Theme Set 1: Human brains experience structural changes throughout life. The adolescent brain undergoes development in the frontal cortex (in addition to other areas that carry out higher order functions). One major structural change in the adolescent brain is the decrease of grey matter and increase of white matter.

1. Experiments on animals, starting in the 1950s, showed that sensory regions of the brain go through sensitive periods soon after birth, during which time environmental stimulation appears to be crucial for normal brain development and for normal perceptual development to occur. These experiments suggested the human brain might be susceptible to the same sensitive periods in early development. Indeed, later experiments demonstrated sensitive periods in the first year of life for sensory capacities such as sound categorization. Based on these experiments, the idea that the human brain may continue to undergo substantial change after early sensitive periods seemed unlikely.

2. It was not until the late 1960s and 1970s that research on post-mortem human brains revealed that some brain areas, in particular the prefrontal cortex, continue to develop well beyond early childhood. Studies carried out in the 1970s and 1980s demonstrated that the structure of the prefrontal cortex undergoes significant changes during puberty and adolescence.

3. An adult brain has about 100 billion neurons; at birth the brain has only slightly fewer neurons. Recent structural volumetric studies have found that the dorsolateral prefrontal cortex does not reach its full volume until the early twenties.

4. Until recently, the structure of the human brain could be studied only after death. The scarcity of post-mortem child and adolescent brains meant that knowledge of the adolescent brain was extremely scanty. Nowadays, non-invasive brain imaging techniques, particularly Magnetic Resonance Imaging (MRI), can produce detailed three-dimensional images of the living human brain. Since the advent of MRI, a number of brain imaging studies have provided further evidence of the ongoing maturation of the frontal cortex into adolescence and even into adulthood.

5. Several MRI studies have been performed to investigate the development of the structure of the brain during childhood and adolescence in humans. One of the most consistent findings from these MRI studies is that there is a steady increase in white matter in certain brain regions during childhood and adolescence. In one MRI study, a group of children whose average age was 9 years, and a group of adolescents whose average age was 14, were scanned. This study revealed differences in the density of white and grey matter between the brains at the two age groups. The results showed a higher volume of white matter in the frontal cortex and parietal cortex in the older children than in the younger group. The younger group, by contrast, had a higher volume of grey matter in the same regions.

6. Giedd et al. performed a longitudinal MRI study on 145 healthy boys and girls ranging in age from about 4 to 22 years. At least one scan was obtained from each of 145 subjects (89 were male). Scans were acquired at two-year intervals for 65 of these subjects who
had at least two scans, 30 who had at least three scans, two who had at least four scans and one who had five scans. Individual growth patterns revealed grey matter development during adolescence. Changes in the frontal and parietal regions were similarly pronounced. The volume of grey matter in the frontal lobe increased during pre-adolescence with a peak occurring at around 12 years for males and 11 years for females. This was followed by a decline during post-adolescence. Additional studies have shown that, at puberty, grey matter volume in the frontal lobe reaches a peak, followed by a plateau after puberty and then a decline throughout adolescence continuing until early adulthood.

Theme Set 2: During adolescence, neurons in the frontal cortex undergo myelination and a reorganization of synapses. The number of synapses increases prior to adolescence and synaptic pruning occurs throughout adolescence based on experience.

7. Whereas sensory and motor brain regions become fully myelinated in the first few years of life, although the volume of brain tissue remains stable, axons in the frontal cortex continue to be myelinated well into adolescence.

8. The first demonstration of synaptogenesis was in 1975, when it was found that in the cat visual system the number of synapses per neuron first increases rapidly and then gradually decreases to mature levels. Further research carried out in rhesus monkeys demonstrated that synaptic densities reach maximal levels two to four months after birth, after which time pruning begins. Synaptic densities gradually decline to adult levels at around 3 years, around the time monkeys reach sexual maturity. However, synaptogenesis and synaptic pruning in the prefrontal cortex have a rather different time course. Histological studies of monkey and human prefrontal cortex have shown that there is a proliferation of synapses in the subgranular layers of the prefrontal cortex during childhood and again at puberty, followed by a plateau phase and a subsequent elimination and reorganization of prefrontal synaptic connections after puberty.
10. Synaptic pruning is believed to be essential for the fine-tuning of functional networks of brain tissue, rendering the remaining synaptic circuits more efficient. Synaptic pruning is thought to underlie sound categorization, for example. Learning one’s own language initially requires categorizing the sounds that make up language. New-born babies are able to distinguish between all speech sounds. Sound organization is determined by the sounds in a baby’s environment in the first 12 months of life – by the end of their first year babies lose the ability to distinguish between sounds to which they are not exposed. For example, the ability to distinguish certain speech sounds depends on being exposed to those distinct sounds in early development. Before about 12 months of age babies brought up in the USA can detect the difference between certain sounds common in the Hindi language, which after 12 months they cannot distinguish. In contrast babies brought up hearing the Hindi language at the same age become even better at hearing this distinction because they are exposed to these sounds in their language. This fine-tuning of sound categorization is thought to rely on the pruning of synapses in sensory areas involved in processing sound.

11. The corpus callosum has also been found to undergo region-specific growth during adolescence and up until the mid-twenties.

12. Researchers analyzed the brain images of 111 children and adolescents aged between 4 and 17 years, and noted an increase in white matter specifically in the right internal capsule and left arcuate fasciculus. Thus the increase in white matter in this region was interpreted as reflecting increased connections between the speech regions.
Excerpts and Themes

Theme Set 3: Inhibition of response and impulse control are key components of executive functions mediated by the frontal cortex. These abilities increase during development possibly due to development of brain structures that link the frontal cortex to the basal ganglion. As these connections increase, the frontal cortex is more able to control the functioning of other parts of the brain.

13. A 10–20% increase in reaction time on the match-to-sample task occurred at the onset of puberty in the 10–11-year-old group of girls and in the 11–12-year-old group of boys, compared to the previous year group of each sex (age 9–10 and 10–11 in girls and boys, respectively) [graph not transferrable]

14. A popular paradigm for studying inhibition is the Go/No-Go task, which involves inhibiting a response when a certain stimulus is shown. In one fMRI study that employed a version of this task, a group of children (7–12 years old) and young adults (21–24 years old) were presented with a series of alphabetic letters and were required to press a button upon seeing each one, except when the letter X appeared. Volunteers were instructed to refrain from pressing any buttons if they saw the letter ‘X’ – the No-Go stimulus. This task requires executive action: the command to inhibit a habitual response. The results showed that in both children and adults, several regions in the frontal cortex, including the anterior cingulate, orbitofrontal cortex and sections of the frontal gyri, were activated during the No-Go task. While the location of activation was essentially the same for both age groups, there was a significantly higher volume of prefrontal activation and lower behavioral response in children than in adults, specifically in the dorsolateral prefrontal cortex and extending into the cingulate. By contrast, adults showed more activity in the orbitofrontal region of the prefrontal cortex and better task performance.

15. To substantiate speculations about brain activation during inhibition during the transition between childhood and adulthood, the study was replicated with a wider age range of participants. In the second study, the same Go/No-Go task was used but participants included children as well as adolescents – this time, subjects ranged in age from 8 to 20 years old. While there was no difference in accuracy on the task with age, reaction times to inhibit responses successfully significantly decreased with age. fMRI data revealed age-related increases in activation in the left inferior frontal gyrus extending to the orbitofrontal cortex and age-related decreases in activation in both the left superior and middle frontal gyrus extending to the cingulate.

16. One recent study examined the association between white matter organization, as measured by DTI, and impulse control in both boys and girls. This investigation found that DTI values correlated most strongly with self-report measures of impulse control in male subjects whereas they correlated most strongly with cognitive measures of inhibitory control in female subjects. These findings support a relationship between changes in white matter microstructure and impulse control during development.

17. A cornerstone of cognitive development is the ability to suppress inappropriate thoughts and actions in favor of goal-directed ones, especially in the presence of compelling incentives. A number of classic developmental studies have shown that this ability
develops throughout childhood and adolescence. Thus goal-directed behavior requires the control of impulses or delay of gratification for optimization of outcomes and this ability appears to mature across childhood and adolescence. Specifically, a review of the literature suggests that impulsivity diminishes with age across childhood and adolescence and is associated with protracted development of the prefrontal cortex, although there are differences in the degree to which a given individual is impulsive or not, regardless of age.

18. Liston et al. (2005) have shown that white matter tracts between prefrontal-basal ganglia and -posterior fiber tracts continue to develop across childhood into adulthood, but only those tracts between the prefrontal cortex and basal ganglia are correlated with impulse control, as measured by performance on a Go/No-Go task. The prefrontal fiber tracts were defined by regions of interests identified in a fMRI study using the same task. Across both developmental DTI studies, fiber tract measures were correlated with development, but specificity of particular fiber tracts with cognitive performance were shown by dissociating the particular tract or cognitive ability.

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Theme Set 4: The amygdala is implicated in emotional responses. During adolescence the connections between the frontal cortex and the amygdala are still developing therefore there is less regulation of amygdala function. At the same time, adolescents might feel less positive affect from positive outcomes, therefore their reward structures might be changing and they might require different types of activities to feel the same level of happiness as they did in childhood.

19. In a recent study a group of adolescents (aged 7 to 17) and a group of adults (aged 25–36) viewed faces showing certain emotional expressions. While viewing faces with fearful emotional expressions, adolescents exhibited greater activation than adults of the amygdala, orbitofrontal cortex and anterior cingulate. When subjects were asked to switch their attention between a salient emotional property of the face, like thinking about how afraid it makes them feel, and a non-emotional property, such as how wide the nose is, adults, but not adolescents, selectively engaged and disengaged the orbitofrontal cortex. These fMRI results suggest that both the brain’s emotion processing and cognitive appraisal systems develop during adolescence.

20. Killgore, Oki, and Yurgelun-Todd studied developmental changes in neural responses to fearful faces in children and adolescents. Results indicated sex-differences in amygdala development: although the left amygdala responded to fearful facial expressions in all children, left amygdala activity decreased over the adolescent period in females but not in males. Females also demonstrated greater activation of the dorsolateral prefrontal cortex over this period, whereas males demonstrated the opposite pattern. The authors interpreted these findings as evidence for an association between cerebral maturation and increased regulation of emotional behavior; the latter mediated by prefrontal cortical systems. It is possible that the pattern of decreased amygdala and increased dorsolateral prefrontal activation in girls with increasing age reflects an increased ability to contextualize and regulate emotional experiences per se.
21. Hariri and colleagues have demonstrated that increased prefrontal activity is associated with significant modulation of amygdala responses to affective stimuli, particularly with regard to fearful and angry faces. It is possible that these affective processing abilities emerge developmentally because functional neuroimaging results have shown that adults produce greater activity than do adolescents in the orbitofrontal cortex when displaying focused attention towards emotional stimuli.

22. Human adolescents exhibit an increase in negative affect/affective disturbances/depressed mood relative to younger or older individuals. In addition to greater negative affect adolescents also appear to experience and expect to experience positive situations as less pleasurable than other aged individuals.

23. A recent neuroimaging study suggests that differences in brain activation in mesolimbic circuitry during incentive-driven behavior between adolescents and adults might account for this. A group of 12 adolescents and 12 young adults were scanned while they carried out a task that involved anticipating the opportunity for both monetary gains and losses and the notification of their outcomes. Compared to adults, adolescents showed reduced recruitment of the right ventral striatum and right amygdala (areas that have been connected to motivational aspects of reward-directed behavior) while anticipating responses for gains. Activation patterns during monetary gain notification did not differ between groups.

24. In an fMRI study that investigated the neural mechanisms that might account for differences between adolescents and adults in decision-making, participants were presented with one-line scenarios (e.g. ‘Swimming with sharks’) and were asked to indicate via a button press whether they thought this was a ‘good idea’ or a ‘not good idea’. There was a significant group by stimulus interaction, such that adolescents took significantly longer than adults on the ‘not good idea’ scenarios relative to the ‘good idea’ scenarios. Furthermore, adults showed greater activation in the insula and right fusiform face area compared to adolescents, during the ‘not good’ ideas. On the other hand, adolescents showed greater activation in the dorsolateral prefrontal cortex (DLPFC) during the ‘not good’ ideas and there was a significant correlation between DLPFC activation and reaction time. However, adolescents relied more on reasoning capacities and therefore activated the DLPFC, hence the relatively effortful responses compared to adults. Although several developmental studies emphasize the decrease in frontal activity with age, in others, activity in this and other regions has been found to increase with age (in response to other clinical tasks).

25. Between late childhood and early adolescence (5th to 7th grade), the number of reports of feeling “very happy” drops by 50%. Even when engaged in the same activities, adolescents find them less pleasurable than do adults. In terms of their expectations for future rewards, adolescents (12–18 years of age) are less optimistically biased when compared with either college students or adults (18– 65 years of age).
Theme Set 5 & 6: The accumbens area of the brain (that is implicated in motivation and reward-predicting) develops much earlier than the frontal cortex. Adolescents show higher activity in the accumbens than adults. Lesion studies have shown that people with lesions in areas of the frontal cortex take increased risks (among other things). Thus, adolescents might make decisions based on miscalculated rewards and consequences because their frontal cortexes are not yet able to regulate accumbens activity.

26. The traditional explanation of adolescent behavior has been suggested to be due to the protracted development of the prefrontal cortex (A). Our model takes into consideration the development of the prefrontal cortex together with subcortical limbic regions (e.g., nucleus accumbens) that have been implicated in risky choices and actions (B).

27. Recent neuroimaging studies have begun to examine reward-related processing specific to risk-taking in adolescents. These studies have focused primarily on the region of the accumbens, a portion of the basal ganglia involved in predicting reward.

28. Risk-taking appears to increase during adolescence relative to childhood and adulthood and is associated with subcortical systems known to be involved in evaluation of rewards. Human imaging studies that will be reviewed, suggest an increase in subcortical activation (e.g., accumbens) when making risky choices that is exaggerated in adolescents, relative to children and adults.

29. Functional magnetic resonance imaging and self-reports of risk perception and impulsivity were acquired in individuals between the ages of 7 and 29 years. There was a positive association between accumbens activity and the likelihood of engaging in risky behavior across development. This activity varied as a function of individual’s ratings of anticipated positive or negative consequences of such behavior. Those individuals who perceived risky behaviors as leading to dire consequences activated the accumbens less to reward. This association was driven largely by the children, with the adults rating the consequences of such behavior as possible. Impulsivity ratings were not associated with accumbens activity, but rather with age.
30. To the extent that the accumbens and related brain regions are critical for integrating the motivational value provided by different inputs, developmental alterations in cortical and limbic systems might well alter the incentive value attributed to different types of motivationally relevant information. Adolescence across a variety of species is typically associated with an increase in importance attributed to social reinforcers outside the family unit. Adolescents also generally seek out new stimuli (novelty seeking; risk taking).

**Theme Set 6: see above**

31. Recent findings are consistent with rodent models imaging studies suggesting enhanced accumbens activity to rewards during adolescence. Indeed, relative to children and adults, adolescents showed an exaggerated accumbens response in anticipation of reward. However, both children and adolescents showed a less mature response in prefrontal control regions than adults. Given evidence of prefrontal regions in guiding appropriate actions in different contexts, immature prefrontal activity might hinder appropriate estimation of future outcomes and appraisal of risky choices, and might thus be less influential on reward valuation than the accumbens. This pattern is consistent with previous research showing elevated subcortical, relative to cortical activity when decisions are biased by immediate over long-term gains. Further, accumbens activity has been shown with fMRI to positively correlate with subsequent risk-taking behaviors.

32. Orbitofrontal Prefrontal Cortex Connectivity: Amygdala, limbic system, striatum, nucleus accumbens
   Functional Deficits: Socially inappropriate behavior, increased "risk taking”, apathy, impaired response suppression
33. Gambling task comparing control responses to responses of participants with orbitofrontal prefrontal (VMF) cortex lesions:

- **Large reward**
  - Larger punishment
  - Result: lose $\$\$\$

- **Small reward**
  - Smaller punishment
  - Result: gain $

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**Normal Control**
(N=13)

- ◊ Disadvantageous decks (A and B)

**Ventromedial Prefrontal (VMF)**
(N=5)

- ○ Advantageous decks (C and D)

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![Graph showing total number of cards selected from decks](image-url)
34. Phineas Gage Case Study

Before: - Loyal & trustworthy
   a. Dedicated to job and community
At the time of the accident
   b. Walked away unassisted
   c. No loss of language
After    -  Capricious, childish, obstinate
   d. Offensive language
   e. Insensitive to external cues
   f. A new plan everyday
   g. Extensive wanderings
   h. Intellect was not greatly affected

He was now “fitful, irreverent, indulging at times in the grossest profanities which was not previously his custom, manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of future operation, which are no sooner arranged than they are abandoned in turn for others appearing more feasible. His mind was radically changed, so decidedly that his friends and acquaintances said he was “no longer Gage”

(Harlow, 1868, “Recovery from the passage of an iron bar through the head.”
Publications of the Massachusetts Medical Society, 2, 327-34)

Theme Set 7: The brain’s natural reward-system ensures that we engage in activities that are essential for survival. This system connects behavior to positive feedback and memory, so that the brain can plan future actions that will allow for gaining the reward. Thus, this system provides motivation for (arguably, all) behaviors. Dopamine is the key neurotransmitter in this pathway. Increased drug use can lead to cellular changes in brain structures.

35. With new imaging techniques, it is now known that addictive drugs cause the activation of a specific set of neural circuits, called the brain reward system. This system controls much of our motivated behavior. Our brain’s reward system motivates us to behave in ways such as eating and having sex that tend to help us survive as individuals and as a species. This system organizes the behaviors that are life-sustaining, provides some tools necessary to take the desired actions, and then rewards us with pleasure when we do. When this happens, not only are we stimulated, but these circuits enable our brains to encode and remember the circumstances that led to the pleasure, so that we can repeat the behavior and go back to the reward in the future. The memory circuitry stores cues to the rewarding stimulus, so previously neutral cues (a perfume, a line of white powder) become salient. In addicts, cues that normally would have no particular importance to
survival or pleasure—such as a line of white powder, a cigarette, or a bottle of brown liquid—activate this same reward system.

36. A critical component of the reward system is the chemical dopamine, which is released from neurons in the reward system circuits and functions as neurotransmitter. Through a combination of biochemical, electrophysiological, and imaging experiments, scientists have learned that all addictive drugs increase the release of dopamine in the brain. Some increase dopamine much more than any natural stimuli. We once held the simplistic view of dopamine as the “pleasure chemical”; when you did something that felt good, the increase in dopamine was the reason. Experimental psychologists now make clear distinctions between “wanting” something and “liking” something, and dopamine seems to be important for the “wanting” but not necessary for the “liking.” This distinction seems to hold in every species in which it has been tested, from rodents to man. “Wanting” turns a set of neutral sensory stimuli (a face, a scent) into a stimulus that is relevant, or has “incentive salience.

37. Most people, when they abruptly stop drinking coffee, begin to suffer some negative effects within about 24 hours: a nagging headache and general feelings of sleepiness and lethargy. Their experience, however, does not signify addiction. They are suffering from the processes of tolerance and withdrawal. Tolerance occurs when the brain reacts to repeated drug exposure by adapting its own chemistry to offset the effect of the drug—it adjusts itself to tolerate the drug. For example, if the drug inhibits or blocks the activity of a particular brain receptor for a neurotransmitter, the brain will attempt to counteract that inhibition by making more of that particular receptor or by increasing the effectiveness of the receptors that remain. On the other hand, if a drug enhances the activity of a receptor, the brain may make less of the receptor, thus adapting to its over-stimulation. Both conditions represent the process of tolerance, and, in either case, withdrawing the drug quickly leaves the brain with an imbalance because the brain is now dependent on the drug.

Theme Set 8: Drug abuse results in a complete take-over of the body’s reward pathway by the need to consume the drug. Therefore, this leads to structural changes at the cellular and systemic levels.

38. The executive area of the brain, located in the prefrontal cortex, enables us to plan and execute complex activities, as well as control our impulses. Humans have a much larger prefrontal cortex and so a greater capacity for planning and executing complex activities than lower animals do, even the nearest primates. When we experience a rewarding event, the executive center of the brain is engaged. It remembers the actions used to achieve the reward and creates the capacity to repeat the experience. Thus, not only does a pleasurable experience result in pleasant memories, but also the executive center of the brain provides motivation, rationalization, and the activation of other brain areas necessary to have the experience again. And each time the experience is repeated all of these brain changes—memories and executive function tasks—become stronger and more ingrained. These planning centers are an important target of dopamine action.
39. The biological memories of the drug can be as profound and long-lasting as any other kinds of memories, and cues can activate the executive system to initiate drug-seeking years after the most recent previous exposure. So addiction is far more than seeking pleasure by choice. Nor is it just the unwillingness to avoid withdrawal symptoms. It is a hijacking of the brain circuitry that controls behavior, so that the addict’s behavior is fully directed to drug seeking and use. With repeated drug use, the reward system of the brain becomes subservient to the need for the drug. Brain changes have occurred that will probably influence the addict for life, regardless of whether or not he continues to use the drug.

40. A simplified model of dopamine pathways:

![Dopamine Pathways Diagram](http://www.nida.nih.gov/Researchreports/methamph/methamph3.html)

In the brain, dopamine plays an important role in the regulation of reward and movement. As part of the reward pathway, dopamine is manufactured in nerve cell bodies located within the ventral tegmental area (VTA) and is released in the nucleus accumbens and the prefrontal cortex. Its motor functions are linked to a separate pathway, with cell bodies in the substantia nigra that manufacture and release dopamine into the striatum.

Mechanisms of Drug Effects

**Some Mechanisms of Drug Action**

**Agonistic Drug Effects**
- Drug increases the synthesis of neurotransmitter molecules (e.g., by increasing the amount of precursor).
- Drug increases the number of neurotransmitter molecules by destroying degrading enzymes.
- Drug increases the release of neurotransmitter molecules from terminal buttons.
- Drug binds to autoreceptors and blocks their inhibitory effect on neurotransmitter release.
- Drug binds to postsynaptic receptors and either activates them or increases the effect on them of neurotransmitter molecules.
- Drug blocks the deactivation of neurotransmitter molecules by blocking degradation or reuptake.

**Antagonistic Drug Effects**
- Drug blocks the synthesis of neurotransmitter molecules (e.g., by destroying synthesizing enzymes).
- Drug causes the neurotransmitter molecules to leak from the vesicles and be destroyed by degrading enzymes.
- Drug blocks the release of the neurotransmitter molecules from terminal buttons.
- Drug activates autoreceptors and inhibits neurotransmitter release.
- Drug is a receptor blocker; it binds to the postsynaptic receptors and blocks the effect of the neurotransmitter.