Chapter 2
Neurodevelopment During Adolescence

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Puberty is a human neuroendocrinological developmental period (see Table 2.1). Individuals naturally enter puberty during adolescence. Adolescence is defined by the World Health Organisation as the timespan between the ages 10 to 19 years, although research on "young people" often also includes youth aged 15 to 24 years old [1]. The neuroendocrinological developments of puberty are accompanied by rapid physical, psychological and behavioural changes. As a result, health risks and the burden of disease can change rather abruptly [2]. Adolescence is, therefore, a critical brain maturation time with an important impact upon cognition, behaviour, and mental health, which will ultimately influence education, employment, and social outcomes. This makes knowledge of adolescent brain development for health-care professionals treating patients in this age group essential.

The investigation of brain development and maturation in the living human is challenging. To better understand and predict the effects on brain maturation when puberty is disrupted, we first need to have a clear picture of 'typical' brain development during this period. To map the trajectory of brain maturation, sizeable datasets of longitudinal data *in vivo* are needed. Advances in neuroimaging techniques allow

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Table 2.1 Endocrine events in puberty. Sex differences of endocrine events show that pubertal development in females starts on average earlier than in males

Endocrine event	Developmental period	References
Adrenarche: characterized by the increase in adrenal androgens (dehydroepiandrosterone (DHEA), DHEA-sulphites and androstenedione)	In females between 6 and 9 years, in males between 7 and 10 years	[3, 4]
Gonadarche: starting with the reactivation of the gonadotropin-releasing hormone neurons which stimulates the secretion of sex steroid hormones (testosterone and oestrogens) from the gonad	In females between 8 and 14 years (mean age 11), in males between 9 and 15 years (mean age 12)	[5, 6]
Activation of the 'growth axis' resulting in a linear growth spurt	In females around age 12, in males around age 14.	[7, 8]

us to obtain these datasets on a large and safe scale; and with the emergence of Magnetic Resonance Imaging (MRI) in particular, our knowledge of brain maturation has grown exponentially. This technique enables us to quantify structure, function, and neurochemical concentrations non-invasively in the living brain. However, there are many possible neuroimaging indices of neurodevelopment, including measures of neuronal integrity, structural and functional connectivity, or temporal change. This can make comparison between studies complex, and it can be difficult to interpret the underlying biological substrates of MR signals.

In this introduction, we provide an overview of typical neurodevelopment in adolescence based on evidence from MRI research. We further address common morbidities and 'neurodivergence' emerging from atypical neurodevelopment.

Anatomy and Brain Functions

Brain tissue is differentiated into 'relatively unmyelinated' grey matter and 'myelinated' white matter. Grey matter is the major component of the cerebral cortex and subcortical structures. In the deep part of the cerebrum lays the white matter, composed of bundles that connect the different grey matter areas to each other. The cerebrum is divided into four lobes: frontal, parietal, occipital, and temporal (See Table 2.2 for their main functional involvement); and subcortical structures including e.g. amygdala, thalamus, hippocampus, and basal ganglia.

The basal ganglia are a group of subcortical 'nuclei' in the cerebrum comprising the striatum (consisting of the caudate nucleus, nucleus accumbens and putamen), globus pallidus, substantia nigra, and subthalamic nucleus. The basal ganglia have strong connections with the thalamus and cortex and coordinate the signal transmission between these regions. The thalamus makes up a central part of basal ganglia-thalamic-cortical connections [18, 19] and acts as mediator in sensory processing and sleep-arousal state regulation. With the amygdala, essential for emotion processing [20], and the hippocampus a key memory hub (Per [21]), correct signalling across these subcortical-cortical pathways is essential for appropriate behavioural control, movement regulation, and reward processing [22].

Table 2.2 Lobes of the cerebrum

Lobe	Function	References
Frontal lobe	Cognitive and executive functions (e.g. control of voluntary movement or activity)	[9–11]
Parietal lobe	Processing information about temperature, taste, touch, and movement	[12, 13]
Occipital lobe	Processing of visual information	[14, 15]
Temporal lobe	Processing memories and integrating sensations (e.g. smell, taste, sound, sight, touch) in memory	[16, 17]

Neuronal Maturation

Neural Structure

As the brain ages, neurons become more connected and specialized, and their function matures. Neural connections (synapses) undergo modifications in response to the internal and external environment. Synapses are removed in a process called "synaptic pruning" or adapt as a result of long-lasting neuronal activation or inactivation [23]; respectively, long-term potentiation (LTP) or long-term depression (LTD). These mechanisms increase synaptic efficacy and hence the efficiency of connections between brain regions. Myelin sheaths are formed around neuronal axons, which increases the signalling speed from neuron to neuron. Synaptic pruning continues into adolescence [24–26], while neuronal myelination continues even longer, up to the 2nd or 3rd decade of life [27, 28]. When the trajectory of brain maturation is disrupted, the resulting developmental outcomes can be atypical.

Brain Chemistry

Alongside structural maturational changes, neurotransmitter systems undergo alterations throughout development. Neurotransmitters mediate the signal transmission between neurons via a cycle of neurotransmitter 'release > binding > signal generation > reuptake' taking place in the synapse [29]. Functional neurotransmission is essential for synaptic pruning, and synaptic pruning is essential for a healthy neurotransmitter circuitry. Disrupted pruning predominantly impacts upon the glutamatergic neurotransmission system [30], which is the brain's most abundant 'excitatory' neurotransmitter. The GABAergic system, the brain's most abundant 'inhibitory' neurotransmitter, is predominantly comprised of GABAergic interneurons that are critical for the regulation of the glutamatergic system [25]. The interplay of glutamate and GABA, which regulates the 'excitation-inhibition' balance in the brain, is responsible for shaping synaptic and hence network connectivity [31].

There are periods in development which are especially 'sensitive' to influences on neuronal growth; very early childhood is one and adolescence another [32, 33]. Many synaptic changes occur during these sensitive periods, with glutamatergic and GABAergic neurotransmitters essential for delimitation of these time windows. Prior to and after these sensitive periods, synaptic adaptation is limited [25]. During adolescence, glutamatergic and GABAergic systems underpin the maturation of excitation-inhibition balance, but also the endocannabinoid system, which is critical for the regulation of the glutamatergic system, also has a key impact [25]. It has been suggested that not only are adolescents more prone to experimentation with substances because of the maturation status of their brain [34], this experiment may then have a substantial effect on the finely balanced neurochemical processes in the brain needed for behaviour control. For example, this age group shows a particular 'sensitivity' to THC, an active compound of cannabis [32]. THC transiently disturbs the endocannabinoid neurotransmitters system and its regulation of glutamate and GABA release. As a result, the maturation of (predominantly frontal) neural circuitries may be affected adversely [32]. Increasing the sensitivity of the brain further [25]. This may lead to more experimentation (i.e. with substances) and subsequently more harm (i.e. neural damage), spiralling into a vicious circle of disrupted neuronal maturation.

Brain Volumetric Changes

Timing and Time Course

The greatest expansion in brain size occurs during pregnancy up to 2 years after birth [24, 35]. Brain growth continues and reaches a peak in adolescence [36]. On average, puberty happens earlier in females compared to males [37]. This is also the case for brain maturation during adolescence; onset is in females at around 10.5 years and later in males at 14.5 years of age on average. [38].

The same pattern is observed for grey matter volume (in frontal and parietal cortices); peaking in females at 11 years and in males at 12 years of age [38, 39]. This peak thus coincides with gonadarche in each sex, suggesting a possible interaction between grey matter development and levels of sex steroid hormones. (Further explained in section "sex-steroid hormones and brain development") Subsequently, grey matter volume declines throughout and after adolescence. This decline is thought to be the result of ongoing synaptic pruning [38], which has been shown to have a direct effect on (reducing) grey matter volume [40].

In contrast, white matter volume increases over the course of childhood throughout adolescence [41, 42], reaching its peak during the 4th decade of life [43]. During adolescence, the volume of white matter in many different tracts (e.g. association tracts) and brain regions (e.g. callosum, putamen, caudate) increases [44–46]. This volume increase has been attributed to ongoing axonal myelination [47] or axonal

enlargement [48]. The sharp increase in white matter volume seen in males is thought to be largely explained by axonal enlargement, which is directly testosterone-related. Studies using diffusion MRI, a technique capable of measuring white matter microstructure (e.g. structural organisation and density), confirm this white matter volume increase in adolescent males is accompanied by advancing (micro) structural organisation and myelination density over the course of adolescence [44, 49, 50]. This maturation trajectory of white matter microstructure is more prolonged in males—*for a review* [27]. Thus, for both grey and white matter, maturation during adolescence peaks on average later in males [37].

In sum, the maturational trajectories of grey matter and white matter in both sexes go hand-in-hand up to adolescence, but deflect in different directions thereafter [51]. Total volume of grey matter in both sexes peaks in mid-childhood to early adolescence and then decreases along with cortical thickness in a U-shaped developmental trajectory [52] *for a review*—[27]. White matter volume expands, and microstructure matures throughout adolescence, but this trajectory is extended in adolescent males compared to females.

It is very important to note that most of the findings of sex differences in the timing of brain changes reported during adolescence were not controlled for 'pubertal timing'. Although it has been assumed that the timing of neuronal maturational changes is linked to the timing of puberty, this has not always been directly examined. In those studies that do control for pubertal timing, there are inconsistencies in approach [53–55]. It is generally accepted that the trajectory of brain maturation in adolescence may be influenced by both pubertal development stage (e.g. Tanner stage,[1] pubertal development score[2]) and related endocrinological changes [51]. However, a recent review highlights a role for additional components of brain development during adolescence, such as the intra-individual 'tempo' of pubertal development and the temporal dynamics of hormone levels, and these can be overlooked when focussing on 'coarse' descriptions of stages or levels [51].

Sex Differentiation

As noted above, sex influences bulk measures of brain; indeed across development, females have smaller average brains than males relative to body size—*for a review* [56]. However, throughout development, sex also has differential impact at a brain regional level. To illustrate; for cortical grey matter, cortical thinning in adolescent males occurs predominantly in the limbic (posterior cingulate), prefrontal (Megan M. [57]) and parietal cortices [58]. Whereas in adolescent females, the most

[1] Tanner stages are divided into five sexual maturation stages, from the pre-pubertal form to the adult form. The Tanner scale provides a rating of sexual maturity [87].

[2] Pubertal development score (PDS) is a self-report measure of pubertal status for young adolescents [88].

pronounced volumetric changes are seen in the parietal (somatosensory) [59], limbic [58], and temporal [57] cortices.

Sexually dimorphic development also occurs in subcortical grey matter. Similar to the cortex, the volumes of the amygdala and thalamus are significantly smaller in adolescent females compared to males [60–62]. In addition, amygdala volume becomes even smaller over the course of puberty in females, whereas it gets larger in males [58]—*for a review* [51]. In contrast, volumes of the basal ganglia and hippocampus are disproportionately larger in adolescent females compared to males [60], but their volumes subsequently increase in females (hippocampus) and decrease in males (basal ganglia) [38, 58]. Precisely how these sex differences in brain regional growth link to cognition, emotion and behaviour in the sexes is not yet understood.

To conclude, cortical and subcortical grey matter exhibit sexually dimorphic volumetric trajectories. For subcortical structures, volume differences between the sexes increase throughout adolescence (Megan M. [63]). It is suggested that the observed dimorphism may be underpinned by a sex-specific propensity for change among these brain regions. Yet we should be cautious before fully accepting that there are very strong sex differences in specific brain regions [51]. There are subtleties we likely do not appreciate, and again, pubertal development stage and/or "tempo" (further explained in section "timing and time course") is thought to impact on neurodevelopment sometimes more than sex per se [51].

Sex-steroid Hormones and Brain Development

Sex steroid hormones are produced by the gonads and adrenal glands and include androgens (e.g. testosterone, dehydroepiandrosterone (DHEA)), oestrogens (e.g. oestradiol), and progestogens. During the perinatal period, the first time window for steroid-dependent changes in neural organisation, these hormones produce sexually differentiated brain circuits [64, 65]. Gonadarche signals the second time window for steroid-dependent changes in neural organisation [66]. Sex steroids cause irreversible structural changes to neuronal systems called "organisational effects". The time windows for these effects to have an impact are limited to sensitive periods for neuronal plasticity (e.g. perinatal, puberty)—*for a review* [51]. Sex steroids can also have 'activational effects' which instead lead to temporary changes in the activity of the neural systems [67]. (Further explained in section "Functional changes".)

It is important to note that different sex steroids play a role in different periods of adolescent development. Testosterone is implicated in late pubertal stages in males only, whereas its 'pro-hormone' DHEA is involved in early puberty in both males and females [68, 69]. Equally, each sex steroid has a distinct pattern of association with structural brain development. Rising testosterone levels are associated with grey matter volume reduction (i.e. cortical thinning) and structural changes in white matter [50, 55, 70]. These effects are most pronounced in males, as is the rise/levels of testosterone across puberty [71]. Less consistent associations are found for

oestradiol levels, although higher oestradiol levels may limit cortical thinning in females [51, 55]. These results indicate that sex steroids relate to sex-specific changes in cortical development across adolescence [57].

Non-steroid hormones (e.g. cortisol, luteinizing hormone) also play a role in pubertal development and may affect the neurodevelopment during adolescence. However, it is beyond the scope of the present review to discuss these further here.

Functional Changes

There is broad agreement that the sensitive period for neuroplastic changes in the brain extends into adolescence [32, 66]. Such changes in neural structure can impact upon functional neural networks such as the social, emotional, and higher-order cognition networks [25, 67]. All of these higher-order networks incorporate the frontal cortex and its targets, and frontal functional maturation continues until or after late adolescence [72, 73]. This predominantly frontal functional maturation can partly explain the wide variations in behaviour seen in this age group. That is, because the frontal lobe contributes to a multiplicity of higher-order processes, frontal maturational changes across adolescence are reflected in marked alterations (and variations) in cognition and behaviour. We present below a brief sample of the neurodevelopmental changes occurring in adolescence that underly some of these behaviours.

Social Cognitive Emotions

The prefrontal and temporal cortical regions associated with emotional processing become gradually more active over the course of adolescent development [74]. Similarly, subcortical brain structures that support emotional processing (i.e. amygdala and ventral striatum) show increasing neural activity by the middle of adolescence [75, 76]. Overall, neural activation during emotional processing increases with advancing metrics of pubertal development. A recent meta-analysis concludes that with advancing pubertal development, processing social information improves [76].

Reward Processing

Nucleus accumbens (striatum) activation is associated with reward processing (e.g. winning in a gambling task). The level of brain activation of the nucleus accumbens during reward-processing peaks by mid-adolescence [77]. This heightened activity

is linearly associated with (saliva) testosterone concentration [78]. These findings are in line with the increase of testosterone levels toward later pubertal stages.

However, despite the relatively large amount of literature focussing on the nucleus accumbens with regards to reward processing, a recent meta-analysis concludes "no convergence" in region or directionality [76]. Note that this is possibly due to the meta-analytical method used, which attaches equal weight to each finding regardless of, for example, sample size in a study. Thus, one should be cautious with the generalization of findings, even from meta-analyses.

Emotional Faces

Facial recognition improves steadily during the first decade of life but shows a decline around age 12 [79]. Specifically, young adolescents (10–11 years in females and 11–12 years in males) seem to have more difficulty with the recognition of emotion-expression, but their abilities improve/return to prepuberty levels by age 16–17 [80]. This has been suggested to be caused by a temporary relative inefficiency in frontal circuitry prior to the pruning of excess (mostly glutamatergic) synaptic contacts [80]. Recent meta-analysis also suggests changes in amygdala activation during face processing are associated with pubertal development [76], though the directionality of the neural activation changes are inconsistent across the constituent studies.

Key Findings

While we have a lot to learn about brain maturation during adolescence, there is reasonable consensus that the following key changes occur:

- Total brain volume peaks in early/mid-adolescence and declines thereafter. This decline is thought to be a result from ongoing neural pruning, which ultimately decreases grey matter volume.

Sex differences: The average age for total brain volume to decline is 4 years later in males than females. The 'deflection point' of increasing difference in total brain volume between males and females is probably a result of the later decline in grey matter volume in males, and continuous increase in white matter volumes that is augmented in males compared to females.

- Total grey matter volume peaks in early adolescence and declines thereafter.

Sex differences: Throughout adolescence, thinning of cortical grey matter is more pronounced in males. This is associated with the exponential increase in testosterone levels in males—showing a positive correlation with cortical thinning, and the exponential increase in oestradiol in females—showing a negative correlation with

cortical thinning [55]. There are differences in grey matter maturation among subcortical structures. Amygdala and thalamus volumes are smaller in adolescent females and decreasing throughout adolescence in females only, whereas the basal ganglia and hippocampus grey matter volumes are smaller in males and decreasing in males only. These structure-dependent sex differentiations are thought to have clinical relevance, considering the involvement of these structures in 'gender-disparate' mental health conditions. For instance, affective disorders (e.g. mood and anxiety disorders) incidence increases sharply in females toward late adolescence and beyond [81–83]. These disorders are known for the implication of the amygdala [84]. This can be linked with the findings of smaller volumes in adolescent females compared to males, which decreases in females away from the volumes found in males.

- Total white matter volume rises during childhood and continues to increase throughout adolescence.

Sex differences: The increase in white matter volume throughout adolescence is augmented in males compared to females. This is thought to be potentially a result of testosterone-related changes to myelinated axons, which predominantly occur in males [48].

- The microstructure of white matter shows increasing organisational maturation during adolescence and a growing myelination density.

Longitudinal studies have contributed to the investigation of potential sex differences in the 'timing' of neurodevelopmental changes during adolescence. Overall, these studies report that indices of neural maturation occur later in males compared to females. However, the findings of sex differentiation are controversial and may be better explained by the generally *later onset* and *longer* pubertal period in males. One explanation for this sex difference could be that different sex steroids affect different brain regions. This has clinical implications because it means that different sexes have a different predisposition for mental health conditions or the development of psychological problems. For example, the (predominantly male) increase in testosterone levels over the course of puberty are positively correlated with nucleus accumbens (part of the basal ganglia/striatum) activation during reward-processing [78]. This suggests that adolescent males may be relatively more responsive to rewards than females. In turn, it is possible that sex-difference in accumbens development in adolescence contributes to, and increase, in risk-seeking behaviours observed mostly in male teens. Adolescents also have an elevated risk for experimentation with substances (i.e. cannabis) as well as an increased vulnerability for neuronal changes during this development period [34]. There is suggested that the increase of sex steroids (both testosterone and oestradiol) in adolescence is associated with increased vulnerability for neurobiological changes during this period [85]. There is a clear sex differentiation, however, concerning the timing of onset, which is typically between 15 and 25 years old, compared to two onset peaks in females at 20 to 29 years, and 45 to 49 years old [86]. Ultimately, the use of substances may lead to the development of mental health conditions (i.e. psychosis or

schizophrenia), depending on the dose used, the exact time window, and the duration of exposure [32]. It is extremely important to supervise the adolescent patient population closely in order to minimize these risks and provide adapted care.

Conclusion

The rising levels of pubertal sex-steroid hormones induce a period of increased neuroplastic sensitivity in the adolescent brain [51, 66]. Neural pruning [24], myelination [27], and maturation of neural circuitries continue into adolescence [66]. With the induction of the 'sensitive' period during adolescence, these processes become more susceptible to influence or disruption. Functional neurochemical systems, and especially the glutamatergic and GABAergic systems [30], which are key regulators of the excitation-inhibition balance in the brain, are essential for delimitation of the 'sensitive' time window in adolescence [25]. An excitation-inhibition imbalance can compromise the maturation of grey and white matter tissue. Thus, physical conditions which disrupt the sex-steroid hormone axis and/or influence brain biochemistry and hence neurotransmitter levels may well have an important impact on the neurodevelopmental trajectory of adolescence. This trajectory provides the foundations for psychological development and shapes adult outcomes, as described in the next chapter.

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