2005

Ethanol Effects on Reward Value Judgment Following Infusions into the Amygdala: Implications for Emotional Processing

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Abstract

Alcohol, when delivered systemically, leads to impaired performance on a variety of tasks, including emotionally-laden or reward value tasks. It is also known that lesions to the amygdala produce emotional or reward value deficits. However, it is unknown whether the emotional deficits observed after alcohol ingestion are due to alcohol's direct effect on the amygdala. The present study examined the effects of alcohol when infused directly into the amygdala on emotional memory and judgment. Eight male Long-Evans rats were trained on a behavioral task to associate one sweetness level with a reward and another sweetness level with no reward. Once the rats learned to discriminate between reward and no reward stimuli, they underwent surgery to implant guide cannulae to directly infuse alcohol into the amygdala. After a week recovery period, rats were given bilateral infusions of a 1.0% solution of alcohol, a 0.1% solution of alcohol, or a saline infusion. It was predicted that rats would perform more poorly on the reward value memory task following alcohol infusions into the amygdala, but that motor skills, motivation, and procedural memory would not be impaired. As predicted, motor skills, motivation and procedural memory were not impaired. However, results did not support the *a priori* hypothesis that intracranial infusions of alcohol into the amygdala would impair reward value memory performance, suggesting that alcohol may be affecting other brain areas involved in emotional decision making, such as the prefrontal cortex.

Ethanol Effects on Reward Value Judgment Following Infusions into the Amygdala: Implications for Emotional Processing

Under the influence of alcohol, people lose control of their emotions and ability to think clearly, leading to poor judgment and involvement in negative situations such as bar fights, promiscuity, and driving while intoxicated (Gengo, Gabos, Straley & Manning, 1990). Good decision-making abilities are significantly hindered by alcohol use, which can result in more serious consequences such as alcohol poisoning, and reckless homicide (Gengo et al., 1990; Steele & Josephs, 1990). While amygdala-damaged patients may not experience all of the behavioral changes related to alcohol use, they do exhibit similar deficits in decision making and emotional judgment as people under the influence of alcohol (e.g., Borrill, Rosen & Summerfield, 1987; Sato, Kubota, Okada, Murai, Yoshikawa & Sengoku, 2002). Based on further examination of the similarity between the individual effects of alcohol on emotion and amygdala damage, it is hypothesized that alcohol use may impair affective judgment by directly hindering amygdalar function.

Alcohol's effects on emotion

Alcohol use leads to emotional changes, which cascade into impaired decision making and judgment. One of alcohol's most behaviorally salient consequences on emotion is an increase in aggression (Bushman & Cooper, 1990; Giancola, 2003; Lyvers, 2000; Norris & Kerr, 1993). Alcohol ingestion led to a greater acceptance of violence in pornography and an increased willingness to engage in such sexual behaviors (Norris & Kerr, 1993). Giancola (2003) found that alcohol consumption was correlated with a greater increase in aggressive behavior when competing against a fictitious opponent, especially in participants low in empathy. Bushman and Cooper (1990) analyzed 30 experimental studies and concluded that

alcohol is not just correlated with an increase in aggression, but in fact produces this observable phenomenon.

While alcohol increases levels of aggression, perception of fearful stimuli and expression of fearful behavior decrease with alcohol intake, which might contribute to impaired decision making and memory for consequences following alcohol use (Christenfeld, & Creager 1996; Curtin, Lang, Patrick & Stritzke, 1998; Gould, 2003; Rimm, Briddell, Zimmerman & Caddy, 1981; Stewart & Pihl, 1994; Weitemier & Ryabinin, 2003). Rimm et al. (1981) found that subjects who had indicated a fear of harmless snakes were less reluctant to approach the snake after imbibing alcohol, but those who had not ingested alcohol were unaffected, regardless of their presumed beverage intake. Alcohol has also been shown to disrupt fear conditioning in mice and rats during the learning period of a task (Gould, 2003; Weitemier & Ryabinin, 2003) and to lessen unconditioned startle responses (Curtin et al., 1998). Similarly, women scoring high in anxiety sensitivity expressed decreased startle anticipation after ingesting alcohol (Stewart & Pihl, 1994).

The decrease in fear from alcohol use may also, then, lead to a similar decrease in anxiety. Christenfeld and Creager (1996) reported a decrease in the number of *ums* uttered in speech among anxious subjects following alcohol consumption. Anxiety also triggers alcohol use (Abrams, Kushner, Medina & Voight, 2002; Cooper, Frone, Russell & Mudar, 1995), which may lead anxious persons into a pattern of alcohol misuse. Alcohol helps alleviate drinkers' anxious state and they are better able to handle social stressors and other anxiety-inducing stimuli under so they feel as though alcohol is necessary for proper functioning.

Alcohol's relieving effects on fear and anxiety increase its use as a self-prescribed emotional analgesic (Abrams et al., 2002; Armeli et al., 2003; Cooper et al., 1995; Russell &

Mehrabian, 1975; Stritzke, Lang & Patrick, 1996). When allowed to drink at leisure, socially phobic participants consumed more alcohol following an anxiety-inducing task than prior to the task (Abrams et al., 2002). Likewise, participants with higher negative outcome expectancy drank significantly more than those with lower negative outcome expectancy (Cooper et al., 1995). Alcohol also reduced the degree of negativity in mood reports following negative experiences when participants were able to drink at will (Armeli et al., 2003). All of these studies point to the use of alcohol as an emotional mediator, allowing the consumer to gain desired short-term emotional relief. However, while immediate gratification is often gained, the long-term effects are often more detrimental and can lead to a pattern of alcohol misuse and unpleasant emotions, which leads to more alcohol use.

The negative cyclical pattern seen in people attempting to self-medicate is often indicative of a more serious problem; alcoholism has frequently been found to be comorbid with emotional disorders such as depression (Litten & Allen, 1995; Steele & Josephs, 1990; Stephens & Curtin, 1995), anxiety (Himle & Hill, 1991; Litten & Allen, 1995), posttraumatic stress disorder (Brown, Stout & Mueller, 1996), schizophrenia (Allen, Goldstein & Aldarondo, 1999), and other personality disorders (Morgenstern, Langenbucher, Labouvie & Miller, 1997; Murphy, Fals-Stewart, O'Farrell & Feehan, 2001; Scheidt & Windle, 1994). In patients diagnosed with comorbid alcoholism, the ability to make sound decisions regarding both the use of alcohol and their emotional state is hindered.

When alcohol decreases fear and anxiety and increases aggression in the consumer, it can increase the likelihood of judgmental errors, based on the inability to comprehend the full range of emotional consequences associated with poor decision making. One of the most salient judgment deficits due to alcohol use is in regard to driving. Alcohol consumption is responsible

for increased response times to physical stimuli and decreased awareness of slower reaction times (Denton & Krebs, 1990; Heacock & Wikle, 1974; Martens, Ross & Mundt, 1991; Maylor, Rabbitt & Connolly, 1989; Mundt, Ross & Harrington, 1992; Salvatore, 1975). Alcohol causes the user to respond differently to behaviors often associated with alcohol use. Chronic heavy drinkers (three or more drinks on one occasion) who participated in a questionnaire study were more likely to report greater acceptance of alcohol misuse and driving while intoxicated than were lighter drinkers and abstainers (Agostinelli & Miller, 1994; Martens et al., 1991). This could be an effect of the impaired judgment for emotional consequences that follows alcohol consumption.

Alcohol also impairs the ability to make intelligent judgments regarding performance on both quantitative and emotional tasks. Gengo et al. (1990) reported cognitive impairment on the ability to determine one's own sobriety levels with larger amounts of alcohol being correlated with greater impairment. Judgmental impairment following alcohol use has also been demonstrated through self-performance ratings when subjects displayed unrealistic optimism in regard to the number of questions answered correctly on a general knowledge test (Tiplady, Franklin & Scholey, 2004). The dampened ability to make accurate assessments after the use of alcohol will also lead to poor decision making during emotionally implicated circumstances as well. Borrill et al. (1987) reported that in participants distinguishing between varying degrees of emotion-laden facial expressions, high doses of alcohol led to decreased accuracy on task performance. Emotional judgment, therefore, is influenced by the presence of alcohol in the blood stream, with greater amounts of alcohol associated with greater impairment.

Alcohol has the ability to change emotions, is frequently comorbid with psychological disorders and impairs emotional judgment and decision making. While there is vast evidence

supporting alcohol's role in emotional alteration, little is known about the specific brain structures that alcohol affects to elicit these behavioral and cognitive changes. One of the brain areas most often associated with emotions is the amygdala, an almond-shaped structure located in the medial temporal lobe anterior to the hippocampus (Davis & Whalen, 2001; Gallagher & Chiba, 1996; Phelps, 2004). Research on amygdala-damaged patients points to a similar pattern of behavioral deficits as seen following alcohol use, suggesting that alcohol may take effect on the amygdala to impair affective functioning.

Amygdala and emotion

The amygdala is involved in a variety of emotions, and problems with the amygdala can lead to deficits in emotional judgment. The amygdala is the main neural structure associated with negative and positive affect, as seen through emotions such as fear and anxiety (Cheng, Knight, Smith & Stein, 2003; Frye & Walf, 2004; Li, Maglinao & Takahashi, 2004; McHugh, Deacon, Rawlins & Bannerman, 2004; Whalen, Shin, McInerney & Fischer, 2001), aggression (Kalynchuk, Pinel & Treit, 1999; Lubin, Elliot, Black & Johns, 2003; Zagrodzka, Hedberg, Mann & Morrison, 1998), sadness (Hamann, Ely, Hoffman & Kilts, 2002; Schneider, Grodd, Weiss, Klose, Mayer, Nagele & Gur, 1997), and happiness (Hamann et al., 2002; Morris et al., 1998; Schneider et al., 1997).

As levels of fear increase, amygdalar activity increases correspondingly (Cheng et al., 2003; Frye & Walf, 2004; Li, Maglinao & Takahashi, 2004; McHugh et al., 2004; Skuse, 2003). Through the use of functional magnetic resonance imaging (fMRI), the amygdala has been shown to increase in activity during human Pavlovian fear conditioning (Cheng et al., 2003) and in response to facial expressions of both fear and anger, but not to affectively-neutral facial expressions (Anderson et al., 2003; Killgore & Yurgelun-Todd, 2001; Whalen et al., 2001; Yang

et al., 2002). The amygdala is necessary for proper fear conditioning and response (McHugh et al., 2004; Frye & Walf, 2004), with freezing behavior in response to a startle stimulus being significantly reduced in rats after lesions to the medial amygdala (Li et al., 2004). In addition, the lesioned animals made more contact with a cloth that contained the scent of a predator (cat) than did controls. The amygdala's involvement with fear is also seen through the human expression of anxiety and social phobia. When the amygdala is activated it operates as an "alarm" mechanism that signals when a specific phobic stimulus is encountered, alerting the presence of potential dangers (Pissiota et al., 2003; Tillfors, 2004). Blood flow to the amygdala increases immediately following a startle stimulus, especially in response to a phobic stimulus as seen in humans (Pissiota et al., 2003). Furthermore, animals diagnosed with the Klüver-Bucy syndrome are classified by having improper responses to emotional stimuli, such as fear or anger (Gazzinaga, Ivry & Mangun, 2002).

Aggressive behavior is also linked with amygdalar activity (Kalynchuk et al., 1999; Lubin et al., 2003; Zagrodzka et al., 1998). Kalynchuk et al. (1999) kindled the amygdala in rats (gradually increased levels of an artificial stimulant applied directly to the amygdala) to reveal greater increases in defensive behavior to an intruder in amygdala-kindled rats and more aggressive behavior in sham-stimulated rats. When rats in a different study were given a gamma aminobutyric acid (GABA) receptor block to the amygdala, aggressive behavior significantly diminished as well (Hansen & Ferreira, 1986). Rats exhibited increased maternal aggression in response to an intruder when infused with an oxytocin antagonist in the central nucleus of the amygdala (Lubin et al., 2003). Aggressive behavior is altered through neurotransmitter and chemical changes in the amygdala.

Through a variety of studies, sadness was found to be associated with an increase in amygdala activity (Yang et al., 2002; Blair, Morris, Frith, Perrett & Dolan, 1999; Schneider et al., 1997). Depression, the mood disorder most closely tied to sadness, is correlated with lower human amygdalar volume and continual decreases in volume after each subsequent depressive episode (Sheline, Gado & Price, 1998). Depressed persons also showed an increase in metabolic rate in the right amygdala during negative affect (Abercrombie et al., 1998). A cross-sectional study of bipolar patients exhibited a smaller left amygdala than normal patients (Chen et al., 2004). In addition, sadness in non-schizophrenic subjects led to greater activation of the amygdala (Schneider et al., 1998). Negative emotions, such as aggression, fear, anxiety, and sadness are all associated with a change in amygdalar activity.

Not only is the amygdala heavily involved with negative affect (Whalen et al., 2001; Cheng et al., 2003), but it is substantially implicated in positive affect as well (Hamann et al., 2002; Morris et al., 1998; Schneider et al., 1997). Several studies revealed increased amygdalar activity during happy emotion on facial recognition tasks through fMRI (Killgore & Yurgelun-Todd, 2001; Morris et al., 1998; Schneider et al., 1997; Yang et al., 2002), as well as positron emission tomography (PET; Hamann et al., 2002). Not only has this been demonstrated through human studies, but amygdalar lesion studies using rats have also reported positive affect deficits following amygdalar damage (Kesner & Williams, 1995; Kesner, Walser & Winzenried, 1989). Since the amygdala is responsible for both positive and negative affect and affective perception, damage to this area should lead to deficits in emotional judgment and decision making.

Indeed, the ability to make productive decisions from knowledge of emotional consequences is significantly impaired following amygdala damage (Adolphs & Tranel, 2004; Baxter et al., 2000; Bar-On, Tranel, Denburg & Bechara, 2003; Skuse, 2003). In an experiment

by Adolphs, Tranel and Damasio (1998), amygdala-damaged patients were more trusting of strangers than non-damaged patients. When emotions are impaired, it is difficult to make accurate assessments of a given situation due to the strong role that emotions play in decision making; decisions are often made based on memory of past outcomes of similar scenarios. If a person has suffered damage to the amygdala, however, they will be less able to remember the emotional consequences of previous behaviors. For example, Skuse (2003) reported that persons with damage to the amygdala often held eye contact for awkward lengths (i.e., too long or too short), which made others feel uncomfortable. This social phenomenon of eye contact duration, thought to have involvement in emotional processing, can alter the reaction of others albeit subtly. The amygdala has an important influence in emotional decision making and behaviors.

The amygdala is clearly a central structure involved in affective functioning seen through changes in a plethora of emotions such as fear, aggression, sadness, and happiness in both intact and damaged amygdalas. The changes in emotional functioning and judgment following both alcohol use and amygdala damage are strikingly similar. For instance, both alcohol intake and amygdala activation are associated with increased aggression, sadness and fear. Alcohol abuse problems are often co-morbid with mood disorders, which are often the result of problems in amygdalar function. One hypothesis is that perhaps these emotionally-laden behavioral changes during alcohol use are due to alcohol directly influencing the functionality of the amygdala.

Alcohol's effects on the amygdala

While alcohol impairs receptor functioning in motor areas to produce impaired balance and coordination (Brick & Erickson, 1998), less is known about its neuronal involvement in emotional changes. However, alcohol has been found to alter several different aspects of neurotransmitter and receptor function prevalent in the amygdala, including neurotransmitter

changes in dopamine, serotonin, noradrenaline and hormonal fluctuations (Baumgartner et al., 1998; Shirao et al., 1988; Yoshimoto et al., 2001); as well as neural receptor alterations in *N*-methyl-D-aspartate (NMDA) and γ-aminobutyric acid (GABA) receptors (Boyce-Rustay & Cunningham, 2004; Calton, Wilson & Moore, 1998; Floyd, Jung & McCool, 2003; Foster et al., 2004; Gean, 1992; Hodge & Cox, 1998; McCool, Frye, Pulido & Botting, 2003; Papadeas, Grobin & Morrow, 2001; Simson et al., 1991).

Dopamine (DA) and serotonin (5-HT) are two very influential neurotransmitters in the limbic system, particularly the amygdala. Ethanol administration both intraperitoneally and through microdialysis into the central amygdala, both led to an increase in DA and 5-HT production (Yoshimoto et al., 2000). Intraperitoneal injections of EtOH also led to a significant increase in noradrenaline (norepinephrine) in the amygdalae of non-stressed rats, but led to a decrease of norepinephrine in the amygdalae of stressed rats (Shirao et al., 1988). In addition, ethanol affects the amygdala to enhance the stimulation of thyroid hormones, which can enhance mood and are often associated with reward (Baumgartner et al., 1998).

Alcohol inhibits the functioning of *N*-methyl-D-aspartate (NMDA) receptors located in the amygdala, as well as other brain regions. The NMDA receptor, an excitatory amino acid receptor, depolarizes neurons in the mammalian central nervous system (CNS; Cooper, Bloom & Roth, 2003). It plays a central role in long-term depression, long-term potentiation (LTP) and in the developmental plasticity of the brain. Alcohol, when delivered to the brain, "dampens the excitatory effects of nerve cell firing" as a result of "its slowing of the gating of sodium and calcium ions in response to the action of glutamate at its NMDA receptor" (Regan, 2001). Simson et al. (1991) found that systemic administration of EtOH at doses capable of producing marked behavioral changes, inhibited NMDA-evoked electrophysiological activity in the medial

striatum *in vivo*. In an *in vitro* experiment using cells from the basolateral amygdala, low-doses of EtOH successfully inhibited NMDA receptor activity (Gean, 1992) – especially when magnesium (Mg^{++}) was also present (Calton, Wilson & Moore, 1998). Acute ethanol administration also led to a decrease in the amplitude of evoked NMDA-mediated EPSP's and EPCP's in the central amygdala (Roberto et al., 2004). Another study used an NMDA blockade to reveal a decrease in conditioned place preference (CPP), as well as conditioned place aversion (CPA) to ethanol (Boyce-Rustay & Cunningham, 2004). Hodge and Cox (1998) provide evidence for the NMDA receptor system's ability to discriminate between EtOH and similar non-EtOH substances in the amygdala and other limbic structures, which suggests an affinity for EtOH in those regions.

While alcohol acts as an antagonist to the main excitatory receptor system (NMDA), it acts as an agonist for the major inhibitory amino acid transmitter in the brain, GABA (Cooper et al., 2003). Since GABA is an inhibitory receptor, when alcohol is administered it stimulates the receptor, thereby increasing inhibition of the target neuron. This concept was validated through an early study which found that GABAergic receptors are sensitive to acute EtOH exposure in the central nucleus of the amygdala (Morales et al., 1998). An intracerebroventricular injection of alcohol into the basolateral amygdala-dentate gyrus complex inhibited the induction of LTP through potentiation of GABAergic transmission only when given prior to the tetanic stimulation (which is typically administered to induce LTP; Abe, Niikura & Misawa, 2004). When EtOH was given after LTP had already occurred, there was no effect on the pre-established LTP, suggesting a time-wise selective mechanism for alcohol's effects on memory and retrieval. Another study found that when EtOH was the sole reinforcer in a self-administration task, where a GABA agonist was administered, the amount of self-administration of EtOH was significantly

decreased (Foster et al., 2004). This suggests that stimulating GABA receptors causes a decline in the seeking out of rewards, which supports the idea that greater doses of EtOH will also lead to such a decline.

Not only does alcohol impair the amygdala at the time of use, but substantial research suggests that permanent damage to GABA and NMDA receptors can result from chronic use of alcohol (Foster et al., 2004; McCool, Frye, Pulido & Botting, 2002; Papadeas, Grobin & Morrow, 2001) and can eventually decrease the mass of the amygdala (Sheline, Gado & Price, 1998). Chronic ethanol treatments in rats led to decreased response of NMDA receptors in the central nucleus of the amygdala (Roberto et al., 2004). Chronic EtOH administration also significantly decreased $GABA_A$ receptor $\alpha 1$ subunit and $\alpha 4$ subunit peptide levels, as well as impaired Cl^- reuptake in the amygdala (Papadeas et al., 2001).

Overall, there is a great deal of support for alcohol's specific role in receptor impairment in the amygdala. While very few studies have utilized intracranial administration of EtOH into the amygdala *in vivo* (e.g., Abe et al., 2004), the evidence taken from *in vitro* studies and systemically injected EtOH *in vivo* lend their support to the possibility that intracranial administration of EtOH into the amygdala will lead to a decline in performance on memory for reward value magnitude. Emotions are highly influenced by alcohol intake with a larger doses of alcohol associated with greater emotional deficits. The amygdala also plays an important role in the perception and regulation of emotions and emotional judgment and decision making. Deficits similar to those seen as a result of alcohol use have also been found in patients with amygdalar lesions (Emery et al., 2001). Therefore, it is hypothesized that infusing alcohol directly into the amygdala should lead to deficits in emotional decision making.

Implications for present study

The present study will examine this issue by infusing alcohol directly into the amygdala on a behavioral task that involves memory for reward value magnitude. Of specific relevance to the present study, Kesner and Williams (1995) found that rats with amygdalar lesions showed deficits in reward value memory on the same behavioral task used in the present study. More recently, Williams (in preparation) found that systemic injections of EtOH led to impairment on the same reward value memory task on which the methods for the present study are based. If lesions to the amygdala lead to impaired affective judgment, and alcohol intake leads to impaired affective judgment, it is plausible that alcohol is affecting the brain at the site of the amygdala to produce these affective reward value deficits. If the amygdala is the brain area mainly responsible for these behavioral deficits, intracranial EtOH administration into the amygdala should lead to greater impairments in emotional judgment in reference to saline administration.

Methods

Subjects

Eight male Long-Evans rats were used in this experiment. Rats were housed individually in standard plastic cages with stainless steel lids and corncob bedding and were kept on a 14/10 hour light/dark cycle. The rats were fed Harlan brand Teklad rat/mouse feed (Indianapolis, Indiana). The rats were maintained at 80-85% of their *ad libitum* weight, with accommodations made for their natural growth throughout the experiment. The treatment of all animals was in accordance with the *Guide for the Care and Use of Laboratory Animals* (1996) and followed the experimental study protocol approved by Illinois Wesleyan University's Institutional Animal Care and Use Committee (IACUC).

Apparatus

A standard radial arm maze with eight arms (67 cm long and 11 cm wide) radiating out from a center platform (34.5 cm in diameter) served as the main apparatus for this experiment (see fig. 1). The maze (raised 91.5 cm above the floor) was walled off by transparent Plexiglas that stood 7.5 cm above the floor of each arm (11.0 cm from base to top) and 42.5 cm tall around the center platform. Vertically sliding doors, raised and lowered by means of a pulley system, allowed access to each arm from the center of the maze. The wood floor was painted black and there was a food well (2.5 cm in diameter) located 2.5 cm from the end of each arm wall. Only two of the arms (located at a 90 degree angle from each other) were used in the experimental procedure.

Procedure

Rats were trained on a behavioral task designed to measure reward value judgment. Rats ran trials five days a week for either 15 minutes or until twenty trials had been completed, whichever came first. In the task, rats differentiated between a stimulus (either low or high sweetness level cereal) that was paired with a reward (positive stimulus), and a stimulus (either low or high sweetness level cereal) that was not paired with a reward (negative stimulus). The two sample stimuli differed in palatable sweetness level, with the low sweetness level cereal being less sweet than the high sweetness level cereal.

Shaping. To habituate the rats to the apparatus, rats were first placed on the center platform and were allowed to explore the two arms used in the experiment (the sample arm and the reward arm). The sample arm was lined with five pieces of the low and high sweetness level cereals placed at equal intervals along the length of the arm. The reward arm was similarly lined with five pieces of the reward stimulus (Apple Jacks), to attract the rats toward the end of the

arm where the food well was located. As the rats became more comfortable eating the food pellets, gradually fewer pellets were placed along the arms until they received only one food pellet, which was located in the food well of each arm as the task required. Once the rats moved back and forth efficiently between arms and reliably consumed the food pellets located within the food wells, they were introduced to another element. Two film canisters (one in the sample arm and one in the reward arm) had been sitting next to the food well in both arms since the rats were first introduced to the maze to habituate them to the presence of a film canister. While the rats never had to move the canister to retrieve the food up until this point, they now were required to move the canister in order to retrieve the food located in the food wells. The canisters were initially placed over one-fourth of the food well and were gradually placed over an increasing area of the food well so that eventually the entire food well was covered for both arms. The purpose of the film canister was to conceal the contents of the food well, and to increase timing reliability by acting as the stop point for trials. The official training period began once the animals were able to confidently move back and forth between arms as well as move the canister aside and consume the food pellet located in each well.

Experimental procedure. The experimental procedure consisted of three main periods: training, surgical procedure, and experimental manipulation. The training period was designed to accustom the rats to the specific task and to bring them up to time criterion. The surgical procedure consisted of surgeries to implant the guide cannulae, through which later infusions would be made, and a recovery period. The experimental manipulation period included the infusions and behavioral retesting on the task.

In the training period, each rat was pseudo-randomly assigned either a low sweetness level cereal or a high sweetness level cereal as their positive stimulus and the opposite as their

negative stimulus, so that four rats received the low sweetness level cereal as their positive stimulus and the high sweetness level cereal as their negative stimulus and four received the high sweetness level cereal as their positive stimulus and the low sweetness level cereal as their negative stimulus.

The task consisted of two phases: a sample phase and a reward phase. The sample phase was initiated by opening the sample arm door and simultaneously starting the stopwatch. After the rats moved into the sample arm, the door was closed behind them. The rats then had to travel to the end of the arm, move the canister to uncover the sample arm food well, and retrieve the sample stimulus (either a low sweetness level cereal or a high sweetness level cereal). As soon as the rats uncovered the food well, the stopwatch was stopped. The entire phase was timed from the opening of the sample door to the uncovering of the food well. Sample phase times were recorded to provide a control for behaviors that may have been altered as a result of impaired motor skills or motivation as opposed to the independent variable.

Following complete consumption of the sample stimulus, the reward phase began. The doors to both the sample and reward arms were opened and the stopwatch was simultaneously started. The rats traveled into the reward arm, moved the canister from the food well at the end of the arm, and revealed the contents of the food well (determined by the contents of the sample arm food well). If the sample well contained the rats' positive stimulus, then the reward well contained the reward stimulus (an Apple Jack piece). If the sample well contained the rats' negative stimulus, then the reward well was empty. After the rats uncovered the food well, the stopwatch was stopped. The entire phase was timed from the opening of the doors to the uncovering of the food well (see fig. 2 for an illustration of the task).

To achieve task criterion, the rats were required to learn that the positive stimulus would always be paired with the reward, and the negative stimulus would never be paired with the reward. Performance was measured by calculating the difference in latency between reward phase trials when given the positive versus the negative sample stimulus. Greater differences in latency indicated strong performance and smaller differences in latency indicated weak performance. Once they reached task criterion, approximately five seconds mean time difference, rats underwent surgery to measure the effects of ethanol (EtOH) on task performance.

Surgical procedure. Each rat was given an injection of ketamine/xylazine anesthesia (0.1 ml/kg) under aseptic conditions in accordance with the *Guide for the Care and Use of Laboratory Animals* (1996). After the anesthesia had taken effect, the rats' scalps were shaved with an electric razor, cleansed with a disinfectant scrub (Betadine), and an incision was made down the center. Sterile cotton swabs were used to clean the area as needed.

Two guide cannulae made of 26 gauge steel tubing were implanted bilaterally into the amygdala (2.3 mm posterior to bregma; 4.4 mm lateral to midline; 5.5 mm ventral to the dural surface) to allow for the infusion of EtOH or saline (see fig. 3). The cannulae were secured to the skull using anchor screws and dental cement. After the surgeries were complete, a stylet was inserted into each guide cannula to prevent clogging and Mycitracin Plus (a local antibiotic/anesthetic) was applied to the edges of the dental acrylic to prevent infection and alleviate irritation. Rats were given an analgesic (Ketamine) to help reduce any potential discomfort. Animals were carefully watched to ensure stable recovery from the surgery.

Experimental Manipulation. After completion of the surgeries, rats were given a seven day recovery period. At the end of this period the rats were re-trained on the task until they returned to task performance criterion (approximately a five second difference between positive

and negative stimulus reward phase trials). When rats performed at the desired level, they received an infusion of 0.1% EtOH solution, 1% EtOH solution or a saline solution prior to performing the task. The saline solution controlled for the possible effects of receiving an infusion on behavioral performance. The present study used a within-subjects design with each rat receiving all solutions on separate days. The infusions were randomly assigned and counterbalanced to prevent order effects. Three days separated each infusion, during which rats continued to perform the task daily to maintain task criterion. The difference in performance between infusions was recorded.

Histology. To verify the accuracy of cannulae placements and to determine the extent of the drug infusions, the rats will be anesthetized with ketamine/xylazine (0.1 ml/kg) and infused with Chicago sky blue dye (2%; 0.5 μl) into the amygdala to mark the location of the placements. Once this is complete, rats will be given a lethal injection of ketamine/xylazine and decapitated. Brains will be removed and placed in a formalin solution for preservation. Brains will then be frozen, sectioned transversely (40 μm), and stained with Cresyl violet. Since secondary data collection is still in progress, this phase of the study has not yet been completed.

Statistical Analyses. Statistical analyses were done to measure the effects of the infusion types on both sample phase times and reward phase times. To control for the effects of the infusions on motor skills, motivation and procedural memory, a within-group one-way analysis of variance (ANOVA) was conducted to compare the post-surgery response times in the sample phase between the saline, 1% EtOH solution, and 0.1% EtOH solution infused rats. Since a reward was always available in the sample phase, it provided an adequate source to determine any effects on motor skill, motivation and procedural memory. To determine whether alcohol infusions impaired reward value memory a within-group ANOVA on the reward phase times

was conducted, using the infusion type (ethanol solution or saline) as the within Ss variable, mean difference in response time between positive and negative trials as the dependent variable. To control for possible effects on the longevity of alcohol in the brain, an ANOVA was conducted to compare the first ten trials with the second ten trials.

Results

Behavior

Eight rats reached task criterion and received intracranial infusions, thus for all analyses $N = 8$. To initially learn the task and reach criterion of three consecutive days of a mean time difference of five seconds between positive and negative trials, rats took an average of 42.88 days (SD = 4.31 days). To become reacquainted with the task following surgery and meet the same criterion of three consecutive days of five second time difference rats took an average of 5.13 days (SD = 2.03 days). The first three consecutive days of adequate performance were included in these analyses.

Main alcohol effects

To examine whether there was an effect of EtOH infusions in the amygdala on memory for reward value magnitude, an analysis of variance (ANOVA) test was done to analyze the statistical difference between low EtOH, high EtOH, and saline infusions, as well as for a non-infusion day. There was not a significant difference between mean time differences for positive and negative trials across infusion types, $F(3, 21) = 1.115$, $p = 0.365$ (see fig. 4). The mean time difference between positive and negative reward phase times following saline infusions was 6.689 sec (SD = 1.202 sec), for low EtOH infusions was 5.636 sec (SD = 1.894 sec), for high EtOH infusions was 6.425 sec (SD = 1.635 sec), and for no infusion was 6.983 sec (SD = 0.935

sec). Alcohol did not significantly impair performance on the task measuring reward value memory.

First ten trials vs. second ten trials

Analyses were also done to examine the possible effects of the time-wise duration of efficacy of infusions to the brain by separating the first ten trials from the second ten trials (see fig. 5). Since the alcohol may have dissipated before completion of all 20 trials, comparisons were made to examine any potential effects that alcohol may have had in the first 10 trials as opposed to the second ten trials. An ANOVA reported no significance between infusion type for the first ten trials alone, $F(3, 21) = 1.789$, $p = 0.180$. However, the mean differences between positive and negative trials for the first ten trials were significantly lower than the mean differences between positive and negative trials for the second ten trials, $F(1, 7) = 12.360$, $p = 0.010$. In addition, there was no interaction effect between infusion type and first ten and second ten trials, $F(3, 21) = 1.012$, $p = 0.407$. The mean difference between positive and negative trials for the first ten trials after infusions of saline was 6.177 sec (SD = 1.668 sec), low EtOH was 4.476 sec (SD = 2.545 sec), high EtOH was 6.255 sec (SD = 1.436 sec), no infusion was 6.395 sec (SD = 0.976 sec). The mean difference between positive and negative trials for the second ten trials of each saline infusion was 7.139 sec (SD = 1.093 sec), low EtOH was 6.617 sec (SD = 1.355 sec), high EtOH was 7.229 sec (SD = 1.556 sec), and no infusion was 7.420 sec (SD = 1.131 sec). There was no significance across infusion types for the first ten trials, but the main effect of time was significant for all infusion types.

Motivation, motor skills, and procedural memory

Alcohol also did not impair motor skills, motivation, or procedural memory (see fig. 6). An ANOVA using infusion as a within Ss factor and sample phase time as a dependent variable

revealed no significance, $F(3, 21) = 0.163$, $p = 0.920$. Mean sample phase time for saline infusions was 1.859 sec (SD = 0.506 sec), low EtOH infusions was 1.858 sec (SD = 0.981 sec), high EtOH infusions was 0.336 sec (SD = 0.119 sec) and no-infusions was 1.881 sec (SD = 0.639 sec). There was no difference between infusion types for motor skills, motivation, or procedural memory.

Histology

Once the data collection process of all rats has been completed and slides have been made, the locations of cannulae placement will be examined.

Discussion

Previous studies have found that both systemic injections of alcohol in rats (Williams, in preparation) and electrolytic lesions of the amygdala (Kesner & Williams, 1995) impair reward value judgment on the same behavioral task that was utilized in the current study. This led to the hypothesis of the current study which stated that the alcohol-induced impairments could be due to alcohol's direct affect on the amygdala. However, results of this study suggest that reward value judgment is not impaired after direct infusions of EtOH into the amygdala. There are several possible explanations for these results. One reason is that brain regions other than the amygdala (subcortical), such as the prefrontal cortex (PFC; cortical), may be responsible for reward value judgment and decision making. Secondly, there might be timing-related issues that may have obscured any potential alcohol-induced impairments. For instance, time delays between sample phase and reward phase used in the present study may have not been appropriate to produce deficits on the task, additionally, the time that alcohol is effective when infused directly into the brain may have altered results. And finally, there may have been concerns regarding the location of cannulae implantation.

Subcortical vs. cortical control

Memory for reward value tasks consists of several aspects including the more immediate response of discriminating between the two sweetness levels, and using that information to make later judgments and responses – a more executive decision related response. At the beginning of a trial, rats must determine the sweetness level of the sample stimulus. They then must consciously evaluate whether the stimulus will lead to a reward and act on this information. These two thought processes involve two different, distinct pathways – the first involves the subcortical pathway (amygdala) which controls the immediate, reflexive emotional behavior, and the second involves the cortical pathway (amygdala sends information to the cortex), which controls higher-order cognitive functions such as evaluation and conscious decision making (Anderson, Christoff, Panitz, de Rosa & Gabrieli, 2003; Pissiota et al., 2003; Shin et al., 2004).

For example, fearful stimuli trigger initial processing in the amygdala (Frye & Walf, 2004; McHugh et al., 2004; Killgore & Yurgelun-Todd, 2001; Yang et al., 2002). When the amygdala is activated, it sends impulses to the sympathetic nervous system, which controls the "fight or flight" response and leads to the freezing behavior often exhibited when one is startled (Pissiota, et al., 2003; Tillfors, 2004). Results from the present study suggest that alcohol does not affect this subcortical route in response to positive affect. The effects of alcohol infusions to the amygdala in a task eliciting negative affect have not yet been studied. However, since systemic injections of alcohol have been shown to impair task performance, it can be inferred that alcohol is in fact having some effect on the brain. When the intact amygdala signals the sympathetic nervous system to produce this automatic response, it simultaneously sends impulses to the cortical brain regions involved in emotional processing. In support of this

phenomenon, Anderson et al. (2003) found that the cortex displayed greater activation than the subcortex when a stimulus was being consciously appraised.

One cortical brain region known to be impaired following systemic alcohol administration is the PFC (Iwamoto et al., 2004; Kahkonen et al., 2003; Mihalick et al., 2001). Alcohol impaired performance on a battery of cognitive tasks that included working memory and planning, but did not impair performance on tasks designed to elicit more subcortical activation (Kirchner & Sayette, 2003). Electrolytic lesions to the PFC significantly impaired performance on the same behavioral task used in the present study (DeCoteau, Kesner, & Williams, 1997). In addition, postmortem human analyses showed that fewer genes were expressed in the prefrontal cortex of alcoholics as compared to control subjects (Iwamoto et al., 2004). Not only did alcohol damage the PFC when taken habitually throughout a lifetime, but there is evidence that prenatal exposure to alcohol significantly reduces cell number in the medial prefrontal cortex in rat pups (Mihalick et al., 2001). Thus, it is possible that while alcohol does not affect the earlier, subcortical stages of reward value processing, it may act on the more cortical stages of reward value processing. The next step in reward value judgment research is to duplicate the present study with infusions of EtOH into the PFC rather than the amygdala. While it is plausible that a region other than the amygdala, the PFC for example, is responsible for the deficits on this behavioral task seen following systemic injections of EtOH, there remain several other alternative explanations for the current results.

Time effects

One explanation involves time between phases on the task and the persistence of EtOH in the amygdala when administered intracranially. It is possible that the delay time from completion of sample phase trials to commencement of reward phase trials plays an important

role on rats' abilities to remember the sweetness level of the sample phase cereal. Since rats were given a 0 second latency between sample phase and reward phase, the effects of EtOH on amygdalar function may have been lessened due to the ease of retaining the sweetness level in working memory. However, in previous studies, electrolytic lesions of the amygdala produced task impairments at all delay periods, including the 1-4 second delay used in the present study (DeCoteau, Kesner, & Williams, 1997; Kesner, & Williams, 1995). In addition, intraperitoneal injections of EtOH also produced significant deficits on this task when the delay time between phases was 1-4 seconds (Williams, in preparation). This suggests that the time delays used in the present study should have been sufficient to detect any effects of intra-amygdalar infusions of alcohol. Therefore, it is unlikely that delays between sample and reward phases were a cause for the current study's results.

Another potential explanation involves the time-wise efficacy of EtOH when intracranially infused. Since most ethanol research has involved oral consumption or intraperitoneal injections, it is unclear how long the effects of EtOH are observed. There are two main ways to determine this concept: recording neurons following direct infusions, or analyzing the behavior following the infusions. Since the present study utilized behavioral observation rather than extra/intracellular recording, the first ten trials and second ten trials were separated to determine potential effects that may not have been observed due to contamination of the data from later trials. Since there were no significant differences between EtOH doses and saline infusions or no-infusion days for the first or second ten trials, it can be concluded that the results found were not due to a depletion of alcohol in the brain prior to the conclusion of all trials. Also, significant impairment was found in rats following direct infusions of EtOH into the medial septal area in a behavioral task that lasted 30 minutes (Givens, & McMahon, 1997).

Further research still needs to be done to examine the duration of efficacy when EtOH is infused directly into the brain.

Histology

One concern with the procedure is insuring correct implantation of the guide cannulae. Since primary and secondary data are still being collected, the brains have yet to be sectioned and put onto slides. Therefore, it is not yet possible to know whether cannulae placements were in the correct area (directly above the amygdala). If several rats had incorrect cannulae placement there is a chance that significant results of the present study were masked by the performance of rats with cannulae placed in an area other than the amygdala. However, this explanation is unlikely to be true given the low variability between individual rat performances. When there was variability it was not consistent across all days. Another possibility is that certain parts of the amygdala may be responsible for entirely separate behaviors. For instance, Kesner, Walser and Winzenried (1989) reported involvement of the central amygdala, but not the basolateral amygdala in an affective memory task. Furthermore, analyzing the differences between cannulae placements of various brain regions may provide important insight to the process of direct infusions into the brain.

Future directions

Studying the effects of alcohol on specific brain regions may lead to pinpointing brain areas responsible for certain types of tasks, or memories. Also, it could eventually lead to further research and possible prevention and treatment for alcoholics. Future studies should assess whether different areas of the amygdala have different levels of involvement in reward value memories, for example, focusing on the basolateral amygdala as compared to the central nucleus of the amygdala. Other studies also need to be conducted to examine the effects of EtOH

infusions to the PFC on the same task. If significant impairment is found when EtOH is directly infused into the PFC, more can be learned about the nature of this subcortical-cortical pathway. Implementing delays between sample phase and reward phase access is another important investigation. Finally, studies also need to be done to specifically investigate the time-wise efficacy of EtOH in the brain during intracranial infusions. The knowledge gained from a study of that nature would be beneficial to the field of neuropsychopharmacology as a whole, and may eventually provide important background knowledge for other future directions of EtOH research.

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Figure 1. Eight arm radial arm maze used in present study.

Figure 2. Schematic of eight arm radial arm maze to illustrate general aspects of the task.

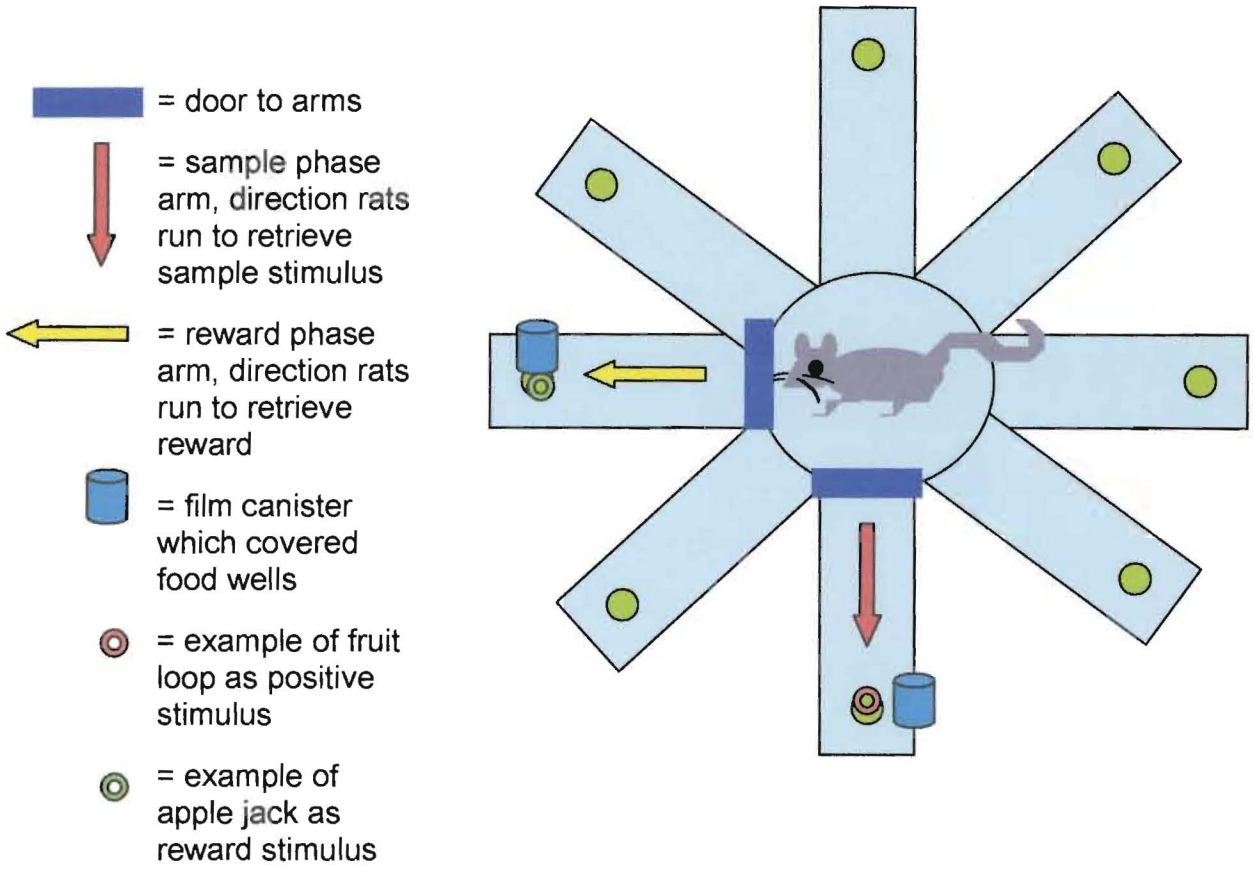

Figure 3. Rat post-surgery with visible guide cannulae attached.

Figure 4.

Alcohol infusions into the amygdala do not significantly impair task performance relative to saline infusions. (*N*=8).

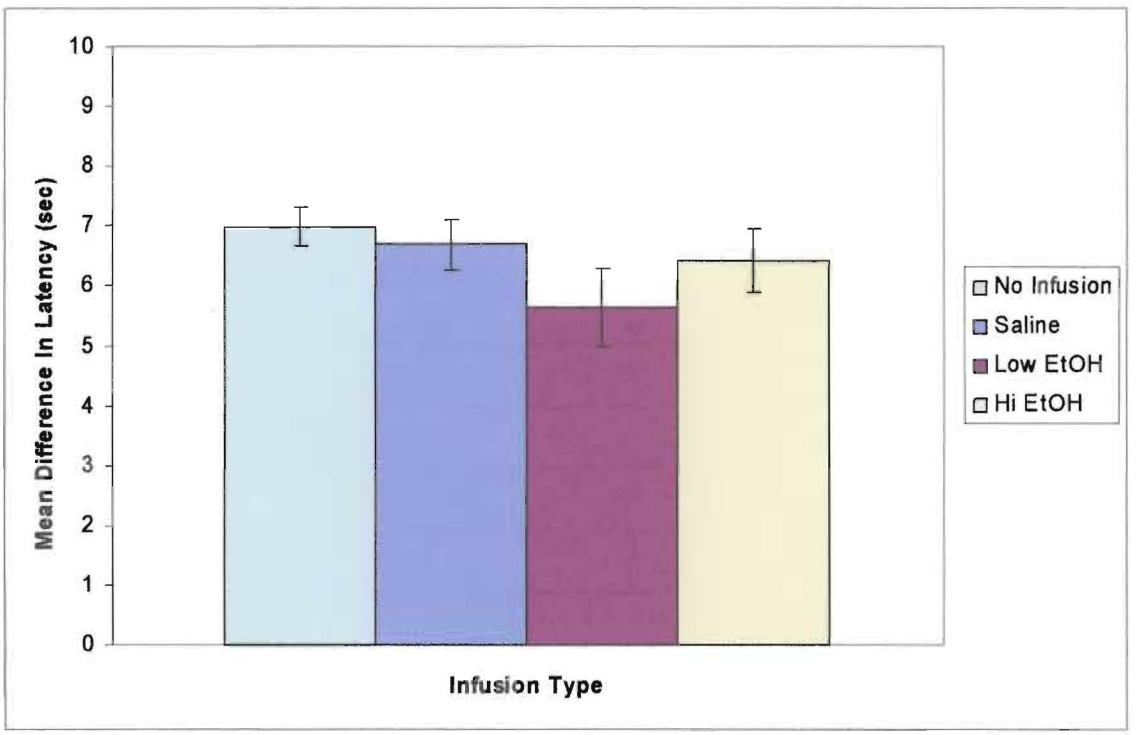

Figure 6.

Alcohol infusions into the amygdala do not impair motivation, motor skills, or procedural memory. (N=8).

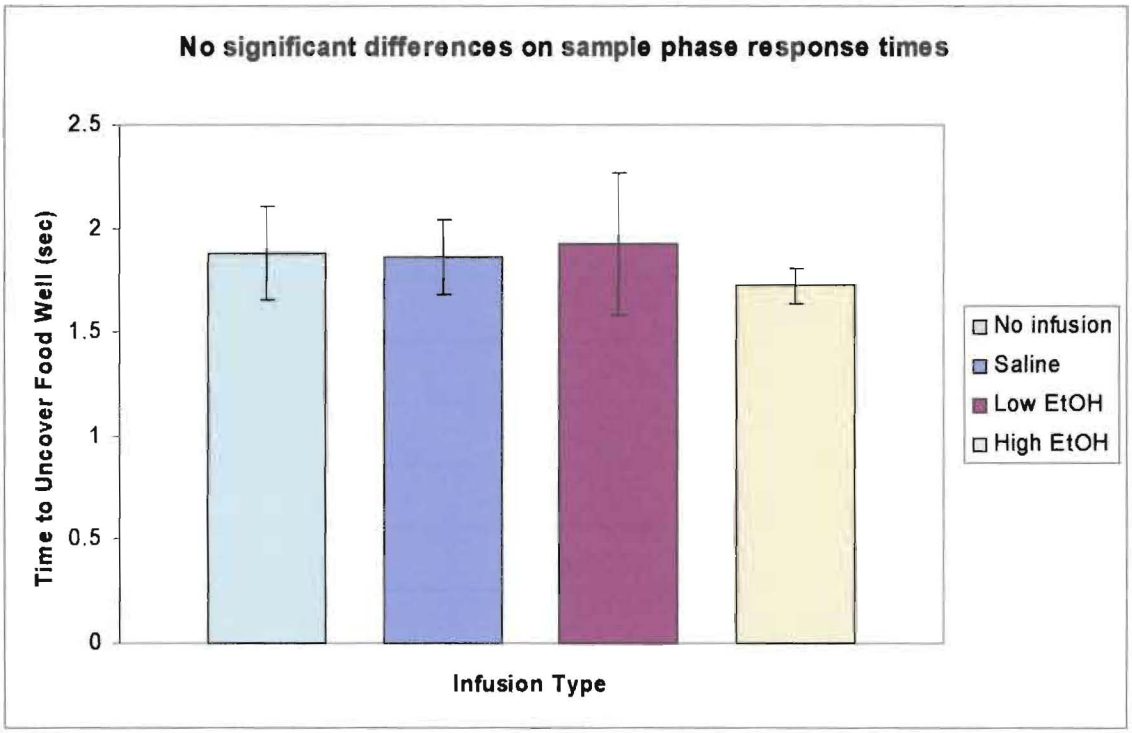

Figure 5.

Performance on 1st ten trials was significantly lower than 2nd ten trials across all infusion types. No effects were found between infusion types and there were no main effects. (N=8).