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Neurotoxic lesions of the medial mediodorsal nucleus of the thalamus disrupt reinforcer devaluation effects in rhesus monkeys

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Abstract

The mediodorsal thalamus is a major input to the prefrontal cortex and is thought to modulate cognitive functions of the prefrontal cortex. Damage to the medial, magnocellular part of the mediodorsal thalamus (MDmc) impairs cognitive functions dependent on prefrontal cortex, including memory. The contribution of MDmc to other aspects of cognition dependent on prefrontal cortex has not been determined. The ability of monkeys to adjust their choice behavior in response to changes in reinforcer value, a capacity impaired by lesions of orbital prefrontal cortex, can be tested in a reinforcer devaluation paradigm. In the present study, rhesus monkeys with bilateral neurotoxic MDmc lesions were tested in the devaluation procedure. Monkeys learned visual discrimination problems in which each rewarded object is reliably paired with one of two different food rewards, and then were given choices between pairs of rewarded objects, one associated with each food. Selective satiation of one of the food rewards reduces choices of objects associated with that food in normal monkeys. Monkeys with bilateral neurotoxic lesions of MDmc learned concurrently-presented visual discrimination problems as quickly as unoperated control monkeys, but showed impaired reinforcer devaluation effects. This finding suggests that the neural circuitry for control of behavioral choice by changes in reinforcer value includes MDmc.

Keywords

amygdala; choice behavior; decision-making; devaluation; medial thalamus; orbitofrontal cortex; prefrontal cortex; reward

The prefrontal cortex (PFC) is involved in multiple aspects of memory, decision-making, and cognitive control. Thalamic input to the PFC is thought to be involved in modulating its functions. Bilateral lesions of the medial, magnocellular part of the mediodorsal thalamus (MDmc) impair learning of object-in-place scenes in rhesus monkeys (Gaffan and Parker, 2000; Mitchell et al., submitted), a task dependent on PFC (Browning et al., 2005). MDmc interacts with both the temporal lobe and ventromedial PFC in rapid learning of single visual discrimination problems in a discrimination learning set paradigm (Gaffan and Murray, 1990; Gaffan et al., 1993). These findings are congruent with the viewpoint that removal of

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input from MDmc to PFC disables the cognitive functions of PFC (Gaffan and Parker, 2000).

The PFC is also involved in decision-making and cognitive control. One function dependent on the PFC, specifically orbital PFC, is the capacity to adjust choice behavior in response to a change in reinforcer value. This adaptive response selection has tremendous survival value as it allows organisms to make choices based on the current value of a reinforcer, rather than its history. The neural circuitry for this ability in monkeys, tested in a reinforcer devaluation paradigm, includes the amygdala and lateral orbital PFC (Malkova et al., 1997; Baxter et al., 2000; Izquierdo et al., 2004; Machado and Bachevalier, 2007), but does not require intact entorhinal and perirhinal cortex (Thornton et al., 1998). The MDmc is interconnected with all of these brain regions. Basolateral amygdala and entorhinal and perirhinal cortex project to MDmc (Aggleton and Mishkin, 1984; Russchen et al., 1987; Saunders et al., 2005). The MDmc has prominent reciprocal connections with ventral and ventromedial orbitofrontal cortex (Goldman-Rakic and Porrino, 1985; Giguere and Goldman-Rakic, 1988; Ray and Price, 1993). The contribution of MDmc to reinforcer devaluation performance has not been determined in nonhuman primates. If MDmc is required for the normal functioning of PFC in response to any demands placed on it, bilateral MDmc lesions would be expected to impair reinforcer devaluation effects just as bilateral orbital prefrontal lesions do.

In the present study we trained rhesus monkeys, either with bilateral neurotoxic lesions of MDmc or intact controls, in the reinforcer devaluation paradigm (Malkova et al., 1997). Monkeys learned 60 visual discrimination problems, presented concurrently once in each training session. Each rewarded object (the correct object in each pair) was consistently associated with one of two different food rewards (a half-peanut or sugar-coated chocolate candy). Once discrimination problems were learned, sessions of critical trials were given in which the 60 rewarded objects were randomly paired to provide 30 choice trials between an object paired with a half-peanut and an object paired with chocolate. Before some of these critical trial sessions, each monkey was allowed to consume one of the two foods to satiety. Normal monkeys make fewer choices of the objects paired with the devalued food after this selective satiation procedure, but this effect is impaired by bilateral lesions of amygdala, orbital PFC, or surgical disconnection of these structures (Malkova et al., 1997; Baxter et al., 2000; Izquierdo et al., 2004; Machado and Bachevalier, 2007).

Method

Subjects

These were 9 rhesus monkeys (*Macaca mulatta*), 7 male and two female. They lived in troops, separated by sex, in large indoor enclosures attached to standard caging. Water was available ad libitum in the home cage, and each monkey's daily food ration was given at the completion of each day's training session. They were behaviorally sophisticated at the time of reinforcer devaluation training. All had been trained on object-in-place scene learning (Gaffan, 1994). Seven of the monkeys (MD1, MD2, MD3, CON1, CON2, CON3, CON4) had also been trained on strategy implementation (Gaffan et al., 2002; Mitchell et al., submitted) as well as concurrent discrimination learning, reversal of concurrent discriminations, and learning and serial reversal of a single visual discrimination problem, all with clip-art stimuli similar to those used in the present study. All of these tasks used 190 mg banana-flavored or sugar pellets (P. J. Noyes, Lancaster, NH) as rewards. Half-peanut and M&Ms were only used as rewards for behavioral test performance in the context of reinforcer devaluation training and selective satiation, although all monkeys were familiar with these foods before they began this training. MDmc lesions were produced between 4 and 6.5 months before the beginning of training on the visual discrimination problems for reinforcer devaluation testing in monkeys MD1-MD5. CON1-CON3 did not undergo any

neurosurgical procedures or anesthesia before or during the present study. CON4 received sterile saline injections into ventrolateral prefrontal cortex. This monkey, operated as part of a separate study of selective neurochemical lesions of ventrolateral prefrontal cortex, was not intended to control for surgical manipulations of the MDmc, but rather provided an additional control case that had undergone anesthesia and neurosurgery, but without sustaining any neuronal damage.

Apparatus

All behavioral testing took place in an automated apparatus, as described in other publications (e.g., Browning et al., 2005). Clip art stimuli were presented on a touch-sensitive screen (380 × 280 mm) located about 150 mm from the front of the transport cage. The monkey could reach through horizontally-oriented bars on the front of the transport cage to touch the screen and obtain rewards. M&Ms and half-peanuts were delivered by automated feeders (Med Associates, St. Albans, VT) to a food cup located centrally below the touchscreen. On the completion of each test session, the monkey was given its daily food by the experimenter and allowed to consume it while still in the transport cage. A clear plastic “lunchbox” (approximately 200 × 100 × 100 mm) that could be attached to the front of the transport cage was used for the specific satiation.

Behavioral testing

This task followed procedures described by Malkova et al. (1997) and Baxter et al. (2000) except that it took place in an automated apparatus instead of a manual one. A set of 60 pairs of clip-art objects, each pair constituting a problem, comprised the visual discrimination problems. One of the two clip-art objects was arbitrarily designated correct in each pair. The objects were presented against a gray background, one on the left side of the screen and one on the right, which was randomized across trials. Touching the correct object resulted in the incorrect object disappearing, delivery of a reward pellet, then the correct object disappearing after 1 sec. Touching the incorrect object caused both objects to disappear immediately and no reward was delivered. The intertrial interval was 30 sec after a choice was made, and a touch to the screen during the intertrial interval reset it. Each problem appeared once in each session.

Half of the rewarded objects resulted in the delivery of a half-peanut, and the other rewarded objects produced an M&M chocolate candy. Training continued until a criterion of 270 or more correct responses over 5 consecutive sessions (90% or greater correct) was reached. At this point a series of sessions of critical trials were presented in which the 60 rewarded objects were randomly assigned to create 30 pairs of critical trials, each offering a choice between a peanut-rewarded object and an M&M-rewarded object. Some sessions of critical trials were preceded by a devaluation procedure in which the monkey was allowed to consume one of the two food rewards to satiation before beginning the critical trial session. For the devaluation, the monkey was moved into the transport cage and remained in the housing room. The plastic lunchbox was affixed to the front of the cage containing a known amount of food reinforcer (either M&Ms or peanuts). The monkey was left undisturbed for 15 minutes to consume the food. If the food was completely eaten the box was refilled. The monkey was then observed closely and once it had not taken any food for 5 minutes, the box was removed from the cage. Once the monkey's cheek pouches were not visibly full of food, it was moved to the testing cubicle and the critical trial session begun. The sequence of critical trial sessions was: baseline, peanut devaluation, baseline, M&M devaluation, and was repeated once. Each critical trial session was separated by at least one standard training session, and monkeys had at least two days of rest following a critical trial session in which devaluation occurred. It is important to note that during these critical trial sessions when one of the foods has been satiated no new learning of object-reward associations can occur as

each pair of objects followed by a food reward is only presented once during the critical trial session.

The critical measure of performance was a score composed of the difference in number of choices of objects paired with a particular food on baseline sessions and in sessions when that food was devalued. These scores were added together for each devalued food. This was calculated separately for each sequence of critical trial sessions and the mean taken as the overall score. For example, a monkey that chose 12 M&M objects and 18 peanut objects in the baseline sessions (mean of the 2 baseline sessions), then chose 5 peanut objects when peanuts were devalued and 7 M&M objects when M&Ms were devalued, would have a difference score of $(18-5) + (12-7) = 18$. If he chose 14 M&M objects and 16 peanut objects in baseline sessions of the second set of critical trial sessions, then 3 peanut objects and 7 M&M objects when each was devalued, this would give a score of 20 for the second set of critical sessions and a difference score of 19 overall.

Monkeys ate an average 98 g food in the selective satiation procedure and spent an average of 15 min in the devaluation sessions. Neither the amounts eaten nor the time spent differed between the groups (t values < 1.46 ; p values > 0.05).

Surgery

Neurosurgical procedures were performed in a dedicated operating theater under aseptic conditions. Monkeys were given steroids (MD1 and MD2, dexamethasone 1 mg/kg, MD3-MD5, methylprednisolone 20 mg/kg) the night before surgery (i.m.), and two (MD1 and MD2, dexamethasone 1-2 mg/kg) or three doses (MD3-MD5, CON4 methylprednisolone, 20 mg/kg) were given i.v. or i.m. on the day of surgery, to protect against intraoperative oedema and postoperative inflammation. Each monkey was sedated on the morning of surgery with both ketamine (10 mg/kg) and xylazine (0.5 mg/kg). Once sedated, the monkey was given atropine (0.05 mg/kg) to reduce secretions, antibiotic (amoxicillin, 8.75 mg/kg) for prophylaxis of infection, opioid (buprenorphine 0.01 mg/kg i.v., repeated twice at 4-6 hour intervals on the day of surgery, i.v. or i.m.) and nonsteroidal anti-inflammatory (meloxicam, 0.2 mg/kg, i.v.) agents for analgesia, and an H₂ receptor antagonist (ranitidine, 1 mg/kg, i.v.) to protect against gastric ulceration as a side-effect of the combination of steroid and nonsteroidal anti-inflammatory treatment. The head was shaved and an intravenous cannula put in place for intraoperative delivery of fluids (warmed sterile saline drip, 5 ml/hr/kg). The monkey was moved into the operating theater, intubated, placed on isoflurane (MD1, MD2, MD4, MD5, CON4, 1.2-2.7%, to effect, in 100% oxygen) or sevoflurane (MD3, 2.25-4.0%, to effect, in 100% oxygen) and then mechanically ventilated. Adjustable heating blankets allowed maintenance of normal body temperature during surgery. Heart rate, oxygen saturation of hemoglobin, mean arterial blood pressure, end tidal CO₂, body temperature, and respiration rate were monitored continuously throughout surgery.

The monkey was placed in a stereotaxic head-holder and the head cleaned with alternating antimicrobial scrub and alcohol and draped to allow a midline incision. The skin and underlying galea were opened in layers. The temporal muscles were retracted as necessary to expose the skull surface over the intended lesion site. A D-shaped bone flap was turned over the right hemisphere and the midline. The dura over the posterior part of the right hemisphere was cut and retracted to the midline. The right hemisphere was retracted with a brain spoon and the splenium of the corpus callosum was cut in the midline with a glass aspirator. The tela choroidea (the membrane covering the third ventricle and the thalamus) was cauterized in the midline posterior and dorsal to the thalamus using a metal aspirator that was insulated to the tip. The posterior commissure, the third ventricle posterior to the thalamus and the most posterior 5 mm of the midline thalamus were exposed. A stereotaxic

manipulator holding a 10- μ l Hamilton syringe with a blunt tipped 26 gauge needle with its hole 1 mm above the base was positioned above the posterior commissure at the midline using the third ventricle as a guide. Neurotoxic bilateral lesions to the magnocellular division of the mediodorsal thalamic nucleus were produced by $10 \times 1 \mu$ l injections of a mixture of ibotenic acid (10 mg/ml; Biosearch Technologies, Novato, CA) and N-methyl-D-aspartic acid (10 mg/ml; Tocris, Bristol, UK) dissolved in sterile 0.1 M phosphate-buffered saline. The monkey brain atlas of Ilinsky and Kultas-Ilinsky (1987) was used to calculate the intended lesion site coordinates. The needle was positioned for the first pair of coordinates, AP, +5.2 mm anterior to the posterior commissure; ML, \pm 1.2 mm lateral to the third ventricle; DV, -4.0 mm (to compensate for the hole positioned 1 mm above the tip of the needle) ventral to the surface of the thalamus directly above the intended lesion site. Each injection was made slowly over 4 minutes and the needle was left in place for approximately 4 minutes before being moved to the next site. The needle was then repositioned for the second pair of coordinates, AP, +4.2 mm; ML, \pm 1.5 mm; DV, -5.0 mm. The third, fourth and fifth pairs of coordinates were AP, +4.2 mm, ML, \pm 1.5 mm and DV, -3.0 mm; AP, +3.4 mm, ML, \pm 1.7 mm and DV, -4.0 mm; and AP, +3.4 mm, ML, \pm 1.7 mm and DV, -3.0 mm, respectively. In each case the DV coordinate was relative to the surface of the thalamus at the injection site. CON4 received a total of 34 (17 per hemisphere) handheld 1- μ l sterile phosphate-buffered saline injections into ventrolateral prefrontal cortex. The boundaries for these injections extended from the ventral lip of the principal sulcus to the fundus of the lateral orbital sulcus. The anterior and posterior limits were lines joining the tips of the principal and lateral orbital sulci.

When the lesions were complete, the dura was repositioned over the brain but not sewn, the bone flap was replaced and held with loose sutures, and the skin and galea were closed in layers. Mechanical ventilation was discontinued intermittently until the monkey was breathing spontaneously; end tidal CO₂ and oxygen saturation of hemoglobin were closely monitored during this process to prevent hypoxia or hypercapnia. The monkey was removed from the head-holder and anesthesia discontinued. The monkey was extubated when a swallowing reflex was observed, returned to the home cage, and monitored continuously until normal posture was regained. Nonsteroidal anti-inflammatory analgesic (meloxicam, 0.2 mg/kg, oral) and antibiotic (8.75 mg/kg, oral) treatment continued following surgery in consultation with veterinary staff, typically for 5 days. Each monkey was returned to his social group as soon as practical after surgery, usually the next day.

Histology

After completion of all behavioral testing each monkey was sedated with ketamine (10 mg/kg), deeply anesthetized with intravenous barbiturate and transcardially perfused with 0.9% saline followed by 10% formalin. The brains were cryoprotected in formalin-sucrose and then sectioned coronally on a freezing microtome at 50 μ m thickness. A 1-in-10 series of sections was collected throughout the thalamus that was expanded to a 1-in-5 series through the area of the lesion; these were mounted on gelatin-coated glass microscope slides and stained with cresyl violet.

Figures 1 and 2 show schematic diagrams depicting the medial thalamus as well as photomicrographs of cresyl violet stained coronal sections corresponding as closely as possible to these schematic diagrams for the five MDmc lesioned monkeys (MD1, MD2, MD3, MD4 and MD5). All five monkeys in the MDmc group had extensive bilateral lesions in the magnocellular division of the mediodorsal thalamic nucleus as intended. The largest lesions were in monkeys MD1, MD3, and MD4 with slight sparing in the most rostral and caudal extents of the MDmc. The MDmc damage in MD2 and MD5 was slightly smaller than the other three lesions, with more extensive atrophy in these lesions within the caudal aspects of the MDmc. In the more rostral parts of MDmc the dorsal area was almost

completely spared in these two monkeys. MD2 also sustained some slight damage to the right posterior cingulate and right retrosplenial cortex. MD1, MD3 and MD5 also sustained unilateral damage to the anterior thalamic nuclei that extended into the anterior portion of the laterodorsal thalamus in MD1 and MD5. Other thalamic damage outside the MDmc was similar in all five lesions within the rhomboid and central medial nuclei. The paraventricular nucleus of the epithalamus was extensively damaged throughout the entire anteroposterior extent of the lesions. All five monkeys also had sagittal section of the splenium of the corpus callosum and hippocampal commissure dorsal to the posterior thalamus.

Results

Monkeys with bilateral neurotoxic lesions of MDmc learned the discrimination problems at a similar rate as controls; mean sessions to criterion \pm SEM, control 19.3 ± 3.8 ; MD 14.0 ± 0.86 (including the criterion run). During the baseline preference testing, there were no significant differences in the object and food pairings selected $t_s < 1.41$, $p_s > 0.05$ (see Figure 3A).

In contrast to their intact learning of the discrimination problems that formed the critical trials for devaluation testing, MD-lesioned monkeys showed attenuated devaluation effects relative to controls. Although the difference scores, on average, were higher for the second devaluation test than the first (mean of 18.88 vs. 15.55) this difference was not statistically significant in the entire sample of monkeys, $t(8) = 1.62$, $p = .13$, nor was it significant in either control or MD monkeys considered separately, t values < 1.70 , p values $> .19$. Thus, our main measure of performance was the mean difference score across the two devaluation tests, although we also considered both separately. This measure is plotted in Figure 3B, and the data from devaluation tests are presented in Table 1. MD-lesioned monkeys were impaired in devaluation as measured by the overall difference score, $t(7) = 2.34$, $p = 0.03$ (one-tailed). This impairment was more prominent on the second devaluation test; comparison of performance on the second test only, $t(7) = 3.43$, $p = 0.01$ (one-tailed) and was not significant on the first test considered alone, $t(7) = 1.31$, $p = 0.12$ (one-tailed). Presumably this reflects the fact that the range of performance is larger on the second devaluation test, as all monkeys tended to show higher devaluation scores when the test was repeated, congruent with previous investigations with this task (e.g., Baxter et al., 2000; Izquierdo and Murray, 2004a).

We note that both groups showed difference scores higher than chance performance (an expected value of zero): controls, $t(3) = 8.49$, $p = .003$; MD, $t(4) = 5.21$, $p = .006$. Thus, although monkeys with MDmc lesions are impaired relative to controls in devaluation performance, they still show performance that is superior to what would be expected based on chance.

Discussion

Bilateral neurotoxic lesions to the MDmc impaired the ability to adjust choice behaviour in response to changes in the reinforcer value. Previous work has shown similar effects following bilateral lesions of orbital PFC (Izquierdo et al., 2004), amygdala (Malkova et al., 1997) or crossed lesions of the amygdala and orbital PFC (Baxter et al., 2000). We predicted deficits in reward devaluation after MDmc lesions due to the interconnections between the amygdala, orbital PFC and the MDmc (Aggleton and Mishkin, 1984; Goldman-Rakic and Porrino, 1985; Russchen et al., 1987; Giguere and Goldman-Rakic, 1988). Thus the current findings provide important evidence regarding a link between the MDmc, the amygdala and the orbital PFC interacting within a neural circuit involved in mediating response selection and goal-directed behavior. This relationship is reinforced by a crossed lesion study of

unilateral MDmc lesions in one hemisphere combined with unilateral orbital PFC and amygdala lesions in the other hemisphere, which also impairs reinforcer devaluation (Izquierdo and Murray, 2004b). The dorsal midline thalamic nuclei, including the paraventricular and parataenial nuclei may have also contributed to the current deficits in reward devaluation as these two nuclei are also interconnected with orbital prefrontal cortex (Hsu and Price, 2007) and they were unavoidably damaged when making the MDmc neurotoxic lesions.

The current results cannot be explained by deficiencies in visual perception or learning abilities because there were no group differences in initial acquisition of the 60 object pairs. It also appears that the MDmc monkeys and controls demonstrated reliable food preferences as performance during baseline testing indicated that most monkeys consistently chose food 1 (M&Ms) objects over food 2 (peanut) objects (see Table 1). Thus the operated group were aware of the values of the reinforcers and their relationships with the specific objects. Furthermore all of the monkeys had participated as subjects in other cognitive tests prior to the devaluation paradigm and demonstrated dissociable cognitive performance between impaired scene learning and an almost normal level of proficiency on a preoperatively acquired strategy implementation task in monkeys MD1, MD2 and MD3 (Mitchell et al., submitted) or impaired new scene learning versus normal retention of 300 preoperatively acquired scenes in monkeys MD4 and MD5 (Mitchell and Gaffan, in prep). Thus the MDmc monkeys did not lack motivation to work for the food rewards. Instead the results of the current study suggest that MDmc lesioned monkeys, like orbital PFC and amygdala lesioned monkeys were unable to adapt their behavior when responding to a choice between two visual objects, which had both previously been rewarding immediately following changes to the value of one of the reinforcers.

It is perhaps surprising that neurotoxic MDmc lesions were without effect on learning the concurrent visual discrimination (object-reward association) problems that formed the pairs of objects used for reinforcer devaluation testing. Aspiration lesions of MDmc impair object-reward association learning (Gaffan and Parker, 2000) as do bilateral lesions of the prefrontal cortex (Parker and Gaffan, 1998). It should be noted that the monkeys with MDmc lesions in the present study were very sophisticated behaviorally by the time these problems were presented (as were the controls), which may mitigate the deficit produced by MDmc ablation in object-reward association learning. Moreover, deficits in object-reward association learning may be less reliable or severe following MDmc lesions relative to impairments in other learning tasks such as scene learning (Mitchell et al., submitted). Bilateral lesions of the ventrolateral or orbital PFC, which reliably impair scene learning, do not impair concurrent object-reward association learning (unpublished observations).

The range of deficits (see Table 1) following bilateral MDmc lesions in the current study were not as severe as those reported following bilateral lesions of orbital PFC (Izquierdo et al., 2004) or amygdala (Malkova et al., 1997), or disconnection of these structures (Baxter et al., 2000). The comparison of magnitude of impairment with these studies is not straightforward, however, because our controls also had higher devaluation scores than previously reported controls (e.g. Izquierdo et al., 2004). The impairment resulting from MDmc lesions in the present study does appear to be a milder impairment than that of monkeys with bilateral orbital PFC lesions tested in precisely the same paradigm (unpublished observations). Furthermore the current testing procedure is not directly comparable with these previously reported studies as they used a manual apparatus whereas the current study used an automated testing design. Nevertheless the milder deficits resulting from MDmc lesions suggest that the MDmc role in the neural circuitry associated with response control may be more regulatory rather than essential. The neuroanatomical connections of the circuit support this proposal, whereby the amygdala and orbital PFC

continue to communicate via a direct route (Porrino et al., 1981; Amaral and Price, 1984; Carmichael and Price, 1996).

The components that account for cognitive deficits after MDmc damage have not yet been identified. Our laboratory has recently proposed that the interactions between PFC and MDmc are critical in rapid new learning (Mitchell et al., submitted). However, the critical trials during the devaluation procedure do not involve new learning as all of the rewarded objects are only presented once during this critical trial session, so there is no opportunity to form new associations between an object and the now-devalued reinforcer. It could be argued that the impairment is related to a deficit in flexible responding or cognitive flexibility more generally. Rats with MD lesions also have reversal learning deficits (Chudasama et al., 2001). However, the effects of lesions on reversal learning and reinforcer devaluation are not identical. Orbital PFC lesions impair both (Izquierdo et al., 2004). But neurotoxic amygdala lesions impair reinforcer devaluation (Malkova et al., 1997) and not reversal learning (Izquierdo and Murray, 2007), whereas rhinal cortex lesions impair reversal learning (Murray et al., 1998) and not reinforcer devaluation (Thornton et al., 1998). Thus, it is not apparent that the involvement of MDmc in reinforcer devaluation can be ascribed with confidence to an impairment in new learning or a generalized impairment in cognitive flexibility.

Interestingly devaluation deficits in an instrumental conditioning paradigm have been shown in rats with mediodorsal thalamus lesions (Corbit et al., 2003), but not with orbitofrontal cortex lesions (Ostlund and Balleine, 2007). Instead orbitofrontal cortex lesions only caused impairments in outcome encoding during Pavlovian conditioning (Ostlund and Balleine, 2007). Basolateral amygdala lesions impair reinforcer devaluation in both instrumental and Pavlovian conditioning paradigms (Hatfield et al., 1996; Balleine et al., 2003; Pickens et al., 2003; Corbit and Balleine, 2005). These results suggest that the brain structures interconnected in this neural circuitry are not simply processing information in the same way, even though lesions of amygdala, orbitofrontal cortex, and MDmc all impair devaluation performance in this procedure in monkeys. Rather the subcortical structures, namely the mediodorsal thalamus and the amygdala, are involved with integration of information about Pavlovian and instrumental outcomes, whereas orbitofrontal cortex is more selectively engaged depending on task demands. The design of our task, at present, does not allow us to distinguish between the contribution of Pavlovian and instrumental processes to performance.

A preliminary report that crossed unilateral lesions of MDmc in one hemisphere, and amygdala and OFC in the other, impair reinforcer devaluation effects (Izquierdo and Murray, 2004b), suggests the involvement of MDmc in this task is via its interaction with these structures. Perhaps the hypothesized involvement of MDmc in PFC-dependent new learning (Mitchell et al., submitted) extends to the modulation of amygdala-orbital PFC interactions in the course of adjusting response selection during the reinforcer devaluation procedure, when choice behavior must be modified in response to the change in the value of the food reinforcer. This would also account for the apparently milder effect of MDmc lesions on reinforcer devaluation than that of bilateral ablation of orbital PFC or amygdala, or their disconnection. Neurophysiological experiments examining neural correlates of reinforcer devaluation in orbital PFC and amygdala in the presence and absence of modulatory input from MDmc would go a long way towards elucidating this issue.

Finally, a role for the MDmc in this neural circuitry associated with response selection suggests that just like humans with orbital PFC and amygdala damage, patients with damage in the mediodorsal thalamus may be impaired in using information about the likely consequences of their actions to guide their behaviour. To our knowledge relatively little

research has investigated these aspects of medial thalamic brain damage. Recent studies have reported that Korsakoff's syndrome patients suffer impairments in affective judgments (Brand et al., 2003) and also make very poor choices and judgments in a laboratory-based gambling task (Brand et al., 2005). Nevertheless in both reports the authors propose that the deficits are mainly the result of frontal lobe pathology. The current findings now suggest that neuronal loss in the mediodorsal thalamic nucleus of Korsakoff's syndrome patients (see (Harding et al., 2000; Kopelman, 2002) may also contribute to the deficits in these affective judgments and irrational responding in gambling-based tasks directly.

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Abbreviations

AD	anterodorsal nucleus
AM	anteromedial nucleus
AV	anteroventral nucleus
Ca	caudate nucleus
CeM	central medial nucleus
CL	central lateral nucleus
CM	center median nucleus
CSL	central superior lateral nucleus
FC	frontal cortex
FX	fornix
HI	lateral habenular nucleus
Hm	medial habenular nucleus
Hpt	habenulopeduncular tract
IT	inferotemporal cortex
LD	lateral dorsal nucleus
Li	limitans nucleus
LP	lateral posterior nucleus
MD	mediodorsal nucleus
MDdc	mediodorsal nucleus, densocellular portion
MDmc	mediodorsal nucleus, magnocellular portion
MDmf	mediodorsal nucleus, multiformis portion
MDpc	mediodorsal nucleus, parvocellular portion
MG	medial geniculate complex
Mm	mamillary complex
Mtt	mamillothalamic tract
Pa	paraventricular nucleus

Pc	paracentral nucleus
Pf	parafascicular nucleus
PFC	prefrontal cortex
Pla	anterior pulvinar nucleus
Pli	inferior pulvinar nucleus
Pl	lateral pulvinar nucleus
Po	posterior nucleus
Pa	parataenial nucleus
R	reticular nucleus
Re	reuniens nucleus
Rh	rhomboid nucleus
SG	suprageniculate nucleus
SN	substantia nigra
St	stria terminalis
Sub	subthalamic nucleus
VA	ventral anterior nucleus
VLa	ventral lateral nucleus, anterior portion
VLp	ventral lateral nucleus, posterior portion
VMb	ventral medial nucleus, basal portion
VMp	ventral medial nucleus, principal portion
VPi	ventral posterior inferior nucleus
VPl	ventral posterior lateral nucleus
VPm	ventral posterior medial nucleus
Zi	zona incerta

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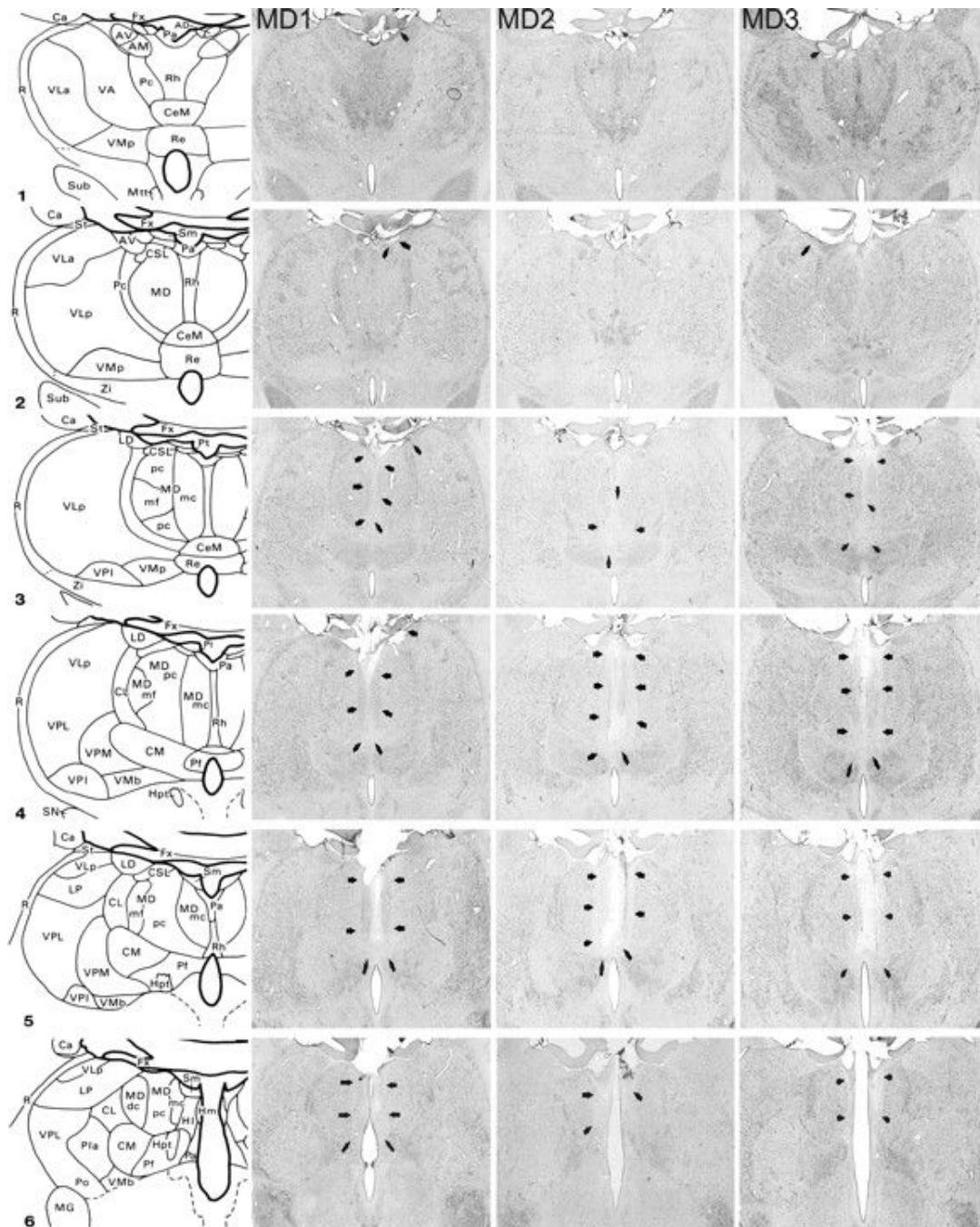


Fig. 1.

MDmc lesions. Schematic diagrams of six sections, 1 mm apart, through the posterior thalamus of a monkey taken from Gaffan and Murray (1990). The next three columns show photomicrographs of the MDmc lesions for MD1, MD2 and MD3 corresponding as closely as possible to the each of the schematic diagrams. (Photomicrographs of MD4 and MD5 are shown in Figure 2). Arrowheads indicate the site of each lesion. For abbreviations see Appendix.

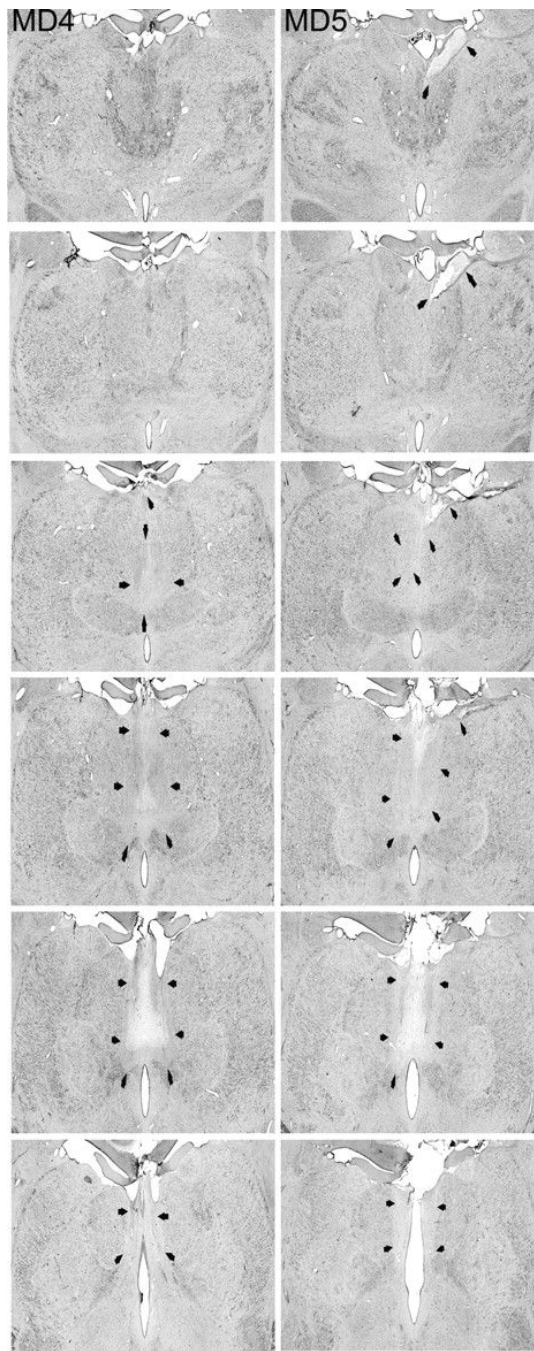


Fig. 2. MDmc lesions cont. The two columns show photomicrographs of the MDmc lesions for MD4 and MD5 corresponding as closely as possible to the each of the schematic diagrams shown in Figure 1. Arrowheads indicate the site of each lesion.

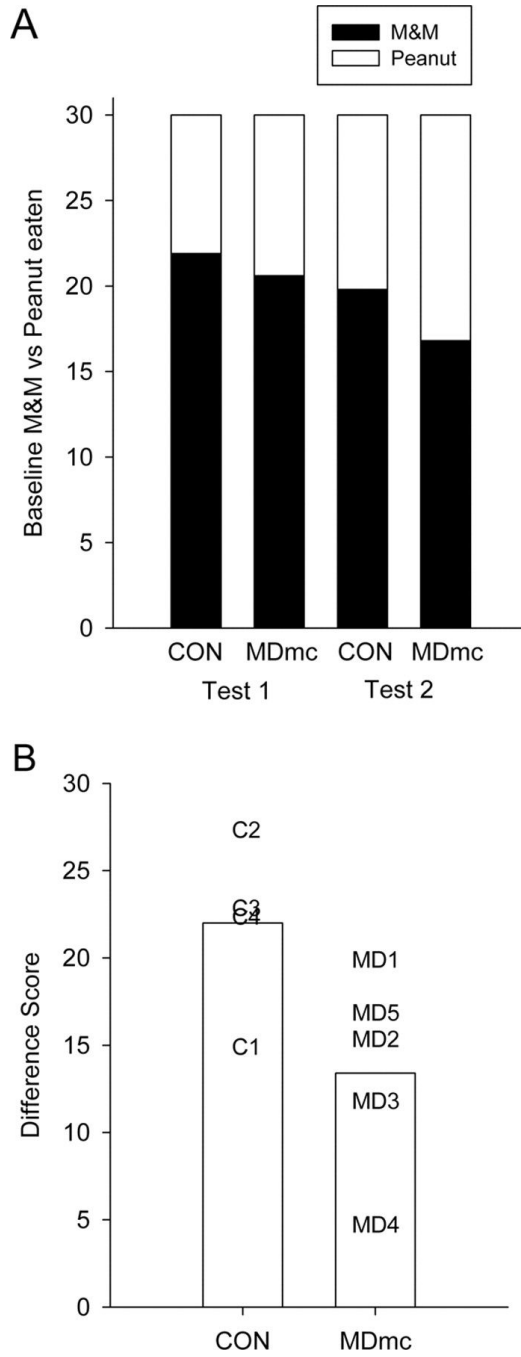


Fig. 3. Devaluation. A: Mean number of objects selected based on either M&M or peanut rewards during baseline preference test sessions of Test 1 and Test 2 for neurotoxic magnocellular mediodorsal thalamus lesion (MDmc) and unoperated control (CON) monkeys. B: Mean difference scores across the two devaluation tests for MDmc and CON monkeys. Data presented are from individual monkeys.

Table 1

Devaluation performance for the two tests. The number of M&M (M) and peanut (P) objects chosen by each monkey (control monkey, Con1-Con4; monkeys with MDmc lesions, MD1-MD5) during the baseline sessions (mean of 2 baseline sessions for each test), and for sessions preceded by devaluation of either peanuts or M&Ms.

Case	Test 1			Test 2			Satiated P	Satiated M	Difference score	Mean
	Baseline M	Satiated P	Difference score	Baseline M	Satiated P	Difference score				
Con1	30:0	21:9	30:0	9	30:0	9:21	30:0	21	15	
Con2	18.5:11.5	2:28	30:0	28	11:19	0:30	27:3	27	27.5	
Con3	18:12	1:29	19:11	18	18:12	2:28	30:0	28	23	
Con4	21:9	7:23	29:1	22	20:10	6:24	29:1	23	22.5	
Mean	21:9:8.1	7.8:22.2	27:3	19.25	19.8:10.2	4.3:25.7	29:1	24.75	22	
MD1	21:9	8:22	27:3	19	15.5:14.5	5:25	25:5	20	19.5	
MD2	19.5:10.5	16:14	27:3	11	13.5:16.5	6:24	25:5	19	15	
MD3	16:14	10:20	21:9	11	17.5:12.5	11:19	23:7	12	11.5	
MD4	29.5:0.5	27:3	29:1	2	25.5:4.5	20:10	27:3	7	4.5	
MD5	17:13	6:24	26:4	20	12:18	6:24	19:11	13	16.5	
Mean	20.6:9.4	13.4:16.6	26:4	12.6	16.8:13.2	9.6:20.4	23.8:6.2	14.2	13.4	