Brief Communication

The Functional Divide for Primary Reinforcement of D-Amphetamine Lies between the Medial and Lateral Ventral Striatum: Is the Division of the Accumbens Core, Shell, and Olfactory Tubercle Valid?

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When projection analyses placed the nucleus accumbens and olfactory tubercle in the striatal system, functional links between these sites began to emerge. The accumbens has been implicated in the rewarding effects of psychomotor stimulants, whereas recent work suggests that the medial accumbens shell and medial olfactory tubercle mediate the rewarding effects of cocaine. Interestingly, anatomical evidence suggests that medial portions of the shell and tubercle receive afferents from common zones in a number of regions. Here, we report results suggesting that the current division of the ventral striatum into the accumbens core and shell and the olfactory tubercle does not reflect the functional organization for amphetamine reward. Rats quickly learned to self-administer D-amphetamine into the medial shell or medial tubercle, whereas they failed to learn to do so into the accumbens core, ventral shell, or lateral tubercle. Our results suggest that primary reinforcement of amphetamine is mediated via the medial portion of the ventral striatum. Thus, the medial shell and medial tubercle are more functionally related than the medial and ventral shell or the medial and lateral tubercle. The current core–shell–tubercle scheme should be reconsidered in light of recent anatomical data and these functional findings.

Key words: **reward; intracranial self-administration; psychomotor stimulants; nucleus accumbens; olfactory tubercle; reinforcing**

Introduction

Brain regions are distinguished and named to identify each region with unique functions. The concept of the ventral striatum emerged when Heimer and Wilson (1975) suggested that the olfactory tubercle is part of the striatal system and that the well established isocortico-dorsal striatopallidal system has a parallel system consisting of limbic (piriform, hippocampal, and amygdaloid) cortices projecting to the olfactory tubercle and nucleus accumbens, which, in turn, project to the ventral pallidum.

The nucleus accumbens, which receives dense dopaminergic projections, plays a key role in motivation and primary reinforcement of psychomotor stimulants (Ikemoto and Panksepp, 1999). Rats learn to self-administer D-amphetamine (Hoebel et al., 1983; Phillips et al., 1994), a dopamine releaser and uptake blocker, and other dopaminergic agents directly into the accumbens. The accumbens can be divided into the core and shell, a distinction that originates from the discovery of differential histochemical profile within the accumbens (Zaborszky et al., 1985). There is now ample evidence for functional heterogeneity between the two zones (Di Chiara, 2002; Kelley, 2004). With respect to primary drug reinforcement, it has been shown that rats learn to self-administer the dopamine uptake inhibitors nomifensine (Carlezon et al., 1995) and cocaine (Rodd-Henricks et al., 2002; Ikemoto, 2003) and mixtures of D_1 and D_2 receptor agonists (Ikemoto et al., 1997) into the shell but not the core. In addition, systemic D-amphetamine-induced conditioned place preference, a measure of reward, can be attenuated by selective lesions of dopaminergic terminals in the shell but not the core (Sellings and Clarke, 2003). However, the evidence used to support functional differences between the core and the shell is applicable only to the medial shell, because most investigators working on this issue compared the core with the medial portion, while ignoring the ventral shell. The crescent-shaped shell lies just medial and ventral to the core, and it is difficult to manipulate the entire shell with a single application of drugs or toxins.

Like the accumbens, the olfactory tubercle receives dense dopaminergic projections from the midbrain. Although it has not received much research attention, the tubercle appears to mediate primary reinforcement of cocaine (Ikemoto, 2003), a process that was widely believed to be mediated by the accumbens. Rats quickly learn to self-administer cocaine into the tubercle. Importantly, the medial tubercle is more responsible than the lateral tubercle for triggering the reinforcing effects of cocaine.

The patterns of the effects of cocaine at various striatal regions do not fit with the currently extant core–shell–tubercle scheme

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but instead support mediolateral functional divisions in the ventral striatum. Indeed, anatomical evidence supports such hypotheses and suggests that the medial shell and medial tubercle receive inputs from common zones in a number of regions, whereas there are significant differences in afferents between the medial and ventral shell and between the medial and lateral tubercle (see Discussion below for detailed information). To examine these functional divisions, we sought for additional behavioral evidence and studied different effects of D-amphetamine within the ventral striatum using intracranial self-administration procedures.

Materials and Methods

Animals. Male Wistar rats (270–350 g at the time of surgery; Harlan, Dublin, VA) were used. Food and water were available *ad libitum* except during testing. The procedures were approved by the Animal Care and Use Committee of the National Institute on Drug Abuse Intramural Research Program and were in accordance with National Institutes of Health guidelines.

Surgery. Rats were stereotaxically implanted with permanent unilateral guide cannulas (24 gauge) under sodium pentobarbital (31 mg/kg, i.p.) and chloral hydrate (142 mg/kg, i.p.) anesthesia. Each rat's guide cannula ended 1.0 mm above one of five target regions. Because efflux from central injections tends to follow a pressure gradient up the cannula shaft (Routtenberg, 1972), the cannulas for medial shell and medial tubercle sites were inserted at a 20° angle from the other hemisphere through the midline (see Fig. 1*A*) to minimize diffusion of drug solution to the core or shell, respectively. The cannulas were inserted vertically for injections in the core, ventral shell, and lateral tubercle. The incisor bar was set at 3.3 mm below the interaural line. The stereotaxic coordinates were 2.0 mm anterior to bregma (A), 2.0 mm lateral to the midline (L), and 8.2 mm ventral to the skull surface (V) (measured along the trajectory of the angled cannula) for medial tubercle placements; A2.0, L1.6, and V7.2 for medial shell placements; A2.0, L2.5, and V8.4 for lateral tubercle placements; A2.0, L2.3, and V7.7 for ventral shell placements; and A2.0, L1.9, and V6.6 for core placements.

Drugs. D-Amphetamine (Sigma, St. Louis, MO) was dissolved in an artificial CSF consisting of the following (in mM): 148 NaCl, 2.7 KCl, 1.2 $CaCl_2$, and 0.85 $MgCl_2$, pH adjusted to 6.8–7.7.

Regional amphetamine effect experiment. The first six sessions were designed to examine the acquisition of self-administration, whereas the last four sessions determined the effects of amphetamine concentrations on self-administration as a function of injection regions. To determine the effectiveness of amphetamine reinforcement in each region, 48 rats with no previous operant training were placed the operant chambers (30 × 22 × 24 cm) equipped with a lever (45 mm wide × 2 mm thick, protruding 20 mm from the wall) below a cue light. Each rat's 31 gauge injection cannula was connected by polyethylene tubing to a micropump (Ikemoto and Sharpe, 2001) hanging a few millimeters above the rat's head. A lever press extinguished the cue light for 5 s and turned on the micropump for 5 s, dispensing a 75 nl infusion; additional lever presses were not rewarded until another 5 s passed, at which time the cue light was reinstated. We chose the following concentrations of amphetamine, considering previous studies on intraaccumbens injections of amphetamine (Hoebel et al., 1983; Phillips et al., 1994; Ikemoto, 2002). Rats received 30 mM amphetamine in sessions 2 and 3, 100 mM in sessions 4 and 5, and vehicle in sessions 1 and 6 (acquisition phase), followed by 10, 30, and 100 mM over three sessions in this order (concentration–response relationship test). The maximum number of infusions available per session was limited to 60 to minimize the possibility of tissue damage. Sessions lasted 90 min or until the rats received a total of 60 infusions.

Two-lever discrimination experiment. To examine the specificity of behavioral effects of amphetamine administered into the medial tubercle, six rats with no previous operant training were placed in operant chambers identical to those described above, except that they had two retractable levers. A response on the "active" lever resulted in a 5 s infusion (75 nl in volume), extinguished a cue light above the lever, and retracted both levers for 30 s. A response on the "inactive" lever did not deliver infusions but retracted both the active and inactive levers for 30 s. The light above the inactive lever was never turned on. The left lever was designated as the active lever for three rats and as the inactive lever for the other three. Responding on the active lever produced vehicle infusions in session 1 and 100 mM amphetamine infusions in sessions 2–4. Sessions lasted 90 min or until the rats received a total of 60 infusions. Numbers of responses on each lever were recorded.

Histology. When each rat completed the experimental procedure, the rat was anesthetized with sodium pentobarbital (31 mg/kg, i.p.) and chloral hydrate (142 mg/kg, i.p.), and its brain was removed and placed in a 4% paraformaldehyde solution. Within 1 week, the brain was cut with a cryostat in coronal 40 μm sections, and the placement of the cannula was confirmed with microscopic examination. Rats with cannula placements outside of target regions were excluded from behavioral analyses.

Statistical analyses. Rates of infusions during the acquisition phase were analyzed with three-by-two within-subjects ANOVAs with concentration (vehicle, 30 mM, and 100 mM) and trial (two) as factors, performed for five regions separately, followed by Newman–Keuls *post hoc* tests. Rates of infusions for the last four sessions were analyzed with a five-by-four mixed ANOVA with two factors: region (the five regions; between-subjects factor) and concentration (0, 10, 30, and 100 mM amphetamine; within-subject factor). Significant main region effect was further analyzed with Newman–Keuls *post hoc* tests. Significant interaction effect between region and concentration was further analyzed with Dunnett's *post hoc* tests, which allowed us to focus on comparisons of concentration effects for each region separately and to avoid all possible comparisons.

For the two-lever discrimination experiment, the numbers of lever-presses were analyzed with a two-by-four within-subjects ANOVA with lever (active and inactive) and session (1–4) as factors, followed by Newman–Keuls *post hoc* tests.

Results

Locations of injection cannulas for the five regions are shown in Figure 1, *B* and *C*. Amphetamine was self-administered at significantly higher rates into the medial tubercle (**$p < 0.001$) or medial shell (*$p < 0.05$) than into the lateral tubercle, ventral shell, or core (a significant region effect; $F_{(4,43)} = 7.84$; $p < 0.0001$) (Fig. 1*D*). In addition, there was an insignificant trend that rats self-administered amphetamine into the medial tubercle at higher rates than into the medial shell. Medial tubercle rats and medial shell rats self-administered 10, 30, and 100 mM amphetamine significantly more than vehicle, whereas the rats in other groups did not self-administer amphetamine more than vehicle (after a significant region-by-concentration interaction effect; $F_{(12,129)} = 4.11$; $p < 0.0001$). Similar results were found in the analysis for the acquisition of self-administration (during sessions 1–6). Rats quickly learned to self-administer amphetamine into the medial tubercle or the medial shell (main concentration effects; $F_{(2,14)} = 8.05$, $p < 0.005$ and $F_{(2,18)} = 6.79$, $p < 0.01$, respectively) but not into the lateral tubercle, ventral shell, or core.

Because the role of the tubercle in reinforcement has not yet been established, it is important to address the alternative interpretation that amphetamine administration into the medial tubercle was not reinforcing but merely arousing. Effects of amphetamine in the tubercle were further studied with a two-lever discrimination procedure. A separate group of rats ($n = 7$) was trained to discriminate an active lever from an inactive lever for intramedial tubercle infusions of amphetamine. As shown in Figure 1*E*, rats learned to discriminate between the two levers and responded on the active lever more than the inactive lever in sessions 3 and 4 (*$p < 0.05$; after a significant lever-by-session interaction; $F_{(3,18)} = 4.49$; $p < 0.05$).

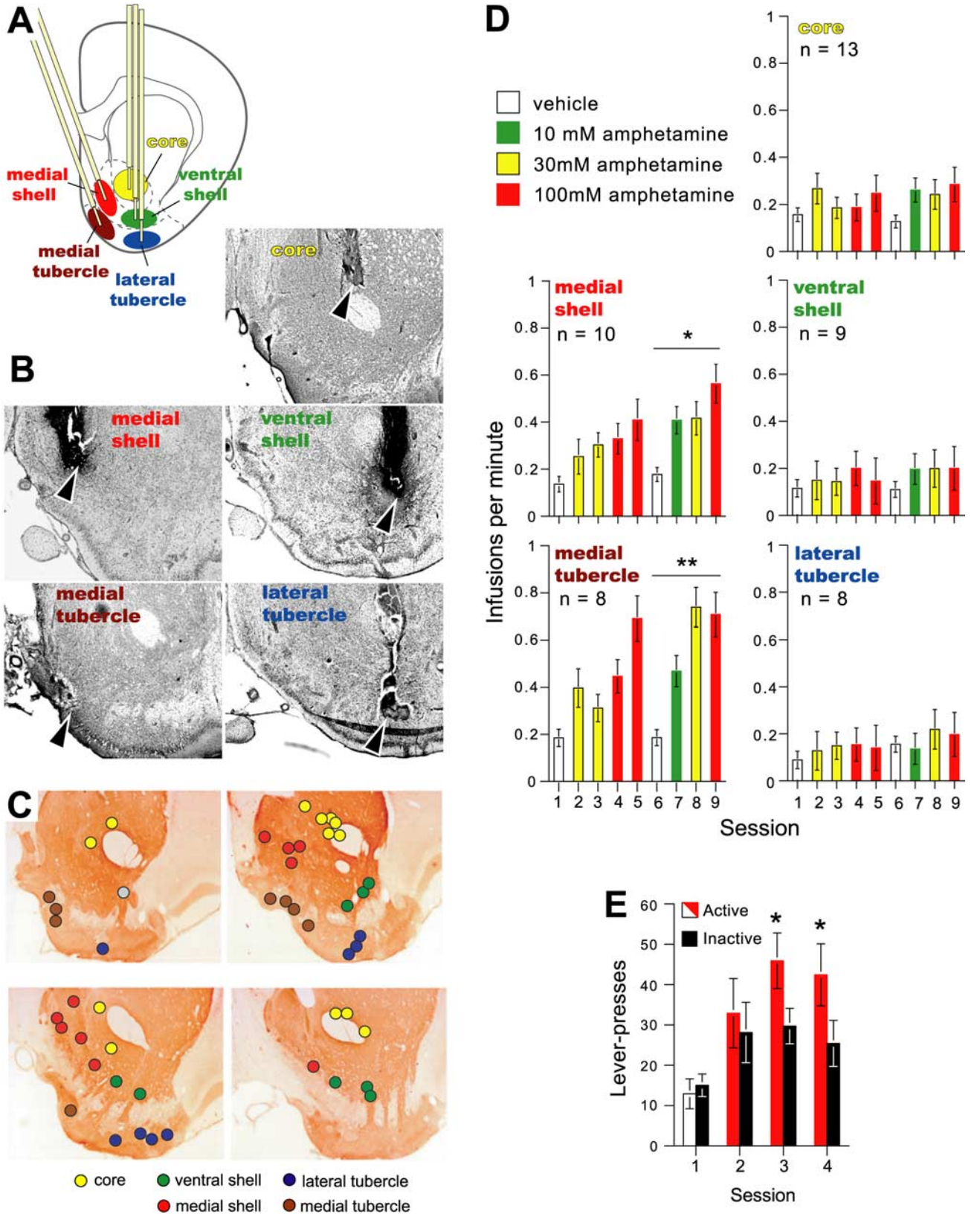

Figure 1. Intracranial self-administration of amphetamine into ventral striatal regions. ***A***, Unilateral guide cannulas aimed at the medial tubercle and medial shell were inserted at a 20° angle from the other hemisphere through the midline, to minimize diffusion of drug solution into the shell or core, respectively. ***B***, Photomicrographs show representative placements of cannulas. Arrowheads indicate the tips of injection cannulas. ***C***, The tips of injection cannulas are plotted for each region on tyrosine hydroxylase-stained sections from top left, the most anterior, to bottom right, the most posterior. ***D***, Mean ± SEM rates of self-administration per session as a function of region are shown. The color of each bar indicates the treatment that the rats received for the session. $*p < 0.05$ and $**p < 0.001$, significant differences compared with corresponding sessions for the core, ventral shell, and lateral tubercle. ***E***, Mean ± SEM lever presses per session over four consecutive sessions are shown. A response on the active lever resulted in a 75 nl infusion, whereas a response on the inactive lever did not deliver an infusion. Rats received vehicle in session 1 and 100 mM amphetamine in sessions 2–4. $*p < 0.05$, significant difference compared with respective inactive lever presses.

Discussion

The findings that rats self-administered amphetamine into the medial shell and medial tubercle but not the core, ventral shell, or lateral tubercle support our hypothesis that the medial ventral striatum (i.e., the medial shell and medial tubercle) is more responsible for the reinforcing effects of amphetamine than the lateral ventral striatum (i.e., the core, ventral shell, lateral tubercle). This hypothesis is consistent with recent data on afferents to the ventral striatum. Although functional evidence has been offered to support the core–shell scheme (Di Chiara, 2002; Kelley, 2004) since the demonstration of anatomical differences between the accumbens core and shell (Zahm and Brog, 1992), the similarities in afferents between the medial shell and medial tubercle and differences between the medial and ventral shell (Groenewegen et al., 1999) and between the medial and lateral tubercle (Newman and Winans, 1980) have not been emphasized. Reviews of recent data on afferents to the ventral striatum in rodents suggest that the medial shell and medial tubercle receive inputs from common zones in a number of regions, whereas there are significant differences in afferents between the medial and ventral shell and between the medial and lateral tubercle [Ikemoto (2002), their Table 1; Voorn et al., 2004]; similar afferent patterns also exist in primates (Haber, 2003).

Dopaminergic inputs to the medial shell and medial tubercle primarily come from the posteromedial ventral tegmental area (VTA) and the central linear nucleus of raphé, whereas inputs to the ventral shell, lateral tubercle, and accumbens core come primarily from the lateral VTA (S. Ikemoto, unpublished observation). Indeed, mediolateral topographic patterns of projections to the accumbens (Fallon and Moore, 1978; Nauta et al., 1978; Beckstead et al., 1979; Phillipson and Griffiths, 1985; Brog et al., 1993) and to the tubercle (Newman and Winans, 1980) from the VTA have been characterized. Other major afferents to the ventral striatum are primarily glutamatergic and play a critical role in determining the actions of dopamine. The medial shell and medial tubercle receive inputs from the infralimbic cortex (Berendse et al., 1992), the posterior basolateral amygdaloid nucleus (Krettek and Price, 1978; Russchen and Price, 1984), the ventral subiculum of the hippocampal formation (Kelley and Domesick, 1982; Groenewegen et al., 1987), and the paraventricular thalamic nucleus (Newman and Winans, 1980; Berendse and Groenewegen, 1990; Moga et al., 1995). On the other hand, the afferent sources to ventral shell and lateral tubercle include the ventral agranular insular area (Berendse et al., 1992), the anterior basolateral amygdala (Krettek and Price, 1978; Russchen and Price, 1984), and the parataenial nucleus (Newman and Winans, 1980; Berendse and Groenewegen, 1990; Moga et al., 1995). The fact that the medial shell and medial tubercle receive inputs from common zones suggests that they engage in related functions; however, on the other hand, the fact that distinct zones project between the medial and ventral shell and between the medial and lateral tubercle suggests that significant functional differences exist between them.

Although these anatomical observations support our behavioral findings, we must address a concern about interpreting microinjection studies before using these findings as evidence. Microinjected drugs do not necessarily act at the site of delivery but diffuse to neighboring regions for action; for instance, amphetamine administration into the tubercle could diffuse to the accumbens shell. To address the issue of possible drug diffusion along the cannula track, we implanted cannulas for the medial tubercle at a lateral angle to avoid the shell. In addition, we examined different concentrations of amphetamine over multiple sessions in the medial shell as well as surrounding regions. Drug concentration and rapidity of drug action decrease markedly as the drug diffuses from one site to another. Thus, if the reinforcing effect of amphetamine delivered into the medial tubercle was caused by diffusion to the medial shell, we would expect to see rewarding effects of amphetamine delivered into the core or lateral shell, which are as close to the medial shell as the medial tubercle. Furthermore, rats receiving infusions into the medal shell would respond to amphetamine at lower concentrations and learn to self-administer amphetamine faster than tubercle rats. We did not observe such effects. Instead, the core and ventral shell rats failed to learn to self-administer amphetamine, and the medial tubercle rats tended to self-administer amphetamine more vigorously than the medial shell rats. These observations are consistent with the previous findings that medial tubercle rats self-administer cocaine at lower concentrations than medial shell rats (Ikemoto, 2003), and core rats do not learn to self-administer cocaine. Therefore, it is most likely that the administration of amphetamine into the medial tubercle is reinforcing on its own right.

The process that amphetamine triggers via the medial tubercle and medial shell may be characterized as concerted motivational process rather than "pure" reinforcement. Although rats learned to discriminate between the active and inactive levers, they continued responding on the inactive lever. These high inactive responses in part indicate an arousing effect of amphetamine and are consistent with the heightened locomotion and rearing induced by microinjections of amphetamine into the medial tubercle (Ikemoto, 2002). Colocalization of arousal and reinforcement has been found in other brain regions including the ventral tegmental area, in which carbachol or endomorphin-1 administration triggers both effects (Ikemoto and Wise, 2002; Zangen et al., 2002; Ikemoto et al., 2003), and the supramammillary nucleus, in which AMPA or picrotoxin administration triggers both (Ikemoto et al., 2004; Ikemoto, 2005). We suspect that drug administration into these regions, including the medial tubercle and medial shell, triggers a coordinated set of changes in mental and bodily states involved in the reward-seeking function (Ikemoto and Panksepp, 1999), leading to hyperactivity and reinforcement. We should add that although the regions that are known to trigger primary drug reinforcement appear to always trigger hyperactivity in rats, anatomical substrates of hyperactivity are not always colocalized with those of reinforcement. The accumbens core, for example, which did not readily trigger primary drug reinforcement, plays an important role in triggering locomotor effects of amphetamine (Ikemoto, 2002; Sellings and Clarke, 2003).

The present study contributes to the existing literature in three ways. First, we provide new information that amphetamine is reinforcing when administered into the medial shell and medial tubercle but not the core, ventral shell, or lateral tubercle. In addition, the results suggest that the ventral shell, which has been neglected for functional investigation, does not mediate reinforcement in the same way that the medial shell does. The present results also provide much needed complements to the cocaine study findings that the accumbens core and the lateral tubercle do not mediate reinforcement in the same way as the medial shell and medial tubercle (Carlezon et al., 1995; Rodd-Henricks et al., 2002; Ikemoto, 2003). It is difficult to interpret the absence of reinforcing effects of cocaine because of its local anesthetic action and regional differences in sensitivity to local anesthesia. In addition to monoamine uptake inhibition, cocaine potently inhib-

its voltage-gated Na^+ channels, which causes local anesthesia (Catterall and Mackie, 1996). Indeed, at the concentrations that cocaine exerts its motor-stimulant and reinforcing effects when injected into the medial tubercle, it induces local anesthesia and motor depression when injected into the accumbens core (Ikemoto and Witkin, 2003). D-Amphetamine, on the other hand, does not inhibit sodium channels when delivered at the concentrations at which amphetamine stimulates dopamine release and inhibits dopamine uptake. Indeed, the core is as responsible for the motor-stimulant effects of D-amphetamine as the medial shell or medial tubercle (Ikemoto, 2002). The present findings, together with the anatomical data, suggest that the medial shell and medial tubercle are more functionally related than the medial and ventral shell or the medial and lateral tubercle. Additional information, such as data on fine efferent projections, would be helpful in determining whether the medial shell and medial tubercle indeed form a functional unit. In any case, the core–shell–tubercle scheme should be reconsidered in light of recent anatomical data and these functional findings.

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