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# Exploring the Connections Between Alcohol Abuse and Cognitive Deficits: A Review of Alcohol's Effects on Brain Development and Memory Formation

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# Exploring the Connections Between Alcohol Abuse and Cognitive Deficits: A Review of Alcohol's Effects on Brain Development and Memory Formation

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# ABSTRACT

Often overlooked and trivialized, Alcohol Use Disorder (AUD) affects 15 million Americans over the age of 18. As of 2015, it was reported that only 6.7% of these individuals received treatment necessary to recover.[34] Perhaps even more alarming, the NIH reports alcohol to be the third leading preventable cause of death in the United States annually.[1,12] As these numbers steadily increase, scientists have become more interested in alcohol addiction and reward pathways, memory deficiencies secondary to alcohol abuse, and the potential development of pathologies like Wernicke-Korsakoff Syndrome.

Previous studies have shown that excessive drinking damages nerve cells that ultimately affect the brain's cognitive functioning. The question the researchers are attempting to answer is at what age are men and women more susceptible to alcohol's damaging effects.[35] Though there is significant understanding of addiction-reward pathways, there is less understanding of the neurological basis of memory loss during periods of binge drinking and severe memory deficiencies that occur during Wernicke-Korsakoff Syndrome. Only more recently have researchers begun using animal models to support their hypothesis that alcohol impairs memory formation by disrupting hippocampal activity.[14] This capstone project is a literature review of different mechanisms of memory loss due to the indirect and direct effects of alcohol on the hippocampus and other brain structures. The research collected explores the neurological basis of memory loss during periods of binge drinking, as well as the effects of alcohol on brain development. Treatment options and psychosocial effects of alcohol addiction will be discussed.

# BACKGROUND

## Alcohol Use Disorder

The National Institute of Alcohol Abuse and Alcoholism defines Alcohol Use Disorder as a "chronic relapsing brain disease characterized by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using."[1] "Alcohol abuse" and "alcohol dependence," are two commonly used categorizations of abnormal alcohol consumption that are merged to form one medical diagnosis: Alcohol Abuse Disorder (AUD).[36] Educators and researchers alike have attempted to eradicate the misuse of the previously accepted disorder classification, "alcoholism," though Alcoholics Anonymous and other recovery establishments continue to incorporate the term in a colloquial manner. In order to be diagnosed with AUD, 2 of 11 of the criteria below must be met.

| | | | |
|---|---|---|---|
| Mild AUD - 2 to 3 symptoms | Moderate AUD - 4 to 5 symptoms | Severe AUD - 6 or more symptoms | Alcohol is often taken in larger amounts or over a longer period than was intended. |
| | | | There is a persistent desire or unsuccessful efforts to cut down or control alcohol use. |
| | | | A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects. |
| | | | Craving, or a strong desire or urge to use alcohol |
| | | | Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home. |
| | | | Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol. |
| | | | Important social, occupational, or recreational activities are given up or reduced because of alcohol use. |
| | | | Recurrent alcohol use in situations in which it is physically hazardous. |
| | | | Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol. |
| | | | Tolerance, as defined by either of the following: a) A need for markedly increased amounts of alcohol to achieve intoxication or desired effect; b) A markedly diminished effect with continued use of the same amount of alcohol. |
| | | | Withdrawal, as manifested by either of the following: a) The characteristic withdrawal syndrome for alcohol (refer to criteria A and B of the criteria set for alcohol withdrawal); b) Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms. |

Table 1. Criteria required to meet an Alcohol Use Disorder Diagnosis.[1]

The severity of AUD is classified as mild, moderate, or severe, depending on the number of criteria met by the individual in question.[1] The consequences of Alcohol Use Disorder (AUD)

are devastating. It is estimated that half of the adults diagnosed with some degree of AUD are free from neurological impairments. However, nearly 2 million Americans suffering from AUD have developed debilitating ailments that require long term and permanent care.[2] These conditions include, but are not limited to, Wernicke-Korsakoff Syndrome, Alzheimer's Dementia, Cardiovascular and Circulatory Disease, numerous types of cancer, metabolic disorders, and stroke.[3]

**The Prefrontal Cortex and the Limbic System**

Numerous studies have discovered the limbic system and frontal lobe's vulnerability to alcohol-related brain damage. The frontal lobes send and receive fibers to subcortical structures and are connected to many other lobes of the brain. The prefrontal cortex is responsible for executive functioning, which includes perception, memory, language, and attention.[6] The limbic system is the control center for urges and emotions and is the fundamental force behind human behavior. Therefore, it is necessary for survival. In addition, the limbic system's main function is involved in memory formation.[4] There is some disagreement about which structures should be classified as parts of the limbic system. For the purpose of this review, the hippocampus, amygdala, nucleus accumbens, and hypothalamus will be the primary focus, as all of these play into the development of alcohol addiction. The brain structure associated with this area of memory formation is the hippocampus, which is minimally involved in non-declarative aspects of memory, such as learning new habits, perceptual reasoning, and motor learning.[5] In addition to this, it is responsible for consolidating information from short-term memory to long-term memory and is vital in spatial learning.[5] The hippocampus must be fully functioning for implicit non-declarative memory to occur. The amygdala is located deep within the anteroinferior region of the temporal lobe.[2,4] It plays a major role in emotional responses, emotional processing, and

decision making which is largely due to the number of connections it fosters. The amygdala has connections to the septal nuclei, medial dorsal nucleus of the thalamus, and the hippocampus.[2] The amygdala causes an individual to feel fear and also jump starts the flight or fight response by sending signals to the brainstem and hypothalamus. Any slight dysregulation in the amygdala can lead to a number of issues in connected areas of the brain. The effect of alcohol is just one factor that may lead to this dysregulation. The amygdala plays a role in detecting danger and self-preservation, and overconsumption of alcohol can detrimentally affect the amygdala and its functioning, which is why individuals are often described as over-emotional and impulsive while intoxicated. Additionally, it is believed that the amygdala allows one to recognize the emotions in another individual, while also lending "emotional coloring to our speech."[4] The hypothalamus is a small structure located within the limbic system, below the thalamus. Its primary roles include regulatory functions, such as temperature control, hormone regulation, eating and drinking, and emotion.[2] Finally, the nucleus accumbens is a small portion of the reward system in our brain. It assists in stimuli analysis, processing, and reinforcement. In addition to this, it appears to be responsible for assigning importance to the alcohol exposure experience.[7]

**Effects of Alcohol on Adolescents**

As the number of adolescents aged 12-17 are diagnosed with AUD skyrockets annually (623,000 adolescents were diagnosed with AUD in 2015), researchers have begun to focus their attention on long term consequences.[1] How do periods of binge alcohol consumption affect an underdeveloped brain? Will these adolescents have problems with memory at a younger age than their non-drinking counterparts?

As one can likely infer, the effects of alcohol differ in adolescents and adults due to structural brain differences and the natural process of maturation. Many studies have

demonstrated that the brain remains highly active during adolescence. More specifically, the process of myelinogenesis, or the generation of myelin sheaths in the central nervous system, continues during puberty and well into an individual's mid twenties.[23] During adolescence, the brain experiences a massive surge of myelinogenesis in the frontal lobe.[24] This surge is responsible for the honing of many cognitive processes fully developed in adulthood, such as logical decision making, planning and prioritizing, and judgment. During a study comparing adolescents' prefrontal cortices to adults' prefrontal cortices, it was determined that adolescents are far less likely to use this structure when making decisions based on interpersonal interactions.[25] Rather, adolescents relied on limbic system structures when reading another person's facial expressions during the attempt to read another's emotions. One study of MRIs of the adolescent brain have indicated the fact that development processes occur in a "front to back" pattern, demonstrating why the prefrontal cortex is not fully developed until the age of 25. In this study, researchers discovered that adults have far more white matter in the frontal lobe when compared to teenagers.[24] From this information, it can be inferred that improved neurocircuitry, or the flow of information between different brain structures, is reached during adulthood. Given the notion that both limbic system structures and the prefrontal cortex are not fully developed during adolescence, it is unsurprising that adolescent brains are more vulnerable to alcohol's effects. Multiple studies were conducted on adolescent rats in order to create animal models of adolescent intermittent exposure to ethanol.[26] In one study, adolescent rats were exposed to high quantities of alcohol via ethanol vapors consistent with the amount of alcohol consumed during a period of binge drinking. Numerous long-lasting neurophysiological changes were recorded, such as reduction in the total amount of time spent in slow-wave sleep.[27] These findings were consistent with sleep patterns observed during advanced aging and are often seen on the pathway

to development of Alzheimer's disease. This research eventually led to a study indicating alteration of 638 genes in the medial prefrontal cortex of adolescent rats exposed to periods of binge alcohol consumption. As the rats aged and eventually reached adulthood, the aforementioned genes belonging to inflammatory pathways and cellular stress were largely increased, indicating long-term damage. The number of genes usually associated with astrocyte production was significantly decreased, thus showing a lower production of prefrontal cortex astrocytes in adult rats exposed to high quantities of alcohol during adolescence.[28] This research sparked numerous questions, mostly along the lines of whether or not damage to this degree would have occurred had the rats been adults rather than adolescents at the time of alcohol exposure. Due to ethical limitations, it is much more difficult to perform these types of experiments on humans. Thus, research on the human brain is currently limited to comparisons of structural MRI studies from a predetermined population. In one notable study, adolescents who partook in binge drinking had larger grey matter volume of the dorsolateral prefrontal cortex compared to those who do not drink alcohol.[29] The dorsolateral prefrontal cortex is one of the most recently derived parts of the human brain and is responsible for higher cognitive processing. Additionally, it undergoes a long maturation period that continues into adulthood.[30] Scientists in Finland conducted a 10 year follow up study. They established that adolescents diagnosed with alcohol use disorder displayed significant reduction in grey matter volumes in the insular cortex, anterior cingulate cortex, and orbitofrontal cortex when compared to non-drinking adolescents.[31] All of these structures belong to the limbic system or prefrontal cortex. These studies were successful in demonstrating alcohol's detrimental effects on the structure and function of the developing adolescent brain.

A common question posed by many scientists is centered around the potential of alcohol's potential during adolescence to affect brain function later down the road. As mentioned previously, adolescence is the time in which the brain is creating new neuronal networks and connections. Due to the constant process of remodeling during this time, it is understood that drinking large consumptions of alcohol can stunt the brain's growth and cause problems with behavior and responses to alcohol during adulthood. When considering binge drinking, adolescents are considered to be the most vulnerable age group. According to the National Institute on Alcohol Abuse and Alcoholism, binge drinking is defined as "repeated episodes of heavy drinking followed by withdrawal."[37] One study was interested in determining whether or not spatial memory deficits exist in adulthood in populations that experienced intermittent chronic alcohol exposure during adolescence. After the adolescent population of rats were given large amounts of alcohol, they were again evaluated as adults via a food maze. The control rats had never received alcohol. It was determined that all rats, those who had never been exposed to alcohol and those who had received it in copious amounts during adolescence, performed the memory experiment with equal success. In a second test, all rats were given alcohol prior to the task. Those who underwent intermittent chronic alcohol exposure did not perform as well as those who were never exposed to alcohol during adolescence.[40] This demonstrated the increased sensitivity to the memory-impeding effects of alcohol during adulthood when previously exposed in adolescence. In order to further discuss their conclusions, a similar test was carried out in college-aged students. Those with binge drinking history did not perform as well during a memory task after being given alcohol as those who had never participated in binge drinking.[41] Another study was conducted on adolescent and adult rats that aimed to show the long term effects of adolescent alcohol abuse. Before this experiment was conducted, it was concluded that

adolescents are typically less sensitive than adults to motor activity under the influence of alcohol. During the experiment, scientists repeatedly exposed adolescent aged rats to elevated amounts of alcohol. They were then later evaluated as adults to determine the ways in which alcohol consumption in adolescence affects motor activity in adulthood. The study found that the rats performed better than expected during the tilted plane test, similarly to how they performed in adolescence. In fact, the rats never showed increased motor deficits in adulthood secondary to alcohol consumption during adolescence.[39] In summary, the alcohol treatment each adolescent rat received did not lead to motor impairment later on. Rather, it was found that the alcohol exposure interferes with brain development processes that eventually cause the motor sensitivity secondary to alcohol exposure seen in adults.

Moving forward, scientists were looking to conduct experiments that could compare the electrical brain activity of adult rats that had or had not been exposed to intermittent chronic alcohol exposure during adolescence in hopes of translating their findings to human populations.[42] Their experiment exhibited drastic changes in the electroencephalogram (EEG) and event-related potentials (ERPs), measures of brain activity denoted by spikes caused by stimulus. Specifically, the hippocampuses of adult rats exposed to alcohol were focal points showing explicit changes during the experiment. Conversely, rats who had not been previously exposed to alcohol during adolescence showed no changes in EEG/ERPs.[43] Finally, following the analysis of results from the aforementioned experiment, scientists sought to link adult rat behavior to EEG and ERP changes. They concluded that rats with EEG/ERP changes in the hippocampus who had previously been exposed to alcohol in adolescence and again in adulthood did not show as many behaviors indicative of intoxication when compared to the control populations.[42] Through this study, they determined that alcohol exposure during adolescence

may lead to persistent changes in brain activity following acute exposure to alcohol in adulthood. Lastly, they noted exposing an adolescent to alcohol can cause responsiveness changes to some of alcohol's effects, such as motor coordination, apparent intoxication, and sedation.[43]

**Structural and Functional Brain Changes Secondary to Acute Alcohol Use**

As mentioned previously, some brain structures are more vulnerable to alcohol's effects than others. Extensive research has been conducted on both rodents and primates demonstrating that the hippocampus is especially vulnerable to alcohol's toxic properties at all ages of life. Morphological and functional changes of the hippocampus have been observed in both animal populations.[32] Rats exposed to alcohol had slower response times and poorer overall performance completing the Morris Water Maze task when compared to those who had not been exposed to alcohol. This task tests both episodic and spatial memory by observing a rat's escape tendencies when placed in a water maze. Alcohol exposed rats generally became confused, took longer to escape, or did not escape at all when compared to non-exposed rats.[33] As mentioned previously, measuring alcohol's effects on the adult brain and memory is more difficult. Memory tests are often adversely affected by alcohol consumption, but generally it is too difficult to eliminate all other confounding variables to get an accurate idea of alcohol's direct effects. Because of this, observing hippocampal volume differences is the most common research method when studying memory function in human subjects.

A recent study aimed to analyze the acute effects of alcohol on human brains via 3D arterial spin-labeling and diffusional kurtosis imaging.[44] According to the scientists conducting the experiment, this allows one to discover functional and structural brain changes following acute alcohol exposure. The methods stated above were performed on 24 volunteers at three distinct time periods: before drinking alcohol, 30 minutes after consumption, and one hour after

consumption. Participants were observed and separated into two groups: blushing and non-blushing. Of the 24 brains from this group, 20 brains were randomly selected and analyzed. The researchers found that in all subjects one hour after drinking, there was increased cerebral blood flow in the frontal regions of the brain, but decreased perfusion in the anterior commissure.[44] Additionally, mean alcohol diffusion within the brain was decreased after one hour in most subjects while mean kurtosis increased after the 30 minute benchmark.[44] In some cases, this may be secondary to a process called cytotoxic edema, in which myelin fiber bundle space is reduced.[46] On the other hand, many studies suggest a decrease in mean brain diffusion may point to vasogenic edema.[45] The results indicated that those in the blushing group, or those with marked increased cerebral blood flow, may experience more severe effects of edema following periods of drinking.[44] This may eventually lead to neurologic injury of the affected brain regions. Their findings after completing both arterial spin-labeling and diffusional kurtosis imaging suggest that structures such as those found in the limbic system, the cerebellum, the thalamus, and the frontal lobes are more susceptible to brain damage secondary to alcohol use than other cerebral areas.[44]

**Brain Reward Circuitry and Reinforcement in Relation to Addiction**

The brain reward system controls primary physiological functions of survival. These include water and food homeostasis and sexual behavior. Perhaps more relevant, many psychoactive substances, such as alcohol, for example, target the reward system directly.[8] Extensive research relating the dopaminergic system and alcohol dependence has been conducted over the years. Dopamine in the central nervous system is largely produced in the substantia nigra.[8] The dopamine system partially controls the amygdala and is responsible for the pleasurable feelings and emotions associated with alcohol intake while the hippocampus is

activated to create memories of this sense of satisfaction.[2,9] In basic terms, addictive drugs, such as alcohol, cause a dopamine rush in the nucleus accumbens. Finally, the amygdala is responsible for producing a conditioned response to a particular stimuli.[10] According to one finding, "alcohol and alcoholism have both positive and negative reinforcing properties."[7] The positive reinforcing effects, secondary to alcohol intoxication after overconsumption, acts via signal transduction pathways which ultimately affect mesocorticolimbic dopamine pathways,[10] the most important reward pathways in the brain. The circuitry starting in the ventral tegmental area (VTA), located in the brainstem, synapses in the nucleus accumbens (VTA-NAc), which is the key structure in detecting a rewarding stimulus. The dopaminergic neurons reside in the VTA and target the nucleus accumbens, also known as the ventral striatum, which is responsible for mediating rewarding effects of alcohol and other substances.[11] The amygdala interacts with the VTA-NAc in that it decides the value, rewarding or unrewarding, of a particular stimulus. With the help of the hippocampus, the amygdala establishes memories of alcohol experiences, making it a necessary aspect of addiction relapse.[11] Perhaps least understood in brain reward circuitry are the portions of the frontal lobe, such as the medial prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex. These areas are responsible for executive control of decision making when pursuing a stimulus in the environment after the primary interaction. In other words, they are involved in the actions that follow and are learned after experiencing a situation that evokes a particular emotion. When a specific experience is repeated, the emotions evoked are recognized, allowing one to make connections leading to an appropriate reaction or response. In turn, this allows an individual to learn from previous mistakes and understand specific triggers of emotions. While this is well understood, much still remains uncovered.

Positive reinforcement, negative reinforcement, and neuroadaptation are all factors that play into the enhancement or inhibition of brain reward circuitry in alcohol addiction. Alcohol has many positive reinforcing factors, and these are generally partially responsible for the eventual development of alcohol dependence. Most studies displaying positive reinforcing factors are animal models of self-administration. In addition to this, there are animal models that mimic binge drinking in human populations. This is also a type of self-administration defined in humans as excessive drinking that causes one's blood alcohol content to rise higher than 0.08 within a 2 hour period.[47] This type of repeated behavior often leads to dependence.

Alcohol's negative reinforcing effects can contribute to addictive-like behavior in those diagnosed with other psychiatric disorders such as anxiety and depression.[47] Often, those individuals use alcohol as a means of self-medication. Generally speaking, non-dependent alcohol use is triggered by positive reinforcing factors. The full dependent state is typically seen as precipitated by both negative and positive reinforcing factors. Chronic exposure to large volumes of alcohol can actually lead to a rewiring of neural circuitry through a process known as neuroadaptation. The three concepts that make up the process of neuroadaptation are sensitization, tolerance, and withdrawal.[48] During sensitization, addictive substances such as alcohol activate a neural system related to incentive and satisfaction which attribute events and stimuli with the substance itself.[49] An individual thus begins to link the substance to general contentment with it, causing one's enjoyment of alcohol to lead to wanting alcohol. As exposure to alcohol increases, the desire becomes much stronger. It then has the ability to morph into a pathological craving.[48] At this point, tolerance is beginning to build. An individual who becomes more dependent on a substance begins to feel less and less of the substance's effects. For example, it takes a larger volume of alcohol for someone who has built a tolerance to feel off-

balance, experience cloudy thinking, and begin to exhibit slurred speech. In order to experience the same desired effects the alcohol had on the individual previously, they require higher amounts of alcohol in the same amount of time.[48] Once alcohol has been present in one's life chronically, the abrupt removal of alcohol from a daily routine may cause a myriad of withdrawal symptoms. Most times, these symptoms urge the victim to seek and ingest the drug for symptom alleviation. Symptoms can last up to 48 hours and may require hospitalization. Common symptoms include tachycardia, sweating, restlessness, motor abnormalities, and convulsions.[48] Long term problems stemming from alcohol withdrawal may include anxiety and irritability.[50]

**Alcohol's Effects on Memory Processing**

As per the National Institute on Alcohol Abuse and Alcoholism, "Alcohol primarily interferes with the ability to form new long–term memories, leaving intact previously established long–term memories and the ability to keep new information active in memory for brief periods."[12] This explains why many adolescents do not remember the occurrences after a long night of binge drinking. One of the most common areas of memory examined in alcohol abuse disorder patients is episodic memory, which is the branch of declarative memory dedicated to voluntary retrieval and storage of specific events.[13] Episodic memory is crucial for the development of a person's identity and the completion of routine and daily tasks.

Though it is true memory loss secondary to long term alcohol abuse is common, memory loss can occur during periods of binge drinking as well. However, the mechanisms are quite different. Blackouts can be thought of as episodes of amnesia. These periods of amnesia are

"anterograde," indicating alcohol's role in blocking the ability to form new memories while the person is intoxicated.[14] As the amount of alcohol consumed increases, so does the level of impairment. Large quantities of alcohol consumed on an empty stomach can be the direct cause of a blackout.[12] It was once thought that periods of binge alcohol consumption directly killed brain cells, resulting in many different types of neurological impairments that go hand in hand with a night out. This was never supported by any scientific evidence, but rather was an extrapolation of what actually occurs on a neurobehavioral and molecular level during periods of binge drinking. A group of scientists decided to test out the previously thought notion that alcohol directly kills neurons. They collected the brains of 55 of alcoholic individuals with the intent of measuring and comparing neocortical neuron loss to control (non-alcoholic) samples. According to their results, there was no significant difference in volume of the ventricles between both groups.[56] Furthermore, there was no significant difference in volume of central grey structures between the non-alcoholic and alcoholic brains.[56] From this and an analysis of similar research done by other investigators, they were able to conclude that there was no neocortical neuron loss found in the brains of the alcoholic samples. This does not, however, take away from the fact that these individuals suffered greatly from their disease and potentially experienced the effects of cognitive decline in other ways. One example of this is the reality that many of these individuals likely experienced short-term memory lapses during their binges.

Neuroscientists at Washington University School of Medicine have identified the brain cells and molecular mechanisms that would account for these short term memory lapses. Instead of brain cell death, studies have shown alcohol damages dendrites within the cerebellum, thus reducing communication between neurons.[15] The damage to these neurons likely explains motor deficits and loss of coordination experienced during heavy periods of drinking. In addition,

alcohol causes a severe interference with key receptors in the brain that produce steroids responsible for the inhibition of long term potentiation. Brain cells affected by alcohol have been localized to the hippocampus and can interfere with the formation of new memories as well.[16] A common structure of interest within the hippocampus is the CA1 cells. Researchers have found that the CA1 region within a rodent's hippocampus correlates strongly with spatial learning and behavior,[37] causing it to be a focal point when testing alcohol's effects on the memory process. Alcohol has been shown to impede the process of long term potentiation in adolescents and adults. Long term potentiation is dependent on the NMDA receptor and glutamate.[37] To sum up numerous studies, it is believed that alcohol interferes directly with the NMDA receptor by inhibiting glutamate. Glutamate's activation of the NMDA receptor allows for an influx of calcium, which allows for many long term structural and functional cell changes that lead to long term potentiation.[37] When alcohol impedes the NMDA receptor, calcium is released in smaller quantities, changing the ways in which vital functional and structural cell changes occur that eventually lead to long term potentiation.[38]

Alcohol induced blackouts have been characterized into two distinct categories: en bloc blackouts and fragmentary blackouts. En bloc blackouts can be thought of as complete anterograde amnesia, in which the individual experiencing it does not remember any detail from the events occurring while he or she was intoxicated. Essentially, the process of converting information from short to long term memory is completely blocked. Because those experiencing en bloc blackouts are able to keep information active in short-term memory for a few seconds at least, they are commonly able to continue with normal activities such as conversation, engagement in complicated behaviors, and unfortunately, automobile operation.[14] If someone says they can remember parts of the events of the night before or remember details when

reminded of what occurred during their period of intoxication, he or she likely experienced a fragmentary blackout. Subjects become aware they are missing pieces of events only after being reminded of what has occurred. Research on these types of blackouts dates back to the 1960s, and many studies indicate fragmentary blackouts are much more common than en bloc blackouts.[17] Many researchers have become concerned with long term memory loss after noting alcohol's extreme effects on short term memory. Some have questioned whether the number of incidents of black outs in adolescence can affect memory formation later on in life. According to a study published in the journal *Neurology,* men who consume 2.5 drinks (classified as beer, wine, or liquor) per day showed earlier signs of memory loss when compared to lighter drinkers.[18] Their study indicated that men drinking 36 grams of alcohol per day or more during midlife were more likely to experience a rapid 10 year cognitive decline. Taking the results collected in the aforementioned studies, a new group of scientists took the research one step further. They aimed to explore whether or not a relationship between type of alcohol and degree of cognitive decline existed. Whiskey, vodka, and gin showed the most rapid declines. No significant differences were found between those who drank wine or beer exclusively.[18] There was weaker evidence of the same effect on middle aged women.[19] This research was in agreement with previous studies suggesting early cognitive decline is likely in men who drink daily during mid-adulthood.[20] Research has also been conducted to determine whether there is a relationship between type of alcohol consumed during adolescence and adulthood and the development of dementia later in life. A few studies reported that individuals who drink wine are at a lower risk for dementia development, though inconsistencies are prevalent [51,52,53]. The preliminary researchers who published their findings in the journal of *Neurology* attempted to uncover the underlying pathways responsible for the cognitive decline they previously discussed.

The hypothesis they focused on states casual to moderate alcohol consumption leads to preferable vascular outcomes,[54] while higher risk of vascular issues are more likely with complete avoidance of alcohol and heavy use that potentially leads to an increase in cognitive impairment.[55]

**Memory Dysfunction Secondary to Wernicke-Korsakoff Syndrome**

Individuals with severe Alcohol Use Disorder who have been drinking for a very long period of time are at risk for developing persistent changes in the brain. It is reported that up to 80% of those with severe AUD also are deficient in thiamine. This is due to the common symptoms of vomiting, diarrhea, and malnutrition endured by many chronically alcohol dependent individuals.[57] In addition to this, those with an alcohol addiction problem experience decreased ability of thiamine absorption in the gastrointestinal tract.[58] Of those persons, some will develop a serious brain disorder known as Wernicke-Korsakoff Syndrome (WKS). WKS are two separate syndromes: "a short–lived and severe condition called Wernicke's encephalopathy and a long–lasting and debilitating condition known as Korsakoff's psychosis."[12] Up to 90% of patients with Wernicke's encephalopathy will develop Korsakoff's psychosis, characterized by severe memory issues. Interestingly, patients have difficulty both recalling old information (retrograde amnesia) and consolidating new information (anterograde amnesia), explaining why patients with Korsakoff's psychosis are often irritable and frustrated in nature.[21] According to a study focusing on MRI studies of patients with Wernicke Encephalopathy, it is "classically described as a triad of encephalopathy, ophthalmoplegia, and gait ataxia; however, studies involving autopsies with confirmed cases demonstrated that only 1/3 of patients present with the triad, with delirium being the most common symptom."[22]

**Structural Brain Changes in Wernicke-Korsakoff Syndrome**

Numerous studies have attempted to analyze structural MRIs in order to determine which areas of the brain are most susceptible to damage during the development of Wernicke-Korsakoff Syndrome. The hallmark MRI of a patient's brain affected by Wernicke encephalopathy generally displays hypersensitivities (bright spots) in the mammillary bodies, area surrounding the cerebral aqueduct, the colliculi, areas near the fornix and thalamus, and area surrounding the third ventricle.[59] (See Figure 1). In addition to this, the MRI findings from this study showed overall mammillary body shrinkage in Wernicke-Korsakoff Syndrome patients.[60]

In a follow-up study, scientists aimed to compare MRIs from healthy patients, patients diagnosed with Wernicke-Korsakoff syndrome, and patients with uncomplicated alcoholism. The MRI findings from this study display mammillary body volume deficits in patients with Wernicke-Korsakoff Syndrome, volume deficits of the hippocampus and thalamus of uncomplicated alcoholics, and no remarkable volume deficits in control patients.[60] These structures discussed are displayed in Figure 2 and show a gradient effect. The volume deficits are seen in the cerebrospinal fluid filled spaces. From the figure it is evident that those diagnosed with Wernicke-Korsakoff Syndrome (Figure 2C) have greater volume deficits than both healthy controls and uncomplicated alcoholic patients (Figure 2B). Uncomplicated alcoholic patients display the second highest volume deficits, followed by healthy controls (Figure 2A).

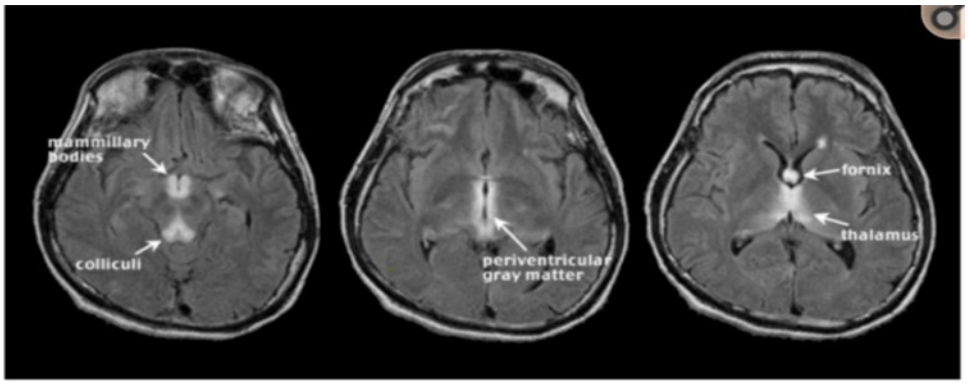


**Figure 1.** MRI of a patient diagnosed with Wernicke encephalopathy.
*Note*. Wernicke encephalopathy. Taken from Alcohol's Effect on the Brain. Zahr, 2017.

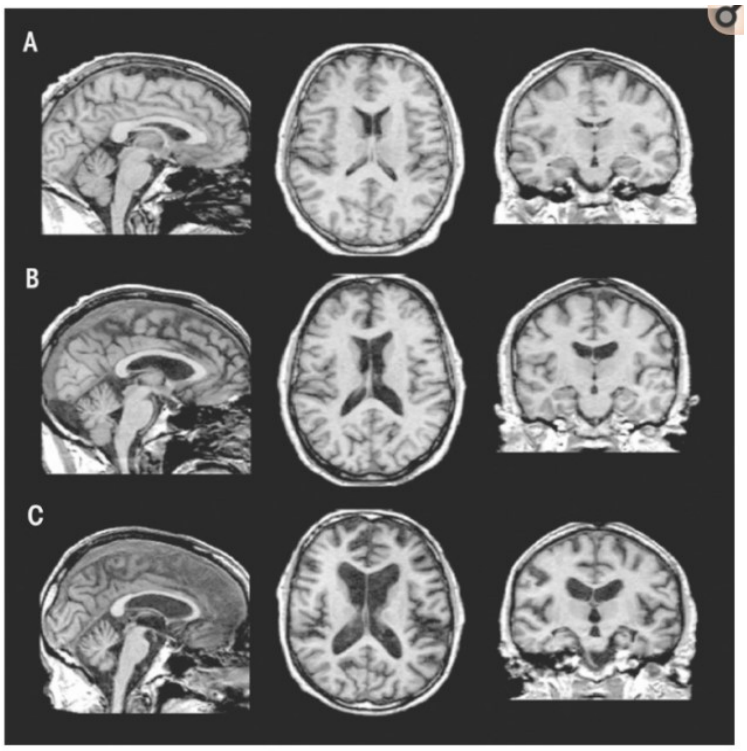


**Figure 2.** A Comparison of MRIs from control patients (A), uncomplicated alcoholics (B) and Wernicke-Korsakoff Syndrome patients (C). *Note*. An MRI Comparison of control brains, Wernicke-Korsakoff Syndrome brains, and Uncomplicated Alcoholics. Taken from Alcohol's Effect on the Brain. Zahr, 2017.

These studies allowed the researchers to create a timeline of potential brain damage that can occur as a person moves through the pathological stages of alcohol addiction. It also encouraged other scientists to look into the ways in which the brain is affected during

uncomplicated alcoholism. Because of these studies and findings, there is hope for healthcare providers to be able to provide a more succinct diagnosis for patients with complicated health histories and comorbidities moving forward.

# DISCUSSION

## Treatment Options

While determining that an individual is suffering from Alcohol Abuse Disorder is fairly straightforward, more difficulties arise when determining to what degree he or she has the disease. Physicians are first required to ask his or her patient a myriad of questions related to drinking habits. A physical examination will also be part of the clinical assessment. In addition to this, laboratory tests will be performed to assess liver enzyme levels and potential organ damage secondary to alcohol abuse. In most cases, a psychological evaluation is performed. Finally, physicians use the guidelines set forth by the DSM-5 in reaching a proper diagnosis.[1]

Treatment varies depending on the individual's specific needs. Treatment includes but is not limited to: Detox and withdrawal, working with alcohol treatment specialists, psychological counseling, oral medications, injected medication, treatment for outside medical problems, and spiritual support. For some cases, residential and rehabilitation treatment centers are an option.[61] It is important to note that most oral medications are used to treat symptoms of withdrawal. With all of these treatment options, it seems as though anyone suffering should be able to fully recover. Sadly, this is not the case. It is estimated that between 40-60% of people who have been treated for alcohol use disorder relapse.[62] Why is this? One of the biggest reasons is the fact that

there is no magic pill or patch to help curb an alcohol addict's desires. Smokers have nicotine patches. Heroin users can seek methadone clinics. While these certainly do not fix the problem, they are important tools an addict has access to. Unfortunately, those suffering from alcohol abuse disorder do not have these options. The best thing they can do is avoid situations in which alcohol is present. This means they may have to make the decision to skip outings with friends and family. They may have to avoid social situations completely, which often adds to the problem and causes relapse. Not only that, some life events are completely unavoidable. Anything can happen at any time, and this could be enough to push a previously recovered alcohol addict back over the edge.

**Psychosocial Aspects of Alcohol Addiction**

As many are aware, alcohol is a part of most cultures. In many places, it is even considered to be part of everyday life. One of the reasons an addiction to alcohol is so dangerous is directly because of how easily it can be concealed. On the outside, you might see your coworker appearing extra tired on Monday mornings. They come into work and do their work, and then goes home. Outsiders do not see them go into a bar immediately after work and down four drinks before heading home to their family, only to continue drinking after they arrive. Maybe your friend has the tendency to get a little bit out of hand when you all go out on the weekends. Surely they don't have a problem, right? The truth is, going out and drinking with friends and getting a little bit carried away is socially acceptable. Going to a public place with friends and shooting up is not only socially unacceptable, it's illegal. Because there is no public shame for a person simply enjoying a drink at a bar, it becomes problematic for an individual suffering from an alcohol addiction. One drink won't hurt, right? Or, will it?

The problem with alcohol addiction is the brass-fisted hold it takes on its victim. Due to fears of social backlash, the problem is often kept within while the person struggling is left alone and defeated. Alcohol addiction is controlling. It has the ability to encourage its victim to lie. It creates world-class actors right before your very eyes. It does not stop when it tears families apart. It won't cease when the individual has lost a job. No one can help the victim but themselves, which is the trickiest and most discouraging aspect of the disease. The desire to loosen the addiction's grip must come from within.

Those who I have heard speak at Alcoholics' Anonymous all have one thing in common. They are misunderstood. Their mental illness is often disregarded. In fact, all of them have been told to "get a grip," which is physically and emotionally impossible without the proper treatment and support groups. They are accomplished artists, parents, and nurses who have lost their way. Alcoholics frequently endure a terrible reputation if they are unable to keep their battle silent. Phrases like "He or she is a drunk," or "I'm such an alcoholic," (when no alcohol dependence issue exists) are problematic. Society should work to develop a more compassionate stance when viewing and handling some of the most vulnerable populations.

# FUTURE STUDIES

Interestingly, there is not much current research being done on active alcohol use disorder sufferers. It was surprising to see the majority of research on neurobehavioral processes, molecular pathways, and neurocircuitry addiction patterns to be from the 1990s-2000s. As mental illness in America continues to climb, it would be interesting to see the effect this has on alcohol use disorder.

Alcohol research definitely needs to expand to further understand brain circuitry and its control over behaviors caused by alcohol. In addition to this, the amount of research on living individuals suffering from alcohol use disorder is minimal. Most of the research discussed in this literature review was conducted on animals or was taken from deceased patients. Perhaps this is the reason there isn't much to offer as a means of treatment aside from therapy and rehabilitation. It could be beneficial to increase funding for clinical trials to see if an alternative treatment option could become available as a therapeutic intervention.

In the future, studies should include larger populations with more diversity. The majority of experiments were conducted on men only, and it is known that alcohol affects women in different ways than it affects men. In addition to this, very little research has been done on individuals in the 25-35 year old age group. However, this could be partially due to the patient not yet reaching a severe degree of alcohol use disorder and neglecting to ask for help. Nonetheless, alcohol research typically targets the elderly male population if it is dealing directly with human subjects.

Finally, I believe more psychosocial studies should be conducted to shed more light on alcohol abuse disorder as a recognized mental disorder. This may encourage the dissipation of social stigmas and motivate victims to seek help. The more we understand as a society, the better equipped we will be to assist those who need us the most.

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