into the anterior cingulate cortex, as well as release and autoreceptor response within the dopaminergic midbrain itself (Albrecht et al., 2014; Buckholtz et al., 2010). However, not every impulsivity task relates to dopamine in the same way: performance on the delay discounting task has been found to have a U-shaped relationship to striatal dopamine release (Joutsa et al., 2015).

The limbic system, specifically, the hippocampus, amygdala and parahippocampal cortex are involved in both the assessment of value of environmental stimuli, the modulation of that signal based on contextual cues, and the inhibition of responses. Hippocampal function specifically, has been linked to multiple aspects of self-control and impulsivity (Johnson et al., 2007; Mizumori and Tryon, 2015). The ability to imagine the acquisition of a future reward, which is needed for tasks involving delayed gratification, like the delay discounting task, relies in part on memories about similar rewards, and contextual cues from the hippocampus and its connectivity to the ventral striatum and prefrontal and cingulate cortex (Bar, 2010; Peters and Büchel, 2010). The limbic system, especially the amygdala, is also related to reward based learning, and specifically,

the processing of cue-based learning, in concert with the striatum (Averbeck and Costa, 2017; Johnson et al., 2007).

However, recently, a third circuit involved in self-control has been identified. Studies by Soutschek et al (2016) found that disruption of the right temporoparietal junction using transcranial magnetic stimulation impairs participants' performance on a delay discounting task (Soutschek et al., 2016). The function of the temporoparietal junction has been previously primarily associated with perspective taking tasks, which were also impaired by transcranial magnetic stimulation in the same study (Soutschek et al., 2016). Further fMRI studies of the same system have supported the finding that the activity of the right temporoparietal junction and its connectivity to the ventromedial prefrontal cortex correlate with reduced delay discounting. They have also found that the corticostriatal networks more typically associated with delay discounting are likewise involved in the social and perspective taking tasks usually associated with the right temporoparietal junction (Connell et al., 2018; Hill et al., 2017; Soutschek et al., 2016).

This relatively recent identification of new elements to a well-established system also raises the question of how complete our understanding of the extended self-control system is, and if further elaborations remain to be discovered.

Neural Correlates of Impulsivity Specific to Adolescence

The Corticostriatal System and Dual Systems Model

Adolescents demonstrate, overall, a heightened reward response and greater reward learning compared to either adults or children (Davidow et al., 2016; Galvan et al., 2006; Geier et al., 2010). This goes along with an increased reward prediction error signal in the ventral striatum and orbitofrontal cortex in response to a given stimulus (Galvan et al., 2006). The prefrontal cortex is one of the latest maturing structures of the brain, and so, remains relatively immature in early and mid-adolescence compared to other regions, as do the white matter tracts connecting the prefrontal cortex to other regions (Adleman et al., 2002). The activation of the prefrontal cortex in tasks of self-control, and executive function more generally, similarly develop throughout adolescence and into adulthood (Adleman et al., 2002).

The dual systems model characterizes the increase in impulsive and risk-taking behaviour which occurs during adolescence as a result of the interaction between the developmental trajectories of the striatal and prefrontal systems (Steinberg, 2010). In general, decisions about

risk versus reward, or short versus long-term goals are driven by the interactions between the striatum, which calculates and processes reward, and the prefrontal cortex, which is involved in the formation and maintenance of long-term goals, self-regulation, and contextual information. During adolescence, the combination of the increase in striatal response to reward without a concomitant increase in response from the prefrontal structures which are still relatively underdeveloped and under-connected, alters value calculations in favour of higher risk and shorter term outcomes (Hofmann et al., 2009; Shulman et al., 2016; Steinberg, 2010; Strang et al., 2013).

The dual systems model can be used to make predictions across multiple tests of impulsive behaviour and multiple measures of neurological structure and function (Casey et al., 2016). A simplified model of a distinct striatal region processing motivation and an inhibitory frontal region can be used successfully to make predictions under this model. However, the corticostriatal system is an integrated system with a complex developmental trajectory which interacts with the other systems of the brain and body. The predictions of the dual systems model also reflect the more complete function and development of the integrated corticostriatal system (Braams et al., 2015; Casey et al., 2016; Ernst, 2014; Haber et al., 2000).

Since the methodological and statistical constraints on imaging studies, especially functional imaging studies, often limit the number of regions or connections which can be examined in a single study the dual systems model allows the generation of a priori hypotheses for studying the neurobiology of adolescence, especially in a neuroimaging context.

Adolescents tend to underperform on tasks of self-control, and behavioural inhibition, and demonstrate a steeper discounting curve on the delay discounting task compared to adults. Behavioural inhibition performance improves with age, not only between adolescence and early adulthood, but during the third decade of life (Christakou et al., 2011, 2009; Cohen et al., 2016). The behavioural improvements in task performance which occur with age are accompanied by increased activation in dorsolateral and ventromedial prefrontal regions, as well as insula, temporal and anterior cingulate cortical regions, decreased activation within the ventral striatum, and connectivity changes between the ventral striatum and ventromedial prefrontal cortex (Bunge and Wright, 2007; Christakou et al., 2011, 2009; Cohen et al., 2016; Rubia et al., 2007, 2006; Van Den Bos et al., 2012). Corticostriatal connectivity and task performance are also less

finely modulated in response to varying sizes of rewards in adolescents as compared to adults (Insel et al., 2017).

Similarly, a relationship between behavioural performance and the activation and connectivity of the corticostriatal system can be seen within samples of adolescents. Younger adolescents who are more impulsive or sensation-seeking show higher volume of the ventral striatum, decreased response to anticipation, and are more likely to develop problematic drug use behaviours later in adolescence (Büchel et al., 2017). Adolescent subjects who scored higher on sensation-seeking, or performed worse on a delay discounting task, showed increased striatal response to anticipation and increased striatal response to reward and decreased reward anticipation and connectivity between the ventral striatum and prefrontal regions (Bjork et al., 2008; van den Bos et al., 2015). This relationship can also be replicated in studies using real world measures of impulsive behaviour, or risk for the same. Adolescents with greater connectivity between the ventral striatum and the amygdala and orbitofrontal cortex smoke at higher rates than those with greater connectivity with the inferior frontal gyrus and medial prefrontal cortex and similar findings differentiate adolescents with family histories of alcohol use disorder from those who do not (Cservenka et al., 2014; Jollans et al., 2016).

Corticostriatal activity in adolescents also varies with sensation-seeking: those with greater trait sensation-seeking have been found to have greater reward response in the insular and lateral prefrontal cortex, but lower activation to reward in the nucleus accumbens (Cservenka et al., 2013; Hawes et al., 2016). The relationship between reward response in the nucleus accumbens and sensation-seeking, however, was also found to be non-linear with age. Adults show the opposite relationship (Hawes et al., 2016).

The Limbic System, the Triadic Model and Other Extensions of the Dual Systems Model

The triadic model of adolescence is an elaboration on the dual systems model, which includes the input from the limbic system, specifically evaluation of aversive stimuli by the amygdala in the evaluation of goals by the corticostriatal system which contribute to increased risk taking in adolescence (Ernst, 2014; Ernst et al., 2006). The original triadic model, as proposed by Ernst et al (2006), emphasizes the role of the amygdala in avoidance of negative stimuli as an additional element in adolescent impulsivity. However, in this model, the hippocampus and parahippocampal cortex also contribute to impulsivity and self-control (Johnson et al., 2007). The overall connectivity between the ventral striatum and limbic regions

are correlated with reward responsivity and decrease with age. The degree to which inputs to the ventral striatum from the limbic regions, and those from the frontal cortex are overlap spatially is similarly correlated (Larsen et al., 2017).

The hippocampus is also involved in the greater reward responsivity seen in adolescents. Improved reward learning seen in adolescents is related to both greater responsivity in the hippocampus during reward learning, and greater connectivity between the hippocampus and ventral striatum. This is believed to be related to increased use of experience via hippocampally mediated memory in decision making (Davidow et al., 2016; Murty et al., 2016). It is possible that altered use of memory, or reduced experience contributes to impulsivity in adolescence.

Both the corticostriatal and limbic systems are innervated by dopaminergic fibres from the substantia nigra and ventral tegmental area in the midbrain. The connectivity between the dopaminergic midbrain, cortex, striatum and limbic system has been found to develop over time, with adolescents showing higher levels of limbic, insula, orbitofrontal cortex and basal ganglia connectivity with the ventral tegmental area and substantia nigra compared to adults (Tomasi and Volkow, 2014). Functional imaging studies of the midbrain are still relatively rare, so these connectivity changes have not been linked directly to changes in impulsivity, but the systems involved in adolescent impulsivity are known to be dopaminergic, and variation in the function of the dopaminergic midbrain has been linked to variation in impulsivity in adults, suggesting that this is a relevant consideration in adolescent behaviour (Buckholtz et al., 2010; Casey et al., 2016; Murty et al., 2014; Tomasi and Volkow, 2014).

Weight Regulation as a Neurological Property

Regulation of appetite in the brain is typically divided into homeostatic regulation, based on nutritional and energy balance inputs, and hedonic regulation, based on the reward value of various food items (Tregellas et al., 2011). Homeostatic control of BMI is regulated by the circuits of the hypothalamus, which receives neuroendocrine input, as well as input from the viscera via the autonomic nervous system. Homeostatic control of BMI implicates hunger and satiety, and is based on ongoing regulation of intake of calories and nutrients, and inhibition of food intake in response to caloric excess (Tregellas et al., 2011).

The hedonic circuits governing eating behaviour evaluate food cues and drive food related decisions based on their perceived rewarding values, including not only perceived nutrition or calories, but also taste, and social or emotional properties. The evaluation of the hedonic

properties of food and related decisions about food choice involves the insular cortex, multiple regions of the corticostriatal system, and the limbic system (Batterink et al., 2010; Gautier et al., 2001; Kanoski and Grill, 2017; Tregellas et al., 2011).

There is also a growing amount of evidence that the neurological circuits controlling BMI are lateralized, with imbalances or injuries which increase the influence of the left over the right hemisphere contributing to reduced exercise and increased food intake and BMI (Alonso-Alonso and Pascual-Leone, 2007; Vainik et al., 2017).

Increased BMI has been associated with widespread structural changes in both grey and white matter of the brain. Higher BMI has been associated with global reductions in cortical thickness or grey matter volume in the cortex and subcortical structures, which becomes more marked in older adults (Ho et al., 2010; Pannacciulli et al., 2006; Ronan et al., 2016; Veit et al., 2014). This reduction in grey matter is observed earliest, in older adolescents and young adults, in the prefrontal and orbitofrontal cortex, and alterations in prefrontal grey and white matter have been associated with worse performance on self-control tasks, and altered food choice (Maayan et al., 2012; Marqués-Iturria et al., 2013; Yau et al., 2011; Yokum et al., 2012). This is also lateralized. Increased volume or cortical thickness in the left prefrontal cortex and reductions on the right contribute to increased weight gain and obesity (Alonso-Alonso and Pascual-Leone, 2007; Vainik et al., 2017). Along with the reductions in grey matter volume, obesity has also been found to decrease efficiency of connections globally, and locally within the basal ganglia. These changes are both also associated with aging, suggesting that obesity exacerbates brain aging (Baek et al., 2017; Betzel et al., 2014; Ronan et al., 2016). Obesity is also associated with morphometric changes in the white matter, seen by changes in fractional anisotropy, which reflects white matter integrity (Medic et al., 2018).

Increased BMI is also associated with reduced volume in the hippocampus and other limbic structures. Reduced hippocampal volume has, similarly been associated with altered eating behaviour, and increased consumption of calorically dense food (Francis and Susman, 2009; Kanoski and Grill, 2017; Stevenson and Francis, 2017). Changes in brain morphometry correlated with BMI may be bidirectional. In older adults especially, reduced cortical thickness and hippocampal volume may result from inflammatory and cerebrovascular damage related to obesity (Hargrave et al., 2016; Ho et al., 2010).

Impulsivity as a Predictor of Body Mass Index

Higher BMI, and greater weight gain, have been correlated with higher levels of impulsivity, based on multiple different impulsivity measures. Adults with higher BMI have been found to show higher rates of delay discounting, and poorer performance on the stop signal task of motor impulsivity (Appelhans et al., 2012; Lawyer et al., 2015; Nederkoorn et al., 2010). Task-based impulsivity has also been related to increased risk for obesity. Obese women who demonstrated higher delay discounting have been found to eat more and higher calorie snack food (Appelhans et al., 2012; Daniel et al., 2013). Reduced capacity for response inhibition, a related task, has also been shown to be associated with increased rates of weight gain (Nederkoorn et al., 2010). Obese women have also been found to demonstrate impulsive choice on the Iowa Gambling Task, as compared to lean ones (Horstmann et al., 2011). It has also been found that increased impulsivity in childhood is correlated with obesity in adulthood (Schlam et al., 2012). In sum, impulsivity is related to higher caloric intake and the consumption of more rewarding high calorie food.

Obese women who exhibit increased delay discounting were found, specifically, to consume higher caloric density pre-prepared food, and less food prepared at home, but, since women still perform the majority of food preparation in most households, it is not known how well this generalizes to men (Appelhans et al., 2012). Obese subjects have been found to have increased habitual and impulsive behaviour towards food specifically, even when their overall level of habit-driven or impulsive responses to other stimuli are not correlated with their BMI. However, general levels of sensation-seeking have been correlated with BMI (Dietrich et al., 2016). Higher BMI, or greater weight gain over time, have also been associated with neuroticism and negatively associated with concientiousness, the more general personality trait of which impulsivity is a facet, and with Extraversion, the factor which contains sensation-seeking, although not as robustly (Gerlach et al., 2015; Jokela et al., 2013; Lunn et al., 2014; Vainik et al., 2013).

Shared Neural Correlates of Impulsivity and Weight in Adults

Neuroimaging of BMI and food response specifically is typically conducted by either by examining changes in activation or connectivity in response to food related cues, or by comparing neuroimaging findings on a non-food tasks, between subjects with differing BMI (Carnell et al., 2012). Multiple circuits are associated in control of BMI, but two of the most

commonly involved are the corticostriatal system, and the limbic system, especially the hippocampus and parahippocampal gyrus.

A 2013 meta-analysis of food response tasks during fMRI found that obese subjects had an increased response in the right inferior, superior and precentral frontal gyri, and left dorsomedial prefrontal cortex, as well as the right parahippocampal cortex, and decreased insular and dorsolateral prefrontal cortex (Brooks et al., 2013). Other studies with differing methods have found similar regional associations. A positron emission tomography study found an overall reduced level of change in cerebral blood flow in response to satiety in an obese group compared to lean controls, which included both a blunted increase in frontal regions, and a blunted decrease in limbic regions (Gautier et al., 2001). A similar resting-state study found that regional homogeneity within the parahippocampal gyrus, a measure of local synchronicity, was associated with a greater degree of food craving as a trait, while dorsal striatal regional homogeneity was negatively correlated with impulsive food choices (Chen et al., 2017; Gao et al., 2018).

Impairment of hippocampal function has also been associated with increased food intake and impaired self-control. Alterations in hippocampal function have been found to impair performance on both food-related and general tests of self-control. The hippocampus and parahippocampal gyri are involved in multiple aspects of appetite including: altering food response during satiety or other contextual factors, and memory for prior meals. Impairment of those functions in obesity can result in increased food intake (Gautier et al., 2001; Hargrave et al., 2016; Kanoski and Grill, 2017; Stevenson and Francis, 2017). This has been found to be a bidirectional relationship. Increased BMI has also been found to impair hippocampal function, most likely mediated by inflammatory or hormonal signalling (Hargrave et al., 2016).

Connectivity at rest between the ventral striatum and the medial prefrontal cortex has been associated with performance on a delay discounting task (Calluso et al., 2015). Occipitoparietal resting-state connectivity with the ventral striatum has been associated with reduced trait risk taking (Cox et al., 2010). Performance on the stop signal task has been simultaneously linked to the function of multiple frontal and frontoparietal networks (Fuentes-Claramonte et al., 2016). Thus, the same frontostriatal system has been simultaneously implicated in impaired delay discounting, greater BMI and weight gain over time, and reduced impact of weight loss interventions (Kishinevsky et al., 2012; Lawyer et al., 2015; Weygandt et al., 2013).

Neuroticism, the broader personality trait of which impulsivity is a sub-factor, has also been associated with greater connectivity between the amygdala and ventromedial prefrontal cortex, and reduced connectivity between it and the anterior cingulate cortex. Neuroticism is also one of the personality traits most often associated with higher BMI or greater weight gain over time (Gerlach et al., 2015; Jokela et al., 2013; Lunn et al., 2014; Vainik et al., 2013).

The dopaminergic midbrain, composed of the substantia nigra and ventral tegmental area has also been independently associated with both BMI and impulsivity (Buckholtz et al., 2010; Dang et al., 2016; Forbes et al., 2009). Greater dopamine availability measured using a fallypride tracer with positron emission tomography has been associated independently with both increased body mass (although only above the age of thirty, not in younger adults or adolescents) and with trait impulsivity. (Buckholtz et al., 2010; Dang et al., 2016). Genes associated with greater dopamine availability in the midbrain, but not the cortex including the DRD2-141C, DAT1-9 repeat and DRD4-7 repeat genotypes, have been associated with greater trait impulsivity as well as increased reward response in the striatum, while lower dopaminergic tone (e.g. with medications) has been associated with weight gain (Forbes et al., 2009; Lee et al., 2018). While these studies were all conducted independently, and so, cannot conclusively demonstrate a link between impulsivity, sensation-seeking and weight, taken as a group they do show that these traits, which are behaviourally correlated, also correlate with similar neural endophenotypes.

Impulsivity and its Neural Correlates and Weight in Adolescents

The relationship between BMI and impulsivity in adolescence begins before puberty. Children begin to show meaningful variation in self-control in very early childhood. Performance on the marshmallow task, the measure most commonly used to assess early-childhood self-control at three or four years of age can predict degree of weight gain over the lifespan. A poor marshmallow test performance at three or four is associated with a higher BMI midlife (Schlam et al., 2012). These effects are also seen on much shorter time scales between childhood and early to mid-adolescence (Duckworth et al., 2010; Francis and Susman, 2009; Tsukayama et al., 2010). The effects of increased BMI can also be seen in younger children. Overweight children have been found to have greater connectivity between the orbitofrontal and ventromedial prefrontal cortex and middle frontal gyri, the frontal regions most associated with reward stimuli, and central adiposity specifically has been associated with impairments in hippocampally mediated memory (Black et al., 2015; Haber et al., 1995; Khan et al., 2015;

Krombholz, 2013). Separate studies have also independently found greater overlap between the default mode network, and task networks in impulsive children, and overweight and sedentary children. In overweight children, the default mode and task networks become more independent in response to increased exercise, similar to findings in overweight adults (Doucet et al., 2017; Inuggi et al., 2014; Krafft et al., 2014; Legget et al., 2016; McFadden et al., 2013). BMI is also correlated with overall reductions in global connectivity in adolescents, similar to what is seen in adults, and these changes are especially large in the connectivity between insular and frontotemporal regions (Baek et al., 2017; Moreno-Lopez et al., 2016).

Adolescents with higher body mass index have been found to be more impulsive than their lean peers according to multiple measures of impulsivity including delay discounting and the UPPS questionnaire. They also underperform on more general measures of self-control including the Stroop task (Batterink et al., 2010; Delgado-Rico et al., 2012). Higher body mass index in adolescents has been correlated with a greater degree of impulsivity on a delay discounting task which is accompanied by reduced activation during the task across multiple prefrontal regions (Batterink et al., 2010).

Structurally, overweight and obese adolescents have reduced volume or thickness in the orbitofrontal cortex, superior and dorsolateral prefrontal cortex and diencephalon, and these reductions in thickness are correlated with increased food related disinhibition and impulsivity, and worse Stroop performance. Higher BMI has also been associated with increased hippocampal volume (Maayan et al., 2012; Moreno-López et al., 2012). Increased hippocampal volume specifically could reflect a number of different processes. Hippocampal function is related to multiple aspects of self-control, but normal hippocampal development of multiple hippocampal subregions involves increases in volume until late childhood or early adolescence, and so this could reflect an immature phenotype, which has also been implicated in higher BMI in functional studies (Gogtay et al., 2006; Krafft et al., 2014; Murty et al., 2016).

Prefrontal, orbitofrontal and anterior cingulate regions, all of which have also been found to be reduced in volume or thickness in adolescent overweight and obesity, are also separately established as part of the corticostriatal system related to adolescent impulsivity (Casey et al., 2016; Yau et al., 2011; Yokum et al., 2012).

Overall, there is substantial evidence that greater impulsivity is behaviourally associated with higher BMI and greater risk for weight gain across the lifespan (Appelhans et al., 2012;

Duckworth et al., 2010; Moreno-López et al., 2012; Schlam et al., 2012). Studies of the neural correlates of food-related impulsivity or of impulsivity in overweight populations have identified a set of networks including the corticostriatal system and limbic system involved in both impulsivity and BMI (Horstmann et al., 2011; Moreno-López et al., 2012; Stevenson and Francis, 2017). This is further substantiated by the fact that separate studies investigating the neural correlates of weight regulation and the neural correlates of impulsivity in general, identify similar networks in both adult and adolescent populations (Buckholtz et al., 2010; Christakou et al., 2011, 2009; Moreno-Lopez et al., 2016; Tomasi and Volkow, 2014, 2013).

Methods

Body Mass Index

Body mass index is equal to weight divided by height squared. Based on population averages standardized cut-offs differentiating healthy weight, overweight and obesity have been established. In children and adolescents normal body mass index is calculated based on age specific ranges, but cut offs for overweight and obesity are calculated based on percentile on a standardized growth curve, and expressed as a body mass index percentile for age, or, a body mass index z-score for age (Flegal et al., 2002; Kuczmarski et al., 2002). Increased body mass index is widely used as a proxy for adiposity, but does not measure it directly, and one of the major limitations of body mass index as a tool is that increased muscle or bone mass will also increase body mass index. Studies of children comparing body mass index to a more precise measure of body composition have found that it corresponds with adiposity more closely as weight increases (Freedman et al., 2005). Extra weight in overweight, and, especially in obese subjects, was found to be predominantly from adipose tissue, while in the normal range subjects with similar body mass indices exhibited a wide range of lean to adipose tissue ratios (Freedman et al., 2005).

Magnetic Resonance Imaging

Magnetic resonance imaging is a tool based on the nuclear magnetic resonance properties of hydrogen atoms in biological tissues. When placed in a strong, static magnetic field, the spin-states of hydrogen atoms will align, with a stronger field producing a more complete state of alignment (Filippi, 2016). When aligned hydrogen atoms gain energy, their alignment will become perturbed, and when the energy source is removed, they will lose that energy and return

to their previous state of alignment. Magnetic resonance imaging briefly applies energy, in the form of radio waves, to tissue in a static magnetic field and then detects the signal that results when energy is released as the hydrogen atoms in that tissue return to alignment within the static field (Filippi, 2016).

To allow for three dimensional imaging the exact strength of the static field is modified by the addition of gradient fields, which vary continuously in strength along a spatial axis, giving each spatial location a distinct field strength. The frequency of the signal is determined by the strength of the static field, and using reverse Fourier transformation the frequency composition of the detected signal can be reconstructed to identify the original spatial location of the varying parts of the signal to create an image of the tissue. The units of resolution the signals are mapped onto form points in a three dimensional grid, called voxels (Filippi, 2016).

Structural Magnetic Resonance Imaging

Different tissues have different magnetic resonance properties, as a result of their differing chemical composition, especially varying water content, since the majority of the hydrogen atoms used in magnetic resonance imaging in biological tissues are within water molecules (Alexander et al., 2008; Filippi, 2016). In the brain, specifically, the three primary tissue types which can be differentiated with magnetic resonance imaging are cerebrospinal fluid, which is mostly free water, grey matter, which consists primarily of cell bodies, where most water is in the form of cellular cytoplasm or extracellular fluid, and white matter, consisting of myelinated axons, which has a relatively low water content which is largely compartmentalized (Alexander et al., 2008; Filippi, 2016).

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging also utilizes the magnetic resonance properties of brain tissue, but uses those properties to infer the timing and location of neural activation. The most commonly used form of functional magnetic resonance imaging is called blood oxygen level dependent imaging. Blood oxygen level dependent imaging uses neurovascular coupling, the relationship between blood flow and neural activity, and the magnetic properties of hemoglobin to generate an image based on neural activity (Filippi, 2016).

Neurovascular coupling is a mechanism by which increased blood flow can be directed to active neurons, which require increased oxygen and glucose to fuel increased metabolic activity,

in a spatially specific manner. This reliably results in an increase in the amount of oxygenated haemoglobin in active regions shortly after neuronal firing (Filippi, 2016).

Haemoglobin, the oxygen carrying molecule in red blood cells, is diamagnetic when oxygen is bound to it, but paramagnetic when it is unbound. This means that deoxygenated haemoglobin molecules will create small disturbances in the magnetic field during magnetic resonance imaging resulting in signal loss, while oxygenated haemoglobin will not. The increased levels of oxygenated blood that immediately follow neuronal firing due to neurovascular coupling therefore result in an increase in signal that is localized to regions with active neurons. This signal is detected in blood oxygen level dependent imaging and used as a proxy for neural activity (Filippi, 2016).

Resting State Functional Magnetic Resonance Imaging

Blood oxygen level dependent imaging can be used to measure neural responses to specific tasks or stimuli, but it can also measure the random baseline activity which occurs in the brain at rest. In task based functional imaging, the time course of activity as compared to the timing of stimuli or specific responses. In resting state functional imaging, the specific time courses are typically non-informative, but the time course correlations between different regions and the amplitude and power of the signal reflect alterations in neural function referred to as functional connectivity (Biswal et al., 1995).

Intrinsic Resting State Networks

Time course correlations between brain regions in resting state functional imaging provides a measure of neural functional connectivity (Biswal et al., 1995). Regions which are known to be coactivated during task performance, tend to be functionally connected at rest. It possible to extract and analyze networks of coactivated regions that have a known relationship to neural function and that can be reliably elicited between subjects and sessions within a single subject (Laird et al., 2011; Smith et al., 2009). These intrinsic resting state networks have been identified in children as well as adults and alterations in intrinsic network activity and connectivity reflect age and gender as well as behavioural measures (Allen et al., 2011; Laird et al., 2011; Smith et al., 2009; Thomason et al., 2011).

Statistical Modelling of the Brain

Independent Component Analysis

Independent components analysis (ICA) is a data driven methodology for identifying underlying patterns of covariation in a dataset. ICA allows the separation of the multivariate fMRI signal into statistically independent subcomponents. ICA has become a widely used method for identifying functional networks within the brain. When applied to functional imaging data ICA can be used to identify independent spatial signal sources within imaging data. Since ICA works without a model it does not require a hemodynamic response function, or other external model, making it a useful method for analyzing resting state data specifically (Shi and Guo, 2014; Calhoun et al., 2001, 2009; Allen et al., 2012; Calhoun et al., 2012; Meier et al., 2012; Liu et al., 2012; Sala-Llonch et al., 2012).

Multiple methodologies for extracting components from imaging data exist. When ICA is applied separately to each individual's resting state fMRI data, the resulting components are not easily comparable; therefore, components are usually generated at a group level (group or GICA) and then reconstructed at an individual level. The information from multiple subjects is most commonly combined using by temporal concatenation, which involves concatenating the scans into a single time course (TC-GICA) (Beckmann et al., 2009; Calhoun et al., 2009). Reconstruction of subject level components is most commonly done using either dual regression or back reconstruction. Dual regression works by first regressing the spatial maps extracted from the GICA onto subjects to extract subject-specific time courses, and then regressing those time courses back onto the original dataset to extract subject-specific spatial maps (Beckmann et al., 2009). During back-reconstruction, the GICA is carried out on a combined matrix which is partitioned by subject. The partitions of the resulting sources can then be isolated to give subject specific sources (Calhoun et al., 2001). Inter-group comparisons can then take place based on multiple elements of each component, including differences in time course, spatial source, or in differences between inter-network correlation. Subject level components can be used in between-group comparisons or correlated against behavioural measures.

Multiple prior studies have found that the components identified by ICA are spatially similar to the networks identified in task-based studies and that variation in the resting state networks identified by ICA is correlated with variation in behaviour (Calhoun et al., 2012; Allen et al., 2012; Meier et al., 2012; Sala-Llonch et al., 2012; Lin et al., 2010).

Components extracted using ICA can be used in multiple ways. A set of biologically relevant intrinsic networks are reliably elicited using ICA the connectivity, time course or signal properties of which can be directly related to aspects of cognitive performance. Another application of ICA is the removal of physiological and motion related noise, which have distinct spatial and signal properties that can be isolated and removed (Pruim et al., 2015; Smith et al., 2009).

Mass Univariate Versus Multivariate Modelling

The majority of neuroimaging studies utilize some form of correlation or regression model, relating some aspect of brain structure or function to behavioural, or other physiological measures (Pernet et al., 2015). Most commonly, especially in older studies, this is done using a mass univariate approach, where a model, usually a variation of the general linear model, is constructed, applied repeatedly to either a set of regions of interest or voxel-wise across the brain, and then significance tested (Pernet et al., 2015).

Mass univariate modelling results must be subjected to some form of multiple comparisons correction to reduce the risk of false positives before they can be interpreted reliably (Pernet et al., 2015). While there are many forms of multiple comparisons procedures, all have the shared effect of reducing the statistical power of an analysis, creating a constant trade-off between type one and type two statistical errors (Pernet et al., 2015).

There are two primary ways of avoiding the problems with mass univariate testing. Firstly, experiments with well-defined anatomical hypotheses can be designed to include only a very limited number of pre-defined tests of those regions, reducing the need for stringent multiple comparisons correction. However, the sort of thoroughly developed anatomically based information this requires is not always available and the level of specificity this entails is not always desirable (Pernet et al., 2015).

Secondly, experimenters can employ multivariate statistical tests. Multivariate analyses employ a single statistical test across larger groups of data, which reduces or obviates the need for multiple comparisons corrections, while still allowing analyses to cover the whole brain, including regions without a specifically hypothesized association with the model (Abdi, 2010; Krishnan et al., 2011; Sawatsky et al., 2015). However, multivariate analyses lack the specificity of univariate models. Because the statistical test in a multivariate analysis is conducted at the level of the pattern (often the whole brain or a large part of it) it becomes much harder to draw

firm conclusions about the specific connections or associations which make up the parts of that pattern (Abdi, 2010; Krishnan et al., 2011; Sawatsky et al., 2015).

Introduction and Rationale

This previous literature has established that weight regulation is related to structural and functional endophenotypes within the brain, especially the structure, task-related activation of the dopaminergic midbrain and ventral striatal structures in the basal ganglia and their connectivity with the prefrontal cortex (Dang et al., 2016; Forbes et al., 2009; Kishinevsky et al., 2012; Lee et al., 2018; Maayan et al., 2012; Weygandt et al., 2013). It has also been established that phenotypes related to impulsivity and sensation-seeking have been identified in similar systems and that impulsivity and sensation-seeking traits change during adolescent development as the result of maturational changes within the same corticostriatal structures. It has also been found that adolescents who display a higher level of impulsivity are at increased risk for being overweight and gaining weight later in life. However, BMI, impulsivity and neurological development during adolescence are all complex, multifactorial phenomena which have different internal subtypes and relate to the function of multiple interacting neurological systems.

This thesis, therefore, aimed to refine our understanding of which systems implicated in adult obesity are relevant to the regulation of BMI in children and how those same systems may relate to the impulsive endophenotype which has been previously found to increase risk for obesity.

In the first study we established that neither a phenotype commonly associated with adult obesity, reduced cortical thickness, nor the more restricted version of the same phenotype, reduced prefrontal cortical thickness, which has been previously identified in older adolescents, are present in children. This established that they neural endophenotypes associated with obesity vary with age.

In the second study we examined the relationship between BMI, impulsivity and sensation-seeking and the connectivity of the basal ganglia and dopaminergic midbrain in a population of young adolescents. However, we identified connections with the limbic system, rather than the expected prefrontal cortical regions, as primarily involved.

In the third study we performed a data-driven, exploratory analysis of the relationship between the connectivity of the brain's large scale intrinsic, resting-state networks and BMI,

impulsivity and sensation-seeking. We identified a pattern of network connectivity related to BMI which encompassed not only subcortical, limbic, and prefrontal regions but also more extensive cortical networks. However, we found that this pattern of network connectivity did not correlate well with impulsivity and sensation-seeking.

In combination, this work firstly expands our understanding of network involvement in the control of body weight in adolescent populations and secondly the relationship between network involvement in body weight and network involvement in the obesity related personality phenotypes of impulsivity and sensation-seeking. It specifically emphasizes the role of subcortical regions in weight and impulsivity in this age group.

Overweight is not associated with cortical thickness alterations in children

Rachel J Sharkey[a], Sherif Karama[a,b], Alain Dagher[a*]

[a]McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, QC, Canada, [b]Douglas Mental Health University Institute, McGill University, Montreal, QC Canada

Correspondence:

Dr Alain Dagher
Montreal Neurological Institute
3801 University Street,
Montreal, PQ, H3A 2B4
Canada

Phone: 514-398-1726
E-mail: alain.dagher@mcgill.ca

Conflicts of Interest: The authors have no conflicts of interest to declare.

Key Words: Obesity, Cortical Thickness, Cortical Development, MRI, Adolescence, Childhood, Gray Matter, Body Mass Index

Word Count in Abstract: 213

Figures and Tables: 4 Figures

Published in Frontiers in Neuroscience; 9(24), 1–7 https://doi.org/10.3389/fnins.2015.00024

Preface

This initial study served two purposes. Firstly, it filled a gap in the literature of the structural neural correlates of obesity, and, secondly, it aimed to provide a basis from which to select appropriate ages, regions of interest and modalities for the following two research studies. Prior to starting this study, there was significant evidence in the literature that increased body weight and adiposity was correlated with a global reduction in cortical thickness in adults, which was most marked in older adulthood (Brooks et al., 2013; Hassenstab et al., 2012; Ho et al., 2010; Maayan et al., 2012; Marqués-Iturria et al., 2013; Pannacciulli et al., 2007, 2006; Taki et al., 2008; Yokum et al., 2012; Horstmann et al., 2011, 2013); however, the evidence pointed to more localized reductions in cortical thickness in emerging adults and older teens (Maayan et al., 2012; Yokum et al., 2012; Yau et al., 2011, 2012).

At the time of the study this latter finding had not been replicated in younger teens or children, and that was the primary aim of the study, based on cortical thickness data taken from the National Institute of Health Study of Normal Brain Development Data Repository (Evans, 2006). This included 716 T1-weighted structural MRI scans from 378 different participants. We extracted cortical thickness across the cortex using CIVET and constructed a multi-level model of the relationship between cortical thickness and BMI Z-score for age (Ad-Dab'bagh et al., 2006; Kuczmarski et al., 2002). Based on this comprehensive sample we produced a very robust negative finding which, based on high statistical power, allowed us to conclude that the relationship between BMI and cortical thickness was not present in children. This was thought to suggest that weight and cortical thickness were not yet associated in younger children. We hypothesized that brain effects on weight in adults might reflect poor control over food choices, and that since children generally do not plan and select their meals, these effects might simply not have appeared by age 18. Conversely, satiety and hunger might be more linked to weight and eating in children, and these might depend on homeostatic control mechanisms not reflected in neocortical anatomy or function.

Abstract

Introduction

Several studies report an association between body mass index (BMI) and cortical thickness in adults. Some studies demonstrate diffuse cortical thinning in obesity, while others report effects in areas that are associated with self-regulation, such as lateral prefrontal cortex.

Methods

This study used multilevel modelling of data from the NIH Pediatric MRI Data Repository, a mixed longitudinal and cross-sectional database, to examine the relationship between cortical thickness and body weight in children. Cortical thickness was computed at 81,942 vertices of 716 MRI scans from 378 children aged between 4 and 18 years. Body mass index Z score for age was computed for each participant. We preformed vertex-wise statistical analysis of the relationship between cortical thickness and BMI, accounting for age and gender. In addition, cortical thickness was extracted from regions of interest in prefrontal cortex and insula.

Results

No significant association between cortical thickness and BMI was found, either by statistical parametric mapping or by region of interest analysis. Results remained negative when the analysis was restricted to children aged 12-18.

Conclusions

The correlation between BMI and cortical thickness was not found in this large pediatric sample. The association between BMI and cortical thinning develops after adolescence. This has implications for the nature of the relationship between brain anatomy and weight gain.

Introduction

Cortical Thickness is both a marker of neurological development and a reflection of cortical function (Giedd et al., 1999b, 1999a; Jernigan et al., 1991; Pfefferbaum et al., 1994; Reiss et al., 1996). Body weight is one factor which has been associated with alterations in cortical thickness. Obesity and overweight has been associated with reduced global gray matter volume in young adults, healthy older adults, and older adults with Alzheimer's disease (Brooks et al., 2013; Hassenstab et al., 2012; Ho et al., 2010; Maayan et al., 2012; Marqués-Iturria et al., 2013; Pannacciulli et al., 2007, 2006; Taki et al., 2008; Yokum et al., 2012; Horstmann et al., 2013, 2011). While some studies report diffuse cortical thinning in obese individuals, others have found reduced cortical thickness specifically in regions associated with self-control and reward (Maayan et al., 2012; Marqués-Iturria et al., 2013; Pannacciulli et al., 2006; Yokum et al., 2012; Hassenstab et al., 2012). These regions include the prefrontal cortex (Ho et al., 2010; Marqués-Iturria et al., 2013), specifically the dorsolateral prefrontal cortex (Brooks et al., 2013), the orbitofrontal cortex (OFC) (Maayan et al., 2012), and the dorsal anterior cingulate cortex (Hassenstab et al., 2012).

The direction of the causal relationship between cortical thickness and body weight is not, however, entirely clear. Thinner gray matter in areas related to self-regulation and motivation could result in excess food intake, but it is also possible that metabolic factors related to excess weight could lead to reduced cortical thickness. A study by Taki *et al* found that body weight was negatively correlated with brain volume in men, but not women. Since women tend to have more subcutaneous fat while men tend to store visceral fat, this would be in line with the hypothesis that increased inflammatory proteins associated with visceral fat play a role in decreased cortical thickness in obesity and overweight (Taki et al., 2008). Alternatively, dysregulation of insulin and leptin, both of which act as neurotrophic factors, has also been associated with reduced frontal cortical thickness in both humans and animal models (Pannacciulli et al., 2006). Humans and animals with leptin mutations have also been found to have reduced cortical thickness, which can be reversed with exogenous leptin treatment (Pannacciulli et al., 2007).

The relationship between obesity and brain volume in older adolescents is less well established. In one study, obese adolescents (ages 14-21) were found to have reduced orbitofrontal cortex volume, high scores on all domains of the Three Factor Eating Questionnaire

and impaired cognitive task performance, notably on tests of inhibitory control. This was hypothesized to reflect a relationship between body weight, OFC function and a tendency to disinhibited eating (Maayan et al., 2012). A second study in women with an average age of 18 years, however, found a global decrease in gray matter in obese individuals, as compared to those classified as lean or overweight (Yokum et al., 2012). The same study, however, found no significant local differences in gray matter volume in a series of regions of interest including the insula, post-central gyrus, caudate , putamen and frontal gyri, between obese, overweight and lean individuals (Yokum et al., 2012).

Cortical thickness in children has been found, overall, to decrease with age, peaking around 4, and decreasing until as late as 30 years of age (Jernigan et al., 1991; Pfefferbaum et al., 1994; Reiss et al., 1996). Different brain regions mature at different rates, but, overall the brain matures from back to front, with the prefrontal cortex being one of the last areas to develop.

Finally, there is limited information on the relationship between BMI and brain volume or cortical thickness in children. The main goal of this study is to assess the relationship between body weight and cortical thickness in children using data from the NIH Pediatric MRI Data Repository, a mixed cross-sectional and longitudinal database of brain development in healthy, normally developing children (Evans, 2006).

Methods

Sampling and Dataset Selection

Data were taken from the NIH Pediatric MRI Data Repository (Evans, 2006). The Repository contains data from the NIH MRI Study of Normal Brain Development. Objective One of this study consisted of 431 children between the ages of 4 and 18 years. Recruitment and scanning occurred at six sites in the United States (US). The institutional review boards at each institution approved the study protocol and both parental consent and participant assent were obtained before testing. Participants were recruited by geocoded mailed survey to reflect the demographic distribution of the US population to prevent any bias and ensure that the sample was representative of the distribution of age, sex, race and socioeconomic status of the zip codes where recruitment occurred (according to 2000 US Census Data). Participants were screened to rule out neurological illness or trauma, axis I psychiatric illness or a family history of the same, language disorders or substance abuse disorders as well as prematurity, exposure to toxins *in*

utero, or most birth complications. Participants with IQ scores below 70 or Child Behaviour Checklist (CBCL) subscale score of over 70 were also excluded. The complete recruitment protocol for the NIH MRI Study of Normal Brain Development can be found at http://pediatricmri.nih.gov/nihpd/info. Each participant was scanned three times, two years apart. Following collection, imaging and behavioural data was stored on a customized database at the Montreal Neurological Institute (MNI).

For this study, only timepoints where age, gender, height and weight (used to calculate BMI) were available and where cortical thickness data passed quality control, were used. This resulted in 378 subjects and 716 datapoints (395 female, 109 overweight, 95 obese according to the CDC guidelines for children and adolescents). Racial distribution in the original sample was 11% Black or African American, 12% Hispanic, 72% White and 5% Other (Evans, 2006). At time point one racial distribution in the subset used in this study was 9.9% Black or African American, 12.5% Hispanic, 76.0% White and 14% Other. At the second time point racial distribution was 10.5% Black or African American, 10.5% Hispanic, 75.7% White and 13.8% Other. At the third time point the distribution was 10.1% Black or African American, 13% Hispanic, 74.5% White and 15.4% Other.

MRI Acquisition and Image Processing Protocol

The full MRI Acquisition protocol for the NIH MRI Study of Normal Brain Development can be found at http://pediatricmri.nih.gov/nihpd.info. Briefly, subjects underwent a sagittal T1 weighted 3D RF-spoiled gradient echo sequence covering the entire head with slice thickness of between 1 and 1.5mm. Shorter alternate sequences with 3mm slice thickness were used for subjects who had difficulty holding still for the scan but none of these were used for the current analyses as the lower spatial resolution is deemed inadequate for precise cortical thickness estimation.

The T1 weighted image was then processed using the CIVET (version 1.1.12) image processing pipeline (Ad-Dab'bagh et al., 2006) to compute gray and white matter boundaries and surfaces, which were then used to calculate cortical thickness. Images were first linearly registered to MNI space based on the ICBM152 template. N3 was used to correct for non-uniformity and INSECT, a neural net classifier, was used to classify all voxels into gray matter, white matter and cerebrospinal fluid. CLASP was used to generate 2D inner and outer cortical surfaces, which are formed from deformable polygon meshes with 81942 vertices (where the

cortical thickness is calculated). The meshes were then registered to the ICBM152 template to ensure the vertices line up between participants. Data were smoothed using a surface based 20mm Gaussian kernel. The full details of the CIVET pipeline can be found at http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET.

BMI Calculations

Healthy BMI in children varies substantially with age, meaning that BMI cannot be compared directly between subjects in our database. Instead a percentile for age was calculated based on a standardized growth curve. BMI, BMI Percentile for age and BMI Z-Score for age were calculated by inputting height, weight and age data into EpiInfo 7 from the Centers for Disease Control (CDC) and Prevention (http://wwwn.cdc.gov/epiinfo/7/). The Z-Scores and percentiles were calculated based on the official CDC growth curves.

Cortical Thickness Analysis

Statistical analysis of the cortical thickness data was conducted using SurfStat (Worsley et al, 2004), a statistical toolbox running in Matlab R2012b (The Mathworks, Inc). A mixed-effects model of the effects on cortical thickness of age, gender, BMI Z-Score for age and scanner, as fixed effects, and subject identity as a random effect, was created using the following model:

$$Y = \beta_0 + \beta_1 \text{BMI Z-Score for age} + \beta_2 \text{Age} + \beta_3 \text{Gender} + \beta_4 \text{Scanner} + \text{random (subject)} + \varepsilon \quad (1)$$

Where Y is cortical thickness, β_0 represents the y-intercept, $\beta_{1\text{-}4}$ are the regression coefficients of the variables and ε is an error term. The regression was run at each of the 81924 vertices. A 0.05 false discovery rate (FDR) was used to account for multiple comparisons. This model was run on the full dataset and also on a subset of all subjects older than age twelve.

Two interaction models were also run. In the first, an interaction term between age and BMI Z Score was added to the original model to account for differing effects of BMI on cortical thickness at different ages:

$$Y = \beta_0 + \beta_1 \text{BMI Z-Score for age} + \beta_2 \text{Age} + \beta_3 \text{Gender} + \beta_4 \text{Scanner} + \beta_5 \text{BMI Z-Score for age*Age} + \text{random(subject)} + \varepsilon \quad (2)$$

In the second interaction model, the three way interaction between BMI Z Score, age and gender was tested using the following model:

$$Y = \beta_0 + \beta_1 \text{BMI Z-Score for age} + \beta_2 \text{Age} + \beta_3 \text{Gender} + \beta_4 \text{Scanner} + \beta_5 \text{BMI Z-Score for Age*Age} + \beta_6 \text{Age*Gender} + \beta_7 \text{BMI Z-Score for age*Gender} + \beta_8 \text{Age*BMI Z-Score for Age*Gender} + \text{random(subject)} + \varepsilon \quad (3)$$

This model sought to account for both potential differences in the effect of BMI on cortical thickness with age, and how the effect might change with gender.

Mean cortical thickness was also calculated for each timepoint and a correlation between mean cortical thickness and BMI Z Score for Age was run.

Region of Interest Analysis

Average cortical thickness values for each participant at each time point were extracted for five regions of interest (ROI) thought to be involved in appetite control. The areas, defined by the AAL atlas (Tzourio-Mazoyer et al., 2002), were the left and right insula, the left and right superior frontal dorsolateral region, the left and right superior orbital frontal region, the left and right middle frontal orbital region and the left and right inferior orbital frontal region. These regions were chosen because their gray matter volume has been previously identified as predicting both BMI (Horstmann et al., 2013, 2011) and personality measures that are predictive of BMI (Vainik et al., 2013; Deyoung et al., 2010) in young adults.

The simple, interaction-free multilevel model used earlier (equation 1) was evaluated using SPSS Version 20 (IBM Corp. Armonk, NY) for each ROI independently.

Analysis of Behavioural Effects

Separate multilevel models of cognitive and demographic effects on BMI Z-Score for age were conducted in SPSS 20. All models accounted for the effects of age and gender. Models were created for the Wechsler Abbreviated Scale of Intelligence IQ score, CBCL attention subscale score, Cambridge Neuropsychological Test Automated Battery Intra-Extra Dimensional (IED) Set Shift score and household income. Household income data in the NIH Pediatric Data Repository was binned into brackets, each of which was assigned an ordinal number. For this analysis the household income data was treated as pseudocontinuous. IED was included as a

measure of executive function, different aspects of which have been shown to predict obesity in adults (Vainik et al., 2013).

$$Y = \beta_0 + \beta_1 \text{Behavioural Variable} + \varepsilon \quad (4)$$

Here Y represents BMI Z-Score for Age, β_0 represents the y-intercept, β_1 is the regression coefficient of the variable and ε is the error term. WASI and IED were found to be redundant in the individual models and were removed, so they were not included in the complete model. Based on the results of the single variable analysis a complete model of all the non-redundant variables was created.

$$Y = \beta_0 + \beta_1 \text{Age} + \beta_2 \text{Gender} + \beta_3 \text{Household Income} + \beta_4 \text{CBCL} + \varepsilon \quad (5)$$

Results

No significant correlations were found between cortical thickness and BMI Z Score using FDR multiple comparison correction (Figure 1). A strong negative correlation between age and cortical thickness was found across the entire brain (Figure 2). Males had significantly thicker cortex than females across large portions of the temporal and parietal lobes and the anterior cingulate cortex (Figure 3). No significant interactions were found in either of the interaction models (equations 2 and 3).

When the FDR threshold was lowered to $q = 0.3$ for exploratory purposes there were four regions of correlation between BMI and cortical thickness in the temporal pole, precuneus, occipital lobe and primary sensory cortex. No negative correlations were found (Figure 4). No correlation between mean cortical thickness and BMI Z Score was found. When only children over twelve ($n = 183$, 291 time points) were included in the analysis there were still no significant effects of BMI found on cortical thickness.

No significant results were found in the ROI analysis. The lowest p-value was $p = 0.60$, and was found in the left insula.

In the individual behavioural and cognitive models, IED and WASI were redundant, and no variables showed a significant correlation with BMI Z-score. The lowest p-value was $p = 0.061$, found for the effect of household income. When the remaining variables were entered

into a model together, a significant negative effect of household income was found (F= -0.071, df=417.785, p=0.038).

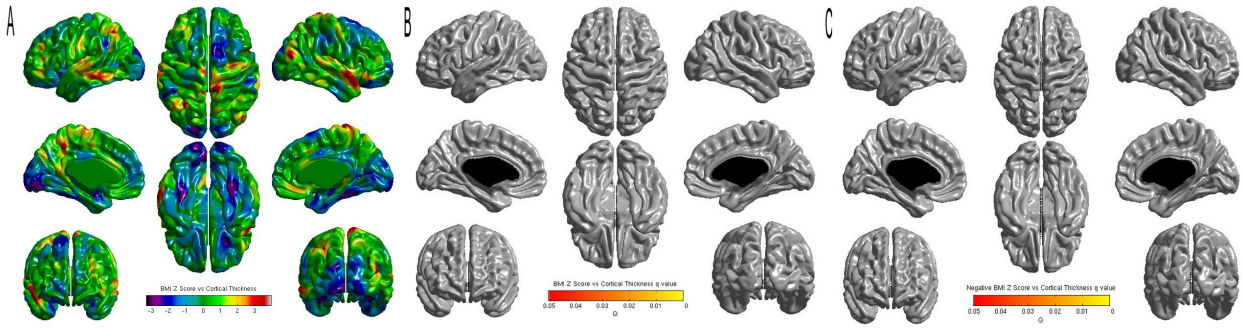

Figure 1. A) Unthresholded correlations between BMI Z-Score for age and cortical thickness across the entire brain, shown here for comparison. Typically T-values of around 4 or greater are needed to reach significance. B) Positive correlations between BMI Z-Score for age and cortical thickness across the entire brain corrected for multiple comparisons with FDR q = 0.05 C) Negative correlations between BMI Z-Score for age and cortical corrected for multiple comparisons with FDR q = 0.05

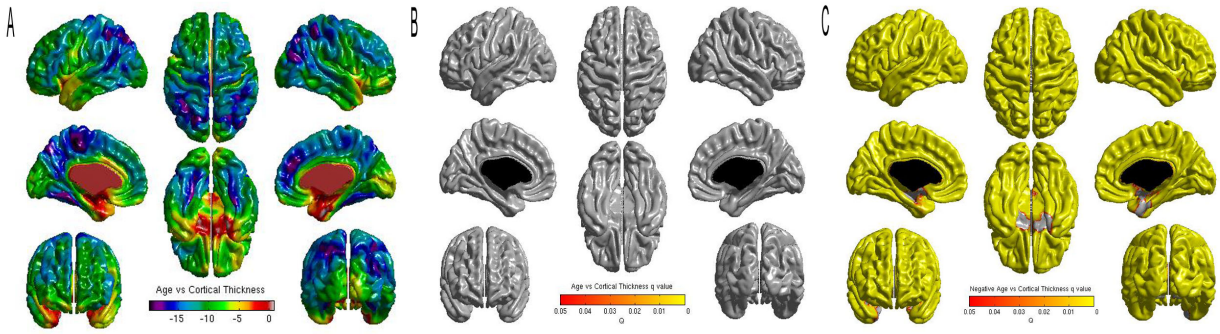

Figure 2. A) Unthresholded correlations between age and cortical thickness across the entire brain, shown here for comparison. B) Positive correlations between age and cortical thickness across the entire brain corrected for multiple comparisons with FDR q = 0.05. C) Negative correlations between age and cortical thickness across the entire brain corrected for multiple comparisons with FDR q = 0.05

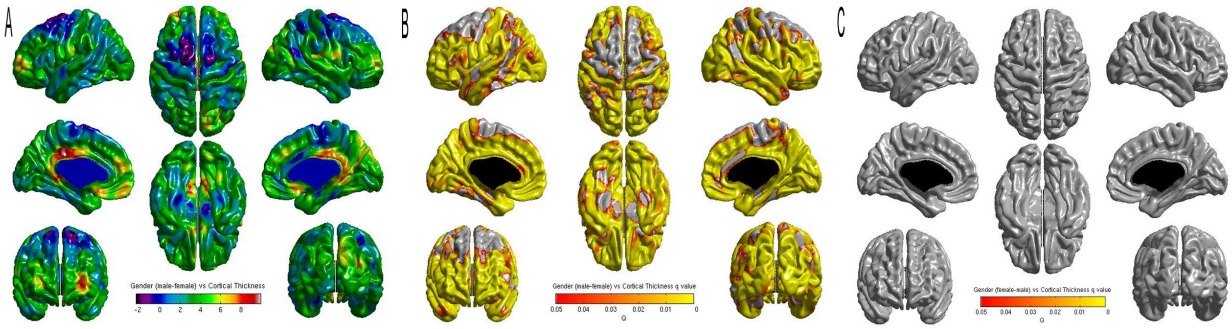

Figure 3. A) Unthresholded correlations between gender (male - female) and cortical thickness across the entire brain, shown here for comparison. B) Positive correlations (male - female) between gender and cortical thickness across the entire brain corrected for multiple comparisons with FDR q = 0.05. C) Negative correlations (female - male) between gender and cortical thickness across the entire brain corrected for multiple comparisons with FDR q = 0.05

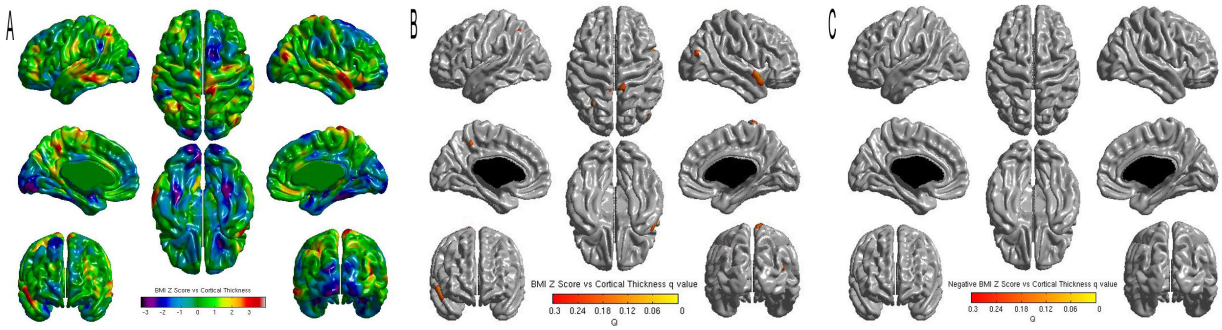

Figure 4. A) Unthresholded correlations between BMI Z-Score for age and cortical thickness across the entire brain, shown here for comparison. Typically T-values of around 4 or greater are needed to reach significance. B) Positive correlations between BMI Z-Score for age and cortical thickness across the entire brain corrected for multiple comparisons with FDR q = 0.3 C) Negative correlations between BMI Z-Score for age and cortical corrected for multiple comparisons with FDR q = 0.3

Discussion

Although there is substantial support for cortical thinning for obese adults and some for older teenagers, we found no association between BMI and cortical thickness in children in this study. A comprehensive power analysis of cortical thickness studies conducted by Pardoe *et al* has found that a sample size of n = 50 is sufficient to detect small cortical thickness differences (less than 0.25mm) (Pardoe et al., 2013). Since our sample is much larger than this, our dataset is likely more at risk of yielding spurious effects than failing to detect real differences. We protected against false positive results by using a false discovery rate of 0.05. The ROI analyses in areas implicated in appetite control failed to detect an effect of BMI on cortical thickness, even when uncorrected for multiple comparisons. The age and gender correlations with cortical thickness identified in this study are also in line with prior research, which supports the overall reliability of our sample and findings (Nguyen et al., 2013; Giedd et al., 1999b, 2006; Pfefferbaum et al., 1994; Jernigan et al., 1991).

The relationship between cortical thickness in prefrontal areas and BMI or weight gain is thought to result from a combination of increased incentive drive and reduced self-control leading to maladaptive decision making with respect to food choices (Horstmann et al., 2011; Vainik et al., 2013). It is most likely the case that, in younger children, other factors are responsible for determining body weight. It could be that both homeostatic satiety mechanisms and parental food choices and meal planning have more influence on food intake. For example, parental control of diet is known to be positively correlated with body weight, and it is hypothesized that rigid external control of meal timing, amount and content by parents may prevent children from learning to attend to internal hunger cues and developing appetite regulation skills. This idea has received some support from existing studies (Birch and Davison, 2001; Crossman et al., 2006; Gray et al., 2007). Differences in satiety between lean and overweight children may also be genetic. Polymorphisms in the FTO gene, which are linked to obesity, have been found to be linked to reduced sensitivity to satiety, which leads to overeating (Wardle et al., 2008). Parental food choices as an environmental factor can also be a major influence on children's weight. Parental choice determines which foods young children have access to, which can cause weight gain when children have reduced access to low energy density foods. Early food access also plays a role in which food children prefer as they develop the ability to make their own food choices (Savage et al., 2008; Scaglioni et al., 2011). Other

environmental factors which have been associated with overweight and obesity in children include high parental weight, low parental education and income and, in girls, low self-esteem(Birch and Davison, 2001; Crossman et al., 2006). One major determinant of weight status for both children and adults is socioeconomic status (SES) (McLaren, 2007). In developed nations, lower SES is associated with higher rates of overweight and obesity due, presumably, to a combination of reduced access to healthy food and fewer opportunities for exercise (McLaren, 2007). Our study replicated this finding.

Impulsivity, and behaviours related to impulsivity are known to be predictive of obesity. Obese adults, especially women, have been shown to exhibit more delay discounting than their lean peers, and increased delay discounting in childhood was correlated with increased BMI as an adult in the Stanford nursery cohort (Schlam et al., 2012; Appelhans et al., 2012; Daniel et al., 2013). A major meta-analysis of neurobehavioural correlates of BMI found that body weight is most strongly influenced by the combined activity of the lateral prefrontal systems mediating executive function and self-control and the striatal network which reacts to novel and rewarding stimuli (Vainik et al., 2013). Obese women, but not obese men, have been show to exhibit a positive correlation between gray matter volume in the putamen and right dorsolateral prefrontal cortex (Horstmann et al., 2011). A study of genetic correlates of body weight found that, in women, a polymorphism near the melanocortin-4-receptor associated with increased body weight was also associated with increased gray matter volume in the amygdala, hippocampus, orbitofrontal cortex and prefrontal cortex, all areas associated with the control of eating and food choice, and with increased scores on the disinhibition scale of the three factor eating questionnaire, and its emotional eating subscale. The same association was not found in men (Horstmann et al., 2013). These endophenotypes may be present in children but may not exert an influence on body weight until late adolescence or early adulthood, when children begin making major food choices for themselves.

If children's weight is determined primarily by external factors then the established cortical thickness effect, which is known to occur in adults, should appear over time as subjects age and develop. This could indicate that as the brain develops, variation in cortical thickness results in variation in regulation of eating behaviour, that different patterns of food consumption affect cortical thickness development, or that both are altered by one or more other factors. A study following children through the transitional period from adolescence to early adulthood,

rather than one which focuses on either period, would be better suited to identifying how associations between weight and cortical thickness emerge during development.

While the age range and diversity of the NIHPD sample allows for very robust conclusions about the population as a whole, it is also possible that the sample's diversity is obscuring associations that are specific to certain demographics. Follow-up studies in selective age groups may reveal specific relationships that are not seen in the general population. Another limitation of this study is that BMI-for-age was used as a measure of obesity. However, BMI does not capture individual variation in fat distribution nor does it differentiate between fat and non-fat mass. In children and adolescents BMI-for-age has been found to have a non-linear relationship with fat mass. BMI was specifically found to be less strongly correlated with fat mass in children with lower body weights (Freedman et al., 2005). Future studies using detailed analyses of body composition such as MR imaging of viscera, which were not available in this dataset, could be used to address the relationship between cortical thickness and fat mass and fat distribution more specifically (Shen et al., 2005). Determining exactly how and when the cortical thickness-obesity relationship emerges could also confirm or disprove our results more robustly, since there is still a chance, despite our high level of statistical power, that an undetectably small effect is present.

Acknowledgements

This research was funded by the CIHR and graduate funding was provided by the Tomlinson Foundation. The authors wish to thank Anton Plavski who helped with the work on this manuscript and Professor Rhonda Amsel and Professor Hsiu-Ting Yu for statistical consultation.

References

Ad-Dab'bagh, Y., Einarson, D., Lyttelton, O., Muehlboeck, J.-S., Mok, K., Ivanov, O., Vincent, R.D., Lepage, C., Lerch, J., Fombonne, E., Evans, A.C., 2006. The CIVET image-processing environment: A fully automated comprehensive pipeline for anatomical neuroimaging research, in: Proceedings of the 12th Annual Meeting of the Organization for Human Brain Mapping, M. Corbetta, Ed.

Appelhans, B.M., Waring, M.E., Schneider, K.L., Pagoto, S.L., DeBiasse, M. a, Debiasse, M. a, Whited, M.C., Lynch, E.B., 2012. Delay discounting and intake of ready-to-eat and away-from-home foods in overweight and obese women. Appetite 59, 576–84. https://doi.org/10.1016/j.appet.2012.07.009

Birch, L.L., Davison, K.K., 2001. Family environmental factors influencing the developing behavioral controls of food intake and childhood overweight. Pediatr. Clin. North Am. 48, 893–907.

Brooks, S.J., Benedict, C., Burgos, J., Kempton, M.J., Kullberg, J., Nordenskjöld, R., Kilander, L., Nylander, R., Larsson, E.-M., Johansson, L., Ahlström, H., Lind, L., Schiöth, H.B., 2013. Late-life obesity is associated with smaller global and regional gray matter volumes: A voxel-based morphometric study. Int. J. Obes. (Lond). 37, 230–6. https://doi.org/10.1038/ijo.2012.13

Crossman, A., Anne Sullivan, D., Benin, M., 2006. The family environment and American adolescents' risk of obesity as young adults. Soc. Sci. Med. 63, 2255–67. https://doi.org/10.1016/j.socscimed.2006.05.027

Daniel, T.O., Stanton, C.M., Epstein, L.H., 2013. The future is now: Comparing the effect of episodic future thinking on impulsivity in lean and obese individuals. Appetite. https://doi.org/10.1016/j.appet.2013.07.010

Deyoung, C.G., Hirsh, J.B., Shane, M.S., Papademetris, X., 2010. Testing predictions from personality neuroscience: Brain structure and the big five. Psychol. Sci. 21, 820–828. https://doi.org/10.1177/0956797610370159.Testing

Evans, A.C., 2006. The NIH MRI study of normal brain development. Neuroimage 30, 184–202. https://doi.org/10.1016/j.neuroimage.2005.09.068

Freedman, D.S., Wang, J., Maynard, L.M., Thornton, J.C., Mei, Z., Pierson, R.N., Dietz, W.H., Horlick, M., 2005. Relation of BMI to fat and fat-free mass among children and adolescents. Int. J. Obes. (Lond). 29, 1–8. https://doi.org/10.1038/sj.ijo.0802735

Giedd, J.N., Blumenthal, J., Jeffries, N., Rajapakse, J.C., Vaituzis, A.C., Liu, H., Berry, Y.C., Tobin, M., Nelson, J., Castellanos, F.X., Jay, N., 1999. Development of the human corpus callosum during childhood and adolescence: A longitudinal MRI study. Prog. Neuropsychopharmacol. Biol. Psychiatry 23, 571–588.

Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, a, Paus, T., Evans, A. C., Rapoport, J.L., 1999. Brain development during childhood and adolescence: A longitudinal MRI study. Nat. Neurosci. 2, 861–3. https://doi.org/10.1038/13158

Giedd, J.N., Clasen, L.S., Lenroot, R., Greenstein, D., Wallace, G.L., Ordaz, S., Molloy, E. a, Blumenthal, J.D., Tossell, J.W., Stayer, C., Samango-Sprouse, C. a, Shen, D., Davatzikos, C., Merke, D., Chrousos, G.P., 2006. Puberty-related influences on brain development. Mol. Cell. Endocrinol. 254–255, 154–62. https://doi.org/10.1016/j.mce.2006.04.016

Gray, V.B., Byrd, S.H., Cossman, J.S., Chromiak, J., Cheek, W.K., Jackson, G.B., 2007. Family characteristics have limited ability to predict weight status of young children. J. Am. Diet. Assoc. 107, 1204–9. https://doi.org/10.1016/j.jada.2007.04.004

Hassenstab, J.J., Sweet, L.H., Del Parigi, A., McCaffery, J.M., Haley, A.P., Demos, K.E., Cohen, R. a, Wing, R.R., 2012. Cortical thickness of the cognitive control network in obesity and successful weight loss maintenance: a preliminary MRI study. Psychiatry Res. 202, 77–9. https://doi.org/10.1016/j.pscychresns.2011.09.008

Ho, A.J., Raji, C. a, Becker, J.T., Lopez, O.L., Kuller, L.H., Hua, X., Lee, S., Hibar, D., Dinov, I.D., Stein, J.L., Jack, C.R., Weiner, M.W., Toga, A.W., Thompson, P.M., 2010. Obesity is linked with lower brain volume in 700 AD and MCI patients. Neurobiol. Aging 31, 1326–39. https://doi.org/10.1016/j.neurobiolaging.2010.04.006

Horstmann, A., Busse, F.P., Mathar, D., Müller, K., Lepsien, J., Schlögl, H., Kabisch, S., Kratzsch, J., Neumann, J., Stumvoll, M., Villringer, A., Pleger, B., 2011. Obesity-Related differences between women and men in brain structure and goal-directed behavior. Front. Hum. Neurosci. 5, 58. https://doi.org/10.3389/fnhum.2011.00058

Horstmann, A., Kovacs, P., Kabisch, S., Boettcher, Y., Schloegl, H., Tönjes, A., Stumvoll, M., Pleger, B., Villringer, A., 2013. Common genetic variation near MC4R has a sex-specific impact on human brain structure and eating behavior. PLoS One 8, e74362. https://doi.org/10.1371/journal.pone.0074362

Jernigan, T.L., Trauner, D. a, Hesselink, J.R., Tallal, P. a, 1991. Maturation of human cerebrum observed in vivo during adolescence. Brain 114 (Pt 5, 2037–49.

Kuczmarski, R.J., Ogden, C.L., Guo, S.S., Grummer-Strawn, L.M., Flegal, K.M., Mei, Z., Wei, R., Curtin, L.R., Roche, A.F., Johnson, C.L., 2002. 2000 CDC growth charts for the United States: Methods and development., Vital and health statistics. Series 11, Data from the national health survey.

Maayan, L., Hoogendoorn, C., Sweat, V., Convit, A., 2012. Disinhibited eating in obese adolescents in associated with orbtofrontal volume reductions and executive dysfunction. Obesity (Silver Spring). 19, 1382–1387. https://doi.org/10.1038/oby.2011.15.Disinhibited

Marqués-Iturria, I., Pueyo, R., Garolera, M., Segura, B., Junqué, C., García-García, I., José Sender-Palacios, M., Vernet-Vernet, M., Narberhaus, A., Ariza, M., Jurado, M.Á., 2013. Frontal cortical thinning and subcortical volume reductions in early adulthood obesity. Psychiatry Res. 1–7. https://doi.org/10.1016/j.pscychresns.2013.06.004

McLaren, L., 2007. Socioeconomic status and obesity. Epidemiol. Rev. 29, 29–48. https://doi.org/10.1093/epirev/mxm001

Nguyen, T.-V., McCracken, J.T., Ducharme, S., Cropp, B.F., Botteron, K.N., Evans, A.C., Karama, S., 2013. Interactive effects of dehydroepiandrosterone and testosterone on cortical thickness during early brain development. J. Neurosci. 33, 10840–8. https://doi.org/10.1523/JNEUROSCI.5747-12.2013

Pannacciulli, N., Del Parigi, A., Chen, K., Le, D.S.N.T., Reiman, E.M., Tataranni, P. a, 2006. Brain abnormalities in human obesity: A voxel-based morphometric study. Neuroimage 31, 1419–25. https://doi.org/10.1016/j.neuroimage.2006.01.047

Pannacciulli, N., Le, D.S.N.T., Chen, K., Reiman, E.M., Krakoff, J., 2007. Relationships between plasma leptin concentrations and human brain structure: A voxel-based morphometric study. Neurosci. Lett. 412, 248–53. https://doi.org/10.1016/j.neulet.2006.11.019

Pardoe, H.R., Abbott, D.F., Jackson, G.D., 2013. Sample size estimates for well-powered cross-sectional cortical thickness studies. Hum. Brain Mapp. 34, 3000–9. https://doi.org/10.1002/hbm.22120

Pfefferbaum, A., Mathalon, D.H., Sullivan, E. V, Rawles, J.M., Zipursky, R.B., Lim, K.O., 1994. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch. Neurol. 51, 874–887.

Reiss, A. L., Abrams, M.T., Singer, H.S., Ross, J.L., Denckla, M.B., 1996. Brain development, gender and IQ in children. A volumetric imaging study. Brain 119 (Pt 5, 1763–74.

Savage, J.S., Fisher, J.O., Birch, L.L., 2008. Parental Influence on Eating Behaviour. J Law Med Ethics 35, 22–34. https://doi.org/10.1111/j.1748-720X.2007.00111.x.Parental

Scaglioni, S., Arrizza, C., Vecchi, F., Tedeschi, S., 2011. Determinants of children's eating behavior. Am. J. Clin. Nutr. 94, 2006S–2011S. https://doi.org/10.3945/ajcn.110.001685

Schlam, T.R., Wilson, N.L., Shoda, Y., Mischel, W., Ayduk, O., 2012. Preschoolers' delay of gratification predicts their body mass 30 years later. J. Pediatr. 10–13. https://doi.org/10.1016/j.jpeds.2012.06.049

Shen, W., Liu, H., Punyanitya, M., Chen, J., Heymsfield, S.B., 2005. Pediatric obesity phenotyping by magnetic resonance methods. Curr. Opin. Clin. Nutr. Metab. Care 8, 595–601. https://doi.org/10.1097/01.mco.0000171150.49248.14

Taki, Y., Kinomura, S., Sato, K., Inoue, K., Goto, R., Okada, K., Uchida, S., Kawashima, R., Fukuda, H., 2008. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. Obesity (Silver Spring). 16, 119–24. https://doi.org/10.1038/oby.2007.4

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273–89. https://doi.org/10.1006/nimg.2001.0978

Vainik, U., Dagher, A., Dubé, L., Fellows, L.K., 2013. Neurobehavioural correlates of body mass index and eating behaviours in adults: a systematic review. Neurosci. Biobehav. Rev. 37, 279–99. https://doi.org/10.1016/j.neubiorev.2012.11.008

Wardle, J., Carnell, S., Haworth, C.M. a, Farooqi, I.S., O'Rahilly, S., Plomin, R., 2008. Obesity associated genetic variation in FTO is associated with diminished satiety. J. Clin. Endocrinol. Metab. 93, 3640–3. https://doi.org/10.1210/jc.2008-0472

Yau, P.L., Castro, M.G., Tagani, A., Tsui, W.H., Convit, A., 2012. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics. https://doi.org/10.1542/peds.2012-0324

Yau, P.L., Kang, E.H., Javier, D.C., Convit, A., 2011. Preliminary evidence of cognitive and brain abnormalities in uncomplicated adolescent obesity. Obesity (Silver Spring). 18, 1492–1501. https://doi.org/10.1016/j.str.2010.08.012.Structure

Yokum, S., Ng, J., Stice, E., 2012. Relation of regional gray and white matter volumes to current BMI and future increases in BMI: a prospective MRI study. Int. J. Obes. (Lond). 36, 656–64. https://doi.org/10.1038/ijo.2011.175

Mesolimbic Connectivity Signatures of Impulsivity and BMI in Early Adolescence

Rachel J Sharkey[a], Josiane Bourque[b], Kevin Larcher[a], Bratislav Mišić[a], Yu Zhang[a], Ayca Altınkaya[a], Abbas Sadikot[a], Patricia Conrod[b,c], Alan C. Evans[a], Hugh Garavan[d], Marco Leyton[e], Jean R. Séguin[b], Robert Pihl[f], Alain Dagher[a]

[a]Montreal Neurological Institute, McGill University, Montreal, QC, Canada, [b]CHU Hospital Ste-Justine, Université de Montreal, Montreal, QC, Canada, [c]Institute of Psychiatry, Psychology and Neuroscience, Kings College, London, United Kingdom, [d]Department of Psychiatry, University of Vermont, Burlington, Vermont, United States, [e]Department of Psychiatry, McGill University, Montreal, QC, Canada, [f]Department of Psychology, McGill University, Montreal, QC, Canada

Corresponding Author:

Rachel J Sharkey
rachel.sharkey.j@gmail.com
3801 University Street. Room NW253
Montreal QC, H3A 2B4
Canada

Conflicts of Interest: The authors have no conflicts of interest to declare.

Keywords: Adolescence, Impulsivity, Sensation-Seeking, BMI, Resting state fMRI

Word Count in Abstract: 275
Figures and Tables: 4 Figures, 3 Tables

Supplementary Figures and Tables: 2 Tables

Published in Appetite 2018 Sept 29; 132: 25-36. Doi: 10.1016/j.appet.2018.09.019.

Preface

Based on the negative findings of the first study early adolescence was identified as a promising age for studying early neural correlates of weight. Early adolescence is a period where, in addition to the developmental changes that accompany puberty, children also undergo rapid social and neurological development, which includes greatly increased independence, including independent food choices.

During adolescence, there is also a well characterized increase in impulsive behaviour and decision making (Collado et al., 2014). This is understood to be a normal aspect of development, however, increased impulsivity puts adolescents at an increased risk of weight gain and becoming overweight and obese (Duckworth et al., 2010; Kelly et al., 2016; Maayan et al., 2012). Increased impulsivity and sensation-seeking, and reduced conscientiousness have been previously established to be related to obesity in earlier studies (Vainik et al., 2013).

The most popular model for explaining increased impulsivity in adolescents, the Dual Systems Model, relates increased impulsivity and sensation-seeking to an imbalance in responses from the early-maturing, and so, relatively fully-developed midbrain and striatum, and the later maturing prefrontal cortex, as well as the white matter tracts that connect the two (Shulman et al., 2016; Steinberg, 2010). This corticostriatal network has also been independently associated with control of appetite and food consumption (Maayan et al., 2012; Ulrich et al., 2016).

This study involved resting state functional MRI from 116 young adolescents, oversampled for impulsive and sensation-seeking traits based on scores on the Substance Use Risk Profile Scale. We used a multivariate technique, partial least squares correlation, to identify relationships between impulsivity, sensation-seeking and body weight and resting state connectivity of two regions from the basal ganglia (the ventral striatum and sub-thalamic nucleus) and two dopaminergic nuclei from the midbrain (the ventral tegmental area and the substantia nigra), with the hypothesis that the weight and personality variables would be related to changes in connectivity between the regions of interest and regions in the prefrontal cortex.

However, the results did not support the original corticostriatal analysis and instead identified a network centered around the connectivity between the midbrain, basal ganglia and the limbic system, primarily the hippocampus, amygdala and parahippocampal cortex. This

network was differentially associated with sensation-seeking, as compared to impulsivity and body mass index.

The limbic system has also been previously implicated in both impulsivity and control of appetite and body weight, and there is previous literature associating it specifically with impulsivity in the context of adolescent development (Ernst, 2014; Stevenson and Francis, 2017). These findings seem to support a more complex view of the neuroscience of adolescent impulsivity and emphasize the role of the limbic system in both increased impulsivity and increased weight.

Abstract

Across age groups, differences in connectivity of the mesolimbic and the prefrontal cortex co-vary with trait impulsivity and sensation-seeking. Impulsivity and sensation-seeking are also known to increase during early adolescence as maturation of subcortical structures outpaces that of the prefrontal cortex. While an imbalance between the striatum and prefrontal cortex is considered a normal developmental process, higher levels of adolescent impulsivity and sensation-seeking are associated with an increased risk for diverse problems, including obesity.

To determine how the relationship between sensation-seeking, impulsivity and body mass index (BMI) is related to shared neural correlates we measured their relationships with the connectivity of nuclei in the striatum and dopaminergic midbrain in young adolescents. Data were collected from 116 children between the ages of 12 and 14, and included resting state functional magnetic resonance imaging, personality measures from the Substance Use Risk Profile Scale, and BMI Z-score for age. The shared variance for the connectivity of regions of interest in the substantia nigra, ventral tegmental area, ventral striatum and sub-thalamic nucleus, personality measures and BMI Z-score for age, were analyzed using partial least squares correlation.

This analysis identified a single significant striato-limbic network that was connected with the substatia nigra, ventral tegmental area and sub-thalamic nuclei ($p = 0.002$). Connectivity within this network which included the hippocampi, amygdalae, parahippocampal gyri and the regions of interest, correlated positively with impulsivity and BMI Z-score for age and negatively with sensation-seeking. Together, these findings emphasize that, in addition to the well-established role that frontostriatal circuits play in the development of adolescent personality traits, connectivity of limbic regions with the striatum and midbrain also impact impulsivity, sensation-seeking and BMI Z-score in adolescents.

Introduction

Adolescence is a developmental period that is characterized, in part, by an increased propensity towards impulsivity (IMP)[1] and sensation-seeking (SS). IMP can be defined as an increased tendency to prioritize short-term rewards over long-term goals, and to act without considering consequences. SS is defined as the desire to seek out new experiences and intense sensations (Christakou et al., 2011; Collado et al., 2014; Duckworth and Kern, 2012; Galvan et al., 2006; Liston et al., 2006; Rubia et al., 2007, 2006; Woicik et al., 2009).

During adolescence, the subcortical and limbic systems develop an adult-like response to task stimuli earlier than the frontal lobes (Braams et al., 2015; Casey et al., 2016; Chick, 2015; Christakou et al., 2011; Collado et al., 2014; Shulman et al., 2016; Steinberg, 2010, 2004; Strang et al., 2013). Subcortical systems, innervated by mesolimbic dopamine projections, include the striatum, amygdala and hippocampus, and their interconnected cortical areas, and are involved in the neural and behavioral response to reward predicting cues. Reward-related tasks provoke greater BOLD response in the faster-maturing mesolimbic regions, as compared to the prefrontal system, possibly creating an imbalance in reward evaluation, which correlates with higher levels of SS and IMP (Braams et al., 2015; van Duijvenvoorde et al., 2016). It is hypothesized that immaturity of prefrontal regions and their white matter connections is associated with a relative inability of these regions to modulate cue responses in mesolimbic areas is associated with impulsive responding, compared to the adult brain. This is referred to as the dual systems model of adolescent development (Collado et al., 2014; Shulman et al., 2016; Steinberg, 2010; Strang et al., 2013). It has been suggested that the reduction in impulsivity that occurs during the transition from adolescence to adulthood may be due in part to maturation of the frontostriatal and frontolimbic white matter connections (Christakou et al., 2011, 2009).

[1] Abbreviations: Impulsivity (IMP), Sensation-Seeking (SS), Substantia Nigra (SN), Ventral tegmental area (VTA), Ventral Striatum (VS), Sub-Thalamic Nucleus (STN), Substance Use Risk Profile Scale (SURPS), Anxiety Sensitivity (AS), BMI Z-Score for Age (BMIZ), Family Affluence Scale (FAS), resting state functional MRI (rsfMRI), FMRIB's Software Library (FSL), Independent Component Analysis (ICA), Partial Least Squares (PLS)

The mesolimbic and mesostriatal systems originate in two dopaminergic midbrain nuclei, the substantia nigra (SN) and ventral tegmental area (VTA) (Gaspar et al., 1992). The SN and VTA have direct connections with the striatum, amygdala, and hippocampus, among other regions (Mizumori and Tryon, 2015). The dopaminergic midbrain, along with the ventral striatum (VS), ventral prefrontal regions and anterior cingulate cortex are involved in reward prediction error and salience processing (Aron et al., 2004; Lohani et al., 2016; Menon, 2015; Zhang et al., 2015). The degree of dopamine signalling from the midbrain to the VS has been previously correlated with trait IMP (Buckholtz et al., 2010). The human SN and VTA are difficult to dissociate structurally in anatomical MRI scans due to their small size and proximity, and are both involved in reward processing and IMP. However, they have also been found to connect to different parts of the frontal-subcortical network (Düzel et al., 2009; Murty et al., 2014). The functional connectivity patterns of the VTA and SN have also been found to change over the course of adolescence, with the prefrontal connectivity of the VTA increasing, and the overall connectivity of the SN decreasing with age (Tomasi and Volkow, 2014).

The sub-thalamic nucleus (STN) is another subcortical nucleus involved, more specifically, in the motor inhibition component of IMP. Lesions of the STN have been found to cause motor IMP (Jahanshahi et al., 2015). The STN is connected to both the supplementary motor cortex, the VS and anterior cingulate cortex. Resting-state connectivity between the STN and the VS-anterior cingulate cortex network has been found to be negatively correlated with IMP and to be reduced in patients with alcohol use disorders (Morris et al., 2015).

The increase in IMP and SS that commonly occurs during early adolescence is believed to be a normal part of development (Shulman et al., 2016; Steinberg, 2010, 2004). However, IMP is also associated with a number of poor outcomes, including increased risk of excessive weight gain and obesity. This association has been seen in in both directions: children and adolescents who demonstrate a high level of IMP are at greater risk for obesity during adolescence and adulthood, and obese patients have higher levels of IMP (Appelhans et al., 2012; Casey et al., 2011; Conrod et al., 2011, 2008; Duckworth et al., 2010; Eigsti et al., 2006; Francis and Susman, 2009; MacPherson et al., 2010; Mischel et al., 1989, 1988; Mitchell and Potenza, 2014; Schlam et al., 2012; Steinberg, 2004; Tsukayama et al., 2010).

Structural and functional fronto-subcortical and mesolimbic connectivity have been negatively correlated with both increased BMI and increased IMP (Black et al., 2015; Calluso et

al., 2015; Casey et al., 2011; Christakou et al., 2011, 2009; Fuentes-Claramonte et al., 2016; Krmpotich et al., 2013; Leong et al., 2016; Morris et al., 2015; Park et al., 2015; Somerville et al., 2011; van den Bos et al., 2015; Whelan et al., 2012; Zhang and Li, 2013). Increased fronto-striatal connectivity is also correlated with age in studies comparing adolescents and young adults (Adleman et al., 2002; Christakou et al., 2011, 2009; Liston et al., 2006; Somerville et al., 2011; Van Den Bos et al., 2012).

This study aimed to identify neural correlates shared between IMP, SS and BMI in early adolescence. Their resting-state functional connectivity correlates were investigated in a sample of healthy young adolescents which is enriched for IMP and SS, using seeds placed in the VS the STN, the SN and the VTA. While the connections of the ventral striatum have been previously fairly well-studied, the addition of the other regions of interest will provide a more complete model of this system. It was hypothesized that, in accordance with the dual-systems model of adolescent IMP and existing connectivity studies, connectivity of dopaminergic nuclei would correlate with IMP and BMI Z-score for age.

Methods

Participants

Neuroventure

Neuroventure is an ongoing longitudinal study of the neurological development of adolescents in relation to IMP, SS, and alcohol use. It is an imaging add-on to the larger Coventure trial, which is testing the effects of a personality trait-specific psychological intervention on reducing the incidence of alcohol use problems in adolescents (Bourque et al., 2016; Conrod et al., 2008; O'Leary-Barrett et al., 2017). The Neuroventure cohort consists of 151 adolescents aged 12 to 14 at entry, free of neurological or psychiatric illness. Participants were selected from three groups: high SS participants and high IMP participants who had a IMP and/or SS score on the Substance Use Risk Profile Scale (SURPS) greater than 1 SD above the mean for their school, and control participants who scored within 1 SD of their school mean on both IMP and SS scores. These participants will be imaged a total of three times and followed for five years. The present paper reports imaging results from the 1st time point and BMI Z-score for age results from the 1st and 2nd , which was collected 24 months later (Bourque et al., 2016).

Final sample

The final sample included in this study consists of 116 participants. Six participants were excluded from the entire sample due to incidental findings on MRI including enlarged ventricles or arachnoid cysts, five were excluded due to missing BMI data, and nine did not complete the full imaging session. Of the remaining 116 participants, 55 were male, 61 were female, with an average age of 13.6 years (163.1±7.8 months) at time point 1. For the following analysis, the whole sample was treated as single group enriched for the variables of interest.

Demographic and behavioural data

Substance Use Risk Profile Scale

Each participant completed the Substance Use Risk Profile Scale (SURPS), which consists of 4 subscales, each measuring one aspect of personality related to risk for drug and alcohol use problems: hopelessness, anxiety sensitivity, SS and IMP (Krank et al., 2011; Woicik et al., 2009). IMP and SS are features more closely related to the causes of adolescent drinking and to excessive weight gain and were the subscales used in the current study (Bourque et al., 2016; Jurk et al., 2015; MacPherson et al., 2010; Moreno-Lopez et al., 2016).

Body mass index and z-score for age

Height and weight were measured before scanning and used to calculate BMI. Participants self-reported their date of birth.

BMI was converted into an age-related z-score based on the standardized CDC growth curves for each subject using EpiInfo (http://www.cdc.gov/epiinfo/7/). The use of BMI Z-score for age (BMIZ) allows comparisons between children of different ages (Kuczmarski et al., 2002).

For each of the participants in the final sample who completed the first follow-up time point at 24 months, BMI and BMIZ were calculated as above. The change in BMI and BMIZ were calculated by subtracting the first time point from the second. The rate of change in BMI and BMIZ were calculated by dividing the difference values by the number of days between the two measurements.

Parental body mass index

The height and weight of the parent who accompanied the subject to the MRI scanning session was available for 74 of the participants at the first time point and 93 at the second. 70% of the accompanying parents were female at the first time point, and 67% were female at the second time point. Height and weight were used to calculate parental BMI.

Family Affluence Scale

The family affluence scale (FAS) assesses the family socio-economic status of teenagers, based on items such as the number of cars and computers the family possesses, the amount of pocket money the teenager has access to and if they have their own bedroom. The FAS has been validated as an accurate measure of socioeconomic status (Boyce et al., 2006; Currie et al., 2008). It was administered to all participants in the Coventure trial. Complete FAS data was available in 113 of the 116 Neuroventure participants included in this analysis.

MRI Data collection

Resting state functional magnetic resonance imaging (rsfMRI) data from Neuroventure was collected as one of a series of MRI acquisitions in a single session. All scans were collected on a Siemens Trio 3.0T scanner. RsfMRI was collected in a single 6-minute run of 152 volumes of 40 axial slices with 3.5mm isotropic voxels in a 224mm FOV (TE = 30ms, TR = 2340ms). Participants were instructed to close their eyes. Acquisition order of the resting state data was changed over the course of the study to improve compliance. The resting state acquisition was initially placed last in the acquisition sequence following to task based fMRI acquisitions and a diffusion tensor acquisition. Due to issues with participants falling asleep, it was later moved to before the diffusion tensor acquisition. Five participants had their resting state acquisition performed before both the task based fMRI and diffusion tensor acquisitions due to an error in the acquisition. There is no relationship between group assignment and scan order.

Also, a high-resolution T1-weighted anatomical image was collected using a MPRAGE sequence (192 sagittal slices, 1.0mm isotropic voxel, 256mm FOV, TE = 2.96ms, TR = 2300 ms).

MRI Data preprocessing

FEAT Preprocessing

Basic rsfMRI data preprocessing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following pre-statistics processing was applied; motion correction using the MCFLIRT tool (Jenkinson et al., 2002); slice-timing correction using Fourier-space time-series phase-shifting; non-brain removal using the BET tool (Smith, 2000); grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor.

Registration

Registration to high-resolution structural and standard space images was carried out using FLIRT, also part of the FEAT toolbox (Jenkinson et al., 2002; Jenkinson and Beckmann, 2001).

Band-pass filtering

Deobliquing and bandpass filtration between 0.1 and 0.01 Hz were carried out using the AFNI 3drefit and 3dFourier tools (Cox, 1996; Cox and Hyde, 1997).

Smoothing

Smoothing was done using a 6mm kernel using fslmaths, part of FSL (www.fmrib.ox.ac.uk/fsl). This degree of smoothing has been previously used by studies focusing on midbrain regions of interest (Tomasi & Volkow, 2014; Murty et. al., 2014; Zhang et. al., 2015).

Detrending

Data for each subject were demeaned. The mean for each subject was calculated using fslmaths, part of FSL. The mean trend was subtracted voxelwise from the image using the AFNI 3dDetrend tool, and the mean value was added back to the data using the AFNI 3dcalc tool, to restore the original mean value (Cox, 1996; Cox and Hyde, 1997).

Nuisance regression of white matter and CSF signals

Seeds for the ventricles and white matter were taken from the avg152T1 SPM canonical template resized to 2mm voxels and eroded using a spherical voxel of 0.1mm to reduce the risk of overlap with non-ventricle or non-white matter voxels. The mean timeseries for each of the two seeds was extracted for each subject using the 'fslmeants' command from FSL (www.fmrib.ox.ac.uk/fsl). Time-series statistical analysis was carried out using FILM, part of FSL (www.fmrib.ox.ac.uk/fsl) with local autocorrelation correction (Woolrich et al., 2001). The white matter and ventricular time-series were both entered as regressors. The residuals image from this regression was used in subsequent analyses.

Independent component analysis based denoising

Independent component analysis (ICA) based denoising was carried out using the ICA based Automatic Removal of Motion Artifacts (ICA-AROMA) toolbox, which is part of the FSL library. ICA-AROMA uses a predetermined set of conservative criteria to classify component networks as noise, which are regressed out of the final image (Pruim et al., 2014a, 2014b).

Analysis was carried out using Probabilistic ICA (Beckmann and Smith, 2004) as implemented in Multivariate Exploratory Linear Decomposition into Independent Components Version 3.14, part of FSL. The following data pre-processing was applied to the input data; masking of non-brain voxels; voxel-wise de-meaning of the data; normalization of the voxel-wise variance. Probabilistic ICA generates a set of spatial independent components (brain maps) and their associated time-courses and power spectra.(Beckmann and Smith, 2004).

ICA-AROMA then identifies the independent components that represent motion artifacts using a predetermined classifier. The classifier applies the following rules: high edge fraction (signal near tissue boundaries in the brain), correlation with head realignment parameters from motion correction, large signal in CSF (> 10%), and high-frequency content (> 35%). Motion-associated components are then removed via linear regression (Pruim et al., 2014b).

Seed selection

Ventral Striatum Seed

The VS seed was taken from the 17-network version of the Choi functional connectivity atlas of the human striatum (Choi et al., 2012). This atlas assigns each striatal voxel based on its functional connectivity with frontal networks. The VS is defined by functional connectivity to limbic regions, especially the orbitofrontal cortex.

The VS region (region 10 in the Choi atlas) was extracted, resized to 2mm resolution and eroded using an 0.1mm spherical kernel using tools from the fslmaths toolbox (www.fmrib.ox.ac.uk/fsl). The left and right VS regions were separated using the FSLView toolbox (Figure 1).

Substantia Nigra and Sub-Thalamic Nucleus Seeds

The SN and STN seeds were taken from a probabilistic structural atlas created by Keuken and Forstmann based on 7T MRI scans (Keuken and Forstmann, 2015). The very high resolution of the 7T scans allow for the delineation of structures that are difficult to identify in standard atlases. Based on structural MRI scans from thirty 24-year olds, the nuclei of the basal ganglia were manually segmented by two raters for each scan independently. The scans were combined in standard space to create a probabilistic map of each of the nuclei.

The SN and STN seeds at a 33% threshold were both resized to 2mm resolution and binarized. The SN seed was eroded using an 0.1mm spherical kernel using tools from the fslmaths toolbox (www.fmrib.ox.ac.uk/fsl). The STN Seed was not eroded as the size and shape

of the seed meant that all voxels would have been removed by spherical erosion. Voxels overlapping between the SN and STN were masked out of the STN seed. The left and right halves of the resulting masks were separated using FSLView (Figure 1).

Ventral Tegmental Area Seed

The VTA seed was derived from the histological images of the BigBrain Project based on midbrain anatomy in the right hemisphere. The BigBrain is a 3D cytoarchitectonic dataset created from histological data from a sliced and stained brain which was then registered to MNI ICBM 152 space (Amunts et al., 2013).

The VTA is composed of five subnuclei; the parabrachial pigmented, the paranigral nucleus, the interfascicular nucleus, the rostral linear nucleus and central linear nucleus (Halliday and Törk, 1986; Oades and Halliday, 1987; Olszewski and Baxter, 1954; Swanson, 1982). We defined VTA borders using neighboring structures and we included all five VTA subnuclei. The borders were drawn by experienced neuroanatomists familiar with this region using display (https://mcin-cnim.ca/technology/visualization/display/) and Atelier3D (https://mcin-cnim.ca/technology/visualization/atelier3d/).

The image was resized to 2mm resolution. The FSL T1 standard image was used as a mask to remove voxels overlapping with CSF. To remove overlap between the VTA and SN a mask of overlapping voxels between the VTA and SN seeds was created and those voxels were subtracted from the VTA mask using the fslmaths toolbox. To generate a left VTA seed, the orientation of the seed was inversed in the X direction (Figure 1).

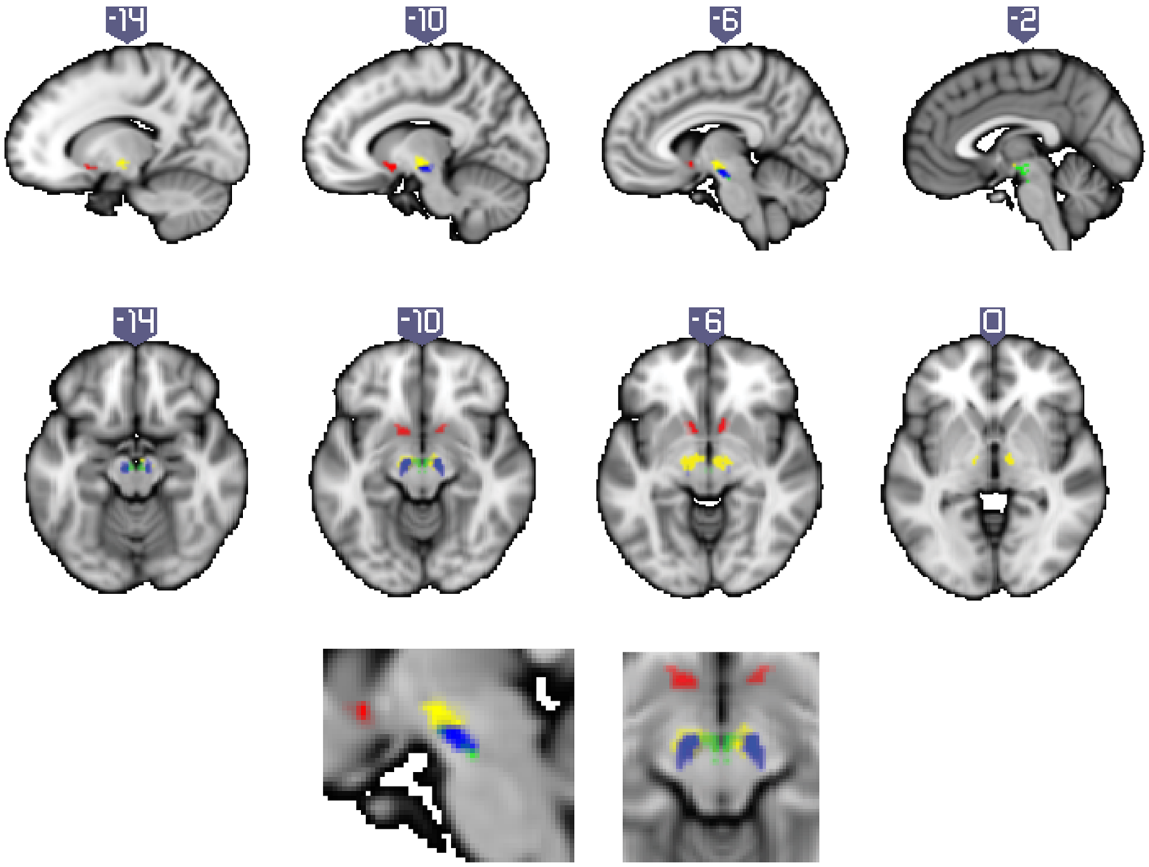

Figure 1. Location of the four regions of interest. The substantia nigra is indicated in blue. The ventral tegmental area is indicated in green. The sub-thalamic nucleus is indicated in yellow. The ventral striatum is indicated in red.

Masking

A whole-brain, standard-space mask based on the output from the CIVET pipeline (Ad-Dab'bagh et al., 2006) was generated for each subject using fslmaths (www.fmrib.ox.ac.uk/fsl) and summed to create a minimal mask for all participants. The minimal mask was applied to each subject in order to include only voxels present in every subject in the analysis.

Subject level analysis

For each subject, the average time-course of each of the four seeds (SN, VTA, VS and STN) was extracted for each hemisphere using tools from the fslmaths toolbox (www.fmrib.ox.ac.uk/fsl). A whole-brain functional connectivity map was generated for each seed region by calculating Pearson correlation coefficients between each seed-timecourse and every grey matter voxel in the residualized maps following motion correction and CSF and white matter regression, based on the ICBM152 atlas. The resultant 3D correlation coefficient maps were converted into Z-scores using Fisher z-transformation. These z-score maps were used in subsequent analyses.

Group level analysis

Personality and Demographic Correlations

A Pearson correlation was run in Matlab between SURPS-IMP, SURPS-SS, BMIZ, FAS Score, age in months and gender, dummy coded as a binary variable.

Regression Analysis

Group level regression analysis of the data was carried out using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The details of the regression analysis, and the results can be found in the supplementary data.

Partial Least Squares Correlation

Focused Partial Least Squares Correlation

A partial least squares (PLS) correlation was conducted using the seed-voxel correlations and the three personality and BMI variables of interest, IMP, SS, and BMI Z-score for age. PLS correlations extract latent variables which explain the covariance between two sets of data. Unlike a linear regression PLS is robust to collinearity, allowing for the correlated personality and BMI variables of interest, and the closely related seed regions, to be considered together (Krishnan et al., 2011; Sawatsky et al., 2015). The PLS analysis was performed using the Baycrest Lab PLS package in MATLAB (Mathworks Inc; https://www.rotman-

baycrest.on.ca/index.php). The PLS correlation was performed as a regular behaviour PLS (option 3 in the Baycrest software), with 10,000 permutations and 2,000 bootstrapping samples.

PLS creates a dimensionally reduced regression test of the shared variance between two sets of data, in the form of the correlation between two matrices, one containing the brain connectivity data and the other the BMIZ and personality data, which is subjected to singular value decomposition. This results in set of singular values, ranked proportionally to the amount of variance they explain, and a pair of orthogonal matrices representing the contributions of the original two tables.

The permutation testing was conducted by randomly permuting the data in the connectivity table, and recalculating the singular value decomposition. The significance represents the proportion of singular values which are greater than the original.

Bootstrapping tests the reliability of the contributions of the connectivity and BMI and personality values. Rows from the original tables were resampled with replacement and the correlation table and singular value decompositions were repeated on the resampled tables. The ratio of the original weight and its bootstrap standard error (called the bootstrap ratio) indicate the strength and stability of each contribution. For a more detailed explanation of PLS correlations refer to Misic et al 2016.

PLS was initially performed with one matrix composed of the three personality and BMI variables from the regression analysis (BMIZ, SURPS-IMP and SURPS-SS scores for each subject) and one matrix composed of the concatenated seed-voxel correlation z-maps for each seed. To reduce the computational demands of the analysis the voxel-wise results were fitted to a composite atlas (Zeighami et al., 2015). The atlas is comprised of cerebral regions from the Hammers atlas, cerebellar segmentation from the Diedrichsen atlas, and manual segmentation of the SN, STN and red nucleus based on the BigBrain, the subject high-resolution T1 scan and the Duvernoy brainstem atlas (Amunts et al., 2013; Diedrichsen et al., 2009; Hammers et al., 2003; Zeighami et al., 2015). The voxels inside each atlas region were averaged using fslmaths (www.fmrib.ox.ac.uk/fsl) to produce a single correlation value with each seed for each of the 133 atlas regions.

PLS was initially performed using all 8 seed regions in the matrix. The resulting singular value decomposition identified a single significant latent variable. The pattern of correlations in the weight matrix between the latent variable and the seed-region correlations with the VTA, SN

and STN seeds were found to be very similar, while the VS connectivity pattern was dissimilar from the other 6 and non-significant. To confirm the analysis of the weight matrix the same analysis was repeated with the VS seed correlations removed, as well as with each pair of seeds separately. A highly similar latent variable was identified in the independent SN, VTA and STN analyses. No significant latent variables were identified when only the VS seed was analyzed. On the basis of these two findings the VS was removed from the model to reduce the overall noise and improve the specificity. Only the results for the combined SN/VTA/STN analysis are reported.

Because the majority of the correlations were negatively associated with the resulting latent variable all the results were multipled by -1 for ease of interpretation.

Extended Partial Least Squares Correlation

To explore the potential effects of some confounding variables, the PLS analysis was repeated using the larger personality, BMI and demographic table including SURPS-IMP, SURPS-SS, BMIZ, FAS, age and gender. FAS was included because of a large and growing body of literature which suggests that socioeconomic status impacts both BMI and impulsive behaviour in teenagers (Jansen et al., 2013; Kidd et al., 2013; Shrewsbury and Wardle, 2008; Watts et al, 2018). Three participants were excluded from this analysis because of a lack of FAS score. All the data were mean-centred, as previously. All eight seed regions of interest were retained in the analysis. Because the majority of the correlations were negatively associated with the resulting latent variable all the results were again multipled by -1 for ease of interpretation.

PLS Loading Correlations

To assess the predictive power of the focused PLS, the subject level loadings onto the latent variable were correlated with parental BMI, BMIZ at the 24 month follow-up, the change in BMI and BMIZ and the rate of the change in BMI and BMIZ between the two time points in MATLAB, with pairwise exclusion of missing data. All the data were mean-centred.

Results

BMI, Personality and Demographics

Significant positive correlations were identified between SURPS-SS and BMIZ ($r = 0.2374$, $p = 0.0114$) as well as between SURPS-SS and SURPS-IMP ($r = 0.2005$, $p = 0.0332$). The complete set of Pearson correlations are displayed in Table 1.

Table 1. Pearson correlation values between personality, body mass index and demographic variables. *Indicates $p < 0.05$.

	Age (Months)	Gender	BMI Z-Score for Age	SURPS Impulsivity	SURPS Sensation-Seeking	Family Affluence Scale
Age (Months)	--					
Gender	0.1030	--				
BMI Z-Score for Age	0.1366	0.0272	--			
SURPS Impulsivity	0.0363	-0.1725	0.1259	--		
SURPS Sensation-Seeking	-0.0451	0.0546	0.2374*	0.2005*	--	
Family Affluence Scale	0.0611	-0.1074	-0.0837	0.0062	0.1727	--

Voxel-Wise Regression Results

The results of the voxel-wise regressions can be found in the supplementary data. The average correlation between the fMRI timecourses of the 8 regions of interest are displayed in the supplementary data.

Partial Least Squares Correlation

Focused Partial Least Squares Correlation

The focused PLS analysis which was designed to test the relationship between resting state connectivity of our brain regions of interest and our three demographic variables of interest, SURPS-SS, SURPS-IMP and BMIZ, identified a single significant latent variable ($p = 0.0075$, $s = 4.5166$). This variable showed a positive relationship with SURPS-IMP and BMIZ scores and a negative relationship with SURPS-SS (Figure 2A).

Three of the four regions of interest, the SN, VTA and STN (bilaterally) loaded significantly onto the latent variable when entered into separate PLS analyses and so were retained in the final analysis. To identify the most relevant brain regions, the bootstrap ratios for the brain regions were thresholded at $z = 3$ (Table 2). This is equivalent to including data at least 3 standard deviations above the mean and contains data which was both strongly associated with the singular values, and stable across bootstrap resampling. This identified a striato-midbrain-limbic network which had connectivity to the seeds positively correlated with BMIZ and SURPS-IMP, including correlations to each seed from the bilateral hippocampus and amygdala and a set of thalamic, cerebellar and midbrain nuclei, and the temporal and anterior cingulate regions. The network had a higher degree of connectivity both in terms of extent and bootstrap values, to the left hemisphere seeds than the right (Figure 2B, 2C). The full, unthresholded maps of bootstrap ratios for each seed for both the focused and extended PLS correlations can be found at https://neurovault.org/collections/3456/.

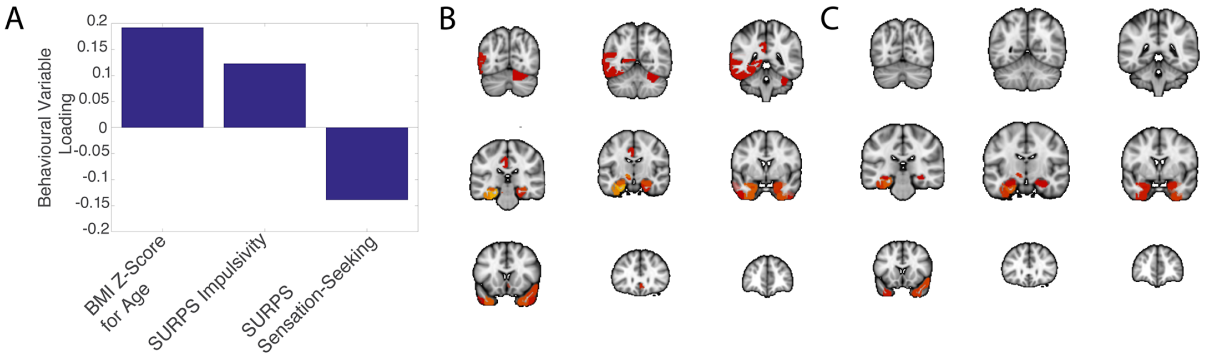

Figure 2. A) Correlations of the three behavioural variables included in the focused PLS correlation with the significant latent variable. B) Bootstrap ratios of the associations of regional connectivity with the left VTA with the significant latent variable in the focused PLS correlation, thresholded at z = 3. C) Bootstrap ratios of the associations of regional connectivity with the right VTA with the significant latent variable in the focused PLS correlation, thresholded at z = 3. All the bootstrap and correlation values were multiplied by -1 during analysis for ease of viewing.

Table 2. Regions which had connectivity with at least one of the regions of interest included in the focused PLS correlation, which was associated with the latent variable, with a bootstrap value of greater than 3. The names and centres of mass for each connected region are listed, and the thresholded bootstrap value of the connectivity with each seed. Empty cells indicate a sub-threshold bootstrap value.

Region Name	Hemisphere	Regional Centre of Mass (mm)			Bootstrap Value of Seed Connectivity					
		X	Y	Z	Left VTA	Right VTA	Left SN	Right SN	Left STN	Right STN
Pontine Nucleus	Right	6	-26	-34			3.69	3.06	3.05	
Pontine Nucleus	Left	-6	-26	-36				3.32		
Red Nucleus	Left	-6	-20	-10	3.04		3.50	3.44	3.77	3.32
Red Nucleus	Right	6	-20	-8			3.45	3.64	4.29	3.55
Substantia Nigra	Right	10	-16	-12					3.00	
Substantia Nigra	Left	-10	-16	-12	3.62		4.03		4.20	
Thalamus	Left	-12	-18	6			3.44		3.22	
Thalamus	Right	12	-18	6			3.44		3.45	
Sub-Thalamic Nucleus	Left	-12	-14	-6	4.37	3.48	3.95	3.70		
Hippocampus	Left	-28	-18	-18	4.03	3.05	4.53	3.73	4.14	3.24
Parahippocampal and Ambient Gyri	Left	-24	-18	-28	4.10	3.90	5.72	4.36	5.07	4.26
Parahippocampal and Ambient Gyri	Right	24	-16	-28	3.20		3.58		3.43	3.13
Hippocampus	Right	28	-16	-18	3.77	3.03	4.32	3.27	4.11	3.31

Amygdala	Left	-24	-4	-22	3.62	3.10	3.44		3.15	3.01
Amygdala	Right	22	-4	-22	3.44	3.08	3.40		3.36	3.11
Posterior Temporal Lobe	Left	-48	-48	-4	3.23	3.01				
Posterior Cingulate	Left	-4	-28	36	3.25				3.15	
Posterior Cingulate	Right	6	-28	36					3.05	
Fusiform Gyrus	Left	-36	-16	-32	4.60	3.56	4.95	4.17	4.65	3.89
Fusiform Gyrus	Right	34	-14	-34			3.22		3.13	3.29
Anterior Inferior Lateral Temporal Lobe	Left	-52	6	-34	3.09					
Anterior Medial Temporal Lobe	Left	-32	8	-38	4.08	3.38	3.73	3.37	3.49	
Anterior Medial Temporal Lobe	Right	30	8	-38	-3.80	3.62	3.29		3.48	3.38
Anterior Inferior Lateral Temporal Lobe	Right	48	10	-38	3.24					
Anterior Superior Temporal Lobe	Right	48	14	-20	3.58	3.77				
Subgenual Anterior Cingulate	Right	4	26	-8	3.47				3.97	
Cerebellar Vermis Crus II		0	-76	-34			4.01			
Cerebellar Vermis VI		0	-72	-22			3.35			

Cerebellar Lobe VI	Right	24	-60	-24	3.06	3.63	3.03		
Fastigial Nucleus	Left	-2	-54	-28				3.19	
Cerebellar Lobe I IV	Left	-6	-46	-16		3.16		3.85	3.10
Cerebellar Lobe I IV	Right	8	-46	-16		3.00		3.21	

Extended Partial Least Squares Correlation

The extended PLS analysis was intended to test the effect of known confounds age, gender and FAS on the model. This extended analysis also identified a single latent variable ($p = 0.0046$, $s = 5.7897$). The identified variable had the same relationship with SURPS-IMP, SURPS-SS and BMIZ as the original analysis above. FAS score and age were both negatively related to the latent variable, while gender was weakly positively associated (Figure 3A).

All four of the regions of interest (bilaterally) loaded significantly onto the latent variable when entered into separate PLS analyses, and so were retained in the final analysis. To identify the most relevant brain regions, the bootstrap ratios for the brain regions were thresholded at $z = 3$ to match the previous analysis. For regions connecting to the SN, VTA and STN the left-lateralized striato-midbrain-limbic network was again identified although the parahippocampal gyri rather than the hippocampus and amygdalae were the most significant regions. There were also a more right lateralized series of regions identified in the frontoparietal cortex. No regions connecting to the VS passed the threshold. The identified regions had connectivity which was positively correlated with BMIZ and SURPS-IMP (Figure 3B, 3C, Table 3). There were also two regions with negative bootstrap ratios of less than -3: the connectivity between the left inferior olivary nucleus and the right VTA and right STN respectively.

The regional bootstrap values for regional connectivity to the SN, VTA and SN from this extended analysis were positively correlated with the same values from the focused PLS correlation ($r = 0.7213$, $p < 0.001$) (Figure 4), indicating that the same latent variable was identified in both analyses.

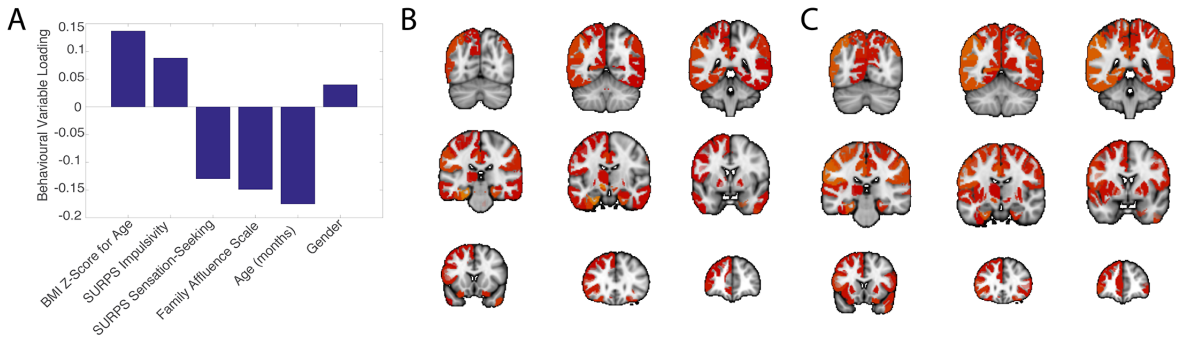

Figure 3. A) Correlations of the six behavioural variables included in the extended PLS correlation with the significant latent variable. B) Bootstrap ratios of the associations of regional connectivity with the left VTA with the significant latent variable in the extended PLS correlation, thresholded at z = 3. C) Bootstrap ratios of the association of regional connectivity with the right VTA with the significant latent variable in the extended PLS correlation thresholded at z = 3. All the bootstrap and correlation values were multiplied by -1 during the analysis for ease of viewing.

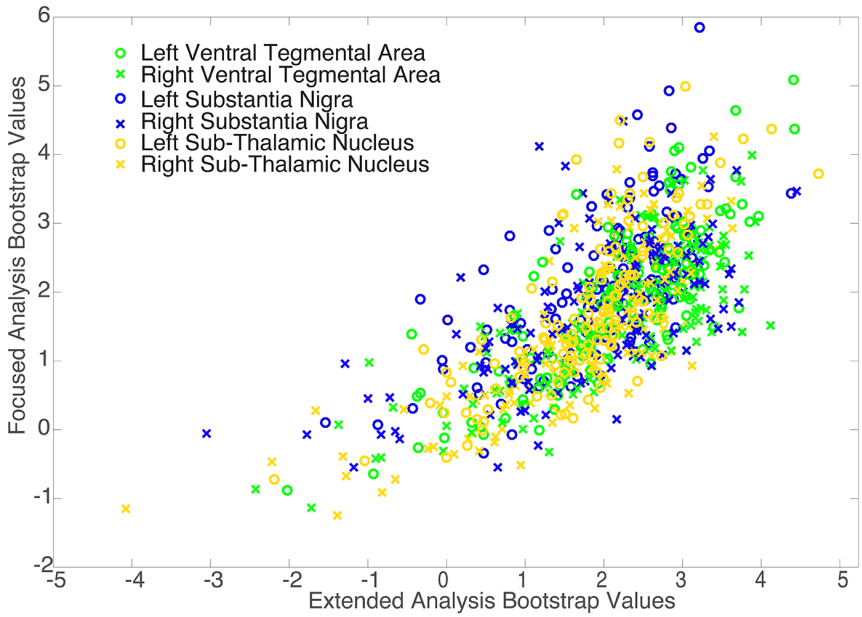

Figure 4. Correlation between the regional bootstrap values of the focused and extended PLS analyses. Points representing the bootstrap values of the connectivity of each region with the seed indicated in the legend. All the bootstrap and correlation values were multiplied by -1 during the analysis for ease of viewing.

24-month follow-up

PLS results at entry were correlated with several variables from the 24 month follow-up, to test the predictive power of the analysis. Subject loadings of regional connectivity onto the first latent variable, prior to being multiplied by -1, of the focused PLS correlation were significantly negatively correlated with BMIZ of the subjects two years later ($r = -0.2280$, $p = 0.0166$) but this does not survive a Bonferroni correction and is almost certainly not independent from BMIZ at timepoint one, which was involved in generating the subject-loadings. Subject loadings were not correlated with either the change in weight ($r = -0.0340$, $p = 0.7247$) or the rate of change ($r = -0.0558$, $p = 0.5623$). When a partial correlation, controlling for the effects of BMIZ at the first time point was run, the relationship between regional connectivity at the first time point, and BMIZ at the 24 month follow-up was no longer significant ($rho = -0.1225$, $p = 0.2045$). It was also not significantly correlated with parental BMI ($r = -0.0618$, $p = 0.5908$).

Table 3. Regions which had connectivity with at least one of the regions of interest included in the extended PLS correlation, which was associated with the latent variable, with a bootstrap value of greater than 3. The names and centres of mass for each connected region are listed, and the thresholded bootstrap value of the connectivity with each seed. Empty cells indicate a sub-threshold bootstrap value.

Region Name	Hemisphere	Regional Centre of Mass (mm)			Bootstrap Value of Seed Connectivity							
		X	Y	Z	Left VTA	Right VTA	Left SN	Right SN	Left VS	Right VS	Left STN	Right STN
Superior Colliculus	Left	-6	-30	-4			3.10					
Pontine Nucleus	Right	6	-26	-34	3.20							
Red Nucleus	Left	-6	-20	-10	3.90	3.42	4.40	4.40			4.73	3.55
Red Nucleus	Right	6	-20	-8	3.85	3.21	3.29	3.34			4.08	3.29
Thalamus	Left	-12	-18	6	3.09	3.00		3.37				
Substantia Nigra	Right	10	-16	-12	3.61	3.05					3.09	
Substantia Nigra	Left	-10	-16	-12	3.81		3.37				3.82	
Sub-Thalamic Nucleus	Right	14	-14	-6		3.15						
Sub-Thalamic Nucleus	Left	-12	-14	-6	4.42	3.71	3.21	3.65				
Pallidum	Left	-20	-4	-0	3.05	3.28						
Pallidum	Right	20	-2	-0	3.16	3.19						
Putamen	Left	-28	0	2		3.10		3.21				
Putamen	Right	26	2	2		3.10		3.05				
Parahippocampal and Ambient Gryi	Left	-24	-18	-28	4.33	3.78	3.17					3.32
Parahippocampal and Ambient Gryi	Right	24	-16	-28	3.74	3.32						
Hippocampus	Right	28	-16	-18	3.04							
Lateral Occipital Lobe	Left	-30	-82	10				3.23				
Cuneus	Left	-6	-82	18		3.14						
Lateral Occipital Lobe	Right	32	-80	10				3.21				

Cuneus	Right	10	-78	22		3.16			
Lingual Gyrus	Left	-12	-72	-4		3.09			
Superior Parietal Gyrus	Right	18	-56	50	3.01	3.24	3.43		
Superior Parietal Gyrus	Left	-16	-54	50	3.10	3.35	3.50		
Posterior Temporal Lobe	Left	-48	-48	-4	3.44	3.85	3.38		3.09
Posterior Temporal Lobe	Right	48	-46	-4	3.00	3.28			
Inferior Lateral Parietal Lobe	Left	-50	-46	36	3.66	4.01	3.64		3.09
Inferior Lateral Parietal Lobe	Right	52	-44	38	3.43	3.77	3.08		
Posterior Cingulate Gyrus	Left	-4	-28	36	3.58	3.82	3.64		
Posterior Cingulate Gyrus	Right	6	-28	36	3.11	3.45	3.20		
Postcentral Gyrus	Right	40	-22	46		3.32			
Postcentral Gyrus	Left	-40	-22	46	3.11	3.78	3.35		3.15
Fusiform Gyrus	Left	-36	-16	-32	3.60				
Central Superior Temporal Gyrus	Left	-54	-14	-0		3.27			
Precentral Gyrus	Left	-34	-8	48	3.01	3.49	3.28		
Precentral Gyrus	Right	36	-8	48		3.27	3.19		
Insula	Left	-36	2	-0		3.14			
Inferior Lateral Anterior Temporal Lobe	Left	-52	6	-34	3.01		3.01		
Inferior Lateral Anterior Temporal Lobe	Right	48	10	-38	3.62	3.50	3.16		3.62

Superior Anterior Temporal Gyrus	Right	48	14	-20		3.28				
Posterior Orbital Gyrus	Left	-28	22	-18	3.54	3.30				
Posterior Orbital Gyrus	Right	26	24	-18	3.41	3.58				3.06
Inferior Frontal Gyrus	Right	48	24	8		3.11				
Inferior Frontal Gyrus	Left	-48	24	8	3.23	3.43	3.50			3.02
Anterior Cingulate Gyrus	Left	-6	32	22	3.02	3.17				
Superior Frontal Gyrus	Left	-12	32	40	3.11	3.09	3.70			
Middle Frontal Gyrus	Left	-36	34	30	3.03	3.08	3.68			
Presubgenual Frontal Gyrus	Left	-5	40	-6	3.19	3.22				
Fastigial Nucleus	Right	4	-54	-28				3.03		
Fastigial Nucleus	Left	-2	-54	-28				3.35		
Cerebellar Lobe I IV	Left	-8	-46	-16			3.06	3.48	3.28	
Cerebellar Lobe I IV	Right	8	-46	-16			3.25	3.24	3.37	

Discussion

The present study's PLS correlation analysis of resting-state connectivity of the SN, VTA and STN with IMP, SS and BMIZ identified a single significant factor consisting of primarily mesolimbic regions connected with the subcortical nuclei of interest. The connectivity of this network was positively correlated with IMP and BMI Z-score for age and negatively correlated with SS (Figure 2). A similar factor was identified in a more complex demographic model, including age, gender, and family income (Figure 3, 4). The network identified in the more complex extended model was more extensive, including a set of primarily frontoparietal cortical regions. It is difficult to draw conclusions about the specific contributions of each element of the PLS analyses but the inverse correlation of the main latent variable with age is consistent with the theory that connectivity changes with maturation are associated with reduced impulsivity. Reduced mesolimbic connectivity and reduced impulsivity have been hypothesized to reflect maturation of prefronto-mesolimbic pathways (Casey et al., 2016; Christakou et al., 2011, 2009). Note however that the age range in the current study was restricted by design. Voxel-wise regression analyses using the same seed regions of interest found peaks in concordant areas (Supplementary Data).

The activity of the limbic system and the connectivity between the hippocampus and the midbrain and striatum has been previously associated with the control of multiple aspects of eating behaviour (Johnson et al., 2007; Mizumori and Tryon, 2015; Ross et al., 2011; Stevenson and Francis, 2017). The hippocampus is responsible for integrating contextual information from memories of earlier food intake, interoceptive information, and environmental information in the calculation of value of food or food cues (Kanoski and Grill, 2017; Stevenson and Francis, 2017). Disruptions to any of these functions can result in increased body weight.

The hippocampus plays a role in behavioural inhibition and altered connectivity or activity can reduce overall capacity for inhibition, as well as food related inhibition specifically. In animal studies most hippocampal outputs are inhibitory and hippocampal lesions have been found to increase response to food cues (Stevenson and Francis, 2017). Alterations to the activity of the hippocampus and limbic system and their connections to the midbrain and striatum have been associated with both general IMP and obesity; so have connections between the hippocampus and prefrontal cortex, which is also implicated in behavioural control (Mizumori and Tryon, 2015; Ross et al., 2011).

The positive correlation between IMP, BMIZ and the connectivity of the limbic-midbrain circuit identified in this study could therefore reflect a number of mechanisms including increased response to food cues, reduced efficiency of inhibition or altered calculation of the value and relevance of food information. The presence of this increased connection could also reflect a single underlying change (increased connectivity) which could ultimately affect multiple mechanisms of food response or of general impulsivity. This would be in keeping with the more general idea of personality predicting behaviour because it reflects underlying properties of brain function (Deyoung and Gray, 2009). A greater response to food cues by the striatum and midbrain has been previously identified in obese and overweight patients (Murdaugh et al., 2012; Stoeckel et al., 2008; Vainik et al., 2013). A greater response to reward stimuli in general has also been identified as a feature of both impulsivity and adolescent development (Christakou et al., 2011; Rubia et al., 2006).

Obesity related changes in the hippocampus can be bidirectional. Alterations in hippocampal function can increase risk for obesity, but inflammatory and metabolic changes associated with obesity can also further modify hippocampal function increasing the risk for further weight gain. This phenomenon has been identified in both overweight and obese adults and adolescent populations with and without metabolic dysfunction (Hargrave et al., 2016; Moreno-Lopez et al., 2016; Yau et al., 2012, 2011).

The parahippocampal gyrus was identified in both our focused and extended PLS analyses. The activity and connectivity of the parahippocampal gyrus has also been found to be altered in obesity. The activity of the parahippocampal gyrus has been specifically associated with appetitive response to food, and to food cravings (Brooks et al., 2013; Chen et al., 2017). The parahippocampal region is also more generally involved in processing the contextual information related to specific stimuli or memories. Increased connectivity between the parahippocampal regions and the dopaminergic midbrain could reflect alterations in how rewarding stimuli, whether food specific or not, are contextualized. Adolescents are also known to utilize contextual information differently than adults in reward tasks. That difference, which was not assessed directly in this study, could be explained by the increased connectivity between parahippocampal and mesolimbic regions (Aminoff et al., 2013; Haddad et al., 2014; Telzer et al., 2013). The amygdala, another region implicated in our analysis, is also known to be involved in determining the salience of different stimuli and rewards based on context, and is also involved in calculating

and responding to risk and reward. The amygdala and its connections are also known to develop substantially over the course of adolescence (Ernst, 2014; Scherf et al., 2013).

We hypothesized that connectivity between frontal regions and mesolimbic nuclei would vary with impulsivity and/or sensation-seeking. Adolescent impulsivity arising from corticostriatal connectivity changes is part of the dual-system hypothesis of adolescent development (Hofmann et al., 2009). Our findings instead identified a mesolimbic network as primarily related to impulsivity and obesity. The data driven nature of the PLS analysis makes it impossible to draw direct conclusions about networks that were not identified by the analysis. However, this finding is not in conflict with the dual-systems hypothesis but it more closely supports the triadic theory of development. The triadic hypothesis is an elaboration on the dual-systems hypothesis, which states that reduced prefrontal control of both the striatum and the limbic system, especially the amygdala is responsible for adolescent impulsivity (Ernst et al., 2006). It is also possible that reduced top-down influence from the prefrontal cortex could result in increased connectivity between the midbrain, striatum and limbic systems, although this has not been investigated previously to the best of our knowledge.

Our data found that SS was differentially associated with our latent variable than IMP. There are few studies which examine SS as an independent trait, rather than as a facet of IMP. However, there is previous research identifying impulsivity and sensation-seeking as being associated with different brain networks, which would support our findings (Castellanos-Ryan et al., 2011). Additionally, Hawes et al. found that the relationship between activity in the striatum during a reward task and SS changed over the course of development. SS was negatively correlated with activity in teens and positively correlated in adults (Hawes et al., 2016). This is difficult to generalize directly to connectivity data, but the negative correlation between midbrain and striatal connectivity identified in our study and sensation-seeking score is consistent with this finding. While the IMP and SS subscale scores are positively correlated with each other, how the midbrain-limbic connectivity relates to each score can still vary. Differential associations at the network level could explain why IMP and SS are negatively associated in the PLS analysis (Figures 2A, 3A), despite being correlated with one another (Table 1).

The findings of this study are limited by the network identified by the PLS correlation. Since our data did not identify a prefrontal network we cannot tell specifically how prefrontal connectivity is correlated with personality or with weight in this sample. The size of our nuclei

of interest relative to the resolution of the data may have impacted the ability of our model to identify multiple latent variables in the PLS analysis. The post-hoc removal of the VS seed from the analysis might also have biased the analysis in favour of the midbrain (SN and VTA) and obscured prefrontal contributions. It is reasonable to assume that other networks, not identified by this study do contribute to both impulsivity and weight. A cortico-striatal network implicating the VS seed would be one likely candidate. It is also not possible based on this set of results to determine the directionality of the obesity related results. Alterations to the limbic-midbrain system have been shown to predict future obesity in previous studies, but have also been shown to be exacerbated by obesity, and reversed by weight loss (Hargrave et al., 2016), although the young age of our sample may favor the first interpretation. This study also did not have data about body composition or exact Tanner stage of pubertal development available.

Acknowledgements

NeuroVenture is funded by an operating grant from the Canadian Institutes of Health Research (Grant Number: 126053). RJS is currently partially funded by a Derek H. Davis award, from the McGill University Faculty of Medicine and has previously been funded by a Tomlinson Doctoral Fellowship and a Alice Chap-Yip Fellowship and a Graduate Excellence Fellowship. AD is funded by the CIHR Foundation Scheme. We thank Brianna Barsanti-Innes for help in data collection and analysis.

References

Ad-Dab'bagh, Y., Einarson, D., Lyttelton, O., Muehlboeck, J.-S., Mok, K., Ivanov, O., Vincent, R.D., Lepage, C., Lerch, J., Fombonne, E., Evans, A.C., 2006. The CIVET image-processing environment : A fully automated comprehensive pipeline for anatomical neuroimaging research, in: Proceedings of the 12th Annual Meeting of the Organization for Human Brain Mapping, M. Corbetta, Ed.

Adleman, N.E., Menon, V., Blasey, C.M., White, C.D., Warsofsky, I.S., Glover, G.H., Reiss, A.L., 2002. A developmental fMRI study of the stroop color-word task. Neuroimage 16, 61–75. https://doi.org/10.1006/nimg.2001.1046

Alonso-Alonso, M., Pascual-Leone, A., 2007. The right brain hypothesis for obesity. JAMA 297, 1819–1822.

Aminoff, E.M., Kveraga, K., Bar, M., 2013. The role of the parahippocampal cortex in cognition. Trends Cogn. Sci. 17, 379–390. https://doi.org/10.1016/j.tics.2013.06.009

Amunts, K., Lepage, C., Borgeat, L., Mohlberg, H., Dickscheid, T., Rousseau, M.E., Bludau, S., Bazin, P.L., Lewis, L.B., Oros-Peusquens, A.M., Shah, N.J., Lippert, T., Zilles, K., Evans, A.C., 2013. BigBrain: An ultrahigh-resolution 3D human brain model. Science (80-.). 340, 1472–1475. https://doi.org/10.1126/science.1235381

Appelhans, B.M., Waring, M.E., Schneider, K.L., Pagoto, S.L., Debiasse, M.A., Whited, M.C., Lynch, E.B., 2012. Delay discounting and intake of ready-to-eat and away-from-home foods in overweight and obese women. Appetite 59, 576–84. https://doi.org/10.1016/j.appet.2012.07.009

Aron, A.R., Shohamy, D., Clark, J., Myers, C., Gluck, M.A., Poldrack, R.A., 2004. Human midbrain sensitivity to cognitive feedback and uncertainty during classification learning 1144–1152.

Beckmann, C.F., Smith, S.M., 2004. Tensorial extensions of independent component analysis for multi-subject FMRI analysis. FMRIB Tech. Rep. TR04CB1 1, 1–23. https://doi.org/10.1017/CBO9781107415324.004

Black, W.R., Lepping, R.J., Bruce, A.S., Powell, J.N., Bruce, J.M., Martin, L.E., Davis, A.M., Brooks, W.M., Savage, C.R., Simmons, W.K., 2015. Tonic hyper-connectivity of reward neurocircuitry in obese children. Obesity (Silver Spring). 22, 1590–1593. https://doi.org/10.14440/jbm.2015.54.A

Bourque, J., Baker, T.E., Dagher, A., Evans, A.C., Garavan, H., Leyton, M., Seguine, J.R., Pihl, R., Conrod, P.J., 2016. Effects of delaying binge drinking on adolescent brain development: A longitudinal neuroimaging study. BMC Psychiatry 16, 445. https://doi.org/10.1186/s12888-016-1148-3.

Boyce, W., Torsheim, T., Currie, C., Zambon, A., 2006. The family affluence scale as a measure of national wealth: Validation of an adolescent self-report measure. Soc. Indic. Res. 78, 473–487. https://doi.org/10.1007/s11205-005-1607-6

Braams, B.R., van Duijvenvoorde, A.C.K., Peper, J.S., Crone, E.A., 2015. Longitudinal changes in adolescent risk-taking: A comprehensive study of neural responses to rewards, pubertal development, and risk-taking behavior. J. Neurosci. 35, 7226–7238. https://doi.org/10.1523/JNEUROSCI.4764-14.2015

Brooks, S.J., Cedernaes, J., Schiöth, H.B., 2013. Increased prefrontal and parahippocampal activation with reduced dorsolateral prefrontal and insular cortex activation to food images in obesity: A meta-analysis of fMRI studies. PLoS One 8. https://doi.org/10.1371/journal.pone.0060393

Buckholtz, J.W., Treadway, M.T., Cowan, R.L., Woodward, N.D., Li, R., Ansari, M.S., Baldwin, R.M., Schwartzman, A.N., Shelby, E.S., Smith, C.E., Kessler, R.M., Zald, D.H., 2010. Dopaminergic network differences in human impulsivity. Science 329, 532. https://doi.org/10.1126/science.1185778

Calluso, C., Tosoni, A., Pezzulo, G., Spadone, S., Committeri, G., 2015. Interindividual variability in functional connectivity as long-term correlate of temporal discounting. PLoS One 10, e0119710. https://doi.org/10.1371/journal.pone.0119710

Casey, B.J., Galván, A., Somerville, L.H., 2016. Beyond simple models of adolescence to an integrated circuit-based account: A commentary. Dev. Cogn. Neurosci. 17, 128–130. https://doi.org/10.1016/j.dcn.2015.12.006

Casey, B.J., Somerville, L.H., Gotlib, I.H., Ayduk, O., Franklin, N.T., Askren, M.K., Jonides, J., Berman, M.G., Wilson, N.L., Teslovich, T., Glover, G., Zayas, V., Mischel, W., Shoda, Y., 2011. Behavioral and neural correlates of delay of gratification 40 years later. Proc. Natl. Acad. Sci. U. S. A. 108, 14998–5003. https://doi.org/10.1073/pnas.1108561108

Castellanos-Ryan, N., Rubia, K., Conrod, P.J., 2011. Response inhibition and reward response bias mediate the predictive relationships between impulsivity and sensation seeking and common and unique variance in conduct disorder and substance misuse. Alcohol. Clin. Exp. Res. 35, 140–155. https://doi.org/10.1111/j.1530-0277.2010.01331.x

Chen, S., Dong, D., Jackson, T., Zhuang, Q., Chen, H., 2017. Trait-based food-cravings are encoded by regional homogeneity in the parahippocampal gyrus. Appetite 114, 155–160. https://doi.org/10.1016/j.appet.2017.03.033

Chick, C.F., 2015. Reward processing in the adolescent brain: Individual differences and relation to risk taking. J. Neurosci. 35, 13539–13541. https://doi.org/10.1523/JNEUROSCI.2571-15.2015

Choi, E.Y., Yeo, B.T.T., Buckner, R.L., 2012. The organization of the human striatum estimated by intrinsic functional connectivity. J. Neurophysiol. 108, 2242–2263. https://doi.org/10.1152/jn.00270.2012

Christakou, A., Brammer, M., Rubia, K., 2011. Maturation of limbic corticostriatal activation and connectivity associated with developmental changes in temporal discounting. Neuroimage 54, 1344–1354. https://doi.org/10.1016/j.neuroimage.2010.08.067

Christakou, A., Halari, R., Smith, A.B., Ifkovits, E., Brammer, M., Rubia, K., 2009. Sex-dependent age modulation of frontostriatal and temporo-parietal activation during cognitive control. Neuroimage 48, 223–236. https://doi.org/10.1016/j.neuroimage.2009.06.070

Collado, A., Felton, J.W., MacPherson, L., Lejuez, C.W., 2014. Longitudinal trajectories of sensation seeking, risk taking propensity, and impulsivity across early to middle adolescence. Addict. Behav. https://doi.org/10.1016/j.addbeh.2014.01.024

Conrod, P.J., Castellanos-Ryan, N., Mackie, C., 2011. Long-term effects of a personality-targeted intervention to reduce alcohol use in adolescents. J. Consult. Clin. Psychol. 79, 296–306. https://doi.org/10.1037/a0022997

Conrod, P.J., Castellanos, N., Mackie, C., 2008. Personality-targeted interventions delay the growth of adolescent drinking and binge drinking. J. Child Psychol. Psychiatry Allied Discip. 49, 181–190. https://doi.org/10.1111/j.1469-7610.2007.01826.x

Cox, R.W., 1996. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173. https://doi.org/10.1006/cbmr.1996.0014

Cox, R.W., Hyde, J.S., 1997. Software tools for analysis and visualization of fMRI data. NMR Biomed. 10, 171–8. https://doi.org/10.1002/(SICI)1099-1492(199706/08)10:4/5<171::AID-NBM453>3.0.CO;2-L

Currie, C., Molcho, M., Boyce, W., Holstein, B., Torsheim, T., Richter, M., 2008. Researching health inequalities in adolescents: The development of the Health Behaviour in School-Aged Children (HBSC) Family Affluence Scale. Soc. Sci. Med. 66, 1429–1436. https://doi.org/10.1016/j.socscimed.2007.11.024

Deyoung, C.G., Gray, J.R., 2009. Personality neuroscience: explaining individual differences in affect, behaviour and cognition, The Cambridge Handbook of Personality Psychology. https://doi.org/10.1017/CBO9780511596544.023

Diedrichsen, J., Balsters, J., Flavel, J., Cussans, E., Ramnani, N., 2009. A probabilistic MR atlas of the human cerebellum. May 15;46(1):39–46. Neuroimage May 15;46, 39–46.

Duckworth, A.L., Kern, M.L., 2012. A meta-analysis of the convergent validity of self-control measures 45, 259–268. https://doi.org/10.1016/j.jrp.2011.02.004.A

Duckworth, A.L., Tsukayama, E., Geier, A.B., 2010. Self-controlled children stay leaner in the transition to adolescence. Appetite 54, 304–308. https://doi.org/10.1016/j.appet.2009.11.016

Düzel, E., Bunzeck, N., Guitart-Masip, M., Wittmann, B., Schott, B.H., Tobler, P.N., 2009. Functional imaging of the human dopaminergic midbrain. Trends Neurosci. 32, 321–328. https://doi.org/10.1016/j.tins.2009.02.005

Eigsti, I.-M., Zayas, V., Mischel, W., Shoda, Y., Ayduk, O., Dadlani, M.B., Davidson, M.C., Lawrence Aber, J., Casey, B.J., 2006. Predicting cognitive control from preschool to late adolescence and young adulthood. Psychol. Sci. 17, 478–84. https://doi.org/10.1111/j.1467-9280.2006.01732.x

Ernst, M., 2014. The triadic model perspective for the study of adolescent motivated behavior. Brain Cogn. 89, 104–111. https://doi.org/10.1016/j.bandc.2014.01.006

Ernst, M., Pine, D.S., Hardin, M., 2006. Triadic model of neurobiology of motivated behaviour in adolescence. Psychol. Med. 36, 299–312. https://doi.org/10.1017/S0033291705005891.Triadic

Francis, L. A., Susman, E.J., 2009. Self-regulation and rapid weight gain in children from age 3 to 12 years. Arch. Pediatr. Adolesc. Med. 163, 297–302. https://doi.org/10.1001/archpediatrics.2008.579

Fuentes-Claramonte, P., Avila, C., Rodriguez-Pujadas, A., Costumero, V., Ventura-Campos, N., Bustamante, J.C., Rosell-Negre, P., Barros-Loscertales, A., 2016. Characterizing individual differences in reward sensitivity from the brain networks involved in response inhibition. Neuroimage 124, 287–299. https://doi.org/10.1016/j.neuroimage.2015.08.067

Galvan, A., Hare, T. a, Parra, C.E., Penn, J., Voss, H., Glover, G., Casey, B.J., 2006. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. J. Neurosci. 26, 6885–6892. https://doi.org/10.1523/JNEUROSCI.1062-06.2006

Gaspar, P., Stepniewska, I., Kaas, J.H., 1992. Topography and collateralization of the dopaminergic projections to motor and lateral prefrontal cortex in owl monkeys. J. Comp. Neurol. 325, 1–21. https://doi.org/10.1002/cne.903250102

Haddad, A.D.M., Harrison, F., Norman, T., Lau, J.Y.F., 2014. Adolescent and adult risk-taking in virtual social contexts. Front. Psychol. 5, 1–7. https://doi.org/10.3389/fpsyg.2014.01476

Halliday, G.M., Törk, I., 1986. Comparative anatomy of the ventromedial mesencephalic tegmentum in the rat, cat, monkey and human. J. Comp. Neurol. 252, 423–445. https://doi.org/10.1002/cne.902520402

Hammers, A., Allom, R., Koepp, M.J., Free, S.L., Myers, R., Lemieux, L., Mitchell, T.N., Brooks, D.J., Duncan, J.S., 2003. Three-dimensional maximum probability atlas of the

human brain, with particular reference to the temporal lobe. Hum. Brain Mapp. 19, 224–247. https://doi.org/10.1002/hbm.10123

Hargrave, S.L., Jones, S., Davidson, T.L., 2016. The Outward Spiral: A vicious cycle model of obesity and cognitive dysfunction. Curr Opin Behav Sci 9, 40–46. https://doi.org/10.1016/j.cobeha.2015.12.001.The

Hawes, S.W., Chahal, R., Hallquist, M.N., Paulsen, D.J., Geier, C.F., Luna, B., 2016. Modulation of reward-related neural activation on sensation seeking across development. Neuroimage 147, 763–771. https://doi.org/10.1016/j.neuroimage.2016.12.020

Hofmann, W., Friese, M., Strack, F., 2009. Impulse and self-control from a dual-systems perspective. Perspect. Psychol. Sci. 4, 1–15. https://doi.org/10.1111/j.1745-6924.2009.01116.x

Jahanshahi, M., Obeso, I., Baunez, C., Alegre, M., Krack, P., 2015. Parkinson's disease, the subthalamic nucleus, inhibition, and impulsivity. Mov. Disord. 30, 128–140. https://doi.org/10.1002/mds.26049

Jansen, P.W., Mensah, F.K., Nicholson, J.M., Wake, M., 2013. Family and neighbourhood socioeconomic inequalities in childhood trajectories of BMI and overweight: Longitudinal study of Australian children. PLoS One 8, e69676. https://doi.org/10.1371/journal.pone.0069676

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved methods for the registration and motion correction of brain images. FMRIB Tech. Rep. TR02MJ1 1. https://doi.org/10.1017/CBO9781107415324.004

Jenkinson, M., Beckmann, C., 2001. ICA in FMRI: A basic introduction. FMRIB Tech. Rep. TR01MJ2 7–9.

Johnson, A., van der Meer, M.A., Redish, A.D., 2007. Integrating hippocampus and striatum in decision-making. Curr. Opin. Neurobiol. 17, 692–697. https://doi.org/10.1016/j.conb.2008.01.003

Jurk, S., Kuitunen-Paul, S., Kroemer, N.B., Artiges, E., Banaschewski, T., Bokde, A.L.W., Büchel, C., Conrod, P., Fauth-Bühler, M., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Heinz, A., Mann, K.F., Nees, F., Paus, T., Pausova, Z., Poustka, L., Rietschel, M., Schumann, G., Struve, M., Smolka, M.N., 2015. Personality and substance use: Psychometric evaluation and validation of the Substance Use Risk Profile Scale (SURPS) in English, Irish, French, and German adolescents. Alcohol. Clin. Exp. Res. 39, 2234–2248. https://doi.org/10.1111/acer.12886

Kanoski, S.E., Grill, H.J., 2017. Hippocampus contributions to food intake control : Mnemonic, neuroanatomical, and endocrine mechanisms. Biol. Psychiatry 81, 748–756. https://doi.org/10.1016/j.biopsych.2015.09.011

Keuken, M.C., Forstmann, B.U., 2015. A probabilistic atlas of the basal ganglia using 7T MRI. Data Br. 4, 577–582. https://doi.org/10.1016/j.dib.2015.07.028

Kidd, C., Palmeri, H., Aslin, R.N., 2013. Rational snacking: Young children's decision-making on the marshmallow task is moderated by beliefs about environmental reliability. Cognition 126, 109–14. https://doi.org/10.1016/j.cognition.2012.08.004

Krank, M., Stewart, S.H., O'Connor, R., Woicik, P.B., Wall, A.-M., Conrod, P.J., 2011. Structural, concurrent, and predictive validity of the Substance Use Risk Profile Scale in early adolescence. Addict. Behav. 36, 37–46. https://doi.org/10.1016/j.addbeh.2010.08.010

Krishnan, A., Williams, L.J., McIntosh, A.R., Abdi, H., 2011. Partial Least Squares (PLS) methods for neuroimaging: A tutorial and review. Neuroimage 56, 455–475. https://doi.org/10.1016/j.neuroimage.2010.07.034

Krmpotich, T.D., Tregellas, J.R., Thompson, L.L., Banich, M.T., Klenk, A.M., Tanabe, J.L., 2013. Resting-state activity in the left executive control network is associated with behavioral approach and is increased in substance dependence. Drug Alcohol Depend. 129, 1–7. https://doi.org/10.1016/j.drugalcdep.2013.01.021

Kuczmarski, R.J., Ogden, C.L., Guo, S.S., Grummer-Strawn, L.M., Flegal, K.M., Mei, Z., Wei, R., Curtin, L.R., Roche, A.F., Johnson, C.L., 2002. 2000 CDC Growth Charts for the United States: methods and development., Vital and health statistics. Series 11, Data from the national health survey.

Leong, J.K., Pestilli, F., Wu, C.C., Samanez-Larkin, G.R., Knutson, B., 2016. White-Matter tract connecting anterior insula to nucleus accumbens correlates with reduced preference for positively skewed gambles. Neuron 89. https://doi.org/10.1016/j.rasd.2014.08.015.Social

Liston, C., Watts, R., Tottenham, N., Davidson, M.C., Niogi, S., Ulug, A.M., Casey, B.J., 2006. Frontostriatal microstructure modulates efficient recruitment of cognitive control. Cereb. Cortex 16, 553–60. https://doi.org/10.1093/cercor/bhj003

Lohani, S., Poplawsky, A.J., Kim, S.-G., Moghaddam, B., 2016. Unexpected global impact of VTA dopamine neuron activation as measured by opto-fMRI. Mol. Psychiatry, 1–10. https://doi.org/10.1038/mp.2016.102

MacPherson, L., Magidson, J.F., Reynolds, E.K., Kahler, C.W., Lejuez, C.W., 2010. Changes in sensation seeking and risk-taking propensity predict increases in alcohol use among early adolescents. Alcohol. Clin. Exp. Res. 34, 1400–8. https://doi.org/10.1111/j.1530-0277.2010.01223.x

Menon, V., 2015. Salience Network, Brain Mapping: An Encyclopedic Reference. Elsevier Inc. https://doi.org/10.1016/B978-0-12-397025-1.00052-X

Mischel, W., Shoda, Y., Peake, P.K., 1988. The nature of adolescent competencies predicted by preschool delay of gratification. J. Pers. Soc. Psychol. 54, 687–96.

Mischel, W., Shoda, Y., Rodriguez, M.I., 1989. Delay of gratification in children. Science 244, 933–8.

Mišić, B., Betzel, R.F., de Reus, M.A., van den Heuvel, M.P., Berman, M.G., McIntosh, A.R., Sporns, O., 2016. Network-Level structure-function relationships in human neocortex. Cereb. Cortex 26, 3285–3296. https://doi.org/10.1093/cercor/bhw089

Mitchell, M.R., Potenza, M.N., 2014. Addictions and personality traits: Impulsivity and related constructs. Curr. Behav. Neurosci. Reports 1, 1–12. https://doi.org/10.1007/s40473-013-0001-y

Mizumori, S.J.Y., Tryon, V.L., 2015. Integrative hippocampal and decision-making neurocircuitry during goal-relevant predictions and encoding, 1st ed, Progress in Brain Research. Elsevier B.V. https://doi.org/10.1016/bs.pbr.2015.03.010

Moreno-Lopez, L., Contreras-Rodriguez, O., Soriano-Mas, C., Stamatakis, E.A., Verdejo-Garcia, A., 2016. Disrupted functional connectivity in adolescent obesity. NeuroImage Clin. https://doi.org/10.1016/j.nicl.2016.07.005

Morris, L.S., Kundu, P., Baek, K., Irvine, M.A., Mechelmans, D.J., Wood, J., Harrison, N.A., Robbins, T.W., Bullmore, E.T., Voon, V., 2015. Jumping the gun: Mapping neural correlates of waiting impulsivity and relevance across alcohol misuse. Biol. Psychiatry 1–9. https://doi.org/10.1016/j.biopsych.2015.06.009

Murdaugh, D.L., Cox, J.E., Cook, E.W., Weller, R.E., 2012. fMRI reactivity to high-calorie food pictures predicts short and long-term outcome in a weight-loss program. Neuroimage 40, 1301–1315. https://doi.org/10.1007/s10439-011-0452-9.

Murty, V.P., Shermohammed, M., Smith, D. V., Carter, R.M., Huettel, S. A., Adcock, R.A., 2014. Resting state networks distinguish human ventral tegmental area from substantia nigra. Neuroimage 100, 580–589. https://doi.org/10.1016/j.neuroimage.2014.06.047

O'Leary-Barrett, M., Mâsse, B., Pihl, R.O., Stewart, S.H., Séguin, J.R., Conrod, P.J., 2017. A cluster-randomized controlled trial evaluating the effects of delaying onset of adolescent substance abuse on cognitive development and addiction following a selective, personality-targeted intervention programme: the Co-Venture trial. Addiction 112, 1871–1881. https://doi.org/10.1111/add.13876

Oades, R., Halliday, G.M., 1987. Ventral tegmental (A10) system: neurobiology. 1. Anatomy and connectivity. Brain Res. 434, 117–165.

Olszewski, J., Baxter, D., 1954. Cytoarchitecture of the human brainstem. S. Karger, Basle & New York.

Park, B.-Y., Seo, J., Yi, J., Park, H., 2015. Structural and functional brain connectivity of people with obesity and prediction of body mass index using connectivity. PLoS One 10, e0141376. https://doi.org/10.1371/journal.pone.0141376

Pruim, R.H.R., Mennes, M., Buitelaar, J.K., Beckmann, C.F., 2014a. Evaluation of ICA-AROMA and alternative strategies for motion artifact removal in resting-state fMRI. Submitt. Publ. 112, 278–287. https://doi.org/10.1016/j.neuroimage.2015.02.063

Pruim, R.H.R., Mennes, M., van Rooij, D., Llera Arenas, A., Buitelaar, J.K., Beckmann, C.F., 2014b. ICA-AROMA: A robust ICA-based strategy for removing motion artifact from fMRI data. Submitt. Publ. 112, 267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064

Ross, R.S., Sherrill, K.R., Stern, C.E., 2011. The hippocampus is functionally connected to the striatum and orbitofrontal cortex during context dependent decision making. Brain Res. 1423, 53–66. https://doi.org/10.1016/j.brainres.2011.09.038

Rubia, K., Smith, A.B., Taylor, E., Brammer, M., 2007. Linear age-correlated functional development of right inferior fronto-striato-cerebellar networks during response inhibition and anterior cingulate during error-related processes. Hum. Brain Mapp. 28, 1163–1177. https://doi.org/10.1002/hbm.20347

Rubia, K., Smith, A.B., Woolley, J., Nosarti, C., Heyman, I., Taylor, E., Brammer, M., 2006. Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. Hum. Brain Mapp. 27, 973–993. https://doi.org/10.1002/hbm.20237

Sawatsky, M.L., Clyde, M., Meek, F., 2015. Partial Least Squares regression in the social sciences. Quant. Method Psychol. 11, 52–62.

Scherf, K.S., Smyth, J.M., Delgado, M.R., 2013. The Amygdala: An agent of change in adolescent neural networks. Horm. Behav. 13, 83–96. https://doi.org/10.1002/ana.22528.Toll-like

Schlam, T.R., Wilson, N.L., Shoda, Y., Mischel, W., Ayduk, O., 2012. Preschoolers' delay of gratification predicts their body mass 30 years later. J. Pediatr. 10–13. https://doi.org/10.1016/j.jpeds.2012.06.049

Shrewsbury, V., Wardle, J., 2008. Socioeconomic status and adiposity in childhood: A systematic review of cross-sectional studies 1990-2005. Obesity (Silver Spring). 16, 275–84. https://doi.org/10.1038/oby.2007.35

Shulman, E.P., Smith, A.R., Silva, K., Icenogle, G., Duell, N., Chein, J., Steinberg, L., 2016. The dual systems model: Review, reappraisal, and reaffirmation. Dev. Cogn. Neurosci. 17, 103–117. https://doi.org/10.1016/j.dcn.2015.12.010

Smith, S.M., 2000. BET: Brain Extraction Tool. FMRIB Tech. Rep. TR00SMS2b. https://doi.org/http://dx.doi.org/10.1016/B978-044451604-6/50001-X

Somerville, L.H., Hare, T., Casey, B., 2011. Frontostriatal maturation predicts cognitive control failure to appetitive cues in adolescents. J Cogn Neurosci 23, 2123–2134. https://doi.org/10.1126/scisignal.2001449.Engineering

Steinberg, L., 2010. A dual systems model of adolescent risk-taking. Dev. Psychobiol. 52, 216–224. https://doi.org/10.1002/dev.20445

Steinberg, L., 2004. Risk taking in adolescence: What changes, and why? Ann. N. Y. Acad. Sci. 1021, 51–58. https://doi.org/10.1196/annals.1308.005

Stevenson, R.J., Francis, H.M., 2017. The hippocampus and the regulation of human food intake 143, 1011–1032.

Stoeckel, L.E., Weller, R.E., Cook, E.W., Twieg, D.B., Knowlton, R.C., Cox, J.E., 2008. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage 41, 636–647. https://doi.org/10.1016/j.neuroimage.2008.02.031

Strang, N.M., Chein, J.M., Steinberg, L., 2013. The value of the dual systems model of adolescent risk-taking. Front. Hum. Neurosci. 7, 223. https://doi.org/10.3389/fnhum.2013.00223

Swanson, L., 1982. The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res. Bull. 9, 321–353.

Telzer, E.H., Fuligni, A.J., Lieberman, M.D., Miernicki, M.E., Galvan, A., 2013. The quality of adolescents peer relationships modulates neural sensitivity to risk taking. Soc. Cogn. Affect. Neurosci. 10, 389–398. https://doi.org/10.1093/scan/nsu064

Tomasi, D., Volkow, N.D., 2014. Functional connectivity of substantia nigra and ventral tegmental area: Maturation during adolescence and effects of ADHD. Cereb. Cortex 24, 935–944. https://doi.org/10.1093/cercor/bhs382

Tsukayama, E., Duckworth, A.L., Toomey, S., 2010. Self-Control protects against overweight status in the transition from childhood to adolescence. Arch Pediatr Adolesc Med 141, 520–529. https://doi.org/10.1016/j.surg.2006.10.010.Use

Vainik, U., Baker, T.B., Alanis, J.C.G., Dadar, M., Michaud, A., Misic, B., Zeighami, Y., Zhang, Y., Collins, D.L., Dagher, A., 2017. Neurobehavioural correlates of obesity are largely heritable. bioRxiv 1–34. https://doi.org/10.1101/204917

Vainik, U., Dagher, A., Dubé, L., Fellows, L.K., 2013. Neurobehavioural correlates of body mass index and eating behaviours in adults: a systematic review. Neurosci. Biobehav. Rev. 37, 279–99. https://doi.org/10.1016/j.neubiorev.2012.11.008

van den Bos, W., Cohen, M.X., Kahnt, T., Crone, E.A., 2012. Striatum-medial prefrontal cortex connectivity predicts developmental changes in reinforcement learning. Cereb. Cortex 22, 1247–1255. https://doi.org/10.1093/cercor/bhr198

van den Bos, W., Rodriguez, C.A., Schweitzer, J.B., McClure, S.M., 2015. Adolescent impatience decreases with increased frontostriatal connectivity. Proc. Natl. Acad. Sci. 112, E3765–E3774. https://doi.org/10.1073/pnas.1423095112

van Duijvenvoorde, A.C.K., Achterberg, M., Braams, B.R., Peters, S., Crone, E.A., 2016. Testing a dual-systems model of adolescent brain development using resting-state connectivity analyses. Neuroimage 124, 409–420. https://doi.org/10.1016/j.neuroimage.2015.04.069

Watts, T.W., Duncan, G.J., Quan, H., 2018. Revisiting the marshmallow test: A Conceptual replication investigating links between early delay of gratification and later outcomes. Psychol. Sci. https://doi.org/10.1177/0956797618761661

Whelan, R., Conrod, P.J., Poline, J.-B., Lourdusamy, A., Stephens, D., Al, E., 2012. Adolescent impulsivity phenotypes characterized by distinct brain networks 15. https://doi.org/10.1038/nn.3092

Woicik, P. a, Stewart, S.H., Pihl, R.O., Conrod, P.J., 2009. The Substance Use Risk Profile Scale: A scale measuring traits linked to reinforcement-specific substance use profiles. Addict. Behav. 34, 1042–55. https://doi.org/10.1016/j.addbeh.2009.07.001

Woolrich, M.W., Ripley, B.D., Brady, M., Smith, S.M., 2001. Temporal autocorrelation in univariate linear modelling of fMRI Data. FMRIB Tech. Rep. TR01MW1 0.

Yau, P.L., Castro, M.G., Tagani, A., Tsui, W.H., Convit, A., 2012. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics. https://doi.org/10.1542/peds.2012-0324

Yau, P.L., Kang, E.H., Javier, D.C., Convit, A., 2011. Preliminary evidence of cognitive and brain abnormalities in uncomplicated adolescent obesity. Obesity (Silver Spring). 18, 1492–1501. https://doi.org/10.1016/j.str.2010.08.012.Structure

Zeighami, Y., Ulla, M., Iturria-Medina, Y., Dadar, M., Zhang, Y., Larcher, K.M.H., Fonov, V., Evans, A.C., Collins, D.L., Dagher, A., 2015. Network structure of brain atrophy in de novo parkinsons disease. Elife 4, 1–20. https://doi.org/10.7554/eLife.08440

Zhang, H.Y., Tang, H., Chen, W.X., Ji, G.J., Ye, J., Wang, N., Wu, J.T., Guan, B., 2015. Mapping the functional connectivity of the substantia nigra, red nucleus and dentate nucleus: A network analysis hypothesis associated with the extrapyramidal system. Neurosci. Lett. 606, 36–41. https://doi.org/10.1016/j.neulet.2015.08.029

Zhang, S., Li, C.R., 2013. Functional networks for cognitive control in a stop signal task: Independent component analysis. Hum. Brain Mapp. 33, 89–104. https://doi.org/10.1002/hbm.21197.Functional

Supplementary Data

Voxel-Wise Regression Analysis

Methods

We used SPM8 (Wellcome Department of Imaging Neuroscience, London, UK) to generate voxel-wise connectivity maps with each subcortical seed. The change from FSL to SPM8 was made because we found it easier to use SPM8 to analyze group data that has already been normalized into standard space. No group level analysis was performed on other software. The analyses were corrected for multiple comparisons using familywise error rate of $p < 0.05$ with a cluster defining threshold of threshold of $p = 0.001$ for cluster based correction (Pernet et al., 2015).

For each of the four seeds per hemisphere, three voxel-wise multiple regressions were carried out, each with a demographic variable of interest (BMIZ, SURPS-SS and SURPS-IMP), and variables controlling for age, gender and scan order along with an intercept variable. All variables were mean-centred. Each behavioural variable of interest was analyzed in a set of separate regressions to control for the effects of the collinearity between SURPS-SS and BMIZ for age and between SURPS-SS and SURPS-IMP detected in the behavioural correlations (section 8.1).

Results

We performed a regression between the voxel-wise connectivity of each region of interest (left and right SN, VTA, VS and STN) and each of the SURPS-IMP, SURPS-SS and BMIZ for a total of 24 comparisons. These results were significant under the original family wise error rate corrected to $p = 0.05$ but not significant when subsequently Bonferroni corrected to $p=0.002$. However, they do show distinct patterns of significance for each comparison.

Connectivity between the left VS and right ventromedial prefrontal cortex ($p = 0.01$), the connectivity between the left STN and the right temporal cortex ($p = 0.03$) and left medial parietal cortex ($p = 0.02$) were all positively correlated with IMP.

Connectivity between the right VTA and the right dorsal anterior cingulate cortex ($p = 0.005$) and the left temporoparietal junction ($p = 0.016$) and the connectivity between the left VTA and the left dorsal anterior cingulate cortex ($p = 0.006$) were negatively correlated with SS.

Connectivity between the right SN and the left entorhinal cortex ($p = 0.055$), the connectivity between the left VTA and the cerebellar vermis ($p = 0.036$), the connectivity between the left

STN and the left entorhinal cortex ($p = 0.003$) and the right parahippocampal gyrus ($p = 0.02$) and the connectivity between the right STN and the left parahippocampal gyrus ($p = 0.034$) were all positively correlated with BMIZ. The peak coordinates for each correlation can be found in Table S1.

Region of Interest Correlations

The mean correlations between the eight regions of interest (left and right, VTA, SN, VS, STN) can be found in Table S2.

References

Pernet, C.R., Latinus, M., Nichols, T.E., Rousselet, G.A., 2015. Cluster-based computational methods for mass univariate analyses of event-related brain potentials/fields: A simulation study. J. Neurosci. Methods 250, 85–93. https://doi.org/10.1016/j.jneumeth.2014.08.003

Table S1. A complete list of significant voxel-wise regression results, based on a threshold of family wise error rate (FWE) = 0.05 per individual analysis

	Regional Connectivity	Peak Coordinates (mm)	Significance
Impulsivity	Left VS – Right ventromedial prefrontal cortex	12 26 -8	0.01 FWE Peak corrected
	Left STN – Right temporal lobe	66 -12 -20	0.03 FWE Peak corrected
	Left STN – Left medial parietal cortex	-8 -52 18	0.02 FWE Cluster corrected
Sensation-Seeking	Right VTA – Right dorsal anterior cingulate cortex	4 -14 44	0.005 FWE Cluster corrected
	Right VTA – Left temporoparietal junction	-50 -56 4	0.016 FWE Cluster corrected
	Left VTA – Left dorsal anterior cingulate cortex	-4 -16 36	0.006 FWE Cluster corrected
BMI Z-Score for Age	Right SN – Left entorhinal cortex	-26 -2 -36	0.055 FWE Peak corrected
	Left VTA – Cerebellar vermis	0 -56 -16	0.036 FWE Cluster corrected
	Left STN – Left entorhinal cortex	-22 -2 -34	0.003 FWE Cluster corrected
	Left STN – Right parahippocampal gyrus	32 -34 -20	0.02 FWE Cluster corrected

	Right STN – Left parahippocampal gyrus	-34 -32 -24		0.034 FWE Cluster corrected

Table S2. Mean Pearson correlation values between the timecourses of the eight regions of interest.

	Left VTA	Right VTA	Left SN	Right SN	Left VS	Right VS	Left STN	Right STN
Left VTA	--							
Right VTA	0.88	--						
Left SN	0.77	0.64	--					
Right SN	0.61	0.67	0.71	--				
Left VS	0.31	0.31	0.39	0.39	--			
Right VS	0.30	0.29	0.37	0.37	0.80	--		
Left STN	0.74	0.66	0.80	0.63	0.36	0.36	--	
Right STN	0.72	0.79	0.66	0.76	0.38	036	0.76	--

Global Internetwork Connectivity Correlates of Body Weight, Impulsivity and Sensation-Seeking in Adolescents

Rachel J. Sharkey[a], Josiane Bourque[b], Bratislav Mišić[a], Alan C. Evans[a], Hugh Garavan[d], Marco Leyton[e], Jean R. Séguin[b], Robert Pihl[f], Patricia Conrod[b,c], Alain Dagher[a]

[a]Montreal Neurological Institute, McGill University, Montreal, QC, Canada
[b]CHU Hospital Ste-Justine, Université de Montreal, Montreal, QC, Canada
[c]Institute of Psychiatry, Psychology and Neuroscience, Kings College, London, United Kingdom
[d]Department of Psychiatry, University of Vermont, Burlington, Vermont, United States
[e]Department of Psychiatry, McGill University, Montreal, QC, Canada
[f]Department of Psychology, McGill University, Montreal, QC, Canada

Corresponding Author:

Rachel J Sharkey
rachel.sharkey.j@gmail.com
3801 University Street. Room NW253
Montreal QC, H3A 2B4
Canada

Conflicts of Interest: The authors have no conflicts of interest to declare

Keywords: Independent component analysis, Internetwork connectivity, BMI, Adolescent development.

Word Count in Abstract: 299
Figures and Tables: 18 figures, 4 tables
Supplementary Figures and Tables: 1 table

Manuscript in Preparation

Preface

The findings of the initial study of seed-based connectivity correlates of weight and impulsivity support the model that both impulsivity and body mass index relate to the function of multiple networks in the brain, and that analysis of single networks will, therefore, yield an incomplete picture of how brain function relates to both personality and weight. This is supported by the overall literature that demonstrates the association between the regions identified in the second study, the midbrain and hippocampus, as well as the regions we initially hypothesized would be involved, the corticostriatal network, and other networks entirely, including the temporoparietal junction.

On that basis we decided to follow up our analysis of seed-based connectivity with a more global, exploratory study of how the large-scale networks of the brain relate to impulsivity and body mass index.

To examine the global connectivity of the brain we used independent component analysis to identify the intrinsic, large-scale networks, and used partial least squares correlation to examine the relationship between internetwork connectivity and body mass index (Allen et al., 2012; Emerson et al., 2015; La et al., 2015; Smith et al., 2009; Thomason et al., 2011). We identified different significant latent variables, depending on whether baseline internetwork connectivity, or change in internetwork connectivity over twenty-four months was considered. The specific network pairs that were most strongly associated with body weight were, individually, either connections, or networks that have been previously associated with impulsivity, with increased weight or obesity, or both (Cole et al., 2013; Coveleskie et al., 2015; Fuentes-Claramonte et al., 2016; Gupta et al., 2018; Inuggi et al., 2014; Krafft et al., 2014; Krmpotich et al., 2013; Kullmann et al., 2012; Lee and Telzer, 2016; Lips et al., 2014; B. Park et al., 2016; Tregellas et al., 2011; Wijngaarden et al., 2015). Different sets of networks seemed to be related to body weight at the first time point and changing weight. These network findings were accompanied by alterations in network efficiency across the cortex and limbic system, but not with significant changes in grey matter density.

This study fills a gap in the literature about the relationship between intrinsic networks and body weight. The previous literature has identified multiple intrinsic network correlates with body weight, spread across multiple methodologies, including not only multiple intrinsic network properties, but also region of interest based connectivity correlated with both resting and

task based fMRI, and graph theory based analyses. To our knowledge this is the first time the full set of intrinsic networks have been considered in the same analysis in a study of neural underpinnings of obesity. This data will provide the basis for future testing, either in the completed Neuroventure dataset or in future cohorts.

Abstract

The regulation of body weight by the brain is a neurologically and behavioural complex phenomenon associated with the activity of multiple networks within the brain. Impulsivity and sensation-seeking are both personality traits associated with weight regulation which are themselves, complex and associated with the function of multiple neurological networks, independently of their connection with weight. Very few existing studies, however, examine more than one or two of these networks concurrently, when studying the neurological control of weight.

This study extracted fifteen canonical independent components from resting state fMRI of a sample of 98 adolescents assessed twice in 24 months. Internetwork connectivity between the canonical networks was calculated using unthresholded Pearson correlation, as a measure of overall interaction between the brain's large scale intrinsic networks. Partial least squares correlation was used to explore the relationship first between the intrinsic internetwork connectivity and body mass index, impulsivity and sensation-seeking; between internetwork connectivity and body mass index in isolation and internetwork connectivity; and between body mass index and change in internetwork connectivity over time.

A single latent variable related to the combination of impulsivity, sensation-seeking and body weight was identified ($p = 0.005$), that was correlated strongly with body weight ($r = 0.37$) but relatively weakly with impulsivity ($r = 0.15$) and sensation-seeking ($r = 0.05$). A latent variable relating only to weight as similarly identified ($p = 0.004$), but correlations with between weight and change in internetwork connectivity over time were non-significant.

These results support the idea that weight is neurologically controlled by the combined activity of multiple different networks, encompassing both cortical and subcortical elements. It also finds that while impulsivity, sensation-seeking and body weight share networks in common, they are neurologically distinct, with numerous networks that are not related to impulsivity or sensation-seeking contributing to regulation of body weight.

Introduction

Global intrinsic connectivity networks are a well-established feature of resting-state functional magnetic resonance imaging (fMRI). They make up a relatively reproducible set of networks which resemble those elicited during task performance, suggesting that they represent groups of brain areas that co-activate during specific cognitive events or tasks (Biswal et al., 1995; Laird et al., 2011; Smith et al., 2009). Canonical resting-state intrinsic networks have been identified both in adults and children and are stable over repeated scanning sessions (Geerligs et al., 2015; Muetzel et al., 2016; Shehzad et al., 2009; Thomason et al., 2011). Group Independent Component Analysis (ICA) is one common method for identifying intrinsic networks in the brain, that allows for networks to be spatially matched between subjects and scan sessions. Multiple properties of ICA derived networks can be related to individual variation in behaviour or task performance (Allen et al., 2012, 2011; Calhoun et al., 2001). Internetwork connectivity in resting state fMRI uses correlation between the time courses of blood oxygen level dependent (BOLD) signal in ICA-based networks as a measure of connectivity on a global level. Internetwork connectivity has been shown to vary with age, gender and task training (Allen et al., 2012; Doll et al., 2015; Emerson et al., 2015; La et al., 2015).

Resting state connectivity has been previously associated with personality, with different traits having different relationships to various intrinsic networks (Adelstein et al., 2011). Connectivity has also, independently, been related to obesity and increased body weight using multiple connectivity metrics, including connectivity within or between specific regions of interest, graph theory metrics and ICA measures (Baek et al., 2017; Coveleskie et al., 2015; Krafft et al., 2014; B. Park et al., 2016; Tregellas et al., 2011). Body weight regulation is a complex phenomenon which has been linked to the functions of multiple networks including those governing homeostatic regulation, reward, executive control and the default mode network, which is associated with interoception (Coveleskie et al., 2015; Krafft et al., 2014; B. Park et al., 2016; Tregellas et al., 2011).

Impulsivity (IMP), a tendency to favour short-term goals and rewards, and sensation-seeking (SS), a desire for novel or intense sensations, are two personality traits that have been associated with higher weight and risk for weight gain (Gerlach et al., 2015; Vainik et al., 2013). Variation in IMP and SS have also, in separate studies, been associated with variation in many of

the same resting-state networks that have been separately associated with variation in body weight (Lee and Telzer, 2016; B.-Y. Park et al., 2016; B. Park et al., 2016).

However, these studies are currently fragmented, with findings coming from multiple methodologies, age groups, and weight groups (obese vs non-obese, healthy weight, continuous samples, etc) and with most studies of the relationship between personality and weight being conducted separately form the neural correlates of personality. This study therefore aimed to examine the relationship between body weight and internetwork connectivity in a data-driven, exploratory manner by analyzing the correlates between body weight and internetwork connectivity in an unbiased set of ICA networks.

Methods

Participants

Neuroventure

Neuroventure is an ongoing longitudinal study of the neurological development of adolescents in relation to IMP, SS and risk for alcohol misuse. It is an imaging add-on to the larger Coventure trial, which is testing the effects of a personality trait-specific psychological intervention on reducing the incidence of alcohol use problems in adolescents (Bourque et al., 2016; Conrod et al., 2008; O'Leary-Barrett et al., 2017). The Neuroventure cohort consists of 151 healthy adolescents imaged during seventh grade (age 12 - 14) during the first data collection. Participants were selected who either had a IMP and/or SS score on the Substance Use Risk Profile Scale (SURPS) greater than 1 SD above the mean for their school, classified as either impulsive or sensation-seeking, and control participants who scored within 1 SD of their school mean on both IMP and SS scores. These participants will be imaged a total of three times across five years. The present paper reports imaging and BMI Z-score for age (BMIZ) results from the first time point and the 24 month follow up (Bourque et al., 2016).

Final Sample

The final sample included in this study consists of 98 participants. Only those with complete resting state MRI scans and BMI data at both time points were included. Six participants from the entire study were excluded due to incidental findings of enlarged ventricles or arachnoid cysts on MRI. Another 47 were missing either imaging or BMI data. Of the remaining 98 participants, 46 were male, 52 were female, with an average age of 163.5 ± 7.7 months at the

first time point and 178.1 ± 5.9 at the second. For the following analysis the Neuroventure sample was treated as a single group enriched for IMP and SS. 65 of the subjects had entered puberty at time point one (assessed based on menarche for females, and voice-breaking for males), and 89 by the second time point.

Demographic and behavioural Data

Substance Use Risk Profile Scale

Each participant completed the SURPS, which assesses four personality traits known to increase risk for drug or alcohol abuse: hopelessness, anxiety sensitivity, SS and IMP (Krank et al., 2011; Woicik et al., 2009). IMP and SS subscale scores were used in this study as they are features thought to be most strongly associated with excessive weight gain (Bourque et al., 2016; Jurk et al., 2015; MacPherson et al., 2010; Moreno-Lopez et al., 2016).

Body Mass Index and Z-Score for Age

Height and weight were measured before scanning at each session and used to calculate BMI. BMI was converted into an age-related z-score based on the standardized CDC growth curves for each subject using EpiInfo (http://www.cdc.gov/epiinfo/7/) and self-reported date of birth. The use of BMIZ allows comparisons between children of different ages (Kuczmarski et al., 2002). The changes in BMI and BMIZ were calculated by subtracting the first time point from the second (Figure 1).

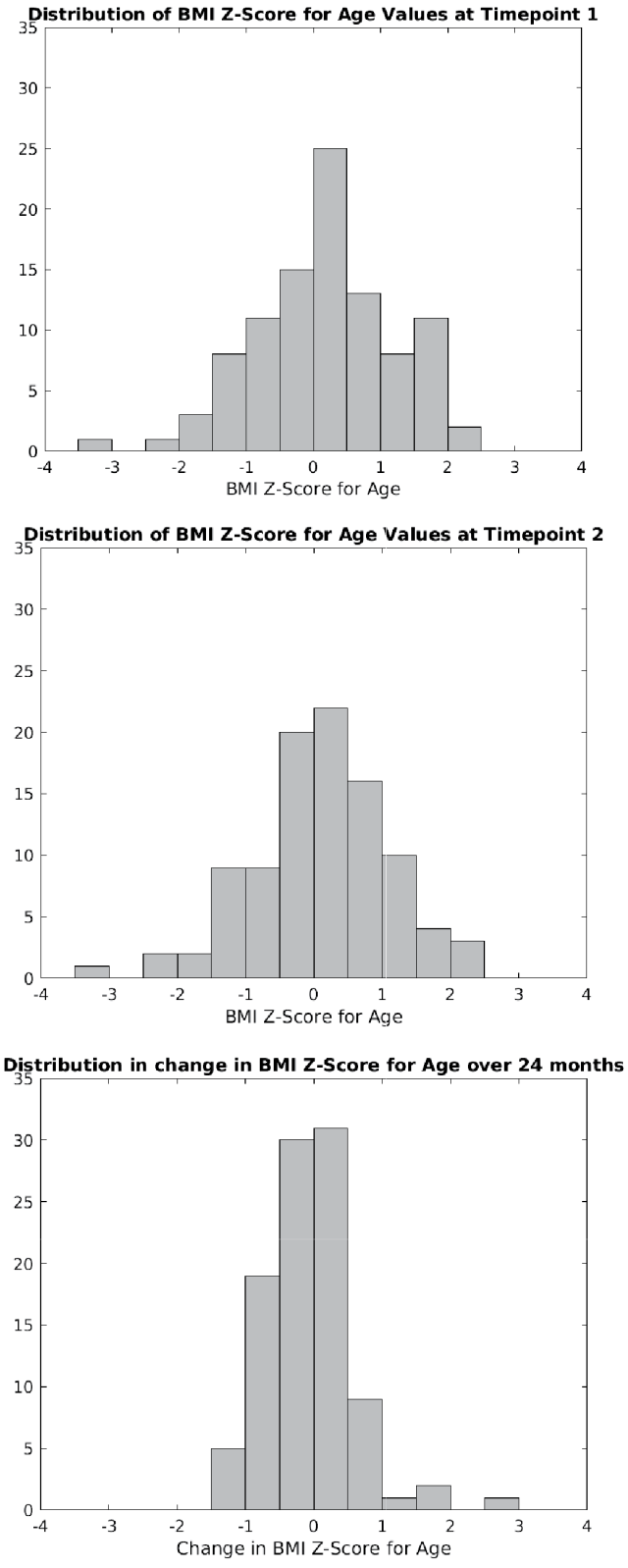

Figure 1. Distribution of BMI Z-score for age in the subset of the Neuroventure cohort used in the present study, at the first and second time points, and the distribution in change over 24 months

MRI Data Collection

At each time point, resting state functional magnetic resonance imaging (rsfMRI) data was collected as one of a series of MRI acquisitions in a single session. All scans were collected on a Siemens Trio 3.0T scanner. BOLD data was collected in the resting state in a single 6-minute run of 152 volumes of 40 axial slices with 3.5mm isotropic voxels in a 224mm FOV (TE = 30ms, TR = 2340ms). Participants were instructed to close their eyes. Acquisition order of the resting state data was changed over the course of the study to improve compliance. The resting state acquisition was initially placed last in the acquisition sequence following task-based fMRI acquisitions and a diffusion tensor acquisition. Due to issues with participants falling asleep, it was later moved to before the diffusion tensor acquisition. Five participants had their resting state acquisition performed before both the task based fMRI and diffusion tensor acquisitions due to an error in the acquisition.

Also, a high-resolution T1-weighted anatomical image was collected using a MPRAGE sequence (192 sagittal slices, 1.0mm isotropic voxel, 256mm FOV, TE = 2.96ms, TR = 2300 ms).

MRI Data Preprocessing

Preprocessing for this study was based on the pipeline previously used by Sharkey et al (2019), on the Neuroventure dataset. Note that previous studies on appropriate denoising for Group ICA data have found that group ICA results are less sensitive to variation in preprocessing than the seed based methods used in Chapter 3 (Andronache et al., 2013; Sharkey et al., 2019).

FEAT Preprocessing

Basic rsfMRI data preprocessing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). This included; motion correction using the MCFLIRT tool; slice-timing correction using Fourier-space time-series phase shifting; non-brain removal using the BET tool and grand mean intensity normalization (Jenkinson et al., 2002; Smith, 2000).

Independent Component Analysis Based Denoising

Independent component analysis (ICA) based denoising was carried out using the ICA based Automatic Removal of Motion Artifacts (ICA-AROMA) toolbox, from the FSL library.

Analysis was carried out using Probabilistic ICA as implemented in Multivariate Exploratory Linear Decomposition into Independent Components Version 3.14, part of FSL. Probabilistic

ICA generates a set of spatial independent components (brain maps) and their associated time-courses and power spectra.(Beckmann and Smith, 2004).

ICA-AROMA then identifies the independent components that represent motion artifacts using a predetermined classifier. The classifier applies the following rules: high edge fraction (signal near tissue boundaries in the brain), correlation with head realignment parameters from motion correction, large signal in CSF (> 10%), and high-frequency content (> 35%). Motion-associated components are then removed via linear regression (Pruim et al., 2015b).

Registration

Registration to high-resolution structural and standard space images was carried out using FLIRT, also part of the FEAT toolbox (Jenkinson et al., 2002; Jenkinson and Beckmann, 2001).

Band Pass Filtering

Deobliquing and bandpass filtration between 0.1 and 0.01 Hz were carried out using the AFNI 3drefit and 3dFourier tools (Cox, 1996; Cox and Hyde, 1997).

Smoothing

Spatial smoothing was done using a 6mm Full Width Half Maximum Gaussian kernel using fslmaths, part of FSL (www.fmrib.ox.ac.uk/fsl).

Group Independent Component Analysis

Group-ICA

Group ICA to identify intrinsic networks was performed once including all participants at both time points. This method ensures matching components in all scans, using the Group ICA of fMRI Toolbox (GIFT) (http://mialab.mrn.org/software/gift/). GIFT is a Matlab based toolbox that utilizes functions from SPM (Wellcome Department of Imaging Neuroscience, London, UK). These analyses were done in GIFT v4.0 and Matlab 2017b (Mathworks Inc.). Minimum description length (MDL) estimated 72 components in the dataset. Because the excessive computing requirements using the MDL estimated number made subsequent analyses unfeasible, a fixed number of 34 components was estimated. This number was chosen to match the number of SCANLab templates of intrinsic resting state components used here (Thomason et al., 2011; www.brainnexus.com/resting-state-fmri-templates).

Spatial Template Selection

Template matching is a method of identifying which components generated using ICA in a given study best reflect previously identified canonical components. This is done by comparing

the spatial distribution of the components to an existing template, derived either from another study, from the aggregate of several studies, or from anatomically derived masks. Generally, correlation between the voxel-wise z-scores of each component and the mask values give a degree of similarity and the template with the highest correlation is used to label the component. Several sets of ICA templates exist, based on different datasets. 13 canonical templates from two sets were combined in this study.

SCANLab Templates

The SCANLab templates are a set of ICA templates of the canonical resting state network components based on a sample of young adolescents. These templates, therefore, reflect a spatial distribution of components that is age-appropriate.

The complete details of the creation of the SCANLab ICA templates are available, along with the templates and associated demographic information from the sample, at the SCANLab website (www.brainnexus.com/resting-state-fmri-templates). These templates were generated from a sample of 62 children and adolescents ranging in age from 9 to 15 years (mean 12.5 ± 2.0). Thirty-Four Group ICA components were extracted using GIFT and were back-reconstructed to the individual scans. The components that most closely corresponded to canonical networks based on automatic template matching were used to form 12 templates corresponding to the default mode, left and right executive, salience, visual, auditory, motor, anterior cingulate/precuneus, parietal association, supplementary motor, posterior default and inferior frontal gyrus (IFG)/middle temporal networks (Thomason et al., 2011; www.brainnexus.com/resting-state-fmri-templates).

Laird Templates

Based on previous research using the Neuroventure cohort the midbrain and limbic systems were thought to be related to impulsivity, sensation-seeking and BMI Z-score for age. To ensure that these regions were well represented in this study, specific midbrain and limbic components from a second set of templates were added.

Refer to Laird et al., 2011, for the complete details of the creation of these templates. Briefly, 20 ICA components were extracted from fMRI meta-analysis data from the brainmap database using the FSL MELODIC toolbox and those components were matched to the behavioural data from the same dataset using hierarchical clustering (Laird et al., 2011). The Laird templates have been previously used in analysis of adolescent resting-state dataset (Lee and Telzer, 2016).

Component Identification

Eleven of the twelve SCANLab templates were used in the study. Only a single default component was used. A previous study done in our lab identified the connectivity between the limbic system and the midbrain as specifically relevant to BMI in the Neuroventure population. Therefore, to ensure good coverage of these regions, two additional templates, specifically identified as Limbic (ICA component 1) and Midbrain (ICA component 5) from the Laird dataset downloaded from the brainmap.org database (www.brainmap.org/icns/) were added to the SCANLab template set.

The spatial correlation between the ICA components identified by GIFT for each session and the selected SCANLab and Laird templates was calculated using the component sorting, spatial correlation tool in the GIFT toolbox. For each template, the maximum spatial correlation was calculated with each of the mean components for session one, session two, and the combined mean. In cases where different components were most strongly associated with a template at the two time points, both were included to maximize the amount of variation over time captured by the data.

Behavioural Correlations

Unadjusted Pearson correlations were performed between age, gender, BMI Z-score for age, impulsivity and sensation seeking at each time point to examine the internal structure of the data.

Motion Correlation

The absolute root mean square displacement is automatically calculated by MCFLIRT, part of the FEAT Preprocessing pipeline (section 4.1). The mean displacement for each subject was calculated, and for each session, it was correlated with the BMI Z-score for age for each subject.

Partial Least Squares Correlation

Impulsivity, Sensation-Seeking, BMI Z-Score for Age and Internetwork Connectivity at Time Point One

To examine the relationships between network features and behavioral measures in the initial dataset a partial least squares (PLS) correlation was conducted using the internetwork connectivity based on component time course correlations and three personality and demographic variables: the impulsivity and sensation-seeking sub-scales from the SURPS IMP, SS and BMI Z-score for age at the first time point. PLS correlations extract latent variables from the covariance between two sets of data. PLS is robust to collinearity and relatively small sample

sizes (Krishnan et al., 2011; Sawatsky et al., 2015). The PLS analysis was performed using the Baycrest Lab PLS package in MATLAB as a behavioural PLS (option 3) with 20,000 permutations and bootstrapping samples (Mathworks Inc; https://www.rotman-baycrest.on.ca/index.php).

PLS creates a dimensionally reduced regression test of the shared variance between two sets of data, in the form of the correlation between two matrices (the brain connectivity and the BMIZ and personality data) that is subjected to singular value decomposition. This results in a set of singular values, ranked proportionally to the amount of variance they explain.

The permutation testing was conducted by randomly permuting the data in the connectivity table. The significance represents the proportion of singular values which are greater than the original.

Bootstrapping tests the reliability of the contributions of the connectivity and BMI and personality values. Rows from the original tables were resampled with replacement and the correlation table and singular value decompositions were repeated on the resampled tables. The ratio of the original weight and its bootstrap standard error (called the bootstrap ratio) indicate the strength and stability of each contribution. For a more detailed explanation of PLS correlations refer to (Mišić et al., 2016).

BMI Z-Score for Age and Internetwork Connectivity at Time Point One

Based on the results of the first PLS correlation, a second PLS correlation was run using only BMI Z-score for age at time point one in one matrix, and the internetwork correlation values in the second (i.e. IMP and SS were omitted). The same PLS parameters were otherwise used.

BMI Z-Score for Age and Internetwork Connectivity at Time Point Two

The second PLS correlation was repeated with the BMI Z-score for age and internetwork connectivity at the second time point, to retest the relationship at twenty-four month follow-up.

BMI Z-Score for Age at Time Point One and Change in Internetwork Connectivity over 24 Months

To examine the relationship between initial weight and changes in intrinsic networks a third PLS correlation, with the same parameters as the first and second, was conducted with BMI Z-score for age at the first time point and the residuals of the internetwork connectivity values at time point two, once the values at time point one had been regressed out.

Change in BMI Z-Score for Age and Internetwork Connectivity over 24 Months

The relationship between change in weight and change in internetwork connectivity a four PLS correlation was conducted including the residuals of BMI Z-score for age at time point two, once BMI Z-score for age at time point one was regressed out, and the residuals of internetwork connectivity at time point two once connectivity at time point one was regressed out.

Grey Matter Density Correlations

CIVET Grey Matter Density Extraction

The T1 weighted image was processed using the CIVET (version 2.0.0) image processing pipeline (Ad-Dab'bagh et al., 2006) to compute gray and white matter boundaries and surfaces. Images were first linearly registered to MNI space based on the ICBM152 template. N3 was used to correct for non-uniformity and INSECT, a neural net classifier, was used to classify all voxels into gray matter, white matter and cerebrospinal fluid. Data were smoothed using a surface based 20mm Gaussian kernel. On the basis of the classification, grey and white matter density maps were calculated for each subject. The complete details of the CIVET pipeline can be found at http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET.

The mean components from each of the original group ICA analysis were binarized using the fslmaths tool to create component masks and the mean grey matter density of the components was extracted from the grey matter density maps for each subject at each time point.

Grey Matter Density Correlation

The grey matter density of three components, the limbic, auditory and first midbrain components were correlated with the PLS brainscores for each of the significant PLS analyses using the corrcoef command in Matlab (Mathworks Inc.).

Graph Theory Analysis

Brainnetome Atlas

The Brainnetome Atlas is a parcellation of the brain designed for connectivity studies. The current version of the atlas has 246 cortical and subcortical regions which were defined based on a combination of multimodal anatomical and connectivity variation. The complete details of the Brainnetome Atlas can be found at atlas.brainnetome.org/index.html.

Regional Data Extraction

For each subject at each of the two study times the BOLD time course of each Brainnetome atlas region was extracted, and a correlation table of complete inter-regional correlations was

calculated in Matlab (Mathworks Inc). The resulting correlation tables were used as connections in a graph for the calculation of the following graph properties.

Global Efficiency

Global efficiency is an average measure of how quickly information can be moved between two nodes of the brain. The weighted efficiency script from the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/), was used to calculate the global efficiency of each subject, at each time point, along with the change in global efficiency between the two time points. The Brain Connectivity Toolbox is a Matlab based toolbox for applying graph-theory measures to functional brain imaging data. Three correlations between the global efficiency and the BMI Z-score for age data were conducted. Global efficiency and BMI Z-score for age at time point one were correlated, change in global efficiency over 24 months was correlated with BMI Z-score for age at time point one, and change in global efficiency over 24 months was correlated with change in BMI Z-score for age over 24 months.

Local Efficiency

Local efficiency is a measure of how efficiently information can be moved within the immediate neighbourhood of a given node. The local efficiency of each node (brainnetome region) for each subject at each time point was calculated using the brain connectivity toolbox weighted efficiency script. Three correlations between the local efficiency and the BMI Z-score for age data were conducted. Local efficiency and BMI Z-score for age at time point one were correlated, change in local efficiency over 24 months was correlated with BMI Z-score for age at time point one, and change in local efficiency over 24 months was correlated with change in BMI Z-score for age over 24 months. To control the false positive rate, the results were corrected for multiple comparisons using the fdr_bh toolbox, a Matlab toolbox for performing Benjamini & Hochberg false discovery rate correction. The fdr_bh toolbox offers two forms of false discovery rate correction; the more rigorous fully-dependent form was used for all corrections in this study (https://www.mathworks.com/matlabcentral/fileexchange/27418-fdr_bh).

Betweenness Centrality

Betweenness centrality is a measurement of how densely connected a given node is, based on how many of the most efficient connections in a network involve that node. The betweenness centrality of each node for each subject at each data collection was calculated using the brain

connectivity toolbox weighted betweenness centrality script. Three correlations between the betweenness centrality and the BMI Z-score for age data were conducted. Betweenness centrality and BMI Z-score for age at time point one were correlated, change in betweenness centrality over 24 months was correlated with BMI Z-score for age at time point one, and change in betweeness centrality over 24 months was correlated with change in BMI Z-score for age over 24 months. To control the false positive rate, the resulting data was corrected for multiple comparisons using the fdr_bh toolbox, a Matlab toolbox for performing Benjamini & Hochberg false discovery rate correction. The more rigorous fully-dependent form of correction was used for all corrections in this study (https://www.mathworks.com/matlabcentral/fileexchange/27418-fdr_bh).

Results

Component Identification

Eight of the templates were maximally correlated to a single resting-state component, indicated by a number in brackets at both study time points: the auditory (1), left executive (9), motor (10), limbic (16), default (18), parietal association (19), right executive (23) and visual (33) networks.

Three templates were maximally correlated to different components at study time point one versus time point two: the supplementary motor (27 and 5), IFG/middle temporal (8 and 22) and midbrain (31 and 25). While these numbers are arbitrary, the use of a single group ICA analysis means that the numbers do identify different and specific networks.

Two of the templates, the anterior cingulate/precuneus and the salience templates both maximally matched to the same component (29) so a single composite label, salience, was used in the following studies.

The spatial maps of all of the components used to generate the internetwork connectivity maps are included in the supplementary material (Figures 2 – 16).

Behavioural correlations

The correlations between the behavioural variables at the first study time point can be seen in Table 1, the correlations between variables at the second time point can be seen in Table 2. SS and BMIZ were significantly correlated at the first study time point, but not at the second.

Table 1. Behavioural correlations between age, gender impulsivity score, sensation-seeking score and BMI Z-score for age, at time point one. *Indicates $p < 0.05$ uncorrected.

	Age (months)	Gender	SURPS Impulsivity	SURPS Sensation-Seeking	BMI Z-Score for Age
Age (months)	--				
Gender	0.064	--			
SURPS Impulsivity	0.059	-0.073	--		
SURPS Sensation-Seeking	-0.004	0.085	0.176	--	
BMI Z-Score for Age	0.130	0.060	0.100	0.215*	--

Table 2. Behavioural correlations between age, gender, impulsivity score, sensation-seeking score and BMI Z-score for age, at time point two *Indicates $p < 0.05$ uncorrected.

	Age (months)	Gender	SURPS Impulsivity	SURPS Sensation-Seeking	BMI Z-Score for Age
Age (months)	--				
Gender	0.036	--			
SURPS Impulsivity	0.039	-0.073	--		
SURPS Sensation-Seeking	-0.077	0.085	0.176	--	
BMI Z-Score for Age	0.100	0.024	0.145	0.014	--

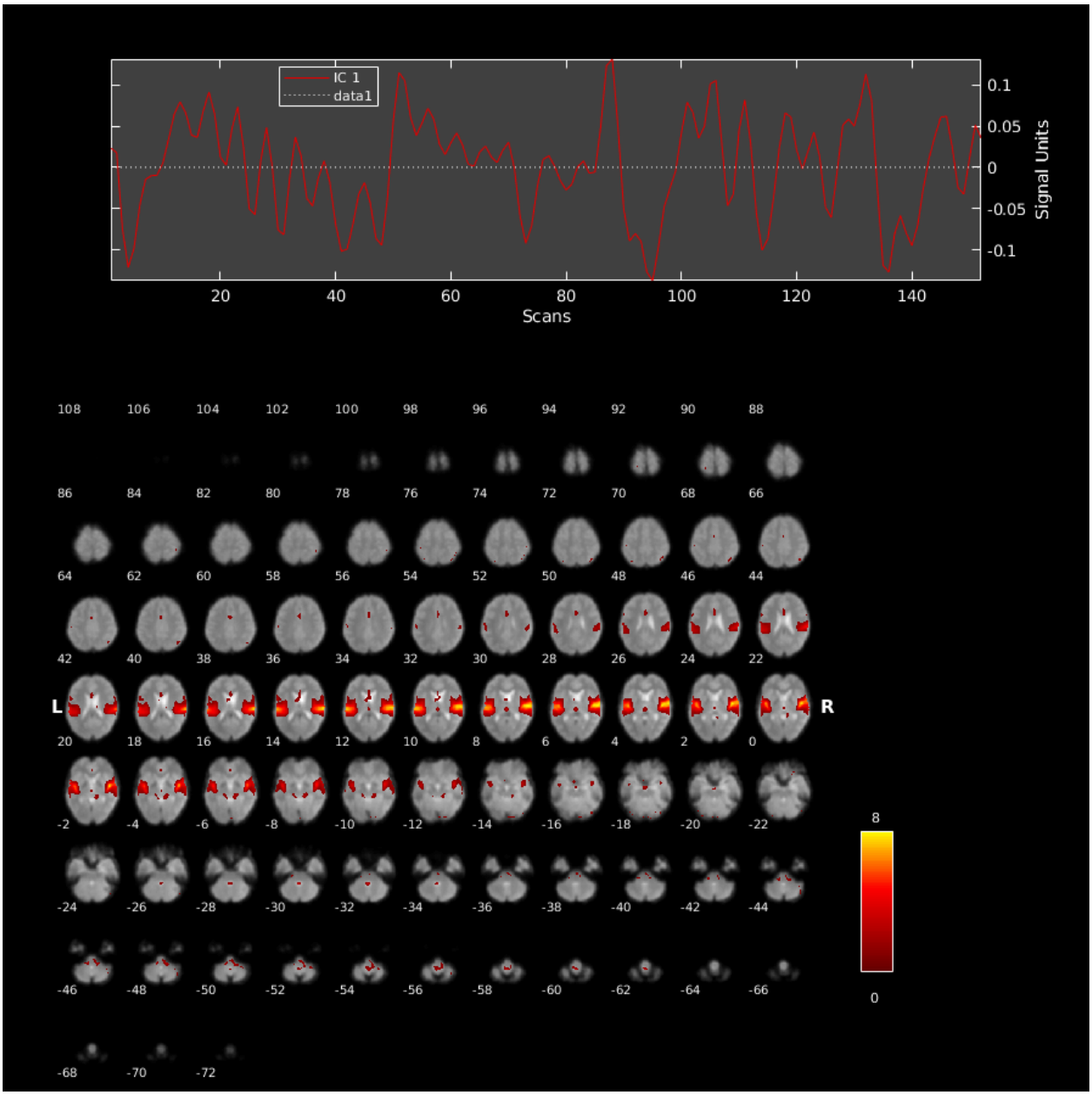

Figure 2. Component 1, which was matched to the auditory template in this dataset.

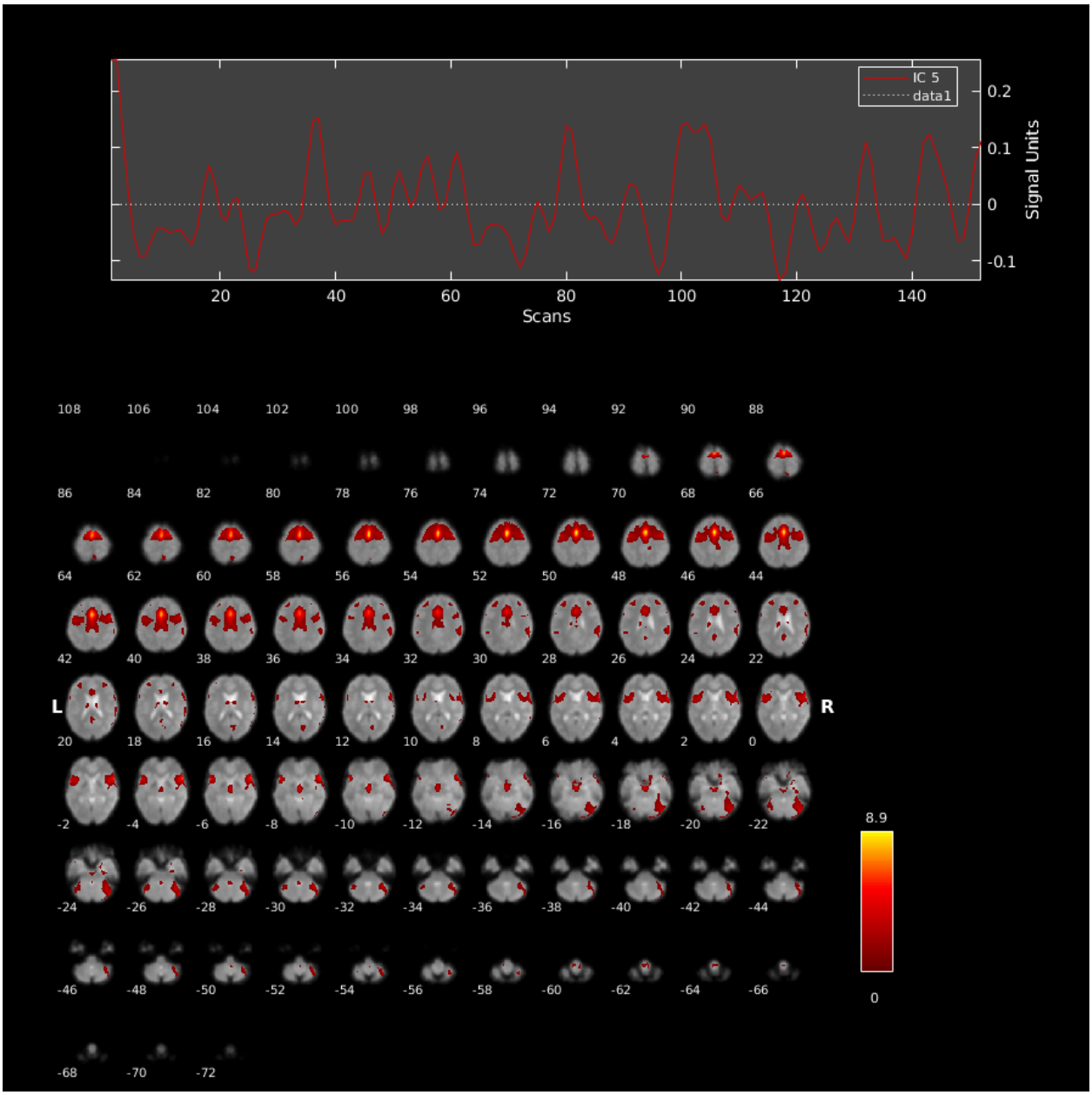

Figure 3. Component 5, which was matched to the supplementary motor template in this dataset.

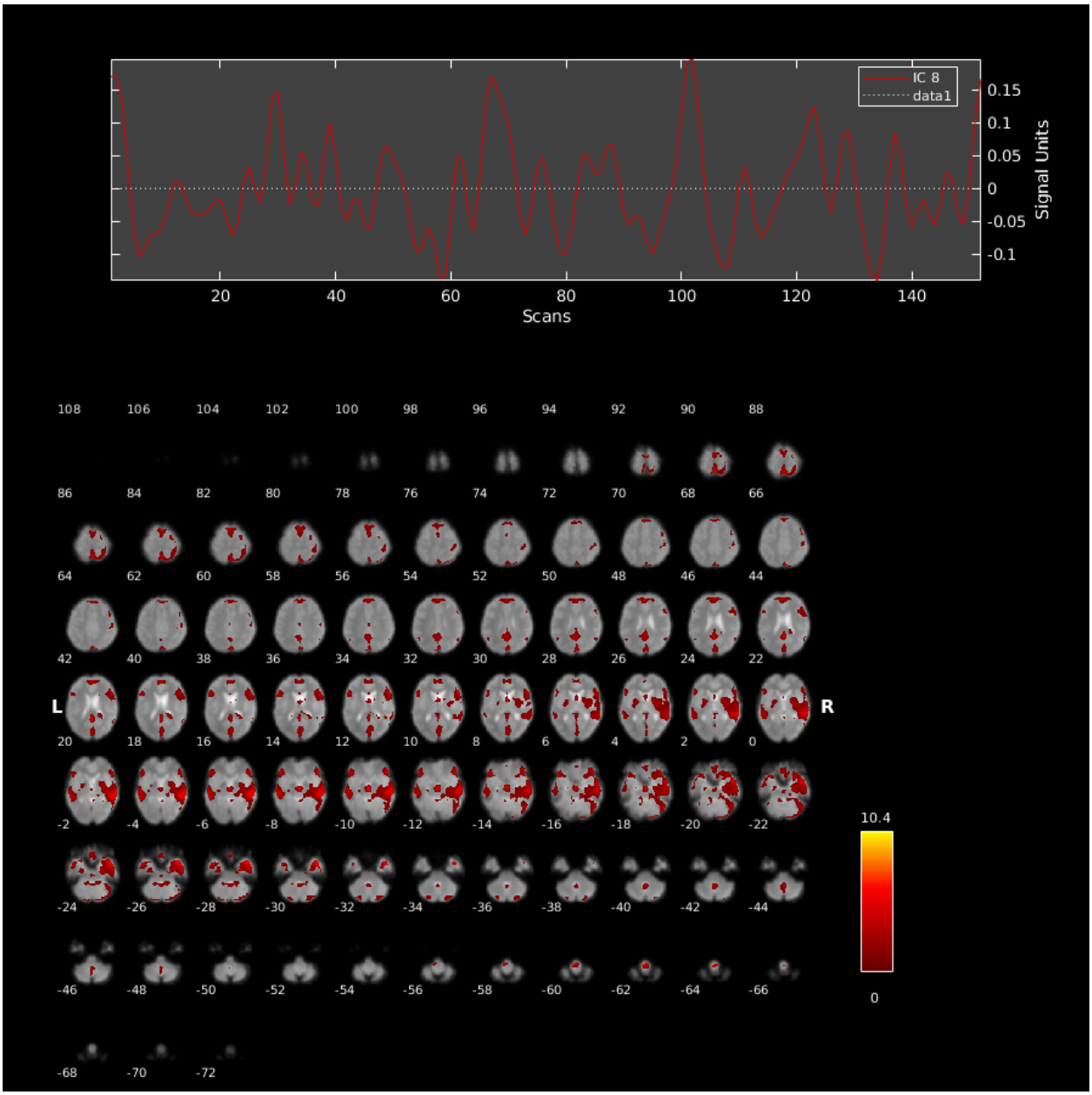

Figure 4. Component 8, which was matched to the IFG/middle temporal template in this dataset.

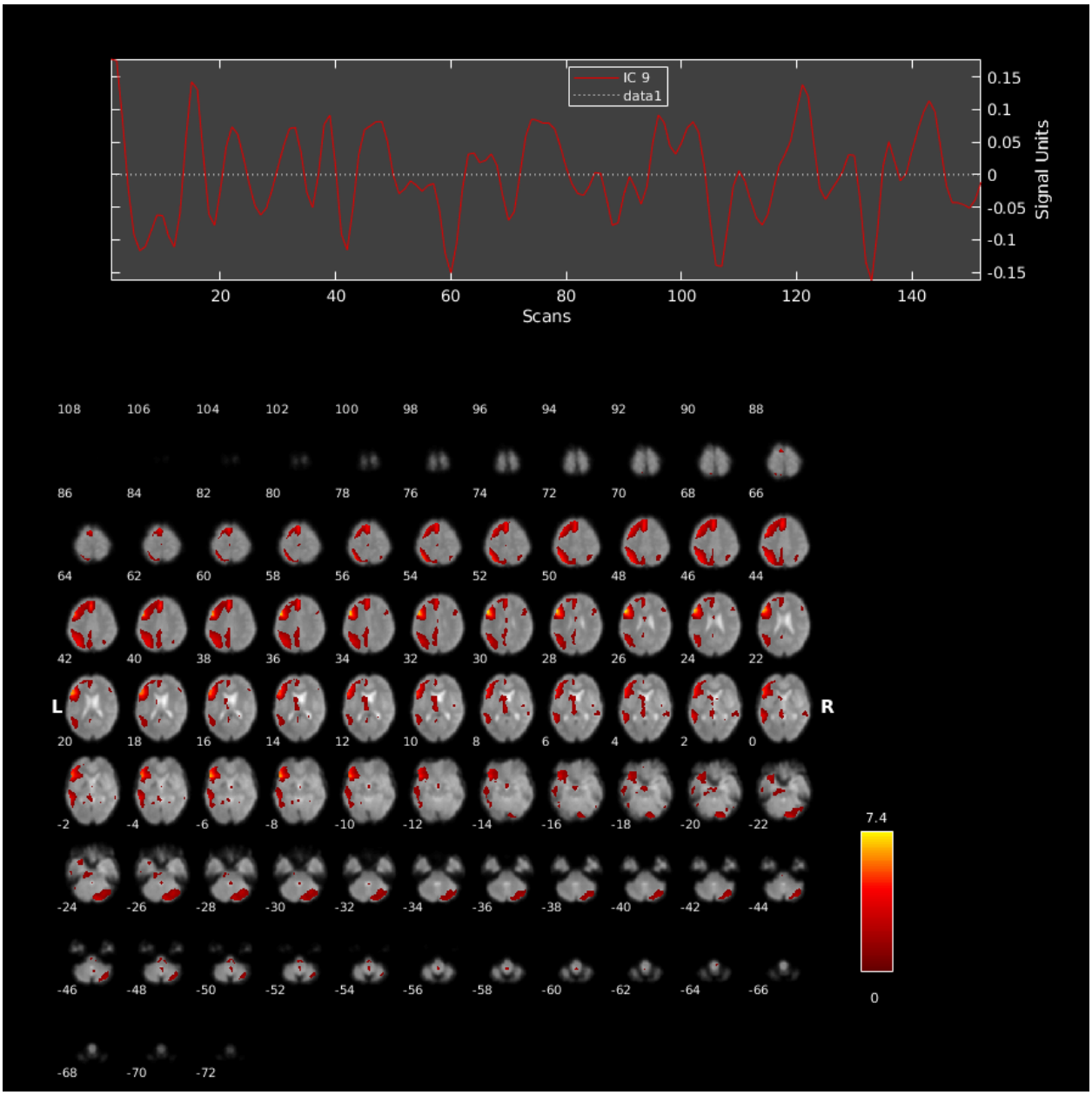

Figure 5. Component 9 which was matched to the left executive template in this dataset.

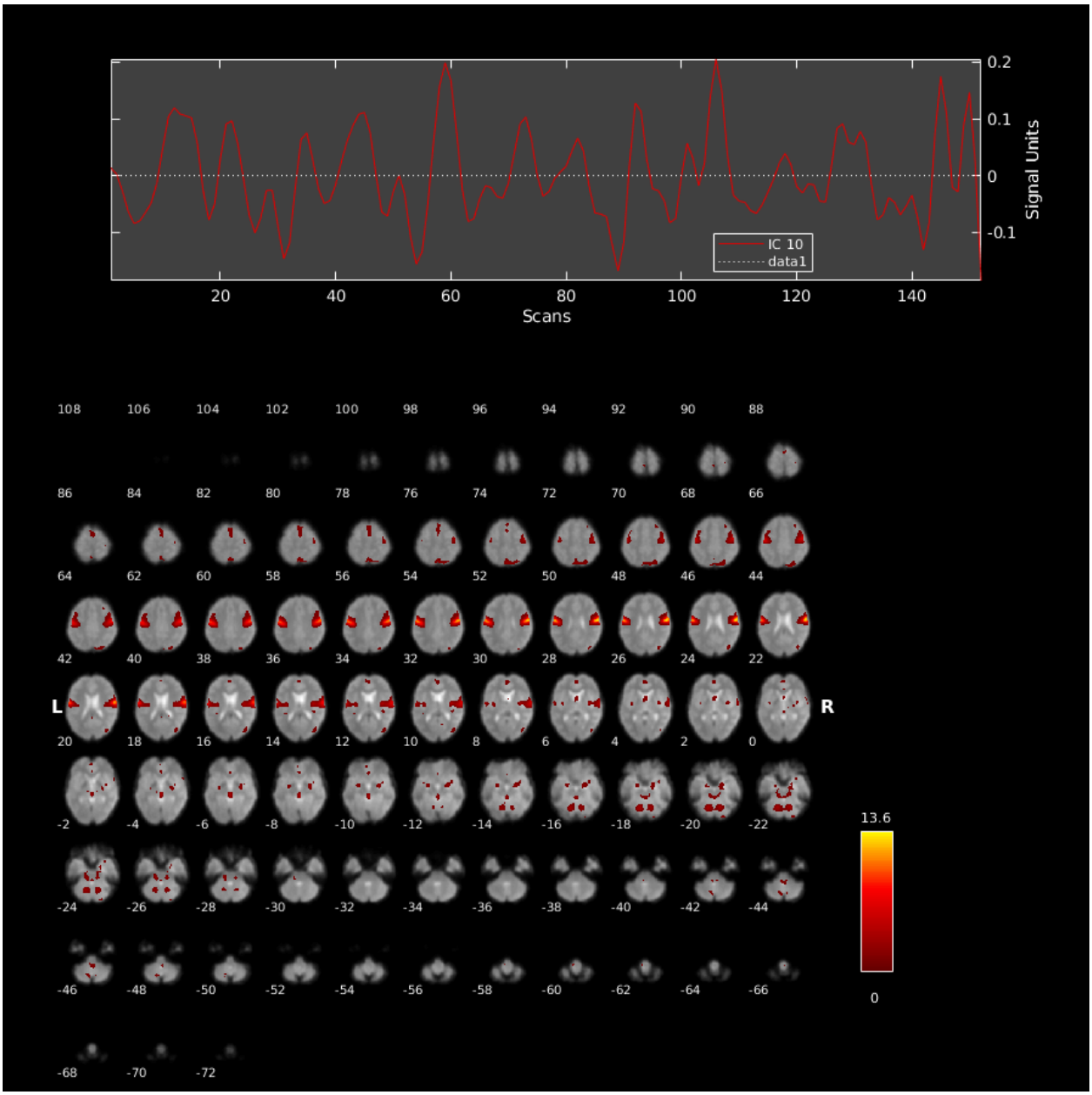

Figure 6. Component 10, which was matched to the motor template in this dataset.

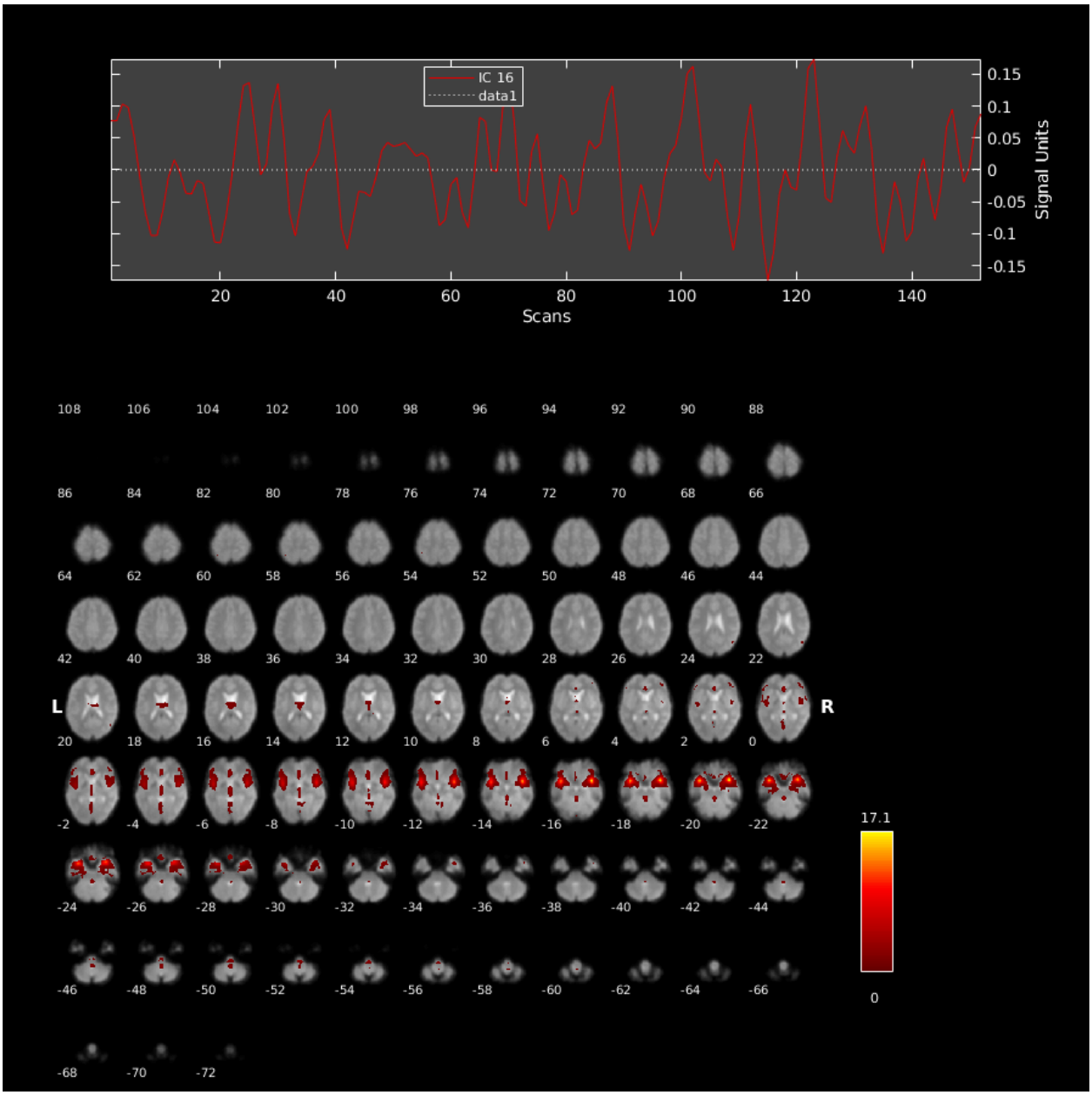

Figure 7. Component 16, which was matched to the limbic template in this dataset.

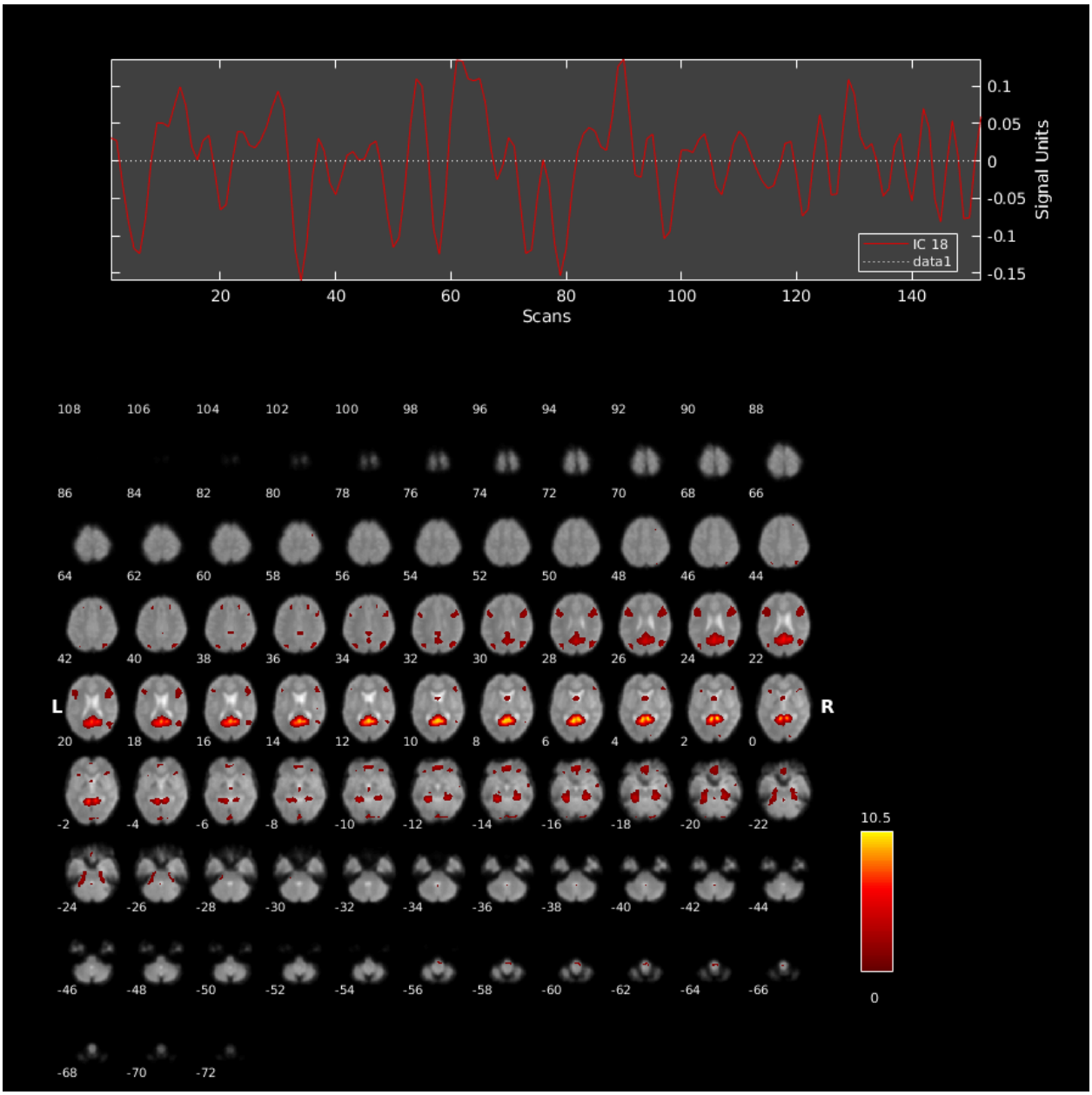

Figure 8. Component 18, which was matched to the default template in this dataset.

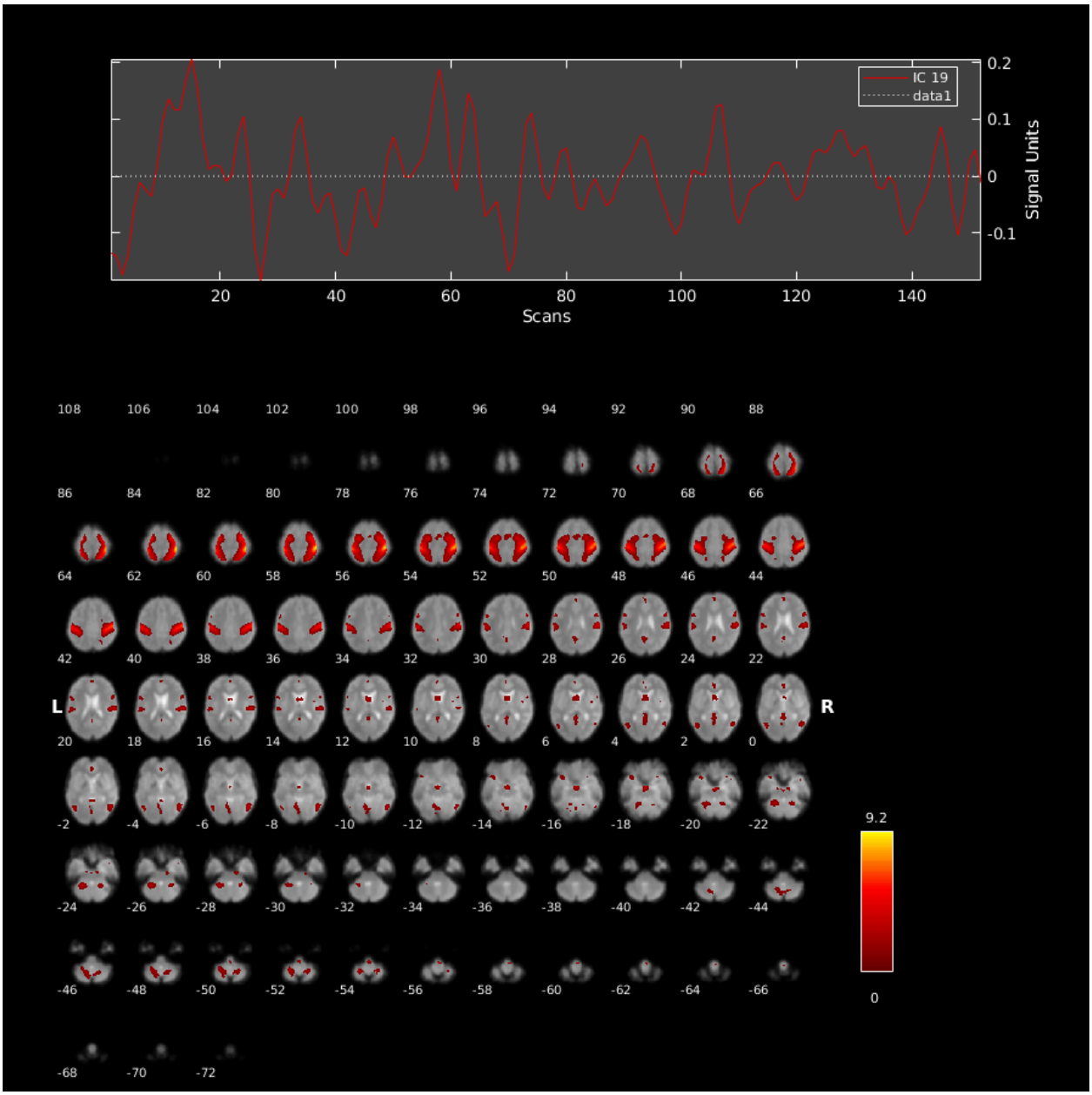

Figure 9. Component 19, which was matched to the parietal association template in this dataset.

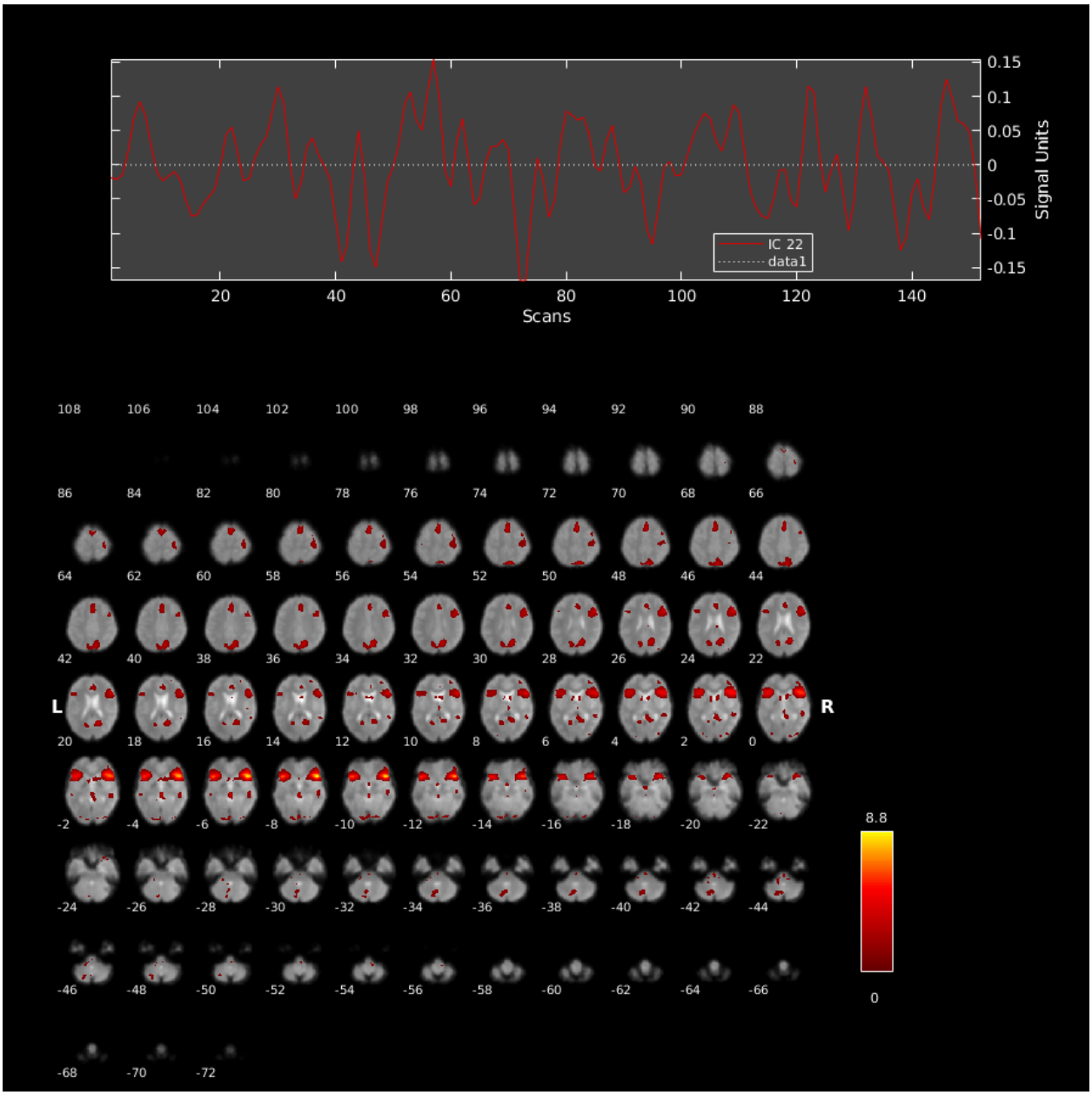

Figure 10. Component 22, which was matched to the IFG/middle temporal template in this dataset.

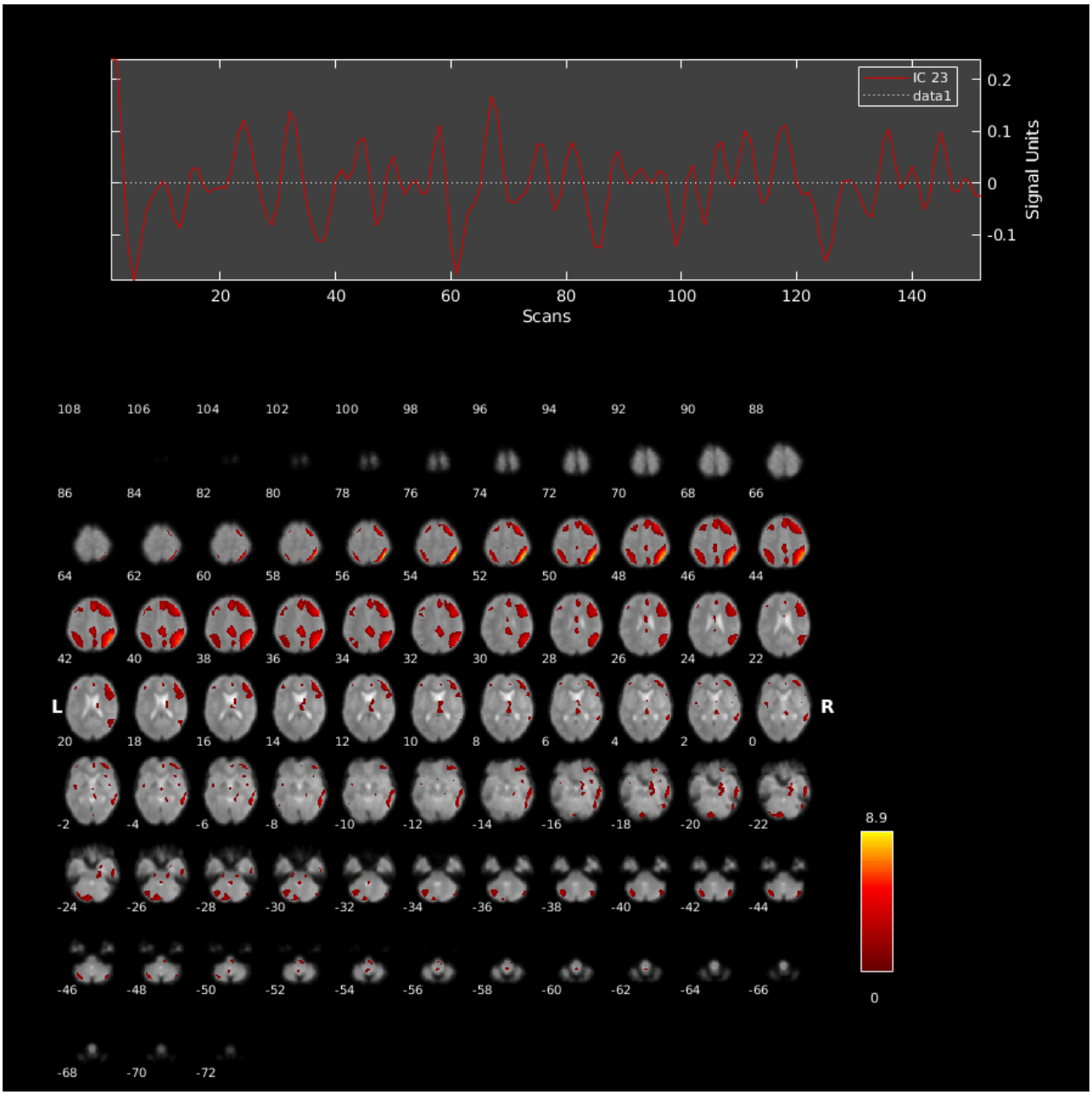

Figure 11. Component 23, which was matched to the right executive template in this dataset.

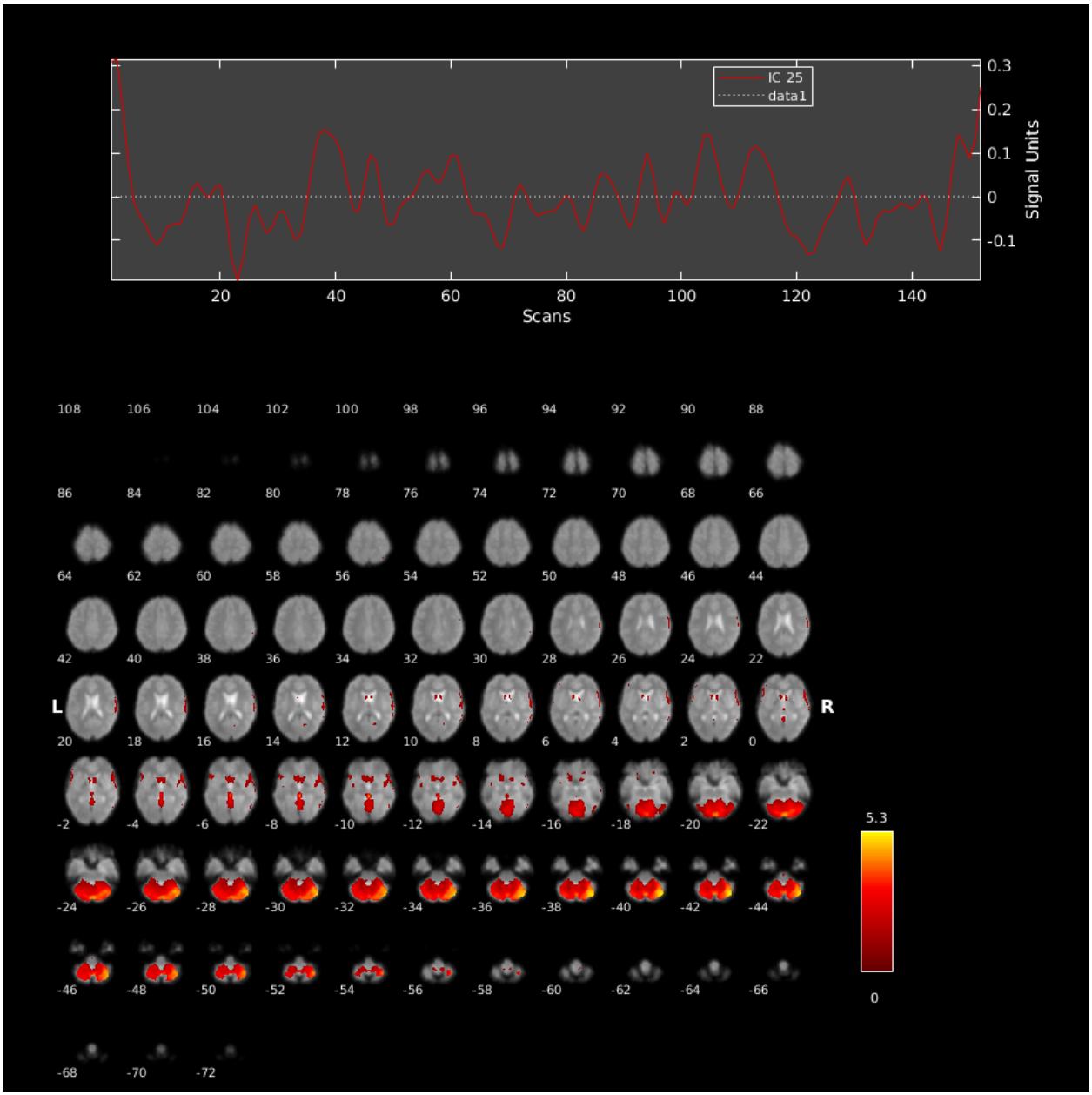

Figure 12. Component 25, which was matched to the midbrain template in this dataset.

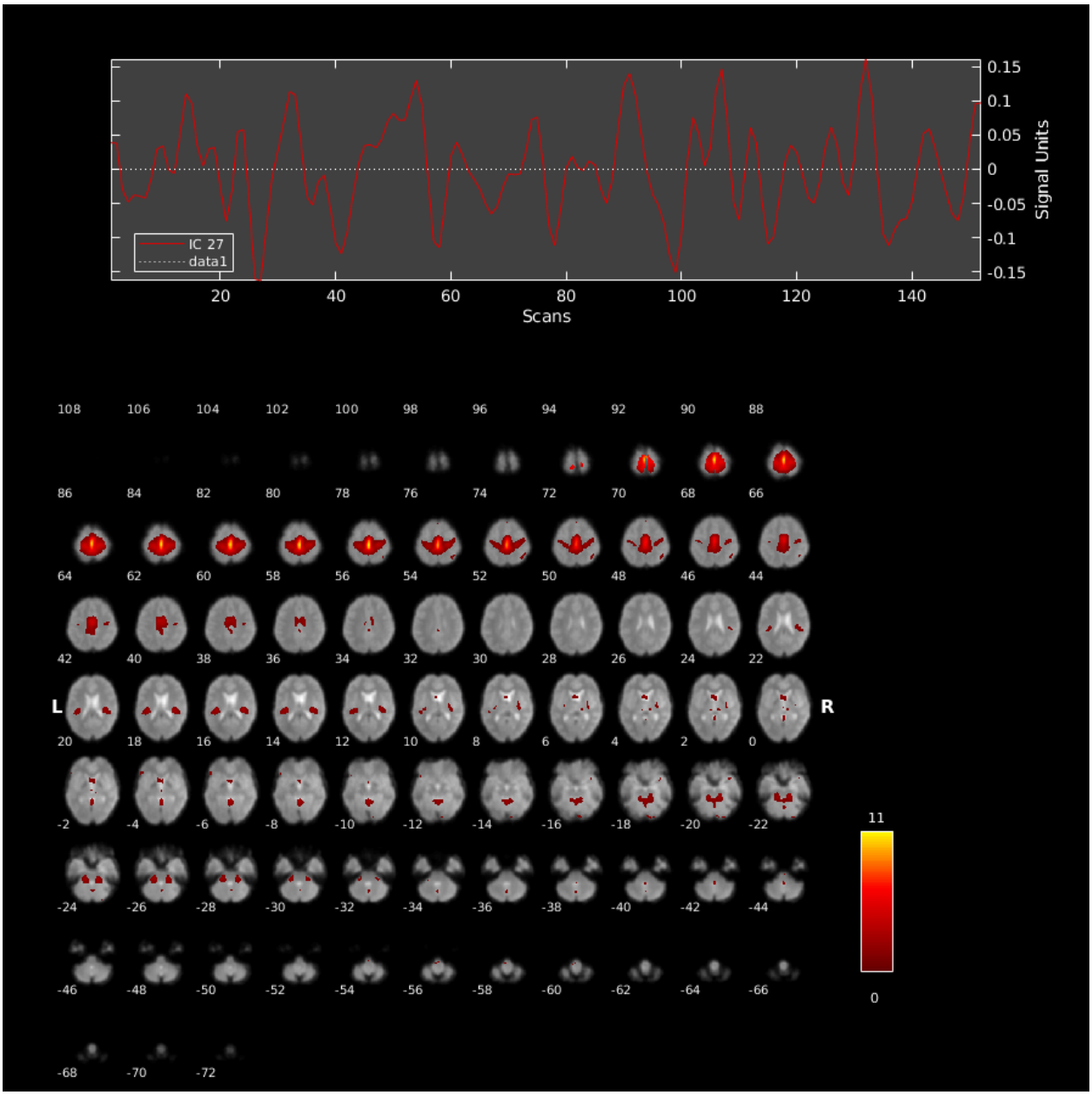

Figure 13. Component 27, which was matched to the supplementary motor template in this dataset.

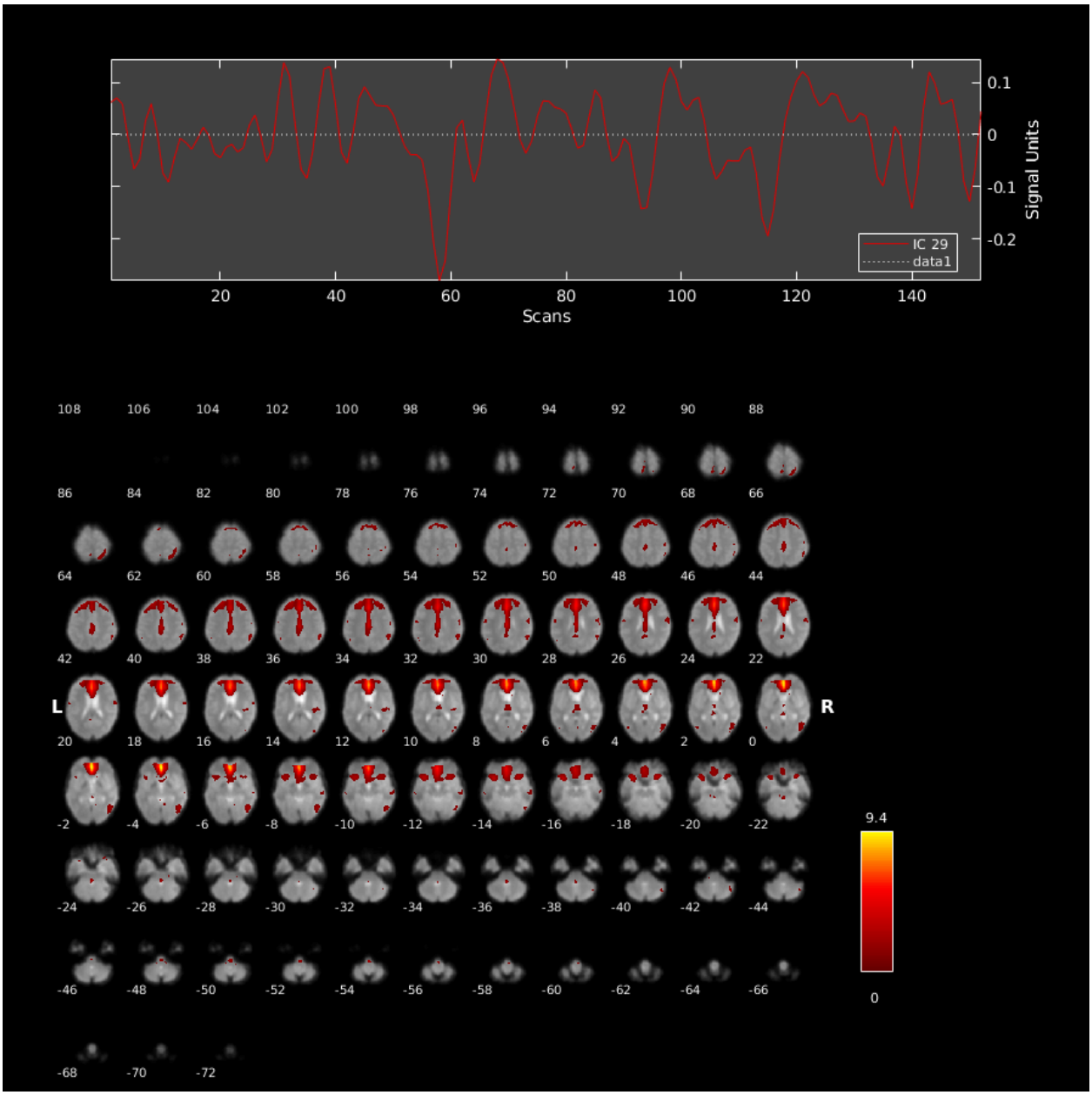

Figure 14. Component 29, which was matched to both the anterior cingulate and salience templates in this dataset. This component has been referred to as the salience component for simplicity.

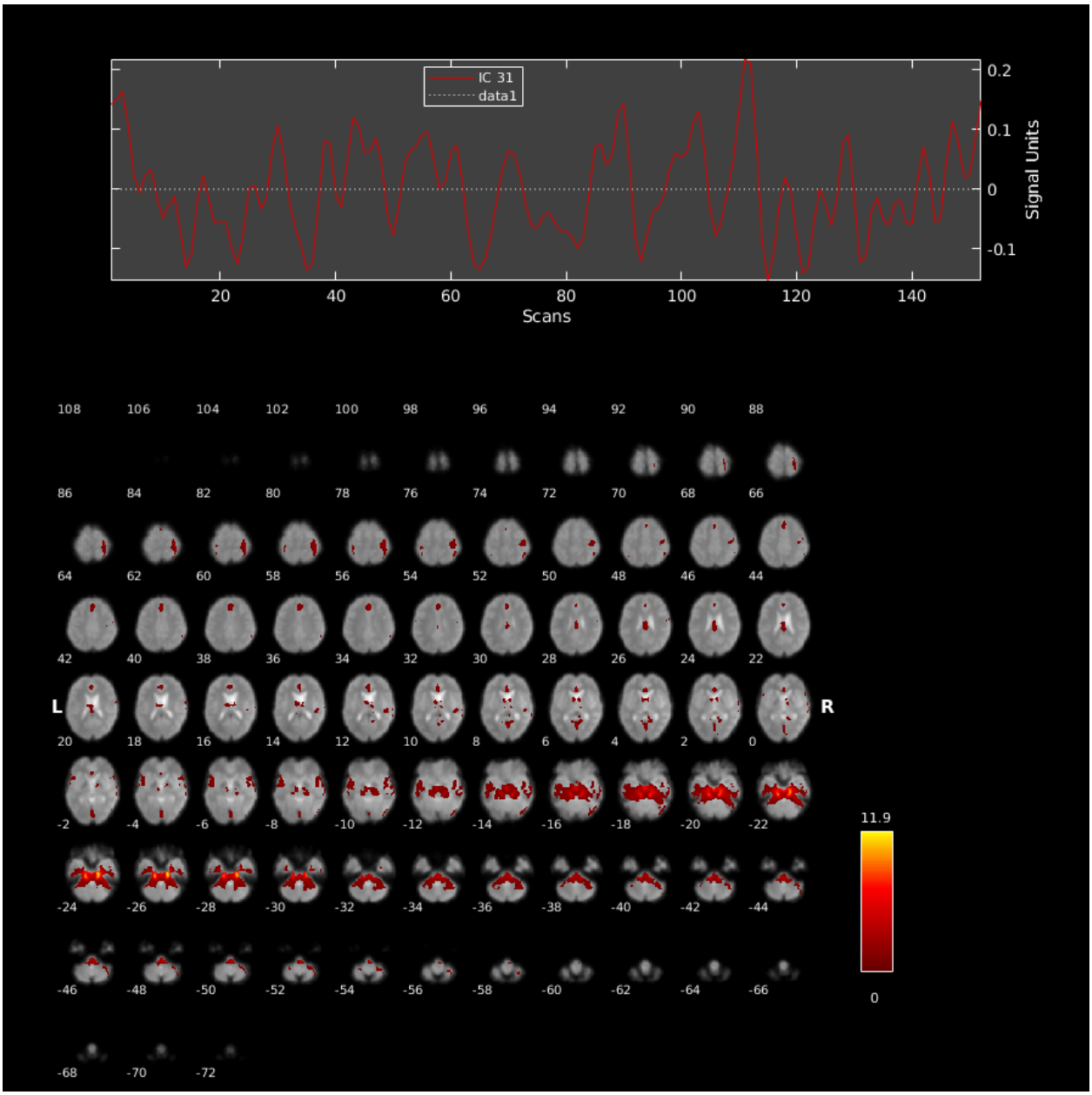

Figure 15. Component 31, which was matched to the midbrain template in this dataset.

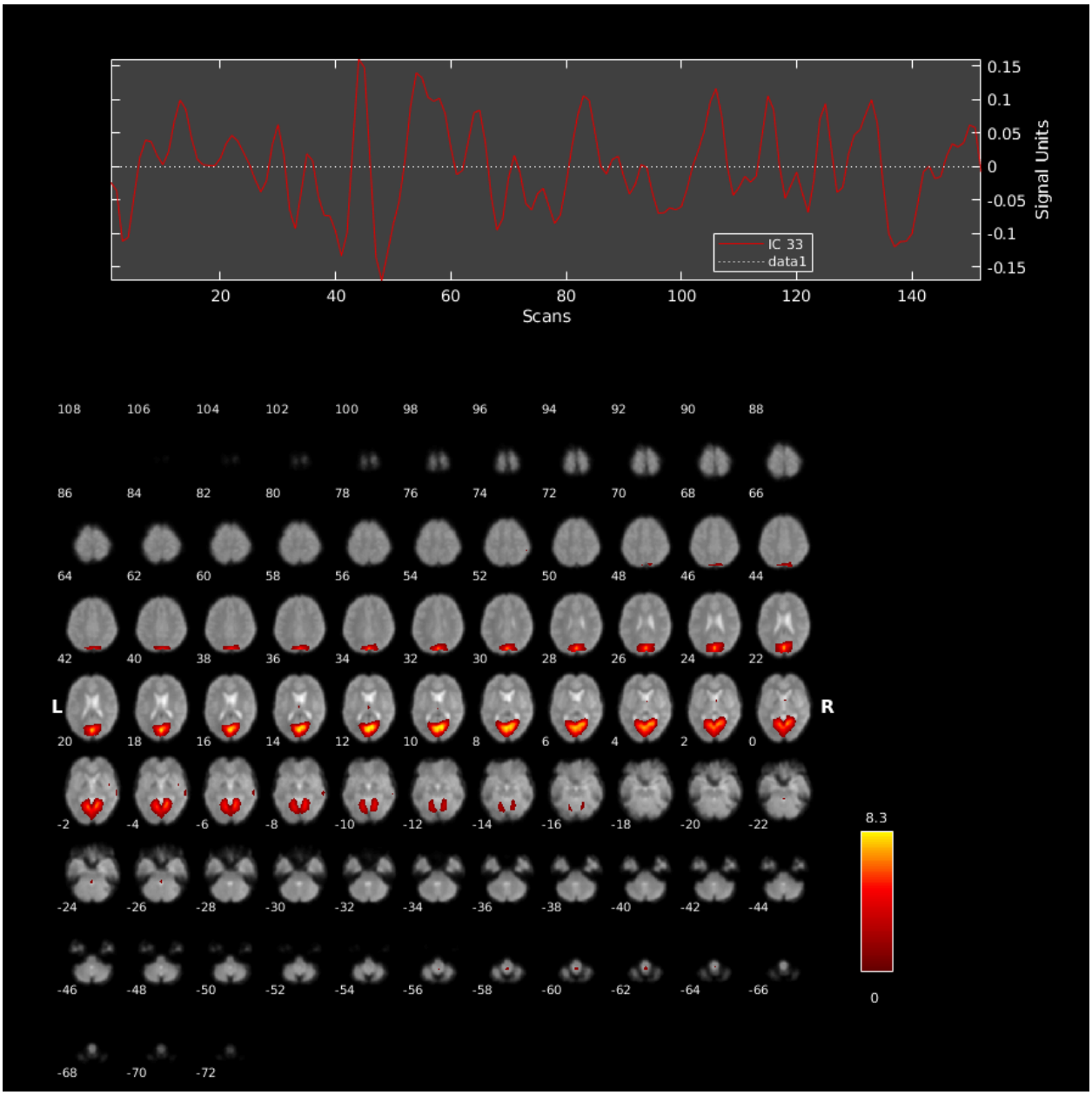

Figure 16. Component 33, which was matched to the visual template in this dataset.

Motion Correlation

Motion was not significantly correlated with BMI Z-score for age at the first ($r = 0.07$, $p = 0.46$) session, but there was evidence of a relationship between the two at the second session ($r = 0.18$, $p = 0.07$). This trend towards significance supports the removal of motion artifacts with AROMA.

Partial Least Squares Correlations

Impulsivity, Sensation-Seeking and BMI Z-Score for Age and Internetwork Connectivity at Time Point One

The first PLS correlation was intended to test the relationship between the internetwork connectivity and BMI Z-score for age, IMP and SS. The analysis identified a single significant latent variable ($p = 0.005$, $s = 1.78$) (Figure 17A). There were positive correlations between all three behavioural variables and the latent variable (Figure 17B). The correlation between the latent variable and BMI Z-score for age was much stronger, 0.37, than the correlations with impulsivity and sensation-seeking, 0.15 and 0.05 respectively (Figure 17B).

To identify the most relevant internetwork correlations, the network pairs were thresholded at a bootstrap ratio of greater than 3 or less than -3, which can be treated equivalently to a similar Z score. This identified the network pairs which were strongly associated with the singular value, and with an association that was stable across bootstrap testing.

Seven network pairs had bootstrap values greater than the chosen threshold, all of which had positive correlations with each other. The connections between the auditory and default and auditory and limbic networks, the limbic and left-executive networks, the right executive and motor networks, the second IFG-Middle Temporal network and the default network, the first supplementary motor network and the right executive network, and the visual and salience networks (Table 3).

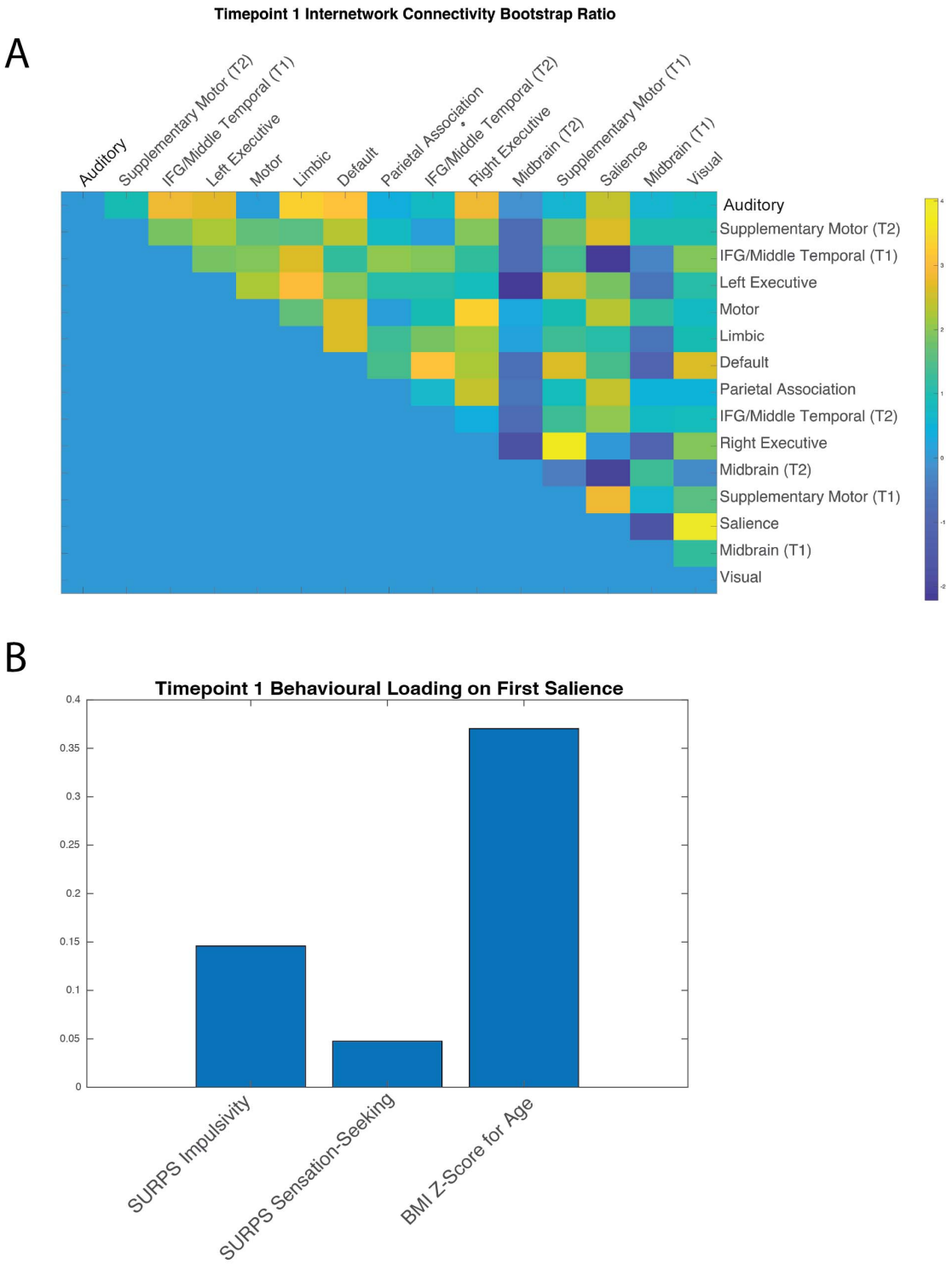

Figure 17. Results of the partial least squares correlation between impulsivity, sensation-seeking and BMI Z-score for age, and internetwork connectivity all at the first time point. A) Bootstrap ratios of the internetwork connectivity values onto the latent variable. B) Correlations with the latent variable and the behavioural variables.

Table 3. The most strongly involved network pairs with the latent variable generated from the partial least squares correlation between impulsivity, sensation-seeking, BMI Z-score for age and internetwork connectivity at time point one, with bootstrap ratios.

Limbic – Auditory	3.33
Default – Auditory	3.08
Limbic – Left Executive	3.02
Right Executive – Motor	3.34
IFG/Middle Temporal (T2) – Default	3.14
Supplementary Motor (T1) – Right Executive	3.67
Visual – Salience	4.04

BMI Z-Score for Age and Internetwork Connectivity at Time Point One

Because the PLS results above were dominated by BMI, we performed a second PLS correlation that tested the relationship between internetwork connectivity and BMI Z-score for age in isolation at time point one. The analysis identified a single significant latent variable ($p = 0.004$, $s = 1.68$) (Figure 18A), which was positively associated with BMI Z-score for age (Figure 18B).

To identify the most relevant internetwork correlations, the network pairs were again thresholded at a bootstrap ratio of greater than 3 or less than -3, which can be treated equivalently to a similar Z score. This identified the network pairs which were strongly associated with the singular value, and with an association that was stable across bootstrap testing.

Six network pairs had bootstrap values of greater than the threshold all of which were positively correlated with each other. The connections between the limbic and auditory networks, the limbic and left executive networks, the right executive and the motor networks, the second IFG/middle temporal network and default mode networks, the supplementary motor and the right executive networks and the visual and salience networks (Table 4). All of these correlations were also present in the earlier PLS containing the personality variables, but one of the networks most strongly related in the first analysis, the correlation between the default and auditory components, was less strongly related to the variable identified in this one.

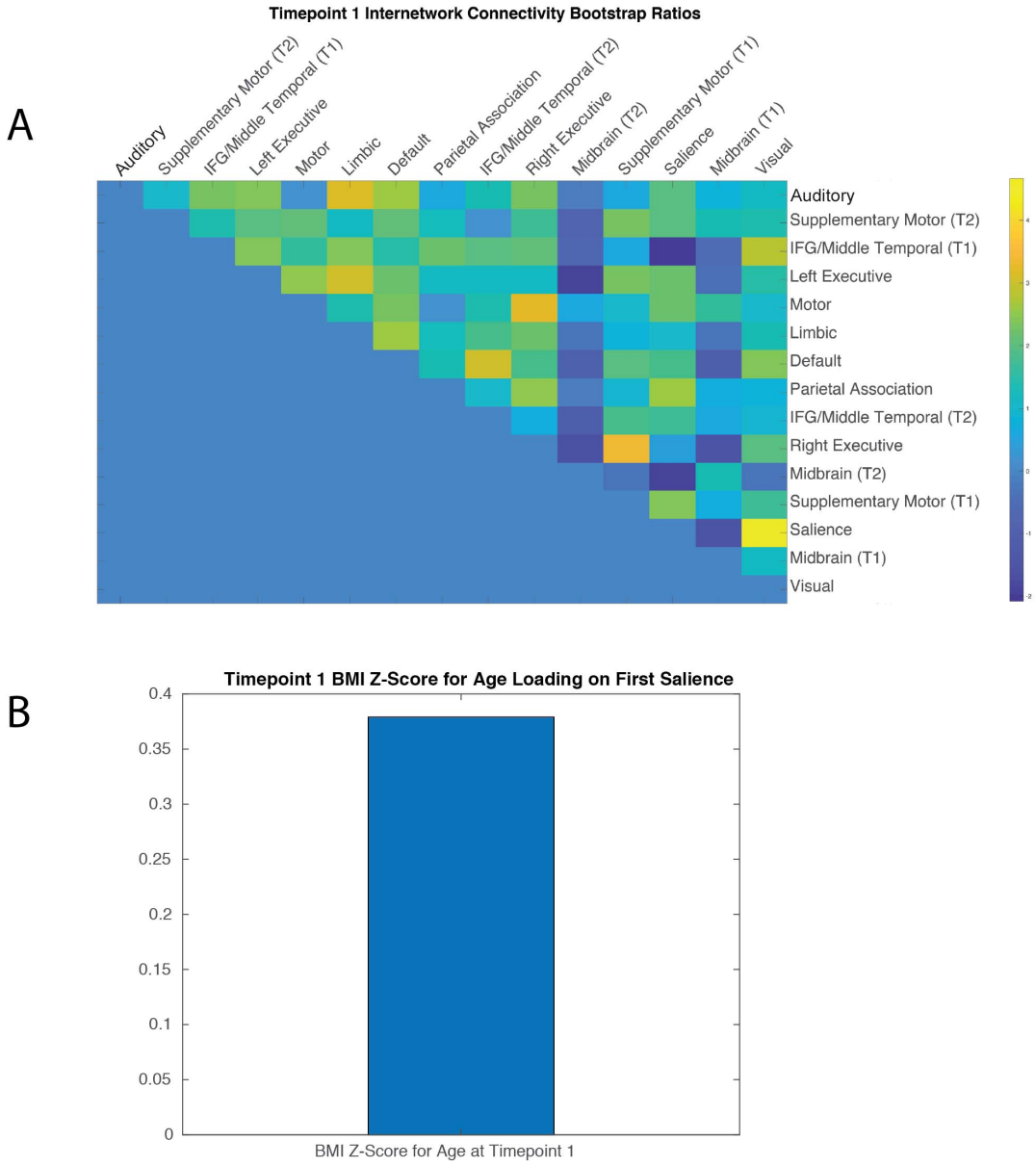

Figure 18. Results of the partial least squares correlation between BMI Z-score for age, and internetwork connectivity all at the first time point. A) Bootstrap ratios of the internetwork connectivity values onto the latent variable. B) Correlations with the latent variable and the behavioural variable.

Table 4. The most strongly involved network pairs with the latent variable generated from the partial least squares correlation between BMI Z-score for age and internetwork connectivity at time point one.

Limbic – Auditory	3.15
Limbic – Left Executive	3.01
Right Executive – Motor	3.29
IFG/Middle Temporal (T2) – Default	3.03
Supplementary Motor (T1) – Right Executive	3.39
Visual – Salience	4.66

BMI Z-Score for Age and Internetwork Connectivity at Time Point Two

The third PLS correlation was intended to test the relationship between internetwork connectivity and BMI Z-score for age at time point two. The partial least squares correlation did not identify any significant latent variables in this dataset ($p = 0.51$, $s = 1.02$).

BMI Z-Score for Age at Time Point One and Change in Internetwork Connectivity over 24 Months

The fourth PLS correlation tested the relationship between BMI Z-score for age at the first time point, and the residualized internetwork connectivity at the first time point, controlling for the second time point. This analysis did not identify any significant latent variables in this dataset ($p = 0.12$, $s = 1.18$).

Change in BMI Z-Score for Age and Internetwork Connectivity over 24 Months

The fifth PLS correlation tested the relationship between residualized BMI Z-score for age at the second time point controlling for the first time point, and residualized internetwork connectivity at the second time point controlling for the first time point. It did not identify any significant latent variables in this dataset ($p = 0.17$. $s = 1.15$).

Grey Matter Density Correlation

None of the PLS brainscores, the relationship of individual subject's internetwork correlation values to the model were significantly correlated with grey matter density in the limbic, auditory or midbrain components.

Graph Theory Analysis

Global Efficiency

BMI Z-score for age at time point one was positively correlated with global efficiency at time point one ($r = 0.22$, $p = 0.029$) and negatively correlated with change in global efficiency over 24 months ($r = -0.32$, $p = 0.001$). Change in BMI Z-score for age and change in global efficiency over 24 months were not significantly correlated ($r = -0.009$, $p = 0.93$).

Local Efficiency

Only correlations between change in local efficiency over 24 months and BMI Z-score for age at time point one were significant following multiple comparisons correction. All the significant regional correlations were negative, indicating that higher initial BMI Z-score for age correlated with reduced change. Significant regions included portions of the frontal, parietal,

temporal and occipital cortex, the limbic system and the globus pallidus (Supplementary Table 1).

Betweenness Centrality

None of the three correlations between measures of betweenness centrality or change in betweenness centrality and BMI Z-score for age or change in BMI Z-score for age remained significant following multiple comparisons correction.

Discussion

This study examined the global internetwork connectivity correlates of BMIZ, and impulsivity and sensation-seeking in a population of young adolescents across 24 months. PLS identified a single significant latent variable, composed of a pattern of connectivity between large-scale intrinsic networks that was strongly correlated with BMIZ, but only weakly correlated with impulsivity and sensation-seeking (Figure 17). A similar latent variable was identified when BMIZ was considered in the absence of personality factors (Figure 18). BMIZ was also found to be positively correlated with global efficiency, and negatively correlated with change in global efficiency over 24 months. BMIZ was also correlated with local efficiency in several cortical and subcortical regions (Supplementary Table 1).

There is a substantial body of research that has previously found degree of impulsivity and sensation-seeking to be correlated with higher body weight (Gerlach et al., 2015; Vainik et al., 2013). There is also evidence that variation in impulsivity is correlated with variation in function or connectivity of networks that are also related to variation in body weight, including previous research on the Neuroventure cohort that identified a limbic-midbrain network using similar PLS methods, which related to both impulsivity and body weight (Sharkey et al., 2019). Body-weight and impulsivity are both multifaceted traits that have been independently related to the function of multiple networks within the brain (Duckworth and Kern, 2012; Vainik et al., 2017, 2013). Our previous study using the Neuroventure cohort focused specifically only on connectivity of subcortical basal ganglia nuclei. The simultaneous examination of a set of large-scale networks in this study aimed to capture a wider scope of the neural relationship between body-weight, impulsivity and sensation-seeking, than is available in more hypothesis driven studies.

The current study identified a pattern of internetwork connectivity that was predominantly related to variation in body-weight, and only weakly associated with impulsivity or sensation-

seeking. PLS, is a multivariate technique meaning that the strength of association presented in this paper reflects a pattern of covariance between internetwork connectivity and BMI that makes up the latent variable as a whole, and does not allow us to assign relative importance to each specific implicated network. Note also that the weak association with impulsivity and sensation-seeking in this study is therefore not reflective of overall relationships between these personality dimensions and function or connectivity of brain networks, many of which have been previously associated with impulsive traits. Instead, it more likely that the network connectivity pattern contains some overlapping elements associated with both body weight and impulsivity and others that reflect some of the other factors known to contribute to weight such as stress vulnerability or emotional eating (Crossman et al., 2006; Kelly et al., 2016).

The most strongly involved set of network connections related to the latent variable, in both analyses, were all positive correlations, reflecting an increase in connectivity between the brain's large-scale networks with increasing weight. This is in line with previous findings which have identified reduced network segregation in overweight adolescents and adults (Doucet et al., 2017; Garcia-Casares et al., 2017; Krafft et al., 2014; Legget et al., 2016; McFadden et al., 2013; Sadler et al., 2018).

The specific networks involved also reflect previous findings in the literature. Increased interactions between the default network and the sensory and task-oriented networks have been previously found in overweight adolescents, and adults. This high level of internetwork connectivity has been found to be reduced by both weight-loss and exercise, also in both adolescent and adult populations (Doucet et al., 2017; Garcia-Casares et al., 2017; Krafft et al., 2014; Legget et al., 2016; McFadden et al., 2013; Sadler et al., 2018). However, increased between network connectivity is a somewhat non-specific finding which has also been found in younger children (which may reflect immaturity), or with other, less related findings, like increased positive mood, suggesting that the exact nature of this finding may be more complex (Krafft et al., 2014; Mirchi et al., 2018; Stevens et al., 2009).

Connectivity between both the limbic and the executive regions, and the limbic and temporal and insular regions (overlapping with the auditory network in this study) as well as alterations in activity in these regions have both been associated with increased weight. Limbic-executive connectivity is also associated with weight and impulsivity in separate studies (Brooks et al., 2013; Lee and Telzer, 2016; Sharkey et al., 2019; Stice and Yokum, 2016). Increased,

relationship between BMI and the activation or responsivity of the right executive network compared to the left has been similarly, previously associated with the right brain theory of obesity (Alonso-Alonso and Pascual-Leone, 2007; Vainik et al., 2017). Similarly, the executive, motor and default networks are also more generally involved in self-regulation (Fuentes-Claramonte et al., 2016). Alterations in regional connectivity within networks including both the default mode network, and temporal networks similar (although not identical to) the IFG/middle temporal networks identified here have also been described. This also, relates to findings of altered within network connectivity of nodes within the large-scale networks (Kullmann et al., 2012). How the between-network connectivity changes identified in this study relate to potential parallel changes in within-network connectivity is a possible avenue for follow-up research.

The IFG/middle-temporal, limbic and left and right executive networks, which are all involved in our study, overlap with the set of regions that have been previously implicated in multiple forms of regulation in the perception-valuation-action (PVA) model, related to both weight and general emotional responses (Etkin et al., 2015; Han et al., 2018).

Under the PVA model, external stimuli are evaluated, and assigned a value, which results in an action in response. There are two major ways in which self-control mechanisms influence the PVA response. Top-down control can inhibit actions based on changing the valuations of perceived stimuli and modulation of the response to these stimuli. Both of these represent forms of self-control associated with dissociable but overlapping networks (Etkin et al., 2015; Langner et al., 2018).

Previous research has identified interactions between the visual and salience networks, like those found in this study, to be involved in valuation modulation of visual food cues, with increased valuation of food cues being associated with higher body weight (Doucet et al., 2017; Han et al., 2018; Kullmann et al., 2013; Sadler et al., 2018).

The increased global efficiency which was also identified in this study is a finding that, reflects, using a different method of analysis, the positive associations between weight and the most heavily involved network pairs, as identified by bootstrap analysis. The overall increase in positive internetwork correlations and the overall increased efficiency both reflect greater information transfer between the large-scale regions and networks of the brain.

However, the finding of increased global efficiency corresponds more strongly to findings related to impulsivity, and the more general trait of neuroticism to which impulsivity is related.

Neuroticism has been previously associated with greater global efficiency (Servaas et al., 2014). Obesity has been previously associated with reduced global efficiency, although that finding may not relate to the more varied weights present in the largely healthy Neuroventure sample (Baek et al., 2017). The age of the sample may also have affected both these findings and the lack of association found in this study between the identified weight related changes in functional connectivity and any differences in grey matter density. Note that previous studies examining structural changes in the brain related to obesity found that findings from adult populations do not necessarily extend to children (Sharkey et al., 2015).

There are two major limitations in this data that merit further follow-up. Firstly, while motion was not significantly correlated with body weight at either time point, there is a pronounced trend towards greater motion at higher weights especially in the second time point. This trend may have affected the data, especially the loss of significance in the second time-point data and the negative correlations with changes in local efficiency seen in the graph theory analysis. It should be noted however that we used a well-validated method to remove BOLD artifacts related to head motion (Pruim et al., 2015b, 2015a).

The Neuroventure dataset also lacks detailed data about pubertal status. Puberty could have potentially influenced the relationship between weight and brain development (since puberty is associated with weight gain) (Ahmed et al., 2009). The effects of puberty on weight are partially accounted for by the use of the BMIZ measure, but only in-so-far as the rate of puberty and amount of weight gained is typical for the subject's age. Neuroventure participants only have a single, binary measure of pubertal status, menarche for female participants and voice-breaking for males, and the majority of subjects had already entered puberty, based on these measures, by the time the initial data was collected, leaving very little variability within the pubertal data. Future work with more detailed data about hormonal and physical maturation will be necessary to further elucidate the role of puberty in adolescent weight changes.

While the sample size of the Neuroventure cohort, 98 people, is large enough to be suitable for this exploratory analysis of neural correlates of weight, it does not have the statistical power to test the multiple specific relationships suggested by the boot-strapping ratios of the latent variables, while accommodating the need for multiple comparisons correction that would entail. However, measuring these relationships simultaneously in a single population provides a

framework for follow-up in subsequent studies that is more comprehensive than previous hypothesis driven findings.

Acknowledgements

NeuroVenture is funded by an operating grant from the Canadian Institutes of Health Research (Grant Number: 126053). RJS has been previously funded by a Derek H. Davis award, from the McGill University Faculty of Medicine, a Tomlinson Doctoral Fellowship and a Alice Chap-Yip Fellowship and a Graduate Excellence Fellowship. AD is funded by the CIHR Foundation Scheme. We thank Brianna Barsanti-Innes, Vincent Mingneron-Foisy, Léa Noirhomme, Marie-Pier Foisy, Gabrielle Généreux, Sean Spinney and Kevin Bastien for help in data collection.

References

Ad-Dab'bagh, Y., Einarson, D., Lyttelton, O., Muehlboeck, J.-S., Mok, K., Ivanov, O., Vincent, R.D., Lepage, C., Lerch, J., Fombonne, E., Evans, A.C., 2006. The CIVET Image-Processing Environment : A Fully Automated Comprehensive Pipeline for Anatomical Neuroimaging Research, in: Proceedings of the 12th Annual Meeting of the Organization for Human Brain Mapping, M. Corbetta, Ed.

Adelstein, J.S., Shehzad, Z., Mennes, M., DeYoung, C.G., Zuo, X.N., Kelly, C., Margulies, D.S., Bloomfield, A., Gray, J.R., Castellanos, F.X., Milham, M.P., 2011. Personality is reflected in the brain's intrinsic functional architecture. PLoS One 6. https://doi.org/10.1371/journal.pone.0027633

Ahmed, M.L., Ong, K.K., Dunger, D.B., 2009. Childhood obesity and the timing of puberty. Trends Endocrinol. Metab. 20, 237–242. https://doi.org/10.1016/j.tem.2009.02.004

Allen, E. A., Erhardt, E.B., Wei, Y., Eichele, T., Calhoun, V.D., 2012. Capturing inter-subject variability with group independent component analysis of fMRI data: A simulation study. Neuroimage 59, 4141–4159. https://doi.org/10.1016/j.neuroimage.2011.10.010

Allen, E. A., Erhardt, E.B., Damaraju, E., Gruner, W., Segall, J.M., Silva, R.F., Havlicek, M., Rachakonda, S., Fries, J., Kalyanam, R., Michael, A.M., Caprihan, A., Turner, J.A., Eichele, T., Adelsheim, S., Bryan, A.D., Bustillo, J., Clark, V.P., Feldstein Ewing, S.W., Filbey, F., Ford, C.C., Hutchison, K., Jung, R.E., Kiehl, K. a, Kodituwakku, P., Komesu, Y.M., Mayer, A.R., Pearlson, G.D., Phillips, J.P., Sadek, J.R., Stevens, M., Teuscher, U., Thoma, R.J., Calhoun, V.D., 2011. A baseline for the multivariate comparison of resting-state networks. Front. Syst. Neurosci. 5, 2. https://doi.org/10.3389/fnsys.2011.00002

Alonso-Alonso, M., Pascual-Leone, A., 2007. The right brain hypothesis for obesity. JAMA 297, 1819–1822.

Andronache, A., Rosazza, C., Sattin, D., Leonardi, M., D'Incerti, L., Minati, L., 2013. Impact of functional MRI data preprocessing pipeline on default-mode network detectability in patients with disorders of consciousness. Front. Neuroinform. 7, 16. https://doi.org/10.3389/fninf.2013.00016

Baek, K., Morris, L.S., Kundu, P., Voon, V., 2017. Disrupted resting-state brain network properties in obesity: Decreased global and putaminal cortico-striatal network efficiency. Psychol. Med. 47, 585–596. https://doi.org/10.1017/S0033291716002646

Beckmann, C.F., Smith, S.M., 2004. Tensorial extensions of independent component analysis for multi-subject FMRI analysis. FMRIB Tech. Rep. TR04CB1 1, 1–23. https://doi.org/10.1017/CBO9781107415324.004

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. Off. J. Soc. Magn. Reson. Med. 34, 537–41. https://doi.org/10.1002/mrm.1910340409

Bourque, J., Baker, T.E., Dagher, A., Evans, A.C., Garavan, H., Leyton, M., Seguine, J.R., Pihl, R., Conrod, P.J., 2016. Effects of delaying binge drinking on adolescent brain development: A longitudinal neuroimaging study. BMC Psychiatry 16, 445. https://doi.org/10.1186/s12888-016-1148-3

Brooks, S.J., Cedernaes, J., Schiöth, H.B., 2013. Increased prefrontal and parahippocampal activation with reduced dorsolateral prefrontal and insular cortex activation to food images in obesity: A meta-analysis of fMRI studies. PLoS One 8. https://doi.org/10.1371/journal.pone.0060393

Calhoun, V.D., Adali, T., Pearlson, G.D., Pekar, J.J., 2001. A method for making group inferences from functional MRI data using independent component analysis. Hum. Brain Mapp. 107, 96–107. https://doi.org/10.1002/hbm.

Cole, D.M., Beckmann, C.F., Oei, N.Y.L., Both, S., van Gerven, J.M.A., Rombouts, S.A.R.B., 2013. Differential and distributed effects of dopamine neuromodulations on resting-state network connectivity. Neuroimage 78, 59–67. https://doi.org/10.1016/j.neuroimage.2013.04.034

Conrod, P.J., Castellanos, N., Mackie, C., 2008. Personality-targeted interventions delay the growth of adolescent drinking and binge drinking. J. Child Psychol. Psychiatry Allied Discip. 49, 181–190. https://doi.org/10.1111/j.1469-7610.2007.01826.x

Coveleskie, K., Gupta, A., Kilpatrick, L.A., Mayer, E.D., Ashe-Mcnalley, C., Stains, J., Labus, J.S., Mayer, E.A., 2015. Altered functional connectivity within the central reward network in overweight and obese women. Nutr. Diabetes 5, e148-7. https://doi.org/10.1038/nutd.2014.45

Cox, R.W., 1996. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173. https://doi.org/10.1006/cbmr.1996.0014

Cox, R.W., Hyde, J.S., 1997. Software tools for analysis and visualization of fMRI data. NMR Biomed. 10, 171–8. https://doi.org/10.1002/(SICI)1099-1492(199706/08)10:4/5<171::AID-NBM453>3.0.CO;2-L

Crossman, A., Anne Sullivan, D., Benin, M., 2006. The family environment and American adolescents' risk of obesity as young adults. Soc. Sci. Med. 63, 2255–67. https://doi.org/10.1016/j.socscimed.2006.05.027

Doll, A., Hölzel, B.K., Boucard, C.C., Wohlschläger, A.M., Sorg, C., 2015. Mindfulness is associated with intrinsic functional connectivity between default mode and salience networks. Front. Hum. Neurosci. 9, 1–11. https://doi.org/10.3389/fnhum.2015.00461

Doucet, G.E., Rasgon, N., McEwen, B.S., Micali, N., Frangou, S., 2017. Elevated body mass index is associated with increased integration and reduced cohesion of sensory-driven and internally guided resting-state functional brain networks. Cereb. Cortex 988–997. https://doi.org/10.1093/cercor/bhx008

Duckworth, A.L., Kern, M.L., 2012. A meta-analysis of the convergent validity of self-control measures 45, 259–268. https://doi.org/10.1016/j.jrp.2011.02.004.A

Emerson, R.W., Short, S.J., Lin, W., Gilmore, J.H., Gao, W., 2015. Network-Level connectivity dynamics of movie watching in 6-year-old children. Front. Hum. Neurosci. 9, 1–8. https://doi.org/10.3389/fnhum.2015.00631

Etkin, A., Büchel, C., Gross, J.J., 2015. The neural bases of emotion regulation. Nat. Rev. Neurosci. 16, 693–700. https://doi.org/10.1038/nrn4044

Fuentes-Claramonte, P., Avila, C., Rodriguez-Pujadas, A., Costumero, V., Ventura-Campos, N., Bustamante, J.C., Rosell-Negre, P., Barros-Loscertales, A., 2016. Characterizing individual differences in reward sensitivity from the brain networks involved in response inhibition. Neuroimage 124, 287–299. https://doi.org/10.1016/j.neuroimage.2015.08.067

Garcia-Casares, N., Bernal-Lopez, M.R., Roe-Vellve, N., Gutierrez-Bedmar, M., Fernandez-Garcia, J.C., Grcia-Arnes, J.A., Ramos-Rodriguez, J.R., Alfaro, F., Santamaria-Fernandez, S., Steward, T., Jimenez-Murcia, S., Garcia-Garcia, I., Valdivielso, P., Fernandez-Aranda, F., Tinahones, F.J., Gomez-Huelgas, R., 2017. Brain functional connectivity is modified by a hypocaloric mediterranean diet and physical activity. Nutrients 9, 685–701. https://doi.org/10.3390/nu9070685

Geerligs, L., Rubinov, M., Cam-CAN, Henson, R.N., 2015. State and trait components of functional connectivity: Individual differences vary with mental state. J. Neurosci. 35, 13949–13961. https://doi.org/10.1523/JNEUROSCI.1324-15.2015

Gerlach, G., Herpertz, S., Loeber, S., 2015. Personality traits and obesity: A systematic review. Obes. Rev. 16, 32–63. https://doi.org/10.1111/obr.12235

Gupta, A., Mayer, E.A., Labus, J.S., Bhatt, R.R., Ju, T., Love, A., Bal, A., Tillisch, K., Naliboff, B., Sanmiguel, C.P., Kilpatrick, L.A., 2018. Sex commonalities and differences in obesity related alterations in intrinsic brain activity and connectivity. Obesity 26, 340–350. https://doi.org/10.1002/oby.22060

Han, J.E., Boachie, N., Garcia-Garcia, I., Michaud, A., Dagher, A., 2018. Neural correlates of dietary self-control in healthy adults : A meta-analysis of functional brain imaging studies. Physiol. Behav. 192, 98–108. https://doi.org/10.1016/j.physbeh.2018.02.037

Inuggi, A., Sanz-Arigita, E., GonzÃ¡lez-Salinas, C., Valero-Garcia, A. V., Garcia-Santos, J.M., Fuentes, L.J., 2014. Brain functional connectivity changes in children that differ in

impulsivity temperamental trait. Front. Behav. Neurosci. 8, 1–14. https://doi.org/10.3389/fnbeh.2014.00156

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved methods for the registration and motion correction of brain images. FMRIB Tech. Rep. TR02MJ1 1. https://doi.org/10.1017/CBO9781107415324.004

Jenkinson, M., Beckmann, C., 2001. ICA in fMRI: A basic introduction. FMRIB Tech. Rep. TR01MJ2 7–9.

Jurk, S., Kuitunen-Paul, S., Kroemer, N.B., Artiges, E., Banaschewski, T., Bokde, A.L.W., Büchel, C., Conrod, P., Fauth-Bühler, M., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Heinz, A., Mann, K.F., Nees, F., Paus, T., Pausova, Z., Poustka, L., Rietschel, M., Schumann, G., Struve, M., Smolka, M.N., 2015. Personality and substance use: Psychometric evaluation and validation of the Substance Use Risk Profile Scale (SURPS) in English, Irish, French, and German Adolescents. Alcohol. Clin. Exp. Res. 39, 2234–2248. https://doi.org/10.1111/acer.12886

Kelly, Y., Patalay, P., Montgomery, S., Sacker, A., 2016. BMI development and early adolescent psychosocial well-being: UK millennium cohort study. Pediatrics 138. https://doi.org/10.1542/peds.2016-0967

Krafft, C.E., Pierce, J.E., Schwarz, N.F., Chi, L., Weinberger, A.L., Schaeffer, D.J., Rodrigue, A.L., Camchong, J., Allison, J.D., Yanasak, N.E., Liu, T., Davis, C.L., McDowell, J.E., 2014. An eight month randomized controlled exercise intervention alters resting state synchrony in overweight children. Neuroscience 256, 445–455. https://doi.org/10.1016/j.neuroscience.2013.09.052

Krank, M., Stewart, S.H., O'Connor, R., Woicik, P.B., Wall, A.-M., Conrod, P.J., 2011. Structural, concurrent, and predictive validity of the Substance Use Risk Profile Scale in early adolescence. Addict. Behav. 36, 37–46. https://doi.org/10.1016/j.addbeh.2010.08.010

Krishnan, A., Williams, L.J., McIntosh, A.R., Abdi, H., 2011. Partial Least Squares (PLS) methods for neuroimaging: A tutorial and review. Neuroimage 56, 455–475. https://doi.org/10.1016/j.neuroimage.2010.07.034

Krmpotich, T.D., Tregellas, J.R., Thompson, L.L., Banich, M.T., Klenk, A.M., Tanabe, J.L., 2013. Resting-state activity in the left executive control network is associated with behavioral approach and is increased in substance dependence. Drug Alcohol Depend. 129, 1–7. https://doi.org/10.1016/j.drugalcdep.2013.01.021

Kuczmarski, R.J., Ogden, C.L., Guo, S.S., Grummer-Strawn, L.M., Flegal, K.M., Mei, Z., Wei, R., Curtin, L.R., Roche, A.F., Johnson, C.L., 2002. 2000 CDC growth charts for the United States: methods and development., Vital and health statistics. Series 11, Data from the national health survey.

Kullmann, S., Heni, M., Veit, R., Ketterer, C., Schick, F., Häring, H.U., Fritsche, A., Preissl, H., 2012. The obese brain: Association of body mass index and insulin sensitivity with resting state network functional connectivity. Hum. Brain Mapp. 33, 1052–1061. https://doi.org/10.1002/hbm.21268

Kullmann, S., Pape, A., Heni, M., Ketterer, C., Schick, F., Häring, H., 2013. Functional network connectivity underlying food processing: Disturbed salience and visual processing in overweight and obese adults. Cereb. Cortex 23, 1247–1256. https://doi.org/10.1093/cercor/bhs124

La, C., Mossahebi, P., Nair, V.A., Bendlin, B.B., Birn, R., Meyerand, M.E., Prabhakaran, V., 2015. Age-related changes in inter-network connectivity by component analysis. Front. Aging Neurosci. 7, 1–12. https://doi.org/10.3389/fnagi.2015.00237

Laird, A.R., Fox, P.M., Eickhoff, S.B., Turner, J.A., Ray, K.L., McKay, D.R., Glahn, D.C., Beckmann, C.F., Smith, S.M., Fox, P.T., 2011. Behavioral interpretations of intrinsic connectivity networks. J. Cogn. Neurosci. 23, 4022–4037. https://doi.org/10.1162/jocn_a_00077

Langner, R., Leiberg, S., Ho, F., Eickho, S.B., 2018. Towards a human self-regulation system: Common and distinct neural signatures of emotional and behavioural control. Neurosci. Biobehav. Rev. 90, 400–410. https://doi.org/10.1016/j.neubiorev.2018.04.022

Lee, T., Telzer, E.H., 2016. Negative coupling between the right fronto-parietal and limbic resting state networks predicts increased self-control and reduced risk-taking behavior in adolescence. Dev. Cogn. Neurosci. 20, 35–42. https://doi.org/10.1016/j.dcn.2016.06.002

Legget, K.T., Wylie, K.P., Cornier, M., Edward, L., Paschall, C.J., Tregellas, J.R., Medical, A., States, U., Campus, A.M., States, U., States, U., Campus, A.M., States, U., States, U., 2016. Exercise-related changes in between-network connectivity in oberweight/obese adults. Physiol. Behav. 158, 60–67. https://doi.org/10.1016/j.physbeh.2016.02.031.Exercise-related

Lips, M.A., Wijngaarden, M.A., Grond, J. Van Der, Buchem, M.A. Van, Groot, G.H. De, Pijl, H., Veer, I.M., 2014. Resting-state functional connectivity of brain regions involved in cognitive control , motivation , and reward is enhanced in obese. Am. J. Clin. Nutr. 100, 524–531. https://doi.org/10.3945/ajcn.113.080671.1

MacPherson, L., Magidson, J.F., Reynolds, E.K., Kahler, C.W., Lejuez, C.W., 2010. Changes in sensation seeking and risk-taking propensity predict increases in alcohol use among early adolescents. Alcohol. Clin. Exp. Res. 34, 1400–8. https://doi.org/10.1111/j.1530-0277.2010.01223.x

McFadden, K.L., Cornier, M.A., Melanson, E.L., Bechtell, J.L., Tregellas, J.R., 2013. Effects of exercise on resting-state default mode and salience network activity in overweight/obese adults. Neuroreport 24, 866–871. https://doi.org/10.1097/WNR.0000000000000013.Effects

Mirchi, N., Betzel, R.F., Bernhardt, B.C., Dagher, A., 2018. Tracking mood fluctuations with functional network patterns. Soc. Cogn. Affect. Neurosci. 14, 47–57. https://doi.org/10.1093/scan/nsy107

Mišić, B., Betzel, R.F., de Reus, M.A., van den Heuvel, M.P., Berman, M.G., McIntosh, A.R., Sporns, O., 2016. Network-Level structure-function relationships in human neocortex. Cereb. Cortex 26, 3285–3296. https://doi.org/10.1093/cercor/bhw089

Moreno-Lopez, L., Contreras-Rodriguez, O., Soriano-Mas, C., Stamatakis, E.A., Verdejo-Garcia, A., 2016. Disrupted functional connectivity in adolescent obesity. NeuroImage Clin. https://doi.org/10.1016/j.nicl.2016.07.005

Muetzel, R.L., Blanken, L.M.E., Thijssen, S., van der Lugt, A., Jaddoe, V.W. V, Verhulst, F.C., Tiemeier, H., White, T., 2016. Resting-state networks in 6-to-10 year old children. Hum. Brain Mapp. 37, 4286–4300. https://doi.org/10.1002/hbm.23309

O'Leary-Barrett, M., Mâsse, B., Pihl, R.O., Stewart, S.H., Séguin, J.R., Conrod, P.J., 2017. A cluster-randomized controlled trial evaluating the effects of delaying onset of adolescent substance abuse on cognitive development and addiction following a selective, personality-targeted intervention programme: the Co-Venture trial. Addiction 112, 1871–1881. https://doi.org/10.1111/add.13876

Park, B.-Y., Hong, J., Lee, S.-H., Park, H., 2016. Functional connectivity of child and adolescent attention deficit hyperactivity disorder patients: Correlation with IQ. Front. Hum. Neurosci. 10, 565. https://doi.org/10.3389/fnhum.2016.00565

Park, B., Seo, J., Park, H., 2016. Functional brain networks associated with eating behaviors in obesity. Sci. Rep. 6, 23891. https://doi.org/10.1038/srep23891

Pruim, R.H.R., Mennes, M., Buitelaar, J.K., Beckmann, C.F., 2015a. Evaluation of ICA-AROMA and alternative strategies for motion artifact removal in resting state fMRI. Neuroimage 112, 278–287. https://doi.org/10.1016/j.neuroimage.2015.02.063

Pruim, R.H.R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J.K., Beckmann, C.F., 2015b. ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage 112, 267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064

Sadler, J.R., Shearrer, G.E., Burger, K.S., 2018. Body mass variability is represented by distinct functional connectivity patterns. Neuroimage 181, 55–63. https://doi.org/10.1016/j.neuroimage.2018.06.082

Sawatsky, M.L., Clyde, M., Meek, F., 2015. Partial Least Squares regression in the social sciences. Quant. Method Psychol. 11, 52–62.

Servaas, M.N., Geerligs, L., Renken, R.J., Marsman, J.-B.C., Ormel, J., Riese, H., Aleman, A., 2014. Connectomics and Neuroticism: An altered functional network organization. Neuropsychopharmacology 1–9. https://doi.org/10.1038/npp.2014.169

Sharkey, R.J., Bourque, J., Larcher, K., Mišić, B., Zhang, Y., Altınkaya, A., Sadikot, A., Conrod, P., Evans, A.C., Garavan, H., Leyton, M., Séguin, J.R., Pihl, R., Dagher, A., 2019. Mesolimbic connectivity signatures of impulsivity and BMI in early adolescence. Appetite 132, 25–36. https://doi.org/10.1016/j.appet.2018.09.019

Sharkey, R.J., Karama, S., Dagher, A., 2015. Overweight is not associated with cortical thickness alterations in children. Front. Neurosci. 9, 1–7. https://doi.org/10.3389/fnins.2015.00024

Shehzad, Z., Kelly, a. M.C., Reiss, P.T., Gee, D.G., Gotimer, K., Uddin, L.Q., Lee, S.H., Margulies, D.S., Roy, A.K., Biswal, B.B., Petkova, E., Castellanos, F.X., Milham, M.P., 2009. The resting brain: Unconstrained yet reliable. Cereb. Cortex 19, 2209–2229. https://doi.org/10.1093/cercor/bhn256

Smith, S.M., 2000. BET: Brain extraction tool. FMRIB Tech. Rep. TR00SMS2b. https://doi.org/http://dx.doi.org/10.1016/B978-044451604-6/50001-X

Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R., Beckmann, C.F., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U. S. A. 106, 13040–13045. https://doi.org/10.1073/pnas.0905267106

Stevens, M.C., Pearlson, G.D., Calhoun, V.D., 2009. Changes in the interaction of resting-state neural networks from adolescence to adulthood. Hum. Brain Mapp. 30, 2356–2366. https://doi.org/10.1002/hbm.20673

Stice, E., Yokum, S., 2016. Gain in body fat is associated with increased striatal response to palatable food cues, whereas body fat stability is associated with decreased striatal response. J. Neurosci. 36, 6949–6956. https://doi.org/10.1523/jneurosci.4365-15.2016

Thomason, M.E., Dennis, E.L., Joshi, A.A., Joshi, S.H., Dinov, I.D., Chang, C., Henry, M.L., Johnson, R.F., Thompson, P.M., Toga, A.W., Glover, G.H., Van Horn, J.D., Gotlib, I.H., 2011. Resting-state fMRI can reliably map neural networks in children. Neuroimage 55, 165–175. https://doi.org/10.1016/j.neuroimage.2010.11.080

Tregellas, J.R., Wylie, K.P., Rojas, D.C., Tanabe, J., Martin, J., Kronberg, E., Cordes, D., Cornier, M.A., 2011. Altered default network activity in obesity. Obesity 19, 2316–2321. https://doi.org/10.1038/oby.2011.119

Vainik, U., Baker, T.B., Alanis, J.C.G., Dadar, M., Michaud, A., Misic, B., Zeighami, Y., Zhang, Y., Collins, D.L., Dagher, A., 2017. Neurobehavioural correlates of obesity are largely heritable. bioRxiv 1–34. https://doi.org/10.1101/204917

Vainik, U., Dagher, A., Dubé, L., Fellows, L.K., 2013. Neurobehavioural correlates of body mass index and eating behaviours in adults: a systematic review. Neurosci. Biobehav. Rev. 37, 279–99. https://doi.org/10.1016/j.neubiorev.2012.11.008

Wijngaarden, M.A., Veer, I.M., Rombouts, S.A.R.B., van Buchem, M.A., Willems van Dijk, K., Pijl, H., van der Grond, J., 2015. Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. Behav. Brain Res. 287, 127–134. https://doi.org/10.1016/j.bbr.2015.03.016

Woicik, P. A., Stewart, S.H., Pihl, R.O., Conrod, P.J., 2009. The Substance Use Risk Profile Scale: a scale measuring traits linked to reinforcement-specific substance use profiles. Addict. Behav. 34, 1042–55. https://doi.org/10.1016/j.addbeh.2009.07.001

Supplementary Data

Supplementary Table 1. Regions, defined by the brainnetome atlas label, where change in local efficiency over 24 months was significantly negatively correlated with initial BMI Z-Score for age, with FDR corrected p values.

Superior Frontal Gyrus A8m, medial area 8	0.04
Superior Frontal Gyrus A8m, medial area 8	0.05
Superior Frontal Gyrus A9l, lateral area 9	0.04
Superior Frontal Gyrus A6m, medial area 6	0.02
Superior Frontal Gyrus A6m, medial area 6	0.03
Superior Frontal Gyrus A10m, medial area 10	0.03
Superior Frontal Gyrus A10m, medial area 10	0.04
Middle Frontal Gyrus IFJ, inferior frontal junction	0.05
Middle Frontal Gyrus IFJ, inferior frontal junction	0.04
Middle Frontal Gyrus A9/46v, ventral area 9/46	0.04
Middle Frontal Gyrus A8vl, ventrolateral area 8	0.04
Middle Frontal Gyrus A8vl, ventrolateral area 8	0.01
Middle Frontal Gyrus A10l, lateral area 10	0.009
Inferior Frontal Gyrus A44d, dorsal area 44	0.03
Inferior Frontal Gyrus IFS, inferior frontal sulcus	0.04
Inferior Frontal Gyrus A45c, caudal area 45	0.05
Orbital Gyrus A14m, medial area 14	0.01
Orbital Gyrus A14m, medial area 14	0.01
Orbital Gyrus A12/47o, orbital area 12/47	0.02
Orbital Gyrus A12/47o, orbital area 12/47	0.02
Orbital Gyrus A11l, lateral area 11	0.04
Orbital Gyrus A11l, lateral area 11	0.04
Orbital Gyrus A11m, medial area 11	0.001
Orbital Gyrus A11m, medial area 11	0.04
Orbital Gyrus A13, area 13	0.03
Orbital Gyrus A13, area 13	0.02
Orbital Gyrus A12/47l, lateral area 12/47	0.05
Precentral Gyrus A4hg, area 4 (head and face region)	0.03
Precentral Gyrus A6cdl, caudal dorsolateral area 6	0.03
Precentral Gyrus A4ul, area 4 (upper limb region)	0.01
Precentral Gyrus A4tl, area 4 (tongue and larynx region)	0.05
Precentral Gyrus A6cvl, caudal ventrolateral area 6	0.03
Paracentral Lobule, A1/2/3ll, area 1/2/3 (lower limb region)	0.02
Paracentral Lobule A4ll, area 4 (lower limb region)	0.04
Superior Temporal Gyrus A38m, medial area 38	0.04

Superior Temporal Gyrus A41/42, area 41/42	0.03
Superior Temporal Gyrus TE1.0 and TE1.2	0.03
Superior Temporal Gyrus A22c, caudal area 22	0.02
Superior Temporal Gyrus A22c, caudal area 22	0.04
Superior Temporal Gyrus A38l, lateral area 38	0.03
Superior Temporal Gyrus A38l, lateral area 38	0.02
Superior Temporal Gyrus A22r, rostral area 22	0.02
Superior Temporal Gyrus A22r, rostral area 22	0.03
Middle Temporal Gyrus A21c, caudal area 21	0.03
Middle Temporal Gyrus A21r, rostral area 21	0.02
Middle Temporal Gyrus A21r, rostral area 21	0.05
Middle Temporal Gyrus A37dl, dorsolateral area 37	0.02
Middle Temporal Gyrus aSTS, anterior superior temporal sulcus	0.01
Middle Temporal Gyrus aSTS, anterior superior temporal sulcus	0.02
Inferior Temporal Gyrus A20iv, intermediate ventral area 20	0.02
Inferior Temporal Gyrus A37elv, extreme lateroventral area 37	0.04
Inferior Temporal Gyrus A37elv, extreme lateroventral area 37	0.04
Inferior Temporal Gyrus A20r, rostral area 20	0.04
Inferior Temporal Gyrus A20il, intermediate lateral area 20	0.04
Inferior Temporal Gyrus A20cl, caudolateral of area 20	0.03
Inferior Temporal Gyrus A20cv, caudoventral of area 20	0.02
Fusiform Gyrus A20rv, rostroventral area 20	0.001
Fusiform Gyrus A37mv, medioventral area 37	0.03
Fusiform Gyrus A37mv, medioventral area 37	0.01
Fusiform Gyrus A37lv, lateroventral area 37	0.04
Fusiform Gyrus A37lv, lateroventral area 37	0.02
Parahippocampal Gyrus A35/36r rostral area 35/36	0.001
Parahippocampal Gyrus A35/36c caudal area 35/36	0.004
Parahippocampal Gyrus A35/36c caudal area 35/36	0.01
Parahippocampal Gyrus TL area TL (PPHC lateral posterior parahippocampal gyrus)	0.003
Parahippocampal Gyrus TL area TL (PPHC lateral posterior parahippocampal gyrus)	0.03
Parahippocampal Gyrus A28/34 area 28/34 (EC, entorhinal cortex)	0.009
Parahippocampal Gyrus A28/34 area 28/34 (EC, entorhinal cortex)	0.04
Parahippocampal Gyrus TH area TH (medial PPHC)	0.03

Superior Parietal Lobule A7r, rostral area 7	0.03
Superior Parietal Lobule A5l, lateral area 5	0.01
Superior Parietal Lobule A5l, lateral area 5	0.05
Superior Parietal Lobule A7pc, postcentral area 7	0.03
Superior Parietal Lobule A7ip, intraparietal area 7(hIP3)	0.03
Superior Parietal Lobule A7ip, intraparietal area 7(hIP3)	0.02
Inferior Parietal Lobule, A39c, caudal area 39(PGp)	0.009
Inferior Parietal Lobule A39rd, rostrodorsal area 39(Hip3)	0.05
Inferior Parietal Lobule A40rd rostodorsal area 40(PFt)	0.03
Inferior Parietal Lobule A39rv rostroventral area 39(PGa)	0.02
Inferior Parietal Lobule A40rv rostroventral area 40(PFop)	0.03
Precuneus A7m, medial area 7 (PEp)	0.05
Precuneus A5m, medial area 5 (PEm)	0.01
Precuneus A5m, medial area 5 (PEm)	0.03
Precuneus dmPOS, dorsomedial parietooccipital sulcus (PEr)	0.01
Precuneus dmPOS, dorsomedial parietooccipital sulcus (PEr)	0.03
Precuneus A31 area 31 (Lc1)	0.01
Precuneus A31 area 31 (Lc1)	0.005
Postcentral Gyrus A1/2/3 ulhf, area 1/2/3 (upper limb, head and face)	0.04
Postcentral Gyrus A1/2/3 ulhf, area 1/2/3 (upper limb, head and face)	0.03
Postcentral Gyrus A1/2/3tonIa area 1/2/3 (tongue and larynx region)	0.04
Postcentral Gyrus A2 area 3	0.04
Cingulate Gyrus, A23d, dorsal area 23	0.004
Cingulate Gyrus, A23d, dorsal area 23	0.006
Cingulate Gyrus, A24rv rostroventral area 24	0.04
Cingulate Gyrus, A24rv rostroventral area 24	0.03
Cingulate Gyrus A32p, pregenual area 32	0.04
Cingulate Gyrus A32p, pregenual area 32	0.03
Cingulate Gyrus A23v, ventral area 23	0.01
Cingulate Gyrus A23v, ventral area 23	0.01
Cingulate Gyrus A24cd, caudodorsal area 24	0.01
Cingulate Gyrus A24cd, caudodorsal area 24	0.04
Cingulate Gyrus A23c, caudal area 23	0.01
Cingulate Gyrus A23c, caudal area 23	0.04
Cingulate Gyrus A32sg, subgenual area 32	0.02
Cingulate Gyrus A32sg, subgenual area 32	0.02
MedioVentral Occipital Cortex, cLinG, caudal lingual gyrus	0.006
MedioVentral Occipital Cortex, cLinG, caudal lingual gyrus	0.006

MedioVentral Occipital Cortex, rCunG, rostral cuneus gyrus	0.009
MedioVentral Occipital Cortex, rCunG, rostral cuneus gyrus	0.01
MedioVentral Occipital Cortex, cCunG, caudal cuneus gyrus	0.02
MedioVentral Occipital Cortex, cCunG, caudal cuneus gyrus	0.02
MedioVentral Occipital Cortex, rLinG, rostral lingual gyrus	0.01
MedioVentral Occipital Cortex, rLinG, rostral lingual gyrus	0.03
MedioVentral Occipital Cortex, vmPOS, ventromedial parietoocipital sulcus	0.01
MedioVentral Occipital Cortex, vmPOS, ventromedial parietoocipital sulcus	0.01
Lateral Occipital Cortex, mOccG, middle occipital gyrus	0.03
Lateral Occipital Cortex, mOccG, middle occipital gyrus	0.03
Lateral Occipital Cortex, V5/MT+, area V5/MT+	0.03
Lateral Occipital Cortex, iOccG, inferior occipital gyrus	0.04
Lateral Occipital Cortex, iOccG, inferior occipital gyrus	0.03
Lateral Occipital Cortex, msOccG, medial superior occipital gyrus	0.02
Lateral Occipital Cortex, msOccG, medial superior occipital gyrus	0.02
Lateral Occipital Cortex, lsOccG, lateral superior occipital gyrus	0.01
Lateral Occipital Cortex, lsOccG, lateral superior occipital gyrus	0.02
Amygdala, lAmyg, lateral amygdala	0.03
Hippocampus, rHipp, rostral hippocampus	0.02
Hippocampus, cHipp, caudal hippocampus	0.03
Basal Ganglia, GP, globus pallidus	0.05

Comprehensive Discussion

Discussion

The overall goal of this thesis is to examine the neural correlates of weight in healthy adolescents and the relationship between those systems and measures of impulsivity and sensation-seeking. There is substantial prior evidence both that impulsivity and sensation-seeking are behavioural risk factors for increased body mass index (BMI) and that this relationship might be reflected in the structural and functional variation in the brain (Delgado-Rico et al., 2012; Gerlach et al., 2015; Jokela et al., 2013; Sutin et al., 2011; Taki et al., 2008; Vainik et al., 2013).

This thesis is comprised of three studies. The first study found that a commonly identified adult phenotype of reduced cortical thickness with increased weight was not replicated in a sample of children (Sharkey et al., 2015). The second study identified the functional connectivity of a midbrain-striato-limbic network related to both weight and impulsivity and sensation-seeking in a population of adolescents (Sharkey et al., 2019). It also found that while sensation-seeking was positively correlated with both weight and impulsivity, it was negatively correlated with the network we identified, while weight and impulsivity were positively correlated (Sharkey et al., 2019). The third study found that interactions between multiple large-scale intrinsic networks involving both cortical and subcortical regions, including the left and right executive networks, the default and limbic networks, and the visual and salience networks, that were related to weight, but that the same, large-scale pattern was only weakly associated with impulsivity and sensation-seeking.

The second two of these findings emphasize the multi-network nature of the neural endophenotype of body weight. The third study identifies multiple networks related to weight directly. Greater BMI was associated with greater interactions between the auditory network and the limbic and default networks, between limbic and left executive networks, the right executive and motor and supplementary motor networks, the default and the IFG/middle temporal network and the visual and salience networks. Greater fronto-occipital connectivity, and increased between-network connectivity in general, but especially between default and task networks have all been previously associated with greater BMI in previous studies, as have alterations to

connectivity between the right executive and temporal and limbic networks (Alonso-Alonso and Pascual-Leone, 2007; Doucet et al., 2017; García-García et al., 2013; Han et al., 2018; Hargrave et al., 2016; Kullmann et al., 2013; Vainik et al., 2017). The work presented here identifies this range of findings in a single population.

The second study was premised around the well-supported role of a frontal corticostriatal network in weight and impulsivity, but instead identified a midbrain striato-limbic network. There is sufficient evidence for the role of the prefrontal cortex in weight and adolescent impulsivity that it is unlikely that our finding genuinely contradicts it, but more likely that we have identified a second network which is simultaneously involved (Sharkey et al., 2019).

Both the second and third study found evidence of subcortical involvement in weight in adolescence and these findings also suggests that the first study, which examined only the cortex and omitted subcortical regions may have overlooked subcortical and limbic associations with weight in this age group. Subcortical and limbic associations with weight may develop earlier than the cortical associations which were hypothesized to be involved. However, greater attention to the role of the limbic system in adult weight may also be valuable (Sharkey et al., 2019, 2015).

The heavily limbic findings of the second study and the involvement of the default mode network, and the connectivity between visual and salience networks identified in the third study, also suggest that value modulation, as a specific mode of self-control, may be particularly relevant to adolescent populations (Braams et al., 2015; Etkin et al., 2015; Langner et al., 2018; Murty et al., 2016). Mechanisms of self-control in response to a specific desirable cue or stimulus can be broadly divided into two categories. Value modulation strategies alter the perceived value of the stimulus which alters how desirable it is perceived to be, while behavioural inhibition strategies inhibit actions in response to the value of a stimulus. The hippocampus and other limbic regions, fronto-occipital networks and the default mode network have all previously been implicated in value and emotional modulation (Etkin et al., 2015; Han et al., 2018; Mirchi et al., 2018). There is also prior evidence that adolescent impulsivity relates to greater response to rewarding stimuli (Braams et al., 2015; Davidow et al., 2016; Geier et al., 2010). In sum, there may be neuroanatomical evidence for greater valuation of food cues in adolescents with obesity.

The second two studies of this thesis also both examine the overlap between neural endophenotypes of weight, and neural endophenotypes of impulsivity and sensation-seeking. All three of these traits have been found to be correlated with each other behaviourally, a finding which was mostly replicated in our second study. However, the second study found that while weight and impulsivity were not directly correlated behaviourally, they did correlate similarly with midbrain-striato-limbic connectivity and that sensation-seeking, despite being correlated with both of them, was negatively correlated with the same network (Sharkey et al., 2019). The third study expanded on this by identifying a pattern of network connectivity which correlated well with weight but only weakly with either sensation-seeking or impulsivity. This strongly suggests that while these traits do relate to each other both behaviourally and neurologically, the networks that make up their neural endophenotypes overlap, rather than reflecting a single underlying neural endophenotype. This likely reflects the range of other factors known to contribute to variation in body weight, which includes genetic and parental influences on food choice and preference, the influence of stress or negative mood, and exercise levels, which were not assessed in these studies (Benton, 2004; Birch and Davison, 2001; Clarke et al., 2015; Krafft et al., 2014; McFadden et al., 2013; Vainik et al., 2013).

Limitations and Future Directions

The three studies which make up this thesis present the opportunity for multiple follow-up investigations. Here we briefly present some of the ways the conclusions of this thesis could be used to guide future studies, but also some of the major limitations of research with this dataset and methods, which could similarly generate questions to be answered in the future.

Comparison Between Adolescent and Adult Populations

All three of the studies in this thesis were conducted on populations of children and adolescents, and so our conclusions are only valid for that age group. There is some prior research which suggests that the degree to which different networks are involved in impulsivity, and weight regulation differ across age groups (Galvan et al., 2006; Tomasi and Volkow, 2014). Future research on the network correlations identified in the studies in this thesis could further develop these lines of inquiry by attempting to replicate these findings in adult populations.

Maturational Curves

Similarly, up to now we have only been able to follow the Neuroventure cohort up to the 24 month time point. A subsequent time point two years later is still being collected. Once three data points are available for each subject it will be possible to examine the trajectories of development in brain, personality, and body weight using a richer dataset than is currently possible.

Structure and Function Relationships

While the studies in this thesis examined both structural and functional neural correlates of weight, there is only a single analysis examining the relationship between the two. While some structural mechanism must necessarily underlie functional connectivity the statistical relationships identified between functional connectivity and structure changes detectable with magnetic resonance imaging methods are more complex. For instance, functional connectivity measures are able to detect relationships between indirectly connected regions, which are hard to establish using structural measures (Damoiseaux and Greicius, 2009).

The Neuroventure dataset, which contains multiple structural and functional measures is well designed for examining relationships between brain structure and function and future studies using this population will hopefully be able to shed more light on this question.

Impacts of Puberty

The Neuroventure dataset measures the onset of puberty in a severely limited manner with a single, binary variable, based on menarche in females and voice-breaking in males. This seriously limits the ability to study the impact of puberty with Neuroventure data (Bourque et al., 2016). Puberty naturally involves an increase in both weight and body mass index (Ahmed et al., 2009; Kuczmarski et al., 2002). The age-matching carried out by converting body mass index to BMI Z-score for age will partly account for that effect, but not for variability in the onset of puberty and puberty associated weight gain.

However, the impact of puberty on weight, impulsivity and brain development is complex. Higher weight is associated bidirectionally with an earlier onset of puberty. Obesity can trigger earlier onset of puberty, but children who enter puberty earlier will tend to gain weight earlier than their peers (Ahmed et al., 2009). But conversely, overweight and obese children and adolescents have been found to have less mature neural phenotypes, which resemble

those of younger subjects than their contemporaries, and to be more impulsive (Braams et al., 2015; Delgado-Rico et al., 2012; Krafft et al., 2014).

Social Influences on Impulsivity and Weight

While adolescent impulsivity and risk-taking behaviour are understood to be normal developmental processes, they are also known to be impacted by external social influences. Adolescents and children of lower socio-economic status show increased levels of impulsivity in comparison to their more affluent peers (Hackman et al., 2010; Ng-Knight and Schoon, 2016). This is at least in part now known to be a reaction to unreliable physical and social environments. Strong positive social relationships, especially family environments, have also been found to reduce adolescent risk-taking, even in the context of low socio-economic status (McCormick et al., 2016; Qu et al., 2015; Telzer et al., 2013). Lower socio-economic status is also independently associated with higher body weight both in children and adolescents. This is partly mediated through socio-economic influences on impulsivity but also partly a reflection of differing access to energy-dense food in lower socio-economic groups.

However, this study considered the impact of social influences in only a very limited fashion in the second study (Chapter 3). Future follow-up either using the Family Affluence Scale data in the Neuroventure cohort, or in other data-sets which include more detailed data about socio-economic status and social relationships, may be able to shed more light both on how these factors relate to impulsivity and weight, but also which neural networks, specifically, are involved in that relationship during different stages of development.

Specific Elements of Impulsivity

The Substance Use Risk Profile Scale, which was the measure of impulsivity used in these studies, is a questionnaire based measure which considers impulsivity as a complete trait (Jurk et al., 2015; Woicik et al., 2009). However, sub-types of impulsivity are not perfectly correlated, and the specific details of how different types of impulsivity differentially relate to different networks could be delineated based on scores on tasks measuring specific aspects of impulsivity (Duckworth and Kern, 2012). The Balloon Analogue Risk Task, the Stop Signal Task, and the Stroop tasks included in the Neuroventure dataset could all be used to more clearly define the neural correlates of specific aspects of impulsivity (Bourque et al., 2016).

This could be a way to clarify the different relationships between sensation-seeking and impulsivity and the midbrain-limbic network identified in the second study (Chapter 3). It could

also help to clarify which of the network contributions to weight identified in the third study (Chapter 4) are also related to impulsivity.

Atlas Choice

The second and third studies of this thesis both use brain atlases for some proportion of the data. This is a major feature of the second study (Chapter 3) and a more minor contributor in the third study (Chapter 4). In both studies, measuring connectivity averaged within atlas regions rather than voxel-wise was used as a method of data reduction (Sharkey et al., 2019). This method of data reduction serves two purposes; firstly it reduces the computational power needed for the analysis, but secondly, and more importantly, it increases the interpretability of the data, by fitting it to a framework which has already been defined. However, the use of an atlas inevitably involves the loss of detail, both from homogenizing neuronal signals which may exist within atlas regions, and from the exclusion of tissue not covered by the atlas. Three of the atlases used in the second study (Chapter 3) were anatomically based atlases, where regions were delineated by anatomical boundaries (Amunts et al., 2013; Choi et al., 2012; Keuken and Forstmann, 2015). However, this can be limiting in studies of connectivity since it can collapse differentially connected sub-regions which can result in overall connectivity being lost. The Brainnetome atlas used in the third study (Chapter 4) and the Choi atlas used to define the ventral striatum in the second study (Chapter 3), were connectivity based atlases, where regional delineation was partly based on voxel-wise connectivity, which reduces the homogenization of sub-regions, although it cannot completely avoid it. However, the Brainnetome is a much more anatomically restricted atlas, which does not cover the midbrain and cerebellum, which means data from those regions was excluded from the graph theoretical analysis (Fan et al., 2016).

The creation of a specialized atlas balancing all of these concerns would be time-consuming, difficult and ideally require access to a reference population not included in the studies the atlas is applied to. The creation of a specialist atlas to suit the needs of a single study is unfeasible in most cases, including the studies in this thesis. It is also an important consideration in any atlas-based study that the idea of an ideal atlas is somewhat misleading. The brain functions simultaneously on multiple levels, and a single atlas, no matter how accurate, confines analysis to a single one of those levels.

Final Conclusions

Taken as a whole, the three studies of this thesis support the model of weight as a phenotype arising from the function and interaction of multiple functional brain networks. The three studies, using two child and adolescent populations, identified relationships between body weight and neural function which were related to but also distinct from earlier findings in adults, and also related to but distinct from networks related to impulsivity and sensation-seeking, personality traits which are known to be related to increased weight. These findings also emphasize the importance of subcortical and limbic networks in the regulation of adolescent weight and personality.

Complete Bibliography

Abdi, H., 2010. Partial least squares regression and projection on latent structure regression (PLS Regression). Wiley Interdiscip. Rev. Comput. Stat. 2, 97–106. https://doi.org/10.1002/wics.51

Ad-Dab'bagh, Y., Einarson, D., Lyttelton, O., Muehlboeck, J.-S., Mok, K., Ivanov, O., Vincent, R.D., Lepage, C., Lerch, J., Fombonne, E., Evans, A.C., 2006. The CIVET image-processing environment: A fully automated comprehensive pipeline for anatomical neuroimaging research, in: Proceedings of the 12th Annual Meeting of the Organization for Human Brain Mapping, M. Corbetta, Ed.

Adelstein, J.S., Shehzad, Z., Mennes, M., DeYoung, C.G., Zuo, X.N., Kelly, C., Margulies, D.S., Bloomfield, A., Gray, J.R., Castellanos, F.X., Milham, M.P., 2011. Personality is reflected in the brain's intrinsic functional architecture. PLoS One 6. https://doi.org/10.1371/journal.pone.0027633

Adleman, N.E., Menon, V., Blasey, C.M., White, C.D., Warsofsky, I.S., Glover, G.H., Reiss, A.L., 2002. A developmental fMRI study of the Stroop color-word Task. Neuroimage 16, 61–75. https://doi.org/10.1006/nimg.2001.1046

Ahmed, M.L., Ong, K.K., Dunger, D.B., 2009. Childhood obesity and the timing of puberty. Trends Endocrinol. Metab. 20, 237–242. https://doi.org/10.1016/j.tem.2009.02.004

Albrecht, D.S., Kareken, D.A., Christian, B.T., Dzemidzic, M., Yoder, K.K., 2014. Cortical dopamine release during a behavioral response inhibition task. Synapse 68, 266–274. https://doi.org/10.1002/syn.21736

Alexander, A.L., Lee, J.E., Lazar, M., Field, A.S., 2008. Diffusion tensor imaging of the brain. Neurotheraputics 4, 316–329.

Allen, E. A., Erhardt, E.B., Wei, Y., Eichele, T., Calhoun, V.D., 2012. Capturing inter-subject variability with group independent component analysis of fMRI data: A simulation study. Neuroimage 59, 4141–4159. https://doi.org/10.1016/j.neuroimage.2011.10.010

Allen, E. A., Erhardt, E.B., Damaraju, E., Gruner, W., Segall, J.M., Silva, R.F., Havlicek, M., Rachakonda, S., Fries, J., Kalyanam, R., Michael, A.M., Caprihan, A., Turner, J. A., Eichele, T., Adelsheim, S., Bryan, A.D., Bustillo, J., Clark, V.P., Feldstein Ewing, S.W., Filbey, F., Ford, C.C., Hutchison, K., Jung, R.E., Kiehl, K. A., Kodituwakku, P., Komesu, Y.M., Mayer, A.R., Pearlson, G.D., Phillips, J.P., Sadek, J.R., Stevens, M., Teuscher, U., Thoma, R.J., Calhoun, V.D., 2011. A baseline for the multivariate comparison of resting-state networks. Front. Syst. Neurosci. 5, 2. https://doi.org/10.3389/fnsys.2011.00002

Alonso-Alonso, M., Pascual-Leone, A., 2007. The right brain hypothesis for obesity. JAMA 297, 1819–1822.

Aminoff, E.M., Kveraga, K., Bar, M., 2013. The role of the parahippocampal cortex in cognition. Trends Cogn. Sci. 17, 379–390. https://doi.org/10.1016/j.tics.2013.06.009

Amunts, K., Lepage, C., Borgeat, L., Mohlberg, H., Dickscheid, T., Rousseau, M.E., Bludau, S., Bazin, P.L., Lewis, L.B., Oros-Peusquens, A.M., Shah, N.J., Lippert, T., Zilles, K., Evans, A.C., 2013. BigBrain: An ultrahigh-resolution 3D human brain model. Science. 340, 1472–1475. https://doi.org/10.1126/science.1235381

Andronache, A., Rosazza, C., Sattin, D., Leonardi, M., D'Incerti, L., Minati, L., 2013. Impact of functional MRI data preprocessing pipeline on default-mode network detectability in patients with disorders of consciousness. Front. Neuroinform. 7, 16. https://doi.org/10.3389/fninf.2013.00016

Appelhans, B.M., Waring, M.E., Schneider, K.L., Pagoto, S.L., DeBiasse, M. A., Debiasse, M. A., Whited, M.C., Lynch, E.B., 2012. Delay discounting and intake of ready-to-eat and away-from-home foods in overweight and obese women. Appetite 59, 576–84. https://doi.org/10.1016/j.appet.2012.07.009

Aron, A.R., Shohamy, D., Clark, J., Myers, C., Gluck, M.A., Poldrack, R.A., 2004. Human Midbrain sensitivity to cognitive feedback and uncertainty during classification learning 1144–1152.

Averbeck, B.B., Costa, V.D., 2017. Motivational neural circuits underlying reinforcement learning. Nat. Neurosci. 20, 505–512. https://doi.org/10.1038/nn.4506

Baek, K., Morris, L.S., Kundu, P., Voon, V., 2017. Disrupted resting-state brain network properties in obesity: Decreased global and putaminal cortico-striatal network efficiency. Psychol. Med. 47, 585–596. https://doi.org/10.1017/S0033291716002646

Bar, M., 2010. Wait for the second marshmallow? Future-oriented thinking and delayed reward discounting in the brain. Neuron 66, 4–5. https://doi.org/10.1016/j.neuron.2010.04.001

Barnea-Goraly, N., Menon, V., Eckert, M., Tamm, L., Bammer, R., Karchemskiy, A., Dant, C.C., Reiss, A.L., 2005. White matter development during childhood and adolescence: A cross-sectional diffusion tensor imaging study. Cereb. Cortex 15, 1848–54. https://doi.org/10.1093/cercor/bhi062

Batterink, L., Yokum, S., Stice, E., 2010. Body mass correlates inversely with inhibitory control in response to food among adolescent girls: An fMRI study. Neuroimage 52, 1696–1703. https://doi.org/10.1016/j.neuroimage.2010.05.059

Beckmann, C.F., Smith, S.M., 2004. Tensorial extensions of independent component analysis for multi-subject FMRI analysis. FMRIB Tech. Rep. TR04CB1 1, 1–23. https://doi.org/10.1017/CBO9781107415324.004

Beckmann, Mackay, Filippini, Smith, 2009. Group comparison of resting-state FMRI data using multi-subject ICA and dual regression, in: OHBM. p. S148. https://doi.org/10.1073/pnas.0811879106

Benton, D., 2004. Role of parents in the determination of the food preferences of children and the development of obesity. Int. J. Obes. Relat. Metab. Disord. 28, 858–69. https://doi.org/10.1038/sj.ijo.0802532

Betzel, R.F., Byrge, L., He, Y., Goni, J., Zuo, X.N., Sporns, O., 2014. Changes in structural and functional connectivity among resting-state networks across the human lifespan. Neuroimage 102, 345–357. https://doi.org/10.1016/j.neuroimage.2014.07.067

Birch, L.L., Davison, K.K., 2001. Family environmental factors influencing the developing behavioral controls of food intake and childhood overweight. Pediatr. Clin. North Am. 48, 893–907.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. Off. J. Soc. Magn. Reson. Med. 34, 537–41. https://doi.org/10.1002/mrm.1910340409

Bjork, J.M., Knutson, B., Hommer, D.W., 2008. Incentive-elicited striatal activation in adolescent children of alcoholics. Addiction 103, 1308–1319. https://doi.org/10.1111/j.1360-0443.2008.02250.x

Black, W.R., Lepping, R.J., Bruce, A.S., Powell, J.N., Bruce, J.M., Martin, L.E., Davis, A.M., Brooks, W.M., Savage, C.R., Simmons, W.K., 2015. Tonic hyper-connectivity of reward neurocircuitry in obese children. Obesity (Silver Spring). 22, 1590–1593. https://doi.org/10.14440/jbm.2015.54.A

Bourque, J., Baker, T.E., Dagher, A., Evans, A.C., Garavan, H., Leyton, M., Seguine, J.R., Pihl, R., Conrod, P.J., 2016. Effects of delaying binge drinking on adolescent brain development: A longitudinal neuroimaging study. BMC Psychiatry 16, 445. https://doi.org/10.1186/s12888-016-1148-3

Boyce, W., Torsheim, T., Currie, C., Zambon, A., 2006. The family affluence scale as a measure of national wealth: Validation of an adolescent self-report measure. Soc. Indic. Res. 78, 473–487. https://doi.org/10.1007/s11205-005-1607-6

Braams, B.R., van Duijvenvoorde, A.C.K., Peper, J.S., Crone, E.A., 2015. Longitudinal changes in adolescent risk-taking: A comprehensive study of neural responses to rewards, pubertal development, and risk-taking behavior. J. Neurosci. 35, 7226–7238. https://doi.org/10.1523/JNEUROSCI.4764-14.2015

Brooks, S.J., Benedict, C., Burgos, J., Kempton, M.J., Kullberg, J., Nordenskjöld, R., Kilander, L., Nylander, R., Larsson, E.-M., Johansson, L., Ahlström, H., Lind, L., Schiöth, H.B., 2013. Late-life obesity is associated with smaller global and regional gray matter volumes: a

voxel-based morphometric study. Int. J. Obes. (Lond). 37, 230–6. https://doi.org/10.1038/ijo.2012.13

Brooks, S.J., Cedernaes, J., Schiöth, H.B., 2013. Increased prefrontal and parahippocampal activation with reduced dorsolateral prefrontal and insular cortex activation to food images in obesity: A meta-analysis of fMRI studies. PLoS One 8. https://doi.org/10.1371/journal.pone.0060393

Büchel, C., Peters, J., Banaschewski, T., Bokde, A.L.W., Bromberg, U., Conrod, P.J., Flor, H., Papadopoulos, D., Garavan, H., Gowland, P., Heinz, A., Walter, H., Ittermann, B., Mann, K., Martinot, J.-L., Paillère-Martinot, M.-L., Nees, F., Paus, T., Pausova, Z., Poustka, L., Rietschel, M., Robbins, T.W., Smolka, M.N., Gallinat, J., Schumann, G., Knutson, B., Arroyo, M., Artiges, E., Aydin, S., Bach, C., Barbot, A., Barker, G., Bruehl, R., Cattrell, A., Constant, P., Crombag, H., Czech, K., Dalley, J., Decideur, B., Desrivieres, S., Fadai, T., Fauth-Buhler, M., Feng, J., Filippi, I., Frouin, V., Fuchs, B., Gemmeke, I., Genauck, A., Hanratty, E., Heinrichs, B., Heym, N., Hubner, T., Ihlenfeld, A., Ing, A., Ireland, J., Jia, T., Jones, J., Jurk, S., Kaviani, M., Klaassen, A., Kruschwitz, J., Lalanne, C., Lanzerath, D., Lathrop, M., Lawrence, C., Lemaitre, H., Macare, C., Mallik, C., Mar, A., Martinez-Medina, L., Mennigen, E., de Carvahlo, F.M., Mignon, X., Millenet, S., Miranda, R., Müller, K., Nymberg, C., Parchetka, C., Pena-Oliver, Y., Pentilla, J., Poline, J.-B., Quinlan, E.B., Rapp, M., Ripke, S., Ripley, T., Robert, G., Rogers, J., Romanowski, A., Ruggeri, B., Schmäl, C., Schmidt, D., Schneider, S., Schubert, F., Schwartz, Y., Sommer, W., Spanagel, R., Speiser, C., Spranger, T., Stedman, A., Stephens, D., Strache, N., Ströhle, A., Struve, M., Subramaniam, N., Theobald, D., Vetter, N., Vulser, H., Weiss, K., Whelan, R., Williams, S., Xu, B., Yacubian, J., Yu, T., Ziesch, V., 2017. Blunted ventral striatal responses to anticipated rewards foreshadow problematic drug use in novelty-seeking adolescents. Nat. Commun. 8, 14140. https://doi.org/10.1038/ncomms14140

Buckholtz, J.W., Treadway, M.T., Cowan, R.L., Woodward, N.D., Li, R., Ansari, M.S., Baldwin, R.M., Schwartzman, A.N., Shelby, E.S., Smith, C.E., Kessler, R.M., Zald, D.H., 2010. Dopaminergic network differences in human impulsivity. Science 329, 532. https://doi.org/10.1126/science.1185778

Bunge, S. a., Wright, S.B., 2007. Neurodevelopmental changes in working memory and cognitive control. Curr. Opin. Neurobiol. 17, 243–250. https://doi.org/10.1016/j.conb.2007.02.005

Calhoun, V.D., Adali, T., Pearlson, G.D., Pekar, J.J., 2001. A method for making group inferences from functional MRI data using independent component analysis. Hum. Brain Mapp. 107, 96–107. https://doi.org/10.1002/hbm.

Calhoun, V.D., Liu, J., Adali, T., 2009. A review of group ICA for fMRI data and ICA for joint inference of imaging, genetic and ERP data. Neuroimage 45, S163–S172. https://doi.org/10.1016/j.neuroimage.2008.10.057.A

Calhoun, V.D., Sui, J., Kiehl, K., Turner, J., Allen, E., Pearlson, G., 2012. Exploring the psychosis functional connectome: Aberrant intrinsic networks in schizophrenia and bipolar disorder. Front. Psychiatry 2, 1–13. https://doi.org/10.3389/fpsyt.2011.00075

Calluso, C., Tosoni, A., Pezzulo, G., Spadone, S., Committeri, G., 2015. Interindividual variability in functional connectivity as long-term correlate of temporal discounting. PLoS One 10, e0119710. https://doi.org/10.1371/journal.pone.0119710

Carnell, S., Gibson, C., Benson, L., Ochner, C., A, G., 2012. Neuroimaging and obesity: Current knowledge and future directions. Obes. Rev. 13, 43–56. https://doi.org/10.1111/j.1467-789X.2011.00927.x.Neuroimaging

Carver, C.S., White, T.L., 1994. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. J. Pers. Soc. Psychol. 67, 319–333. https://doi.org/10.1037/0022-3514.67.2.319

Casey, B.J., 2014. Beyond simple models of self-control to circuit-based accounts of adolescent behavior. Annu. Rev. Psychol. 1–25. https://doi.org/10.1146/annurev-psych-010814-015156

Casey, B.J., Galván, A., Somerville, L.H., 2016. Beyond simple models of adolescence to an integrated circuit-based account: A commentary. Dev. Cogn. Neurosci. 17, 128–130. https://doi.org/10.1016/j.dcn.2015.12.006

Casey, B.J., Giedd, J.N., Thomas, K.M., 2000. Structural and functional brain development and its relation to cognitive development. Biol. Psychol. 54, 241–57.

Casey, B.J., Somerville, L.H., Gotlib, I.H., Ayduk, O., Franklin, N.T., Askren, M.K., Jonides, J., Berman, M.G., Wilson, N.L., Teslovich, T., Glover, G., Zayas, V., Mischel, W., Shoda, Y., 2011. Behavioral and neural correlates of delay of gratification 40 years later. Proc. Natl. Acad. Sci. U. S. A. 108, 14998–5003. https://doi.org/10.1073/pnas.1108561108

Castellanos-Ryan, N., Rubia, K., Conrod, P.J., 2011. Response inhibition and reward response bias mediate the predictive relationships between impulsivity and sensation seeking and common and unique variance in conduct disorder and substance misuse. Alcohol. Clin. Exp. Res. 35, 140–155. https://doi.org/10.1111/j.1530-0277.2010.01331.x

Chen, S., Dong, D., Jackson, T., Zhuang, Q., Chen, H., 2017. Trait-based food-cravings are encoded by regional homogeneity in the parahippocampal gyrus. Appetite 114, 155–160. https://doi.org/10.1016/j.appet.2017.03.033

Chick, C.F., 2015. Reward processing in the adolescent brain: Individual differences and relation to risk taking. J. Neurosci. 35, 13539–13541. https://doi.org/10.1523/JNEUROSCI.2571-15.2015

Choi, E.Y., Yeo, B.T.T., Buckner, R.L., 2012. The organization of the human striatum estimated by intrinsic functional connectivity. J. Neurophysiol. 108, 2242–2263. https://doi.org/10.1152/jn.00270.2012

Christakou, A., Brammer, M., Rubia, K., 2011. Maturation of limbic corticostriatal activation and connectivity associated with developmental changes in temporal discounting. Neuroimage 54, 1344–1354. https://doi.org/10.1016/j.neuroimage.2010.08.067

Christakou, A., Halari, R., Smith, A.B., Ifkovits, E., Brammer, M., Rubia, K., 2009. Sex-dependent age modulation of frontostriatal and temporo-parietal activation during cognitive control. Neuroimage 48, 223–236. https://doi.org/10.1016/j.neuroimage.2009.06.070

Clarke, T.-K., Hall, L.S., Fernandez-Pujals, a M., MacIntyre, D.J., Thomson, P., Hayward, C., Smith, B.H., Padmanabhan, S., Hocking, L.J., Deary, I.J., Porteous, D.J., McIntosh, a M., 2015. Major depressive disorder and current psychological distress moderate the effect of polygenic risk for obesity on body mass index. Transl. Psychiatry 5, e592. https://doi.org/10.1038/tp.2015.83

Cohen, A.O., Breiner, K., Steinberg, L., Bonnie, R.J., Scott, E.S., Taylor-Thompson, K.A., Rudolph, M.D., Chein, J.M., Richeson, J.A., Heller, A.S., Silverman, M.R., Dellarco, D. V., Fair, D.A., Galván, A., Casey, B.J., 2016. When is an adolescent an adult? Assessing cognitive control in emotional and nonemotional contexts. Psychol. Sci. 0956797615627625-. https://doi.org/10.1177/0956797615627625

Cole, D.M., Beckmann, C.F., Oei, N.Y.L., Both, S., van Gerven, J.M.A., Rombouts, S.A.R.B., 2013. Differential and distributed effects of dopamine neuromodulations on resting-state network connectivity. Neuroimage 78, 59–67. https://doi.org/10.1016/j.neuroimage.2013.04.034

Collado, A., Felton, J.W., MacPherson, L., Lejuez, C.W., 2014. Longitudinal trajectories of sensation seeking, risk taking propensity, and impulsivity across early to middle adolescence. Addict. Behav. https://doi.org/10.1016/j.addbeh.2014.01.024

Connell, G.O., Hsu, C., Christakou, A., 2018. Thinking about others and the future: Neural correlates of perspective taking relate to preferences for delayed rewards. Cogn. Affect. Behav. Neurosci. 18, 35–42.

Conrod, P.J., Castellanos-Ryan, N., Mackie, C., 2011. Long-term effects of a personality-targeted intervention to reduce alcohol use in adolescents. J. Consult. Clin. Psychol. 79, 296–306. https://doi.org/10.1037/a0022997

Conrod, P.J., Castellanos-Ryan, N., Strang, J., 2010. Brief, personality-targeted coping skills interventions and survival as a non-drug user over a 2-year period during adolescence. Arch. Gen. Psychiatry 67, 85–93. https://doi.org/10.1001/archgenpsychiatry.2009.173

Conrod, P.J., Castellanos, N., Mackie, C., 2008. Personality-targeted interventions delay the growth of adolescent drinking and binge drinking. J. Child Psychol. Psychiatry Allied Discip. 49, 181–190. https://doi.org/10.1111/j.1469-7610.2007.01826.x

Costa, P.T., McCrae, R.R., 1995. Domains and facets: Hierarchical personality assessment using the revised NEO personality inventory. J. Pers. Assess. 64, 21–50.

Costa, P.T., Terracciano, a, McCrae, R.R., 2001. Gender differences in personality traits across cultures: robust and surprising findings. J. Pers. Soc. Psychol. 81, 322–331. https://doi.org/10.1037/0022-3514.81.2.322

Costa, P.T.J., McCrae, R.R., 1997. Stability and change in personality assessment: The revised NEO personality inventory in the year 2000. J. Pers. Assess. 68, 69–85. https://doi.org/10.1207/s15327752jpa6801

Coveleskie, K., Gupta, A., Kilpatrick, L.A., Mayer, E.D., Ashe-Mcnalley, C., Stains, J., Labus, J.S., Mayer, E.A., 2015. Altered functional connectivity within the central reward network in overweight and obese women. Nutr. Diabetes 5, e148-7. https://doi.org/10.1038/nutd.2014.45

Cox, C.L., Gotimer, K., Roy, A.K., Castellanos, F.X., Milham, M.P., Kelly, C., 2010. Your resting brain CAREs about your risky behavior. PLoS One 5. https://doi.org/10.1371/journal.pone.0012296

Cox, R.W., 1996. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173. https://doi.org/10.1006/cbmr.1996.0014

Cox, R.W., Hyde, J.S., 1997. Software tools for analysis and visualization of fMRI data. NMR Biomed. 10, 171–8. https://doi.org/10.1002/(SICI)1099-1492(199706/08)10:4/5<171::AID-NBM453>3.0.CO;2-L

Crone, E.A., Van Duijvenvoorde, A.C.K., Peper, J.S., 2016. Annual Research Review: Neural contributions to risk-taking in adolescence - developmental changes and individual differences. J. Child Psychol. Psychiatry Allied Discip. 57, 353–368. https://doi.org/10.1111/jcpp.12502

Crossman, A., Anne Sullivan, D., Benin, M., 2006. The family environment and American adolescents' risk of obesity as young adults. Soc. Sci. Med. 63, 2255–67. https://doi.org/10.1016/j.socscimed.2006.05.027

Cservenka, A., Casimo, K., Fair, D. a., Nagel, B.J., 2014. Resting state functional connectivity of the nucleus accumbens in youth with a family history of alcoholism. Psychiatry Res. - Neuroimaging 221, 210–219. https://doi.org/10.1016/j.pscychresns.2013.12.004

Cservenka, A., Herting, M.M., Seghete, K.L.M., Hudson, K.A., Nagel, B.J., 2013. High and low sensation seeking adolescents show distinct patterns of brain activity during reward processing. Neuroimage 66, 184–193. https://doi.org/10.1016/j.neuroimage.2012.11.003

Currie, C., Molcho, M., Boyce, W., Holstein, B., Torsheim, T., Richter, M., 2008. Researching health inequalities in adolescents: The development of the Health Behaviour in School-

Aged Children (HBSC) Family Affluence Scale. Soc. Sci. Med. 66, 1429–1436. https://doi.org/10.1016/j.socscimed.2007.11.024

Damoiseaux, J.S., Greicius, M.D., 2009. Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. Brain Struct. Funct. 213, 525–533. https://doi.org/10.1007/s00429-009-0208-6

Dang, L.C., Samanez-Larkin, G.R., Castrellon, J.J., Perkins, S.F., Cowan, R.L., Zald, D.H., 2016. Associations between dopamine D2 receptor availability and BMI depend on age. Neuroimage. https://doi.org/10.1016/j.neuroimage.2016.05.044

Daniel, T.O., Stanton, C.M., Epstein, L.H., 2013. The future is now. Comparing the effect of episodic future thinking on impulsivity in lean and obese individuals. Appetite. https://doi.org/10.1016/j.appet.2013.07.010

Davidow, J.Y., Foerde, K., Galván, A., Shohamy, D., 2016. An upside to reward sensitivity: The hippocampus supports enhanced reinforcement learning in adolescence. Neuron 92, 93–99. https://doi.org/10.1016/j.neuron.2016.08.031

Defoe, I.N., Dubas, J.S., Figner, B., van Aken, M.A.G., 2015. A meta-analysis on age differences in risky decision making: Adolescents versus children and adults. Psychol. Bull. 141, 48–84. https://doi.org/10.1037/a0038088

Delgado-Rico, E., Río-Valle, J.S., González-Jiménez, E., Campoy, C., Verdejo-García, A., 2012. BMI predicts emotion-driven impulsivity and cognitive inflexibility in adolescents with excess weight. Obesity 20, 1604–1610. https://doi.org/10.1038/oby.2012.47

Deyoung, C.G., Gray, J.R., 2009. Personality neuroscience: explaining individual differences in affect, behaviour and cognition, The Cambridge Handbook of Personality Psychology. https://doi.org/10.1017/CBO9780511596544.023

Deyoung, C.G., Hirsh, J.B., Shane, M.S., Papademetris, X., 2010. Testing predictions from personality neuroscience: Brain structure and the big five. Psychol. Sci. 21, 820–828. https://doi.org/10.1177/0956797610370159.Testing

Di Martino, A., Scheres, A., Margulies, D.S., Kelly, A. M.C., Uddin, L.Q., Shehzad, Z., Biswal, B., Walters, J.R., Castellanos, F.X., Milham, M.P., 2008. Functional connectivity of human striatum: A resting state fMRI study. Cereb. Cortex 18, 2735–2747. https://doi.org/10.1093/cercor/bhn041

Diedrichsen, J., Balsters, J., Flavel, J., Cussans, E., Ramnani, N., 2009. A probabilistic MR atlas of the human cerebellum. Neuroimage 46, 39–46.

Dietrich, A., de Wit, S., Horstmann, A., 2016. General habit propensity relates to the sensation seeking subdomain of impulsivity but not obesity. Front. Behav. Neurosci. 10, 1–14. https://doi.org/10.3389/fnbeh.2016.00213

Doll, A., Hölzel, B.K., Boucard, C.C., Wohlschläger, A.M., Sorg, C., 2015. Mindfulness is associated with intrinsic functional connectivity between default mode and salience networks. Front. Hum. Neurosci. 9, 1–11. https://doi.org/10.3389/fnhum.2015.00461

Doucet, G.E., Rasgon, N., McEwen, B.S., Micali, N., Frangou, S., 2017. Elevated body mass index is associated with increased integration and reduced cohesion of sensory-driven and internally guided resting-state functional brain networks. Cereb. Cortex 988–997. https://doi.org/10.1093/cercor/bhx008

Duckworth, A.L., Kern, M.L., 2012. A meta-analysis of the convergent validity of self-control measures 45, 259–268. https://doi.org/10.1016/j.jrp.2011.02.004.A

Duckworth, A.L., Tsukayama, E., Geier, A.B., 2010. Self-controlled children stay leaner in the transition to adolescence. Appetite 54, 304–308. https://doi.org/10.1016/j.appet.2009.11.016

Düzel, E., Bunzeck, N., Guitart-Masip, M., Wittmann, B., Schott, B.H., Tobler, P.N., 2009. Functional imaging of the human dopaminergic midbrain. Trends Neurosci. 32, 321–328. https://doi.org/10.1016/j.tins.2009.02.005

Eigsti, I.-M., Zayas, V., Mischel, W., Shoda, Y., Ayduk, O., Dadlani, M.B., Davidson, M.C., Lawrence Aber, J., Casey, B.J., 2006. Predicting cognitive control from preschool to late adolescence and young adulthood. Psychol. Sci. 17, 478–84. https://doi.org/10.1111/j.1467-9280.2006.01732.x

Emerson, R.W., Short, S.J., Lin, W., Gilmore, J.H., Gao, W., 2015. Network-Level connectivity dynamics of movie watching in 6-year-old children. Front. Hum. Neurosci. 9, 1–8. https://doi.org/10.3389/fnhum.2015.00631

Ernst, M., 2014. The triadic model perspective for the study of adolescent motivated behavior. Brain Cogn. 89, 104–111. https://doi.org/10.1016/j.bandc.2014.01.006

Ernst, M., Pine, D.S., Hardin, M., 2006. Triadic model of neurobiology of motivated behaviour in adolescence. Psychol. Med. 36, 299–312. https://doi.org/10.1017/S0033291705005891.Triadic

Etkin, A., Büchel, C., Gross, J.J., 2015. The neural bases of emotion regulation. Nat. Rev. Neurosci. 16, 693–700. https://doi.org/10.1038/nrn4044

Evans, A.C., 2006. The NIH MRI study of normal brain development. Neuroimage 30, 184–202. https://doi.org/10.1016/j.neuroimage.2005.09.068

Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A.R., Fox, P.T., Eickhoff, S.B., Yu, C., Jiang, T., 2016. The Human Brainnetome Atlas: A new brain atlas based on connectional architecture. Cereb. Cortex 26, 3508–3526. https://doi.org/10.1093/cercor/bhw157

Filippi, M., 2016. fMRI Techniques and Protocols.

Flegal, K.M., Wei, R., Ogden, C., 2002. Weight-for-stature compared with body mass index-for-age growth charts for the United States from the Centers for Disease Control and Prevention. Am. J. Clin. Nutr. 75, 761–6.

Forbes, E.E., Brown, S.M., Kimak, M., Ferrell, R.E., Manuck, S.B., Hariri, a R., 2009. Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. Mol. Psychiatry 14, 60–70. https://doi.org/10.1038/sj.mp.4002086

Francis, L. A., Susman, E.J., 2009. Self-regulation and rapid weight gain in children from age 3 to 12 years. Arch. Pediatr. Adolesc. Med. 163, 297–302. https://doi.org/10.1001/archpediatrics.2008.579

Freedman, D.S., Wang, J., Maynard, L.M., Thornton, J.C., Mei, Z., Pierson, R.N., Dietz, W.H., Horlick, M., 2005. Relation of BMI to fat and fat-free mass among children and adolescents. Int. J. Obes. (Lond). 29, 1–8. https://doi.org/10.1038/sj.ijo.0802735

Fuentes-Claramonte, P., Avila, C., Rodriguez-Pujadas, A., Costumero, V., Ventura-Campos, N., Bustamante, J.C., Rosell-Negre, P., Barros-Loscertales, A., 2016. Characterizing individual differences in reward sensitivity from the brain networks involved in response inhibition. Neuroimage 124, 287–299. https://doi.org/10.1016/j.neuroimage.2015.08.067

Galvan, A., Hare, T. A., Parra, C.E., Penn, J., Voss, H., Glover, G., Casey, B.J., 2006. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. J. Neurosci. 26, 6885–6892. https://doi.org/10.1523/JNEUROSCI.1062-06.2006

Gao, X., Liang, Q., Wu, G., She, Y., Sui, N., Chen, H., 2018. Decreased resting-state BOLD regional homogeneity and the intrinsic functional connectivity within dorsal striatum is associated with greater impulsivity in food-related decision-making and BMI change at 6-month follow up. Appetite 127, 69–78. https://doi.org/10.1016/j.appet.2018.04.024

Garcia-Casares, N., Bernal-Lopez, M.R., Roe-Vellve, N., Gutierrez-Bedmar, M., Fernandez-Garcia, J.C., Grcia-Arnes, J.A., Ramos-Rodriguez, J.R., Alfaro, F., Santamaria-Fernandez, S., Steward, T., Jimenez-Murcia, S., Garcia-Garcia, I., Valdivielso, P., Fernandez-Aranda, F., Tinahones, F.J., Gomez-Huelgas, R., 2017. Brain functional connectivity is modified by a hypocaloric mediterranean diet and physical activity. Nutrients 9, 685–701. https://doi.org/10.3390/nu9070685

García-García, I., Jurado, M.Á., Garolera, M., Segura, B., Sala-Llonch, R., Marqués-Iturria, I., Pueyo, R., Sender-Palacios, M.J., Vernet-Vernet, M., Narberhaus, A., Ariza, M., Junqué, C., 2013. Alterations of the salience network in obesity: A resting-state fMRI study. Hum. Brain Mapp. 34, 2786–2797. https://doi.org/10.1002/hbm.22104

Gaspar, P., Stepniewska, I., Kaas, J.H., 1992. Topography and collateralization of the dopaminergic projections to motor and lateral prefrontal cortex in owl monkeys. J. Comp. Neurol. 325, 1–21. https://doi.org/10.1002/cne.903250102

Gautier, J.F., Del Parigi, A., Chen, K., Salbe, A.D., Bandy, D., Pratley, R.E., Ravussin, E., Reiman, E.M., Tataranni, P.A., 2001. Effect of satiation on brain activity in obese and lean women. Obes. Res. 9, 676–84. https://doi.org/10.1038/oby.2001.92

Geerligs, L., Rubinov, M., Cam-CAN, Henson, R.N., 2015. State and trait components of functional connectivity: Individual differences vary with mental state. J. Neurosci. 35, 13949–13961. https://doi.org/10.1523/JNEUROSCI.1324-15.2015

Geier, C.F., Terwilliger, R., Teslovich, T., Velanova, K., Luna, B., 2010. Immaturities in reward processing and its influence on inhibitory control in adolescence. Cereb. Cortex 20, 1613–1629. https://doi.org/10.1093/cercor/bhp225

Gennatas, E.D., Avants, B.B., Wolf, D.H., Satterthwaite, T.D., Ruparel, K., Ciric, R., Hakonarson, H., Gur, R.E., Gur, R.C., 2017. Age-related effects and sex differences in gray matter density, volume, mass, and cortical thickness from childhood to young adulthood. J. Neurosci. 37, 3550–16. https://doi.org/10.1523/JNEUROSCI.3550-16.2017

Gerlach, G., Herpertz, S., Loeber, S., 2015. Personality traits and obesity: A systematic review. Obes. Rev. 16, 32–63. https://doi.org/10.1111/obr.12235

Giedd, J.A.Y.N., Blumenthal, J., Jeffries, N., Rajapakse, J.C., Vaituzis, A.C., Liu, H., Berry, Y.C., Tobin, M., Nelson, J., Castellanos, F.X., Jay, N., 1999. Development of the human corpus callosum during childhood and adolescence: A longitudinal MRI study. Prog. Neuropsychopharmacol. Biol. Psychiatry 23, 571–588.

Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, a, Paus, T., Evans, a C., Rapoport, J.L., 1999. Brain development during childhood and adolescence: A longitudinal MRI study. Nat. Neurosci. 2, 861–3. https://doi.org/10.1038/13158

Giedd, J.N., Castellanos, F.X., Rajapakse, J.C., Vaituzis, A.C., Rapoport, J.L., 1997. Sexual dimorphism of the developing human brain. Prog. Neuropsychopharmacol. Biol. Psychiatry 21, 1186–1201.

Giedd, J.N., Clasen, L.S., Lenroot, R., Greenstein, D., Wallace, G.L., Ordaz, S., Molloy, E. A., Blumenthal, J.D., Tossell, J.W., Stayer, C., Samango-Sprouse, C. A., Shen, D., Davatzikos, C., Merke, D., Chrousos, G.P., 2006. Puberty-related influences on brain development. Mol. Cell. Endocrinol. 254–255, 154–62. https://doi.org/10.1016/j.mce.2006.04.016

Giedd, J.N., Rapoport, J.L., 2010. Structural MRI of pediatric brain development: What have we learned and where are we going? Neuron 67, 728–34. https://doi.org/10.1016/j.neuron.2010.08.040

Gogtay, N., Iii, T.F.N., Herman, D.H., Ordonez, A., Greenstein, D., Hayashi, K.M., Clasen, L., Toga, A.W., Giedd, J.N., Rapoport, J.L., Thompson, P.M., 2006. Dynamic mapping of normal human hippocampal development 672, 664–672. https://doi.org/10.1002/hipo

Gray, V.B., Byrd, S.H., Cossman, J.S., Chromiak, J., Cheek, W.K., Jackson, G.B., 2007. Family characteristics have limited ability to predict weight status of young children. J. Am. Diet. Assoc. 107, 1204–9. https://doi.org/10.1016/j.jada.2007.04.004

Gupta, A., Mayer, E.A., Labus, J.S., Bhatt, R.R., Ju, T., Love, A., Bal, A., Tillisch, K., Naliboff, B., Sanmiguel, C.P., Kilpatrick, L.A., 2018. Sex commonalities and differences in obesity-related alterations in intrinsic brain activity and connectivity. Obesity 26, 340–350. https://doi.org/10.1002/oby.22060

Haber, S.N., 2003. The primate basal ganglia: parallel and integrative networks. J. Chem. Neuroanat. 26, 317–330. https://doi.org/10.1016/j.jchemneu.2003.10.003

Haber, S.N., Fudge, J.L., McFarland, N.R., 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J. Neurosci. 20, 2369–82.

Haber, S.N., Kunishio, K., Mizobuchi, M., Lynd-Balta, E., 1995. The orbital and medial prefrontal circuit through the primate basal ganglia. J. Neurosci. 15, 4851–4867.

Hackman, D. A., Farah, M.J., Meaney, M.J., 2010. Socioeconomic status and the brain: Mechanistic insights from human and animal research. Nat. Rev. Neurosci. 11, 651–659. https://doi.org/10.1038/nrn2897

Haddad, A.D.M., Harrison, F., Norman, T., Lau, J.Y.F., 2014. Adolescent and adult risk-taking in virtual social contexts. Front. Psychol. 5, 1–7. https://doi.org/10.3389/fpsyg.2014.01476

Halliday, G.M., Törk, I., 1986. Comparative anatomy of the ventromedial mesencephalic tegmentum in the rat, cat, monkey and human. J. Comp. Neurol. 252, 423–445. https://doi.org/10.1002/cne.902520402

Hammers, A., Allom, R., Koepp, M.J., Free, S.L., Myers, R., Lemieux, L., Mitchell, T.N., Brooks, D.J., Duncan, J.S., 2003. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. Hum. Brain Mapp. 19, 224–247. https://doi.org/10.1002/hbm.10123

Han, J.E., Boachie, N., Garcia-garcia, I., Michaud, A., Dagher, A., 2018. Neural correlates of dietary self-control in healthy adults : A meta-analysis of functional brain imaging studies. Physiol. Behav. 192, 98–108. https://doi.org/10.1016/j.physbeh.2018.02.037

Hargrave, S.L., Jones, S., Davidson, T.L., 2016. The outward spiral: A vicious cycle model of obesity and cognitive dysfunction. Curr Opin Behav Sci 9, 40–46. https://doi.org/10.1016/j.cobeha.2015.12.001.The

Hassenstab, J.J., Sweet, L.H., Del Parigi, A., McCaffery, J.M., Haley, A.P., Demos, K.E., Cohen, R. a, Wing, R.R., 2012. Cortical thickness of the cognitive control network in obesity and successful weight loss maintenance: a preliminary MRI study. Psychiatry Res. 202, 77–9. https://doi.org/10.1016/j.pscychresns.2011.09.008

Hawes, S.W., Chahal, R., Hallquist, M.N., Paulsen, D.J., Geier, C.F., Luna, B., 2016. Modulation of reward-related neural activation on sensation seeking across development. Neuroimage 147, 763–771. https://doi.org/10.1016/j.neuroimage.2016.12.020

Hill, P.F., Yi, R., Spreng, R.N., Diana, R.A., 2017. Neural congruence between intertemporal and interpersonal self-control: Evidence from delay and social discounting. Neuroimage 162, 186–198. https://doi.org/10.1016/j.neuroimage.2017.08.071

Ho, A.J., Raji, C. A., Becker, J.T., Lopez, O.L., Kuller, L.H., Hua, X., Lee, S., Hibar, D., Dinov, I.D., Stein, J.L., Jack, C.R., Weiner, M.W., Toga, A.W., Thompson, P.M., 2010. Obesity is linked with lower brain volume in 700 AD and MCI patients. Neurobiol. Aging 31, 1326–39. https://doi.org/10.1016/j.neurobiolaging.2010.04.006

Hofmann, W., Friese, M., Strack, F., 2009. Impulse and self-control from a dual-systems perspective. Perspect. Psychol. Sci. 4, 1–15. https://doi.org/10.1111/j.1745-6924.2009.01116.x

Horstmann, A., Busse, F.P., Mathar, D., Müller, K., Lepsien, J., Schlögl, H., Kabisch, S., Kratzsch, J., Neumann, J., Stumvoll, M., Villringer, A., Pleger, B., 2011. Obesity-Related differences between women and men in brain structure and goal-directed behavior. Front. Hum. Neurosci. 5, 58. https://doi.org/10.3389/fnhum.2011.00058

Horstmann, A., Kovacs, P., Kabisch, S., Boettcher, Y., Schloegl, H., Tönjes, A., Stumvoll, M., Pleger, B., Villringer, A., 2013. Common genetic variation near MC4R has a sex-specific impact on human brain structure and eating behavior. PLoS One 8, e74362. https://doi.org/10.1371/journal.pone.0074362

Insel, C., Kastman, E.K., Glenn, C.R., Somerville, L.H., 2017. Development of corticostriatal connectivity constrains goal-directed behavior during adolescence. Nat. Commun. 8, 1605. https://doi.org/10.1038/s41467-017-01369-8

Inuggi, A., Sanz-Arigita, E., Gonzalez-Salinas, C., Valero-Garcia, A. V., Garcia-Santos, J.M., Fuentes, L.J., 2014. Brain functional connectivity changes in children that differ in impulsivity temperamental trait. Front. Behav. Neurosci. 8, 1–14. https://doi.org/10.3389/fnbeh.2014.00156

Jahanshahi, M., Obeso, I., Baunez, C., Alegre, M., Krack, P., 2015. Parkinson's disease, the subthalamic nucleus, inhibition, and impulsivity. Mov. Disord. 30, 128–140. https://doi.org/10.1002/mds.26049

Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved methods for the registration and motion correction of brain images. FMRIB Tech. Rep. TR02MJ1 1. https://doi.org/10.1017/CBO9781107415324.004

Jenkinson, M., Beckmann, C., 2001. ICA in fMRI: A basic introduction. FMRIB Tech. Rep. TR01MJ2 7–9.

Jernigan, T.L., Trauner, D. A., Hesselink, J.R., Tallal, P. A., 1991. Maturation of human cerebrum observed in vivo during adolescence. Brain 114 (Pt 5, 2037–49.

Johnson, A., van der Meer, M.A., Redish, A.D., 2007. Integrating hippocampus and striatum in decision-making. Curr. Opin. Neurobiol. 17, 692–697. https://doi.org/10.1016/j.conb.2008.01.003

Jokela, M., Hintsanen, M., Hakulinen, C., Batty, G.D., Nabi, H., Singh-Manoux, A.., Kivimäki, M., 2013. Association of personality with the development and persistence of obesity: A meta-analysis based on individual-participant data. Obes. Rev. 14, 315–323. https://doi.org/10.1111/obr.12007

Jollans, L., Zhipeng, C., Icke, I., Greene, C., Kelly, C., Banaschewski, T., Bokde, A.L.W., Bromberg, U., Buchel, C., Cattrell, A., Conrod, P.J., Desrivieres, S., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Martinot, J.-L., Artiges, E., Nees, F., Papadopoulos Orfanos, D., Paus, T., Smolka, M.N., Walter, H., Schumann, G., Whelan, R., 2016. Ventral striatum connectivity during reward anticipation in adolescent smokers. Dev. Neuropsychol. 5641, 1–16. https://doi.org/10.1080/87565641.2016.1164172

Joutsa, J., Voon, V., Johansson, J., Niemelä, S., Bergman, J., Kaasinen, V., 2015. Dopaminergic function and intertemporal choice. Transl. Psychiatry 5, e491. https://doi.org/10.1038/tp.2014.133

Jurk, S., Kuitunen-Paul, S., Kroemer, N.B., Artiges, E., Banaschewski, T., Bokde, A.L.W., Büchel, C., Conrod, P., Fauth-Bühler, M., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Heinz, A., Mann, K.F., Nees, F., Paus, T., Pausova, Z., Poustka, L., Rietschel, M., Schumann, G., Struve, M., Smolka, M.N., 2015. Personality and substance use: Psychometric evaluation and validation of the Substance Use Risk Profile Scale (SURPS) in English, Irish, French, and German adolescents. Alcohol. Clin. Exp. Res. 39, 2234–2248. https://doi.org/10.1111/acer.12886

Kanoski, S.E., Grill, H.J., 2017. Hippocampus contributions to food intake control: Mnemonic, neuroanatomical , and endocrine mechanisms. Biol. Psychiatry 81, 748–756. https://doi.org/10.1016/j.biopsych.2015.09.011

Kelly, Y., Patalay, P., Montgomery, S., Sacker, A., 2016. BMI development and early adolescent psychosocial well-being: UK millennium cohort study. Pediatrics 138. https://doi.org/10.1542/peds.2016-0967

Keuken, M.C., Forstmann, B.U., 2015. A probabilistic atlas of the basal ganglia using 7T MRI. Data Br. 4, 577–582. https://doi.org/10.1016/j.dib.2015.07.028

Khan, N.A., Baym, C.L., Monti, J.M., Raine, L.B., Drollette, E.S., Scudder, M.R., Moore, R.D., Kramer, A.F., Hillman, C.H., Cohen, N.J., 2015. Central adiposity is negatively associated with hippocampal-dependent relational memory among overweight and obese children. J. Pediatr. 166, 302–308. https://doi.org/10.1016/j.jpeds.2014.10.008

Kishinevsky, F.I., Cox, J.E., Murdaugh, D.L., Stoeckel, L.E., Cook, E.W., Weller, R.E., 2012. fMRI reactivity on a delay discounting task predicts weight gain in obese women. Appetite 58, 582–92. https://doi.org/10.1016/j.appet.2011.11.029

Krafft, C.E., Pierce, J.E., Schwarz, N.F., Chi, L., Weinberger, A.L., Schaeffer, D.J., Rodrigue, A.L., Camchong, J., Allison, J.D., Yanasak, N.E., Liu, T., Davis, C.L., McDowell, J.E., 2014. An eight month randomized controlled exercise intervention alters resting state synchrony in overweight children. Neuroscience 256, 445–455. https://doi.org/10.1016/j.neuroscience.2013.09.052

Krank, M., Stewart, S.H., O'Connor, R., Woicik, P.B., Wall, A.-M., Conrod, P.J., 2011. Structural, concurrent, and predictive validity of the Substance Use Risk Profile Scale in early adolescence. Addict. Behav. 36, 37–46. https://doi.org/10.1016/j.addbeh.2010.08.010

Krishnan, A., Williams, L.J., McIntosh, A.R., Abdi, H., 2011. Partial Least Squares (PLS) methods for neuroimaging: A tutorial and review. Neuroimage 56, 455–475. https://doi.org/10.1016/j.neuroimage.2010.07.034

Krmpotich, T.D., Tregellas, J.R., Thompson, L.L., Banich, M.T., Klenk, A.M., Tanabe, J.L., 2013. Resting-state activity in the left executive control network is associated with behavioral approach and is increased in substance dependence. Drug Alcohol Depend. 129, 1–7. https://doi.org/10.1016/j.drugalcdep.2013.01.021

Krombholz, H., 2013. Motor and cognitive performance of overweight preschool children 1. Percept. Mot. Skills 116, 40–57. https://doi.org/10.2466/22.25.PMS.116.1.40-57

Kuczmarski, R.J., Ogden, C.L., Guo, S.S., Grummer-Strawn, L.M., Flegal, K.M., Mei, Z., Wei, R., Curtin, L.R., Roche, A.F., Johnson, C.L., 2002. 2000 CDC growth charts for the United States: Methods and development., Vital and health statistics. Series 11, Data from the national health survey.

Kullmann, S., Heni, M., Veit, R., Ketterer, C., Schick, F., Häring, H.U., Fritsche, A., Preissl, H., 2012. The obese brain: Association of body mass index and insulin sensitivity with resting state network functional connectivity. Hum. Brain Mapp. 33, 1052–1061. https://doi.org/10.1002/hbm.21268

Kullmann, S., Pape, A., Heni, M., Ketterer, C., Schick, F., Häring, H., 2013. Functional network connectivity underlying food processing: Disturbed salience and visual processing in

overweight and obese adults. Cereb. Cortex 23, 1247–1256. https://doi.org/10.1093/cercor/bhs124

La, C., Mossahebi, P., Nair, V.A., Bendlin, B.B., Birn, R., Meyerand, M.E., Prabhakaran, V., 2015. Age-related changes in inter-network connectivity by component analysis. Front. Aging Neurosci. 7, 1–12. https://doi.org/10.3389/fnagi.2015.00237

Laird, A.R., Fox, P.M., Eickhoff, S.B., Turner, J.A., Ray, K.L., McKay, D.R., Glahn, D.C., Beckmann, C.F., Smith, S.M., Fox, P.T., 2011. Behavioral Interpretations of Intrinsic Connectivity Networks. J. Cogn. Neurosci. 23, 4022–4037. https://doi.org/10.1162/jocn_a_00077

Langner, R., Leiberg, S., Ho, F., Eickho, S.B., 2018. Towards a human self-regulation system: Common and distinct neural signatures of emotional and behavioural control. Neurosci. Biobehav. Rev. 90, 400–410. https://doi.org/10.1016/j.neubiorev.2018.04.022

Larsen, B., Verstynen, T.D., Yeh, F.-C., Luna, B., 2017. Developmental changes in the integration of affective and cognitive corticostriatal pathways are associated with reward-driven behavior. Cereb. Cortex 1–12. https://doi.org/10.1093/cercor/bhx162

Lawyer, S.R., Boomhower, S.R., Rasmussen, E.B., 2015. Differential associations between obesity and behavioral measures of impulsivity. Appetite 95, 375–382. https://doi.org/10.1016/j.appet.2015.07.031

Lee, T., Telzer, E.H., 2016. Negative coupling between the right fronto-parietal and limbic resting state networks predicts increased self-control and reduced risk-taking behavior in adolescence. Dev. Cogn. Neurosci. 20, 35–42. https://doi.org/10.1016/j.dcn.2016.06.002

Lee, Y., Kroemer, N.B., Oehme, L., Beuthien-, B., Goschke, T., Smolka, M.N., 2018. Lower dopamine tone in the striatum is associated with higher body mass index. Eur. Neuropsychopharmacol. https://doi.org/10.1016/j.euroneuro.2018.03.009

Legget, K.T., Wylie, K.P., Cornier, M., Edward, L., Paschall, C.J., Tregellas, J.R., Medical, A., States, U., Campus, A.M., States, U., States, U., Campus, A.M., States, U., States, U., 2016. Exercise-related changes in between-network connectivity in oberweight/obese adults. Physiol. Behav. 158, 60–67. https://doi.org/10.1016/j.physbeh.2016.02.031.Exercise-related

Leong, J.K., Pestilli, F., Wu, C.C., Samanez-Larkin, G.R., Knutson, B., 2016. White-Matter tract connecting anterior insula to nucleus accumbens correlates with reduced preference for positively skewed gambles. Neuron 89. https://doi.org/10.1016/j.rasd.2014.08.015.Social

Li, N., Ma, N., Liu, Y., He, X.-S., Sun, D.-L., Fu, X.-M., Zhang, X., Han, S., Zhang, D.-R., 2013. Resting-State functional connectivity predicts impulsivity in economic decision-making. J. Neurosci. 33, 4886–4895. https://doi.org/10.1523/JNEUROSCI.1342-12.2013

Lin, Q.H., Liu, J., Zheng, Y.R., Liang, H., Calhoun, V.D., 2010. Semiblind spatial ICA of fMRI using spatial constraints. Hum. Brain Mapp. 31, 1076–1088. https://doi.org/10.1002/hbm.20919

Lips, M.A., Wijngaarden, M.A., Grond, J. Van Der, Buchem, M.A. Van, Groot, G.H. De, Pijl, H., Veer, I.M., 2014. Resting-state functional connectivity of brain regions involved in cognitive control , motivation , and reward is enhanced in obese females. Am. J. Clin. Nutr. 100, 524–531. https://doi.org/10.3945/ajcn.113.080671.1

Liston, C., Watts, R., Tottenham, N., Davidson, M.C., Niogi, S., Ulug, A.M., Casey, B.J., 2006. Frontostriatal microstructure modulates efficient recruitment of cognitive control. Cereb. Cortex 16, 553–60. https://doi.org/10.1093/cercor/bhj003

Liu, J., Ghassemi, M.M., Michael, A.M., Boutte, D., Wells, W., Perrone-Bizzozero, N., Macciardi, F., Mathalon, D.H., Ford, J.M., Potkin, S.G., Turner, J. a., Calhoun, V.D., 2012. An ICA with reference approach in identification of genetic variation and associated brain networks. Front. Hum. Neurosci. 6, 1–10. https://doi.org/10.3389/fnhum.2012.00021

Lohani, S., Poplawsky, A.J., Kim, S.-G., Moghaddam, B., 2016. Unexpected global impact of VTA dopamine neuron activation as measured by opto-fMRI. Mol. Psychiatry, 1–10. https://doi.org/10.1038/mp.2016.102

Lunn, T.E., Nowson, C. A., Worsley, A., Torres, S.J., 2014. Does personality affect dietary intake? Nutrition 30, 403–409. https://doi.org/10.1016/j.nut.2013.08.012

Maayan, L., Hoogendoorn, C., Sweat, V., Convit, A., 2012. Disinhibited eating in obese adolescents in associated with orbtofrontal volume reductions and executive dysfunction. Obesity (Silver Spring). 19, 1382–1387. https://doi.org/10.1038/oby.2011.15.Disinhibited

MacPherson, L., Magidson, J.F., Reynolds, E.K., Kahler, C.W., Lejuez, C.W., 2010. Changes in sensation seeking and risk-taking propensity predict increases in alcohol use among early adolescents. Alcohol. Clin. Exp. Res. 34, 1400–8. https://doi.org/10.1111/j.1530-0277.2010.01223.x

Marqués-Iturria, I., Pueyo, R., Garolera, M., Segura, B., Junqué, C., García-García, I., José Sender-Palacios, M., Vernet-Vernet, M., Narberhaus, A., Ariza, M., Jurado, M.Á., 2013. Frontal cortical thinning and subcortical volume reductions in early adulthood obesity. Psychiatry Res. 1–7. https://doi.org/10.1016/j.pscychresns.2013.06.004

McCormick, E.M., Qu, Y., Telzer, E.H., 2016. Adolescent neurodevelopment of cognitive control and risk-taking in negative family contexts. Neuroimage 124, 989–996. https://doi.org/10.1016/j.neuroimage.2015.09.063

McCrae, R.R., John, O.P., 1992. An introduction to the five-factor model and its applications. J. Pers. 60, 175–215. https://doi.org/10.1111/j.1467-6494.1992.tb00970.x

McFadden, K.L., Cornier, M.A., Melanson, E.L., Bechtell, J.L., Tregellas, J.R., 2013. Effects of exercise on resting-state default mode and salience network activity in overweight/obese adults. Neuroreport 24, 866–871. https://doi.org/10.1097/WNR.0000000000000013.Effects

McLaren, L., 2007. Socioeconomic status and obesity. Epidemiol. Rev. 29, 29–48. https://doi.org/10.1093/epirev/mxm001

Medic, N., Kochunov, P., Ziauddeen, H., Ronan, L., Fletcher, P.C., Ersche, K.D., Nathan, P.J., Fletcher, P.C., 2018. BMI-related cortical morphometry changes are associated with altered white matter structure. Int. J. Obes. https://doi.org/10.1038/s41366-018-0269-9

Meier, T.B., Wildenberg, J.C., Liu, J., Chen, J., Calhoun, V.D., Biswal, B.B., Meyerand, M.E., Birn, R.M., Prabhakaran, V., 2012. Parallel ICA identifies sub-components of resting state networks that covary with behavioral indices. Front. Hum. Neurosci. 6, 1–14. https://doi.org/10.3389/fnhum.2012.00281

Menon, V., 2015. Salience Network, Brain Mapping: An Encyclopedic Reference. Elsevier Inc. https://doi.org/10.1016/B978-0-12-397025-1.00052-X

Mirchi, N., Betzel, R.F., Bernhardt, B.C., Dagher, A., 2018. Tracking mood fluctuations with functional network patterns. Soc. Cogn. Affect. Neurosci. 14, 47–57. https://doi.org/10.1093/scan/nsy107

Mischel, W., Ebbesen, E.B., Zeiss, a R., 1972. Cognitive and attentional mechanisms in delay of gratification. J. Pers. Soc. Psychol. 21, 204–18.

Mischel, W., Shoda, Y., Peake, P.K., 1988. The nature of adolescent competencies predicted by preschool delay of gratification. J. Pers. Soc. Psychol. 54, 687–96.

Mischel, W., Shoda, Y., Rodriguez, M.I., 1989. Delay of gratification in children. Science 244, 933–8.

Mišić, B., Betzel, R.F., de Reus, M.A., van den Heuvel, M.P., Berman, M.G., McIntosh, A.R., Sporns, O., 2016. Network-Level structure-function relationships in human Neocortex. Cereb. Cortex 26, 3285–3296. https://doi.org/10.1093/cercor/bhw089

Mitchell, M.R., Potenza, M.N., 2014. Addictions and personality traits: Impulsivity and related constructs. Curr. Behav. Neurosci. Reports 1, 1–12. https://doi.org/10.1007/s40473-013-0001-y

Mizumori, S.J.Y., Tryon, V.L., 2015. Integrative hippocampal and decision-making neurocircuitry during goal-relevant predictions and encoding, 1st ed, Progress in Brain Research. Elsevier B.V. https://doi.org/10.1016/bs.pbr.2015.03.010

Moreno-Lopez, L., Contreras-Rodriguez, O., Soriano-Mas, C., Stamatakis, E.A., Verdejo-Garcia, A., 2016. Disrupted functional connectivity in adolescent obesity. NeuroImage Clin. https://doi.org/10.1016/j.nicl.2016.07.005

Moreno-López, L., Soriano-Mas, C., Delgado-Rico, E., Rio-Valle, J.S., Verdejo-García, A., 2012. Brain structural correlates of reward sensitivity and impulsivity in adolescents with normal and excess Weight. PLoS One 7, 1–8. https://doi.org/10.1371/journal.pone.0049185

Morris, L.S., Kundu, P., Baek, K., Irvine, M.A., Mechelmans, D.J., Wood, J., Harrison, N.A., Robbins, T.W., Bullmore, E.T., Voon, V., 2015. Jumping the gun: Mapping neural correlates of waiting impulsivity and relevance across alcohol misuse. Biol. Psychiatry 1–9. https://doi.org/10.1016/j.biopsych.2015.06.009

Muetzel, R.L., Blanken, L.M.E., Thijssen, S., van der Lugt, A., Jaddoe, V.W. V, Verhulst, F.C., Tiemeier, H., White, T., 2016. Resting-state networks in 6-to-10 year old children. Hum. Brain Mapp. 37, 4286–4300. https://doi.org/10.1002/hbm.23309

Murdaugh, D.L., Cox, J.E., Cook, E.W., Weller, R.E., 2012. fMRI reactivity to high-calorie food pictures predicts short and long-term outcome in a weight-loss program. Neuroimage 40, 1301–1315. https://doi.org/10.1007/s10439-011-0452-9.Engineering

Murty, V., Calabro, F., Luna, B., 2016. The role of experience in adolescent cognitive development: Integration of executive, memory and mesolimbic systems. Neurosci. Biobehav. Rev. 70, 46–58. https://doi.org/10.1016/j.neubiorev.2016.07.034.The

Murty, V.P., Shermohammed, M., Smith, D. V., Carter, R.M., Huettel, S. A., Adcock, R.A., 2014. Resting state networks distinguish human ventral tegmental area from substantia nigra. Neuroimage 100, 580–589. https://doi.org/10.1016/j.neuroimage.2014.06.047

Myerson, J., Green, L., Warusawitharana, M., 2001. Area under the curve as a measure of discounting. J. Exp. Anal. Behav. 76, 235–43. https://doi.org/10.1901/jeab.2001.76-235

Nederkoorn, C., Houben, K., Hofmann, W., Roefs, A., Jansen, A., 2010. Control yourself or just eat what you like? Weight gain over a year is predicted by an interactive effect of response inhibition and implicit preference for snack foods. Health Psychol. 29, 389–393. https://doi.org/10.1037/a0019921

Ng-Knight, T.., Schoon, I.. b, 2016. Disentangling the influence of socioeconomic risks on children's early self-control. J. Pers. 1–14. https://doi.org/10.1111/jopy.12288

Nguyen, T.V., McCracken, J.T., Ducharme, S., Cropp, B.F., Botteron, K.N., Evans, A.C., Karama, S., 2013. Interactive effects of dehydroepiandrosterone and testosterone on cortical thickness during early brain development. J. Neurosci. 33, 10840–8. https://doi.org/10.1523/JNEUROSCI.5747-12.2013

O'Leary-Barrett, M., Mâsse, B., Pihl, R.O., Stewart, S.H., Séguin, J.R., Conrod, P.J., 2017. A cluster-randomized controlled trial evaluating the effects of delaying onset of adolescent substance abuse on cognitive development and addiction following a selective, personality-targeted intervention programme: the Co-Venture trial. Addiction 112, 1871–1881. https://doi.org/10.1111/add.13876

Oades, R., Halliday, G.M., 1987. Ventral tegmental (A10) system: neurobiology. 1. Anatomy and connectivity. Brain Res. 434, 117–165.

Olszewski, J., Baxter, D., 1954. Cytoarchitecture of the human brainstem. S. Karger, Basle & New York.

Østby, Y., Tamnes, C.K., Fjell, A.M., Westlye, L.T., Due-tønnessen, P., Walhovd, K.B., 2009. Heterogeneity in subcortical brain development: A structural magnetic resonance imaging study of brain maturation from 8 to 30 Years 29, 11772–11782. https://doi.org/10.1523/JNEUROSCI.1242-09.2009

Pannacciulli, N., Del Parigi, A., Chen, K., Le, D.S.N.T., Reiman, E.M., Tataranni, P. a, 2006. Brain abnormalities in human obesity: a voxel-based morphometric study. Neuroimage 31, 1419–25. https://doi.org/10.1016/j.neuroimage.2006.01.047

Pannacciulli, N., Le, D.S.N.T., Chen, K., Reiman, E.M., Krakoff, J., 2007. Relationships between plasma leptin concentrations and human brain structure: A voxel-based morphometric study. Neurosci. Lett. 412, 248–53. https://doi.org/10.1016/j.neulet.2006.11.019

Pardoe, H.R., Abbott, D.F., Jackson, G.D., 2013. Sample size estimates for well-powered cross-sectional cortical thickness studies. Hum. Brain Mapp. 34, 3000–9. https://doi.org/10.1002/hbm.22120

Park, B.-Y., Hong, J., Lee, S.-H., Park, H., 2016. Functional connectivity of child and adolescent attention deficit hyperactivity disorder patients: Correlation with IQ. Front. Hum. Neurosci. 10, 565. https://doi.org/10.3389/fnhum.2016.00565

Park, B.-Y., Seo, J., Yi, J., Park, H., 2015. Structural and functional brain connectivity of people with obesity and prediction of body mass index using connectivity. PLoS One 10, e0141376. https://doi.org/10.1371/journal.pone.0141376

Park, B., Seo, J., Park, H., 2016. Functional brain networks associated with eating behaviors in obesity. Sci. Rep. 6, 23891. https://doi.org/10.1038/srep23891

Paus, T., 2010. Growth of white matter in the adolescent brain: myelin or axon? Brain Cogn. 72, 26–35. https://doi.org/10.1016/j.bandc.2009.06.002

Pernet, C.R., Latinus, M., Nichols, T.E., Rousselet, G.A., 2015. Cluster-based computational methods for mass univariate analyses of event-related brain potentials/fields: A simulation study. J. Neurosci. Methods 250, 85–93. https://doi.org/10.1016/j.jneumeth.2014.08.003

Perrin, J.S., Hervé, P.-Y., Leonard, G., Perron, M., Pike, G.B., Pitiot, A., Richer, L., Veillette, S., Pausova, Z., Paus, T., 2008. Growth of white matter in the adolescent brain: Role of testosterone and androgen receptor. J. Neurosci. 28, 9519–24. https://doi.org/10.1523/JNEUROSCI.1212-08.2008

Petanjek, Z., Judas, M., Simic, G., Rasin, M.R., Uylings, H.B.M., Rakic, P., Kostovic, I., 2011. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. Proc. Natl. Acad. Sci. 108, 13281–13286. https://doi.org/10.1073/pnas.1105108108

Peters, J., Büchel, C., 2010. Episodic future thinking reduces reward delay discounting through an enhancement of prefrontal-mediotemporal interactions. Neuron 66, 138–48. https://doi.org/10.1016/j.neuron.2010.03.026

Pfefferbaum, A., Mathalon, D.H., Sullivan, E. V, Rawles, J.M., Zipursky, R.B., Lim, K.O., 1994. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch. Neurol. 51, 874–887.

Postuma, R.B., Dagher, A., 2006. Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. Cereb. Cortex 16, 1508–1521. https://doi.org/10.1093/cercor/bhj088

Pruim, R.H.R., Mennes, M., Buitelaar, J.K., Beckmann, C.F., 2015a. Evaluation of ICA-AROMA and alternative strategies for motion artifact removal in resting state fMRI. Neuroimage 112, 278–287. https://doi.org/10.1016/j.neuroimage.2015.02.063

Pruim, R.H.R., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J.K., Beckmann, C.F., 2015b. ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage 112, 267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064

Qu, Y., Fuligni, A.J., Galvan, A., Telzer, E.H., 2015. Buffering effect of positive parent-child relationships on adolescent risk taking: A longitudinal neuroimaging investigation. Dev. Cogn. Neurosci. 15, 26–34. https://doi.org/10.1016/j.dcn.2015.08.005

Raznahan, A., Lee, Y., Stidd, R., Long, R., Greenstein, D., Clasen, L., Addington, A., 2010. Longitudinally mapping the influence of sex and androgen signaling on the dynamics of human cortical maturation in adolescence. Proc. Natl. Acad. Sci. U. S. A. 107, 16988–16993. https://doi.org/10.1073/pnas.1006025107/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1006025107

Reiss, A. L., Abrams, M.T., Singer, H.S., Ross, J.L., Denckla, M.B., 1996. Brain development, gender and IQ in children. A volumetric imaging study. Brain 119 (Pt 5, 1763–74.

Ronan, L., Alexander-Bloch, A.F., Wagstyl, K., Farooqi, S., Brayne, C., Tyler, L.K., Fletcher, P.C., 2016. Obesity associated with increased brain age from midlife. Neurobiol. Aging 47, 63–70. https://doi.org/10.1016/j.neurobiolaging.2016.07.010

Ross, R.S., Sherrill, K.R., Stern, C.E., 2011. The hippocampus is functionally connected to the striatum and orbitofrontal cortex during context dependent decision making. Brain Res. 1423, 53–66. https://doi.org/10.1016/j.brainres.2011.09.038

Rubia, K., Smith, A.B., Taylor, E., Brammer, M., 2007. Linear age-correlated functional development of right inferior fronto-striato-cerebellar networks during response inhibition and anterior cingulate during error-related processes. Hum. Brain Mapp. 28, 1163–1177. https://doi.org/10.1002/hbm.20347

Rubia, K., Smith, A.B., Woolley, J., Nosarti, C., Heyman, I., Taylor, E., Brammer, M., 2006. Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. Hum. Brain Mapp. 27, 973–993. https://doi.org/10.1002/hbm.20237

Sadler, J.R., Shearrer, G.E., Burger, K.S., 2018. Body mass variability is represented by distinct functional connectivity patterns. Neuroimage 181, 55–63. https://doi.org/10.1016/j.neuroimage.2018.06.082

Sala-Llonch, R., Peña-Gómez, C., Arenaza-Urquijo, E.M., Vidal-Piñeiro, D., Bargalló, N., Junqué, C., Bartrés-Faz, D., 2012. Brain connectivity during resting state and subsequent working memory task predicts behavioural performance. Cortex 48, 1187–1196. https://doi.org/10.1016/j.cortex.2011.07.006

Savage, J.S., Fisher, J.O., Birch, L.L., 2008. Parental influence on eating behaviour. J Law Med Ethics 35, 22–34. https://doi.org/10.1111/j.1748-720X.2007.00111.x.Parental

Sawatsky, M.L., Clyde, M., Meek, F., 2015. Partial Least Squares regression in the social sciences. Quant. Method Psychol. 11, 52–62.

Scaglioni, S., Arrizza, C., Vecchi, F., Tedeschi, S., 2011. Determinants of children's eating behavior. Am. J. Clin. Nutr. 94, 2006S–2011S. https://doi.org/10.3945/ajcn.110.001685

Scherf, K.S., Smyth, J.M., Delgado, M.R., 2013. The amygdala: An agent of change in adolescent neural networks. Horm. Behav. 13, 83–96. https://doi.org/10.1002/ana.22528.Toll-like

Schlam, T.R., Wilson, N.L., Shoda, Y., Mischel, W., Ayduk, O., 2012. Preschoolers' delay of gratification predicts their body mass 30 years later. J. Pediatr. 10–13. https://doi.org/10.1016/j.jpeds.2012.06.049

Servaas, M.N., Geerligs, L., Renken, R.J., Marsman, J.-B.C., Ormel, J., Riese, H., Aleman, A., 2014. Connectomics and Neuroticism: An altered functional network organization. Neuropsychopharmacology 1–9. https://doi.org/10.1038/npp.2014.169

Sharkey, R.J., Bourque, J., Larcher, K., Mišić, B., Zhang, Y., Altınkaya, A., Sadikot, A., Conrod, P., Evans, A.C., Garavan, H., Leyton, M., Séguin, J.R., Pihl, R., Dagher, A., 2019. Mesolimbic connectivity signatures of impulsivity and BMI in early adolescence. Appetite 132, 25–36. https://doi.org/10.1016/j.appet.2018.09.019

Sharkey, R.J., Karama, S., Dagher, A., 2015. Overweight is not associated with cortical thickness alterations in children. Front. Neurosci. 9, 1–7. https://doi.org/10.3389/fnins.2015.00024

Shehzad, Z., Kelly, A. M.C., Reiss, P.T., Gee, D.G., Gotimer, K., Uddin, L.Q., Lee, S.H., Margulies, D.S., Roy, A.K., Biswal, B.B., Petkova, E., Castellanos, F.X., Milham, M.P., 2009. The resting brain: Unconstrained yet reliable. Cereb. Cortex 19, 2209–2229. https://doi.org/10.1093/cercor/bhn256

Shen, W., Liu, H., Punyanitya, M., Chen, J., Heymsfield, S.B., 2005. Pediatric obesity phenotyping by magnetic resonance methods. Curr. Opin. Clin. Nutr. Metab. Care 8, 595–601. https://doi.org/10.1097/01.mco.0000171150.49248.14

Shi, R., Guo, Y., 2014. Modeling covariate effects in group independent component analysis with applications to functional magnetic resonance imaging. Ann. Appl. Stat. 1–36.

Shulman, E.P., Smith, A.R., Silva, K., Icenogle, G., Duell, N., Chein, J., Steinberg, L., 2016. The dual systems model: Review, reappraisal, and reaffirmation. Dev. Cogn. Neurosci. 17, 103–117. https://doi.org/10.1016/j.dcn.2015.12.010

Smith, S.M., 2000. BET: Brain extraction tool. FMRIB Tech. Rep. TR00SMS2b. https://doi.org/http://dx.doi.org/10.1016/B978-044451604-6/50001-X

Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R., Beckmann, C.F., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U. S. A. 106, 13040–13045. https://doi.org/10.1073/pnas.0905267106

Somerville, L.H., Hare, T., Casey, B., 2011. Frontostriatal maturation predicts cognitive control failure to appetitive cues in adolescents. J Cogn Neurosci 23, 2123–2134. https://doi.org/10.1126/scisignal.2001449.Engineering

Soutschek, A., Ruff, C.C., Strombach, T., Kalenscher, T., Tobler, P.N., 2016. Brain stimulation reveals crucial role of overcoming self-centeredness in self-control. Sci. Adv. 2, 2–10. https://doi.org/10.1126/sciadv.1600992

Sowell, E.R., Thompson, P.M., Leonard, C.M., Welcome, S.E., Kan, E., Toga, A.W., 2004. Longitudinal mapping of cortical thickness and brain growth in normal children. J. Neurosci. 24, 8223–31. https://doi.org/10.1523/JNEUROSCI.1798-04.2004

Sowell, E.R., Trauner, D.A., Gamst, A., Jernigan, T.L., 2002. Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. Dev. Med. Child Neurol. 44, 4–16.

Sripada, C.S., Gonzalez, R., Luan Phan, K., Liberzon, I., 2011. The neural correlates of intertemporal decision-making: Contributions of subjective value, stimulus type, and trait impulsivity. Hum. Brain Mapp. 32, 1637–1648. https://doi.org/10.1002/hbm.21136

Steinberg, L., 2010. A dual systems model of adolescent risk-taking. Dev. Psychobiol. 52, 216–224. https://doi.org/10.1002/dev.20445

Steinberg, L., 2004. Risk taking in adolescence: What changes, and why? Ann. N. Y. Acad. Sci. 1021, 51–58. https://doi.org/10.1196/annals.1308.005

Stevens, M.C., Kiehl, K. a., Pearlson, G., Calhoun, V.D., 2007. Functional neural circuits for mental timekeeping. Hum. Brain Mapp. 28, 394–408. https://doi.org/10.1002/hbm.20285

Stevens, M.C., Pearlson, G.D., Calhoun, V.D., 2009. Changes in the interaction of resting-state neural networks from adolescence to adulthood. Hum. Brain Mapp. 30, 2356–2366. https://doi.org/10.1002/hbm.20673

Stevenson, R.J., Francis, H.M., 2017. The hippocampus and the regulation of human food intake. Psychol. Bull. 143, 1011–1032.

Stice, E., Yokum, S., 2016. Gain in body fat is associated with increased striatal response to palatable food cues, whereas body fat stability is associated with decreased striatal response. J. Neurosci. 36, 6949–6956. https://doi.org/10.1523/jneurosci.4365-15.2016

Stoeckel, L.E., Weller, R.E., Cook, E.W., Twieg, D.B., Knowlton, R.C., Cox, J.E., 2008. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage 41, 636–647. https://doi.org/10.1016/j.neuroimage.2008.02.031

Strang, N.M., Chein, J.M., Steinberg, L., 2013. The value of the dual systems model of adolescent risk-taking. Front. Hum. Neurosci. 7, 223. https://doi.org/10.3389/fnhum.2013.00223

Sussman, D., Leung, R.C., Chakravarty, M.M., Lerch, J.P., Taylor, M.J., 2016. The developing human brain: Age-related changes in cortical , subcortical , and cerebellar anatomy. Brain Behav. 6, 1–15. https://doi.org/10.1002/brb3.457

Sutin, A.R., Ferrucci, L., Zonderman, A.B., Terracciano, A., 2011. Personality and obesity across the adult life span. J. Pers. Soc. Psychol. 101, 579–592. https://doi.org/10.1037/a0024286

Swanson, L., 1982. The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res. Bull. 9, 321–353.

Taki, Y., Kinomura, S., Sato, K., Inoue, K., Goto, R., Okada, K., Uchida, S., Kawashima, R., Fukuda, H., 2008. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. Obesity (Silver Spring). 16, 119–24. https://doi.org/10.1038/oby.2007.4

Tamnes, C.K., Herting, M.M., Goddings, A.-L., Meuwese, R., Blakemore, S.-J., Dahl, R.E., Güroğlu, B., Raznahan, A., Sowell, E.R., Crone, E.A., Mills, K.L., 2017. Development of the cerebral cortex across adolescence: A multisample study of interrelated longitudinal

changes in cortical volume, surface area and thickness. J. Neurosci. 37, 3302–16. https://doi.org/10.1523/JNEUROSCI.3302-16.2017

Telzer, E.H., Fuligni, A.J., Lieberman, M.D., Galván, A., 2013. Meaningful family relationships: Neurocognitive buffers of adolescent risk taking. J. Cogn. Neurosci. 25, 374–87. https://doi.org/10.1162/jocn_a_00331

Telzer, E.H., Fuligni, A.J., Lieberman, M.D., Miernicki, M.E., Galv??n, A., 2013. The quality of adolescents peer relationships modulates neural sensitivity to risk taking. Soc. Cogn. Affect. Neurosci. 10, 389–398. https://doi.org/10.1093/scan/nsu064

Thomason, M.E., Dennis, E.L., Joshi, A.A., Joshi, S.H., Dinov, I.D., Chang, C., Henry, M.L., Johnson, R.F., Thompson, P.M., Toga, A.W., Glover, G.H., Van Horn, J.D., Gotlib, I.H., 2011. Resting-state fMRI can reliably map neural networks in children. Neuroimage 55, 165–175. https://doi.org/10.1016/j.neuroimage.2010.11.080

Tomasi, D., Volkow, N.D., 2014. Functional connectivity of substantia nigra and ventral tegmental area: Maturation during adolescence and effects of ADHD. Cereb. Cortex 24, 935–944. https://doi.org/10.1093/cercor/bhs382

Tomasi, D., Volkow, N.D., 2013. Striatocortical pathway dysfunction in addiction and obesity: Differences and similarities. Crit. Rev. Biochem. Mol. Biol. 48, 1–19. https://doi.org/10.3109/10409238.2012.735642

Tregellas, J.R., Wylie, K.P., Rojas, D.C., Tanabe, J., Martin, J., Kronberg, E., Cordes, D., Cornier, M.A., 2011. Altered default network activity in obesity. Obesity 19, 2316–2321. https://doi.org/10.1038/oby.2011.119

Tsukayama, E., Duckworth, A.L., Toomey, S., 2010. Self-Control protects against overweight status in the transition from childhood to adolescence. Arch Pediatr Adolesc Med 141, 520–529. https://doi.org/10.1016/j.surg.2006.10.010.Use

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273–89. https://doi.org/10.1006/nimg.2001.0978

Ulrich, M., Steigleder, L., Grön, G., 2016. Neural signature of the Food Craving Questionnaire (FCQ). Appetite 107, 303–310. https://doi.org/10.1016/j.appet.2016.08.012

Vainik, U., Baker, T.B., Alanis, J.C.G., Dadar, M., Michaud, A., Misic, B., Zeighami, Y., Zhang, Y., Collins, D.L., Dagher, A., 2017. Neurobehavioural correlates of obesity are largely heritable. bioRxiv 1–34. https://doi.org/10.1101/204917

Vainik, U., Dagher, A., Dubé, L., Fellows, L.K., 2013. Neurobehavioural correlates of body mass index and eating behaviours in adults: a systematic review. Neurosci. Biobehav. Rev. 37, 279–99. https://doi.org/10.1016/j.neubiorev.2012.11.008

Van Den Bos, W., Cohen, M.X., Kahnt, T., Crone, E.A., 2012. Striatum-medial prefrontal cortex connectivity predicts developmental changes in reinforcement learning. Cereb. Cortex 22, 1247–1255. https://doi.org/10.1093/cercor/bhr198

van den Bos, W., Rodriguez, C.A., Schweitzer, J.B., McClure, S.M., 2015. Adolescent impatience decreases with increased frontostriatal connectivity. Proc. Natl. Acad. Sci. 112, E3765–E3774. https://doi.org/10.1073/pnas.1423095112

van Duijvenvoorde, A.C.K., Achterberg, M., Braams, B.R., Peters, S., Crone, E.A., 2016. Testing a dual-systems model of adolescent brain development using resting-state connectivity analyses. Neuroimage 124, 409–420. https://doi.org/10.1016/j.neuroimage.2015.04.069

Veit, R., Kullmann, S., Heni, M., Machann, J., Häring, H.U., Fritsche, A., Preissl, H., 2014. Reduced cortical thickness associated with visceral fat and BMI. NeuroImage Clin. 6, 307–311. https://doi.org/10.1016/j.nicl.2014.09.013

Vigil, P., Orellana, R.F., Cortés, M.E., Molina, C.T., Switzer, B.E., Klaus, H., 2011. Endocrine modulation of the adolescent brain: a review. J. Pediatr. Adolesc. Gynecol. 24, 330–7. https://doi.org/10.1016/j.jpag.2011.01.061

Wardle, J., Carnell, S., Haworth, C.M. a, Farooqi, I.S., O'Rahilly, S., Plomin, R., 2008. Obesity associated genetic variation in FTO is associated with diminished satiety. J. Clin. Endocrinol. Metab. 93, 3640–3. https://doi.org/10.1210/jc.2008-0472

Weygandt, M., Mai, K., Dommes, E., Leupelt, V., Hackmack, K., Kahnt, T., Rothemund, Y., Spranger, J., Haynes, J.D., 2013. The role of neural impulse control mechanisms for dietary success in obesity. Neuroimage 83, 669–678. https://doi.org/10.1016/j.neuroimage.2013.07.028

Whelan, R., Conrod, P.J., Poline, J.-B., Lourdusamy, A., Stephens, D., Al, E., 2012. Adolescent impulsivity phenotypes characterized by distinct brain networks 15. https://doi.org/10.1038/nn.3092

Whiteside, S.P., Lynam, D.R., 2001. The five factor model and impulsivity: Using a structural model of personality to understand impulsivity. Pers. Individ. Dif. 30, 669–689. https://doi.org/10.1016/S0191-8869(00)00064-7

Wijngaarden, M.A., Veer, I.M., Rombouts, S.A.R.B., van Buchem, M.A., Willems van Dijk, K., Pijl, H., van der Grond, J., 2015. Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. Behav. Brain Res. 287, 127–134. https://doi.org/10.1016/j.bbr.2015.03.016

Woicik, P. a, Stewart, S.H., Pihl, R.O., Conrod, P.J., 2009. The Substance Use Risk Profile Scale: a scale measuring traits linked to reinforcement-specific substance use profiles. Addict. Behav. 34, 1042–55. https://doi.org/10.1016/j.addbeh.2009.07.001

Woolrich, M.W., Ripley, B.D., Brady, M., Smith, S.M., 2001. Temporal autocorrelation in univariate linear modelling of fMRI data. FMRIB Tech. Rep. TR01MW1 0.

Yau, P.L., Castro, M.G., Tagani, A., Tsui, W.H., Convit, A., 2012. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics. https://doi.org/10.1542/peds.2012-0324

Yau, P.L., Kang, E.H., Javier, D.C., Convit, A., 2011. Preliminary evidence of cognitive and brain abnormalities in uncomplicated adolescent obesity. Obesity (Silver Spring). 18, 1492–1501. https://doi.org/10.1016/j.str.2010.08.012.Structure

Yokum, S., Ng, J., Stice, E., 2012. Relation of regional gray and white matter volumes to current BMI and future increases in BMI: a prospective MRI study. Int. J. Obes. (Lond). 36, 656–64. https://doi.org/10.1038/ijo.2011.175

Zeighami, Y., Ulla, M., Iturria-Medina, Y., Dadar, M., Zhang, Y., Larcher, K.M.H., Fonov, V., Evans, A.C., Collins, D.L., Dagher, A., 2015. Network structure of brain atrophy in de novo Parkinsons disease. Elife 4, 1–20. https://doi.org/10.7554/eLife.08440

Zhang, H.Y., Tang, H., Chen, W.X., Ji, G.J., Ye, J., Wang, N., Wu, J.T., Guan, B., 2015. Mapping the functional connectivity of the substantia nigra, red nucleus and dentate nucleus: A network analysis hypothesis associated with the extrapyramidal system. Neurosci. Lett. 606, 36–41. https://doi.org/10.1016/j.neulet.2015.08.029

Zhang, S., Li, C.R., 2013. Functional networks for cognitive control in a stop signal task: Independent component analysis. Hum. Brain Mapp. 33, 89–104. https://doi.org/10.1002/hbm.21197.Functional