Title: Adolescence as a sensitive period of brain development

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Abstract: The human brain undergoes substantial changes in adolescence, especially in frontal, parietal and temporal cortices. It has been proposed that these changes in brain structure and function are characterised by relatively high levels of plasticity, making adolescence a sensitive period of development for environmental influences such as drugs, stress or cognitive training. Drugs, such as cannabis, have a particularly deleterious effect on cognitive performance and brain function during adolescence, and social stress during this period of life confers long-lasting negative effects on mental health. Heightened plasticity in adolescence might lead not only to increased vulnerabilities. Plasticity in cognitive control and memory performance during this period of life might also be heightened, making adolescence a window of opportunity for education.

Brain development in adolescence

Neuroimaging studies in the past two decades have demonstrated that the human brain undergoes protracted development, including during adolescence, the period of life that starts at puberty and ends at the point at which an individual attains an independent role in society [1, 2].

White matter volume and integrity increases throughout childhood and adolescence into adulthood. The pattern of increase differs between brain regions with frontal and temporal regions showing particularly pronounced changes in adolescence [3]. White matter volume increases are thought to reflect an increase in axonal calibre [4] or myelination [5, 6]. Myelin acts as an electrical insulator of high resistance and low capacitance, which increases signal conduction velocity [7].
Grey matter consists mainly of neuronal cell bodies, glia, dendrites and synapses. In many cortical regions, grey matter volume increases from infancy through childhood, then declines throughout adolescence and into the twenties [6]. Grey matter volume undergoes particularly substantial decreases in frontal and temporal grey matter during adolescence [8]. It has been proposed that the reduction in grey matter during adolescence is due to a number of factors, including increasing white matter encroaching on grey matter [3], environmentally-driven synaptic pruning [9], and a reduction in glia [10].

The ongoing development in white and grey matter during adolescence is accompanied by marked changes in cognition. Piaget conceptualized adolescence as a formal operational stage of development during which individuals increasingly rely on abstract thought and reasoning [11]. This dovetails with recent evidence from Diffusion Tension Imaging (DTI) studies suggesting that adolescent white matter maturation in frontal and parietal regions and their connections is associated with improvements in IQ [12] and working memory performance [13]. Similarly, grey matter reductions in frontal and parietal regions as well as regions surrounding the central sulci are longitudinally associated with improvements in working memory during adolescence [14] and thinner parietal cortices in early adolescence predict better problem solving, planning and verbal learning [15]. Social cognition also undergoes pronounced changes during this period of life, including significant maturation of perspective taking [16] and face processing [17] during human adolescence.

The evidence for the reorganisation of brain structure and cognition during adolescence has led to the suggestion that adolescence is a sensitive period of brain development [18, 19]. It has been proposed that neural plasticity, the way the brain adapts to internal or external changes, is heightened, rendering the adolescent brain particularly susceptible to
environmental input. We will explore three areas in which adolescence is particularly likely
to be characterised by heightened plasticity: the effects of drug use; the social environment;
and cognitive control and memory.

The effects of drug use on adolescent brain development
The developing brain may be particularly sensitive to drugs such as cannabis. Cannabis is
one of the most widely recreationally used drugs among adolescents and adults in the US
and UK [20, 21]. Cannabinoid exposure during early adolescence is thought to initiate
neuroplasticity, resulting in lasting changes in brain structure and cognitive deficits [22, 23].
A recent study suggested that significant grey matter atrophy in the adult temporal pole,
parahippocampal gyrus and insula was linked to heavy cannabis consumption during
adulthood or adolescence, or moderate (recreational) use before the age of 18 [24].
Longitudinal data indicated that self-reported persistent cannabis use between 13 and 15
years of age was associated with a significant decline in cognitive abilities [25]. See Figure 1.
The longer the period of cannabis consumption, the greater the decline in cognitive abilities
[25]. This cognitive decline was more pronounced for participants who used cannabis before
age 18 as compared to after. It should be noted that alternative explanations, such as pre-
existing mood or anxiety disorders mediating both cannabis-use and cognitive problems,
cannot be ruled out [26].
Molecular and cellular data on the effects of cannabis in adolescence is scarce and it is not
yet clear what makes the developing brain particularly sensitive to cannabis. Cannabis
affects the endocannabinoid system, which, along with other neurotransmitter systems (e.g.
the glutamatergic and dopaminergic systems), undergoes extensive restructuring during
adolescence [27]. Cannabis may disturb neurodevelopmental processes known to be
mediated by the endocannabinoid system, including neuronal genesis, neural specification,
neuronal migration, axonal elongation and glia formation [28-30].

Cannabis use during adolescence may increase the risk of developing psychotic disorders
such as schizophrenia [31-33]. Research has shown that individuals with a genetic
predisposition to schizophrenia and a history of cannabis use are at higher risk of developing
schizophrenia compared to those without [34]. Animal models have suggested a causal link
between first-time cannabis consumption in adolescence and schizophrenic-like symptoms.
Cannabinoid exposure in adolescent rodents predicted schizophrenia-like symptoms such as
long-term cognitive deficits in adulthood (e.g. object recognition memory), whereas similar
exposure in adult rodents was not linked to such symptoms [35-38].

Recent studies in humans and animals support the notion as adolescence as a period of
particular sensitivity to cannabis consumption compared to adulthood. More studies
investigating the effect of cannabis during development are needed, however. Sensitivity to
cannabis during childhood remains unclear. As cannabis is one of the most widely
recreationally used drugs and consumption is typically initiated during adolescence, it is
important to understand the impact of cannabis use for social and cognitive development
during this time.
Adolescence as a sensitive period for social stress

Adolescents are especially sensitive to the social environment, particularly to the influence of peers. Peers influence risk taking behaviours such as drug use and academic performance [40]. Social stress and social exclusion have a significant impact on adolescents [41], and peer victimization and lack of social support has particularly detrimental effects for mental health [42].

Studying rodents provides the opportunity to manipulate experimentally exposure to social stress, and has provided valuable insights into the deleterious effects of stress in adolescence. Adolescent rats respond differently to social stress compared to adult and juvenile rats [43, 44]. Adolescent rats subjected to repeated defeat by a dominant individual present with different behavioural patterns (more avoidance rather than aggression), and recover less from renewed stress, compared with adult rats. Exposure to stress in adolescence in rats (compared with adulthood) was also associated with less neuronal activation in areas of the prefrontal cortex, cingulate and thalamus [44]. Social deprivation in rats has been shown to have irreversible effects on some aspects of exploratory behaviour, but only if the deprivation occurs between late childhood and mid-adolescence (postnatal day 25-45), but not after 45 days [43]. This early study is also one of the few to investigate plasticity in the juvenile, adolescent and adult period (see textbox ‘Models of plasticity in adolescence’).
Many mental illnesses have their onset in adolescence and early adulthood \([47, 48]\). See Figure 3. A representative, longitudinal study showed that 73.9% of adult cases with a mental disorder have already had a diagnosis before 18 years of age and 50.0% before 15 years of age \([49]\). It is thought that psychiatric disorders may in part be triggered by stress-exposure in childhood or adolescence \([19]\). The experience of acculturation stress by immigrant-origin adolescents in US-American schools, for instance, has been shown to predict longitudinally internalizing symptoms such as depression and anxiety \([50]\).

For psychiatric disorders such as post-traumatic stress disorder (PTSD), stress may persist even if the stressor is no longer present. Fear extinction learning is key for a healthy response to stress and the basis for desensitization treatments for PTSD \([51]\). Fear extinction learning has been found to be attenuated in adolescence as compared to childhood and adulthood – both in humans and in mice \([51]\). The rodent data in the study indicated that a lack of synaptic plasticity in the ventro-medial prefrontal cortex during adolescence is associated with decreased fear extinction.

### Models of plasticity in adolescence

Unless pre-pubertal as well as adult groups are compared to adolescents, the question of whether adolescence is a sensitive period cannot be assessed. There are several possible plasticity profiles \([45, 46]\). Adolescence may be stand-alone period of heightened plasticity in certain domains, before and after which plasticity is lower (Model A, Figure 2). Alternatively, childhood and adolescence might form a continuous sensitive period after which plasticity declines (Model B, Figure 2). A third possibility is that plasticity may decline more or less continuously from childhood through adolescence and into adulthood (Model C, Figure 2). In this case adolescence would not be categorised as a sensitive period even though plasticity is heightened as compared with adulthood.
Adolescence is not a clear-cut period of vulnerability to stress, however. In some cases, adolescent animals may show higher resilience to certain stressors than adults [52] and social stress in adolescence can be buffered if rats are socially housed after exposure to stress [53]. Early and targeted mental health interventions aimed at strengthening resilience and providing support during adolescence may help buffer the effects of social stress and bullying, which may in turn improve life-long mental health outcomes.

Adolescence as a sensitive period for cognitive control and memory
The protracted development in frontal and parietal regions has been linked to changes in cognitive control, including planning [54], measures of executive function and working memory [55]. Mnemonic abilities also generally increase from childhood, through adolescence and into adulthood [56]. Aspects of memory requiring strategic, effortful components are usually found to develop later than those that require less cognitive control [57].

Plasticity in working memory
Working memory (WM), the ability to hold and manipulate information [58], has been shown to undergo changes beyond childhood. While basic aspects of spatial WM may reach maturity in childhood, complex spatial WM abilities continue to improve during early adolescence [55]. WM tasks recruiting frontal areas show protracted development throughout adolescence [59].

There is some evidence for plasticity of WM in development. For children and young adolescents, gains in WM training, but not knowledge-based training, transferred to
improvements in fluid intelligence [60]. Improvements were sustained over a 3-month period during which time no further training was implemented. WM training may also be effective in adolescents with poor executive functioning, as well as in typically-developing controls [61]. However, we do not yet know how effects of training differ in adolescents as compared to children or adults, which limits conclusions for adolescence as a sensitive period for WM.

Memory in adolescence and the reminiscence bump

Memory capacities appear to be heightened in adolescence. The number of autobiographic memories recalled at age 35 or after shows a peak in adolescence, a phenomenon referred to as the reminiscence bump [62]. The lifespan retrieval curve (Figure 4) shows a period of childhood amnesia before around 5 years when autobiographic memories are virtually absent [63]. Memories then increase and reach a maximum between 10 and 30 years, which is followed by a period of fewer recalled memories. Recency effects lead to a better recall of events in the later decades of life. The reminiscence bump is remarkably robust and shows a similar pattern when tested with different mnemonic tests and in different cultures [62, 63].

In addition to autobiographical events, the recall of music, books, films and public events from adolescence is also superior compared with from other periods of life [64, 65]. Even mundane events that happened in adolescence and early adulthood appear to be overrepresented in memory, suggesting that mnemonic capacity is heightened during this time of life [66]. A large-scale study showed a peak of other aspects of memory like verbal and visuospatial memory between 14 and 26 years of age [67].

Future studies are required that manipulate experimentally environmental input in child, adolescent and adult groups. Developmental training studies in which different aged
participants undergo cognitive training and effects are compared to active control groups that receive placebo training may be particularly useful here [68]. Such studies may also directly inform clinical and educational interventions.

Conclusion

Adolescence is a period of protracted brain development that is characterised by gross transformations in white and grey matter that are concomitant with changes in socio-emotional and cognitive processing. The development of some of these processes may be particularly susceptible to environmental influences, such as drugs, social stress or cognitive training, making adolescence a sensitive period of development.

The findings discussed here highlight the importance of adolescent health care and education. It has been estimated that 40% of the world’s teenagers do not have access to secondary school education [69]. Even in countries that have compulsory education, schooling often ends between 14 and 16 years of age [70]. In Western countries, such as the UK or US, much attention and resources have been devoted to early development, sometimes creating the impression that experiences in the first few years of life determine lifelong health, education and social outcomes [71, 72]. This status quo is now changing, however, and heightened awareness is emerging of the importance of later stages in development. A recent WHO report argues for the importance of adolescence for world-wide health [73] and a UK Royal Society report underscored the significance of STEM-subjects education post-16 for the national economy [74].
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The Royal Society
Figure legends

**Figure 1.** The effects of cannabis consumption on IQ in adolescence and adulthood. 1,037 participants were followed from birth to age 38. Cannabis dependence was diagnosed in interviews at ages 18, 21, 26, 32 and 38. The change in IQ from childhood to adulthood is shown here for participants with 1, 2 or 3+ diagnoses of cannabis dependence as a function of onset of cannabis dependence. Black bars represent individuals with adolescent-onset cannabis dependence and grey bars individuals with adult-onset cannabis dependence [25].

**Figure 2.** Models of plasticity in adolescence. Adolescence may be a stand-alone period of heightened plasticity (A) or form a continuous sensitive period with childhood (B). Alternatively, plasticity may decline continuously from childhood through adolescence and into adulthood (C). Adapted from [45, 46].

**Figure 3.** The interquartile ranges of the age of onset (AoO) of selected psychiatric disorders. The AoO data for Schizophrenia Spectrum Diagnosis was adapted from the Early Psychosis Prevention and Intervention Centre in Melbourne, Australia, as reviewed by Kessler et al. [47]. The AoO for the remaining disorders stems from the National Comorbidity Survey Replication in the United States [48].

**Figure 4.** The lifespan retrieval curve. The retrieval curve shows a peak of autobiographical memories around adolescence and early adulthood – the reminiscence bump. Adapted from [62].