2 The Anatomical, Hormonal and Neurochemical Changes that Occur During Brain Development in Adolescents and Young Adults

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Case Study

At age 17, Jessica Platt was admitted to an adult ward in a UK hospital with an illness requiring admission for some days. She was distressed by the lack of understanding staff appeared to have of her situation. She undertook her own research and wrote a pamphlet. One of its pages is reproduced here; note especially the clarity of the middle paragraph Fig. 2.1.

The full pamphlet and background are available at: https://sites.google.com/site/yphsig/networking/the-blog/participationinactionteensinhospital. Reprinted with permission from Jessica Platt.

Fig. 2.1 Adolescent Brain Pamphlet

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Anatomical, Hormonal and Neurochemical Changes

By age 6 years, the brain is at 95% of its peak volume [2]. Total cerebral volume peaks at 14.5 years in males and 11.5 years in females.

Cortical Grey Matter

Grey matter consists of neurones, synapses and unmyelinated axons. In the adolescent brain, there is a gradual increase in grey matter followed by reduction—the so-called inverted U [2, 3]. The sensory and motor regions mature first, followed by the remainder of the cortex, which follows a posterior to anterior loss of grey matter with the last area to change being the superior temporal cortex (Fig. 2.2) [2]. Histological studies, mainly in animals, show that there is a massive synaptic proliferation in the prefrontal area in early adolescence, followed by a plateau phase and subsequent reduction and reorganisation. Longitudinal imaging studies in humans have recently confirmed histological studies. It is the rarely used synaptic connections that are assumed to be pruned, leading to a more efficient and specialised brain [3, 4]. This prefrontal region is the site of executive control of short- and long-term planning, emotional regulation, decision-making, multi-tasking, self-awareness, impulse control and reflective thought (see Table 2.1, below). It is important to realise that when the posterior cortices for vision and sensory-motor control are approaching the end of their inverted U trajectories at about age 10–13 years (i.e. synaptic proliferation stopped some time ago and pruning is almost complete), the prefrontal cortex is still in a state of massive synaptic proliferation.

Table 2.1 Prefrontal cortex functions

The prefrontal cortex is the site of:
• Executive control of short- and long-term planning
• Emotional regulation
• Decision-making
• Multi-tasking
• Self-awareness
• Impulse control
• Reflective thought

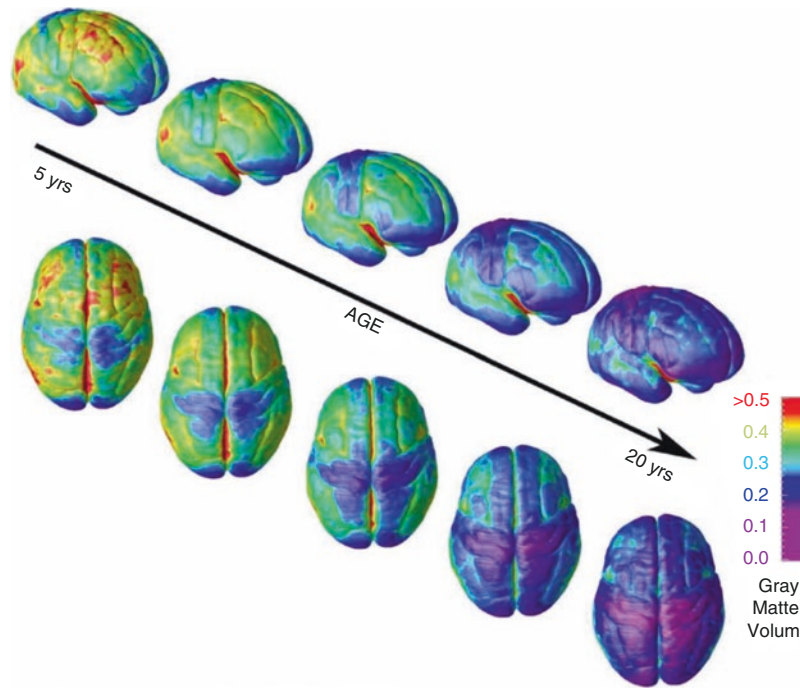

Fig. 2.2 Right lateral and top views of the dynamic sequence of grey matter maturation over the cortical surface. The side bar shows a colour representation in units of grey matter volume. Fifty-two scans from thirteen subjects each scanned four times at approximately 2-year intervals. Reprinted with permission from [2]

Sub-Cortical Grey Matter

The basal ganglia or nuclei are the striatum (caudate nucleus and putamen), ventral striatum (nucleus accumbens), globus pallidus, subthalamic nucleus and substantia nigra. These nuclei are involved in transmission circuits which control movement and higher-order cognitive and emotional functioning. The limbic system, consisting of the hippocampus, amygdala, septic nuclei and limbic lobe, is closely involved in emotional regulation, reward processing, appetite and pleasure seeking.

Due to their small size, accurate visualisation of these regions is more difficult than for cortical grey matter; however, the caudate nucleus follows a similar 'inverted U' shape trajectory and limbic structures develop sooner than the basal ganglia [2].

White Matter

White matter tracts between the prefrontal cortex and subcortical structures develop in a steady but non-linear manner [1], with more rapid development of functional tracts in early adolescence and levelling off in young adulthood. The changes reflect a mixture of ongoing myelination and increased axonal diameter. In contrast to grey matter changes, the white matter increases occur in all lobes of the brain simultaneously [5, 6]. Recent studies, using diffusion tensor imaging, show that this increase in myelination and axon density in white matter tracts between the prefrontal cortex and basal ganglia continues to develop throughout adolescence [1, 7].

Pubertal Hormones

Grey matter changes in the same sequence in boys and girls, but girls' grey matter peaks about 1 year before that of boys [8]. This difference corresponds with pubertal maturity, suggesting brain development and puberty may be interrelated [9]. The behavioural changes of adolescence correspond to the timing of puberty, not chronological age, as do the gender differences in mental health problems such as depression.

Although there are many associations between pubertal hormone levels, behaviours and grey and white matter changes, it is difficult to know if these are causative. Studies need first to control for age, sex and onset of puberty before examining if there are residual associations with pubertal hormone levels. Until recently the causal effects of pubertal hormones on brain structure and function were thought to occur only in the perinatal and late gestation periods; effects in adolescence were thought at most to sensitise certain brain structures. However, recent developments in the field are challenging this view and are reviewed by Schulz [10]. Studies in rodent models suggest there might be a causal link. Studies which involve castration or oophorectomy at various ages and injection of pubertal hormones show that sexually dimorphic (i.e. different in male and female) behaviours are influenced by the presence of pubertal hormones during adolescence, whether these come from the gonad or are administered by injection [10]. Further, there is evidence of sexual dimorphism in aspects of brain structure maturation in the limbic, basal ganglia and frontal cortex systems [10]. Extrapolated to humans, this might indicate the pubertal hormones determine to some extent the patterns of adolescent brain maturation, rather than just facilitating changes generated independently. There is now some evidence for this in humans. Striatal volumes are unrelated to puberty stage or testosterone level, but larger grey matter volumes in the limbic system in both sexes are associated with later stages of puberty and higher levels of circulating testosterone. The sensitivity of the limbic system to testosterone is sexually dimorphic, and this may be responsible for the greater risk of anxiety and depression in girls [11]. There are also associations between white matter microstructure and sex and pubertal level—and a small residual effect of pubertal hormones [12].

Neurotransmitters

Dopamine is the neurotransmitter involved in priming and firing reward-seeking circuits and in reinforcing learning. There are two significant

dopaminergic pathways, the mesolimbic from the midbrain to the limbic structures and the mesocortical from the midbrain to the frontal cortex [13]. Both primates and rodents exhibit increases in functionally available dopamine during adolescence as compared to other life periods and the brain's sensitivity to dopamine [14]. Dopamine receptors increase in the striatum and prefrontal cortex in adolescence and then decline, but this is not due to underlying pubertal hormone levels [15]. This elevation of dopamine levels affects the efficiency with which synaptic signalling can regulate behaviour in an adaptive manner. The neuro-circuitry of reward seeking is thought to be determined by dopamine signals received by the nucleus accumbens [14, 16].

Oxytocin is the hormone commonly known for its role in a variety of social behaviours, including social bonding in maternal behaviour and hostility to those outside a person's core social group [17]. Oxytocin can also act as a neurotransmitter and may play an important role during adolescence [18]. Pubertal hormone levels are strongly correlated with oxytocin-mediated neurotransmission in the limbic areas [19, 20] where there is proliferation of oxytocin receptors during adolescence. These changes in oxytocin transmission may explain why adolescents show heightened responses to emotional stimuli in comparison to children and adults [21].

Endocannabinoids are substances produced from within the body that activate cannabinoid receptors. Although endocannabinoids are intercellular signallers, they differ in numerous ways from dopamine. For instance, they use retrograde signalling between neurons. This allows the postsynaptic cell to control its own incoming synaptic traffic. The ultimate effect on transmission depends on the nature of the more conventional anterograde transmission by other neurotransmitters. So, as is often the case when the anterograde excitatory neurotransmitter is dopamine, the retrograde signalling by the endocannabinoids exercises inhibitory modulation. This is a relatively new field of enquiry which is likely to influence how we understand the development of emotional behaviour [22, 23].

Summary

New imaging techniques show unequivocal changes in the white and grey matter of the brain which take place between 11 and 25 years of age and increased dopaminergic activity in the prefrontal cortices, the striatum and limbic system and the pathways linking them. The brain is dynamic, with some areas developing faster and becoming more dominant until other areas catch up. These changes represent a period of 'pruning, re-wiring and insulation' that sees predominant neural circuits surviving and becoming more efficient. This happens first in primary systems (such as motor and sensory) in early adolescence, with executive systems (memory, planning, emotional regulation, decision-making and behavioural inhibition) only maturing in young adulthood. Broadly, changes start in **functional units** of the brain (such as limbic system, basal ganglia, prefrontal cortex) and progress to changes in **functional networks** as white matter steadily increases. Changes in the neurotransmitters and their receptors, especially dopamine, facilitate these processes. The importance of pubertal hormones in brain maturation is still uncertain. These points are summarised in Table 2.2.

Plausible mechanisms link these changes to the cognitive and behavioural features of adolescence. The changing brain may generate abrupt behavioural change with the attendant risks; but it also produces a brain which is flexible and able to respond quickly and imaginatively. Ideally, the young person's immediate environment and wider society set a context that allows adolescent exuberance and creativity to be bounded in relative safety, thus allowing them to experiment and explore the opportunities available to them, in order to develop their sense of self and make decisions about their future. Whilst these changes apply to all young people, there are additional

Table 2.2 The adolescent brain—all you need to know

• It is certain that the brain changes much during adolescence
• The changes continue from 11 to 25 years
• Pubertal hormones are probably not the main determinant of change

challenges for young people with chronic illness and disability in the context of their transition to adulthood, who need to learn to manage their health condition during this dynamic phase of life. Further, their health care providers need to understand how to facilitate this.

References

1. Lebel C, Beaulieu C. Longitudinal development of human brain wiring continues from childhood into adulthood. J Neurosci. 2011;31(30):10937–47.
2. Lenroot RK, Giedd JN. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev. 2006;30(6):718–29. PubMed PMID: WOS:000241208800002. English.
3. Casey BJ, Jones RM, Hare TA. The adolescent brain. Ann N Y Acad Sci. 2008;1124:111–26. PubMed PMID: 18400927. Pubmed Central PMCID: 2475802.
4. Giedd JN. The teen brain: insights from neuroimaging. J Adolesc Health. 2008;42(4):335–43.
5. Giedd JN, Castellanos FX, Rajapakse JC, Kaysen D, Vaituzis AC, Vauss YC, et al. Cerebral MRI of human brain development—ages 4–18. Biol Psychiatry. 1995;37:657.
6. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. Nat Neurosci. 2003;6(3):309–15. PubMed PMID: 12548289.
7. Hasan KM, Sankar A, Halphen C, Kramer LA, Brandt ME, Juranek J, et al. Development and organization of the human brain tissue compartments across the lifespan using diffusion tensor imaging. Neuroreport. 2007;18(16):1735–9. PubMed PMID: WOS:000250329300020. English.
8. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci. 1999;2(10):861–3. PubMed PMID: 10491603.
9. Blakemore SJ, Burnett S, Dahl RE. The role of puberty in the developing adolescent brain. Hum Brain Mapp. 2010;31(6):926–33. PubMed PMID: 20496383. Pubmed Central PMCID: 3410522.
10. Schulz KM, Sisk CL. The organizing actions of adolescent gonadal steroid hormones on brain and behavioral development. Neurosci Biobehav Rev. 2016;70:148–58. PubMed PMID: 27497718. Pubmed Central PMCID: PMC5074860.
11. Neufang S, Specht K, Hausmann M, Gunturkun O, Herpertz-Dahlmann B, Fink GR, et al. Sex differences and the impact of steroid hormones on the developing human brain. Cereb Cortex. 2009;19(2):464–73. PubMed PMID: WOS:000262518800021. English.
12. Herting MM, Maxwell EC, Irvine C, Nagel BJ. The impact of sex, puberty, and hormones on white matter microstructure in adolescents. Cereb Cortex. 2012;22(9):1979–92. PubMed PMID: 22002939. Pubmed Central PMCID: PMC3412439.
13. Wahlstrom D, Collins P, White T, Luciana M. Developmental changes in dopamine neurotransmission in adolescence: behavioral implications and issues in assessment. Brain Cogn. 2010;72(1):146–59. PubMed PMID: 19944514. Pubmed Central PMCID: PMC2815132.
14. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Rev. 1998;28(3):309–69. PubMed PMID: WOS:000078202000003. English.
15. Andersen SL, Thompson AP, Krenzel E, Teicher MH. Pubertal changes in gonadal hormones do not underlie adolescent dopamine receptor overproduction. Psychoneuroendocrinology. 2002;27(6):683–91.
16. Braams BR, van Duijvenvoorde AC, Peper JS, Crone EA. Longitudinal changes in adolescent risk-taking: a comprehensive study of neural responses to rewards, pubertal development, and risk-taking behavior. J Neurosci. 2015;35(18):7226–38. PubMed PMID: 25948271.
17. Insel TR, Fernald RD. How the brain processes social information: searching for the social brain. Annu Rev Neurosci. 2004;27:697–722. PubMed PMID: 15217348.
18. Sannino S, Chini B, Grinevich V. Lifespan oxytocin signaling: maturation, flexibility, and stability in newborn, adolescent, and aged brain. Dev Neurobiol. 2017;77(2):158–68. PubMed PMID: 27603523.
19. Chibbar R, Toma JG, Mitchell BF, Miller FD. Regulation of neural oxytocin gene expression by gonadal steroids in pubertal rats. Mol Endocrinol. 1990;4(12):2030–8. PubMed PMID: 2082196.
20. Insel T, Young L, Witt D, Crews D. Gonadal steroids have paradoxical effects on brain oxytocin receptors. J Neuroendocrinol. 1993;27:697–722.
21. Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, Siddhanti S, et al. Oxytocin modulates neural circuitry for social cognition and fear in humans. J Neurosci. 2005;25(49):11489–93. PubMed PMID: 16339042.
22. Lee TT, Gorzalka BB. Evidence for a role of adolescent Endocannabinoid signaling in regulating HPA Axis stress Responsivity and emotional behavior development. Int Rev Neurobiol. 2015;125:49–84. PubMed PMID: 26638764.
23. Vanderschuren LJ, Achterberg EJ, Trezza V. The neurobiology of social play and its rewarding value in rats. Neurosci Biobehav Rev. 2016;70:86–105. PubMed PMID: 27587003. Pubmed Central PMCID: PMC5074863.