The Hippocampus and Blackout

Aaron White (2003):

Subsequent research with other patients confirmed that the hippocampus, an irregularly shaped structure deep in the forebrain, is critically involved in the formation of memories for events (see figure 2 for a depiction of the brain, with the hippocampus and other relevant structures highlighted). Patient R.B. lost a significant amount of blood as a result of heart surgery. He survived but showed memory impairments similar to those exhibited by H.M. Upon his death, histology revealed that the loss of blood to R.B.'s brain damaged a small region of the hippocampus called hippocampal area CA1, which contains neurons known as pyramidal cells because of the triangular shape of their cell bodies (Zola–Morgan et al. 1986). Hippocampal CA1 pyramidal cells assist the hippocampus in communicating with other areas of the brain. The hippocampus receives information from a wide variety of brain regions, many of them located in the tissue, called the neocortex, that blankets the brain and surrounds other brain structures.

(Neocortex literally means "new bark" or "new covering." When one looks at a picture of the human brain, most of what is visible is neocortex.) The hippocampus somehow ties information from other brain regions together to form new autobiographical memories, and CA1 pyramidal cells send the results of this processing back out to the neocortex. As is clear from patient R.B., removing CA1 pyramidal cells from the circuitry prevents the hippocampal memory system from doing its job.

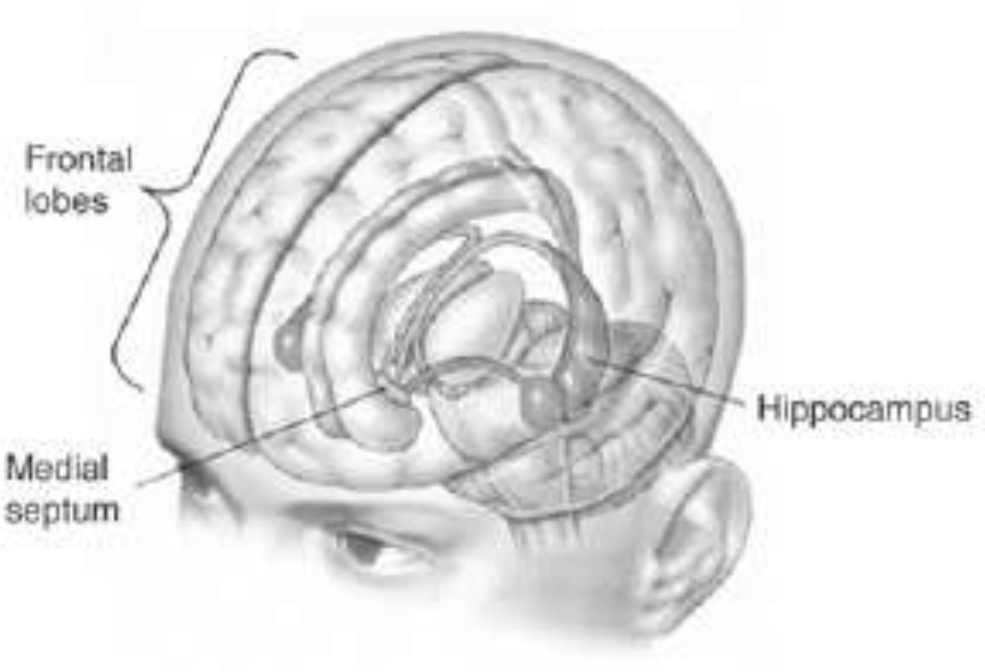

Figure 2 The human brain, showing the location of the hippocampus, the frontal lobes, and the medial septum.

The second barrier to understanding the mechanisms underlying alcohol's effects on memory was an incomplete understanding of how alcohol affects brain function at a cellular level. Until recently, alcohol was assumed to affect the brain in a general way, simply shutting down the activity of all cells with which it came in contact. The pervasiveness of this assumption is reflected in numerous writings during the early 20th century. For instance, Fleming (1935) wrote, "The prophetic generalization of Schmiedeberg in 1833 that the pharmacological action of alcohol on

the cerebrum is purely depressant has been found, most pharmacologists will agree, to characterize its action in general on all tissues" (p. 89). During the 1970s, researchers hypothesized that alcohol depressed neural activity by altering the movement of key molecules (in particular, lipids) in nerve cell membranes. This change then led to alterations in the activity of proteins, including those that influence communication between neurons by controlling the passage of positively or negatively charged atoms (i.e., ions) through cell membranes (e.g., Chin and Goldstein 1977). This view persisted into the late 1980s, at which time the consensus began to shift as evidence mounted that alcohol has selective effects on the brain's nerve–cell communication (i.e., neurotransmitter) systems, altering activity in some types of receptors but not others (e.g., Criswell et al. 1993). Substantial evidence now indicates that alcohol selectively alters the activity of specific complexes of proteins embedded in the membranes of cells (i.e., receptors) that bind neurotransmitters such as gamma–aminobutyric acid (GABA), glutamate, serotonin, acetylcholine, and glycine (for a review, see Little 1999). In some cases, only a few amino acids appear to distinguish receptors that are sensitive to alcohol from those that are not (Peoples and Stewart 2000). It remains unclear exactly how alcohol interacts with receptors to alter their activity.

Alcohol, Memory, and the Hippocampus

More than 30 years ago, both Ryback (1970) and Goodwin and colleagues (1969a) speculated that alcohol might impair memory formation by disrupting activity in the hippocampus. This speculation was based on the observation that acute alcohol exposure (in humans) produces a syndrome of memory impairments similar in many ways to the impairments produced by hippocampal damage. Specifically, both acute alcohol exposure and hippocampal damage impair the ability to form new long–term, explicit memories but do not affect short–term memory storage or, in general, the recall of information from long–term storage.

Research conducted in the past few decades using animal models supports the hypothesis that alcohol impairs memory formation, at least in part, by disrupting activity in the hippocampus (for a review, see White et al. 2000b). Such research has included behavioral observation; examination of slices of and brain tissue, neurons in cell culture, and brain activity in anesthetized or freely behaving animals; and a variety of pharmacological techniques.

As mentioned above, damage limited to the CA1 region of the hippocampus dramatically disrupts the ability to form new explicit memories (Zola–Morgan et al. 1986). In rodents, the actions of CA1 pyramidal cells have striking behavioral correlates. Some cells tend to discharge electrical signals that result in one cell communicating with other cells (i.e., action potentials) when the rodent is in a distinct location in its environment. The location differs for each cell. For instance, while a rat searches for food on a plus–shaped maze, one pyramidal cell might generate action potentials primarily when the rat is at the far end of the north arm, while another might generate action potentials primarily when the rat is in the middle of the south arm, and so on. Collectively, the cells that are active in that particular environment create a spatial, or contextual map that serves as a framework for event memories created in that environment. Because of the location–specific firing of these cells, they often are referred to as "place–cells," and the regions of the environment in which they fire are referred to as "place–fields" (for reviews, see Best and White 1998; Best et al. 2001). Given that CA1 pyramidal cells are critically important to the formation of memories for facts and events, and the clear behavioral correlates of their activity in rodents, it is possible to assess the impact of alcohol on hippocampal output in an intact, fully functional brain by studying these cells.

In recent work with awake, freely behaving rats, White and Best (2000) showed that alcohol profoundly suppresses the activity of pyramidal cells in region CA1. The researchers allowed the

rats to forage for food for 15 minutes in a symmetric, Y–shaped maze and measured the animals' hippocampal activity using tiny wires (i.e., microelectrodes) implanted in their brains. Figure 3 displays the activity of an individual CA1 pyramidal cell. The activity—which corresponds to the middle portion of the lower left arm of the maze—is shown before alcohol administration

(A), 45 to 60 minutes after alcohol administration (B), and 7 hours after alcohol administration (C). The dose of alcohol used in the testing session was 1.5 grams per kilogram of body weight—enough to produce a peak BAC of about 0.16 percent. (A corresponding BAC in humans would be twice the legal driving limit in most States.) As the figure illustrates, the cell's activity was essentially shut off by alcohol. Neural activity returned to near–normal levels within about 7 hours of alcohol administration.

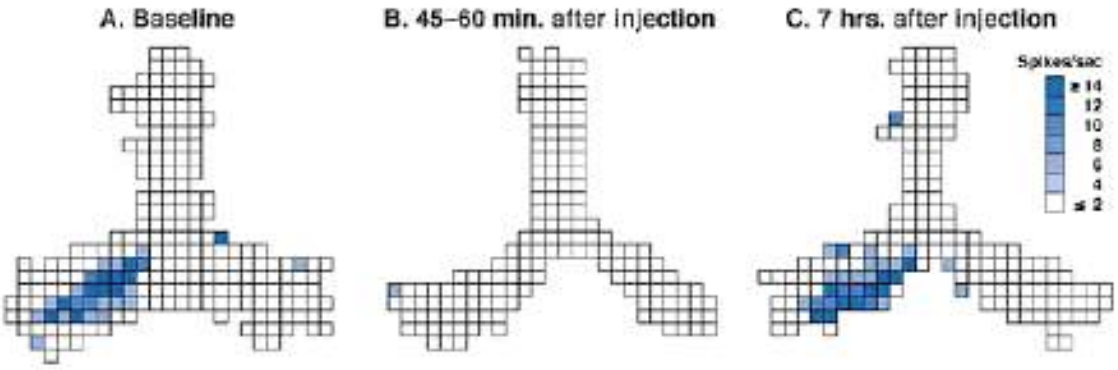

Figure 3 Alcohol suppresses hippocampal pyramidal cell activity in an awake, freely behaving rat. Pyramidal cells often fire when the animal is in discrete regions of its environment, earning them the title "place–cells." The specific areas of the environment where these cells fire are referred to as place–fields. The figure shows the activity of an individual pyramidal cell before alcohol administration (baseline), 45 to 60 minutes after alcohol administration, and 7 hours after alcohol administration (1.5 g/kg). Each frame in the figure shows the firing rate and firing location of the cell across a 15–minute block of time during which the rat was foraging for food on a symmetric, Y–shaped maze. White pixels are pixels in which the cell fired at very low rates, and darker colors represent higher firing rates (see key to the right of figure). As is clear from a comparison of activity during baseline and 45 to 60 minutes after alcohol administration, the activity of the cell was essentially shut off by alcohol. Neural activity returned to near normal levels within roughly 7 hours after alcohol administration.

White and Best administered several doses of alcohol in this study, ranging from 0.5 g/kg to 1.5 g/kg. (Only one of the experiments is represented in figure 3.) They found that the dose affected the degree of pyramidal cell suppression. Although 0.5 g/kg did not produce a significant change in the firing of hippocampal pyramidal cells, 1.0 and 1.5 g/kg produced significant suppression of firing during a 1–hour testing session following alcohol administration. The dose–dependent suppression of CA1 pyramidal cells is consistent with the dose–dependent effects of alcohol on episodic memory formation.

Alcohol and Hippocampal Long–Term Potentiation

In addition to suppressing the output from pyramidal cells, alcohol has several other effects on hippocampal function. For instance, alcohol severely disrupts the ability of neurons to establish long–lasting, heightened responsiveness to signals from other cells (Bliss and Collinridge 1993). This heightened responsiveness is known as long–term potentiation (LTP). Because researchers have theorized that something like LTP occurs naturally in the brain during learning (for a review,

see Martin and Morris 2002), many investigators have used LTP as a model for studying the neurobiology underlying the effects of drugs, including alcohol, on memory.

In a typical LTP experiment, two electrodes (A and B) are lowered into a slice of hippocampal tissue kept alive by bathing it in oxygenated artificial cerebral spinal fluid (ACSF). 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 is used to record how the cells in the area respond to the incoming signals. This response is 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. When the original stimulus that elicited the baseline response is delivered again through electrode A, the response recorded at electrode B is larger (i.e., potentiated). In other words, as a result of the patterned input, cells at position B now are more responsive to signals sent from cells at position A. The potentiated response often lasts for an extended period of time, hence the term long–term potentiation.

Alcohol interferes with the establishment of LTP (Morrisett and Swartzwelder 1993; Givens and McMahon 1995; Pyapali et al. 1999; Schummers and Browning 2001), and this impairment begins at concentrations equivalent to those produced by consuming just one or two standard drinks (e.g., a 12–oz beer, 1.5–oz of liquor in a shot or mixed drink, or a 5–oz glass of wine) (Blitzer et al. 1990). If sufficient alcohol is present in the ACSF bathing the slice of hippocampal tissue when the patterned stimulation is given, the response recorded later at position B will not be larger than it was at baseline (that is, it will not be potentiated). And, just as alcohol tends not to impair recall of memories established before alcohol exposure, alcohol does not disrupt the expression of LTP established before alcohol exposure.

One of the key requirements for the establishment of LTP in the hippocampus is that a type of signal receptor known as the NMDA2 receptor becomes activated. (2 N–methyl–D–aspartate [NMDA] is a receptor for the neurotransmitter glutamate.) Activation of the NMDA receptor allows calcium to enter the cell, which sets off a chain of events leading to long–lasting changes in the cell's structure or function, or both. Alcohol interferes with the activation of the NMDA receptor, thereby preventing the influx of calcium and the changes that follow (Swartzwelder et al. 1995). This is believed to be the primary mechanism underlying the effects of alcohol on LTP, though other transmitter systems probably are also involved (Schummers and Browning 2001).

Indirect Effects of Alcohol on Hippocampal Function

Like other brain regions, the hippocampus does not operate in isolation. Information processing in the hippocampus depends on coordinated input from a variety of other structures, which gives alcohol and other drugs additional opportunities to disrupt hippocampal functioning. One brain region that is central to hippocampal functioning is a small structure in the fore brain known as the medial septum (Givens et al. 2000). The medial septum sends rhythmic excitatory and inhibitory signals to the hippocampus, causing rhythmic changes in the activity of hippocampal pyramidal cells. In electroencephalograph recordings, this rhythmic activity, referred to as the theta rhythm, occurs within a frequency of roughly 6 to 9 cycles per second (hertz) in actively behaving rats. The theta rhythm is thought to act as a gatekeeper, increasing or decreasing the likelihood that information entering the hippocampus from cortical structures will be processed (Orr et al. 2001). (For more information on the role of electrophysiology in diagnosing alcohol problems, see the article in this issue by Porjesz and Begleiter.) Information entering the hippocampus when pyramidal cells are slightly excited (i.e., slightly depolarized) has a better chance of influencing hippocampal circuitry than signals that arrive when the cells are slightly suppressed (i.e., slightly hyperpolarized).

Manipulations that disrupt the theta rhythm also disrupt the ability to perform tasks that depend on the hippocampus (Givens et al. 2000). Alcohol disrupts the theta rhythm in large part by suppressing the output of signals from medial septal neurons to the hippocampus (Steffensen et al. 1993; Givens et al. 2000). Given the powerful influence that the medial septum has on information processing in the hippocampus, the impact of alcohol on cellular activity in the medial septum is likely to play an important role in the effects of alcohol on memory. Indeed, in rats, putting alcohol directly into the medial septum alone produces memory impairments
(Givens and McMahon 1997).

Other Brain Regions Involved in Alcohol–Induced Memory Impairments

The hippocampus is not the only structure involved in memory formation. A host of other brain structures also are involved in memory formation, storage, and retrieval (Eichenbaum 2002). Recent research with humans has yielded compelling evidence that key areas of the frontal lobes play important roles in short–term memory and the formation and retrieval of long–term explicit memories (e.g., Shastri 2002; Curtis and D'Esposito 2003; Ranganath et al. 2003). Damage to the frontal lobes leads to profound cognitive impairments, one of which is a difficulty forming new memories. Recent evidence suggests that memory processes in the frontal lobes and the hippocampus are coordinated via reciprocal connections (Wall and Messier 2001; Shastri 2002), raising the possibility that dysfunction in one structure could have deleterious effects on the functioning of the other.

Considerable evidence suggests that chronic alcohol use damages the frontal lobes and leads to impaired performance of tasks that rely on frontal lobe functioning (Kril and Halliday 1999; Moselhy et al. 2001). "Shrinkage" in brain volume, changes in gene expression, and disruptions in how performing certain tasks affects blood flow in the brain all have been observed in the frontal lobes of alcohol–dependent subjects (Kril and Halliday 1999; Lewohl et al. 2000; Tapert et al. 2001; Kubota et al. 2001; Desmond et al. 2003).

Although much is known about the effects of chronic (i.e., repeated) use of alcohol on frontal lobe function, little is known about the effects of one–time (i.e., acute) use of alcohol on activity in the frontal lobes, or the relationship of such effects to alcohol–induced memory impairments. Compelling evidence indicates that acute alcohol use impairs the performance of a variety of frontal lobe–mediated tasks, like those that require planning, decisionmaking, and impulse control (Weissenborn and Duka 2003; Burian et al. 2003), but the underlying mechanisms are not known. Research also suggests that baseline blood flow to the frontal lobes increases during acute intoxication (Volkow et al. 1988; Tiihonen et al. 1994), that metabolism in the frontal lobes decreases (Wang et al. 2000), and that alcohol reduces the amount of activity that occurs in the frontal lobes when the frontal lobes are exposed to pulses from a strong magnetic field

(Kahkonen et al. 2003). Although the exact meaning of these changes remains unclear, the evidence suggests that acute intoxication alters the normal functioning of the frontal lobes. Future research is needed to shed more light on this important question. In particular, research in animals will be an important supplement to studies in humans, affording a better understanding of the underlying prefrontal circuitry involved in alcohol–induced memory impairment.

Aaron M. White, *What Happened? Alcohol, Memory Blackouts, and the Brain* (2003).
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