A systematic review of adolescent physiological development and its relationship with health-related behaviour

NHS Health Scotland

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Acknowledgements

Glossary

Brain regions

ACC	anterior cingulate cortex
dACC	dorsal anterior cingulate cortex
NAcc	nucleus accumbens
PFC	prefrontal cortex
dlPFC	dorso-lateral prefrontal cortex
dmPFC	dorso-medial prefrontal cortex
lPFC	lateral prefrontal cortex
mPFC	medial prefrontal cortex
vlPFC	ventro-lateral prefrontal cortex
vmPFC	ventro-medial prefrontal cortex
VS	ventral striatum

Brain measures

FRN	feedback-related negativity
MRI	magnetic resonance imaging
fMRI	functional magnetic resonance imaging
DTI	diffusion tensor imaging

1. Background

Adolescence is characterised by the transition from childhood to adulthood.[1] This period has implications for health as a result of interactions between early childhood development, specific biological, psychological and social role changes, and wider social determinants.[2]

While a great deal of focus has been placed on the importance of healthy early childhood development,[3-5] the adolescent years are a similarly unique period. During adolescence, there is increased opportunity to engage in health-harming behaviours such as excessive alcohol and substance use. These behaviours, in conjunction with emerging social influences such as the pressure to conform to peer group norms, can contribute to the establishment of behaviour patterns with consequences for both current and future health status.[6] While there is often an emphasis on risky and harmful health behaviours in adolescence,[7] these years also provide significant opportunities for behaviour to be shaped in health enhancing and sustaining ways, with consequences for longer-term health outcomes.[8] Public health interventions targeting this stage have the potential to foster positive health outcomes throughout adolescence and the remainder of the life span.

Young people from poorer backgrounds consistently face greater challenges, including in relation to education, youth employment and health, with such challenges contributing to health inequalities. Increasing the development of health-promoting behaviours alongside reducing harmful behaviours during adolescence is therefore a key goal for public health professionals and policy makers. This is in keeping with current Scottish Government policy emphasising prevention as a means to achieving health and social equity.[9] In order to achieve this, it is necessary to understand the fundamental landscape of adolescent development and the myriad influences at play during this developmental period.

In December 2012, NHS Health Scotland and the Scottish Collaboration for Public Health Research and Policy (SCPHRP) established a Youth Health Behaviour Development and Change (YHBD&C) Advisory Group, consisting of academic, policy and practice experts in adolescent health, to consider health behaviour

development and change during adolescence. The overall goal of the group was to provide information on evidence and theory related to health behaviour development and change for children and young people, in order to support health improvement policy and practice development in Scotland. A subgroup formulated research priorities around adolescent health behaviour development and agreed that the first step should be an understanding of theories of adolescent development across six key dimensions, as shown in Figure 1 below.

Micro Environment (Individual or proximal determinants)		Macro environment (Wider or distal determinants)			
Physiology/ biology E.g. brain and other physiological systems	**Psychological** E.g. cognition, autonomy, resilience	**Environment: Physical** E.g. housing, transport, green spaces, safety	**Environment: Social** E.g. family, peers, school, community	**Environment: Socio-economic** E.g. income, occupation, education, poverty	**Environment: Cultural** E.g. social norms/ attitudes, media
Phase 1	Phase 2	Phase 3		Phase 4	

Stage 1: Identify candidate theories

Stage 2: Search and synthesise empirical evidence that uses the theories to explain or predict the development of health behaviours

Stage 3: Cross-study synthesis of the evidence to identify commonalities and time-points where interventions may be most effective

Stage 4: Dissemination and incorporation of evidence into policy and practice

Stage 5: Cross-synthesis of all evidence obtained from all phases

Health behaviours could include: tobacco use, alcohol and drug misuse, sexual risk taking, physical activity, healthy eating, sleep, either alone or in combination
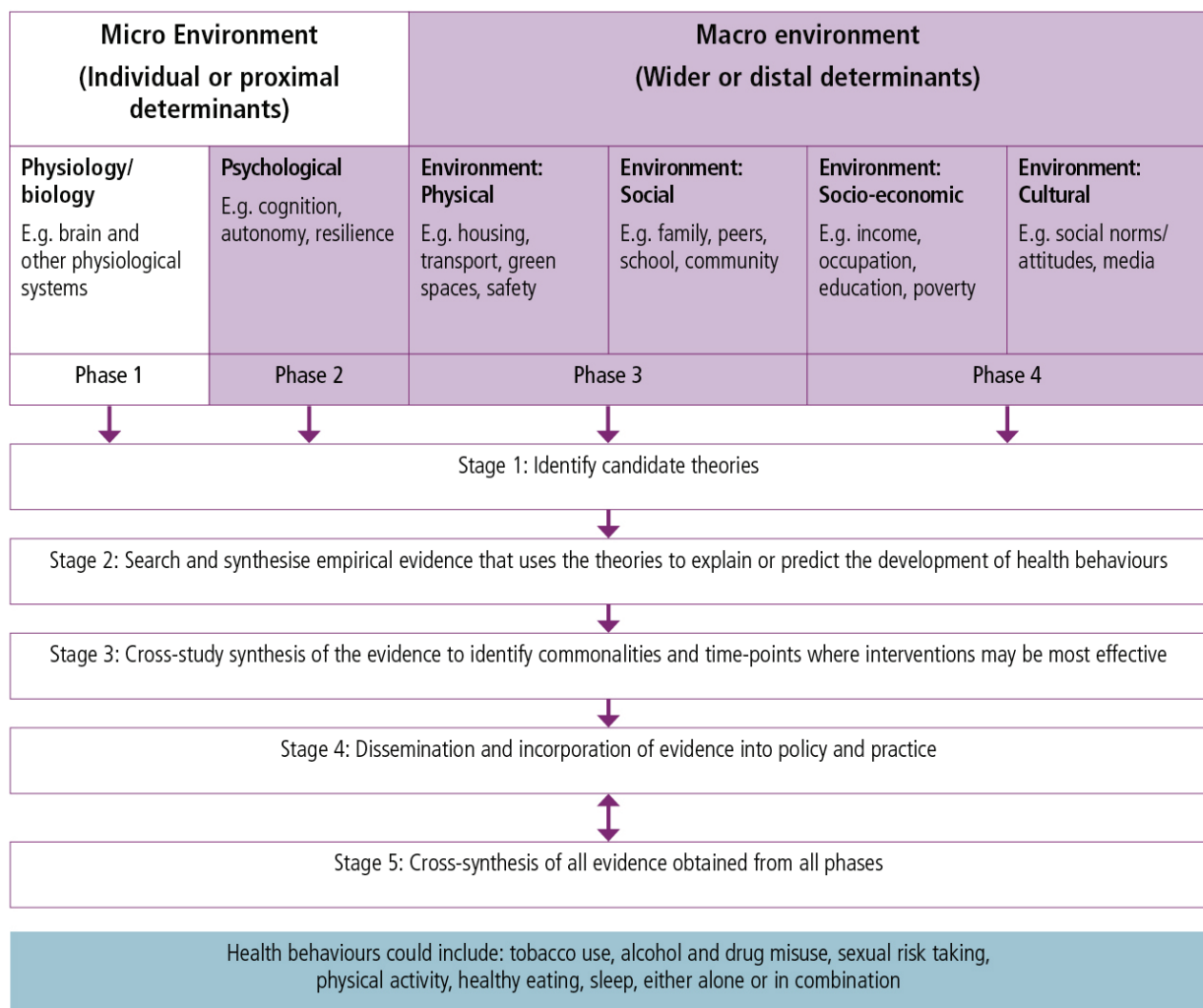
Figure 1. Dimensions of adolescent development (purple shaded boxes are not included in this particular project)

Theories developed to explain, predict or describe the determinants of adolescent health-related behaviour are mainly constructed within separate disciplines (silo-working), which do not necessarily value or understand theories from other

disciplines.[10] A silo-approach to the development and exploration of theories means learning and research opportunities across theories have not been fully recognised. Social, cultural, and economic approaches to the study of adolescence are often separated from biological analyses. However, neural and hormonal changes during adolescence play an important role in influencing the ways adolescents think, feel, and behave.[11]

1.1 Focus of this review

With the advisory group's consensus it was agreed to first focus upon synthesising theories of physiological development, followed by subsequent dimensions. Theories across domains will be synthesised upon completion of reviews in relation to the five other determinants.

Adolescence is a time in which substantial physiological changes are occurring in parallel with changing environments and opportunities. An understanding of the complex physiological changes that are taking place within the human body during this period and relationships with health-related behaviours is the first step towards recognising adolescence as a transition period that warrants specific focus as a unique period of opportunity. Such knowledge can help to inform health policy and intervention development. The aim of this systematic review is to gain an understanding of the relationship between physiological development and health-related behaviours in adolescence, as a fundamental step in the wider project outlined in Figure 1.

The objectives are to:
- identify and describe the range of theories that explore the relationship between physiological development and health behaviours in adolescence
- identify and describe the range of evidence which explores and/or explains the relationships between physiological development and health behaviours in adolescence
- determine which theories are underpinned by rigorous scientific evidence and which are not

- provide recommendations in relation to the findings that could be used to develop policy and practice
- provide recommendations to inform future research priorities.

2. Method

The method for this review is described in full elsewhere.[12] This systematic review is based on the principles of an integrative review in order to identify a broad range of studies, following PRISMA guidelines.[13] Integrative reviews are the most comprehensive of all review approaches, facilitating the inclusion of different methodological approaches, and both published and unpublished literature.[14] The method involves standard systematic review procedures – specifying inclusion/exclusion criteria, literature searching, data extraction and data synthesis. In-depth formal quality assessment was not feasible due to the breadth and scope of papers included in the review, in terms of discipline, focus and study design. However, quality of the studies is highlighted where relevant in the narrative summary. Papers were screened by two reviewers to assess eligibility and relevance.

Studies with participants aged between 10 and 24 (inclusive) years were included, although no definitive age barriers were used to avoid excluding potentially relevant research, with the proviso that the topic focus related to the adolescent life stage. The main variables of interest were theories and hypotheses related to physiological development during adolescence and relationships with health-related behaviour. Physiological development was defined as encompassing a broad range of biological systems (e.g. musculo-skeletal, nervous, endocrine, integumentary, cardiovascular, respiratory, digestive, reproductive) and associated biochemical and hormonal processes. Health-related behaviours included areas such as diet and nutrition, physical activity, substance use, smoking, sexual behaviours, and sleep. Outcome measures potentially referred to any of these systems or behaviours. All research designs and types of papers were considered. Theoretical or discussion papers were included if they contributed to our understanding of mechanisms or effects. We excluded protocols that did not contain results. We further excluded studies in which

the direction of effect was unclear or focused explicitly upon the impact of health behaviour upon physiological outcomes and not vice versa. Studies dating from 1980 were included.

A project advisory group monitored all stages of the review process and is comprised of researchers with a background in public health, neuroscience, adolescence, and systematic reviews, as well as policy/decision makers with a remit to improve youth health across Scotland.

3. Results

In total, 13,633 papers were identified. Figure 2 (below) maps the numbers of papers identified at each stage of the selection process. Following narrow screening, 341 papers were selected. Due to the large volume of studies relating to brain physiology (n=181), these studies were grouped together. Papers that did not fall into the category of brain physiology (n=108) were grouped separately. These studies generally referred to other aspects of physiological development, e.g. the endocrine or musculoskeletal systems. Supplementary tables describing study characteristics are available as appendices at www.healthscotland.scot/publications/a-systematic-review-of-adolescent-physiological-development-and-its-relationship-with-health-related-behaviour

The remainder of the report is split into papers reporting findings with implications for health behaviours in adolescence (i.e. papers where health behaviour itself has not been measured and reported), and those reporting findings where health behaviour data have been directly measured and reported. Implications for practice and research recommendations are given where appropriate.
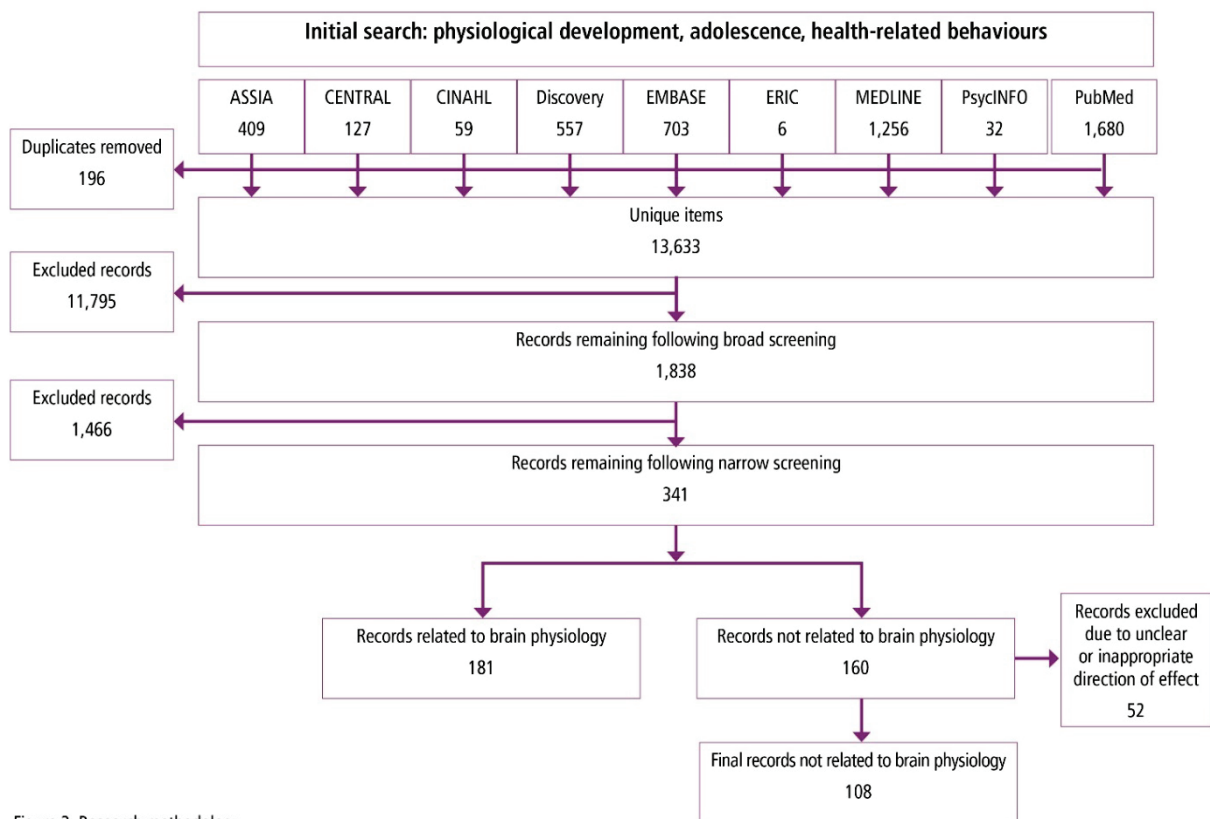
Figure 2. Research methodology

3.1 Papers reporting findings with implications for health behaviours in adolescence

A total of 58 papers reported findings with implications for health behaviours in adolescence (see supplementary material). These papers were exclusively focused upon brain physiology, and were primarily theory papers or laboratory studies that investigated the broad cognitive and affective processes thought to be involved in health-related behaviour in adolescence.

3.1.1 Theory papers: Scientific theories of brain physiology

There are several theories as to how brain maturation relates to health-related decision making and behaviour in adolescence. These are outlined below, with specific hypotheses described in detail.

Hormonal influences on brain development

The brain contains receptors for the suite of hormones associated with puberty, with hormonal changes during puberty affecting brain development.[15] Exposure to stress during adolescence might alter the development of the brain's structure and function (in relation to learning and emotion regulation), given that the brain also has receptors for stress hormones (e.g. cortisol).[16]

Changes in the dopaminergic system

Adolescence is a time of increasing approach motivation, or drive to explore novel situations. Some researchers have hypothesised that adolescents have higher levels of incentive motivation (drive to engage in behaviours in anticipation of reward) than children or adults, due to heightened dopamine transmission within the brain.[17] Specifically, it has been hypothesised that 'stereotypical' adolescent behaviours such as risk taking, in addition to decreased capacity to control behaviour (behavioural regulation) are related to heightened dopamine activity during adolescence, relative to childhood or adulthood.[18] Neurophysiological evidence from primate and rodent studies and molecular genetic studies in humans supports this hypothesis.[19] For example, in adolescent rats, the ability to learn from the consequences of actions is related to the delayed maturation of dopaminergic pathways within the brain.[20] In a similar vein, Luciana and colleagues have proposed that failures in cognitive control or self-regulation during adolescence are the product of increased incentive motivation placing high demand on cognitive resources.[21] There is, however, some conflicting evidence to suggest that dopamine activity is underactive during adolescence.[22]

Developmental timing

There are several models of adolescent behaviour that are based on the idea that different neural systems mature at different rates. These models stemmed from earlier models that primarily implicated the protracted development of the prefrontal cortex as underlying changes in adolescent behaviour. Modern theories of the prefrontal cortex take into account its heterogeneity, as well as its connections to

other parts of the brain. For example, different areas of the prefrontal cortex are involved in distinct networks that relate to distinct cognitive processes, such as regulation of cognitive versus affective processes.[23]

Social information processing network model

The Social Information Processing Network model hypothesises that distinct brain systems involved in processing social signals in the environment develop at different rates.[24] [25] The staggered development of these different systems therefore make certain periods of development more sensitive to specific signals in the environment, and their interactions contribute to establishing long-term patterns of brain function and behaviour. Originally, they proposed three systems within an overarching social information processing network: the detection system involved in basic social perceptual processes, e.g. face processing; the affective system involved in perception of emotional signals, e.g. processing guilt; and the cognitive-regulation system involved in both inhibiting motivated response tendencies and understanding the minds of others.[25]

Triadic model

The triadic model proposes that adolescent behaviour can potentially be understood by the balance between neural systems involved in approach and avoidance behaviours.[26-28] This model focuses on three key brain regions and the connections between them: the amygdala, the striatum and the prefrontal cortex (PFC). The theory asserts that these three regions are the centres of specific systems, with the striatum representing the motivation/approach system, the amygdala representing the emotion/avoidance system, and the PFC representing the regulatory system – specifically regulating the two other 'systems' in this model. Quite simply, this theory asserts that the striatal system is responsible for risk seeking and cognitive impulsivity and the amygdala system for emotional intensity and lability. The theory also asserts that PFC develops linearly with age, whereas the striatal system is more responsive to positive contexts and less responsive to certain cognitively demanding situations, and the amygdala system is more responsive to threat and less responsive to rewarding contexts, in adolescence compared to childhood or

adulthood. The theory has been met with significant opposition given its relatively simplistic way of assigning brain regions to certain cognitive or behavioural processes (e.g. Somerville, van den Bulk and Skwara, 2014[29]).

Dual systems model

Any dual systems model simply posits that two different systems interact to influence behaviour. In adolescent neuroscience, there are several dual systems models, but each model has an overall flavour of pitting 'cognitively controlled' against 'emotionally driven' behaviour. Indeed, behavioural studies have shown that, in adolescence, deliberative thinking is impaired in states of heightened emotional arousal.[30] However, the brain regions are involved in these two systems, and the specific hypotheses derived from these dual systems models, vary across research groups as well as publications.

The most well-known dual systems model for adolescent behaviour was proposed by Steinberg, which posited specifically that risk-taking behaviour increases from childhood to adolescence due to changes in the brain's 'socio-emotional system', and that risk-taking behaviour decreases from adolescence to adulthood due to changes in the brain's 'cognitive control system'.[31-33] In this original model, the dopaminergic changes occurring around puberty in the regions of the socio-emotional system were hypothesised to make adolescents more susceptible to signalling from these regions and therefore more affected by socio-emotional contexts, e.g. relationships and the contexts in which these take place. The protracted development of regions related to cognitive control means that adolescence is a period of heightened socio-emotional arousal and reduced cognitive capacity to regulate such arousal. In contrast, adults are hypothesised to be better able to regulate behaviour in socio-emotional contexts because of their mature cognitive control regions.

There have been variations of the original dual systems model for adolescent behaviour that use slightly different terminology and brain regions when describing the interaction between two systems. For example, another dual systems model describes two brain networks involved in risky decision making and behaviour: a

'decision-making system' including regions in the dorsolateral prefrontal cortex, parietal cortex, insular cortex, and anterior cingulate; and a 'reward system' including regions in the ventral striatum, and ventromedial prefrontal cortex.[34]

Imbalance model

The imbalance model is similar to the dual systems models described above, but extends it further by discussing how differential timing of distinct brain systems can lead to an 'imbalance' in neural processing during adolescence.[35-38] Specifically, the model hypothesises that the brain regions involved in processing affect and reward mature around adolescence, whereas the regions involved in cognitive control mature in adulthood. Thus, the model proposes that there is greater activity in the regions of the brain responsible for processing affect and reward during adolescence. The model has since been refined to emphasise the role of communication (e.g. connectivity) between these regions of the brain, to explain developmental differences in behaviour.[39]

Critiques of dual systems models

Dual systems neurobiological models of adolescent development have been questioned in recent years.[40] [41] Some have argued that risk-taking behaviour, and novelty seeking in general, is necessary to optimise brain development in adolescence.[42] Others have addressed how risk-taking behaviour may aid in the personal trajectory of the individual – namely to aid in the development of agency over one's life.[43] Sercombe suggests that neuroscientists are possibly importing their own value-driven and moral leanings when operationalising adolescent risk-taking behaviour. A critical examination of common assumptions present in fMRI studies of risk-taking in adolescents found that public health data did not support many of the common assumptions made in laboratory studies.[44]

One longitudinal study directly tested the basis of the 'mismatched brain development' accounts of adolescent behaviour by examining the developmental trajectories of the prefrontal cortex, amygdala, and nucleus accumbens within participants.[45] This study found although most participants showed an earlier

developing amygdala compared with the PFC (and some participants likewise showed an earlier development of the nucleus accumbens compared to the PFC), there was substantial heterogeneity in brain development patterns across participants. Furthermore, there was no clear relationship between the presence of a mismatch and adolescent risk-taking or sensation-seeking behaviours (although these were measured retrospectively).

3.1.2 Laboratory studies investigating cognitive and affective processes thought to be involved in health-related behaviour in adolescence

Emotion regulation

Emotion regulation involves both cognitive and affective processes, and is an essential ability for making healthy decisions in scenarios that might evoke emotional reactions. The four studies examining emotion regulation in adolescence were carried out by teams in the USA over the past decade. One study was longitudinal, and three were cross-sectional.

One of the first developmental neuroimaging investigations of emotional regulation reported heightened recruitment of the amygdala in emotional contexts in adolescents compared to children and adults.[46] In this cross-sectional study, Hare and colleagues investigated participants' neural responses in an emotional go/no-go task that involved detecting fearful, happy, or calm emotional expressions (target expression) while ignoring non-target expressions. Although adolescents recruited the amygdala more during this task relative to children and adults, this difference decreased with repeated exposures to the stimuli. In other words, the amygdala habituated to the stimuli. Further, there was also a relationship between individual differences in self-reported ratings of anxiety and the extent of habituation in amygdala, with more anxious participants showing less habituation over repeated exposures. The less a participant habituated over time was negatively related to functional connectivity between vPFC and amygdala. Overall, this study supported the imbalance model of neural development in adolescence, and the authors

suggested that adolescents were able to suppress a competing response in emotional contexts with the appropriate level of prefrontal PFC recruitment.

A cross-sectional study comparing adolescent and adult males examined whether adults would show greater recruitment of brain regions involved in emotional regulation than adolescents during an emotionally challenging context.[47] To do so, they employed a task fMRI paradigm in which participants were instructed to perform an intellectually challenging task while also undergoing social evaluation. The heart rates for adults and adolescents increased during the challenge condition, and both groups recruited the dlPFC and dACC similarly. However, adults additionally recruited the anterior insula during the challenge condition, and this region was more highly connected to prefrontal regions in adults compared to adolescents. The authors concluded that adolescents and adults utilised the PFC to different degrees for behavioural and emotional regulation.

A cross-sectional study comparing adolescents, emerging adults and adults investigated how these different age groups would perform on an inhibition task that required participants to regulate behaviour based on threat or safety cues present in facial expressions.[48] They found that older participants were more cautious in their behaviour, and were less likely to impulsively respond in emotional contexts. Younger participants were less able to inhibit behaviour in emotional contexts. Overall, this study suggests that the ability to inhibit behaviour in emotional contexts continues to develop from adolescence and into adulthood.

In a longitudinal study spanning puberty, Spielberg and colleagues tested the hypothesis that puberty increases in the capacity to experience (some) fear-evoking experiences as an exciting thrill.[49] Specifically, they examined if pubertal surges in testosterone were related to increases in the tendency to experience threat cues (in the form of threatening faces) as thrilling. They found that increases in testosterone over a two-year period of pubertal maturation was positively related to recruitment of both the amygdala and nucleus accumbens when perceiving stimuli typically associated with threat. The level of recruitment of these regions was further related to greater approach behaviour – in this case, responding faster to threatening faces. Overall, the authors suggest that the experience of threat shifts to a more complex

process during pubertal maturation, which is specifically associated with changing testosterone levels.

The studies identified suggest that the physiological underpinnings of emotional regulation continue to mature in adolescence, and an individual's ability to regulate her/his emotions has implications for health-related behaviours.[46][47][48-49] Specifically, adolescents might respond faster, and with less inhibition, in emotionally charged situations. Also, there are individual differences in how adolescents adapt to emotionally charged contexts, with more anxious adolescents less likely to show neural habituation to emotional cues than less anxious adolescents. More anxious adolescents may therefore find it harder to regulate behaviour in emotional situations.

Cognitive control

Cognitive control is commonly defined as the ability to 'override or augment reflexive and habitual reactions in order to orchestrate behaviour in accord with [one's] intentions'[50] and is associated with a suite of brain regions spanning the frontal and parietal cortices. Other theories of cognitive control suggest that changes in self-control during adolescence is related to changes in connections within fronto-limbic circuitry.[39] Of the 24 studies examining cognitive control in adolescence, 15 were carried out by teams based in the USA; three were carried out by teams based in Canada; two were carried out by teams based in the UK; two were carried out by teams based in the Netherlands; with single studies being conducted in Australia and Ireland. These studies were conducted within the last 15 years, with the majority of the studies occurring within the last six years. Three studies were longitudinal, and 21 were cross-sectional.

In one of the first studies to examine the relationship between a form of cognitive control – response inhibition – and brain development, participants between ages 8–20 years performed a go/no-go task while undergoing fMRI.[51] Behaviourally, older participants were faster to respond correctly to the task, and the authors suggest this might also illustrate an increased ability to inhibit reflexive reactions. There were, however, no age differences in accuracy on the task. On correct trials of response

inhibition, younger participants showed increased recruitment of that left superior and middle frontal gyri during than older participants, whereas older participants showed increased recruitment of the left inferior frontal gyrus. Overall, the authors suggest that distinct prefrontal regions are involved in inhibitory control across developmental periods.

It has been hypothesised that adolescents need to recruit more neural resources than adults when exerting cognitive control, and that this is related to behavioural differences between these groups. This hypothesis was tested in a cross-sectional study comparing inhibitory control during a go/no-go task between adolescents and adults.[52] These researchers found that adults showed more right dominant inferior frontal activity recruitment when inhibiting responses, whereas adolescents showed more left dominant, bilateral activity recruitment in the inferior frontal cortex. This supplemental cortical recruitment was interpreted by the authors as helping their adolescent sample maintain adequate inhibitory performance.

Male adolescents showed poorer performance on a sustained attention task than adults, as indexed by greater error rates and greater response variability in a Sustained Attention to Response Task.[53] When displaying successful response inhibition, young adolescents showed increased recruitment of many brain regions compared to adults, which included frontal gyri, insula and posterior cingulate cortices, and inferior parietal cortices. However, the group differences in recruitment of the frontal cortex disappeared when the authors matched adolescents and adults on task performance, suggesting that recruitment of the frontal cortex during response inhibition in a sustained attention task is more related to individual differences in executive control than developmental changes. The authors suggest that these results support the idea that the progressive maturation of the developing brain between adolescence and adulthood might shift the specific neural networks that underlie response inhibition.

Inhibitory control can be measured with an antisaccade task, which requires participants to look away from a cue when prompted. Two studies from the same group of researchers examined both behavioural and neural responses to this task in children, adolescents and adults. They found that children were worse at inhibiting

themselves from looking at the cue than adolescents, and that adults were best at inhibitory control.[54] Across age groups, regions of the brain involved in voluntary control of eye movements were recruited more when participants were able to successfully inhibit, compared to when they failed to inhibit, looking at the cue.[54] One region of the brain involved in cognitive control, the dACC, was recruited more during error trials, and this effect was stronger in younger participants.[54] Overall, children recruited the dlPFC more when engaging in the task than either adolescents or adults.[54] The authors suggest that functional changes in the dACC are associated with error regulation and the utilisation of feedback to correct subsequent errors, and this developmental change contributes to age-related improvements in cognitive control.[54] Further, in a separate publication of the same dataset and task, these researchers reported that the attention processes necessary to sustain performance on this task continued to mature even after competence in performing the task was established.[55] Overall, these researchers found that momentary recruitment in prefrontal regions supporting cognitive controlled processing decreased with age, whereas sustained prefrontal recruitment increased until young adulthood.[55]

A longitudinal study examined non-linear changes in neural recruitment during an antisaccade task across ages 9–26 years.[56] Behaviourally, the ability to inhibit eye movements (a marker of cognitive control) continued to improve throughout adolescence. Recruitment of regions of the brain involved in motor response control did not show developmental changes, suggesting that brain functioning regarding this aspect of cognitive control matures in late childhood. There was, however, an age-relationship between recruitment of brain regions and error-processing, with decelerating rates of recruitment of the right dlPFC between childhood and adolescence. Recruitment of brain regions involved in error processing was associated with performance, which mediated the relationship between age and successful response inhibition. The authors suggest that the continued maturation of error-processing abilities underlies the protracted development of inhibitory control over adolescence.

In a cross-sectional study, neural responses during a stop signal task, which involved participants withholding motor responses if an error signal followed a 'go' cue, were compared between adolescent and adult males.[57] These researchers

found that adolescents and adults were both able to successfully inhibit reflexive responses in the task, but that adults showed increased recruitment of the right inferior PFC during successful response inhibition trials, and increased recruitment of the rostral anterior cingulate gyrus ACC during unsuccessful response inhibition trials, compared with adolescents. The authors suggest that the functional maturation of fronto-subcortical pathways of motor inhibition continue to mature throughout adolescence, and that this maturation process contributes to inhibitory control capacity.

Another cross-sectional study by the same group investigated the differences in neural recruitment between adolescent and adults during three different inhibitory control tasks.[58] They found that increased recruitment of task-specific fronto-striatal networks in adults compared to adolescents during each of the three inhibitory tasks. Overall, the authors argue that fronto-subcortical as well as fronto-cortical networks that support cognitive control continue to mature between adolescence and adulthood.

Most functional imaging studies rely on the BOLD signal to infer neural activity. However, one cross-sectional study did examine actual levels of a specific neurotransmitter – GABA – in living healthy human adolescents compared with young adults.[59] They hypothesised that 12–14 year old adolescents would have lower GABA levels than emerging adults in the ACC, and that lower GABA in this region would be positively correlated with impulsivity and negatively correlated with response inhibition across both groups. Indeed, they found that adolescents have lower GABA than adults, and that lower GABA in the ACC was positively correlated with impulsivity and negatively correlated with cognitive control. They conclude that the frontal cortex in adolescence is still integrating inhibitory GABAergic neurotransmission with inhibitory control.

A cross-sectional EEG study comparing children, adolescents and adults examined theta activity in the mPFC during a go/no-go task.[60] Behaviourally, the ability to inhibit inappropriate responses improved linearly with age. Theta power also increased with age during response inhibition, and this developmental effect was localised to ACC. Theta power in the ACC also correlated with behavioural

performance across all ages, which partially mediated the age-related improvement in response inhibition. Based on this EEG findings, the authors concluded that improvements in cognitive control can be linked to maturing cortical activity.

Proactive versus reactive cognitive control

Certain models posit that cognitive control is a heterogeneous construct consisting of both proactive and reactive control mechanisms. For example, the Cascade-of-Control model distinguishes between cognitive control processes that help implement and maintain attention to a given task (proactive control), from those processes that are implemented transiently through response selection and evaluation (reactive control).[61] This model hypothesises that certain regions of the brain are involved in proactive cognitive control such as the posterior dorsolateral prefrontal cortex dlPFC, and other regions are involved in reactive cognitive control, such as the anterior cingulate cortex ACC.

Using the Cascade-of-Control model, one cross-sectional study compared brain activity of adolescents and young adults on a task requiring cognitive control.[62] The authors hypothesised that adolescents and adults would show differential recruitment of brain regions involved in different aspects of cognitive control. They found that young emerging adults showed greater recruitment of brain regions associated with proactive control compared to adolescents. While younger adolescents did not show increased recruitment of brain regions associated with reactive control, older adolescents did show heightened recruitment of these regions. Further, for the adolescent group, recruiting regions of the brain involved in proactive cognitive control during this task was positively associated with self-reported measures of impulse control, planning ahead, and resistance to peer influence. Based on these findings, the authors suggest that different aspects of cognitive control are still developing through adolescence and into young adulthood.

In a cross-sectional study, reactive inhibitory control in a reaction task improved across ages 10–25 years, with older participants reacting faster and showing greater suppression of motor cortex activity than younger participants.[63] Proactive inhibitory control also improved with age, with older participants showing slower responses

than younger participants when anticipating a cue signifying that they would need to stop. Improved proactive inhibition was positively correlated with increased recruitment of the right striatum, right ventral and dorsal inferior frontal gyrus, and supplementary motor area. Further, older participants showed greater functional connectivity between the striatum and frontal cortex during proactive inhibition than younger participants. The authors of this study suggest that developmental improvements in proactive inhibition are paralleled by increases in recruitment of, and functional connectivity between, the fronto-striatal network.[63]

Regions of the brain involved in cognitive control undergo substantial structural development in adolescence. One longitudinal study of adolescents assessed how structural development of the ACC, dlPFC, and vlPFC related to changes in proactive and reactive cognitive control between at age 12 and 16 years.[64] Behaviourally, male participants improved in reactive control between early- and mid-adolescence, and the degree of improvement in reactive control was associated with less cortical thinning of the left ACC. While there was no significant behavioural improvement in proactive control across the sample, the degree to which individuals improved in proactive control was associated with less cortical thinning of the right vlPFC. The authors suggest that individual differences in the structural maturation of the cognitive control regions ACC and vlPFC underlie the development of proactive versus reactive cognitive control between early- and mid-adolescence.

One cross-sectional study found that children, adolescents and adults will shift to proactive cognitive control in the context of reward, suggesting that there is some relationship between the development of cognitive control and reward-related neural systems across development.[65]

Connectivity and cognitive control

One theory is that developmental increases in cognitive control ability could be related to changes in connections within and between certain brain networks. One cross-sectional study comparing 8–12 year olds and 20–47 year olds hypothesised that brain networks would show increasing specialisation (more within-network connectivity and less between-network connectivity) across age, and that this

increasing specialisation would be related to response inhibition.[66] However, these researchers found that only the left dlPFC showed differences in connectivity between 8–12 year olds and adults, but that adults showed greater specialisation in a brain network related to focusing on a given task than the 8–12 year olds. Further, response inhibition performance was positively related to the integrity (specialisation) of brain networks. Overall, the authors suggest that the greater specialisation of brain networks is a maturational process related to achieving mature inhibitory control.

One cross-sectional study aimed to identify functionally integrated networks associated with response inhibition in healthy adolescents and adults.[67] They found three distinct neural networks involved in response inhibition: a fronto-striatal-thalamic network (specifically, the indirect pathway); a network comprising bilateral precentral gyri, inferotemporal cortex, anterior insula, and right inferior frontal cortex; and a frontal-parietal circuit. While adolescents and adults both displayed engagement of these networks during response inhibition, the level in which participants engaged the networks, as well as how the regions within the networks communicated with one another, differed between groups. The authors suggest that these findings support the hypothesis that developmental differences in fronto-striatal connectivity impact response inhibition performance.

In an early, and relatively underpowered cross-sectional study, white matter integrity in fronto-striatal pathways was positively related to cognitive control abilities in children, adolescents and adults.[68] While fronto-striatal integrity was associated with the age-related increase in cognitive control ability, individual differences in fronto-striatal integrity was also related to individual differences in performance independent of age. In another study of children aged 5–16 years, white matter integrity in frontal and posterior white matter regions was negatively correlated with response inhibition.[69] However, white matter integrity in posterior and brainstem regions was positively correlated with cognitive flexibility.

A recent longitudinal study showed that the majority of white matter tracts reach maturation at some point during adolescence, with the latest developing tracts being those that connect to prefrontal regions.[70] The differences in timing of white matter

maturation across the whole brain were related to variability in reaction times during an inhibitory task. Overall, the authors suggest that white matter matures in a hierarchical manner, with tracts that support inhibitory control showing continued development through adolescence.

One cross-sectional study investigating the development of white matter integrity and cognitive performance across the lifespan found evidence for age-independent relationships between white matter integrity and executive functioning.[71] Specifically, the integrity of cingulum bundle was related to higher executive functioning, and the integrity of the inferior fronto-occipital fasciculus was related to higher global cognitive functioning, respectively, independent of the effect of age.

Cognitive control in affective contexts

In a study comparing children, adolescents and adults on an emotional go/no-go task (using faces as stimuli), adolescents were less able to suppress reflexive responses to happy (compared to calm) faces more than children or adults.[72] Further, adolescents showed more recruitment of the ventral striatum when viewing happy faces, than children or adults. When asked to suppress reflexive responses, recruitment of the PFC was greater in younger individuals, and this level of recruitment predicted overall performance on the task. Across age, the participants who showed greater ability to suppress reflexive responses also recruited the right inferior frontal gyrus less during successful suppression trials. The connections between the striatum and cortex were more cohesive in teens and adults relative to children. The authors suggest that these findings show that adolescents can suppress reflexive responses in neutral contexts, but that they are more likely to have trouble doing so in the face of appetitive cues (e.g. happy faces). This is one of the first experimental studies to suggest that the maturation trajectories of cognitive and affective processes might interact in such a way that adolescents are less able to exert cognitive control in emotional or socially stimulating contexts, which could underlie the increased propensity to engage in health risks during this period of life.

One cross-sectional study found that adolescents are more sensitive to incentives than adults, and can perform equally as well as adults on cognitive control tasks

when a reward was at stake.[73] Adolescents were overall slower than adults when performing a non-rewarded sustained attention task, but equally as fast during the rewarded version of the same task. In the non-rewarded condition, there was a linear developmental increase in recruitment of brain regions associated with sustained attention such as the right hemispheric lateral inferior frontal, superior temporal and inferior parietal cortices, and a linear developmental decrease in recruitment of regions involved in saliency detection, such as limbic and paralimbic medial temporal, posterior insular and posterior cingulate regions. Developmental effects were amplified in the rewarded condition for recruitment of the inferior frontal, temporal and cerebellar brain regions, and further effects were found for brain regions involved in executive attention and motivation control, including the dorsolateral and ventromedial orbital PFC and dorsal striatum. The authors suggest that this study supports the hypothesis that reward can enhance sustained attention processing.

A cross-sectional fMRI study comparing the impact of incentives on inhibitory control in adolescents and adults found that adolescents make less inhibitory errors when a reward is at stake.[74] Further, both adolescents and adults are faster at correctly inhibiting a specific eye movement when a reward is at stake. During rewarded trials, adolescents showed greater recruitment than adults when preparing for the task in both the ventral striatum as well as the precentral sulcus. As this region is involved in correctly performing the inhibitory task of this study (an oculomotor task), the reward incentives may help adolescents modulate neural responses to correctly inhibit responses.

Using a rewarded antisaccade task, a cross-sectional study examined the effects of cognitive control on reward processing in childhood, adolescence and adulthood.[75] In this task, the presence of rewards improved cognitive control across all ages, with participants responding faster and making fewer errors. Adolescents were the only age group to show greater recruitment of the ventral striatum during rewarded trials compared to neutral trials. Further, the presence of rewards increased the recruitment of brain regions associated with oculomotor and inhibitory control. The authors suggest this increased recruitment of task-relevant regions suggest that the

presence of reward could enhance motivation to engage in cognitive control during adolescence.

Integrating the results from these studies provides several conclusions about brain development in adolescence in relation to cognitive control. There appears to be broad consensus that maturing brain physiology is associated with maturing cognitive control abilities between childhood and early adulthood. Prefrontal regions appear to be involved in inhibiting one's actions throughout adolescence and into adulthood. There is some evidence that adolescents engage the PFC even more than adults when inhibiting behaviour. Other studies suggest that adolescents might use completely different neural networks than adults when inhibiting behaviour. It could be that brain networks involved in cognitive control become more specialised with age. The ability to track when one makes errors continues to develop across adolescence, and this ability is directly related to the ability to control one's behaviour. Several studies found that brain regions and networks involved in error-monitoring develop across adolescence, and that these brain changes parallel increased cognitive control abilities. Several studies suggest that developmental changes in frontal-subcortical pathways mediate the increase in cognitive control abilities between childhood and adulthood.

It is important to note, however, that cognitive control is not one standalone construct that develops in isolation. Several studies noted that different aspects of cognitive control develop at different rates during adolescence, which is likely related to the differential development of related brain regions and networks. Other studies found that cognitive control abilities were impacted by the presence of a rewarding or affective context. Adolescents find it harder than adults to suppress inappropriate behaviour in the face of appetitive cues like happy faces. However, adolescents also appear to be better at inhibiting inappropriate behaviour, as well as sustaining attention, when a reward is at stake.

Temporal discounting

Temporal discounting involves deciding whether to take an immediate smaller reward, or wait for a later, larger reward. As certain health-related behaviours involve

weighing the relative value of waiting for a later reward (delaying gratification) versus taking an immediate reward (e.g. snacking frequently during the day, versus waiting for an evening meal), it is important to understand how brain maturation during adolescence could be related to this cognitive process. It is worth mentioning that this process also goes by other names, including intertemporal choice or delayed discounting. Of the five studies examining cognitive control in adolescence, two were carried out by teams in the USA; two were carried out by teams based in Germany; and one study was conducted in the UK. These studies were conducted within the last seven years. All five studies were cross-sectional.

One of the first neuroimaging studies investigating the development of temporal discounting examined how white matter integrity related to temporal discounting preferences across ages 9–23 years.[76] The study found that greater white matter integrity in pathways connecting the frontal and temporal cortices with other areas of the brain were positively correlated with the preference for delayed rewards across adolescence.[76] Some of these correlations were developmentally related, whereas some of the effects appeared to be age-independent. For example, the relationship between greater white matter integrity in right frontal and left temporal regions and increased preference for delayed reward was not attributable to age. However, the relationship between integrity of white matter in left frontal, right temporal, right parietal (as well as some subcortical-cortical circuits), and the preference for delayed reward was age-dependent, given that as these white matter tracts also increased in integrity across the age range studied. These results show that both developmental age as well as individual differences in neural circuitry are related to an individual's preference for immediate versus delayed rewards.

In a study comparing male adolescents aged 12–18 years versus male adults aged 18–32 years, having a preference for delayed rewards was related to patterns of brain activity when making a choice for an immediate reward.[77] For both groups, increased recruitment of the vmPFC was positively related to an individual's preference for a delayed reward, whereas recruitment of the ventral striatum showed the opposite pattern. Further, these patterns of brain activity were also correlated with age, suggesting a linear relationship between chronological maturation and the tendency to choose later, larger rewards. In addition, communication between the

ventral striatum and vmPFC was also positively correlated with the preference for later rewards, as well as chronological age. Overall, this study suggests that developmental changes in functional connections between the vmPFC and ventral striatum are related to the developmental changes in the preference for delayed rewards.

However, one study found that, when controlling for discounting behaviour, neural processing of the value of delayed rewards does not differ between adolescents and adults.[78] Instead, these researchers found the same pattern of neural activity – recruitment of the ventral striatum, posterior cingulate gyrus and medial prefrontal cortex (PFC) – was elicited when processing delayed rewards in both the adolescent and adult groups, with those who discounted future rewards more steeply showing overall lower brain responses to delayed rewards than individuals who were less impulsive.[78] Further, they did not find evidence for adolescents showing either a hypo- or hyper- ventral striatal response to reward processing. Overall, the authors of this study suggest that processing the value of waiting for a larger reward is more dependent on an individual's discounting preference rather than their chronological age.

In a later study, these researchers also examined the relationship between IQ and temporal discounting preferences in the adolescents.[79] They found that IQ was positive correlated with greater activation of the perigenual ACC, inferior frontal gyrus, vmPFC, and ventral striatum when processing the value of delayed rewards. There was also a positive relationship between this pattern of brain activity and an individual's preference for delayed rewards. Further, the consistency of one's choices was related to a specific pattern of brain activity during value-independent decision making (including the dlPFC, precuneus, and the occipital lobe), which was also positively correlated with IQ. Overall, this study suggests that IQ is related to the neural processing of temporal discounting during adolescence.

One theory is that neural systems involved in three cognitive processes: valuation (i.e. the value placed on a certain stimuli or outcome), cognitive control (i.e. engaging in goal-directed cognitive processes), and prospection (i.e. thinking about the future), are involved in the process of temporal discounting.[80] Using this framework, Banich

and colleagues (2013)[81] compared the behavioural and neural correlates of temporal discounting in younger (14–15 years) and older (17–19 years) adolescents, and how these measures related to an individual's self-reported tendency to think beyond the present. Behaviourally, older adolescents were more likely to choose a delayed reward over an immediate reward, and were slower than younger adolescents to choose the immediate reward.[81] Neurally, the pattern of brain activity related to intertemporal decision making was more distinct when choosing between immediate versus delayed rewards in the older adolescents compared to the younger adolescents.[81] Across groups, individuals who reported a greater tendency to think beyond the present showed decreased activity in recruitment of cognitive control regions during the temporal discounting task. These results show that both developmental age as well as individual differences affect the neural processing of temporal discounting. The authors suggest that choosing an immediate but smaller reward might be due to a failure to inhibit urges, an overvaluation of rewards, or a failure to conceptualise the future.

In summary, the studies suggest that, on average, as adolescents get older, they show increasing tolerance to wait for larger rewards rather than take immediate smaller rewards. However, there are individual differences across development in this preference, and these individual differences are related to differences in neural architecture as well as processing. How one comes to choose a smaller immediate reward over a larger distant reward could be related to how that individual values the proposed reward, or it could be related to how well that individual can inhibit reflexive urges or is able to think about the future. The development of brain systems involved in evaluating rewards, cognitive control, and thinking about the future all appear to contribute to the developmental changes in how we process situations that involve us making a choice between an immediate outcome and a distant outcome.

Impulsivity

While impulsivity is related to both cognitive control and temporal discounting, it can also be considered a separate construct, especially when it is measured through self-report. Self-reported impulsivity involves an individual's ability to reflect on their own behaviour and report how likely they are to be involved in a number of

behaviours not directly related to cognitive control or temporal discounting, such as an individual's proclivity for planning versus spontaneity. Therefore, we have chosen to describe studies that focused on self-reported impulsivity as a primary outcome separately from the other constructs. Only one study, carried out by a team based in the USA, focused on impulsivity as a main outcome. This cross-sectional study of 10–22 year olds examined how age-related changes in cortical thickness in a specific region, the insular cortex, related to self-reported impulsivity.[82] Overall, cortical thickness and impulsivity both showed negative relationships with age. Further, the age-related rate of cortical thinning in the anterior insula was related to the age-related reduction in impulsivity. This study suggests that the structure of the brain is related to impulsive behaviour, and perhaps the maturational changes in brain structure that occur over adolescence relate to improvements in impulse control.

Probabilistic learning

We all use probabilistic learning when adapting to new situations. Our brain is constantly assessing the likelihood of given outcomes based on what has been previously observed, and there are even neural markers for when we are surprised that someone did not occur as expected (called 'prediction errors'). We experience a positive prediction error when we observe an outcome that was better than expected, and we experience a negative prediction error when we observe an outcome that was worse than expected. Probabilistic learning involves integrating this feedback from the environment in order to make better subsequent decisions – an ability that is essential for making healthy decisions. Of the five studies examining probabilistic learning, two were carried out in Germany, with single studies being conducted by teams in the USA, Netherlands, and the UK. Four of these studies were conducted within the last five years, and one study was conducted 12 years ago. All five studies were cross-sectional.

The ability to integrate feedback from the environment in order to make better subsequent decisions continues to improve across adolescence and into young adulthood. Young adolescents are more likely to continue making disadvantageous decisions even when given negative feedback longer than older adolescents placed

in the same context. While there are mixed results on whether adults are more or less likely to learn from observing an outcome that was worse than expected, it appears that adolescents are just as likely to learn from both positive and negative surprising outcomes. Adolescents might have a harder time integrating feedback from uncertain environments in order to make better subsequent decisions. These studies suggest that the continued development of the PFC, ACC, and their connections with subcortical regions involved in reward and learning, is related to the development of probabilistic learning strategies.

Reward processing

Reward processing involves the anticipation and receipt of a reward, and is essential to learning about one's environment. In humans, processing the receipt of reward engages the ventral striatum and mPFC.[83] These regions are part of the dopaminergic system, which has been proposed to be overactive,[18] as well as underreactive,[22] in adolescence. Of the 12 studies examining reward processing in adolescence, 10 were carried out by teams in the USA and two were carried out by teams based in the Netherlands. These studies were conducted within the last 11 years. Nine of these studies were cross-sectional, two were longitudinal, and one was a systematic review.

Taken together, the studies echo the conclusions of a previous systematic review which noted a lack of consistency across studies.[84] There appears to be evidence supporting the claim that adolescents process rewards differently from children and adults, although it is unclear what drives the shift. The few studies that included measures of puberty found a relationship between pubertal changes and reward processing in both females and males. Perhaps pubertal changes drive some of the differences between children and adolescents, but it is likely that other factors drive the differences between adolescents and adults.

The context and characteristics of the rewarding scenario affect how adolescents process the potential reward at stake. For example, one study in this section emphasised that having a choice in making a decision mattered in terms of how adolescents processed potentially rewarding outcomes. Indeed, when adolescents

have a choice in a situation, their neural processing of rewards is more similar to that of adults. There were mixed findings regarding how adolescents processed negative outcomes compared to adults, and it is unclear which age group is more sensitive to negative outcomes as compared to the other. Two studies in this section suggest that adolescents might be more sensitive to negative feedback or aversive stimuli than are adults, whereas a study discussed in the previous section suggested that adults are more sensitive to surprising negative feedback.

These studies challenge the theories that adolescents are overall 'hyper' or 'hypo' sensitive to rewards, with several showing great individual variability within age groups, as well as differential recruitment patterns for different stages of reward processing. There is increasing support for the idea that reward processing regions are recruited more during the receipt of reward in younger individuals, whereas these same regions are recruited more during reward anticipation in older individuals. This pattern mimics what occurs across a shorter timescale regarding how individuals learn about a specific rewarding outcome, namely, dopaminergic firing will shift from the receipt of a reward to the anticipation of a reward overtime.

Risky decision making

Of the nine studies examining risky decision making in adolescence, three were carried out by teams in the Netherlands; two were carried out by collaborations between the USA and the Netherlands, with single studies being conducted by teams based in the USA, Switzerland, as well as collaborations between the USA and Switzerland and between Spain and Germany. These studies were conducted within the last seven years. All studies included cross-sectional data, with one study including both cross-sectional and longitudinal datasets.

Health-related behaviours sometimes involve making a decision that involves weighing the benefits of risking something to obtain a potentially rewarding outcome. Therefore, it is essential to understand how we weigh risk across the lifespan, including during the period of adolescence. Contrary to popular belief, these studies do not suggest that adolescents are more likely to choose the riskier option, but instead support the idea that adolescence is a time of differentiation in how an

individual responds to risk: with some adolescents showing increasing risk aversion and some showing increasing risk tolerance. As with other cognitive processes, decision making under risk is affected by contextual factors, and adolescents are less likely to select risky decisions when they have been given expert advice, but could be more prone to select a risky decision when the potential reward is highly valued.

3.1.3 Implications

General implications

- Physiological changes occurring during adolescence should be considered when designing or delivering interventions to improve adolescent health outcomes.

- These changes should be viewed in the context of the wider social environment, and not in isolation.

Interventions – general

- Interventions designed to help adolescents respond healthily in emotionally charged situations may benefit from targeting 'gut' responses to potentially problematic situations rather than relying solely on deliberative processes.

- Interventions should emphasise the rewarding aspects of engaging in healthy behaviours as well as the rewarding aspects of not engaging in unhealthy behaviours.

- Situations that require high attentional demand may predispose adolescents to failing at inhibiting unhealthy behaviours. Interventions and support should take this into consideration when discussing strategies to combat unhealthy behaviours.

- Interventions should support young people during the early formation of associations between health-related experiences and outcomes (positive or negative). These early associations have the potential to stem future negative health behaviours, as well as spur future positive health behaviours.

- Interventions that focus upon impulse control may not be appropriate for younger adolescents, who might not be physiologically ready to benefit from this approach.

- Interventions might focus on the anticipation of an outcome for older adolescents, whereas focusing on the receipt of an outcome might be more rewarding in case of younger adolescents.

- Interventions should be tailored to both 'hot' (emotional) contexts as well as 'cold' (deliberative) contexts. Adolescents use different processes to make decisions under these different contexts.

Research implications

- More longitudinal, robust studies are needed in this area, enabling the inference of causality and to further categorise trajectories of adolescent development.

- Follow-through data into adulthood is necessary to clarify the links between adolescent physiological development, behaviours in adolescence and subsequent behaviours and outcomes in adulthood.

- The inclusion of lay summaries and explanatory comments would increase the accessibility of research papers of this sort to practitioners and policy makers.

3.2 Papers reporting health behaviour data

A total of 283 papers reported health behaviour data in relation to adolescent physiological development (see supplementary material). These papers spanned both brain physiology and other physiological systems, and focused upon sleep, eating behaviours, physical activity, substance use, sexual behaviour and risk behaviours in general. A separate short section has been included related to genetic influences upon behaviour. The decision was taken to present this section separately as it is qualitatively different and a relatively new field of research.

3.2.1 Sleep

Sleep and brain physiology

Five empirical studies conducted in the USA examined adolescent sleep patterns in relation to brain measures. Two of the studies were longitudinal studies, and three were cross-sectional.

Changes in daytime sleepiness is not just a function of shifting sleep schedule preferences, but is also linked to changes in brain function as captured by sleep EEG.[85] Specifically, this longitudinal study found that delta power density during non-rapid eye movement sleep declined across early adolescence. However, the sleep behaviours that adolescents have some control over, such as bedtime or time in bed, have been found to be more related to chronological age than maturational changes in brain functioning during sleep.[86] In this study, when age was controlled for, the relationship between delta power density during sleep EEG and factors such as sleep behaviour, puberty, or other physiological measures like height and weight were no longer significant.[86]

A suite of studies conducted by researchers at University of Pittsburgh suggests that changes in sleep during adolescence are related to neural changes in reward-processing. For one, adolescents with lower sleep quality show decreased activity in the caudate when anticipating rewards or processing reward outcomes.[87] Further studies suggest that the sleep schedules of adolescence relate to reward processing beyond subjective measures of sleep quality. For example, adolescents who have a

later sleep midpoint – an index of the influence of circadian function on sleep timing – show less reward-related activity in the medial prefrontal cortex.[88] When examined further, it appears that a shift in sleep schedule on the weekend also affects reward processing in adolescents, with those who go to sleep much later on the weekend than weekday showing less reward-related activation of the medial prefrontal cortex and ventral striatum.[89] Taken together, these studies suggest that circadian misalignment might contribute to alterations in reward processing in adolescence.

The studies identified suggest that, while there are physiological changes in brain functioning in relation to sleep during adolescence, these do not seem to underlie changes in bedtime routines, which are more related to age than brain physiology. Changes in bedtime routines, however, do have an impact on brain activity when processing rewarding outcomes. Of particular concern is the finding that the impact of lower sleep quality can impact brain physiology even when participants did not report low sleep quality. Finally, shifting sleep schedules between the weekend and weekday (school nights), have a separate impact on brain physiology, which could impact how adolescents process rewards. As many health-related situations involve assessing rewards, it is possible that shifts in sleep schedules during adolescence could alter health-related decision making, but further work linking sleep, reward processing, and behavioural outcomes is needed.

Sleep and other physiological systems

Studies relating to sleep and adolescence in relation to other physiological systems fell into two broad categories: those studies relating to sleep patterns (n=15), and those discussing the relationship between sleep and obesity (n=12).

Of the 15 studies examining adolescent sleep patterns, six were review articles. The majority of studies or reviews (n=9) were carried out by teams in the USA; two studies were carried out by teams based in Israel, with single studies being conducted in Switzerland, Canada, Japan and Germany. With the exception of the early Japanese study,[90] the remaining studies were all conducted within the last 15 years, perhaps reflecting the more recent global focus on adolescent health in general.[91]

Across the studies relating to the changing sleep patterns that occur during adolescence, there seemed to be agreement across many studies that pubertal onset heralds later sleep times, while wake times are often dictated by school hours, resulting in sleep deprivation due to the unchanged or increased need for sleep.[92 -102] Hagenauer and Lee (2013)[103] and Hagenauer et al (2009)[104] indicated that the delayed sleep phase in adolescence is a probable common phenomenon across mammals, not specifically human beings. This perhaps reflects the shared influence of gonadal hormones during puberty between mammalian species.[105]

While some of these studies were limited in their individual claims due to cross-sectional data collection, the cumulative effect, including evidence from several systematic reviews, lends weight to assertions that adolescents are commonly sleep-deprived, due to the altered sleep patterns following pubertal onset.

With regard to gender differences in the onset of these changes in sleep preference patterns, Knutson et al (2005)[98] and Laberge et al (2001)[100] suggest that the gender differences commonly reported in adolescents' sleep patterns are most likely explained by girls' higher pubertal status; girls typically enter puberty between 10–11 years, about two years earlier than boys.[106] Females have been shown to engage in a delayed sleep phase preference pattern at the onset of pubertal changes, until approximately five years after menarche.[107] Thereafter, sleep patterns start to show an advancing, rather than a delaying pattern.[107]

In addition to the influence of gonadal hormones, changes in the circadian timing system and circadian period (internal day length) are associated with changes in melatonin secretion.[92] Data from an earlier study by Murata and Araki (1993)[90] suggest that the onset of menarche is affected by hours of sleep, as well as body weight and height, indicating that the direction of influence may be complex. Menarche onset may be influenced by depression of melatonin concentration during the night, resulting from (or as a result of) a decrease in mean hours of sleep. The long-term effect of melatonin on the reproductive organs was a recommendation for further research by the authors.

While recorded total sleep time declined with age during adolescence, according to Feinberg et al (2011)[95] this was entirely related to a reduction in non-rapid eye movement (NREM) sleep. In contrast, rapid eye movement (REM) sleep increased slightly but significantly. Reduced sleep, including reduced NREM sleep, may have a detrimental effect on immune systems and mental health.[108] [109]

With further regard to the impact on health, Shochat et al (2014)[102] and Carskadon et al (2011)[94] discussed the fact that insufficient sleep has potential effects on mood, attention levels, behaviour, and examination grades. Sleep deficit may also lead to increased caffeine use to feel alert, with potential impacts on health, and learning capacity that require further research.[92] Insufficient sleep in combination with alcohol can be particularly dangerous for adolescent drivers.[99]

Sleep deficit therefore has the potential to have significant health risks during adolescence. In relation to managing these issues, those involved with adolescents are urged to encourage good sleep patterns, consider later school start times, and limit late evening activities.[94] Carskadon et al (2011)[94] and Hagenauer et al (2009)[104] recommend minimising exposure to light at night, as well as reducing the use of electronic devices. However, guidelines relating to the timing and duration of changing sleep patterns need to be provided,[107] and (Dahl and Lewin, 2002)[99] pointed to a paucity of robust evidence to guide such decision making. For example, adequate and inadequate sleep duration for adolescents needs to be defined.[102] It is also questionable from this review whether the sleep amount required for optimal or adequate functioning equates to the optimal amount for health outcomes.

In addition, Maume (2013)[93] found that social relational factors out-performed developmental factors in determining youths' sleep patterns. Stressful social ties, excess school homework, TV and computer use, and family poverty, were found to disrupt sleep in general. Indeed, Carskadon et al (1998)[101] concluded that psychosocial influences and changes in bio-regulatory systems controlling sleep may limit teenagers' capacities to make adequate adjustments to an early school schedule. The imposition of an early start time may require unrealistic, if not unattainable, bedtimes to provide adequate time for sleeping.

Sleep deprivation during adolescence, related to increasing pubertal hormone levels, is common and potentially detrimental to health, both in immediate day-to-day activities, and for future health. Dewald-Kaufmann et al (2013)[110] found evidence of vulnerability to impaired daytime functioning due to (chronic) sleep loss in adolescents. The results also indicated that adolescents obtaining sufficient and/or good sleep show nearly no daytime functioning problems. Interventions that help adolescents to shift to an earlier sleep pattern have been suggested in several studies, and may indeed help adjustment to societal needs and pressures. However, the review has highlighted the pubertal changes and influences are out-with the control of adolescents. Attempting to try and alter sleep patterns could ostensibly be opposing physiological drivers. Whether making such changes is better than modifying structures to accommodate the natural adolescent processes by, for example, changing school start times, is debatable and worthy of involving the views of adolescents themselves in further research.

Several studies pointed to the limitations in the data collected due to the self-report nature of many of the outcome measures. Recording of sleep in a laboratory setting, or by other objective means, and the use of hormonal assays to augment pubertal development scales, would assist validity of findings.[96] [97] Sleep diaries over long periods of time and actigraphy may also contribute to the robustness of the future research findings.[100]

In similarity to studies relating to sleep patterns, much of the data reported in studies[111–113] related to sleep and obesity were from self-report accounts and would have been subject to the vagaries of memory and social desirability bias, especially with regard to diet and weight issues.[114] In addition, there was variation in whether analyses were adjusted to account for age or pubertal stage; as noted above, pubertal stage has recognised associations with sleep patterns, and therefore the recording of age and pubertal stage would be beneficial for the interpretation of results. It is worth noting that in addition to its function in relation to circadian rhythms, melatonin plays an important role in energy metabolism and body weight regulation.[115] In recent research Overberg et al (2015)[115] found a strong association between lower nocturnal melatonin secretion and insulin resistance in obese

adolescents. The physiological influences are therefore complex, and likely to be multi-directional.

3.2.2 Eating behaviour

Brain physiology

There have now been several studies investigating how neurobiology in adolescence can predispose teenagers to healthy food choices. Of the 10 studies examining adolescent eating behaviours in relation to brain measures, five were carried out by the same team based in the USA, one was carried out by a research collaboration between China and the USA, and three were carried out by the same research team in Spain. These studies were conducted over the past six years. Two of the studies were longitudinal studies, seven were cross-sectional, and one was a systematic review.

It has been hypothesised that neural responses to images of appetising foods can predict future increases in BMI.[116] [117] This hypothesis was tested in a group of adolescents who first underwent an fMRI experiment that required imagining eating appetising foods, and were then followed up one year later to assess changes in BMI.[118] In this study, neural responses at baseline were unable to predict changes in BMI over the following year unless the group was divided into subgroups based on genotype. The genotypes examined in this study were two alleles related to dopamine signalling, which is involved in reward processing and brain circuitry. When the groups were analysed separately, the results suggest that individuals who a) possess genetic variants associated with reduced dopamine signalling, and b) also show less recruitment of brain reward circuitry when imagining eating appetising food, are at elevated risk for future weight gain.[118]

This same group investigated how adolescents process real-world cues for unhealthy foods, specifically advertisements for Coca Cola products.[119] In this study, the neural response patterns between regular teenage consumers of Coca Cola were compared to non-consumers while undergoing three different fMRI paradigms: anticipation and receipt of Coca Cola, anticipation and receipt of milkshake, and

viewing Coca Cola advertisements. While this study found multiple differences in neural activation patterns between the groups, the meaning of these differences were difficult to untangle. However, the authors of the study suggest that the heightened salience response to viewing Coca Cola logos, and the decreased inhibitory response during anticipation of Coca Cola receipt, could indicate a predisposition to habitual consumption.

This same group also conducted a longitudinal study using a realistic food-related reward paradigm by examining neural adaptation to the cues preceding, and the response to, receipt of a high-fat, high-sugar substance, namely a milkshake.[120] They found that repeated exposures to the cue preceding milkshake receipt was associated with greater caudate responses over time, whereas the neural response in the putamen and ventral pallidum decreased over time in response to the receipt of the milkshake. By tracking the sample of 35 adolescent females over the next two years, this study was able to investigate if neural adaptation to the receipt of milkshake predicted increase in weight over time. This analysis revealed that the females who showed the greatest increase in ventral pallidum recruitment when viewing cues, and the greatest decrease in caudate recruitment during receipt of the milkshake, were more likely to show greater increases in BMI over the next two years.[120] Taken together, these studies potentially suggest that the typical way in which adolescents' neurobiology respond to repeated exposure to cues for, and receipt of, unhealthy foods is adaptive to making healthy choices, and that adolescents who show deviations in the typical response might be at higher risk for increasing weight.

There are multiple theories as to why certain individuals are predisposed to engage in unhealthy eating behaviours. As eating palatable food can sometimes be an affect-driven decision, it is hypothesised that individuals who engage neural systems associated with 'urge' responses to a greater degree when making decisions under affective contexts, or show dampened engagement in neural systems involved in reflective decision making, will also show greater unhealthy food behaviours in real life.[121] One study tested this hypothesis by examining the neural responses to decision making on the Iowa Gambling Task, a task that has been previously shown to capture decision making preferences in affect contexts, in a group of adolescents

and then comparing these neural responses to real world food consumption behaviours.[121] Indeed, responses in brain regions associated with the reflective system were positively correlated with vegetable consumption and negatively correlated with snack consumption, whereas responses in brain regions associated with the urge network were negatively correlated with vegetable consumption and positively correlated with snack consumption.[121] The authors suggest that perhaps the decision-making processes involved in unhealthy eating behaviour are part of a more general urge-driven style that extends into other domains of decision making.[121]

Brain responses related to body mass index (BMI)

There have also been studies investigating the relationship between BMI and neural responses to certain stimuli in adolescents. While BMI is not necessarily an indicator of health behaviour, it is of interest to understand how neural responses might differ between adolescents with unhealthy weights versus adolescents with healthy weights. For example, it is possible that individuals with higher BMI have different neurocognitive strategies when it comes to assessing the advantages or disadvantages of eating an appetising food. This hypothesis was examined in an fMRI experiment in which adolescents of varying BMI (lean, overweight, and obese) were instructed to use different cognitive reappraisal strategies when viewing images of appetising foods.[122] However, no differences in neural responses to the cognitive reappraisal strategies were observed, suggesting that adolescents of differing BMI levels have similar neurocognitive strategies when it comes to reappraising the benefits and costs of eating appetising foods.[122] Across the whole group, engaging in reappraisal strategies involving either assessing the benefits or assessing the costs of eating an appetising food elicited greater activity in a region of the brain associated with inhibitory control, the left ventrolateral prefrontal cortex.[122] This result suggests that adolescents of all BMI levels are amenable to interventions that involve cognitive reappraisal strategies for eating behaviours.

It is also hypothesised that overweight adolescents might also show reduced recruitment of brain regions involved in inhibition when responding to food cues, which could lead to an increased propensity towards overeating.[123] To test this hypothesis, Batterink et al (2010)[123] examined if BMI in adolescent females

correlated with brain responses during a go/no-go task with vegetables being a 'go' stimuli and desserts being a 'no-go' stimuli. They found that adolescent females with higher BMI responded more slowly to vegetable cues and failed to inhibit responses to desserts. When the participants were instructed to inhibit responses to images of appetising foods, participants with higher BMI showed less recruitment of regions involved in response inhibition and more recruitment of regions involved in reward processing. Despite these differences in neural responses between high- and low-BMI females, behavioural or neural responses did not predict BMI at the one-year follow-up.

It has also been proposed that adolescents with excess weight will respond to cognitive tasks involving risky decision making differently than adolescents with typical weight.[124] In an fMRI study of adolescents performing a Risky-Gains task, excess weight adolescents showed increased midbrain and decreased left insular cortex recruitment when making a risky decision.[124] Additionally, the adolescents with excess weight showed increased recruitment in various regions of the brain when responding to reward receipt, compared to adolescents with typical weight.[124] While this study does provide evidence for differential brain responses to risky decision making and response to rewards for adolescents of varying BMI levels, it is hard to interpret exactly what these neural differences signify.

These same investigators have also compared structural brain differences in adolescents of varying BMI. In this study, they found that adolescents with excess weight had, on average, larger right hippocampi.[125] While it is not clear why adolescents with higher BMI would have larger hippocampi, this same study also investigated relationships between brain structural volumes and individual differences in reward sensitivity, impulsivity, and inhibitory control. They found that, in the group of adolescents with typical BMI, the size of the second somatosensory cortex was negatively correlated with reward sensitivity and the size of the dlPFC was positively correlated with inhibitory control, whereas these relationships were absent in the groups of adolescents with excess weight.[125]

This same lab also explored the neuropsychological performance of adolescents with excess weight compared to normal-weight adolescents.[126] They hypothesised

that adolescents with excess weight would not perform as well as normal-weight adolescents on neuropsychological measures of the ability to inhibit reflexive or reward-driven responses but that excess weight adolescents would perform similarly to normal-weight adolescents on measures of 'cold' executive functions. They found that adolescents with excess weight performed worse on measures of response inhibition, cognitive flexibility, and decision making than adolescents with normal weight, but all adolescents in both groups performed similarly on measures of working memory, planning, and analogical reasoning. These findings suggest that adolescents with excess weight may have specific needs in relation to impulse control and cognitive flexibility.

A systematic review of studies examining the link between obesity and neurocognitive performance suggests that adolescents with excess weight are more likely to show deficits in executive functioning, attention, visuo-spatial performance, and motor skill.[127] Further, adolescents with deficits in executive functions are more likely to exhibit unhealthy eating behaviours such as increased intake and disinhibited eating.[127] However, since many of these studies reviewed included both children and adolescents, and this review did not compare results across these two developmental groups, it is unclear if these relationships are specific to the adolescent period.

Taken together, these studies suggest that typical adolescent neurobiology predisposes adolescents to make healthy eating decisions. The way the brain in adolescence responds to unhealthy foods makes adolescents less likely to engage in unhealthy eating. However, certain individual factors put adolescents at risk for future weight gain, including deviations in the typical brain responses to food cues, as well as possessing genetic variants associated with reduced dopamine signalling. It is possible that healthy eating behaviours are related to an individual's overall style of decision making, and that an urge-driven style could predispose adolescents to engage in unhealthy eating under emotional contexts. Adolescents with healthy, as well as high BMI levels, appear to be amenable to interventions that involve cognitive reappraisal strategies for eating behaviours. However, carrying excess weight in adolescence is also related to decreased impulse control and cognitive flexibility, which could make some intervention strategies less effective.

Other physiological systems

In this section of the review, there were 17 studies relating to eating behaviours during adolescence. Dates ranged from 1996–2014, indicating that the topic has been of interest for some time. There were studies from the USA (n=8), Australia (n=4), and single studies from Ethiopia, France, Switzerland, Europe, and India, demonstrating global interest in the topic.

Sixteen studies were further subdivided into the themes of hormonal influences on eating behaviour, physiological influences on food preference, and the influence of sleep on eating behaviour. In addition, one review[128] formulated the influences that impact on child and adolescent diet and weight into an explanatory model (the Six-Cs Model). This model framed the influences at cellular, individual (child), family (clan), community, country, and cultural levels. The authors concluded that unidimensional intervention approaches may be inadequate, and that multiple level approaches, and acknowledgement of interactions between levels, are necessary. This model offers an interesting perspective against which to discuss the remaining studies, and provides detail of the scope that potential interventions need to consider.

Hormonal influences on eating behaviour

With regard to the hormonal influences on eating behaviour, the majority of studies (n=12) were included in this section. There appeared to be gender differences. For example, a study by McCabe et al (2002)[129] reported that girls were more likely to adopt strategies to lose weight, and boys to increase muscle but not weight, during their adolescent years. The main predictor for such behaviours was pubertal hormonal changes for boys, while girls were influenced by both puberty and the media to lose weight. In older girls the main predictor of body dissatisfaction and desire to increase muscle tone was perceived popularity with the opposite sex. Girls were more dissatisfied with their bodies in general, and both genders perceived sociocultural pressures to conform to ideals, which increased with age. However, the media appeared to be less influential than expected in this study. All data was from

self-report questionnaires; interviews in addition might have yielded more explanatory findings.

Also specific to girls, a study by Abraham and O'Dea (2001)[130] reported that the concept of dieting in relation to weight loss, and the behaviours and feelings associated with dieting, did not develop until menarche for girls, and were likely to be associated with the rapid increases in height, weight, and body fat during that time. The authors suggested that educational interventions aimed at preventing disordered eating behaviours among prepubescent girls may be inappropriate, ineffective, and potentially dangerous.* Although this was a small qualitative study, it gives insight into the dieting and weight perceptions of female adolescents around the age of menarche.

With regard to pubertal timing, Ayele et al (2013)[131] found that, for girls living in Ethiopia, a low menarche age was independently associated with high calorie intake, high protein diet, increased coffee intake, low physical activity, adequate sleep, and parents' low educational background. Low body mass index, low parental income, greater exercise levels, and Amhara ethnic background were associated with late menarche age. However, the impact of ethnicity and the exact direction of the influence(s) were unclear from this paper. It was therefore difficult to make inferences from the results.

Bordini et al (2009)[132] and McCartney (2009)[133] also examined obesity and hormonal influences in girls. These authors reported that obesity in pre-pubertal and early pubertal girls was associated with reduced lutenising hormone secretion, and reduced lutenising hormone amplitude in later puberty. The authors suggested that excess adiposity may subtly suppress hypothalamic-pituitary-gonadal function in pre-menarcheal pubertal girls. Also discussed is the fact that excess adiposity may slow pubertal tempo, although less so than pre-pubertal adiposity appears to advance puberty onset, i.e. excess adiposity delayed the transition through puberty, but

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* It is worth noting that a review of interventions related to obesity prevention did not find any adverse outcomes relating to obesity prevention in pre or post pubescent children. (Waters E et al. Interventions for preventing obesity in children. Cochrane Database of Systematic Reviews, 2011.)

puberty tended to start earlier in those who were already overweight/obese; the nature of directional influence would benefit from further research.

Investigating the effects of puberty on dietary habits in both genders, Clavien et al (1996)[134] found that the type of diet which has been linked with several chronic diseases in adults living in developed countries already prevails before pubertal maturation. This dietary pattern only changes marginally during pubertal development. The study indicated that food education should start earlier than puberty. The study did not gather data before the age of 9, and earlier (and later) dietary preferences would have been interesting.

In relation to other hormonal effects, the study by Ruttle et al (2013)[135] examined the associations between the 'stress' hormone, cortisol, and body mass index (BMI) across adolescence. Cortisol regulates energy by selecting the right type and amount of carbohydrate, fat, or protein the body needs to meet the physiological demands placed on it.[136] When chronically elevated, cortisol can have detrimental effects on weight, the immune system, and chronic disease risk. Ruttle et al (2013)[135] reported that blunted patterns of adolescent cortisol (as opposed to fluctuating) were associated with increased measures of BMI. The findings suggested that the association between cortisol and BMI were developmentally influenced and that blunted diurnal cortisol patterns can be identified in overweight individuals at a younger age than previously thought. The study was unable to establish causation, since earlier childhood BMI and cortisol data were not captured. Further research would benefit from including such measures. However, the links are nevertheless of interest.

In further relation to cortisol and stress, DeVriendt et al (2012)[137] examined the relationship between perceived stress and diet quality in European adolescents as part of the HELENA study (Healthy Lifestyle in Europe by Nutrition in Adolescence). This was clinician-assessed using the Diet Quality Index for Adolescents (DQI-A). They reported that in both boys and girls, perceived stress was a significantly independent negative predictor of overall diet quality. This inverse relationship was observed for all dietary components, except for dietary diversity in boys, and it was unaltered when additionally adjusted for moderate-to-vigorous physical activity or

sleep duration. These results support the hypothesis that stress influences dietary behaviour, thus emphasising the need for preventive stress-coping strategies for adolescents. The cross-sectional nature and self-report nature of the data were limitations, as were the proportion of females and adolescents with 'highly educated parents'.

Regarding further hormonal influences, a study by Miller et al (2014)[138] reported that loss of control eating was associated with higher fasting leptin in youth, beyond the contributions of body weight. Leptin is one of a group of hormones regulating appetite and energy balance.[139] The relationships between leptin (the 'satiety' hormone), eating behaviour, and weight are complex.[140] Miller et al (2014)[138] found that the association between loss of control eating and leptin appeared to be significant for adolescent females only. The cross-sectional design did not inform the directionality of the relationship between leptin and eating behaviours, however. Prospective studies are therefore required to elucidate whether loss of control eating promotes greater leptin or whether greater leptin resistance may promote loss of control eating. Only a single fasting blood measure of leptin was taken. Given natural diurnal variations in leptin levels, this was a study limitation.

King et al (2010)[141] conducted a review into appetite control, the regulation of energy, and physical activity in adolescence. They reported that the energy balance hormones, gherlin and obestatin, were associated with alterations in the drive to eat (i.e. hunger), eating behaviours and appetite regulation. Furthermore, there is some evidence that these peptides might also be associated with physical activity behaviours. Since these hormones are some of the more recently identified, further research would clearly be beneficial.

Two further studies that investigated indirect hormonal influences were Johnson et al (2012)[142] and Bitar et al (1999)[143]. Johnson et al (2012)[142] reported that overweight and obese young adults had been more advanced in terms of skeletal maturity throughout childhood, peaking during puberty. Potential causative factors need to be examined to provide further information about this potential period of risk identification.

Bitar et al (1999)[143] reported that daily energy expenditure and sleeping energy expenditure were significantly higher in adolescent boys than in girls, irrespective of pubertal stage. The daily energy expenditure of children and adolescents could be predicted from fat-free mass, sex, and season. However, links between physiology and health-related behaviour were not emphasised in this study, making any associations speculative.

Physiological influences on food preference

Two studies examined physiological influences on taste preferences: Coldwell et al (2009)[144] reported that bone growth and plasma leptin were significantly lower in a low sweet taste-preference group. The authors concluded that a change in sugar preference from high to low during adolescence appears to be associated with the cessation of growth. They also speculated that there may be biological reasons for seemingly unhealthy behaviour in earlier childhood; for example, a dislike of bitter tastes in children could be a developmental defence against accidental poisoning from plant consumption. One study limitation was that the authors did not assess the effects of menstrual cycle stage in girls, which may have been a modifying factor. For example, Barbosa et al (2015)[145] suggest that there are changes in the taste perception during the luteal phase of the menstrual cycle, potentially influencing unhealthy food choices; the study by Barbosa et al (2015)[145] also suggests the possibility that hormones ghrelin and insulin influence taste, acting to control food intake. These considerations may assist further research in this area to develop the most appropriate data variables. The point at which preferences change during adolescence could be an indicator of an advantageous point for health interventions.

Also investigating food preferences, an Indian study by Sharma and Kaur (2013)[146] reported that more sensitive phenylthiocarbamide (PTC) (bitter) tasters had a low preference for raw vegetables and bitter-tasting foods, and higher preference for sweet-tasting foods. More sensitive PTC tasters overtook their PTC non-taster counterparts from age 14–16 years in having higher mean average skinfold, percentage body fat, fat mass index and fat-free mass index. Further research is needed to confirm these indications across other adolescent populations, but these two studies show that interesting associations between taste preferences and body composition may be present.

The influences of sleep on eating behaviour

Studies relating to the impact of sleep on weight and obesity are discussed in detail in the section focussing on sleep, but in summary, many studies in that section reported an association between short sleep duration and being overweight or obese.[147] [148] [149] [150] [151] [152] However, patterns were not consistent across studies, and further research is needed.

In further research regarding sleep and eating behaviour in this section of the review, Landis et al (2009)[153] found that greater food craving was associated with increased daytime sleep. They concluded that insufficient night sleep may have resulted in increased day napping, and predicted food cravings that could potentially lead to obesity. This study was limited by its cross-sectional study design, however; a longitudinal design with more objective measures (e.g. serum leptin and ghrelin) would be beneficial. Sleep and food intake/cravings were from self-report data. Calorie intake was also estimated by 24-hour recall, which may have been subject to variation and recall bias. Nevertheless, findings indicate potential links that may be worth investigating further.

Golley et al (2013)[154] reported additional potential links between sleep patterns and eating behaviours, indicating that late bed, late risers had higher BMI scores and lower diet quality, independent of sleep duration or activity level.

3.2.3 Physical activity

Brain physiology

There have been few studies examining how adolescent brain structure or function relates to physical activity during this time. Indeed, only one empirical study was found through our systematic review that would fit these criteria. This cross-sectional study was conducted in the USA, examining how aerobic fitness in a group of adolescent males related to white matter integrity,[155] which is a marker for brain function. While unable to parse apart the direction of influence, this study found that aerobic fitness in adolescence was positively associated with higher integrity in white

matter tracts that connect regions of the frontal and motor cortices.[155] To summarise, aerobic fitness in adolescence is related to healthier brain signalling between areas of the brain involved in motor function and executive functions.

Other physiological systems

Physical activity was the most frequently examined topic in this section of the review, with 32 studies examining aspects of physical activity during adolescence. There was a wide range of dates, spanning from 1992–2015. The majority of studies were conducted by teams in the USA (n=10) and the UK (n=10); there were five from Canada, two from Italy, and single studies were conducted by teams from Africa, France, Norway, Portugal and Taiwan. This would indicate that the topic has been of international interest for a significant period of time.

This section of the review included two early systematic reviews. Bale et al (1992)[156] examined the influence of growth and maturation on functional performance/exercise and metabolic response to exercise from childhood into adolescence and adulthood. They reported that respiratory factors such as expiratory volume were lower in females after puberty. Cardiac output may also be reduced, with females having faster heart rates and smaller hearts over this developmental period. Although limited information was available, these results indicated associations which may help to explain observed patterns in adolescent female physical activity; however, directional influences need to be examined further, as reported in later research, which will be detailed below. The review by Kohl and Hobbs (1998)[157] reported that a variety of factors are potential determinants of physical activity in children and adolescents. Interaction between factors is likely, and correlations rather than true predictors were present in the examined evidence in their review. The authors concluded that research must focus on integrating data on physical activity and diet to determine energy balance in relation to weight, to be more meaningful. Further longitudinal rather than cross-sectional research was called for, with less reliance on self-report measures. There is some evidence that later research teams have heeded such advice, with 17 of the 26 empirical studies in the review being longitudinal in design, and 16 using some objective outcome measures.

Gender differences relating to physical activity

In the studies that examined the differences between male and female physical activity in our review, this disparity was illustrated in the research by Cumming and colleagues.[158] [159] [160] [161] [162] Early cross-sectional data suggested that in a same chronological age cohort, boys reported significantly greater exercise behaviour than girls.[158] However, when biological age was controlled for, gender differences were no longer apparent. The same authors reported on a longitudinal pilot study in a later paper[159] and found that maturity status was positively, but weakly, associated with exercise in males, and negatively associated with strenuous exercise in females. Maturation was assessed by height predictions only in both studies. This method of maturation assessment has been validated in USA samples, but may not be as accurate as a more direct measure of pubertal stage. The questionnaires also used self-report measures of physical activity, with the associated risk of bias.

Further cross-sectional work by Cumming et al (2011)[160] reported that advanced maturation was associated with less involvement in physical activity for girls, and perceptions of being less attractive. In contrast, a later longitudinal study by Cumming et al (2014)[162] reported that maturation was associated with less physical activity and more sedentary time in boys, but not girls. Early maturity at 11 years did not predict physical activity or sedentary behaviour at 13 years in either gender, but only these two time points were included. The authors concluded that their results suggest that the effects of maturity on physical activity and sedentary behaviours in girls may be less marked than previously suggested (or more complex). Again, pubertal stage was not explicitly detailed in this study, and maturation assessed by height predictions only. At age 13 years, some participants may not have reached puberty, given the age range over which this occurs.[106] Psychological factors were also not included; as other authors[163] [164] have reported, negative perceptions can influence physical activity levels, especially in girls.

Dumith et al (2012)[165] also found associations between maturity and physical activity that were different between the genders: they reported that early male maturation and later menarche in females were associated with positive physical activity change, as was positive maternal physical activity change. Among related

psychosocial factors, adolescents remained inactive if they were fearful of their neighbourhood, and became inactive if they were of higher socio-economic status (males) or engaged in more screen time (females).

In further relation to sociological factors, a study conducted in the USA investigated differences in racial backgrounds. Andreacci et al (2004)[166] reported higher physical inactivity levels in pre-pubertal black children of both sexes. Differences in maximum oxygen intake (VO2 max) between the pubertal racial groups was independent of body composition and physical activity level. The authors concluded that the results could be attributed to comparatively lower haemoglobin and more sedentary lifestyle in black children. The authors recommended further research to investigate links, including genetic links.

Further evidence relating to whether chronological or biological age is the more important factor varied. Cairney et al (2014)[167] reported that rate of decline in physical activity was greater in girls, and that biological age was a stronger predictor of participation than chronological age in both sexes. However, follow-up was only through until 14 years; data relating to later years would have been beneficial.

Both Machado et al (2010)[168] and Thompson et al (2003)[169] reported few gender differences in the pattern of physical activity when the confounding effects of biological age were controlled. Jackowski et al (2011),[170] Wickel et al (2009)[171] and Duncan et al (2007)[172] reported that physical activity decreased with increasing chronological age from late childhood into adolescence in both sexes, but concluded that girls were generally less active than boys. Duncan et al (2007)[172] found that early maturing boys had greatest initial physical activity levels, and greatest decline. In comparison to Cairney et al (2014)[167] all these studies, apart from Wickel et al (2009),[171] involved data collection beyond 14 years of age, with Thompson et al (2003)[169] having a year age range from 9–18 years. Such longitudinal study is beneficial in showing trends across the pubertal period, rather than just specific short periods of time.

In studies relating to slightly different aspects, Murdey et al (2004)[173] reported that after controlling for sleep time, no differences in sedentary time were seen at

pubertal onset or with increased pubertal development in either gender. However, only sedentary time was measured, with no measures of activity level being reported in this cross-sectional study. With regard to enjoyment of physical activity, Gebremariam et al (2012)[174] reported only small decreases in enjoyment for girls over the early pubertal period (10–13 years). However, the findings were not clear, and the follow-up period was relatively short (20 months).

By way of helping to summarise adolescent physical activity research, a review by Sherar et al (2010)[175] stated that available findings (at that date) generally supported the stage termination hypothesis, suggesting that early biological maturation is associated with poorer body image and negative initial reactions to puberty. These factors were felt to impact on physical activity. The review found that results were generally inconsistent among studies examining maturity and physical activity, partly due to variations in the assessment of biological maturity status, and whether it was self or clinically assessed; methods used to create maturity groups could also vary, and maturity homogeneity may not have been present. The review also found that small sample sizes were often used, and ethnicity and social circumstances were not fully acknowledged in studies. The authors suggest that chronological age may be more important than some studies suggest. Tempo (the rate at which the individual progresses through puberty) is another fluctuating factor not always considered.

In addition to the studies discussed above, a further eight studies in the review focussed on factors affecting females only in relation to activity levels: papers by Baker et al (2007),[176] Davison et al (2010)[177] and Labbrozzi et al (2013)[178] reported that 13 year old girls, and those more developed at 11 years, displayed poorer physical perception and enjoyment/engagement in physical activity. Of the 13 year old girl participants in the study by Labbrozzi et al (2013),[178] two thirds were already overweight or obese. Labbrozzi et al (2013)[178] question whether puberty induces weight gain, or vice versa, since the evidence is not clear. Further research would be beneficial. In conclusion, Labbrozzi et al (2013)[178] highlighted the need to encourage active lifestyles to prevent overweight prior to pubertal onset. Davison et al (2010)[177] and Baker et al (2007)[176] also suggested that physical activity programmes for adolescent girls should address the issues of self-consciousness and discontent,

and identify settings and activities that make differences in body shape less conspicuous.

Baker and Davison (2011)[179] found that more advanced development at age 9 related to declines in perceive athletic competence between ages 11 and 13. The authors concluded that perceived athletic competence is a suitable target for intervention efforts designed to increase adolescent girls' physical activity. In this study, sports were classified as either 'aesthetic' (gymnastics, dance, baton-twirling etc), or 'non-aesthetic' (volleyball, basketball, soccer etc). Such classification may be rather limiting and open to subjectivity, as well as potentially deterring.

In contrast to the above studies, Fawkner et al (2013)[180] reported that relatively more mature girls may be more active than their less mature peers. The authors argue that few studies have demonstrated more than a modest effect of maturation on reduced physical activity levels. The results were based on physical activity self-assessment, and the reasons for the findings are speculative rather than explanatory. This study was also conducted over a relatively short period of time, during the early pubertal period only.

Sherar et al (2009)[181] also found conflicting evidence, reporting no differences in physical activity between early and late maturing girls. However, the decline described was marked: daily minutes spent in moderate to vigorous physical activity decreased by 40% between 8 years and 16 years. Girls aged 8–10 years cited more interpersonal or social barriers. Girls in the older age range (15–16 years) cited more institutional barriers, such as school programmes.

A further study that points to the complexity of the relationship between physical activity and maturation is that of Knowles et al (2009).[182] This study reported that a decrease in overall physical activity was not influenced by maturational status or physical characteristics. Physical self-perception partially accounted for this, with body mass being a predictor of change. However, as the authors indicate, 12 months may not have been sufficient for changes in physical activity related to maturity to develop.

In research with a slightly different focus, Devlin et al (2010)[183] examined the relationship between physical activity, hormone levels and bone strength. Devlin et al (2010)[183] reported that oestrogen levels in the first year after menarche and physical activity are positively associated with bone strength in young adulthood. The results indicate that interactions between oestrogen and exercise around the time of menarche affect maximum bone strength at the end of adolescence. Findings also suggested that specific populations may be at risk of skeletal fragility, such as adolescents with amenorrhea, anorexia, or hypogonadism. This may help to target preventative interventions, and adds to the evidence relating to the importance of maintaining, encouraging and facilitating physical activity throughout adolescence.

Energy balance and physical activity

Studies in this section were diverse, but pointed to associations between reduced physical activity and obesity, due to an energy imbalance. In a systematic review relating to these issues, Katzmarzyk et al (2008)[184] examined physical activity and obesity in children in the 5–17 years age range; they concluded that there is, in general, a negative relationship between physical activity and adiposity in children. In addition, the authors asserted that available data suggested that high levels of physical activity reduce the likelihood of weight gain over time. As evidenced in this review, studies are often limited by correlational designs and measures that do not necessarily meet high psychometric standards. However, further research would be beneficial to determine the importance of environmental and social factors in mediating changes in physical activity.

A study by Benefice et al (2001)[185] examined the energy expenditure and physical activity levels of rural Senegal adolescent girls. They reported that girls in this sample had high levels of energy expenditure due to their considerable contribution to household tasks. However, as with other populations, activity levels declined with age. Micronutrient deficiency was of concern, indicating that dietary deficiency may exist even where energy/macro nutrition is sufficient, and girls are active. The study highlighted the necessity to consider variations between area and cultures. Overall dietary and activity levels need to be taken into account to provide a full picture.

Grassi et al (2006)[186] reported that almost all their participants (aged 14–18 years) could be labelled as sedentary due to a lack of physical activity, and thereby energy expenditure. Apart from the compulsory classes run by their school, there was little engagement in physical activity. A negative association between BMI and VO2 max was also found in overweight adolescents. Aerobic fitness declined with age in both sexes, with the reduction being greater in females. The authors recommended that detection of nutritional levels and aerobic performance should be encouraged in schools.

Armstrong et al (2000)[187] also examined the influence of gender, growth, and maturation on peak oxygen consumption. However, the conclusions from the finding were not clear. Peak VO2 and potential links to activity levels and energy expenditure were implicit rather than explicit, making any possible any implications uncertain.

The study by Chen et al (2012)[188] concurred with the hypothesis that obesity in children is associated with a dysfunction of the autonomic nervous system. The study found that decreases in sympathetic activity could promote excess storage of energy. The authors concluded that overweight/obese children should be encouraged to engage in physical activity during puberty to improve their autonomic nervous system function.

Bitar et al (1999)[143] reported that the daily energy expenditure of adolescents varied with gender, body composition, and season, but not with stage of puberty. Increases in metabolic rate due to changes in hormonal status were compensated for by decreases in energy expenditure resulting from alterations in body composition. Energy expenditure results were significantly higher in boys than in girls, and energy expenditure could be predicted from fat-free mass, sex, and season. Data in this study were from objective measures; however links between physiology and health-related behaviour were not emphasised, making results of lesser relevance to this review.

Findings from many of the studies in this section of the review were conflicting, particularly regarding the influence of maturity on levels of physical activity, and

activity engagement in girls. Disparities were due to a variety of factors, including differing means of measuring biological maturity, the use of maturity status rather than maturation rates, and the range/classification of physical activities used in studies. However, concern about reducing activity levels across adolescence for both genders appears to be widespread. The evidence suggests that the relationship between maturation and physical activity is complex and influenced by psychosocial, racial, and biological factors. Maintaining good physical activity levels across adolescence may improve autonomic nervous system function, and positively influence weight and bone strength. Physical differences in cardio-pulmonary systems may influence physical ability in females during and following puberty. Bi-directional influences may be at play, but there is limited evidence relating to this. Information regarding personal and situational barriers is needed to identify the most relevant intervention strategies.

3.2.4 Substance use

Brain physiology

The suite of physiological and environmental changes occurring during early adolescence has been related to the risk of using alcohol.[189] It has been hypothesised that adolescents may be more vulnerable to the effects of addictive substances because of the ongoing neural maturation processes that occur over this period.[190] Of the 12 empirical studies examining adolescent substance use in relation to brain measures, eight were carried out by teams based in the USA, two were carried out by the same team based in Australia, with single studies conducted by a team based in Canada and France. The studies were conducted over the past seven years. Six of the studies were longitudinal studies, and five were cross-sectional, with one of the longitudinal studies being a rodent study.

One hypothesis is that the presence of certain externalising behaviours (e.g. impulsive risk-taking, social gregariousness, and oppositional behaviours) in childhood and adolescence reflects individual differences in how dopaminergic circuits respond to emotionally salient stimuli.[191] That is, adolescents with these externalising behaviours might show more dopaminergic response to emotionally

salient stimuli, and this could predispose them to engage in novel behaviours such as substance use. Further, heightened sensitivity to emotionally salient stimuli could also predispose these adolescents to addiction if substance use is initiated. Overall, this theory supports the idea that individual differences in one's neurobiology, especially concerning the dopaminergic system, makes certain individuals more vulnerable to substance abuse. However, they caution against biological determinism, suggesting that interventions involving impulse control training are able to reduce substance use in adolescents with high externalising behaviours.

As adolescence is a period of continued cortical development, it may represent a time of heightened sensitivity to environmental influences.[192] It has been hypothesised that neurotypical development during adolescence could be disrupted by exposure to alcohol and drugs, and produce subtle changes that could have an impact on adult behaviours as well as the quality of adult life.[192] Specifically, engaging in heavy substance use in adolescence can impair the development of executive functions relating to impulse control and decision making, which could promote even further substance use in the individual.[192]

It has been hypothesised that the changes occurring in the brain during adolescence render it as a period of increased vulnerability for substance use. Specifically, it's thought that the relatively greater signal capacity of regions involved in approach motivation, coupled with the decreased influence of regions involves in inhibitory control, interact with adolescents' drive for novel experiences to promote experimentation with substances.[193]

Increased sensitivity to the effects of alcohol during adolescence is related to increased alcohol consumption in adolescence, which might affect how an individual's neurobiology adapts to chronic alcohol exposure. In a longitudinal study of college students, the authors found that greater exposure to alcohol cues early in college changed the pattern of communication between brain regions in response to alcohol-related cues.[194] The researchers of this study suggest that developmental changes in patterns of brain activity could influence the perception of alcohol cues in late adolescence.

One study directly evaluated the role of response inhibition on the frequency of adolescent unprotected sexual behaviour and substance use in a sample of high-risk adolescents.[195] High-risk adolescents were recruited from a court-ordered diversion program, and were excluded if they were not sexually active or if they had never used cannabis or alcohol. This study examined the relationship between brain responses during a response inhibition task and past month risk behaviour. They found a negative correlation between substance use and brain responses in the left inferior frontal gyrus and right insula during response inhibition, and a positive correlation between risky sex and brain responses in the right inferior frontal gyrus and left middle occipital gyrus during response inhibition. The authors suggest that these findings show that different health risk behaviours are related to different neurocognitive patterns.

Brain structure predicting substance use

A cross-sectional study comparing marijuana and alcohol using adolescents to non-using age-matched controls found differences in how white matter integrity related to cognitive processes between the groups.[196] In the marijuana and alcohol using group, decreased integrity of white matter in the temporal lobe was related to poorer attention, working memory, and processing speed, but greater integrity in the occipital cortex was related to better working memory and complex sequencing performance. These relationships between regional white matter integrity and cognition were not present in the non-user group. This work suggests that exposure to marijuana and alcohol in adolescence might affect how white matter development relates to cognitive processes.

A cross-sectional study of 'high-risk' adolescents recruited from juvenile justice services investigated how subcortical brain structures differ between daily marijuana-users and non-users.[197] Interestingly, and contrary to their hypothesis, these researchers did not find any differences in brain structure between daily users and non-users after controlling for alcohol and tobacco use, gender, age, personality traits and mental health. In a separate study, this research group compared measures of brain structure in emerging adults (ages 18–23 years) with early substance use and associated problems to age-matched controls.[198] The group with early substance use had smaller brain volumes in the left frontal cortex after

controlling for potential confounders such as lifetime substance use and family history.

It is hypothesised that alcohol use in adolescence can alter brain development, which could potentially make an individual more likely to abuse alcohol in adulthood.[199] In a longitudinal study, a group of adolescents with no reported history of alcohol use underwent a structural MRI assessment, and were assessed again two years later. In this period, half of the sample had initiated alcohol use, and measures of structural brain development were compared between these two groups of adolescents (initiators vs. non-users). These researchers found that adolescents who had initiated alcohol use showed a larger decline in cortical thickness in the right middle frontal gyrus, whereas several right hemisphere regions showed an attenuated increase in cortical white matter volume. Further, the adolescents who had not initiated alcohol during this period of adolescence showed a greater increase in white matter integrity in the left dorsal caudate and right mid-temporal region of the inferior fronto-occipital fasciculus compared to the initiator group. The authors suggest that subclinical alcohol use during mid-to-late adolescence is related to alterations in structural brain development.

Some studies have examined how individual differences in brain structure relate to later use of substances. As the brain continues to undergo significant changes in structure through adolescence, it is possible that some individuals show 'markers of vulnerability' by showing alterations in certain brain structures early in adolescence. Two longitudinal studies from Australia have found evidence for structural brain differences in early adolescence preceding the onset of substance use. One study found that the size of the ACC at age 12 was related to the prevalence of alcohol use problems at age 16 years.[200] These results remained even after the authors controlled for other substance use and psychopathology among their sample.[200] Another study by the same group found that the size of the orbitofrontal cortex at age 12 years was related to cannabis use at age 16 years.[201]

Orbitofrontal thickness has also been found to associate with the number of drugs used by adolescents, although with different patterns observed for adolescents exposed prenatally to maternal cigarette smoking compared to non-exposed

adolescents.[202] The number of drugs tried by adolescents aged 12–18 years was positively correlated with orbitofrontal thickness in the non-exposed group, but negatively correlated in the exposed group. Further, the genotype of the non-exposed group mediated the relationship between oribitofrontal thickness and the number of drugs tried, with Val/Val carriers of the BDNF gene showing a strong positive relationship, and the Met carriers showing no relationship.

One study examined if white matter integrity could predict risk-taking behaviours at an 18-month follow-up, and if this relationship differed between substance-using adolescents versus age-matched controls.[203] They found that adolescents with less white matter integrity in certain white matter tracts (the fornix and superior corona radiata) were more likely to use substances at the 18-month follow-up. Further, they found that less fronto-limbic white matter integrity was predictive of future risk taking behaviours, but only in the group of substance-using adolescents.

Rodent studies

Rodent studies are essential to understand the underlying mechanisms relating physiological development to health behaviours in adolescence. A recent mini-review proposed that adolescent intermittent ethanol exposure can cause lifelong changes in brain structure in rodents, which relate to how the mature rodent responds to ethanol.[204] For example, when young adolescent rats are exposed to 'binge' amounts of ethanol, they are more likely to seek out and consume more ethanol as adults.[205] However, this effect was not observed in older adolescent rats, suggesting that exposure to alcohol in young adolescence is more likely to have an impact on alcohol use in adulthood than alcohol exposure in late adolescence. This difference could be related to the rapid and dynamic changes occurring in the nucleus accumbens during adolescence, as the rats that went on to use more ethanol in this study showed alterations in their nucleus accumbens functionality.[205]

Taken together, these studies suggest that developmental changes occurring in the adolescent brain could impact on how likely individuals are to use substances in both adolescence and adulthood. It is clear that there is a complex and bidirectional relationship between brain structure in adolescence and substance use, with certain individual differences in brain structure appearing to predispose individuals to

increasing substance use risk. Further, individuals who begin to use substances in adolescence show different patterns of brain development than individuals who remain substance naïve through adolescence. However, as with many studies in which the variable of interest cannot be manipulated (for ethical reasons), it is difficult to discern the direction of effect. Studies that have utilised animal models could potentially fill in the gaps, given the similarity of neurobiological circuits between humans and other mammals.

There is evidence that different substances have distinct relationships with the brain. While several studies found evidence for a relationship between brain development and alcohol use, one study here found that daily use of cannabis during adolescence was not associated with differences in brain structure once other health-related confounders were taken into consideration. However, cannabis and alcohol use have been found to alter the relationship between brain structural integrity and cognition in adolescence, suggesting that individuals who use these substances in adolescence follow a different trajectory of brain development than non-users. Finally, one study reviewed provided evidence that even exposure to alcohol-related cues in late adolescence are related to how brain communication networks develop in this period of life.

Other physiological systems

In this section of the review, there were 19 studies relating to substance use. Publication dates ranged from 1999–2014. The majority of studies (n=12) were conducted in the USA; there were four German studies, two UK studies and one study conducted in Holland.

Multiple substance use behaviours

Studies examining substance use either discussed one type of behaviour, such as smoking or alcohol, or considered multiple different types of behaviour. Six studies investigated multiple substance use behaviours. For example, the study by Martin et al (2002)[206] examined sensation seeking in relation to pubertal development, and the use of nicotine, alcohol and marijuana. Sensation seeking was positively associated with pubertal development in both sexes, even when controlling for age, and may

help explain the changes in drug use propensity seen after the onset of puberty.[206] All measures in this study were self-report; objective measures and a longitudinal design would have given greater generalisability to the findings.

Halpern et al (2007)[207] reported that advanced physical maturity was associated with higher risk in relation to alcohol and substance use in general, and in particular in girls with an older partner. Monitoring pubertal development may therefore assist in identifying at-risk adolescents.

Reynolds et al (2007)[208] also examined hormonal influences on substance use, and reported that testosterone influenced aggressive and antisocial behaviour; these factors, alongside peer affiliations, predicted illicit substance use by late adolescence, and subsequent substance use disorders in young adulthood. The study underscores the potential influence of biological processes on patterns of socialisation leading to the use of illicit drugs. Although objective measures of testosterone and Tanner stage were taken, much of the other data were from self-report measures.

Another study that examined substance use more broadly was that of Moss et al (1999).[209] The authors reported that hypo-reactivity as an adaptation to chronic stress may be associated with an increased likelihood of substance use between different generations of the same family. However, data collection limitations made any specific inferences from this study problematic.

In addition to these primary studies, Stanis and Andersen (2014)[210] conducted a systematic review into factors that influence vulnerability to addiction, including developmental stage, exposure to early life adversity, drug exposure, and genetic predisposition. The review concluded that while a considerable amount is known about the functional neuroanatomy and/or pharmacology of risky behaviours, relatively little has been directly translated into strategies to reduce the impact on addiction in high-risk children or teenagers. An opportunity exists to effectively intervene before adolescence, when substance use is likely to emerge. Concordant with this, an earlier review by Waylen and Wolke (2004)[211] concluded that biological

and genetic factors may interact with social factors (e.g. peers, parenting style, neighbourhood) making adolescence either an adaptive or a challenging transition.

Single behaviours

Alcohol

Ten studies had a specific focus on alcohol use during adolescence. Papers by Blomeyer et al (2013)[212] and Buchmann et al (2009)[213] indicated that pubertal stage at age of first drink had an impact on increased future alcohol consumption and a strong predictor of heavy consumption in early adulthood.

Also related to these two studies was the research of Laucht et al (2009)[214] who presented data drawn from the same overall study as Blomeyer et al (2013)[212] and Buchmann et al (2009)[213]. The study found that male adolescents with specific genotypes (5-HTTLPR) and family adversity exhibited more hazardous drinking than girls, those with other genotypes, or those without exposure to adversity. In contrast to these gender-related findings, Hinkers et al (2006)[215] concluded that associations between response to alcohol and genotype seemed to be higher in girls than in boys; further research is needed to explain such gender differences. Adult follow-up is also required for both genders to examine subsequent risks in adulthood to make results more meaningful. Also much of the data reported were from self-reports, rather than objective measures, which may have strengthened the relevance of findings.

Irons et al (2012)[216] discussed the fact that certain genetic factors (the presence of ALDH2 alleles) may be associated with lower risk for alcohol dependence and reduced alcohol use. The protective effect of the ALDH2 allele appears to increase over the course of adolescence and young adulthood and is modified by the environmental influence of parental alcohol use. There may therefore be both protective and risk factors present in genetic structures that influence behaviour in relation to drinking.

Both De Water et al (2013)[217] and Costello et al (2007)[218] examined pubertal maturation and associations with levels of alcohol use, when controlling for age. The results indicated that advanced pubertal maturation was related to increased alcohol use in both boys and girls. Higher testosterone and estradiol levels correlated with

the onset of alcohol use in boys, and higher estradiol levels were associated with larger quantity of alcohol use. However, correlations between sex steroids and alcohol use were not significant in girls.[217] Findings suggested that higher sex steroid levels could be one of the underlying influences of alcohol use in boys, possibly by stimulating brain regions implicated in reward processing. Influence of peer behaviour, lax supervision in girls, and family problems/poverty in boys were further predictive.[218] These studies support the theory that the earlier the onset of puberty, the longer the period of risk, and indicate influencing sociological factors.

In addition to these primary studies, there were three review papers: Varlinskaya et al (2013)[219] conducted a review into pubertal-related changes and adolescent behaviours connected to alcohol use. The results from rodents suggested that androgens may moderate ethanol intake in males. The authors concluded that converging evidence from both primary scientific studies, and research with human adolescents, is necessary to more fully explore the dynamic interrelationships between neural, hormonal and behavioural changes during adolescence.

Windle et al (2009)[189] also reviewed evidence relating to alcohol use in adolescence and concluded that among the most influential alcohol-specific risk factors are a family history of alcoholism and the influences of siblings and peers, all of which shape an adolescent's views about alcohol; these in turn help determine alcohol use behaviours. This review highlighted the bidirectional influences at play during early- to mid-adolescence regarding alcohol use.

Spear et al (2014)[204] reviewed the literature relating to adolescent alcohol exposure, both in humans and rodents. The results indicated that adolescent rodents were more insensitive to cues that may moderate alcohol intake. The review also highlighted that neurocognitive deficits may be apparent years after exposure to excess alcohol, although some neural changes may be evident prior to alcohol exposure; this raises questions relating to the determinants and consequences of adolescent alcohol exposure, the answers to which may help identify protective factors.

Smoking

In relation to smoking behaviours, three studies[220-222] were included in this part of the review. Li et al (2011)[222] indicated that specific genes may influence smoking initiation in adolescent females. They concluded that further research is needed to understand the influence of psychological traits and other psychosocial mediating factors in addition to genetic factors. While a gender variation was mentioned, this was not expanded upon, and clearly further research would be beneficial.

Summary

Evidence from the studies reviewed in this section indicates that a younger age of alcohol exposure increases risk of future harm, including potential addiction. There may also be defined effects of specific genes or alleles, in conjunction with other socio-economic factors, which influence drinking behaviour during adolescence. Complex influencing factors in relation to drinking behaviour are therefore beginning to emerge, but do not appear to be fully clear at present. Despite rapid progress in this field, many questions remain, and further research is still required to help inform health guidelines and professional practice for those involved with adolescents.

3.2.5 Sexual behaviour

Other physiological systems

In this section, 12 papers discussed sexual behaviour. All but two were conducted in the USA: one study involved Zimbabwean boys, and one was conducted by a Dutch research team. Dates of publication were broad, ranging from 1981–2015. All papers examined factors affecting the onset of sexual activity.

With regard to the onset of sexual activity, several papers examined the role of testosterone in this respect. Although an earlier study by Halpern et al (1993)[223] did not provide support for the idea of a direct causal link between testosterone levels and change in sexual motivation or behaviour, two later studies with more frequent data collection were able to demonstrate such links: Halpern et al (1998)[224] reported that higher levels of salivary testosterone were associated with more frequent sexual activity in adolescent males. In addition, Halpern et al (1997)[225] reported similar

findings with regard to testosterone levels in adolescent girls and the timing of first coitus. For adolescent females, frequency of attendance at religious services was found to moderate effects of testosterone on sexual transition, and is consistent with a biosocial model suggesting that biological effects are moderated by relevant social variables.

In contrast, Udry et al (1985)[226] examined hormonal and social effects on adolescent male sexual behaviour, and concluded that testosterone appeared to affect sexual motivation directly in boys, and did not operate through the social influences accompanying pubertal development. In addition to the effects of testosterone, Campbell et al (2005)[227] reported that first spontaneous nocturnal emission was a stronger predictor of sexual behaviour than secondary sexual characteristics, and concluded that this event be of use as a marker of pubertal timing.

Hormonal and peer influences during adolescence may account for gender variations. For example, Smith et al (1985)[228] found that the sexual behaviour of female adolescents was positively affected by the hormones androgen and oestrogen, as well as the sexual behaviour of friends. Whereas for males, greater pubertal development (regardless of age) was associated with greater sexual involvement, but not associated with friends' sexual behaviour.

Such gender differences were also found by Graber and Sontag (2006)[229] who concluded that sexuality begins to develop more fully during puberty, develops extensively over adolescence, and is interconnected with changes in self and social context for girls during this period. Research by Moore et al (2014)[230] found that girls' perceived pubertal timing, in addition to actual age at menarche, predicted age of first sex.

With regard to associated behaviours, in a review of the factors that precede the onset of adolescent sexual intercourse, Zimmer-Gembeck and Helfand (2008)[231] reported that this was connected to alcohol use, delinquency, school problems, and (for girls engaging in early sexual activity) depressive symptoms. With regard to other consequences, early sexual activity may also result in greater risk, including infection or unwanted pregnancy.[232]

Zimmer-Gembeck and Collins (2008)[233] found that adolescents accumulated a higher number of sexual partners by age 16 years when they looked older, drank alcohol more frequently, and were more involved with dating in early to middle adolescence. Male gender was associated with accumulation of sexual partners more rapidly between ages 16 and 26 years. There was little indication that the accumulation of different sexual partners had begun to slow by age 26 in this study. These findings indicate that interventions targeted at teens to reduce sexual risk behaviour may be just as necessary in the later teen years/emerging adulthood, and may need to be gender sensitive.

In further relation to the exact specifics of sexual activity, most of the studies detailed engagement in vaginal intercourse as being a definition of this. However, an early study by Dornbusch et al (1981)[234] reported on data limited to a simple yes or no response relating to whether participants had ever been on a date. Conclusions drawn from this study may therefore not be comparable with more specific romantic or sexual activity data from other studies. This perhaps reflects the less open attitudes that prevailed during that earlier era, in terms of actual behaviour, prevailing cultural and social pressures at that time, and possibly the acceptability of researching such personal topics. It does, however, provide a historical view of past research approaches and findings, to help situate current research findings.

The papers relating to adolescent sexual behaviour highlighted the effects of differing hormonal profiles, and associated gender differences. Females appeared to be more influenced by psychosocial factors, including the effect of peers. The included studies varied in terms of the sexual behaviours examined and the method(s) of assessing pubertal status, which made direct comparisons more difficult. Pubertal status measures ranged from Tanner staging assessed by a professional, to parental or self-assessment. Although these latter measures have been considered valid and reliable, there may also be elements of self-assessed psychological and behavioural maturity incorporated in such considerations,[235] which may not be acknowledged as confounding factors. Halpern et al (2007)[207] used 'perceived physical maturity' as a proxy for relative pubertal status, and concluded that although advanced physical maturity was associated with increased risk (in

terms of alcohol, substance use, sexual risk-taking etc), it was also associated with greater likelihood of having a romantic partner, which further increased risks, especially for girls with an older (≥ two years) partner. However, as the authors noted themselves, although self-perceived measures are meaningful, and may be valid, they are not the same as objective measures. Also, it is possible that adolescents with older partners may see themselves as more mature by association. In addition, girls typically enter puberty two years in advance of boys,[106] so an age gap of this range would indicate a physical maturity match, and potentially a match with regard to readiness to engage in sexual activity; however, as the review has highlighted, this latter consideration may be mediated by culture, society or religion. While these factors may be acknowledged as influencing issues, the impact on individual behaviours is difficult to ascertain, unless these are specific elements under study.

With further regard to sexual behaviours, these may not be specified in sufficient detail for comparison between studies; for example, intercourse may or may not be specified as vaginal, and there is often little acknowledgement that sexual activity may involve actions other this. Similarly, homosexual sexual activity, either as a behaviour, or in relation to greater risk, is not acknowledged. Baams et al (2015),[232] for example, noted one study (out of 50 studies in their review) as specifically relating to homosexual activity; however, this was not discussed in their analysis. Similarly, Halpern et al (2007)[207], although noting such behaviour as increasing risk, did not discuss data from within this category.

3.2.6 Risky behaviours in general

Brain physiology

Six studies utilised measures of self-reported engagement in health-risk behaviour as a dependent or independent variable. As these measures encompass a suite of health-risk behaviours, it is difficult to parse apart which health behaviour is being assessed in the study. Therefore, the studies including such measures are featured in this section. Of the six empirical studies examining adolescent health-risk behaviours in relation to brain measures, four were carried out by teams based in the USA, with single studies conducted by teams based in New Zealand as well as a

collaboration between the USA and the UK. The studies were conducted over the past five years. Three of the studies were longitudinal studies, and three were cross-sectional.

One cross-sectional study of typically developing adolescents examined how self-reported endorsement of engagement in health-risk behaviours, and psychosocial problems experienced from these behaviours, related to patterns of brain activity when performing a basic monetary reward task.[236] When anticipating rewards, the adolescents who endorsed more psychosocial problems and engagement in risk behaviours showed increased recruitment of the mesolimbic circuitry involved in incentive processing. When presented with the opportunity to obtain a reward, these adolescents also showed greater changes in signalling between the nucleus accumbens and frontal cortex. The authors suggest that these findings support the theory that individual differences in the motivational neurocircuitry in adolescence is related to impulsivity and engagement in health-risk behaviours.

Another cross-sectional study assessed how self-reported engagement in risky behaviours (including health risk) was related to neurocognitive functioning as well as personality traits in a group of adolescents and adults.[237] These researchers found that individual differences in the personality traits of impulsivity, sensation-seeking, aggression, and sociability were positively correlated with self-reported engagement in risky behaviour. However, they found that individual differences in neurocognitive functioning was related to self-reported engagement in risky behaviour even after taking into account these individual differences in personality, as well as age, and gender. Overall, the participants with lower neurocognitive functioning reporting greater engagement in risky behaviour than participants with higher neurocognitive functioning. This study suggests that neurocognitive functioning is a better predictor of real-life risk taking behaviour than age for adolescents and adults.

A longitudinal study of children transitioning into adolescence examined how changes in neural reactivity to emotional faces related to real-world health-risk behaviour as well as susceptibility to peer influence.[238] These researchers found increased recruitment of the ventral striatum and vmPFC over time in response to

emotional faces. Further, the increased recruitment of the ventral striatum was negatively correlated with risk-taking as well as susceptibility to peer influence. The results of this study suggest that adolescents' heightened recruitment of the ventral striatum in emotional contexts could be adaptive, and a possible mechanism related to increased ability to avoid engaging in health-risks.

Another longitudinal behavioural study examined how individual differences in working memory, impulsivity, and sensation seeking related to real-world engagement in health risks in developing adolescents.[239] In this study, overall levels of engaging in health-risk behaviour, impulsivity, and working memory all increased across ages 10 to 14 years. However, while an individual's working memory in early adolescence was negatively related to engagement in health-risk behaviour in mid-adolescence, an individual's sensation seeking behaviour in early adolescence was positively related to engagement in health-risk behaviour in early-to-mid adolescence. The authors concluded that this pattern of development suggests that engaging in health-risk behaviours during adolescence can be a product of either a 'dysfunctional' form of impulsivity, which is characterised by deficient executive function capacities as well as a tendency to act without thinking, or a more 'controlled' form of impulsivity, which is characterised by high sensation seeking and high executive function capacities.

An integrative cross-sectional study that combined both self-reported engagement in health-risk behaviour, as well as an fMRI task assessing risky decision making and cognitive control, investigated how feelings of family obligation related to both risky decision making, cognitive control and real-life risk behaviour.[240] These researchers found that self-reported feelings of family obligation were negatively correlated with risky decision making, as well as dampened recruitment of the ventral striatum to increasing monetary rewards. However, family obligation was positively correlated with recruitment of the dlPFC when participants exerted cognitive control to inhibit reflexive behaviour during successful behavioural inhibition. Overall, less recruitment of the ventral striatum was related to less self-reported engagement in health-risk behaviour. The results suggest that family obligation influences the neural processing of reward and cognitive control, and that these differences have an impact on real-life engagement in health-risk behaviour. The authors conclude that

adolescents who report greater family obligation might be less inclined to take risks, and are less sensitive to rewards.

Taken together, these studies suggest that individual differences in brain circuitry, neurocognitive function, as well as feelings of family obligation, can impact on how likely an adolescent will engage in health-risk behaviours. Lower neurocognitive functioning is related to greater engagement in health-risk behaviours, and could be a better predictor of real-life risk taking behaviour than age for adolescents as well as adults. An adolescent's feeling of family obligation appears to be related to less engagement in health-risk behaviour. Contrary to the theory that increased recruitment of ventral striatum during adolescence is a marker of vulnerability, one study found that increased recruitment of the ventral striatum was related to less engagement in health-risk behaviours, as well as less susceptibility to peer influence. Another study reviewed here suggests that there are distinct roads that could lead to engaging in health-risk behaviours during adolescence. One road could be related to deficient executive function capacities as well as a tendency to act without thinking, whereas another road, to a more 'controlled' form of engagement in risk behaviours, might be characterised by high sensation seeking and high executive function capacities. Overall, these studies suggest that environmental factors could interact with individual differences in neurobiological predispositions to influence how likely an individual will engage in health-risk behaviours.

3.2.7 Genetic influences

Genes are units of heredity passed from parents to offspring and contained in a person's cells – every human cell contains about 20,000 to 25,000 genes.[241] Genes vary greatly from person to person and influence personality, intelligence, physical appearance, and health. While some genetic traits cannot be altered (e.g. having blue eyes), other attributes can be modified by education, behaviour, and environment.[241]

With regard to the influence of genetic factors on health behaviour during adolescence, the review identified 12 studies. These studies are all dated within the last decade, indicating the recent emergence of this research field. Three studies

were conducted in Germany and three in the USA; there were two Dutch studies; one study involved populations from China and the USA, with one study each in Norway, India and Estonia. Interest in this field is therefore spread over a number of diverse countries and cultures.

The majority of studies were concerned with either alcohol consumption (n=4) or obesity (n=4); two studies focused on physical activity, one on smoking, and one on self-regulation[242] in general. The studies are reviewed under these headings below. All the papers reviewed assumed prior in-depth knowledge of genetics, and did not offer explanations of the terminology used, as will be illustrated.

The studies suggest that there are emerging connections between genetic make-up and health behaviours that are complex and worthy of ongoing research. It appears to be too early to relate such links to intervention development. However, in the future, genetic data may provide indications of greater propensity for certain behaviours, which may help to identify risk populations and allow interventions to be targeted more accurately. Studies relating to genetic influences on alcohol use were the most commonly reported in this review. However, even controlling for such genetic factors, early alcohol exposure appears to be a strong predictor of heavy alcohol use in adulthood, as discussed in the section relating to substance use.

This review has indicated some of the complexities involved, including the influence of psychosocial factors on alcohol consumption. As further research emerges, these links will become clearer, giving evidence to help determine how to best focus efforts, resources and advice on adolescent alcohol consumption.

Although limited in number, interesting genetic links relating to the likelihood of becoming obese are also emerging[243]. All studies are fairly recent, and signify the need for further research.

Similarly in the studies[244] relating to genetic influences on physical activity, there appear to be associations that may become more apparent and of greater importance as further indicators emerge. Such evidence will help to identify the most appropriate target groups for interventions.

With regard to smoking, the study by Li et al (2011)**Error! Bookmark not defined.** was a large longitudinal study carried out over seven years, with almost 3,000 participants. However, it relied on self-report data relating to smoking, rather than more objective measures, such as cotinine blood or urine samples. The fact that only one study was available for review also limited any conclusions beyond those inferred by the authors. In further more recent research not included in this review, O'Loughlin (2014)[245] conducted an analysis of 24 candidate genes in a longitudinal study of adolescents. The authors identified seven genetic loci that were associated with number of cigarettes smoked in the past three months. However, because none of the associations remained statistically significant after correction for multiple testing, the findings in this study must be viewed as preliminary. Clearly further research is necessary, and will be of benefit to those working with adolescents.

3.2.8 Implications

General implications

- Physiological changes occurring during adolescence should be considered when designing or delivering interventions to improve adolescent health outcomes.
- These changes should be viewed in the context of the wider social environment, and not in isolation.

Interventions – specific behaviours

Sleep
- Those developing interventions should consider how shifts in sleep schedule may impact on health behaviour, in addition to the role of use of social media and IT equipment.
- Involving the views of adolescents on what would be most helpful to them with regard to optimising sleep and functioning is a vital part of intervention development.

Eating behaviour

- Early dietary advice predating puberty may help to prevent unhealthy dietary behaviours from being exacerbated during adolescence.
- Interventions targeting eating behaviour should consider including components related to optimal sleep and physical activity.
- Effective coping strategies may reduce the likelihood of unhealthy eating. These could be incorporated into Life Skills interventions present already in school curricula as a general, and inclusive, preventative measure.

Physical activity

- Gender and maturation-rate differences, and perceptions of body image and self-esteem, may inform the development of appropriate strategies to encourage physical activity levels.

Substance use

- Early adolescence might be a particularly vulnerable period. Younger adolescents and older adolescents should be given distinct intervention efforts tailored to their specific age group.
- Early maturity appears to be associated with increased risk of substance use, and an increased length of risk, which may then impact on adult behaviours and health problems. Interventions to target those who mature early may be more beneficial than blanket coverage.
- Psychosocial aspects, including peer influence, family poverty, romantic partners, and parental behaviours, need to be taken into account, and may also help identify the most appropriate intervention target groups.

Sexual behaviour

- Gender differences in maturity need to be taken into account when designing interventions to promote sexual health. Stage of readiness to receive interventions may differ according to maturity levels.
- Social context, cultural and religious influences need to be acknowledged in, and adaptability built into intervention development in this area.

Research implications

- More longitudinal, robust studies are needed in this area, enabling the inference of causality and to further categorise trajectories of adolescent development.
- Follow-through data into adulthood is necessary to clarify the links between adolescent physiological development, behaviours in adolescence and subsequent behaviours and outcomes in adulthood.
- The inclusion of lay summaries and explanatory comments would increase the accessibility of research papers of this sort to practitioners and policy makers.

4. Discussion

Interventions to improve adolescent health and subsequent health outcomes in later life are implemented within the context of many changes unique to this stage of the life course. This review has considered health behaviours in general, and more specifically sleep, eating behaviours, physical activity, substance use and sexual behaviour, within the context of the physiological changes occurring during adolescence. To our knowledge, this review is the first of its kind and represents an up-to-date primer of research that has applicability to those working with and for young people across the policy, practice and research sectors.

Our findings support calls for greater focus in public health upon adolescent development as a unique period in its own right.[246] Physiological changes during adolescence – for example, changes outlined occurring within the brain and directly affecting cognitive and emotional regulation, and their links with health behaviours, suggest that adolescence is a critical opportunity to support healthy, positive change in ways that may offset trajectories into ill health. One key point derived from this review is that although physiological changes on occasion seem to have their independent impact on adolescent health behaviour development, they do not occur in isolation. Rather, they exist alongside a myriad of other influences, i.e. socio-

environmental determinants, shaping and reshaping adolescent health and life trajectories.

The findings of this review indicate a number of nuances specific to adolescent development, which have clear implications for how we can support young people towards better health. For example, our findings suggest the adolescent brain is wired in such a way that interventions should be tailored to both 'hot' emotional contexts as well as 'cold' deliberative contexts, since different processes are used to make decisions under these contexts. Adolescents therefore need to be equipped to deal with both. Thus, interventions to reduce risk-taking behaviour may have more success if they provide adolescents with strategies for dealing with impulsive action (hot) in addition to strategies to support decision making (cold). Other implications are listed throughout this report, with the intention of serving as a guide for those involved in youth health.

The findings of the review were split into two sections: brain physiology, and other physiological systems. This grouping suggests that in terms of content, there is a greater amount related to brain physiology. Other physiological systems included the musculoskeletal and hormonal systems, in addition to general changes related to puberty. The abundance of material related to brain physiology may reflect where the majority of theory and empirical evidence lies in relation to adolescent development and health behaviour. This may be due to the fundamental role that the brain plays in many of the capacities and processes directly influencing behaviour and behaviour change, e.g. emotion and emotion regulation, cognition and decision making, perception, etc. It is worth noting, however, that almost half of the papers related to brain physiology were considered to have implications for health behaviour but did not measure this directly or discuss it explicitly. Many studies were conducted in laboratory settings, given the inherent difficulties of measuring brain function in non-laboratory settings. The controlled context of many of these studies is markedly different from the environments in which our young people grow up on a day-to-day basis, and their attendant challenges and opportunities. It could therefore be argued that while these studies provide valuable insight into the adolescent brain, there is still much to learn about brain function in relation to how it operates in complex non-laboratory contexts.

The review aimed to identify theories exploring the relationship between physiological development and health behaviours in adolescence. A further aim was to identify the extent to which these were underpinned by rigorous scientific evidence. As stated previously, in-depth formal quality assessment was not feasible due to the breadth and scope of papers included in the review, in terms of discipline, focus and study design. Quality of the studies was highlighted when relevant in the narrative summaries. It should be noted that many of the studies were cross-sectional, using correlational designs, as described in the narrative reports. This type of study design is particularly problematic since it is difficult to disentangle the direction of any effect, or to rule out the influences of other confounding variables. Indeed, one of our key recommendations is that there is a need for more longitudinal studies. While the cumulative effect of studies lends support to the findings reported, it would be unwise to rank theories or evidence on the basis of the current literature. A more cautious approach is to identify all theories and to consider these on a case by case basis, as we have presented throughout the review.

This review represents the foundation for a larger project that aims to understand the full breadth of influences impacting upon adolescent health behaviour, as shown in Figure 1. A comprehensive understanding of such influences will enable an understanding of how these might interact with one another, and further support effective public health policy and practice. This understanding could be used to fine tune and optimise interventions for young people. Undertaking this work will require collaboration between public health professionals working across disciplines. This review presents an example of where such collaborative working – in this case, between neuroscientists, public health practitioners, and public health researchers – has proved fruitful.

It is important to note that the way in which we discuss biological influences on behaviour has real consequences on how individuals perceive themselves and one another. While the results of this report show that there is no shortage of brain imaging studies investigating how brain development could have an impact on health behaviours during adolescence, there have been few studies assessing how adolescents, or people in general, process these widely disseminated research

experiments. One study sought to examine how adolescents take up the vocabulary of the teenage brain by conducting a survey at a science museum, but also by interviewing adolescent females at a secondary school.[247] When asked to choose from a list of possible explanations for a specific scenario regarding a teenager's behaviour, adolescents were most likely to endorse explanations referring to the difficulty of teenage life and the generation gap between parents and their children compared to biological explanations (e.g. neuroplasticity, neurochemicals, and evolution, with the exception of hormones). Results of interviews emphasised how adolescents felt that neuroscience research had the potential to combat negative stereotypes and dehomogenise teenagers as a group, but the current focus of neuroscientists on teenage behaviours misrepresented adolescence. They expressed an overall fear that brain-based explanations of teenage behaviour could reinforce negative stereotypes of teenagers in society. It is therefore important to be mindful of how the findings from such studies are presented.

In conclusion, this review has identified and described theories and empirical evidence related to physiological development and adolescent health behaviour. The findings have clear implications for public health policy, research and practice, as outlined throughout this report. Our findings emphasise the critical importance of viewing adolescence as a unique period of the life course, and are in line with calls for increased focus upon adolescent development within the public health domain. This review represents the foundation for a larger project that aims to understand the full breadth of influences, proximal, distal and their interaction, impacting upon adolescent health behaviour. A comprehensive understanding of such influences will enhance our understanding to allow us to further fine tune and optimise interventions to support young people towards healthy outcomes.

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