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The use of acute ethanol administration as a tool to investigate multiple memory systems☆

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Abstract

The discovery of multiple memory systems supported by discrete brain regions has been one of the most important advances in behavioral neuroscience. A wealth of studies have investigated the role of the hippocampus and related structures in supporting various types of memory classifications. While the exact classification that best describes hippocampal function is often debated, a specific subset of cognitive function that is focused on the use of spatial information to form hippocampal cognitive maps has received extensive investigation. These studies frequently employ a variety of experimental manipulations including brain lesions, temporary neural blockade due to cooling or discrete injections of specific drugs. While these studies have provided important insights into the function of the hippocampus, they are limited due to the invasive nature of the manipulation. Ethanol is a drug that is easily administered in a non-invasive fashion, is rapidly absorbed and produces effects only in specific brain regions. The hippocampus is one brain region affected by acute ethanol administration. The following review summarizes research from the last 20 years investigating the effects of acute ethanol administration on one specific type of hippocampal cognitive function, namely spatial memory. It is proposed that among its many effects, one specific action of acute ethanol administration is to produce similar cognitive and neurophysiological effects as lesions of the hippocampus. Based on these similarities and the ease of its use, it is concluded that acute ethanol administration is a valuable tool in studying hippocampal function and multiple memory systems.

1. Introduction

The discovery that memory can be subdivided into categories based on content was a significant advancement in the study of cognition. The specific categories that best explain memory have been often debated. These categories include, but are not limited to, spatial memory (locale memory), non-spatial memory (taxon memory), representational memory, configural memory, declarative memory, procedural memory, and episodic memory (Eichenbaum, 2001; Eichenbaum, Otto, & Cohen, 1993; O'Keefe & Nadel, 1978; Sutherland & Rudy, 1989; Zola et al., 2000). Furthermore, specific brain regions are thought to be critical for specific memory categories with particular emphasis placed on the hippocampus, caudate, and cerebellum.

In recent years, the role of the hippocampus as it relates to categories of specific memory types is being redefined. For example, current research is exploring the hypothesis that the hippocampus is critical for information that composes specific episodes (Eichenbaum, 1998; Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999). An episode contains all information that defines a particular place (spatial memory) and the particular sequence of events (non-spatial memory) that happen within that particular spatial location. For example, it has been demonstrated that the hippocampus is critical for remembering the specific sequences of events, such as odors, which are distinctively non-spatial (Agster,

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Fortin, & Eichenbaum, 2002; Fortin, Agster, & Eichenbaum, 2002) and is also critical for remembering specific locations, which are distinctively spatial (Morris, Garrud, Rawlins, & O'Keefe, 1982).

Spatial memory is memory based on spatial information as defined by 3-dimensional Euclidian space and is external to the organism while non-spatial memory is based on information independent of this external space. Spatial memory is dependent on the integrity of the hippocampus (O'Keefe & Nadel, 1978) while non-spatial memory can be independent of the hippocampus in some specific tasks and is likely dependent on the function of additional brain regions such as the caudate (Nadel, 1991; O'Keefe & Nadel, 1978; Packard, Hirsh, & White, 1989).

The experimental framework that the hippocampus is critical for spatial information and less critical for non-spatial information was initially proposed as the spatial cognitive mapping hypothesis (Nadel, 1991; O'Keefe & Nadel, 1978). The cognitive mapping hypothesis makes several specific predictions concerning memory and the effect of hippocampal lesions on memory performance. For example, it is predicted that animals will have an inherent bias to process and use spatial information as demonstrated by Tolman (1948). Additionally, tasks that can be learned via spatial information should be learned faster than tasks that depend on non-spatial information. Furthermore, if a task can be learned using either spatial or non-spatial information, animals will preferentially use spatial information when performing the task as demonstrated by Hebb (1938). Finally, it is predicted that hippocampal function is required for animals to learn tasks using spatial information, and, if the hippocampus is compromised, non-spatial tasks should be learned at a faster rate. While this framework likely addresses only a subset of hippocampal sensitive cognitive tasks, it provides a useful basis to explore multiple memory systems, namely spatial and non-spatial memory.

2. Experimental support for the spatial mapping theory

A wealth of experimental data support the underlying predictions of the spatial mapping hypothesis. Specifically, animals, including rats, mice, and pigeons, have an inherent bias to use spatial information when learning a task (Matthews & Best, 1997; Tolman, 1948). Furthermore, spatial information will overshadow non-spatial information during learning as evidenced by preferential use of spatial information during a memory test (Hebb, 1938; Matthews, Ilgen, White, & Best, 1999). Furthermore, lesions to the hippocampus or its primary connections selectively block spatial learning and memory (Jarrard, 1983, 1993; Morris et al., 1982; O'Keefe, Nadel, Keightley, & Kill, 1975). Interestingly, following lesions to the hippocampal system, animals learn a non-spatial task significantly faster than control animals, presumable due to the fact that the lesion removes the inherent bias to use spatial information (Matthews & Best, 1995; Packard et al., 1989). Recordings of hippocampal pyramidal neurons in awake freely behaving animals have also provided additional support for the function of the hippocampus in processing spatial information. Specifically, hippocampal pyramidal neurons (often termed place cells) are sensitive to a variety of memory specific information chunks including recent outcomes, anticipation of future events and the current spatial location of the animal (Ferbinteanu & Shapiro, 2003). In fact, if neural activity is recorded as an animal performs a simple task that contains a strong spatial component, place cells often display a strong bias to fire only in specific locations, termed the place field (McNaughton, Barnes, & O'Keefe, 1983; Muller, Kubie, & Ranck, 1987; O'Keefe & Dostrovosky, 1971; Thompson & Best, 1990). As expected, lesions to hippocampal afferents (Miller & Best, 1980) or reversible inactivation of hippocampal afferents (Mizumori, Miya, & Ward, 1994) disrupt the spatial sensitivity of place cells and provide a direct measure of hippocampal function in awake freely behaving animals.

Research has consistently supported the hypothesis that the hippocampus is critical for the use of spatial memory. However, many of the study procedures require invasive techniques, such as brain lesions, cooling probes or infusion of drugs into brain to investigate memory processes. To further investigate how hippocampal function modulates multiple memory systems, we believed that the use of a short acting pharmacological agent that effected specific brain regions in a reversible manner would be beneficial.

Ethanol (alcohol) is a short chain lipid soluble compound whose initial mechanism of action was thought to be diffuse in brain due to a "lipid membrane disordering" effect resulting from a significant correlation between the number of alcohols and their partition coefficient between oil and water (Chin & Goldstein, 1977). However because of work from a variety of disciplines, it is now clear that ethanol alters brain neurobiology only in specific brain regions. The specificity of ethanol's action is most likely due to the drug interacting with subsets of specific neurotransmitter systems, such as $GABA_A$ and NMDA-preferring glutamate systems (see Crews, Morrow, Criswell, & Breese, 1996; Grobin, Matthews, Devaud, & Morrow, 1998; Morrow, 1995 for review).

Direct investigation of the effect of ethanol in the hippocampus has shown that acute administration of the drug potentiates GABA-mediated inhibition via $GABA_A$ receptors. For example, inclusion of intracellular ATP (Weiner, Zhang, & Carlen, 1994), cold shock treatment of hippocampal slices (Weiner, Gu, & Dunwiddie, 1997) or blockade of $GABA_B$ receptors (Wan, Berton,

Madamba, Francesconi, & Siggins, 1996) all led to ethanol potentiation of GABA-mediated inhibition in hippocampus. Moreover, low ethanol concentrations can potentiate GABA-mediated inhibition in hippocampal CA1 pyramidal cells following proximal but not distal stimulation (Weiner, Valenzuela, Watson, Frazier, & Dunwiddie, 1997).

In addition to ethanol's effects on $GABA_A$ receptors, it has also been shown that ethanol blocks NMDA-evoked neural activity both in vitro (Lovinger, White, & Weight, 1989) and in vivo (Simson, Criswell, & Breese, 1993). In fact, the hippocampus and medial septum are two brain regions in which ethanol blockade of NMDA-evoked activity is readily observed (Lima-Landman & Albuquerque, 1989; Simson et al., 1993). Finally, it has been demonstrated that ethanol blocks the induction, but not the expression, of NMDA-dependent long-term potentiation in the hippocampus (e.g., Blitzer, Gil, & Landau, 1990). Given that ethanol interacts with neurotransmitter systems found in the hippocampal system, it is reasonable to assume that ethanol will affect hippocampal neurophysiology.

Over the last several years, a variety of projects have demonstrated that hippocampal neurophysiology is altered by ethanol. For example, acute ethanol administration selectively attenuates stress-induced c-fos expression in the rat hippocampus (Ryabinin, Melia, Cole, Bloom, & Wilson, 1995; Ryabinin, Criado, Henriksen, Bloom, & Wilson, 1997; see Crabbe, 1997 for review) but not in the cerebral cortex suggesting that the hippocampus is one site of ethanol action. Furthermore, similar doses of ethanol decrease the hippocampal theta rhythm (Givens, 1995) while moderate doses of ethanol inhibit the spontaneous neural activity of both hippocampal pyramidal neurons (Steffensen & Henriksen, 1992; Tokunaga, McDaniel, Morrow, & Matthews, 2003) and medial septal neurons (Givens & Breese, 1990; VanDoren et al., 2000). Interesting, acute ethanol administration does not increase c-fos expression in the cerebral cortex (Ryabinin et al., 1995) nor alters the spontaneous neural activity of lateral septal neurons (Simson et al., 1991). These studies demonstrate that one effect of acute ethanol administration is to alter hippocampal neurophysiology and perhaps hippocampal function. Given the fact that ethanol ready crosses the blood–brain barrier and produces selective neurophysiological effects in the hippocampus, it seemed reasonable to investigate if acute ethanol administration selectively altered hippocampal-dependent spatial memory.

3. Acute ethanol administration as a tool to study spatial and non-spatial memory

Initial studies investigating if acute ethanol administration impairs spatial learning or spatial memory concluded that ethanol did not degrade the performance of animals on spatial tasks (Devenport, Stidham, & Hale, 1989). However, particular training conditions were included in these studies that might have interfered with a selective effect of ethanol on spatial learning and memory performance. To determine if ethanol does, in fact, alter spatial memory the following tests were conducted. To directly test if acute ethanol administration alters spatial memory, animals were trained either a spatial reference memory task or a non-spatial reference memory task on a radial arm maze (Olton & Samuelson, 1976) sober then tested following either a saline challenge (control) or one of three ethanol challenges (0.75, 1.5 or 2.25 g/kg). Using this procedure, it was found that acute ethanol administration impaired spatial memory in a dose-dependent manner but did not alter non-spatial memory (Matthews, Simson, & Best, 1995). This finding has been replicated and extended by several studies from multiple laboratories; it has been demonstrated that the selective impairment produced by acute ethanol administration is not due to the specific ethanol challenge doses (White, Simson, & Best, 1997) or the inability of the animal to visualize salient distal information (White, Elek, Beltz, & Best, 1998). Furthermore, ethanol degradation of spatial memory was not specific to reference memory as evidenced by the fact that ethanol also selectively impaired spatial working memory (Gibson, 1985; Givens, 1995; Hoffmann & Matthews, 2001).

Several tests have investigated how the selective effects of ethanol generalize to additional tasks or species. Acute ethanol administration impairs spatial, but not non-spatial memory, in the Morris water maze task (Matthews, Morrow, Tokunaga, & McDaniel, 2002; Shimizu, Matsubara, Uezono, Kumura, & Shiono, 1998; Wright et al., 2003) indicating that ethanol impairs hippocampal function regardless of task demands (walking vs. swimming) or motivation (food deprivation vs. escape). Furthermore, similar doses of acute ethanol will selectively impair context-dependent learning but not cue-dependent learning in standard fear conditioning paradigms (Gould, 2003; Melia, Ryabinin, Corodimas, Wilson, & Ledoux, 1996) and impair trace fear conditioning but not delayed fear conditioning (Weitemier & Ryabinin, 2004). The fact that acute alcohol administration also selectively impairs context memory (i.e., spatial memory) is interesting given that context memory is often assessed by freezing, thus demonstrating that motor movement is not a confounding variable in the radial arm maze or water maze studies. The effect of acute ethanol administration on spatial memory is not limited to rats. Recently, it has been demonstrated that alcohol also selective impairs spatial memory in mice (Berry & Matthews, 2004) demonstrating that ethanol's degradation of hippocampal function is not species dependent.

These studies demonstrate that animals injected with ethanol have very similar performance impairments compared to animals subjected to traditional hippocampal lesions. Furthermore, the similarities are not dependent on the task demands or the motivational properties of the tasks. However, hippocampal lesion also can facilitate non-spatial memory performance under certain task demands (Matthews & Best, 1995; Packard et al., 1989). If acute ethanol administration does produce a similar pattern of results then one might predict that acute ethanol administration could impair non-spatial memory performance under particular task demands.

To investigate if acute ethanol administration can facilitate the use of non-spatial memory performance, we trained rats when sober a task on an 8-radial arm maze that could be learned using either spatial or non-spatial information (Matthews et al., 1999). Specifically, animals were trained six trials/day to navigate to one particular goal arm for a food reward. Each of the six trails started from a unique arm. The goal arm remained in a constant spatial location and was identified by a single proximal cue located on the arm (i.e., a piece of wood covered in fine wire mesh the rat had to walk over to obtain the food reward). Using this procedure, animals could learn to navigate to the food reward using either spatial (go to a place) or non-spatial (go to the arm containing the cue) information. Following learning, animals' memory was tested using a procedure that allowed for independent assessment of the use of both spatial and non-spatial information. Specifically, the maze was rotated 90° thereby placing an un-cued arm in the rewarded spatial location and the rewarded cued arm in a new spatial location. Prior to testing, animals were injected with saline, 1.0, 1.5 or 2.0 g/kg ethanol. If the number of test trials solved using spatial memory (i.e., going to the rewarded spatial location even though it contained a new un-cued arm) was analyzed, it was found that acute ethanol administration impaired spatial memory, as previously reported. Interestingly though, acute ethanol administration did not produce general memory errors. Instead if the number of test trials solved using non-spatial memory (i.e., going to the reward cued arm even though it was in a new spatial location) was analyzed, acute ethanol administration significantly facilitated performance (see Fig. 1). The striking similarity between the cognitive effects of acute ethanol administration and hippocampal lesions begins to establish the use of ethanol as a tool to selectively study hippocampal function.

4. Cellular mechanisms underlying the degradation of spatial memory and the facilitation of non-spatial memory by acute ethanol

One specific, but not the only (Ferbinteanu & Shapiro, 2003), behavioral correlate of hippocampal pyramidal neurons is their sensitivity to spatial location. Specifically, it has been repeated demonstrated that hippocampal CA1 or CA3 neurons have preferential firing fields (place fields) when recorded in awake freely behaving animals if the task demands are constructed such that spatial information is an important component (McNaughton et al., 1983; Muller et al., 1987; O'Keefe & Dostrovosky, 1971; Thompson & Best, 1990). Hippocampal place cells have been proposed as the cellular map underlying spatial information processing in the hippocampus (Nadel, 1991; O'Keefe & Nadel,

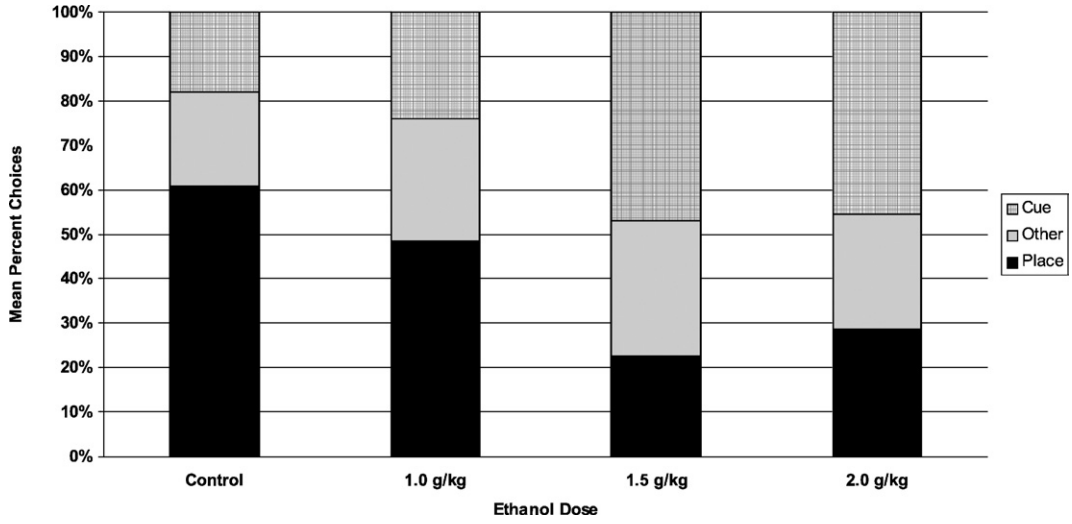

Fig. 1. Acute ethanol administration impairs spatial memory performance while facilitating non-spatial memory performance in rats. The mean percent of choices during testing for each challenge dose of ethanol. Place choices are choices to the rewarded place that contains a non-rewarded cue, cue choices are choices to the rewarded cue which is in a new spatial location and other choices are neither cue nor place choices. Adapted from Matthews et al. (1999).

1978). Given that acute ethanol administration impairs spatial memory, it seem reasonable to predict that similar doses of ethanol should alter the spatial specificity of hippocampal place cells.

It was first reported that ethanol altered the spatial specificity of hippocampal place cells by showing that a 1.0 g/kg ethanol injection decreased the number of place "units" recorded from awake freely behaving rabbits (Alexandrov et al., 1993). A more systematic study using rats investigated the effect of a higher dose of ethanol, 2.0 g/kg, on the spatial specificity of place cells. It was found that the spatial specificity of place cells recorded in awake freely behaving rats was significantly reduced 30 min following the ethanol injection compared to pre-ethanol levels. Interestingly, this is the time point when acute ethanol administration has been shown to impair spatial memory and facilitate non-spatial memory (Matthews et al., 1999). Furthermore, the level of spatial sensitivity completely recovered 24 h after the ethanol injection (Matthews, Simson, & Best, 1996), a time point when acute ethanol administration no longer impairs spatial memory (Hoffmann & Matthews, 2001). More recently, the reduced spatial specificity has been shown to be due to a reduction in the firing rate of the hippocampal place cells in the place field regardless of the route by which ethanol is administered (Ludvig, Fox, Kubie, Altura, & Altura, 1998; White & Best, 2000). This reduction in firing rate and decrease in spatial sensitivity of hippocampal place cells has been argued to be the cellular mechanism by which acute ethanol administration impairs spatial memory (Matthews & Morrow, 2000).

The hypothesis that degradation in the spatial specificity of hippocampal place cells as the cellular mechanism impairing spatial memory is supported by work showing that inactivation of the lateral dorsal thalamus by tetracaine resulted in hippocampal place cells displaying a reduction in the spatial sensitivity and a corresponding reduction in the accuracy of the same animals in a spatial memory test (Mizumori et al., 1994). In a more recent study, it has been demonstrated that acute injections of scopolamine, at similar doses that impair spatial memory (for review, see, Gold, 2003), also reduce the spatial specificity of hippocampal place cells (Brazhnik, Muller, & Fox, 2003). While still correlational in nature, data from these studies suggest that acute ethanol administration degrades the spatial specificity of hippocampal place cells and also degrades spatial memory.

The exact cellular mechanism by which acute ethanol administration impairs spatial memory and can facilitate non-spatial memory is unknown. However, at least three possible cellular mechanisms exist: (A) the degradation of hippocampal place cells; (B) a potential "facilitation" of neurophysiological function in other brain regions such as the caudate; or (C) a combination of both degraded hippocampal place cell spatial specificity and changes of the neurophysiology in the caudate.

Recording of multiple unit activity has demonstrated that specific brain regions display differential sensitivity to acute injections of ethanol. For example, it has been shown that multiple unit activity recorded in the hippocampus, along with the cerebellum and cortex, is altered at relatively low ethanol doses while other brain regions such as the caudate are effected at relatively higher doses (Klemm et al., 1976). These data suggest that acute ethanol administration alters cognition by changing both hippocampal and caudate neurophysiology.

5. Potential mechanisms by which ethanol alters hippocampal and caudate neurophysiology

Ethanol interacts with a variety of neurotransmitter systems including glutamate and GABAergic systems (for review, see, Valenzuela, 1997) and both of these likely contribute to the degradation of hippocampal neurophysiology. For example, acute ethanol administration will inhibit both hippocampal NMDA-dependent LTP (Blitzer et al., 1990; Givens & McMahon, 1995; Roberto et al., 2003) and NMDA-independent LTP (Hendricson, Thomas, Lippmann, & Morrisett, 2003). In addition to blocking the induction of both NMDA-dependent and non-dependent LTP, ethanol will also *enhance* NMDA-dependent long-term depression (LTD) (Hendricson, Alek Miao, Lippmann, & Morrisett, 2002). These studies clearly demonstrate one potential mechanism by which ethanol can alter hippocampal neurophysiology.

Acute ethanol administration also modulates hippocampal $GABA_A$ receptors, but only following particular experimental conditions (see above). Recently however it was discovered that acute ethanol administration, at doses that impair spatial memory and enhance non-spatial memory, also dramatically increases the levels of allopregnanolone (3α-hydroxy-5α-pregnan-20-one), a specific neuroactive steroid, in the hippocampus (Khisti, VanDoren, Matthews, & Morrow, in press). Allopregnanolone is a potent, positive modulator of $GABA_A$ receptors (Harrison, Majewska, Harrington, & Barker, 1987) and has recently been proposed as a critical intermediary by which ethanol produces some effects at $GABA_A$ receptors (Khisti et al., in press; Morrow, Khisti, Tokunaga, McDaniel, & Matthews, 2003; VanDoren et al., 2000). In addition, we have recently proposed that ethanol-induced increases in hippocampal allopregnanolone levels are a biochemical mechanism leading to impairments in spatial memory (Silvers, Tokunaga, Berry, White, & Matthews, 2003).

The hypothesis that ethanol-induced increases in allopregnanolone are critical for ethanol's impairments in spatial memory have recently been supported. For

example, it has been demonstrated that acute allopregnanolone administration impairs both spatial learning (Johansson, Birzniece, Lindblad, Olsson, & Backstrom, 2002) and spatial memory (Matthews et al., 2002). Furthermore, both acute ethanol administration (Steffensen & Henriksen, 1992) and acute allopregnanolone administration (Tokunaga et al., 2003) inhibits the spontaneous neural activity of hippocampal pyramidal neurons. These data suggest that allopregnanolone might modulate ethanol's effects in the hippocampus. To directly test if ethanol-induced increases in allopregnanolone levels are the mechanism producing a decrease in hippocampal pyramidal cell firing rates, animals were pre-treated with finasteride, a type I and II 5α-reductase inhibitor (Normington & Russell, 1992). Previous research has shown that finasteride pre-administration reduces ethanol-induced cortical allopregnanolone levels by 48% (VanDoren et al., 2000). Interestingly, finasteride pre-administration completely blocked ethanol-induced inhibition of hippocampal pyramidal neurons (Tokunaga et al., 2003) and ethanol-induced spatial memory impairments (Morrow et al., 2003). These data suggest that ethanol-induced increases in allopregnanolone might modulate ethanol's degradation in hippocampal function.

The nature by which ethanol-induced increases in hippocampal allopregnanolone levels might modulate degradation in memory systems is unknown. However, one possibility is an interaction between hippocampal GABAergic systems and acetylcholine systems. A developing body of evidence suggests that GABA modulation of limbic acetylcholine systems might be related to spatial memory impairments produced by acute ethanol administration. Specifically, reduced hippocampal acetylcholine levels (either natural reductions due to aging or pharmacological reductions) produce impairments in spatial memory (Ikegami, 1994; Mishima et al., 2000; for review see Gold, 2003). Interestingly, acute administration of ethanol (Melis, Stancampiano, Imperato, Carta, & Fadda, 1996) and acute administration of allopregnanolone (Dazzi, Sanna, Cagetti, Concas, & Biggio, 1996) also inhibit acetylcholine release in hippocampus. Taken together, these data suggest that ethanol increases hippocampal allopregnanolone levels which (1) potentiate $GABA_A$ receptor activity in the hippocampus and (2) reduce hippocampal acetylcholine levels. It is quite likely that these factors, in addition to blockade of LTP induction and facilitation of LTD, are mechanisms causing ethanol-induced spatial memory impairments.

As previously discussed, acute ethanol administration can facilitate the use of cue-based non-spatial memory (Matthews et al., 1999), a task that is often associated with normal caudate function (Packard et al., 1989; Packard & McGaugh, 1992). Furthermore, it has been demonstrated that dopaminergic activity enhances memory performance of cue-based tasks (e.g., Packard & White, 1991). These data would suggest that pharmacological manipulations that increase dopamine release in the caudate would also improve non-spatial memory performance.

Acute ethanol administration has often been shown to increase the release of dopamine in many brain regions including the caudate (Di Chiara & Imperato, 1988; Imperato & Di Chiara, 1986; Signs, Yamamoto, & Schechter, 1987; however see Budygin et al., 2001). Furthermore, dopamine levels in the cauduate peak at 35 min following ethanol injection (Signs et al., 1987), a time point that correlates with facilitated cued-based memory performance (Matthews et al., 1999). Hence it is possible that acute ethanol administration facilitates caudate function by increasing dopamine release.

In summary, one possible systems approach to acute ethanol impairing spatial memory while facilitating non-spatial memory is a concomitant degradation in hippocampal neurophysiology and a facilitation in caudate neurophysiology. As such, the performance of animals in memory tasks that can be solved using either spatial or non-spatial memory is likely to be biased to the use of non-spatial performance when subjects are intoxicated.

6. Does acute ethanol exposure alter hippocampal function in humans?

The cognitive mapping theory also was intended to explain memory formation in humans (O'Keefe & Nadel, 1978), although this segment of the theory has received little experimental attention (Nadel, 1991). However, it has been demonstrated that acute ethanol administration can alter spatial cognition in humans (Stokes, Belger, Banich, & Taylor, 1991; however see Weissenborn & Duka, 2003). A potential link between ethanol and spatial memory impairments in humans would be very interesting and additional research should be focused on this area.

In addition to a spatial function in humans, the hippocampus has also been proposed to play a role in declarative memory (Scoville & Milner, 1957). The declarative memory impairments resulting from removal of the hippocampus are similar to declarative memory impairments produced by alcohol, often called ethanol-induced "blackouts" (for review see Silvers et al., 2003). The term blackout refers to an inability of an individual to recall events that occurred while the person was intoxicated (Jellinek, 1946) with blackouts being an indicator of alcoholism. Recently, it has been demonstrated that acute ethanol exposure in males and females increases serum allopregnanolone levels (Torres & Ortega, 2003, 2004), suggesting similar mechanisms might lead to degradation of declarative memory in humans. The field of

Table 1
Summery of similar effects produced by acute ethanol administration and hippocampal lesions (adapted and expanded from Silvers et al., 2003)

Effect	Hippocampal/septum lesion	Acute ethanol
Impaired spontaneous alteration	Douglas and Isaacson (1964) Means et al. (1971)	Cox (1970)
Facilitated two-way avoidance	Isaacson et al. (1961)	Pallares et al. (1997)
Impaired contextual fear conditioning	Phillips and LeDoux (1992)	Melia et al. (1996)
Impaired performance on spatial reference memory tasks	O'Keefe et al. (1975) Morris et al. (1982) Jarrard (1993)	Matthews et al. (1995) White et al. (1997) Markweise et al. (1998)
Facilitated performance on non-spatial reference memory tasks	Packard et al. (1989) Matthews and Best (1995)	Matthews et al. (1999)
Increased response preservation	Kimble and Kimble (1965) Hirsh and Segal (1972)	Devenport et al. (1989)
Impaired performance on spatial working memory tasks	Olton et al. (1978)	Gibson (1985) Givens (1995) White et al. (1997, 2000)
Impaired performance on non-spatial working memory tasks	Raffaele and Olton (1988) Rawlins et al. (1993)	Givens (1995)
Alterations in the hippocampal theta rhythm	Rawlins et al. (1979) Bland and Bland (1986) Leung et al. (1994)	Whishaw (1976) Givens (1995)
Decreased spatial specificity of hippocampal place cells	Miller and Best (1980)	Alexandrov et al. (1993) Matthews et al. (1996) White and Best (2000)
Reduced hippocampal LTP	Molnar et al. (1994)	Swartzwelder and Wilson (1995)
Impaired performance in morris water task	Morris et al. (1982)	Matthews et al. (2002)
Impaired spatial performance in mice	Liu et al. (2002)	Berry and Matthews (2004)

ethanol impairments in declarative memory, while not often investigated, provides additional support for the framework that acute ethanol administration degrades cognitive performance dependent on the hippocampus.

7. Summary of ethanol effects on hippocampus and hippocampal-dependent behaviors

The hippocampus is critical for the use of spatial information to organize and guide behaviors. In addition, lesions of the hippocampus impair performance in many types of tasks that are dependent on the use of spatial information and can facilitate performance of tasks that are dependent on the use of non-spatial information. Acute ethanol administration produces dose-dependent impairments in the use of spatial information and facilitation in the use of non-spatial information that are strikingly similar to the effects produced by lesions to the hippocampus. In addition, acute ethanol administration degrades the spatial specificity of hippocampal place cells in a manner similar to the reduced spatial specificity produced by lesions to hippocampal afferents. Thus, it is reasonable to assume that ethanol-induced impairments in the use of spatial information are due to ethanol altering, either directly or indirectly, the function of the hippocampal system. Acute ethanol administration and traditional lesions to the hippocampal system produce similar effects in many experimental preparations (see Table 1). Given that investigations using acute ethanol administration as an experimental manipulation are much easier, less invasive and temporary compared to investigations using brain lesions, it is tantalizing to speculate that acute ethanol administration might be a suitable tool for studying hippocampal function. However, further investigations into the effect of acute ethanol administration of a variety of learning and memory tasks (e.g, episodic, configural, representational) are needed.

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