

Opposing effects of 5,7-DHT lesions to the core and shell of the nucleus accumbens on the processing of irrelevant stimuli

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Abstract

There is good evidence that forebrain serotonergic systems modulate cognitive flexibility. Latent inhibition (LI) is a cross-species phenomenon which manifests as poor conditioning to a stimulus that has previously been experienced without consequence and is widely considered an index of the ability to ignore irrelevant stimuli. While much research has focused on dopaminergic mechanisms underlying LI, there is also considerable evidence of serotonergic modulation. However, the neuroanatomical locus of these effects remains poorly understood. Previous work has identified the nucleus accumbens (NAc) as a key component of the neural circuit underpinning LI and furthermore, this work has shown that the core and shell subregions of the NAc contribute differentially to the expression of LI. To examine the role of the serotonergic input to NAc in LI, we tested animals with 5,7-dihydroxytryptamine (5,7-DHT) lesions to the core and shell subregions on LI assessed under experimental conditions that produce LI in shams and subsequently with weak stimulus pre-exposure designed to prevent the emergence of LI in shams. We found that serotonergic deafferentation of the core disrupted LI whereas 5,7-DHT lesions to the shell produced the opposite effect and potentiated LI.

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Introduction

Prior exposure to a stimulus without consequence retards the acquisition of a conditioned response to that stimulus when it is subsequently paired with a biologically significant event (Lubow & Moore, 1959). This latent inhibition (LI) effect is reliably disrupted by the indirect catecholamine agonist amphetamine in both humans and rodents and is absent in acute schizophrenia patients (Baruch *et al.* 1988; Gray *et al.* 1992; Kumari *et al.* 1999; Solomon *et al.* 1981; Weiner *et al.* 1984). Disrupted LI is reversed by both typical and atypical antipsychotics that also potentiate LI (Shadach *et al.* 2000; Weiner & Feldon, 1987; Williams *et al.* 1997). As a loss of selectivity in attentional processes is considered a hallmark of schizophrenia, the neural substrates of LI have aroused considerable

interest in recent years (Gray *et al.* 1991, 1997, 1999; Weiner, 1990, 2003). Much of this work has focused on the role of forebrain dopaminergic systems and related corticolimbic structures. These studies have shown that the nucleus accumbens (NAc) and its dopamine (DA) innervation as well as major sources of input to the NAc including entorhinal cortex, medial prefrontal cortex (mPFC), hippocampus and basolateral amygdala all play a key role in the regulation of LI (Coutureau *et al.* 1999; Gal *et al.* 2005; George *et al.* 2010; Honey & Good, 1993; Nelson *et al.* 2010, 2011a, b; Schiller & Weiner, 2004; Tai *et al.* 1995).

There is also compelling evidence of serotonergic modulation of LI. Central serotonin (5-HT) depletion induced by electrolytic lesions as well as 5,7-dihydroxytryptamine (5,7-DHT) lesions to the medial raphe nucleus attenuate LI (Asin *et al.* 1980; Lorden *et al.* 1983; Solomon *et al.* 1980). Similarly, pharmacological manipulations designed to reduce 5-HT transmission or block its actions post-synaptically have generally been shown to disrupt LI (Cassaday *et al.*

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1993a; Shadach *et al.* 2000; Solomon *et al.* 1978) whereas increases in 5-HT release can potentiate LI (Loskutova, 1998). However, little work has addressed the neuroanatomical locus of these effects. One study has shown that destruction of 5-HT hippocampal innervation by 5,7-DHT lesions to the fornix-fimbria attenuates LI (Cassaday *et al.* 1993b). More recently, there has been some evidence that 5,7-DHT lesions to the NAc can similarly disrupt LI (Loskutova, 2001). However, it is clear from studies that have employed electrolytic and excitotoxic lesions that the core and shell subregions of the NAc are differentially involved in LI: LI is abolished by shell lesions but spared or potentiated by core lesions (Gal *et al.* 2005; Tai *et al.* 1995; Weiner *et al.* 1996).

Thus to dissociate the potential role of 5-HT within different neuroanatomical subdivisions of the NAc, we tested the effects of 5,7-DHT lesions to serotonergic terminals within the core and medial shell NAc on LI measured in a conditioned emotional response procedure. As the effects of neural manipulations on LI may only emerge with the use of appropriate experimental parameters that can reveal lesion-induced abolition or potentiation of LI (Nelson *et al.* 2010; Weiner & Arad, 2009), we tested the effects of the 5,7-DHT lesions under conditions that produce robust LI in controls (30 stimulus pre-exposures in expt 1) as well as with parameters designed to prevent the emergence of LI in normal rats (10 stimulus pre-exposures in expt 2).

Methods

Animals

The subjects were 68 adult male Wistar rats (Charles River, UK) that were caged in pairs on a 12-h light/dark cycle (lights on 07:00 hours) with food and water available *ad libitum*. Rats were handled for approximately 10 min per day for 1 wk and then at mean weight 242 g (range 213–263 g) underwent surgery. Twenty-three rats were randomly allocated to the core group and 24 to the shell group and a total of 21 rats were allocated to the sham condition (11 rats were sham-operated at the core coordinates and 10 rats were sham-operated at the shell coordinates).

All procedures were carried out in accordance with the United Kingdom (UK) Animals Scientific Procedures Act 1986, Project License no.: PPL 40/3163. The UK Act ensures full compliance with the 'Principles of laboratory animal care' (NIH publication No. 86-23, revised 1985).

Stereotaxic infusion of 5,7-dihydroxytryptamine

In order to protect dopaminergic terminals, animals received injections of the DA reuptake inhibitor GBR12909 (15 mg/kg). The NA reuptake inhibitor desipramine (25 mg/kg) was also administered to protect noradrenergic terminals. Both desipramine and GBR12909 were administered by subcutaneous injection approximately 30 min prior to the stereotaxic infusion of 5,7-DHT. Anaesthesia was induced by isoflurane (4%) in a N₂O/O₂ (1:2, v/v) mixture and maintained thereafter with isoflurane (1–2%). Stereotaxic surgery was conducted with the incisor bar set at –3.3 mm below the intra-aural line. The bone above the NAc was removed and the dura was cut to expose the cortex. Rats received bilateral infusions of 5,7-DHT or vehicle into either core or medial shell at the following stereotaxic coordinates – core: AP +1.6 mm, ML ±1.8 mm, DV –6.8 mm; medial shell: AP +1.3 mm, ML ±0.8 mm, DV –6.4 and 7.0 mm; one infusion at each DV coordinate (Paxinos & Watson, 2005). DV coordinates were taken from dura. Infusions were made via a 31-gauge stainless-steel injector attached by polythene tubing to a 1 µl Hamilton syringe. 5,7-DHT creatinine sulfate (15 mg/ml as salt dissolved in vehicle; Sigma, UK) or vehicle (0.9% saline/ascorbic acid, 0.2% w/v) was infused manually over 2 min in a volume of 0.5 µl (core) or as two infusions of 0.25 µl (medial shell). The injectors were left *in situ* for 5 min to allow absorption of the bolus and to minimize spread of the toxin. Control animals were injected with the saline vehicle at shell or core coordinates and otherwise treated identically. Rimadyl (0.03 ml s.c.) provided post-operative analgesia. Animals were allowed a minimum of 7 d recovery before the commencement of behavioural testing.

Quantification of 5,7-DHT lesion by high-pressure liquid chromatography with electrochemical detection (HPLC-ECD)

Following the completion of behavioural testing, the rats were humanely killed by dislocation of the neck and decapitated. The brains were removed rapidly and dissected on a cold tray. Using ice-chilled razor blades, three 2-mm coronal brain sections were cut. The posterior side of the slices corresponded to approximately +3, +1 and –3 from bregma according to the atlas of Paxinos & Watson (2005). The brain samples were then immediately frozen on dry ice and stored at –80 °C. Subsequently, the three 2-mm coronal sections were placed posterior side up onto an ice-chilled plate. From the first section (+3 mm bregma)

a 0.84-mm-diameter stainless-steel micropunch was used to remove the infralimbic (IL) cortex and the prelimbic (PL) cortex from the same brain slice. From the second section (+1 bregma), the 0.84-mm-diameter stainless-steel micropunch was also used to remove samples of tissue from core NAc and medial shell NAc and a 1.6-mm-diameter stainless-steel micropunch was used to remove sample tissue from the caudate putamen (CPu). From the third section (−3 mm bregma) a 1.6-mm-diameter stainless-steel micropunch was used to remove the amygdala. In each case, one punch was used per brain hemisphere, except in IL and PL cortices where hemisphere punches were combined. Tissue punch samples were stored in 1.5 ml Eppendorf tubes and frozen at −80 °C.

Neurotransmitter levels in the samples were determined by HPLC-ECD. The tissue samples were homogenized in 0.1 M PCA solution by sonication and centrifuged at 17400 g for 20 min at 4 °C. The supernatant was injected onto the HPLC system. The mobile phase consisted of 50 mM citric acid, 0.1 mM EDTA, 8 mM KCl, 50 mM phosphoric acid, 30 mg/l octanesulfonic acid, and 6% methanol, pH adjusted to 4.15 by the addition of sodium hydroxide. The mobile phase was pumped at a flow rate of 0.2 ml/min by an Alexys LC100 pump connected via an Alexys AS100 autosampler to an Antec Leyden reverse-phase analytical column (ALF-215 150 × 2.1 mm i.d.) maintained at 35 °C. Neurotransmitter levels were detected using a glassy carbon flow cell (VT-03 Antec) with an ISAAC Ag/AgCl reference electrode. An external standard consisting of DA and 5-HT and their metabolites in concentrations of 10^{-7} , 0.5×10^{-7} and 10^{-8} M was injected at a volume of 4 μ l for calibration. Samples were injected onto the column at 4 μ l volumes, except for PL and IL samples which were injected at 8 μ l due to the higher detection thresholds in the mPFC. Results were analysed using Alexys software data system. Bradford assay was used to adjust for protein content using the pellet remaining after sample centrifugation.

Latent inhibition

Apparatus

Six identical fully automated conditioning chambers, housed within sound-attenuating cases containing ventilation fans (Cambridge Cognition, Cambridge, UK) were used. Each of the inner conditioning chambers consisted of a plain steel box (25 × 25 × 22 cm high) with a Plexiglas door (27 × 21 cm) at the front. The floor was a shock grid with steel bars 1 cm apart and 1 cm above the lip of a 7-cm-deep sawdust tray.

A waterspout was mounted on one wall. The spout was 5 cm above the floor and connected to a lickometer supplied by a pump. Licks were registered as a break in the photo beam within the spout, which also triggered water delivery of 0.05 ml per lick. The waterspout was illuminated when water was available. A loudspeaker for the presentation of auditory stimuli was set in the roof. A 5-s flashing light, provided by the three wall-mounted stimulus lights and the house-light flashing both on (0.5 s) and off (0.5 s) served as the conditioned stimulus (CS) in expt 1. In expt 2, to avoid generalization across experiments, the CS was a 5-s mixed-frequency noise set at 85 dB (including background). Footshock of 1 s duration and 1 mA intensity provided the unconditioned stimulus (UCS) in both experiments. This was delivered through the grid floor by a constant current shock generator (pulsed voltage: output square wave 10 ms on, 80 ms off, 370 V peak under no load conditions; MISAC Systems, UK). Stimulus control and data collection were by an Acorn Archimedes RISC computer programmed in Basic with additional interfacing using an Arachnid extension (Cambridge Cognition).

Procedure

Expt 1: LI assessed with 30 CS pre-exposures (light CS)

Water deprivation was introduced 1 d prior to shaping. Thereafter, the animals received 1 h and 15 min of *ad libitum* access to water in their home cage in addition to water in the experimental chambers. The stages of the conditioned emotional response (CER) procedure used in expt 1 were as follows:

Pre-training. Rats were shaped for 1 d until all drank from the waterspout and individually assigned to a conditioning box for the duration of the experiment. There then followed 5 d of pre-training, in which rats drank in the experimental chamber for 15 min each day (timed from first lick). The drinking spout was illuminated throughout, but no other stimuli were presented in this phase. Latency to first lick was measured as an indicator of habituation to the experimental context. Total number of licks was also recorded each day to assess any pre-existing differences in drinking (prior to conditioning).

Pre-exposure with 30 CS presentations. Animals were placed in the chambers where the pre-exposed (PE) animals received thirty 5-s light CS presentations with an average inter-stimulus interval of 60 s. The non-pre-exposed (NPE) control animals were confined to the chambers for an identical period of time (30 min)

without receiving the light CS presentations. Water was not available within the chamber and the waterspout was not illuminated during the pre-exposure session.

Conditioning. Conditioning was conducted on the day following pre-exposure. No water was available within the chamber and the waterspout was not illuminated. There were two conditioning trials in which the UCS footshock was delivered following termination of the light CS. The first pairing of CS and UCS was presented after 5 min had elapsed, and the second pairing was 5 min after the first, followed by a further 5 min left in the apparatus. In the absence of drinking, there were no behavioural measures to record.

Reshaping. On the day following conditioning, animals were reshaped following the same procedure as in pre-training sessions. This was in order to re-establish drinking after conditioning. Reshaping also provided measures of conditioning to the box context (latency to first lick).

Light test. On the day following reshape, the animals were placed in the conditioning chambers and conditioned suppression to the light was determined. Water was available throughout the test and the waterspout was illuminated. Once the animals had made 50 licks, the light CS was presented for 15 min. The latency to make 50 licks in the absence of the CS (the A period) provided a measure of any individual variation in baseline lick responding. This was compared with the time taken to complete 50 licks following CS onset (B period) in a suppression ratio $[A/(A+B)]$ to assess the level of conditioning to the CS, adjusted for any individual variation in drinking rate.

Expt 2: LI assessed with 10 CS pre-exposures (noise CS)

Following the completion of expt 1, the animals were given one session of baseline training conducted in exactly same manner as above. They then underwent the same procedure as above except that the CS was now a noise CS and the PE animals only received 10 CS presentations. Briefly, the stages of expt 2 were as follows:

Pre-exposure 10 CS presentations. This was conducted in exactly the same manner as expt 1 except that the PE animals received 10 CS presentations of the noise CS. NPE controls remained in the box for 10 min without any CS presentations.

Conditioning. This was as described above except the CS was the 5-s noise CS.

Reshape. This was as described for expt 1.

Noise test. This was conducted in the same way as the light test in expt 1 except that CS was the 5-s mixed-frequency noise. As lesion-induced changes in the level of LI after weak pre-exposure (i.e. enhanced LI) are not always apparent after a single test of conditioning to the CS, the animals underwent a second test to the noise CS in expt 2 (Joseph *et al.* 2000; Nelson *et al.* 2011b).

Design and analysis. In each experiment, there were six experimental groups run in a 3×2 independent factorial design with lesion placement (at levels sham, core or shell) and pre-exposure (levels of NPE and PE) as between-subject factors. Statistical analysis was performed using analysis of variance (ANOVA) with alpha set at $p < 0.05$ for the rejection of the null hypothesis. Significant interactions were explored with simple main effects using the pooled error term. In expt 2, the animals underwent two tests of conditioning to the noise CS (Joseph *et al.* 2000). Thus the test data from expt 2 were subject to an additional within-subjects factor with two levels (test 1 and test 2). *t* tests were used to explore differences between groups in neurotransmitter levels.

Results

Neurochemical assay

Initial analysis revealed that three animals showed no evidence of 5-HT depletion and a further 10 animals had only unilateral depletions. These animals were therefore excluded from all subsequent neurochemical and behavioural analyses. After these exclusions, there were 15 shell-lesioned animals (8 NPE, 7 PE) with a mean 5-HT depletion of 65.5% (range 95.2% to 30.2% loss) in the target structure and 19 core-lesioned animals (11 NPE, 8 PE) with a mean 5-HT depletion of 76.0% (range 95.7 to 48.7% loss) in the target structure. There were 21 shams (11 NPE, 10 PE).

The levels (pmol/ μ g protein) of 5-HT and DA as well as their metabolites 5-HIAA and DOPAC in the six brain regions from which samples were taken are presented as absolute levels (Table 1) and as the percentage depletion relative to sham

Table 1. Mean absolute levels (\pm S.E.M.) of 5-HT and DA and their metabolites 5-HIAA and DOPAC after 5,7-DHT lesions to either the core or shell NAc in the six brain regions assayed. Values are expressed as pmol/ μ g protein

	Vehicle	5,7-DHT core	5,7-DHT shell
5-HT			
Core	0.556 \pm 0.042	0.139 \pm 0.024*†	0.609 \pm 0.120
Shell	0.921 \pm 0.086	0.632 \pm 0.095*†	0.327 \pm 0.049*†
Caudate putamen	0.299 \pm 0.017	0.258 \pm 0.018	0.301 \pm 0.028
Amygdala	0.745 \pm 0.039	0.808 \pm 0.073	0.801 \pm 0.043
Prelimbic cortex	0.351 \pm 0.033	0.164 \pm 0.028*	0.117 \pm 0.170*
Infralimbic cortex	0.390 \pm 0.034	0.163 \pm 0.032*	0.112 \pm 0.031*
5-HIAA			
Core	0.756 \pm 0.067	0.469 \pm 0.078*†	0.995 \pm 0.169†
Shell	0.878 \pm 0.089	0.707 \pm 0.073	0.596 \pm 0.067*
Caudate putamen	0.512 \pm 0.032	0.463 \pm 0.027	0.530 \pm 0.049
Amygdala	0.673 \pm 0.043	0.703 \pm 0.037	0.793 \pm 0.031*†
Prelimbic cortex	0.487 \pm 0.051	0.265 \pm 0.037*	0.189 \pm 0.022*
Infralimbic cortex	0.467 \pm 0.069	0.243 \pm 0.041	0.181 \pm 0.034
DA			
Core	10.545 \pm 1.03	10.026 \pm 1.12	15.15 \pm 1.810*†
Shell	11.521 \pm 1.63	8.650 \pm 0.861	9.742 \pm 1.960
Caudate putamen	8.990 \pm 0.697	10.20 \pm 0.887	9.343 \pm 0.608
Amygdala	1.604 \pm 0.190	1.682 \pm 0.288	1.446 \pm 0.242
Prelimbic cortex	0.202 \pm 0.026	0.162 \pm 0.013	0.181 \pm 0.020
Infralimbic cortex	0.122 \pm 0.012	0.097 \pm 0.011	0.104 \pm 0.009
DOPAC			
Core	3.628 \pm 0.373	4.475 \pm 0.533	5.748 \pm 0.683*†
Shell	4.635 \pm 0.747	4.505 \pm 0.554	5.682 \pm 1.308
Caudate putamen	2.583 \pm 0.249	3.739 \pm 0.434*	3.599 \pm 0.421
Amygdala	0.360 \pm 0.051	0.366 \pm 0.050	0.313 \pm 0.036
Prelimbic cortex	0.062 \pm 0.006	0.080 \pm 0.010	0.079 \pm 0.007
Infralimbic cortex	0.059 \pm 0.007	0.065 \pm 0.011	0.067 \pm 0.012

*Significant difference from sham,

† significant difference from other lesion group, $p < 0.05$, t test.

levels (Table 2). As is clear from the tables, the shell lesion was anatomically selective in that it depleted 5-HT in the shell without any significant changes in the adjacent core. Injection of 5,7-DHT into the core produced an overall larger depletion in the target structure but also led to some 5-HT loss in the shell sample (-33.4%). Both lesions also resulted in significant changes in 5-HT levels in both subregions of the mPFC sample. However, there was no evidence of 5-HT loss in the CPu sample which was dorsal to the injection sites. Although the shell lesion did lead to significant increases in DA levels measured in the core sample ($+54.6\%$), the 5,7-DHT lesions were otherwise neurochemically selective to 5-HT, producing a maximal loss of 25.4% in DA in the other brain regions

sampled, indicating that GBR12909 had protected DA terminals.

Behavioural

Expt 1: LI assessed with 30 CS pre-exposures

Pre-conditioning. By day 5, there were no differences between the lesion groups and the animals to be conditioned in terms of the latency to first lick or total amount drunk (max $F_{2,49} = 1.47$, n.s.).

Reshape. There were no effects of lesion or pre-exposure on the latency to first lick in the reshape session following conditioning (max $F_{2,49} = 1.51$, n.s.). Similarly, there were no differences in the total number of licks made during the reshape session (max $F_{2,49} = 1.82$, n.s.).

Table 2. Mean percentage (\pm S.E.M.) depletions of 5-HT and DA and their metabolites 5-HIAA and DOPAC after 5,7-DHT lesions to either the core or shell NAc in the six brain regions assayed. Percentages are expressed relative to vehicle-infused animals

	5,7-DHT core		5,7-DHT shell	
5-HT				
Core	-76.0%*†	± 4.2	+13.5%	± 22.1
Shell	-33.4%*†	± 10.1	-65.5%*†	± 5.3
Caudate putamen	-9.7%	± 6.1	-3.2%	± 8.9
Amygdala	+7.7%	± 9.7	$\pm 8.2\%$	± 5.9
Prelimbic cortex	-54.5%*	± 7.9	-65.9%*	± 4.9
Infralimbic cortex	-53.0%*	± 9.3	-73.0%*	± 7.8
5-HIAA				
Core	-42.4%*†	± 9.5	+40.3%†	± 23.6
Shell	-21.4%	± 8.1	-30.8%*	± 7.7
Caudate putamen	-8.1%	± 5.3	+2.3%	± 9.5
Amygdala	-5.4%	± 5.0	+30.2%*†	± 5.8
Prelimbic cortex	-48.2%*	± 7.1	-59.7%*	± 4.4
Infralimbic cortex	-42.7%	± 9.6	-63.5%	± 7.1
DA				
Core	-12.2%	± 9.8	+54.6%*†	± 15.5
Shell	-25.4%	± 7.4	-15.0%	± 17.1
Caudate putamen	+8.3%	± 9.4	+8.4%	± 7.1
Amygdala	-14.4%	± 14.6	+13.7%	± 19.7
Prelimbic cortex	-23.2%	± 6.1	-6.4%	± 10.6
Infralimbic cortex	-10.9%	± 10.0	-22.4%	± 6.8
DOPAC				
Core	+18.2%	± 13.8	+68.0%*†	± 19.9
Shell	-1.1%	± 12.2	-15.0%	± 17.1
Caudate putamen	+50.1%*	± 17.4	+35.0	± 15.6
Amygdala	-17.3%	± 11.2	+9.5%	± 13.2
Prelimbic cortex	+21.9%	± 15.5	+34.5%	± 12.8
Infralimbic cortex	+26.2%	± 20.8	+0.9%	± 17.4

* Significant difference from sham,

† significant difference from other lesion group, $p < 0.05$, t test.

Light test. The A period (time to make licks 2–50 in the absence of the light CS) did not differ between any of the groups (max $F_{1,49} = 1.35$, n.s.). The mean suppression ratios to the light are presented in Fig. 1. As expected with 30 CS pre-exposures, there was a robust LI effect in the sham-lesioned animals, but the effect of pre-exposure clearly differed by lesion group. This description of the data was confirmed by ANOVA which yielded no effect of lesion ($F < 1$), an effect of pre-exposure ($F_{1,49} = 15.02$, $p = 0.0003$) but also an interaction ($F_{2,49} = 3.25$, $p = 0.047$). Simple effects analysis of this interaction confirmed an effect of pre-exposure in the sham ($F_{1,49} = 11.21$, $p = 0.0016$) and shell-lesioned ($F_{1,49} = 9.92$, $p = 0.0028$) animals, but in

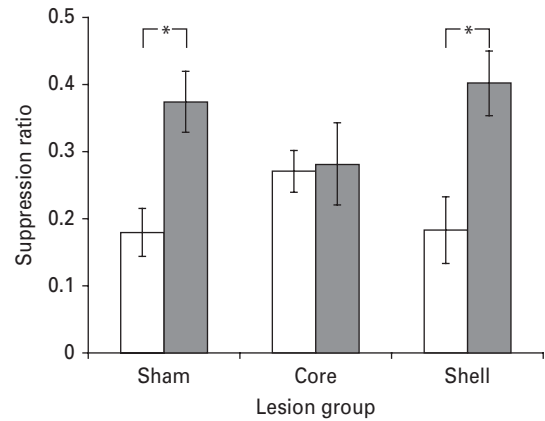


Fig. 1. The effect of 5,7-DHT lesions to the core and shell of the nucleus accumbens on latent inhibition produced with 30 conditioned-stimulus (CS) pre-exposures. Bars represent suppression ratios (\pm S.E.M.) to the CS for non-pre-exposed controls (□) and pre-exposed animals (■). Significant difference between pre-exposure groups ($p < 0.05$).

the core-lesioned animals there was no difference in conditioning to the light CS between the NPE and PE animals ($F < 1$).

Expt 2: LI assessed with 10 CS pre-exposures

Pre-conditioning. None of the experimental groups differed in terms of time to first lick or total number of licks (max $F_{2,49} = 2.49$, n.s.).

Reshape. Analysis of the times (s) to complete the first lick in the reshape session following conditioning revealed no effects of pre-exposure, lesion or an interaction between these factors (max $F_{2,49} = 1.86$, n.s.). Nor were there any differences between the groups in the total number of licks made in the reshape session (max $F_{1,49} = 1.38$, n.s.).

Noise test. None of the experimental groups differed in the time to make the first lick in the absence of the tone (A period) in either test (max $F_{2,49} = 2.69$, n.s.). Analysis of the two tests revealed an effect of test ($F_{1,49} = 47.44$, $p = 0.0001$) consistent with extinction to the CS. This factor did not interact with either the pre-exposure or lesion (max $F_{1,49} = 1.55$, n.s.) and hence the data are presented in Fig. 2 collapsed across the two tests. Inspection of this figure reveals that under conditions of weak pre-exposure there was no evidence of LI in shams. Similarly, the core NPE and PE animals showed equivalent levels of conditioning to the CS. However, 5,7-DHT lesions to the shell appeared to potentiate LI as there was a clear pre-exposure effect in

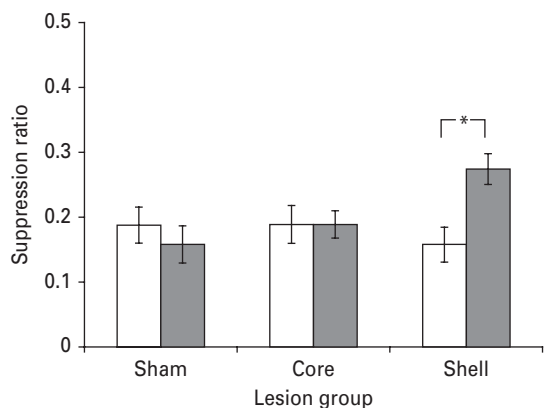


Fig. 2. The effect of 5,7-DHT lesions to the core and shell of the nucleus accumbens on latent inhibition produced with 10 conditioned-stimulus (CS) pre-exposures. Bars represent suppression ratios (\pm s.e.m.) to the CS for non-pre-exposed controls (\square) and pre-exposed animals (\blacksquare). Significant difference between pre-exposure groups ($p < 0.05$).

these animals. ANOVA revealed no effect of either lesion or pre-exposure (max $F_{1,49} = 1.61$, n.s.) but a significant interaction between these factors ($F_{2,49} = 3.56$, $p = 0.036$). Simple effects of this analysis confirmed the absence of LI in both the sham and core-lesioned animals (both $F_s < 1$) but a clear pre-exposure effect in shell-lesioned animals ($F_{1,49} = 6.89$, $p = 0.012$).

Discussion

The current experiments tested the effects of 5-HT depletion within the core and shell of NAc on LI using experimental parameters designed to produce (expt 1) and prevent (expt 2) the emergence of LI in sham-lesioned animals. Under conditions that yielded reliable LI in shams, core but not shell 5-HT depletion attenuated LI. Conversely, 5,7-DHT lesions to the shell potentiated LI.

Neuroanatomical and neurochemical selectivity of the 5,7-DHT lesions

The 5,7-DHT lesions to the medial shell were anatomically highly selective in that they produced significant 5-HT depletions within the shell (-65.5%) but only minimal changes in the adjacent core ($+13\%$). The core lesion depleted core 5-HT (-76.0%) but also resulted in some 5-HT loss in the shell sample (-33.4%). This pattern of greater anatomical selectivity of shell lesions compared to core lesions is consistent with what we and others have found with 6-hydroxydopamine (6-OHDA) lesions to the NAc

core and shell, although the selectivity of the core 5,7-DHT lesion in the present study was far greater than that previously produced by 6-OHDA (Nelson *et al.* 2011a; Sellings *et al.* 2008). There are direct connections between the core and shell NAc, with particularly strong connections from the core to the shell which may account for the greater anatomical selectivity of the shell lesion (Van Dongen *et al.* 2005). The lesions were neurochemically selective to 5-HT as neither lesion had significant effects on DA content in the target structure. This may indicate that treatment with the DA reuptake inhibitor GBR12909 successfully protected DA terminals. However, given the evidence of DA/5-HT interactions (see below), compensatory increases in DA levels following 5-HT depletion may underlie this apparent sparing of DA content. Consistent with this proposition, the shell lesion produced significant increases in both DA and DOPAC within the core sample and the core lesion also increased DOPAC levels within the CPu.

Both lesions led to reduced 5-HT levels in the mPFC. We and others have also found changes in mPFC DA levels after NAc 6-OHDA lesions (Nelson *et al.* 2011a; Parkinson *et al.* 2002). Similarly, other studies have shown comparable reductions in 5-HT levels in the mPFC following 5,7-DHT lesions to the NAc (Fletcher *et al.* 2009; Ludwig & Schwarting, 2007; Mohr *et al.* 2009). It is not clear why 5,7-DHT lesions to the NAc should produce 5-HT loss in distal regions but simple diffusion of the neurotoxin is a poor account of these effects as there were no significant changes in 5-HT content in the CPu which is dorsal to the infusion site. In principle, the 5,7-DHT toxin may have produced 5-HT depletion within the mPFC through retrograde degeneration of the raphe nuclei but the sparing of 5-HT content in the amygdala indicates that this is unlikely. Perhaps more likely, the neurotoxin may have been taken up by 5-HT transporters on axons that pass through the NAc and which in turn project to the mPFC (Fletcher *et al.* 2009; Ludwig & Schwarting, 2007; Van Bockstaele *et al.* 1993; Zhou *et al.* 1998).

5,7-DHT lesions to the core attenuate LI

The 5,7-DHT lesion to the core disrupted the expression of LI as there was no difference in conditioning to the CS between the NPE and PE animals. This finding may at first seem surprising given the considerable body of evidence demonstrating that both electrolytic and excitotoxic lesions to the core spare or potentiate LI depending on experimental parameters (Gal *et al.* 2005). However, it is becoming increasingly apparent that lesions that are neurochemically

selective can produce different or even opposing effects on LI to those produced by standard lesioning techniques. For example both electrolytic and excitotoxic lesions to the shell NAc consistently abolish LI (Gal *et al.* 2005; Tai *et al.* 1995; Weiner *et al.* 1996) but we have found that 6-OHDA lesions to the shell spare LI and under appropriate experimental parameters (weak pre-exposure) actually enhance LI (Nelson *et al.* 2011a,b). Similarly, we have also shown that amphetamine exerts its disruptive effects on LI via actions in the core rather than shell NAc (Nelson *et al.* 2011a). According to the switching hypothesis of LI (Weiner, 1990, 2003), the core mediates responding to CS-reinforcement contingencies at conditioning and the shell inhibits this core-based switching mechanism. Within this framework, the current data suggest that reducing 5-HT function within the core serves to activate the switching mechanism so that the animal responds according to the CS-reinforcement association acquired at conditioning leading to disrupted LI. This in turn suggests that within the core NAc, 5-HT depletion produces a similar behavioural outcome as that found after activation of DA.

There is a venerable history of research indicating that 5-HT can modulate dopaminergic function in an opposing manner (Lucki & Harvey, 1979). This work broadly shows that increases in 5-HT can inhibit DA-dependent behaviours while reducing 5-HT function exerts the opposite effect and enhances DA-dependent behaviours (Fletcher, 1991, 1995; Fletcher *et al.* 1993, 1999; Wogar *et al.* 1991). Based on this evidence, reducing the actions of 5-HT could be expected to produce the same behavioural outcome (disrupted LI) as has been found with increasing DA release in the NAc core (Joseph *et al.* 2000; Nelson *et al.* 2011a). Interestingly, it appears that effects of 5-HT depletion on mesolimbic DA function and DA dependent-behaviours are only seen when impulse-dependent activation of DA neurons is required, that is calcium-dependent phasic DA release in response to behaviourally relevant stimuli (Fletcher *et al.* 1999; Grace, 1991; Lyness & Moore, 1981). Similarly, impulse-dependent DA release is required to disrupt LI (Young *et al.* 2005). For example, LI is not disrupted by direct DA agonists such as apomorphine, while amphetamine given systemically or directly into NAc core only abolishes LI when there has been a previous sensitizing injection which promotes calcium-dependent DA release (Feldon *et al.* 1991; Joseph *et al.* 2000; Nelson *et al.* 2011a; Warburton *et al.* 1996). Thus the current findings of reduced LI after 5,7-DHT lesions to NAc core are consistent with the effects of 5-HT/DA opponent interactions and the

impulse-dependent release associated with this interaction.

5,7-DHT lesions to the shell potentiate LI

The behavioural results of the shell 5,7-DHT lesions were markedly different to those produced by the core lesions as LI was enhanced rather than attenuated by these lesions. Previously, reduced DA function induced by either 6-OHDA lesions or microinfusions of the D₂ antagonist haloperidol has similarly been shown to produce LI under conditions of weak pre-exposure that do not yield LI in shams. We have recently reported that the locus of these effects within the NAc is the medial shell (Nelson *et al.* 2011b). Thus in the case of NAc shell, both 5-HT and DA depletion appear to produce the same functional outcome.

Given the well-established evidence for 5-HT/DA opponent interactions (see above) it may seem surprising that 5-HT depletion can produce the same behavioural effect as DA depletion. However, the nature of this interaction may be influenced by several factors. First, the stimulatory effect of 5-HT on DA may depend on different 5-HT receptor subtypes. In view of the bewildering complexity of the multifarious pre- and post-synaptic sites at which 5-HT acts, it is perhaps not surprising that DA/5-HT interactions cannot simply be defined as opponent (for a review see Alex & Pehek, 2007). For example within the NAc, 5-HT-induced increases in DA activity appear to be modulated by 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and 5-HT₃ receptor subtypes (Jiang *et al.* 1990; Parsons & Justice, 1993; Yan & Yan, 2001; Yoshimoto & McBride, 1992). Conversely, 5-HT_{2C} receptors inhibit both tonic and phasic DA release in NAc (Di Matteo *et al.* 2000). Hence regional differences in the distribution of the various 5-HT subtypes may influence the exact nature of 5-HT/DA interactions. For example, there appears to be a greater density of 5-HT₂ and 5-HT₄ receptors in the shell relative to the core NAc (Zahm, 1999).

Second, the forebrain is innervated by two anatomically distinct sets of 5-HT axons which may also be functionally distinct (Mamounas *et al.* 1991). Consistent with the subdivision of the NAc into core and shell, there is good evidence that the 5-HT innervation of the core and shell differ in terms of density, axon morphology and expression of the 5-HT transporter SERT (Brown & Molliver, 2000). The serotonergic axons of the shell lack SERT, are thicker and more varicose relative to those of the core (Van Bockstaele & Pickel, 1993). This distinct pattern of 5-HT innervation to the core and shell NAc 5-HT may also underlie functional differences. For example,

core and shell 5-HT axons are differentially sensitive to the neurotoxic effects of methamphetamine (Brown & Molliver, 2000). Thus regional differences in the morphology of 5-HT axons in the NAc may also contribute to the functional differences we have found after selective serotonergic deafferentation of the NAc.

It is possible that the enhancement of LI we found following 5,7-DHT lesions to the shell was not in fact mediated by changes in 5-HT within the shell but rather by secondary changes in monoamines and their metabolites that were observed in distal brain regions. These changes were most pronounced in the mPFC where there was a significant loss of 5-HT. Although lesions to the mPFC potentiate LI (George *et al.* 2010; Nelson *et al.* 2010), the current results are most unlikely to be due to these secondary changes in mPFC 5-HT content as there was substantial loss of mPFC 5-HT after both lesions and yet enhanced LI was only seen in the shell lesion group. The 5,7-DHT shell lesion also produced significant increases in DA, DOPAC and 5-HIAA in the core, as well as 5-HIAA in the amygdala. However, increased DA function within the core has been shown to disrupt rather enhance LI (Nelson *et al.* 2011a) and although lesions to the basolateral amygdala can potentiate LI (Schiller & Weiner, 2004) it is unlikely that the moderate increase in 5-HIAA observed in the current study can account for the behavioural results found at test.

Conclusions

The current findings provide evidence of a marked behavioural dissociation in the effects of 5-HT depletion within subregions of the NAc on the processing of irrelevant stimuli. These data have important implications for our understanding of the neurobiological basis of LI. First, they show that neurochemically selective lesions do not always produce the same pattern of results as obtained with standard lesioning techniques. This is consistent with what we have found with manipulations to forebrain DA systems (Nelson *et al.* 2010; 2011a, b). Indeed, the dissociation in function between the core and shell found here is diametrically opposed to that which is found with standard lesions (Gal *et al.* 2005; Tai *et al.* 1995; Weiner *et al.* 1996). Similarly, the demonstration that both 6-OHDA and 5,7-DHT lesions to the shell NAc enhance LI (Nelson *et al.* 2011a), suggests that interactions between DA and 5-DHT in LI are more complicated than has previously been assumed and cannot be accommodated by a simple opponency account. However, given the well-established role of 5-HT in the behavioural response to punishment

(Cools *et al.* 2008), it remains to be seen whether the dissociable roles of core and shell 5-HT in modulating the expression of LI would be found in an appetitively motivated task. Although there is some evidence that appetitive and aversive LI paradigms may share the same neural substrates (Norman & Cassaday, 2004), there is also evidence that the sensitivity of LI to various neural manipulations can depend on the associative learning paradigm in use (Coutureau *et al.* 2001; Pothuizen *et al.* 2006; Weiner *et al.* 1995). Thus further experiments will be required to test the generality of the current findings.

The current data complement emerging evidence of the modulation of cognitive flexibility by forebrain serotonergic systems (Brigman *et al.* 2010; Clarke *et al.* 2004; Kehagia *et al.* 2010). Cognitive flexibility can be broadly defined as the ability to modify behaviour in response to changes in situational demands and is mediated by fronto-striatal systems. Disrupted LI, produced here by 5-HT depletion in the NAc core, manifests as conditioning to stimuli that should normally be treated as irrelevant and amounts to excessive behavioural switching. Conversely, enhanced LI after deafferentation of the 5-HT input to the shell represents retarded behavioural switching and a failure to switch cognitive resources to pertinent environmental stimuli. As such the current findings may have important implications for understanding the aetiology and treatment of disorders such as schizophrenia that are marked by cognitive inflexibility.

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Statement of Interest

None.

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