Impulsive choice induced in rats by lesions of the nucleus accumbens core, but not of anterior cingulate or medial prefrontal cortex

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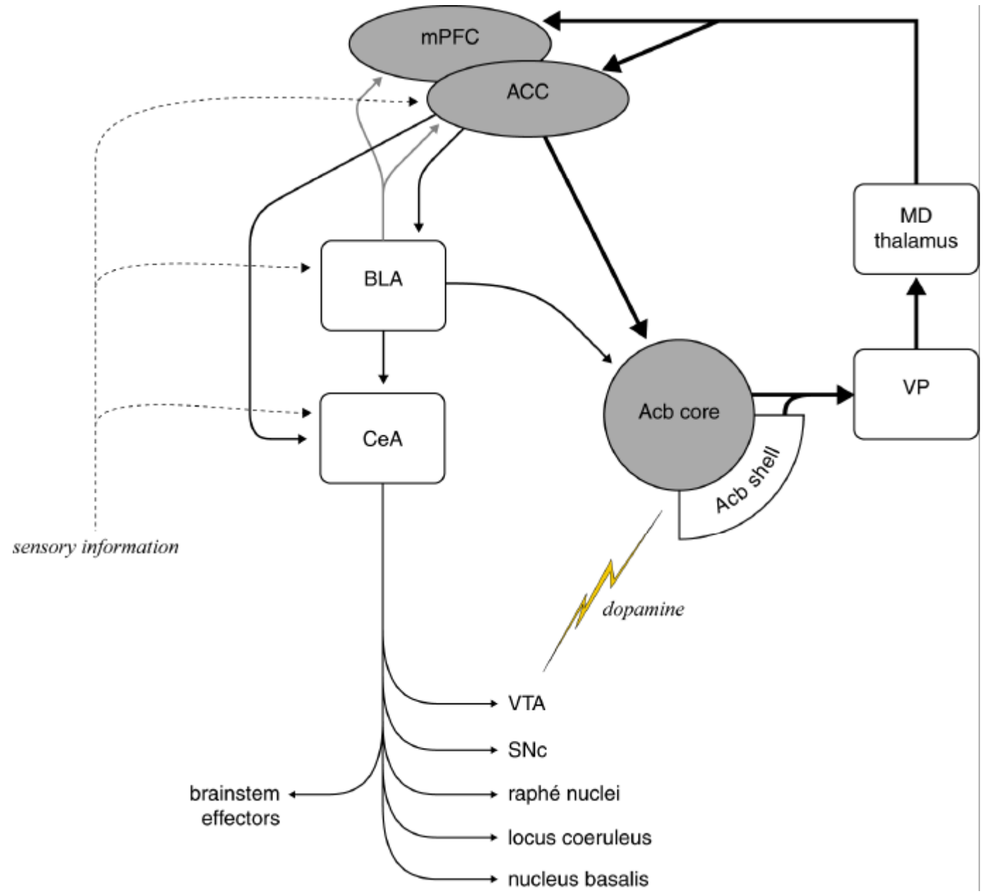
Abstract. Impulsive choice is exemplified by the choice of reward that is small, poor, or ultimately disastrous, but is available immediately, in preference to a larger reward obtainable only after a delay. Impulsive choice contributes to neuropsychiatric disorders such as drug addiction as well as attention-deficit/hyperactivity disorder (ADHD), mania, and personality disorders. Impulsive choice hypothetically results from dysfunction of limbic corticostriatal circuitry implicated in reinforcement processes, via convergence on the nucleus accumbens. In this first study of the neuroanatomical basis of impulsive choice, we show that lesions of the nucleus accumbens core (AcbC) induce impulsivity by dramatically and persistently impairing rats' ability to choose a delayed reinforcer. In contrast, lesions of the anterior cingulate cortex (ACC) or medial prefrontal cortex (mPFC) had no effect on this capacity, although mPFC lesions appeared to affect general behavioural timing mechanisms. Thus, dysfunction of the AcbC may be a key element in the neuropathology of impulsivity.

Introduction

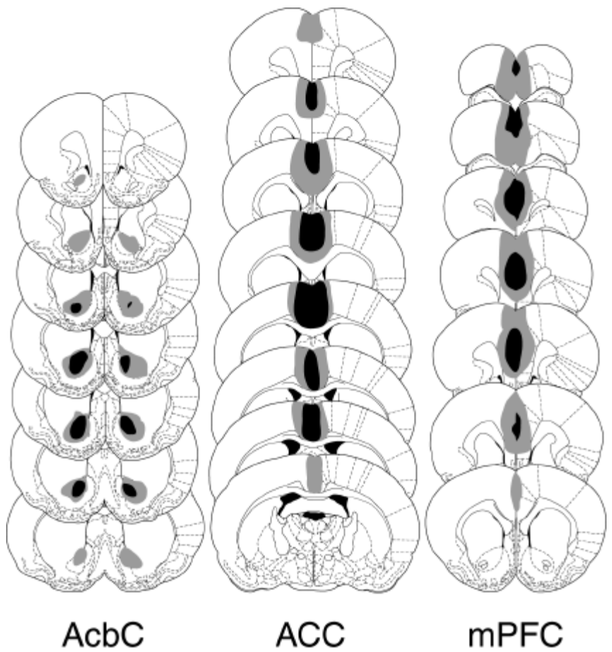
- When animals act to obtain reward, there is always some delay between the action and its outcome; thus, to control the world successfully, animals must be able to use delayed reinforcement. This ability varies: impulsive individuals are influenced less by delayed rewards than self-controlled individuals [2].
- The neural basis of delayed reinforcement is not presently understood, but several lines of evidence suggest the nucleus accumbens (Acb) and its cortical afferents, including the anterior cingulate and medial prefrontal cortices (ACC, mPFC), as candidate structures that may be involved in regulating choice between alternative reinforcers. These structures:
  - have been implicated in reinforcement processes [4, 5, 8, 15, 19];
  - receive major dopaminergic and serotonergic afferents, and pharmacological manipulations of these systems affect impulsive choice in rats [6, 9, 13, 16, 29];
  - have been found to be abnormal in impulsive individuals, be they humans with ADHD [7, 12, 23] or spontaneously hypertensive rats (SHR), widely used as an animal model of ADHD [24-26].
- The present study used a task developed by Evenden and Ryan [14] to investigate the effects of excitotoxic lesions of the AcbC, ACC, and mPFC on rats' capacity to choose a delayed reward.



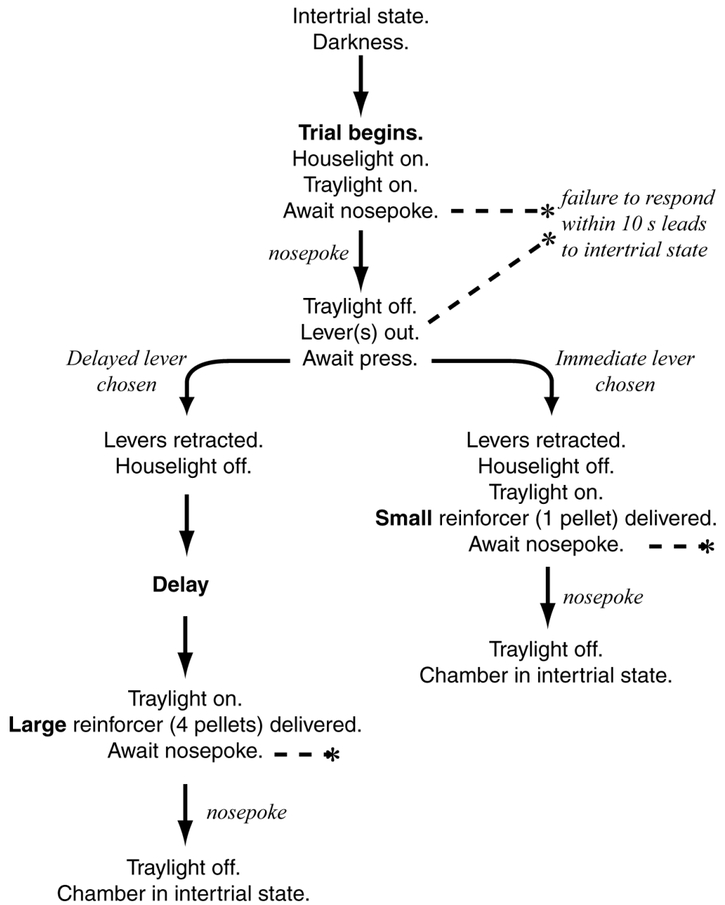
A simplified schematic of part of the 'limbic loop' of the basal ganglia. Grey shading indicates the regions lesioned in the present study. *(Abbreviations: Acb – nucleus accumbens; ACC – anterior cingulate cortex; mPFC – medial prefrontal cortex; BLA – basolateral amygdala; CeA – central nucleus of the amygdala; VTA – ventral tegmental area; VP – ventral pallidum.)*

Methods

- Evenden and Ryan [14] developed a model of impulsive choice in which food-restricted rats choose between a small, immediate reward and a large, delayed reward in discrete trials, the delay to the large reinforcer being increased in steps as the session progresses. Subjects were trained on this task (*figure, right*) and assigned to matched groups; they then received excitotoxic lesions of the AcbC, ACC, or mPFC, or sham lesions before being retested.
- Before surgery, rats exhibited a within-session shift in preference from the large to the small reward as the large reward was progressively delayed (*left-hand figures in subsequent pages*), as is typical for trained subjects performing this task [9, 14]. There were no pre-operative differences between corresponding sham and lesion groups.

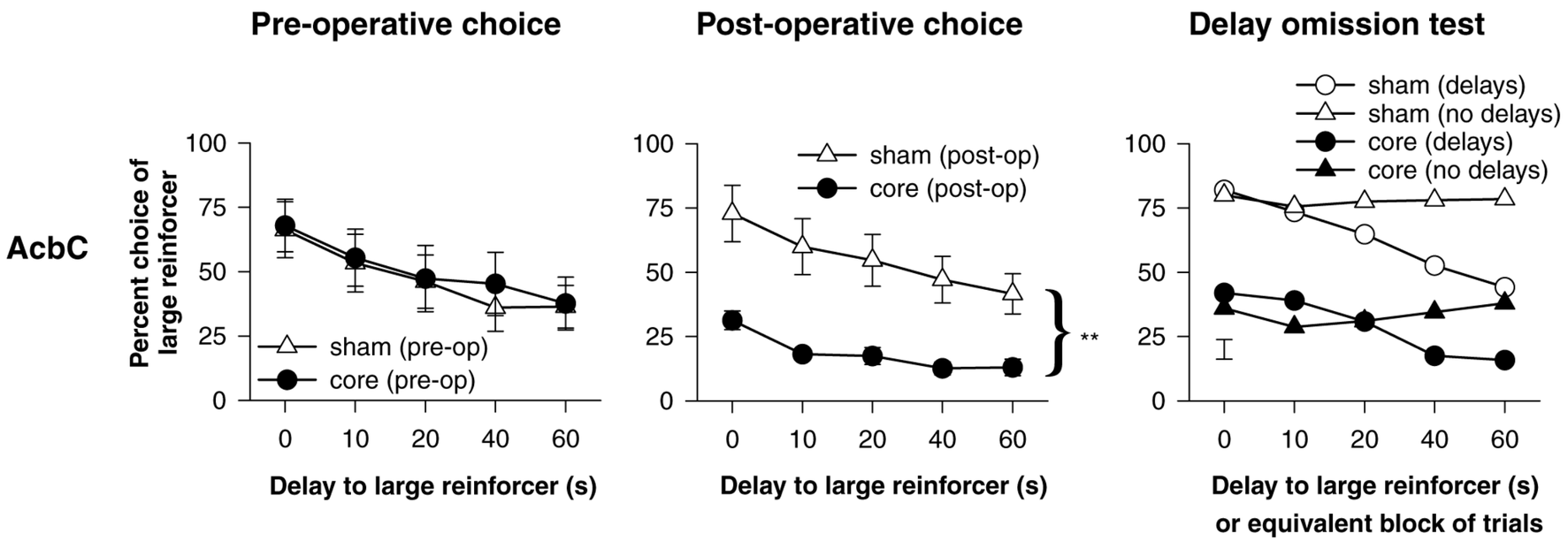


Lesion schematics *(black shading indicates the extent of neuronal loss common to all subjects; grey indicates the area lesioned in at least one subject).[21]*



Task schematic. *The figure shows the format of a single trial. Each session contained 5 blocks; each block comprised two single-lever trials and 10 choice trials. The delay to the large reinforcer was varied systematically across the session: delays for consecutive blocks were 0, 10, 20, 40, and 60 s respectively.*

1. Effects of nucleus accumbens core (AcbC) lesions

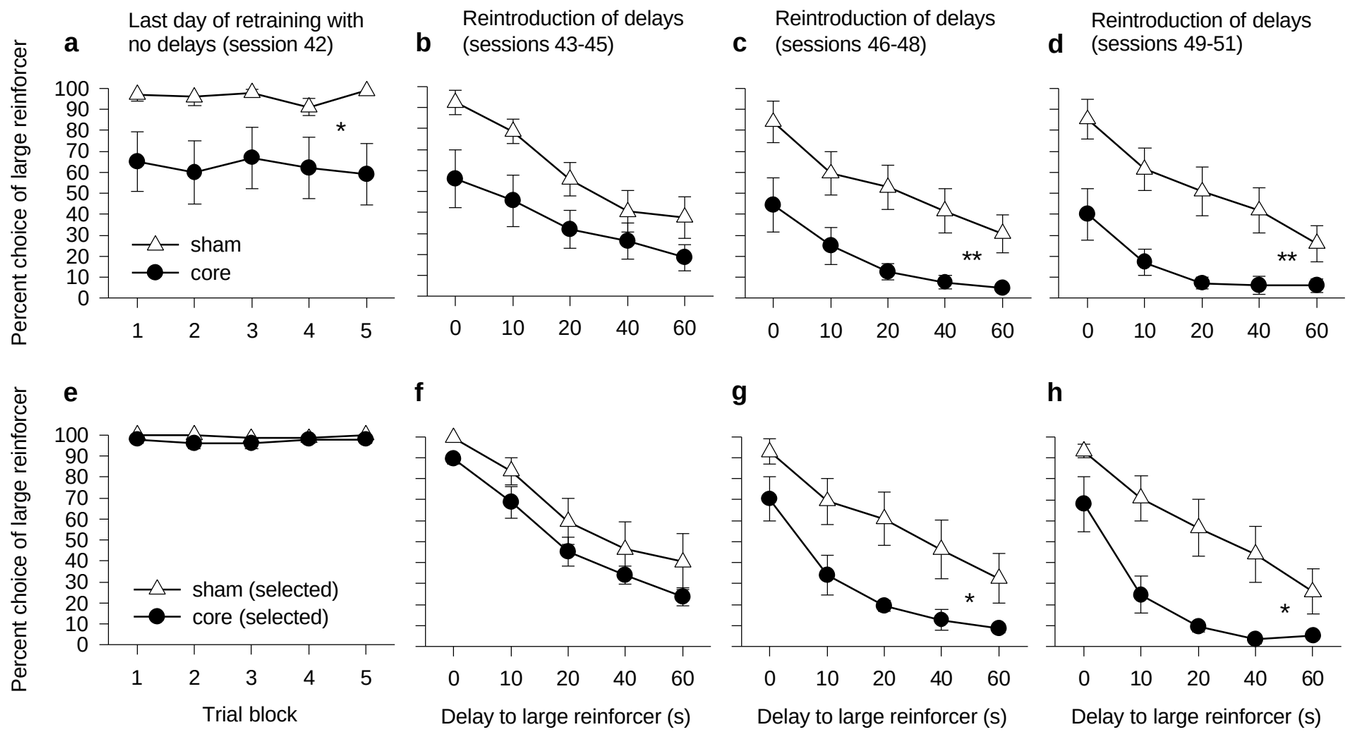


** $p < .01$

- **Lesions of the AcbC induced a profound and lasting deficit in subjects' ability to choose the delayed reward — lesioned subjects made impulsive choices** (*middle panel*). This was not due to an inflexible bias away from the lever producing the delayed reinforcer, as AcbC-lesioned rats still chose the large reinforcer more frequently at zero delay than at other delays, and removal of the delays resulted in a rapid and significant increase in the rats' preference for the large reinforcer (*right-hand panel*). Thus, the pattern of choice clearly reflected a reduced preference for the large reinforcer when it was delayed, suggesting that delays reduced the effectiveness or value of rewards much more in AcbC-lesioned rats than in controls.

- AcbC-lesioned subjects were **hyperactive** and slower to habituate to the novel environment of the locomotor testing apparatus, as described previously [20]. They were also ~10% lighter than controls ($p < .01$ throughout testing). However, it is unlikely that differences in primary motivation contributed to the impulsive choice of AcbC-lesioned rats. Firstly, they did not differ in consumption of the sucrose reinforcer used in the task. Secondly, manipulation of motivational state does not affect choice on this task [9]. Thirdly, performance of Acb-lesioned animals was not comparable in other respects to that of sated rats [9].

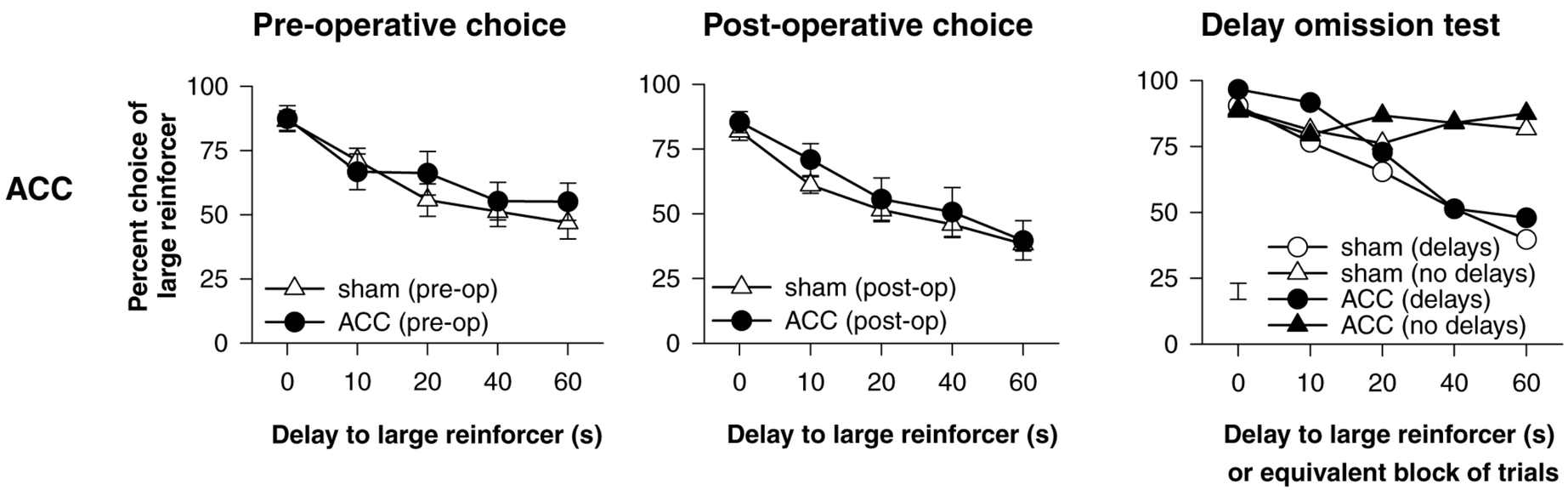
2. Further testing of AcbC-lesioned rats



Panel a: *Preference of AcbC-lesioned rats following extended training in the absence of any delays.* ***Panels b–d:*** *Performance over consecutive blocks of sessions upon the reintroduction of delays (* $p < .05$, ** $p < .01$, *between-group difference). Panels* ***e–h*** *are identical in form to panels* ***a–d,*** *but only includes data from those rats selected on the basis of a criterion of ³90% preference for the large reinforcer on the last day of training with no delays. The groups were therefore matched in panel e. In panels f–h, upon reintroduction of the delays, preference for the large reinforcer collapsed in the core group.*

- Initially, AcbC-lesioned subjects also failed to choose the large reward as often as shams when it was not delayed. However, prolonged training in the absence of delays re-established preference for the large reinforcer in a majority (60%) of lesioned subjects; thus, they discriminated the two reinforcers, and the difference observed at zero delay (*previous page*) did not reflect a true preference for the small immediate reward over the large immediate reward.
- Even those AcbC-lesioned subjects who exhibited a near-absolute preference for the large reinforcer when given prolonged training without delays (≥90% preference in every trial block, a criterion met by 50% of lesioned and 70% of sham subjects) remained hypersensitive to the effects of reintroducing the delays subsequently ($p < .05$ compared to similarly-selected shams).

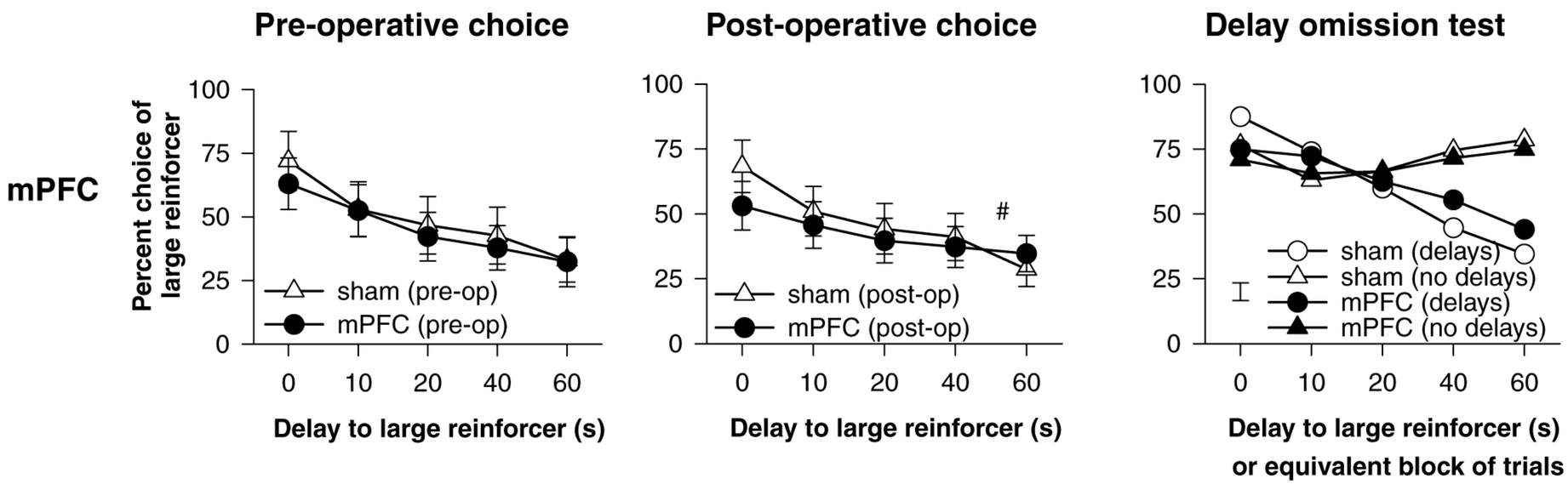
3. Effects of anterior cingulate cortex (ACC) lesions



- **Lesions of the ACC did not affect subjects' ability to choose a delayed reward;** their pattern of choice was indistinguishable from that of sham-operated controls (*centre*), and their behaviour remained equally sensitive to unexpected removal of the delays (*right*).

- This finding stands in apparent contrast to previous reports of motor impulsivity or disinhibited responding in ACC-lesioned rats. For example, such rats have been found to over-respond to unrewarded stimuli [8], and to respond prematurely in situations where they are required to wait [18]. However, a dissociation between motor impulsivity and impulsive choice is not unprecedented [13].

4. Effects of medial prefrontal cortex (mPFC) lesions



 # $p < .05$, group ´ delay interaction

- **Lesions of the mPFC 'flattened' the normal within-session shift in preference** — that is, the mean preference for the large reward was *below* that of shams at zero delay, but *above* that of shams at the maximum delay (*centre panel*).
- However, a shift from large to small reward (albeit small) persisted in lesioned subjects (*centre*) and they remained sensitive to removal of the delays (*right*).
- A plausible interpretation is that mPFC lesions disrupted the control over behaviour by the passage of time in each session. Normal rats acquire a tendency to shift from the large to the small reward as the session progresses [9]. Disruption of such temporal stimulus control might be expected to produce a flattening of this within-session shift, consistent with the effects of aspirative mPFC lesions on timing [11].

Discussion and conclusions

- AcbC-lesioned animals exhibited at least two signs of **ADHD** [3, 26]: locomotor hyperactivity and impulsive choice. However, attentional deficits are not evident in such animals [10] (A. Christakou, T.W.R. & B.J.E., unpublished results). Thus, AcbC-lesioned rats may represent an animal model of the hyperactive–impulsive subtype of ADHD [3].

- The present results show that **the integrity of the Acb is critical for animals to tolerate delays to reward.**

- The possibility that **the AcbC is required to maintain the value of a reinforcer over a delay** may provide a novel insight into Acb function. Neuronal activity in the primate ventral striatum is related to the expectation of reward across a delay; such activity is a candidate representation of the goals of behaviour [28]. Striatal neurons also respond to past events, maintaining a form of memory that might assist the association of past acts with reinforcement [28]. These findings are the basis for computational models of striatal function [17] and indicate the nature of the information that the AcbC may use to promote actions leading to delayed rewards.

- Additionally, the present results demonstrate **a role for the Acb in action selection even when those actions do not differ in response effort or cost.** Thus, reduced preference for delayed reinforcement may also explain the observation that Acb dopamine depletion prevents rats working hard for a preferred food [27] and impairs responding on high-effort schedules [1], as such schedules also impose delays to reinforcement.

- While lesions of the AcbC induced impulsive choice, lesions of two of its cortical **afferents** did not. An important task for further investigations is to specify which afferents to the AcbC contribute to its ability to promote the choice of delayed rewards. One obvious candidate that may convey specific information concerning reinforcer value to the Acb is the basolateral amygdala [15]. Another is the orbitofrontal cortex, also implicated in the assessment of reward value and probability [22, 28].

- In summary, the present results provide the first direct evidence that the Acb is involved in the **pathogenesis of impulsive choice.** In addition to providing neuroanatomical insight into the normal process through which delayed reinforcement affects behaviour, and demonstrating a previously unknown function of the Acb, this finding suggests a mechanism by which Acb dysfunction may contribute to addiction, ADHD, and other impulse control disorders.

Acknowledgements

- Supported by the Medical Research Council (UK) and a Wellcome Trust Programme Grant.
- Conducted within the MRC Co-operative for Brain, Behaviour and Neuropsychiatry.
- RNC was supported by a research studentship from the UK Medical Research Council and a James Baird award from the University of Cambridge School of Clinical Medicine.
- The authors thank Caroline Morrison and Helen Sweet-Gossage for assistance with histological procedures.
- Presented at the Society for Neuroscience 31st Annual Meeting, 10–15 November 2001, San Diego, California, USA.

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