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# Deep brain stimulation of the nucleus accumbens reduces ethanol consumption in rats

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ABSTRACT

Recent studies have shown that deep brain stimulation (DBS) of the nucleus accumbens (NAcc) has an inhibitory effect on drug-seeking behaviors including reinstatement responding for cocaine. The objective of the present study was to expand on these findings by assessing the effects of DBS on behaviors related to alcohol consumption. The specific aim of this study was to determine whether DBS delivered to either the shell or core of the NAcc would reduce ETOH intake in rats using a two-bottle choice limited access procedure. Long Evans rats were induced to drink a 10% ethanol solution using a saccharin fading procedure. Bipolar electrodes were implanted bilaterally into either the core or shell of the NAcc. During testing animals received DBS 5 min prior to and during a 30-minute test session in which both ETOH and water bottles were accessible. Current was delivered at amplitudes ranging from 0 to 150 μA. ETOH consumption was significantly reduced from baseline levels at the 150 μA current for both shell and core electrode placements. A significant current effect was not found for water consumption for either site. These results provide evidence that DBS delivered either to the nucleus accumbens core or shell subregions can significantly reduce ethanol intake in the rat.



## 1. Introduction

Deep brain stimulation (DBS) involves the continuous electrical low intensity stimulation of select brain areas. DBS has been found to have a number of therapeutic applications including the treatment of movement disorders such as Parkinson's disease (Krack et al., 2003) and of psychiatric disorders that include depression (Lozano et al., 2008) and obsessive compulsive disorder (Greenberg et al., 2008). A few recent preclinical studies have focused on the effects of deep brain stimulation in models of substance abuse disorders. With respect to psychomotor stimulants, delivery of deep brain stimulation over a two hour long test session to the shell of the nucleus accumbens has been found to selectively block reinstatement responding for cocaine induced by the priming dose of this psychomotor stimulant (Vassoler et al., 2008). Morphine-induced conditioned place preference has been reported to be attenuated by the delivery of deep brain stimulation to the nucleus accumbens core during the conditioning phase (Liu et al., 2008). This finding suggests that DBS delivered to the core of the accumbens may either alter the rewarding effects of opioids or may otherwise disrupt other mechanisms involved in the acquisition of opioid-related conditioned responses.

Stimulation of the nucleus accumbens was associated with decreased ethanol consumption by an alcohol dependent patient (Kuhn et al., 2007). Other than this single case study there appear to be no other published reports concerning the effects of DBS on alcohol consumption. The finding that stimulation of the nucleus accumbens may produce this effect is consistent with evidence that this structure may play a role in regulating ethanol consumption behaviors. Other evidence that implicates the nucleus accumbens in regulating the processes associated with ethanol consumption includes findings that spike activity in this structure is altered during operant responding for alcohol (Janak et al., 1999). Also energy metabolism is increased in the shell of the accumbens of rats while they are drinking ethanol (Porrino et al., 1998a,b). Pharmacological manipulations such as the injection of the $GABA_A$ receptor agonist muscimol (Hodge et al., 1995) or the dopamine receptor antagonist fluphenazine (Rassnick et al., 1992) into the nucleus accumbens have an inhibitory effect on responding for ethanol. During periods of alcohol consumption dopamine levels in the accumbens may be increased (Doyon et al., 2003). Some results do suggest, however, that dopamine within the nucleus accumbens regulates ethanol seeking but not consummatory behaviors (Ikemoto et al., 1997; Samson and Chappell, 2004).

The objective of the present study was to assess whether DBS delivered to the nucleus accumbens would alter ethanol consumption by rats given limited access to 10% alcohol–water solutions. A second bottle containing water was also made available to animals during test sessions to assess whether DBS had any effect on the small amounts of water that rats consumed during these sessions.

The nucleus accumbens has core and shell subregions that have somewhat distinct projection patterns (Heimer et al., 1991). These

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subregions also differ with respect to relative distribution of certain neuropeptides such as cholecystokinin (Lança et al., 1998) and in the density of some receptor populations including high affinity neurotensin receptors (Pickel et al., 2001). The differences between these two subregions may have functional significance with regard to their response to the presence of ethanol. For example, dopamine release produced by the acute administration of ethanol may be more pronounced in the shell than in the core of the accumbens (Howard et al., 2008) and chronic ethanol treatment results in greater expression of the transcription factor ΔFosB in the core as compared to the accumbens shell (Perrotti et al., 2008). Because of possible differences in the role played by the accumbens core and shell in regulating ethanol consumption separate core and shell targeted groups of animals were tested in the present study.

## 2. Methods

### 2.1. Animals and housing

Animals were used in this investigation with the approval of the Boston University Medical Center's Institutional Animal Care and Use Committee.

Male Long Evans (Taconic Laboratories, Germantown, NY) rats weighing between 200 and 225 g were obtained for this study. Prior to surgery animals were housed in pairs and were then housed individually following electrode implantation to protect these implants. Animals were maintained under a 12/12 hour light/dark cycle, with lights being turned on at 7:00 AM. Animals were trained and tested during the lights-on condition. Food and water were always accessible to animals when they were in their home cages.

### 2.2. Testing environment, apparatus, stimulation parameters

Animals drank alcohol in an acrylic drug self-administration chamber that was housed in a sound-attenuating chamber. Fans provided a white noise background in the test environment.

Ethanol/water and ethanol/saccharin solutions were delivered from 15-ml graduated centrifuge tubes (SP Industries Lab Glass, Warminster, PA) with custom designed wide mouths for placement of #5 rubber stoppers and sipper tubes. Water was available from 40-ml graduated centrifuge tubes.

Stimulation was delivered from Med Associates Stimulators (East Fairfield, VT). These stimulators were controlled by Med PC for Windows software. The stimulation current consisted of biphasic square pulses. Stimulation parameters were set at a pulse width of 200 μs, a delay between positive and negative pulses of 200 μs, with a frequency set at 160 Hz. Current intensities ranged from 0 to 150 μA. The train duration was set at 5 min in length with no delay between trains, resulting in essentially continuous stimulation. These stimulation parameters are the same as those used in prior work on the effects of deep brain stimulation on cocaine reinstatement responding (Vassoler et al., 2008) and are within the range we have utilized in brain stimulation reward experiments (Bird and Kornetsky, 1990). They would be expected to produce levels of stimulation similar to those used by other investigators who have examined the effects of deep brain stimulation delivered to a variety of brain regions including the nucleus accumbens (Chang et al., 2003; Liu et al., 2008; McCracken and Grace 2007).

### 2.3. Surgery

Rats received 80 mg/kg ketamine and 12 mg/kg xylazine IP as anesthesia. After the induction of anesthesia rats were placed into stereotaxic apparatus (Kopf Instruments, CA). Two bipolar stainless steel electrodes (Plastics One, Roanoke, VA) were then implanted into either the shell or the core of the nucleus accumbens. Shell electrode placements were targeted to the medial portion of this subregion based on the prior finding that deep brain stimulation delivered to this area suppressed reinstatement responding for cocaine (Vassoler et al., 2008). The following coordinates were used for implanting electrodes: 1) nucleus accumbens core — stereotaxic arms were set at a 12° angle: 1.2 mm anterior to bregma, ±3.5 mm lateral to the midline, and 6.9 ventral to the surface of the skull 2) nucleus accumbens shell — stereotaxic arms were set at a 17°angle: 1 mm anterior to bregma, ±3.0 mm lateral to the midline, and 7.3 mm ventral to the surface of the skull. Electrodes were affixed to the skull using dental cement (Ortho-Jet; Lang Dental Manufacturing Co., Inc, Wheeling, Il.).

### 2.4. Induction of drinking and testing

Animals were given access to ethanol in 30-minute sessions during the induction, stabilization and test phases of this experiment. A second bottle containing tap water was always made available to animals during all of the experimental sessions. The position of the ethanol and water bottles remained fixed throughout the training and testing periods. This was done to decrease the possibility that DBS might influence ethanol consumption by disrupting the cognitive processes needed to keep track of alternating bottle positions. Rats were first induced a drink of 10% ethanol solution using a saccharin fading procedure. The target schedule for this procedure was as follows: Days 1–3, 0.2% saccharin (S)/0% ethanol (E); Days 4–7, 0.15% S/0.05% E; Days 8–10, 0.125% S/0.5% E; Days 11–15, 0.05%S/5% E; Days 16–20, 0.01%S/8% E; thereafter 10%E.

After the induction period rats were given access to 10% ethanol solution for between 4 and 6 weeks to stabilize their ethanol intake. After drinking was stabilized (by weeks 5–7), i.e. no systematic change in ethanol intake over a course of several days immediately prior to surgery from the preceding weeks of testing, rats then under went electrode implantation surgery. Animals were given one week to recovery from the surgical procedure. After recovery rats were given access during experimental sessions to 10% ethanol solutions. Prior to testing stimulation wire leads were connected to the implanted electrodes to allow animals to acclimate to these wires over a period of several days.

On test days subjects received deep brain stimulation for 5 min prior to being given access to ethanol solutions and for the full 30 min of the access period. Animals received a minimum of 4 levels of stimulation at levels 0, 50, 75, 100, and 150 μA's. Rats in the core targeted group also received stimulation at the 87 μA level. The 0 μA stimulation level was repeated at least every other day. In most cases, stimulation at other intensities was repeated once.

### 2.5. Brain histology

At the end of the experiment animals were injected with pentobarbital 100 mg/kg IP. Normal saline was then administered intracardially. This was followed by intracardial perfusion with 10% formalin. The brain was then removed and coronal sections were prepared from regions located from just anterior to the nucleus accumbens to regions just posterior to this structure. Brain sections were stained with cresyl violet prior to examination under a light microscope. Electrode placements were determined using the atlas of Paxinos and Watson (2005).

### 2.6. Statistical analysis

The mean for all of the days in which no current was delivered following recovery from surgery was used as a baseline value for each animal. Means for each current level above 0 μA were used as the value for that level. The values for the grams of ethanol/kg consumed by animals were used in the primary analysis in this experiment. The total volume of 10% ethanol/water solution and water consumed during test sessions were also analyzed. Data were analyzed using a

one-way repeated measures analysis of variance with current level as a factor. Post-hoc testing using Dunnett's test was conducted for significant current effects with mean baseline values acting as the control value.

## 3. Results

Electrode placement sites for animals analyzed for the accumbens core and shell groups are shown in Fig. 1. Five of the animals in the core-targeted group were confirmed to have electrode tips placed into the core of the nucleus accumbens with one animal having only one placement in the core. Four animals were found to have electrode placements in the shell of the accumbens with placements located in the medial portion of this subregion. This includes one animal that was originally in the core-targeted group that was found to have only an electrode placement in the shell. Three rats did not have any electrode placements in either the core or shell subregions, and consequently, results for these three animals were not used in the analysis of data for the present study. One of these rats was found to have a placement at bregma level −0.36 mm in the anterior portion of the medial division of the bed nucleus of the stria terminalis (BNST) and in the caudate putamen at level 0.0 mm to bregma. A second animal had two electrode placements directly into the anterior commissure at −0.12 mm to bregma. A third rat had a placement at −0.36 mm from bregma, in the posterior part of the lateral division of the BNST and second placement at 0.0 mm to bregma in the ventral part of the medial division of the BNST.

Mean (±SE) values for the 5 values for g/kg of ethanol consumed obtained during test sessions immediately prior to surgery and after recovery for all of the animals tested were 0.68 (±0.08) and 0.72 (±0.08), respectively. This indicates that surgical procedure did not alter animals' levels of ethanol intake. Within animal comparisons of these pre- and post-surgery ethanol intake measures were not found to be significant. The mean (±SE) weights of the five animals analyzed in the core group were immediately prior to start of deep brain stimulation testing 463.6 (±12.5) g and 489 (±11.6) g at the end of testing. For the shell group, the mean weight of rats was 482.2 (±29.7) g prior testing and 501.5 (±30.3) g at the completion of testing. These results indicate that intermittent delivery of DBS did not have a marked impact on animals' weights.

The mean consumption of ethanol in grams/kg as a function of DBS current intensity by animals with electrode placements in either the core or the shell of the nucleus accumbens is shown in Fig. 2. The current effect was significant for animals in the core [$F(4,16)=3.67$; $p=0.03$], and shell [$F(3,9)=5.67$; $p=0.02$] placement groups. Post-hoc testing indicated a significant difference between the 0 and 150 μA current levels for animals in the both placement groups. Results for the volume of alcoholic liquid consumed paralleled those obtained for the grams/kg of ethanol consumed (see Fig. 2) with the current effect being significant for the core [$F(4, 16)=4.45$; $p=0.01$] and shell [$F(3,9)=4.76$; $p=0.03$] placement groups. The difference in the volume of ethanol consumed by rats between 0 and 150 μA current levels was shown to be significant by post-hoc testing. In contrast to the findings for the alcoholic solution, the current effect on the mean

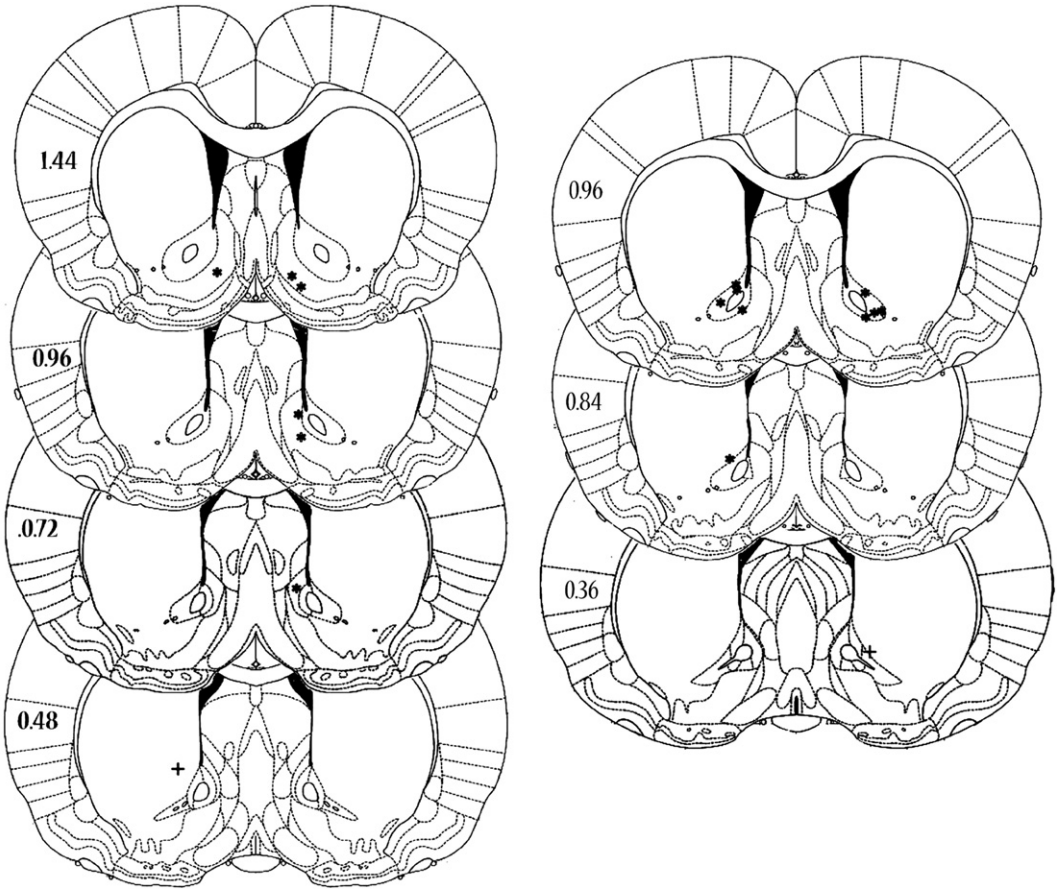


**Fig. 1.** Coronal section sections showing electrode placements for the nucleus accumbens shell [$n=4$] (left) and core [$n=5$] (right) analysis groups. * indicates on-target placement. + indicates incorrect placement. Sections shown are adapted from the atlas of Paxinos and Watson (2005).

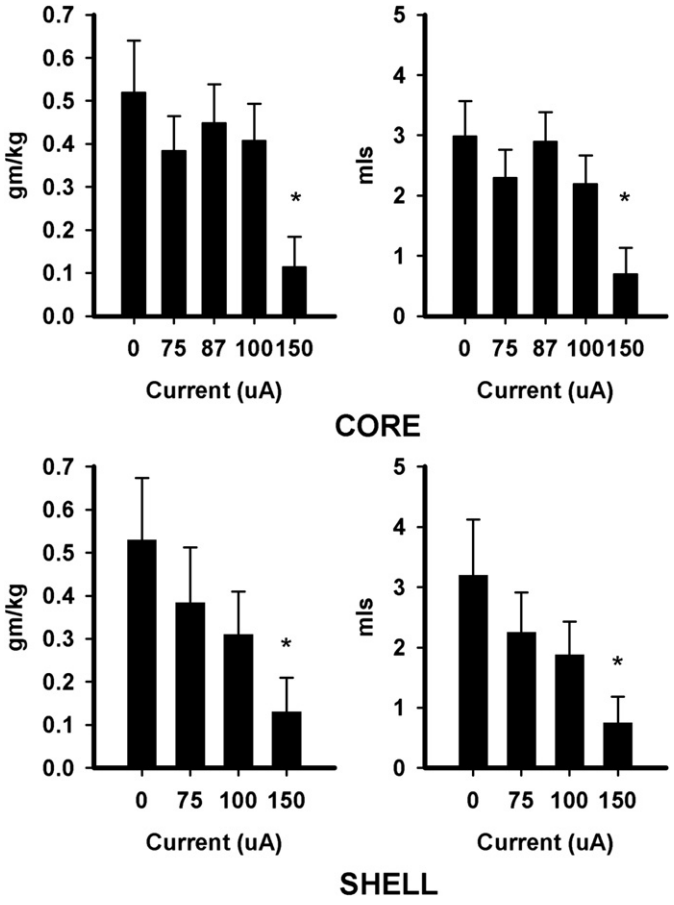


**Fig. 2.** The effects of deep-brain stimulation as a function of current intensity on the grams of ethanol/kg consumption of ethanol (left) and volume of alcoholic solution consumed (right) for DBS delivered to either the nucleus accumbens core (top) or shell (bottom). * indicates $p<0.05$ for comparison with 0 μA current intensity.

volume of water consumed by rats in either the core or shell groups was not found to be significant (Fig. 3).

The core targeted rat with an electrode placements in the anterior division of the medial BNST showed a changed in mean g/kg of ethanol consumed from a baseline value of 0.42 to 0 at the 150 μA current intensity. In contrast, for the two shell targeted animals with no confirmed accumbens placements the change from baseline to the 150 μA current intensity in g/kg consumption of ethanol was from 0.62 to 0.51 for one rat and from 0.90 to 0.87 for the other animal.

During periods of DBS delivery animals did not display behaviors such as freezing, vocalization, or jumping that would be consistent with the presence of fear, pain, or other discomfort. One core placement animal did become highly active while receiving the highest level of stimulation.

## 4. Discussion

The results of this study indicate that deep brain stimulation delivered to either the shell or core of the nucleus accumbens may produce marked reductions in the consumption of an ethanol/water solution by rats. This appears to be the first study in which the effects of DBS on the self-administration of an abused substance were examined. In the present study, water consumption during test sessions was not significantly reduced by DBS delivered to either the accumbens shell or core, although a trend towards a reduction in water intake was seen for the shell group. The volumes of water consumed during the limited access test sessions, however, were comparatively low and may not be indicative of the effects of DBS on more important measures of water consumption such as total daily water intake.

In prior work DBS delivered to the shell of the nucleus accumbens, at stimulation levels identical to those used in the present study, suppressed cocaine-induced reinstatement responding in animals with a history of cocaine self-administration (Vassoler et al., 2008). In contrast, shell DBS failed to significantly reduce reinstatement responding for sucrose pellets, indicating the selectivity of its effect on responding for cocaine. This finding suggests that DBS delivered to the nucleus accumbens does not produce non-specific disruption of behavior. Other evidence of this is provided in a report that DBS delivered to either the core or shell of the nucleus accumbens fails to significantly alter reaction times for cued lever pressing for food (Sesia et al., 2008). Low, but not high frequency shell stimulation did, however, significantly increase premature responding for food, a putative sign of increased impulsivity. High frequency core DBS appeared to have an opposite effect.

DBS delivered to the dorsal striatum using the same stimulation parameters and apparatus that were used in the present study, did not result in a significant alteration in reinstatement responding for cocaine, again suggesting the specificity of the shell DBS effect (Vassoler et al., 2008). Although a control group of animals receiving stimulation outside of the nucleus accumbens was not included in this study alcohol consumption was not greatly altered in two animals with no confirmed nucleus accumbens placements. In a third animal, however, with an electrode placement in the anterior portion of the medial division of the bed nucleus of the stria terminalis, DBS, at the maximal current delivered, did suppress all consumption of alcohol. The suppressant effects of DBS on ethanol consumption in this animal might be related to activation of bed nucleus of the stria terminalis pathways that project to the nucleus accumbens (Alheid, 2003).

The neuronal mechanism that mediates the behavioral effects of accumbens deep brain stimulation described in the present study remains to be established. High frequency stimulation of several brain structures including the hippocampus (Lian et al., 2003), subthalamic nucleus (Filali et al., 2004; Magariños-Ascone et al., 2002) have been shown to produce inhibition of local neuronal activity. Thus, deep brain stimulation may suppress ethanol consumption by inhibiting the activity of neurons within the accumbens, thereby disrupting the activity of the ventral striatopallidal and associated cortico-thalamic pathways that have been implicated in mediating the reinforcing effects of ethanol and other drugs of abuse (Pierce and Kumaresan, 2006). Deep brain stimulation, however, also has been shown to alter activity in structures distant from the site of stimulation through axonal activation (Lujan et al., 2008). In anesthetized rats deep brain stimulation delivered to the core of the nucleus accumbens reduced the firing rate of cells in the orbital frontal cortex (McCracken and Grace, 2007). This may result from the antidromic activation of axons that excite inhibitory interneurons in the orbital frontal cortex. Whether accumbens deep brain stimulation-

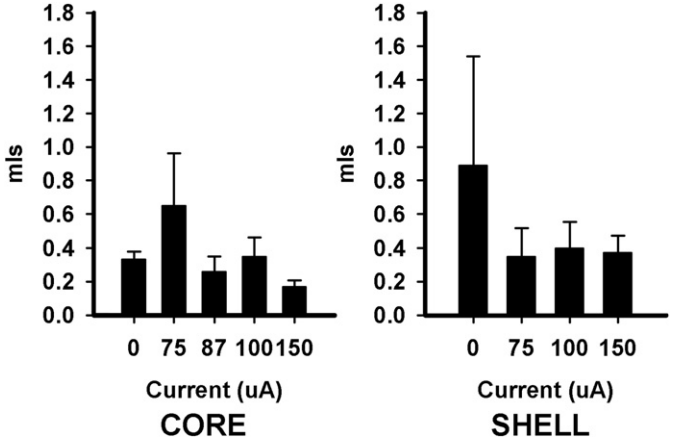


**Fig. 3.** The effects of deep-brain stimulation on the volume of water consumed during test sessions for stimulation delivered to the core (top) and shell (bottom) of the nucleus accumbens.

induced alterations in the activity in structures such as the orbital frontal cortex contribute to the suppressant effects on alcohol consumption of such stimulation remains to be investigated.

In so far as the DBS effects on ethanol consumption are the result of local inhibition of accumbens neuronal activity the results of the present study are consistent with the idea that the medial shell of the accumbens may mediate the reinforcing effects of ethanol. Additional evidence of the role of the medial shell of the accumbens in alcohol reinforcement includes the finding that infusion of the dopamine antagonist fluphenazine into this subregion blocks the induction of conditioned place preference produced by intracerebroventricular infusion of ethanol (Walker and Ettenberg, 2007). Results showing that ethanol is self-administered into the posterior portion of the ventral tegmental, a region that may project to the medial shell, is consistent with the idea that this subregion mediates ethanol reinforcing effects (Rodd et al., 2004; Ikemoto, 2007).

The medial shell may play a role in mediating the reinforcing effects of a variety of drugs of abuse other than alcohol (Ikemoto, 2007). Animals will self-administer psychomotor stimulants directly into the medial shell of the accumbens (Ikemoto, 2007). Cocaine self-administration is antagonized by the infusion of dopamine receptor antagonists into the medial shell (Bari and Pierce, 2005). These results suggest that the shell may also mediate the reinforcing actions of psychomotor stimulants. The finding that DBS delivered to the accumbens shell blocks reinstatement responding resulting the administration of a priming dose of cocaine, then, may reflect suppression of reinforcing stimuli produced by the priming dose.

The results of the present study fail to demonstrate separate effects of core versus shell DBS on alcohol consumption. This may indicate that each of these subregions plays crucial roles in processes that mediate ethanol consumption, although there is little direct evidence that the core of the nucleus is involved in the production of the reinforcing effects of ethanol per se. There is, however, evidence from both electrophysiological and brain metabolism studies that activity in both the core and the shell of the nucleus accumbens is increased when animals are drinking alcoholic solutions (Porrino et al., 1998a,b; Robinson and Carelli, 2008).

Several models of patterns of current distribution from DBS electrode indicate that activated regions may be at least a millimeter in diameter (Butson and McIntyre, 2005; Gimsa et al., 2006; Hemm et al., 2005; Kuncel et al., 2008). This would mean that it would be difficult to separate the shell versus core effects of different electrode placements in a structure as small as the rat nucleus accumbens. It should be noted, however, that none of these models is designed to reflect the activity of the configuration of the bipolar electrodes of the sort used in the present study. The sharp electrode tips that are separated by a small gap such as were used in the present experiment would be expected to produce a high intensity current in a very discrete area (Chang et al., 2008).

The results of the present study are consistent with the idea that DBS delivered to either the core or shell of the nucleus accumbens suppresses the consumption of alcohol. DBS administered to the accumbens might be of value as a tool for studying the neuronal regulation of alcohol consumption and possibly as a therapeutic intervention for severe treatment resistant alcoholism. Future studies, however, of accumbens DBS administered for prolonged periods of time to animals with high levels of ethanol intake are needed to further determine the viability of DBS as a mode of treatment for alcohol use disorders. The limited available evidence does indicate that stimulation delivered to the nucleus accumbens in treatment of depression (Schlaepfer et al., 2008) and obsessive compulsive or anxiety disorders (Sturm et al., 2003) is well tolerated by human subjects, suggesting that DBS may eventually provide a unique treatment for alcoholism.

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