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Substance use and the adolescent brain: An overview with a focus on alcohol

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JUST THE FACTS

Adolescence

- Adolescence is the transition from childhood (dependence) to adulthood (independence).
- No distinct beginning and end, but roughly 10-20 years of age is a good approximation.
- Normal adolescent behavior consists of changes in sleeping and eating habits, an increase in conflicts with family members, a desire to be with one's friends around the clock, resistance to messages from authority, irritability, risk taking, and proclamations of sheer boredom!
- These changes compel adolescents to explore the deeper end of the gene pool and acquire the skills, competence, and confidence necessary to survive on their own.
- A biological wedge is naturally driven between parents and adolescents to aid the transition from dependence to independence. The closer the family, the harder this process can be.

Adolescent drug use

- More than half of all adolescents will experiment with alcohol (80%) and/or marijuana (50%) by the time they become seniors in high school. Fortunately, most move through this stage of experimentation smoothly with no lingering drug problems.
- Levels of marijuana use have really skyrocketed in the past ten years, though they are still lower than they were in the early-mid 1980s.
- Alcohol misuse is by far the biggest drug problem among our kids. Alcohol kills more young people than all other drugs combined. Where do they get it? From us.

Adolescent brain development: Possibilities and pitfalls

- It is now quite clear that the brain undergoes a tremendous amount of development during the teen years, including a major remodeling of the frontal lobes, which are involved in planning, decision-making, impulse control and language.
- Changes in the frontal lobes and other areas are influenced by experience, which means that the decisions that kids make can have a big impact on how their own brains develop!
- Healthy choices = healthy brains, unhealthy choices = unhealthy brains.
- Because of the changes occurring in the brain during the teen years, alcohol affects teenagers and adults differently – for instance, it appears to produce bigger impairments in learning and more widespread brain damage in adolescents than in adults.
- Repeated alcohol exposure might alter the trajectory, or path, of teen brain development.
- The moldability, or plasticity, of the brain decreases as we enter the early 20s, which means that we might not be able to make up entirely for the poor decisions that we make as teenagers.

How to help teenagers make the most of it

- Embrace the changes in adolescents rather than fight them. Help them find healthy forms of risk taking so that they can build confidence and explore the world in a relatively safe way.
- Talk to them about different drugs and other issues of safety and health – be certain they know how you feel about them. Communication between parents and kids on this topic really seems to diminish the odds that they will become substance abusers.

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Introduction

Adolescence, broadly defined as the second decade of life, is the period of time during which many people begin to use alcohol and other drugs, and often do so heavily. According to the 2002 Monitoring the Future survey, roughly 30% of 12th graders reported drinking five or more drinks in a row in the two weeks before being surveyed (Johnston et al, 2003). This pattern of heavy, intermittent drinking is also prevalent among college students (White et al, 2002a) and young military personnel (Bray, 1996). While levels of alcohol use among adolescents remain high, the perceived risk associated with such use appears to be declining. From 1992 to 2002, the percentage of 12th graders perceiving "great risk of harm" associated with drinking four or five drinks per day, nearly everyday, dropped from 71% to 59% (Johnston et al, 2003). It does not appear that adolescent alcohol abuse is a problem that will soon disappear.

High levels of drinking among adolescents are particularly troubling given recent evidence that, in contrast to long-held assumptions, a tremendous amount of structural and functional brain development takes place during the teenage years (Geidd et al., 1999; for review see Spear, 2000;2002). Evidence is accruing that alcohol, and perhaps other drugs, impact brain function and behavior differently during adolescence than during adulthood. Further, preliminary data suggest that adolescents might be more vulnerable than adults to impairments following repeated alcohol exposure.

The purpose of this summary is to briefly discuss recent findings regarding adolescent substance use, adolescent brain development, and the impact of alcohol on adolescent behavior and brain function.

What is adolescence?

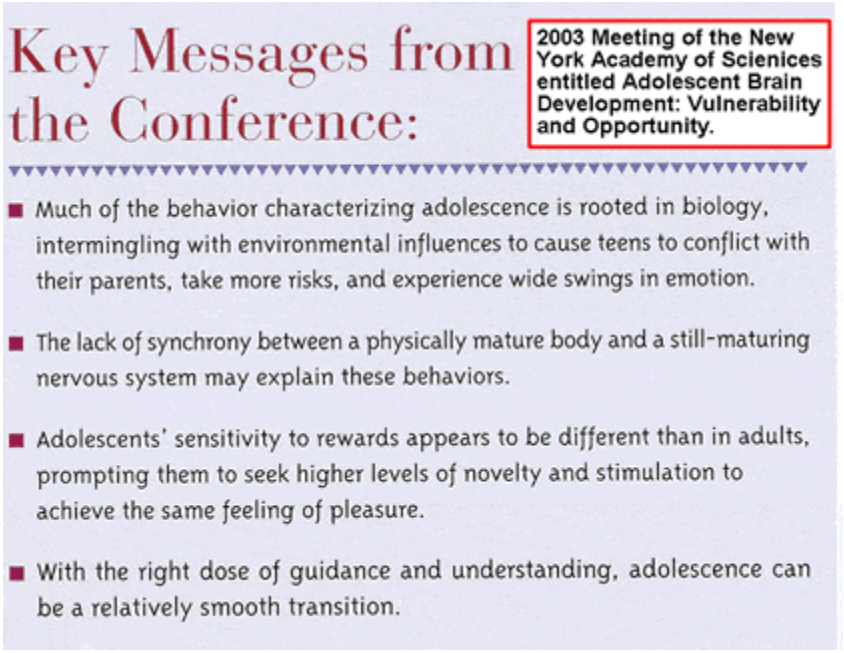
Adolescence is a transition

Adolescence is the transition from childhood to adulthood, a period during which an individual acquires the skills necessary to survive on his/her own away from their parents or other caregivers. The age range during which this transition occurs can vary, but often encompasses the entire second decade of life or longer.

Adolescence can be a very confusing time for everyone involved. Happy, fun-loving children can somehow morph into bitter malcontents in no time flat. How do I know this? Because I remember being one! For some reason, many of my friends and colleagues have forgotten just how strange, confusing, exciting, frightening, exhilarating, etc., the adolescent years are. Adolescence is a time of intense flux -- emotionally, behaviorally, and physically. If one grabbed a copy of the DSM and examined the diagnostic criteria for adult psychopathologies, they would find that even normal adolescents exhibit symptoms that would be considered causes of concern if exhibited by adults. Changes in sleep, diet, mood, weight, attitude, decreased pleasure from daily activities, and the list goes on, are all normal, and probably very adaptive, during adolescence. If an adult rattled this list of behaviors off to their family doctor during a routine checkup, there is a good chance they would leave with a referral to a

psychiatrist!

Adolescence is a very misunderstood stage of development. As should be clear from the discussion below, much of the chaos that occurs during the adolescent years is both normal and necessary, regardless of how painful it can be for both parents and kids. The image to the right highlights some of the take home messages from a recent meeting of the NY Academy of Sciences on the topic of adolescent development. We will explore some of these issues in this and subsequent sections.



Evolution and the value of being flexible

Some animals must fend for themselves immediately after hatching from an egg or shortly after leaving the womb. Being born prepared for independence has its pluses and minuses. On the plus side, the animal does not require an extended period of nurturing and can immediately go out and find its own food. It does not have to compete with siblings for the attention of the mother and can survive without adult help. However, on the negative side, and there are some big negatives here, essentially all of the instructions that the animal is going to have to assist in its survival come with it into the world. While it might be able to learn a new trick or two, it will not be able to roll with major changes in the environment. If your brain tells you that you simply must eat green bugs and there are NO green bugs in the world, then you're in trouble!

In stark contrast to that scenario, humans are born with an incredible ability to roll with changes in the demands of an environment. While our brains have probably not changed at all in the past thousand years, the repertoire of skills necessary to survive certainly has. Humans take these demands in stride. Unfortunately, this flexibility comes at a great price -- we are born incredibly dependent on others. Imagine a one month old, or even an 18 month old, human trying to survive by itself without support. This trade off is clearly more than fair, or we would not have survived as long as we have.

An amazing amount of learning takes place during the first decade of life, a time period characterized by our dependence on adult caregivers. During that time, we explore ourselves and our worlds using the family, or other caregivers, as a home base. Eventually, in order for our species to survive another generation, we need to venture out away from the family, out into the deeper end of the gene pool, and create families of our owns. That clearly can not happen overnight. Most of us would not have

made it had our parents just dropped us off at a bus stop when we were 10 and said, "Well, it's been great, now it's time for you to do this on your own!" For humans, as for many other mammalian species, there is a transitional stage between childhood and adulthood. That stage is adolescence.

When is adolescence?

Adolescence does not have a distinct onset and offset. While it is possible to offer a rough beginning and a rough end, there are simply no absolute boundaries. This is true for rats, humans, and any other species that you could imagine studying. In general, as mentioned above, adolescence is considered a transition from childhood to adulthood, a period during which an individual acquires the skills necessary to survive on his/her own. It involves changes at numerous levels, some of which are defined biologically and some of which are defined behaviorally. In humans, some have suggested that adolescence encompasses the entire second decade of life (i.e., 10-20 years of age), while others suggest that 12-18 is a more conservative range (Spear, 2000a,b). In rats, adolescence is even trickier to define than in humans. A rough estimate of the age range for adolescence in rats is between 30-50 days of age (Little et al., 1996).

As you can see, there is simply no fixed age range to define the boundaries of adolescence. In fact, the transition from childhood to adulthood could actually be extended or shortened depending on the individual and the demands placed on the individual by his/her surroundings. For example, in the United States, many college students remain dependent on their families and do not join the work force until after they graduate, which means that they technically remain adolescents into their early- or mid-20s. In contrast, in other countries, the individual might be required to work and provide for an entire family during their early teen years, thus forcing the transition to be complete at a much earlier age, closer to the completion of puberty. It is also important to recognize that, because adolescence is a period of development during which a multitude of changes are taking place, the onset and offset of adolescence is, in the end, determined by how it is operationally defined.

In my opinion, if a time frame must be chosen, it is safest to consider that adolescence encompasses the entire second decade of life. That is how the term will be used in this site. Again, in the end, it is the collection of changes that truly defines adolescence, not the specific age range.

What are some of the basic changes that occur during adolescence?

Linda Spear (2000a,b) has written extensively about adolescence and notes that there are several common themes in adolescence that humans share with other species, including rats. Here are a few of those themes and a brief discussion of each.

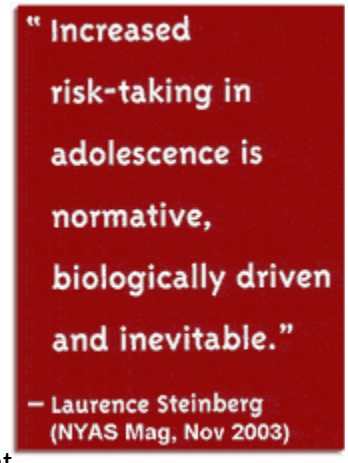
1. An increase in time spent with peers and a decrease in time spent with one's family

Given total freedom, most teenagers would not choose to stay at home with their families, at least not for very long or often! They would much prefer to IM their friends, talk on their cell phones with friends, page their friends, communicate via courier pigeon, etc. I am certain it has always been this way for humans. It is just far easier now to communicate around the clock than it ever has been. The reason why this is

adaptive should be obvious. In order to jockey for position in the social hierarchy, find mates, acquire the skills necessary to compete with peers, form alliances with peers, etc., it is very important to spend time around one's peers. Indeed, one could look at sports and other competitive play behavior, parties, and even just hanging out, as training or preparation for the social competition of adulthood.

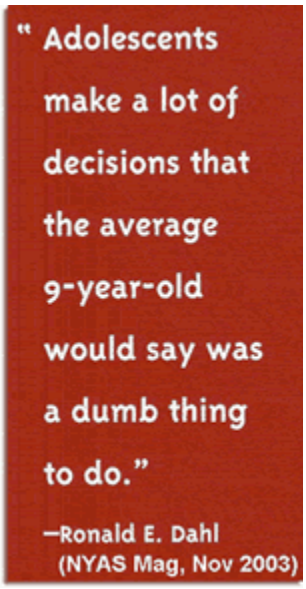
It certainly seems that being a teenager these days is very risky business, perhaps more so than in previous generations. I am well aware that many parents feel the urge to simply prevent their kids from ever leaving the house. While this might help ensure their safety, it can also put them at a terrible disadvantage socially. They will eventually have to compete with their peers for mates, money, and other resources, and form social networks to help them succeed. To use an analogy, watching basketball from the sidelines all day long is no substitute for playing the game. Opting not to play the game, or being prevented from doing so, can make competing as an adult even more difficult.

2. Increased risk-taking and exploration



This is perhaps one of the most important and poorly understood aspects of normal adolescent development. If adolescents were perfectly content staying at home with their families all of the time and had no desire to explore the world, meet new people, etc., then they would never venture into the deep end of the gene pool and the species would quickly die out. They simply must be driven to explore, seek novelty, and take risks. The repertoire of skills that an individual needs to acquire during adolescence changes from generation to generation. It is critical to the survival of the species that adolescents are willing to take chances, have novel experiences, and learn new skills.

Risk-taking and novelty seeking can take some forms that are hard to approve of or even comprehend. As a graduate student, I recall taking a break from studying for comprehensive exams and walking to the window (a big mistake as it was a nice spring day and I was stuck in the lab!). Below the window was a group of teenage boys taking turns rollerblading as fast as they could, backwards, with no pads, down several flights of very steep concrete steps. Clearly, this was probably not the best decision that any of them had ever made and it could have had disastrous consequences. However, their behavior and all of the processes leading up to it (e.g, decision-making, impulse control, risk-taking and reward-seeking) were simply prime examples of what takes place during adolescence. As the quote on the right captures, adolescence really is a unique stage with regard to the kinds of decisions that people make and the risks they are willing to take.



Exploring altered states of consciousness through experimentation with substances is another common

manifestation of risk taking and novelty seeking during adolescence. As will be discussed in a subsequent section, more than 1/2 of all high school seniors have smoked marijuana and roughly 80% have consumed alcohol. Fortunately, the vast majority of adolescents do not engage in such activities regularly and do not go on to develop problems with substances.

One key message here is that adolescents are built to take risks and seek novel experiences. Trying to prevent them from doing so is typically futile, as it is simply part of their biology. What we can do as parents, friends, and members of the community is to create opportunities for adolescents to take healthy risks (yes, there is such a thing) and reinforce them for doing so. For instance, the data tell us that the more extracurriular activities that an adolescent is involved in, the less likely they are to drink heavily or do other substances. Creating opportunities for kids to explore and take some chances can minimize the likelihood that they choose less healthy, riskier options to satisfy their need to do so. Not every parent can afford to let their child go sky diving, bungee jumping, or snowboarding. However, what about finding a YMCA or community center with a basketball court that stays open late on the weekends? Not every kid will want to take advantage of an opportunity like playing basketball on a Friday night, but some will. The point is simply that there are things we can do to diminish the risks that adolescents take besides trying to force them to change their nature, which typically does not work and might be detrimental to their development.

4. Increase in conflicts with authority, including parents

This is essential for several reasons. For one, as discussed above, adolescents must push away from their parents, and the parents must push the adolescent away from them to some extent, in order to propel the adolescent into the deeper end of the gene pool. If adolescence was characterized by a growing satisfaction with authority, this simply would not happen!

Human are social animals. Mating and obtaining resources involves competition. Those at higher rungs on the social ladder enjoy better odds of mating and obtaining resources. Jockeying for position in the hierarchy involves conflict. For males, such conflict is typically more overt or physical. Research indicates that, for females, such conflict is more likely to involve sabotaging social relationships, manipulating friendships, etc. Regardless, an increase in conflict during adolescence, whether the conflict is with peers or authority, makes sense given the purpose of this stage of development.

One of the key benefits of the adolescent period is that it allows the individual to acquire the skills necessary to succeed as an adult in the *current* environment. These skills might differ from the skills that allowed one's parents to survive. In other words, it is not necessarily healthy or adaptive for adolescents to take on all of the characteristics of the existing adults. This would limit the true utility of the adolescent period with regard to our evolution as a species. A natural tendency to be in conflict with adults helps propel adolescents to find their own paths.

5. Changes in sleep patterns, including a tendency to go to sleep later and wake up later

I wish I had a good explanation for this one. It probably is not adaptive or healthy

in its own way. It is probably a consequence of some other set of changes taking place in the body that is adaptive and healthy. Regardless, the sleep patterns of teenagers can be fragmented and unfulfilling. Many individuals, including some pediatricians, believe that schools should actually start later in the morning to accommodate the sleeping habits of a typical adolescent.

6. Puberty (sexual maturation)

Puberty refers to a constellation of hormonal and physical changes that prepare the male and female bodies for procreation and physical confrontation (particularly males). Puberty and adolescence overlap but are *not* the same thing.

This transition can be particularly hard on healthy families!

As the changes mentioned above suggest, evolution seems to have equipped us with a set of behavioral tendencies that helps aid the transition into adulthood. At a very deep level, the adolescent is driven to push away from the family. At the same time, many parents might feel driven to push back. The closer the family, the harder this transition can be. In the end, however, it has to happen. If it did not, then our species simply would not survive.

Brain development during adolescence

The brain is an amazingly complex, still poorly understood, organ. Hundreds of billions of cells bathe one another in chemical messengers that influence moment to moment changes in brain function, behavior, and experience. Some chemical messengers can also trigger changes in gene expression in other cells, leading to long-term changes in how they look and operate, and how the individual thinks and acts. The current chemical milieu of your brain governs how you feel at this very moment -- how attentive you are, whether you are deeply satisfied with your life, whether your foot itches, you name it.

During adolescence, brain organization and function enter a unique period of flux. As an individual makes the transition from childhood to adulthood, from dependence to independence, the changes in behavior are dramatic. Not surprisingly, so are the changes in brain function that give rise to these behaviors. As we will see, the circuits that coordinate our behaviors, help us make good decisions and control our impulses, react appropriately in different situations, govern our eating and sleeping habits, etc., are being remodeled during the teen years. Much of this remodeling is influenced by an individual's interactions with the outside world, a fact that makes perfect sense given the nature of adolescence as a stage of intense personal evolution that prepares one to survive on their own outside of the nuclear family. The brain of an adolescent is highly moldable by experience, more so than the brain of a full grown adult. The fact that people are willing to completely disrupt their lives to return to their high school reunions 50 years after they graduate is, I think, a pretty clear indication of just how important the adolescent years are for shaping who we are and how our brains function. In this section, we will explore some of the many changes taking place in the brain during the adolescent years.

Shaping the brain

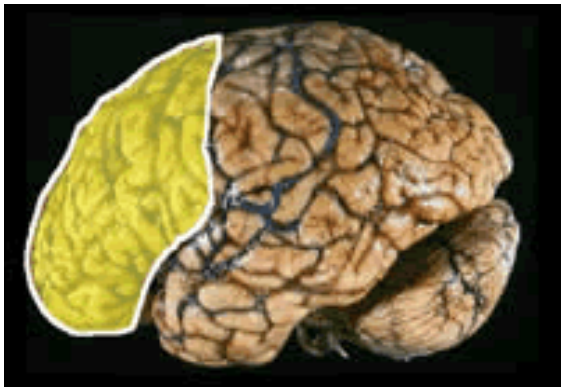
Overproduction of neuronal tissue is a central theme in early brain development, from the womb to late childhood. Human infants are born with far more neurons than are present in the adult brain. The selection process that determines whether an individual cell lives or dies is based on several factors, including the transmission of neurotrophic factors from the post-synaptic cell to the pre-synaptic cell in response to excitatory synaptic activity. In this way, cells that fire together wire together, and those that do not make meaningful contacts with other cells do not survive. One key benefit of this process is that it allows a child's brain to be sculpted by his/her interactions with the outside world (Chugani, 1998).

In recent years, it has become clear that, during adolescence, as in childhood, the brain is highly plastic and shaped by experience. A substantial number of synapses are eliminated, or pruned, in the cortex during adolescence, and this process is presumably influenced, at least in part, by interactions with the outside world (Huttenlocher, 1979; Lidow et al., 1991; Seeman, 1999). It is tempting to conclude that adolescent brain development must simply be an extension of childhood brain development; that it represents a transition stage between childhood and adulthood in a manner similar to how adolescence itself has long been viewed. In actuality, it appears that many of the changes that take place during the second decade of life are novel and do not simply represent the trailing remnants of childhood plasticity.

Some of the most intriguing changes observed thus far occur in the frontal lobes, brain regions that play critical roles in memory, voluntary motor behavior, impulse control, decision-making, planning, and other higher order cognitive functions. Frontal lobe gray matter volumes, which represent dense concentrations of neuronal tissue, increase throughout childhood and do not reach their peak until roughly the age of 12, at which point they decline throughout the second decade of life. The decreased gray matter volumes appear to reflect both an elimination of synapses and an increase in myelination, a process by which glial cells surround neuronal axons and enhance the speed and distance of signal transmission. A parallel increase in overall metabolism occurs in the frontal lobes during the first decade of life and then decreases during early adolescence to reach adult levels by the age of 16-18 (Chugani, 1998). Importantly, such declines during adolescence do not reflect a diminution of frontal lobe function. Indeed, there appears to be an increased reliance on the frontal lobes in the control of behavior, a process commonly referred to as *frontalization* (Rubia et al., 2000). At the

The frontal lobes

The frontal lobes (highlighted at right) play important roles in a variety of higher psychological processes - like planning, decision making, impulse control, language, memory, and others. There is mounting evidence that neuronal circuitry in the frontal lobes is shaped and fine tuned during adolescence, and that experience plays a prominent role in these changes.



same time that gray matter volumes and metabolism decrease, neural activity during the performance of certain tasks becomes more focused and efficient (Casey, 1999; Rubia et al., 2000; Luna et al., 2001). Thus, it appears that adolescent brain development, at least in the frontal lobes, represents a very unique stage of change.

Additional research suggests that similar changes occur elsewhere in the cortex during adolescence. As in the frontal lobes, gray matter volumes in the parietal lobes, which are involved in processing sensory information and evaluating spatial relationships, peak at around age 11 and decrease throughout adolescence (Geidd et al., 1999). Gray matter volumes in the occipital lobes, which are dedicated to processing visual information, increase throughout adolescence and into the early 20s (Geidd et al., 1999). Gray matter volumes in the temporal lobes, which are critically involved in memory formation, as well as visual and auditory processing, do not reach maximum until the age of 16-17 (Geidd et al., 1999).

A variety of changes in subcortical structures have also been noted. For instance, the corpus collosum, a thick bundle of axons that allows the two cerebral hemispheres to communicate with one another, increases in size during adolescence (Geidd et al., 1999). Also, in the rat, levels of dopamine receptors in the nucleus accumbens increase dramatically between PD 25-40 (Teicher et al., 1995), an age range that falls within the window of periadolescent development (Spear, 2002). Dopamine receptor levels in the striatum also increase early in adolescence and then decrease significantly between adolescence and young adulthood (Teicher et al., 1995). Further, the numbers of GABA-A receptors increase markedly in a variety of subcortical structures during early adolescence (PD 28-36), including the cerebellum and medial septal nucleus (Moy et al., 1998). As in the frontal lobes, age-related changes in brain activation during task performance have been observed in the cerebellum, superior colliculus, thalamus, striatum, parietal cortex, and hippocampus (Luna et al., 2001; Mueller et al., 1998).

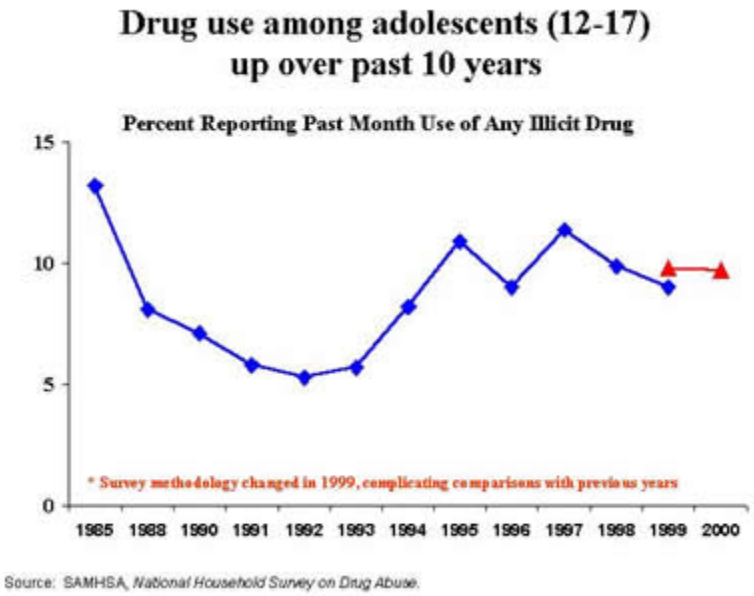
It has become quite clear over recent years that alcohol impacts both behavior and brain function differently in adolescents and adults (Smith, 2003). For instance, the available evidence suggests that adolescents are more vulnerable than adults to the effects of alcohol on both memory and memory-related brain function, while being less vulnerable to other effects of the drug. Following a brief overview of current levels of substance use among adolescents in the US, age-related differences in the effects of alcohol will be discussed.

Substance use during adolescence

Despite an intense and costly war on drugs, substance use among adolescents in the United States has generally risen during the past decade after declining in the late 1980's (please see the chart below). Use of tobacco, marijuana, cocaine and heroin all increased between 1991 and 1999 (Kann et al., 2000; Johnston et al., 2001). In 2000, heroin use was the highest it had been in 25 years, and use of ecstasy nearly doubled from 6% in 1996 to 11% (Johnston et al., 2001). To make matters worse, the purity of both cocaine and heroin has risen considerably in the past decade while the prices of these and other drugs have fallen (ONDCP, 2001). Increases in use and changes in

purity have contributed to a sharp rise in emergency room visits related to drug use (DAWN, 2001).

The proportion of high school students consuming alcohol, as well as the rate of heavy drinking, remained relatively stable during the past 10 years (Kann et al., 2000; Johnston et al., 2001). Current estimates suggest that roughly 50% of high school seniors consume alcohol at least once per month, while 17% regularly smoke cigarettes and nearly 50% have smoked marijuana (Kann et al., 2000; Johnston et al., 2001). By the time an adolescent reaches 8th grade, nearly 1/2 have had at least one drink, and 1/5 have been "drunk" (NIAAA, 2003). Alcohol use continues to kill more adolescents than all illegal drugs combined (NIAAA, 2003).



As the use of many drugs has increased during the past decade, the perceived risk associated with such use has decreased. From 1991 to 2000, the percentage of 12th graders who considered regular use of marijuana to pose a “great risk of harm” dropped from 79% to 58%, while those perceiving great risk associated with drinking four or five drinks per day, nearly everyday, dropped from 70% to 60% (Johnston et al., 2001). Similar decreases in the perception of risk were observed for use of powder and crack cocaine, crystal methamphetamine, and LSD (Johnston et al., 2001).

At the same time, both attitudes toward drug use and perceived ease of access to drugs also changed. Disapproval of regular marijuana use dropped from 90% in 1991 to 80% in 2000, and disapproval of regular cocaine, LSD, heroin, tobacco, and heavy alcohol use either decreased slightly or remained relatively stable during this time period (Johnston et al., 2001). In addition, the data suggest that it is easier now for high school students to get many drugs, including marijuana, LSD, ecstasy, and heroin, than it was a decade ago (Johnston et al., 2001).

Given these trends, it is not surprising that the number of adolescents in drug and alcohol treatment programs has increased dramatically in recent years. Between 1993 and 1998, the number of adolescents entering treatment rose more than 45%, from roughly 95,000 to 138,000 (SAMSHA, 2000). Most of the growth in the patient population was due to an increase in admissions for marijuana abuse/dependence. Enrollments in which marijuana was the primary drug of abuse increased from 32% in 1993 to 57% in 1998. During this same period, enrollments in which alcohol was the primary drug of abuse dropped significantly, from roughly 50% to 25% (SAMSHA, 2000).

Under any circumstances, increases in the abusive use of drugs among

adolescence should be troubling. Findings from recent neurobiological studies make these surges in use a serious cause for concern. As summarized above, it has recently become clear that, in contrast to previous assumptions, there is a tremendous amount of brain development taking place during adolescence. We will now discuss evidence that 1) alcohol, and perhaps other drugs, affect both behavior and brain function differently in adolescents than adults, and 2) adolescents may be more vulnerable to the long-term effects of alcohol abuse.

Before discussing these recent findings, it is important to note that this research is still in its infancy. Much of what is known right now regarding differences in the impact of substances on behavior and brain function in adolescents and adults pertains to alcohol use. As research proceeds, much more will be learned regarding differences in the effects of other drugs. In addition, for a variety of fairly obvious reasons, most of the research on this topic has been conducted using non-human animal models. It has yet to be determined whether all of the differences observed in other animals map onto the human condition, though we certainly expect this to be the case.

Alcohol affects adolescents and adults differently in many ways

It has become quite clear over recent years that alcohol impacts both behavior and brain function differently in adolescents and adults. This general finding should perhaps not be surprising given the dramatic changes in brain occurring during the adolescent period. Recent studies suggest that adolescents are more vulnerable to some effects of alcohol exposure, while being less vulnerable to others. These findings will be reviewed below, beginning with the impact of alcohol on memory and memory-related brain function in general, and then focusing on developmental differences in these effects. Differences in the impact of alcohol on sedation and motor coordination in adolescents and adults will then be discussed.

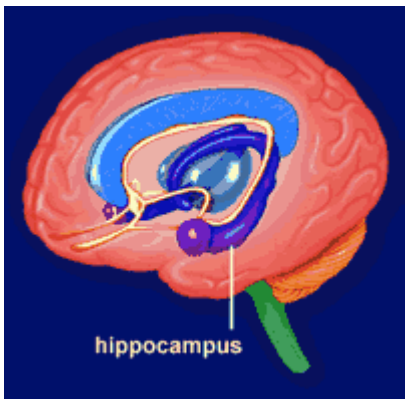
Learning and memory

It is well known that alcohol produces learning and memory impairments. These effects are reviewed in detail on a separate page (click here). Briefly, alcohol primarily interferes with the establishment of new memories rather than the recollection of previously stored information. Alcohol produces what Ryback (1971) referred to as a continuum of encoding deficits. That is, as the dose of alcohol goes up, the magnitude of the memory impairments go up, as well. For instance, while a few drinks might make it more difficult for you to learn a new person's name, a bunch of drinks might completely impair your ability to remember ever having met the person at all. The inability to remember entire events that occurred while drinking is commonly referred to as a *blackout*.

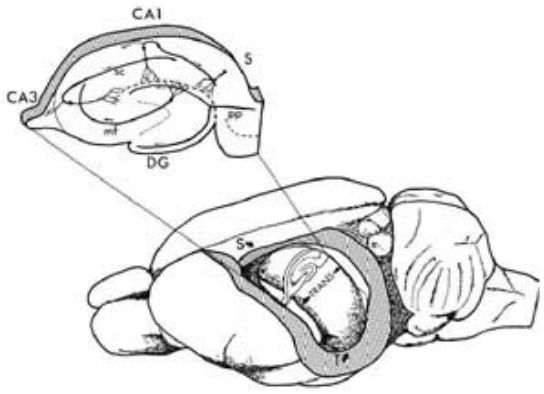
The specific mechanisms by which alcohol impairs memory are still under investigation. However, it seems likely that alcohol does so by disrupting neural plasticity in brain regions involved in memory formation. Neural plasticity refers to the ability of circuitry in the brain to reorganize itself as a result of experience. The altered activity in neural circuits somehow represents the acquired information and allows for the recollection of the information at a later time. Alcohol appears to interfere with the changes in circuitry that occur during learning.

One brain region that is highly involved in memory formation and exhibits a tremendous amount of neural plasticity is the hippocampus. The hippocampus is an old cortical structure located deep within a region of the brain known as the temporal lobes (see the figure below). The temporal lobes run along the sides of your brain at about the level of the temples.

Location of the hippocampus in the human brain
(This image was borrowed from www.morphonix.com, a site offering multimedia software aimed at educating children and adults about the brain)

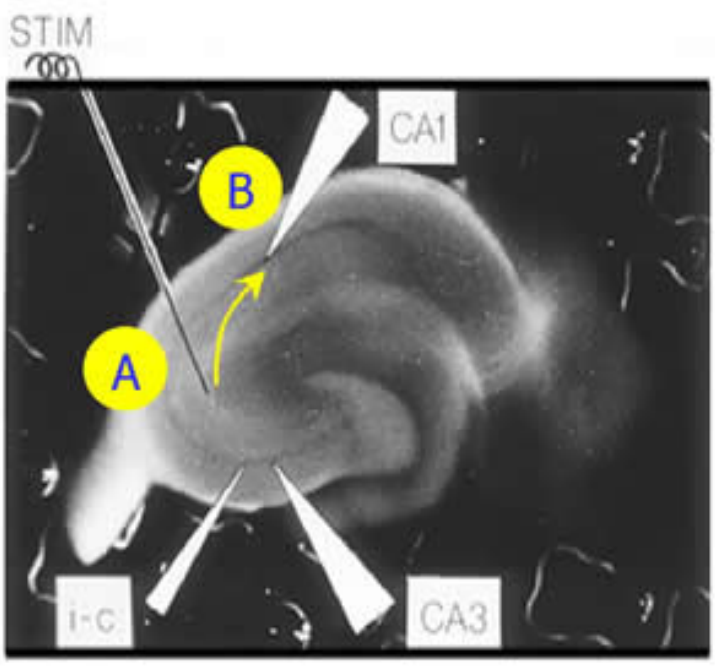


Alcohol disrupts the functioning of the hippocampus. This has been demonstrated using a variety of methods, including the recording of hippocampal neurons in freely behaving animals (White and Best, 2000). The effects of alcohol on hippocampal function have also been assessed in a variety of experiments examining the impact of alcohol on Long-Term Potentiation (LTP). LTP is a model of the changes in hippocampal circuitry that might occur during learning. LTP is not learning. It is simply a model for what might occur in the brain during learning. Nonetheless, LTP offers an interesting way of assessing the impact of drugs like alcohol on neural plasticity, and for comparing the effects of alcohol on memory-related brain function in adolescent and adults subjects. LTP experiments are typically carried out using slices of tissue removed the brain and kept alive by bathing them in oxygenated artificial cerebral spinal fluid (ACSF), which is essentially the same stuff that keeps our brains alive inside of our bodies. The figure above shows the location of the hippocampus in the rat brain and a diagram of a slice of hippocampal tissue.



Location of the hippocampus in the rat brain [From: Fuster, J.M. Memory in the Cerebral Cortex: An Empirical Approach to Neural Networks in the Human and Nonhuman Primate. Cambridge, Massachusetts: The MIT Press, 1995, p26.]

In a typical LTP experiment, two electrodes are lowered into the slice of tissue. The positioning of these electrodes is indicated by the letters A and B in the figure below. A small amount of current is passed through electrode A, causing the neurons in this area to send signals to cells located near electrode B. Electrode B then records the response of cells in the area to the incoming signals. This response is referred to as the baseline response. Next, a specific pattern of stimulation intended to model the pattern of activity that might occur during an actual learning event is delivered through electrode A. Now, when you return to the original stimulus delivered during baseline, the response recorded at B is bigger (i.e., potentiated). In other words, as a result of the patterned



input, cells at position B are now more responsive to signals sent from cells at position A. The potentiated response often lasts for a long time, hence the label Long-Term Potentiation.

Alcohol interferes with the establishment of LTP. If there is enough alcohol in the brain when you give the patterned stimulus, the response recorded later at position B will not be bigger than it was during baseline. Because drugs that interfere with the establishment of LTP also cause memory impairments in humans, many people believe that LTP serves as a good model for studying the neurobiology underlying the effects of drugs like alcohol on memory. Two recent studies have revealed that adolescent brains are much more sensitive to the effects of alcohol on LTP than adults (Swartzwelder et al., 1995; Pyapali et al., 1999).

One of the key requirements for the establishment of LTP in the hippocampus is that a particular type of neurotransmitter recepter, called the NMDA receptor, becomes activated. Activation of the NMDA receptor allows calcium (CA++) to enter the cell, which sets off a chain of events leading to long-lasting changes in the structure and/or function of the cell. Alcohol interferes with the activation of the NMDA receptor, thereby preventing the influx of CA++ and the changes that follow. This is believed to be the mechanism underlying the effects of alcohol on LTP induction. (Click here for a diagram of an NMDA receptor and more on the effects of alcohol on NMDA receptor functioning). It is now clear that alcohol has a much bigger impact on NMDA receptor activation in adolescents than in adults (Swartzwelder et al., 1995). Differences in the affects of alcohol on NMDA receptor activity in the hippocampus of adolescents and adults provides a logical explanation for differences in the affects of alcohol on LTP in these age groups. Further, these differences suggest that we might expect adolescents to be more vulnerable than adults to the affects of alcohol on learning and memory.

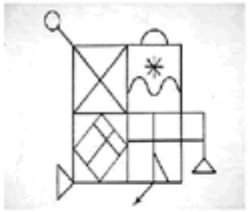
The available evidence suggests that adolescents are more vulnerable than adults to the affects of alcohol on learning and memory, though much more work needs to be done in this area. In rats, one task commonly used to assess learning and memory is called the Morris water maze task. This task requires rats to locate a platform submerged an inch or so beneath the surface of the water in a big circular tub (see below). The ability to learn this task is very sensitive to changes in activity in the hippocampus, so it provides an easy way to assess whether drugs that disrupt hippocampal function also disrupt learning that is dependent on this structure. Markwiese et al. (1998) discovered that adolescent rats are much more vulnerable to alcohol-induced learning impairments in the water maze than adults.

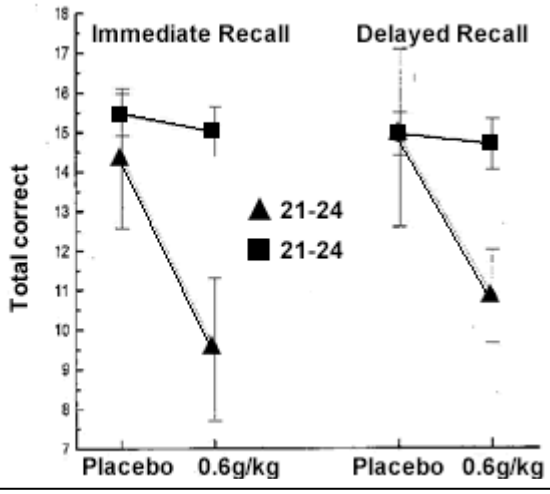
It is difficult to determine whether adolescent humans, like adolescent rats, are more vulnerable than adults to the effects of alcohol on learning and memory. For obvious legal and ethical reasons, this research has not been carried out in young adolescent humans. However, the neurobiology underlying memory formation is considered to be, at a basic level, similar between rats and humans, leading us to expect similar outcomes at the behavioral level. In fact, recent evidence suggests that people in their early twenties are actually more vulnerable to alcohol-induced memory impairments than those in their late twenties (Acheson et al., 1999). While people in their early twenties are arguably outside of the adolescent age range, the data certainly suggest that younger subjects are more vulnerable to alcohol-induced memory impairments than slightly older subjects, raising the possibility that true adolescents are even more vulnerable still.

The Morris water maze task
The rat is required to learn the location of a platform submerged an inch or so beneath the surface of the water. Alcohol impairs performance in this task, and does so more potently in adolescents than adults.

In the aforementioned study, subjects were tested using a variety of tasks, including the complex figure task. In this task, subjects were shown a line drawing and were required to reproduce the drawing immediately after it was shown to them (immediate recall) and then again twenty minutes later (delayed recall). The figure below shows an example of a complex figure, and the effects of alcohol on performance of subjects in the two age groups. When tested under placebo, all subjects performed similarly in both the immediate and delayed components of the task. However, when tested under alcohol (the equivalent of about 2-3 drinks), subjects in their early twenties performed worse than subjects in their late twenties on both components of the task.

Alcohol and the complex figure task
Subjects were shown a figure like the one in the upper left and were asked to recreate it both immediately after seeing it and twenty minutes later. Alcohol impaired performance more in subjects between 21-24 years of age than in subjects 25-29 years of age.





Sleepiness (sedation) and problems with balance and muscle coordination

While younger subjects appear to be more sensitive than adults to the affects of alcohol on learning and memory, recent evidence suggests that they might actually be less sensitive to other effects. For instance, a number of reports suggest that adolescent rats are less vulnerable than adults to alcohol-induced sedation. Sedation refers to the calming or tranquilizing effects a drug. In rats, sedation is often assessed by examining something called the righting reflex. If you lay a rat on its back, it quickly turns over (i.e., rights itself). Drugs with sedative effects, like alcohol, suppress the righting reflex. For instance, after being given a big dose of alcohol, rats will let you lay them on their backs without attempting to right themselves. The extent of sedation is commonly assessed by simply testing how long it takes after drug treatment for a rat to regain its righting reflex. It has been demonstrated numerous times over the past few years that adolescent rats are significantly less sensitive than adults to the effects of alcohol on the righting reflex (Little et al., 1996; Swartzwelder et al., 1998; Silveri and Spear, 1998). These findings suggest that the sedative effects of alcohol are weaker in adolescents than adults.

It also appears that adolescents might be less sensitive than adults to the effects of alcohol on motor coordination. Motor coordination refers to the ability to maintain balance, to walk without stumbling, to drive a car with a manual transmission, etc. As is well known, alcohol disrupts motor coordination. Indeed, the impact of alcohol on motor coordination serves as the basis for field sobriety tests. A limited amount of research, again with rats, suggests that alcohol affects motor coordination to a lesser degree in adolescents than adults (Hollstedt and Rydberg, 1985; White et al., 2001; White et al., submitted). The effects of alcohol on motor coordination are commonly assessed using a simple device called a tilting plane (see Figure below). As the name implies, the rat is placed on a flat, typically glass, surface and one end of the surface is slowly raised. Staying on the surface without sliding requires coordinated motor activity. The angle at which the subject slides is assessed while sober and intoxicated, and the data are then compared. It is quite clear that adolescent rats are much less affected by alcohol in this task than adults, suggesting that they might be less vulnerable to alcohol-induced motor impairments.

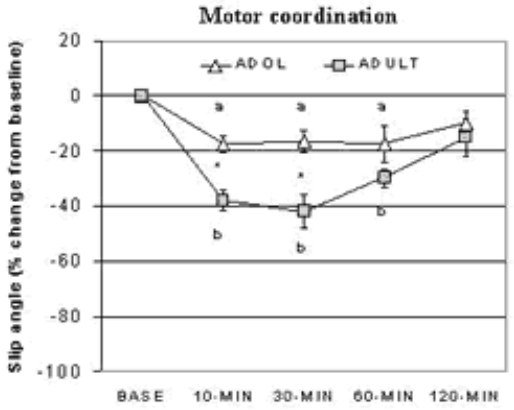
Alcohol impairs balance and muscle coordination

The tilting plane apparatus and depictions of performance of a subject while sober (a) and intoxicated (b). Alcohol reduces the angle at which subjects begin to slide

The figure below shows the effects of alcohol on performance of the tilting plane test in adolescent and adult rats (White et al., 2001). It is quite clear that adolescent rats are much less affected by alcohol in this task than adults, suggesting that they might be less vulnerable to alcohol-induced motor impairments.

Alcohol impairs balance and muscle coordination more in adult rats than in adolescent rats

The graph shows the effects of 1.5 g/kg alcohol on balance and muscle coordination in adolescent and adult rats (n=6 per group). Adolescent subjects were less impaired than adults at both 10 and 30 min post-injection. (* = between group difference, a = difference relative to baseline for adolescent subjects, b = difference relative to baseline for adult subjects. All p-values less than 0.05)



The existing research regarding alcohol-induced sedation and motor impairments in adolescents and adults has all involved the use of rats. In humans, the sedative and motor incoordinating effects of alcohol can limit the amount of alcohol an individual consumes. That is, the individual might find him/herself incapacitated at some point during the evening and unable to continue drinking even if they desired to do so. If the findings observed with rodents extend to humans, the decreased vulnerability of adolescents to the sedative and motor impairing effects of alcohol might allow adolescents to continue drinking for longer periods of time than adults, and perhaps achieve much higher BACs, without becoming incapacitated. As we have seen, adolescents appear to be more vulnerable than adults to some of the cognitive impairments produced by alcohol. Thus, the reduced susceptibility to alcohol-induced sedation and motor incoordination, combined with an enhanced susceptibility to alcohol-induced cognitive deficits, could be a potentially very dangerous combination of effects. Clearly, the above model depends upon the assumption that adolescent humans are, in fact, less vulnerable than adults to the sedative and motor incoordinating effects of alcohol. This has not yet been demonstrated scientifically, though we expect it to be the case.

In addition to greater short-term risks associated with alcohol use during adolescence, recent research strongly suggests that adolescents might also be at greater risk for long-term deficits following alcohol abuse. These findings will be covered in the next section.

Long-term effects of alcohol abuse during adolescence

In addition to reacting differently to the acute, or initial, effects of alcohol, it appears that adolescents are also affected differently than adults by repeated, heavy drinking. Many adolescents engage in a pattern of chronic intermittent exposure (CIE)

sometimes referred to as binge drinking. Chronic intermittent exposure is a special case of chronic alcohol administration that involves discrete, repeated withdrawals. There is compelling evidence that it is the repeated withdrawals from alcohol that are responsible for many of the CNS effects of chronic alcohol exposure. For example, in laboratory animals, repeated withdrawals from alcohol result in a higher rate of seizures during withdrawal than are observed after continuous exposure of the same duration (Becker and Hale, 1993). The association of repeated withdrawals with withdrawal seizure susceptibility is also indicated in humans. In studies of alcohol detoxification, patients with a history of previous detoxifications were more likely to exhibit seizures during withdrawal (Brown et al, 1988). Although these data from human studies are correlational, the convergence of these findings with those from animal models strongly suggests that discrete, repeated withdrawals from alcohol exposure presents a unique risk for subsequent neurobehavioral impairments.

There is mounting evidence that repeated exposure to alcohol during adolescence leads to long-lasting deficits in cognitive abilities, including learning and memory, in humans. Much of this work has been pioneered by Drs. Susan Tapert and Sandra Brown, alcohol researchers at the University of California, San Diego (UCSD). Drs. Tapert and Brown have conducted a series of studies examining the impact of alcohol abuse on neuropsychological functioning in adolescents and young adults. In one such study (Brown et al., 2000), adolescents in an in-patient substance abuse treatment program, at least three weeks sober, were compared to controls from the community on a battery of neuropsychological tests. Ages ranged from 15-16. Frequent drinkers (100 or more total drinking sessions), particularly those that had experienced alcohol withdrawal, performed more poorly than controls on several tests, including tests of learning, memory, and visuospatial functioning. In a longitudinal study of subjects recruited from treatment programs (ages 13-19), the authors observed that a return to drinking after the program led to further decline in cognitive abilities, particularly in tests of attention, over the next four years (Tapert et al., 1999). Once again, withdrawal from alcohol was a powerful predictor of such impairments. Similarly, Tapert and colleagues (2002) assessed neuropsychological functioning and substance use involvement at seven time points during an eight year period in subjects beginning, on average, at the age of 16 and ending at 24. Many of the subjects were initially assessed while in treatment and then tracked after their stay in the facility ended. Others were recruited from the community and then followed during the eight year period. Cumulative levels of substance use, including alcohol use, were correlated with impairments in verbal learning and memory during the final assessment. That is, the heavier one was involved in substance use during adolescence, the lower their scores on tests of learning and memory at year eight, when subjects were in their early twenties. Heavier drinking alone was associated with lower scores on tests of attention, and experiencing withdrawal symptoms from alcohol predicted additional deficits in visuospatial abilities. These studies suggest that heavy use of alcohol and other drugs during the teenage years predicts lower scores on test of memory and attention when one is in their early-mid twenties.

Research by Tapert and Brown clearly suggest that alcohol use during the teen years, particularly when such use is heavy enough to precipitate withdrawal symptoms, negatively impacts memory and attention, abilities necessary for negotiating the tasks of

adolescence and successfully making the transition into adulthood. These impairments presumably stem from changes in brain function, and that is exactly what additional projects by Tapert and Brown have observed. The authors have conducted several studies employing fMRI to investigate changes in brain activity following alcohol abuse during the teen years. While MRI is used to create images of the anatomy of the brain, fMRI is used to measure changes in oxygen levels in the brain over time, like while subjects perform different tasks. The changes in oxygen levels are used to measure, indirectly, changes in brain activity. In one study on this topic (Tapert et al., 2001), alcohol-dependent young women and healthy controls between the ages of 18-25 performed tests of working memory and vigilance (attention) while brain oxygen levels were measured using fMRI. The sample sizes were not quite big enough to detect significant impairments in working memory, though a clear trend toward such impairments was observed. However, alcohol-dependent subjects exhibited significantly less brain activity while performing the working memory task. Weaker activity was observed in several parts of the frontal lobes and in the parietal lobes. Alcohol-dependent subjects performed just fine during the vigilance task, and their brain activation during the task appeared normal. Such data suggest that the trend toward impaired working memory and the week brain activity that went with it can not simply be explained by lack of interest or motivation on the part of the subject. A subsequent study with alcohol-dependent young women showed that alcohol-related cues (e.g., words associated with drinking) elicited craving and led to greater increases in brain activity in a variety of regions relative to controls (Tapert et al., 2004), thus establishing a link between craving for alcohol and brain function in key areas and indicating that the brains of alcohol-dependent young women function differently than their peers.

As discussed above, 15-16 year olds in in-patient treatment for alcohol-dependence perform more poorly on test of memory and attention than healthy control subjects from the surrounding community. The image at the right shows representative brain images from such subjects. Details regarding the image can be found in the caption. This image appeared in

The brain images below show how alcohol may harm teen mental function. Compared with a young non-drinker, a 15-year-old with an alcohol problem showed poor brain activity during a memory task. This finding is noted by the lack of pink and red coloring.

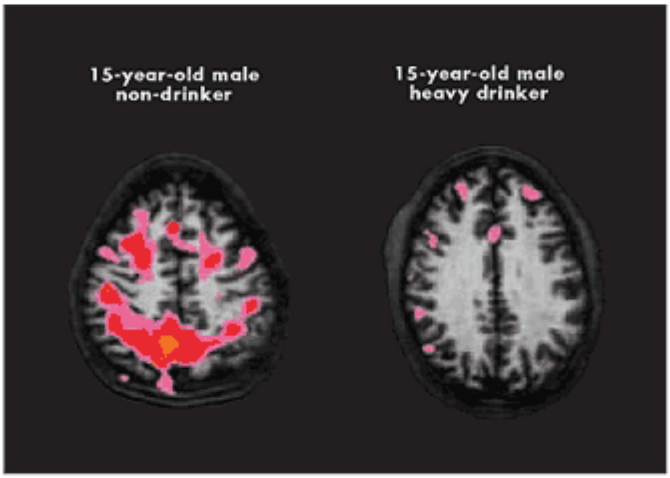
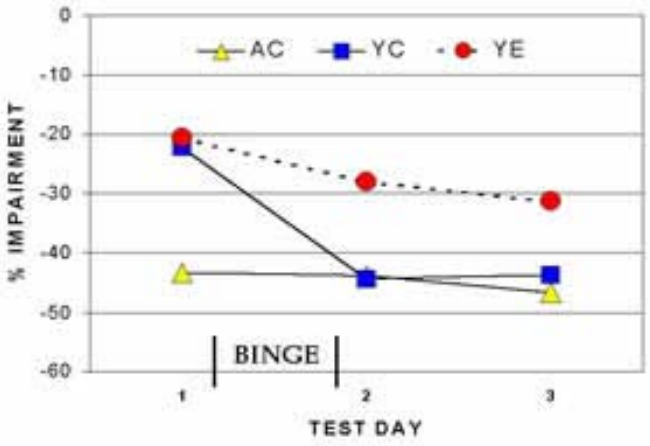


Image from Susan Tapert, PhD, University of California, San Diego.

an information sheet from the Society for Neuroscience entitled, *Brain Briefings: Brains on Alcohol*. Additional images based on Tapert's and Brown's research can be found on the Alcohol Policy Solutions website.

Research with human adolescents clearly suggests that alcohol abuse during the teen years has deleterious effects. For obvious legal and ethical reasons, there are limits to the amount of control a researcher can exert on the variables that might impact the magnitude of the adolescent's impairments or the time course of the recovery. Many researchers have turned to rodents to address these issues. In one of our recent studies, we observed what we believe is a striking, long-term effect of developmental alcohol exposure in rats (White et al, 2002c). We found that CIE treatment (5.0 g/kg IP, every 48 hrs for 20 days) during adolescence interferes with the normal increase in sensitivity to alcohol-induced motor impairments that occurs between adolescence and adulthood. As expected, under control conditions (i.e. repeated saline exposure), rats were more sensitive to the effects of alcohol on postnatal day 65 (young adulthood) then they had been on postnatal day 30 (adolescence). This is consistent with the previous reports that rats become more sensitive to the motor impairing effects of alcohol as they progress from adolescence to adulthood (White et al., 2002b). However, animals that received CIE during adolescence did not show the normal pattern of increased sensitivity to alcohol as they aged into adulthood. In these subjects, the impact of acute alcohol on motor coordination remained unchanged before, two days after, and 16 days after CIE treatment. In contrast to the effects of CIE in adolescents, CIE treatment during adulthood had little



Alcohol exposure during adolescence has lasting effects

The above figure shows the effects of alcohol on motor coordination during three different test days (Test Day 1,2,3). The lower on the chart the data point is (i.e., the closer it is to this sentence), the bigger the impairment. Between Test 1 and Test 2, rats received 10 injections (one very 48 hrs) of either saline or alcohol. Test 3 occurred 16 days after the treatment period ended. The purpose of the experiment was to determine whether this pattern of alcohol treatment (sometimes called binge pattern treatment) has a lasting influence on the way adolescents and adults respond to alcohol later in life. The chart above shows that the effects of alcohol on motor coordination in adult rats treated with saline between Test 1 and Test 2 (group AC) remained quite stable across the three test days. The effects of alcohol on motor coordination in adolescent rats treated with saline increased dramatically between Test 1 and Test 2 (group YC), showing the clear age-related increase in senstivity to alcohol-induced motor impairments. Notice that adolescent rats treated with alcohol between Test 1 and Test 2 (group YE) do not show the same age-related increase in sensitivity. In fact, even a few weeks later, they continued to exhibit the same level of sensitivity shown during the first test day. While the data aren't shown in this particular graph, adult rats treated in the binge pattern exhibited only a short-lasting change in sensitivity alcohol.

impact on the subsequent effects of alcohol on motor coordination. This suggests the possibility that the chronic exposure during adolescence may have “locked in” the adolescent insensitivity to alcohol’s sedative effects, or at least significantly delayed the normal progression to greater sensitivity in adulthood. The data raise the distinct possibility that repeated exposure to alcohol during adolescence might alter the normal trajectory of brain development in long-lasting, perhaps permanent, ways.

Long-lasting cognitive deficits have also been observed in rodents exposed to alcohol repeatedly during adolescence. For instance, our preliminary data indicate that CIE treatment in adolescent rats results in exacerbated alcohol-induced learning deficits in adulthood (White et al, 2000). Adolescent and adult subjects were treated with CIE (5.0 g/kg, IP every 48 hrs for 20 days) and then trained on a spatial memory task. All subjects acquired the task at similar rates. However, when their memory was tested under acute alcohol (1.5 g/kg), subjects treated with CIE during adolescence performed more poorly than the other groups. This finding is consistent with a recent report on the impact of alcohol on memory in college students. Weissenborn and Duka (2003) assessed the impact of acute alcohol exposure on memory in college students. Those with a history of binge-pattern drinking performed more poorly while intoxicated than other subjects.

Cognitive impairments following repeated alcohol exposure and withdrawal may stem from neurotoxicity in the hippocampus and related structures. Crews et al. (2000) reported that adolescent rats exposed to alcohol in a four-day binge pattern suffer extensive brain damage that includes structures that provide the hippocampus with the information that it needs to form memories. This damage was more extensive in adolescent subjects than in adults exposed to alcohol in the same pattern. A study by De Bellis et al. (2000) provides preliminary evidence that, in humans, alcohol abuse during adolescence is associated with a reduction in the volume of the hippocampus. The authors utilized magnetic resonance imagine (MRI) to assess the size of the hippocampus in subjects with adolescent-onset alcohol use disorders and in normal control subjects. Hippocampal volumes were smaller in those who abused alcohol during adolescence, and the amount of apparent hippocampal damage increased as the number of years of alcohol abuse increased (i.e., the longer one abused alcohol, the smaller the hippocampus became). Total intracranial, cortical gray and white matter, corpus callosum and amygdala volumes did not differ between groups. Such data suggest that the adolescent hippocampus is sensitive to the neurotoxic effects of alcohol, and that the earlier in adolescence one begins abusing alcohol, the greater the risk for producing hippocampal damage. However, whether adolescents are truly more vulnerable than adults to hippocampal damage following alcohol exposure remains to be seen.

Damage to the hippocampus following repeated alcohol exposure might stem from too much activity at the NMDA receptor, a particular type of receptor for the neurotransmitter glutamate, during alcohol withdrawal. Too much activity at these receptors could allow intracellular levels of calcium (Ca2+) to become too high, which can damage and even kill a cell. Evidence for this remains indirect, but such an effect is certainly feasible based on research examining the impact of alcohol on NMDA receptor activity in slices of brain and cultured neurons (Grant et al, 1990; Hoffman and Tabakoff, 1994; Snell et al, 1993; Crews and Chandler, 1993)

While the long-lasting effects of alcohol abuse during adolescence might reflect brain damage in the traditional sense, there is certainly reason to believe that such effects might also involve alterations in normal brain development. As discussed above, the adolescent brain is a brain in flux. There are a number of important changes taking place during this stage of development. It is possible that alcohol, and other drugs, alters the course of brain development in a way that might be hard to correct if the abuse persists throughout the adolescence period. Such changes would clearly be considered "damage", but not in the traditional sense of the word (i.e., this type of damage could occur without the death of a single cell).

Summary

While the overall size of the brain increases little beyond early childhood, important structural and functional changes take place as one progresses from childhood to adulthood (Giedd et al., 1999). Recent evidence suggests that, as a result of the changes in brain function that occur during adolescence, alcohol affects adolescents differently than it affects adults (for review see Spear, 2000). Adolescent rats are more vulnerable than adults to the effects of alcohol on memory (Markweise et al., 1998), a finding that might stem from developmental changes in the impact of alcohol on the functioning of a part of the brain known as the hippocampus (Pyapali et al., 1999).

It also appears that adolescents might be particularly vulnerable to the long-lasting effects of alcohol use. Preliminary data suggest that alcohol exposure during adolescence makes rats more sensitive to alcohol-induced memory impairments later in life (White et al., 2000). In humans, cognitive impairments have been detected in adolescent alcohol abusers weeks after they stop drinking. The causes of these long-lasting changes are unclear, but they might involve brain damage and/or alterations in normal brain development. In rats, alcohol exposure produces more extensive brain damage in adolescents than adults (Crews et al., 2000). In humans, alcohol abuse during adolescence has been associated with a decrease in the size of the hippocampus (DeBellis et al., 2000).

The available evidence suggests that adolescents might actually be less sensitive than adults to some of the effects of alcohol. Adolescent rats are less vulnerable than adults to the sedative effects of alcohol, as well as to the effects of alcohol on balance and motor coordination (Little et al., 1996; White et al., 2001). While it is not known whether these differences occur in humans, the findings suggest that adolescents might be able to stay awake and mobile at higher blood alcohol levels than their adult counterparts, all the while being more vulnerable to alcohol-induced cognitive impairments and, perhaps, brain damage.

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