Increased release of acetylcholine and noradrenaline in the rat medial prefrontal cortex during contingent and non-contingent performance of a visual attentional task

837.9

Jeffrey W. Dalley, Jill McGaughy, Rudolf N. Cardinal, Liat Levita, Barry J. Everitt and Trevor W. Robbins

Department of Experimental Psychology,
University of Cambridge,
Downing Street,
Cambridge
England CB2 3EB

Introduction

- The locus coeruleus (LC) noradrenergic system is thought to contribute to processes concerned with the selective attention of salient unexpected stimuli (Aston-Jones and Bloom, 1981). Thus, LC neurons show increased activity to simple and conditioned sensory stimuli and various stimuli, including novelty, increase noradrenaline (NA) release in the rat frontal cortex (Dalley and Stanford, 1995). Similar functional changes have been reported for the basal forebrain cortical cholinergic system however unlike the LC system, cortical cholinergic inputs are presumed to play a more general role in stimulus detection and information processing (Sarter and Bruno, 2000).

- Cortical acetylcholine (ACh) efflux has been shown to increase during sustained attention performance (Passetti et al., 2000; Himmelheber et al., 2000). However, the specificity of this response to attentional processing requires further evaluation since many factors related to instrumental (action-outcome) performance, including reinforcement density and motoric activity, are known to affect cortical ACh efflux.

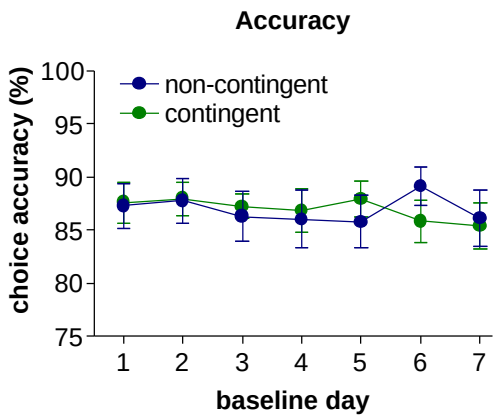
- In this study we measured cortical NA and ACh efflux in the medial prefrontal cortex using in-vivo microdialysis during sustained attention performance on the 5-choice task. Two experimental manipulations were used. The first, an attention performance group, assessed the relative effects of performance on cortical ACh and NA efflux. The second manipulation involved degrading the instrumental contingency of the task such that reinforcement was made contingent on the performance of a second trained rat. Subjects in this group could freely engage in the task but they were no longer rewarded or punished for correct or incorrect responses as before.

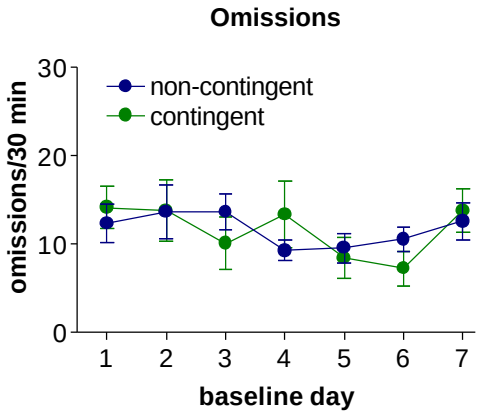
Methods

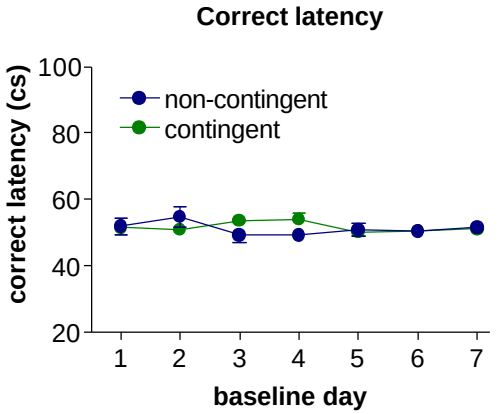
5-Choice apparatus

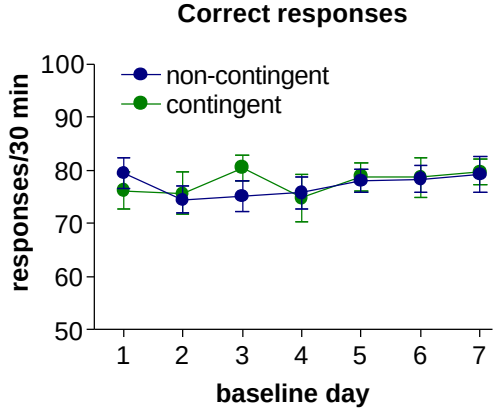
- Male LH rats (n=20) were trained on the 5-choice task to criterion performance (choice accuracy >80%, omissions <20%). Subjects were randomly assigned to two groups. Baseline measures of performance were taken over seven consecutive sessions to ensure that both groups were evenly matched (see Fig 1).
- Microdialysis probes (AN 69 membrane, 2 mm) were implanted in the medial prefrontal cortex (AP 3mm; L 1.2 mm; V -4.0 mm; 12^{o} to the vertical) under ketamine/xylazine anaesthesia.
- Behavioral dialysis was conducted over two consecutive days. The task was initiated two hours after the rat was placed in the chamber. Six 10-min baseline samples were collected immediately prior to task onset (HL light off).
- Six 10-min 'task' samples collected. Perfusate delivered at 2 µl/min via a dual channel liquid swivel (composition [mM]: NaCl [147]; $CaCl_2$ [1.3]; KCl [3]; $MgCl_2$ [1]; sodium phosphate buffer [1.5]; pH 7.4; neostigmine 50 nM.
- Non-contingent behavioral subjects received the same reinforcement density and visual stimuli as contingent subjects but were not rewarded or punished for correct or incorrect responses.
- NA and ACh were analysed by HPLC-ECD (Dalley and Stanford, 1995; Haung et al., 1995).

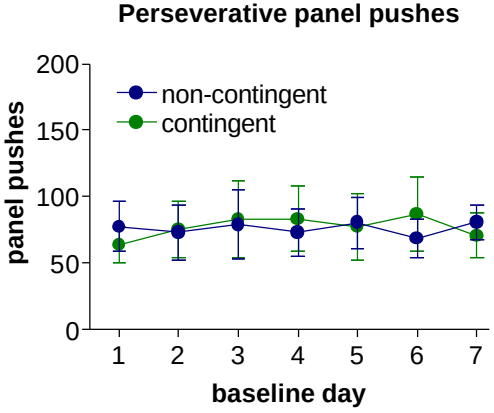
Baseline performance prior to in-vivo microdialysis

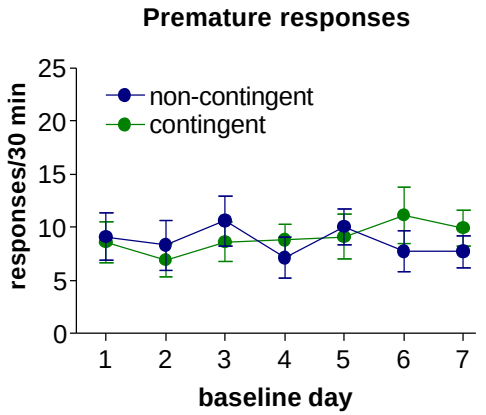




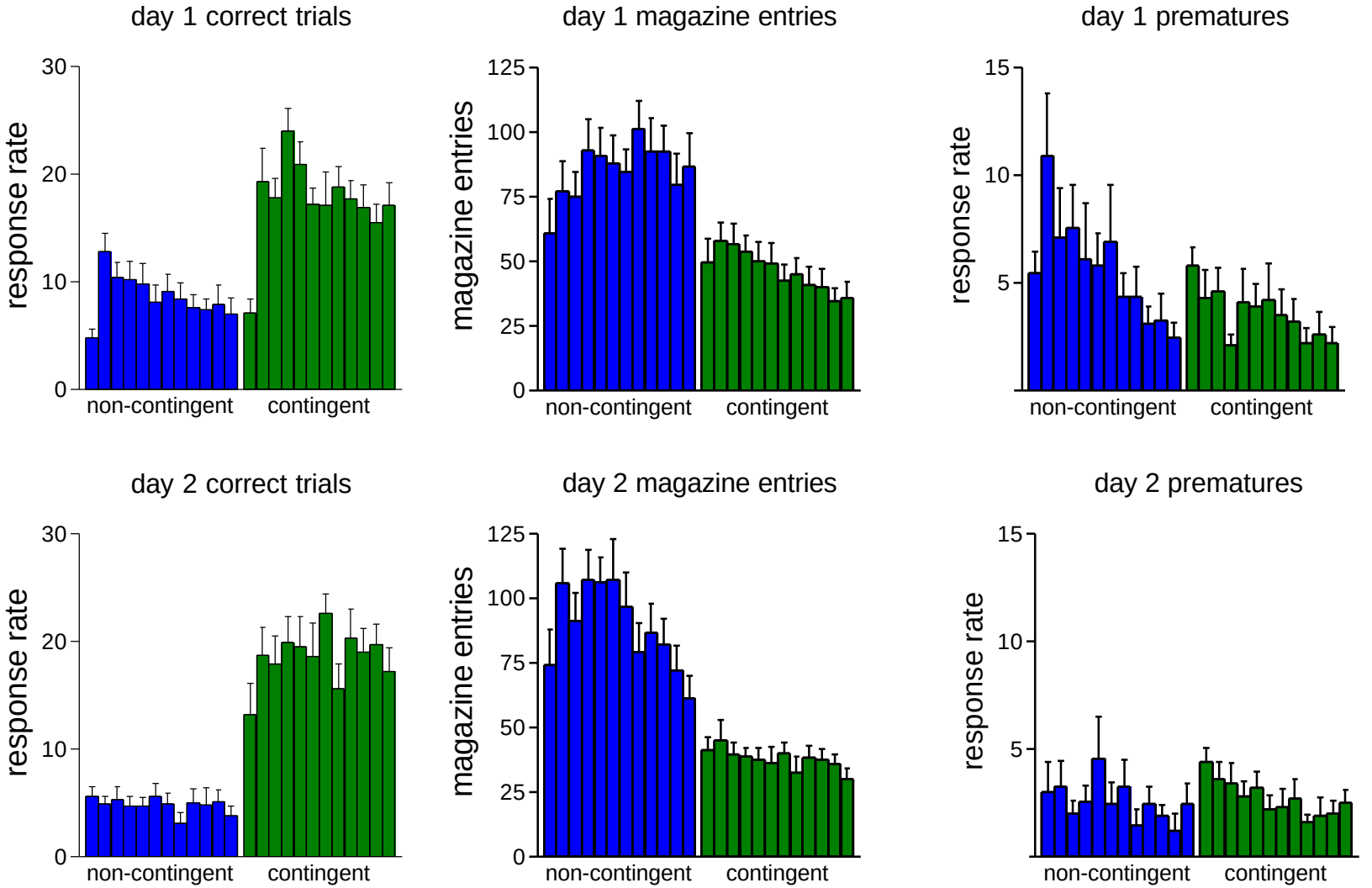








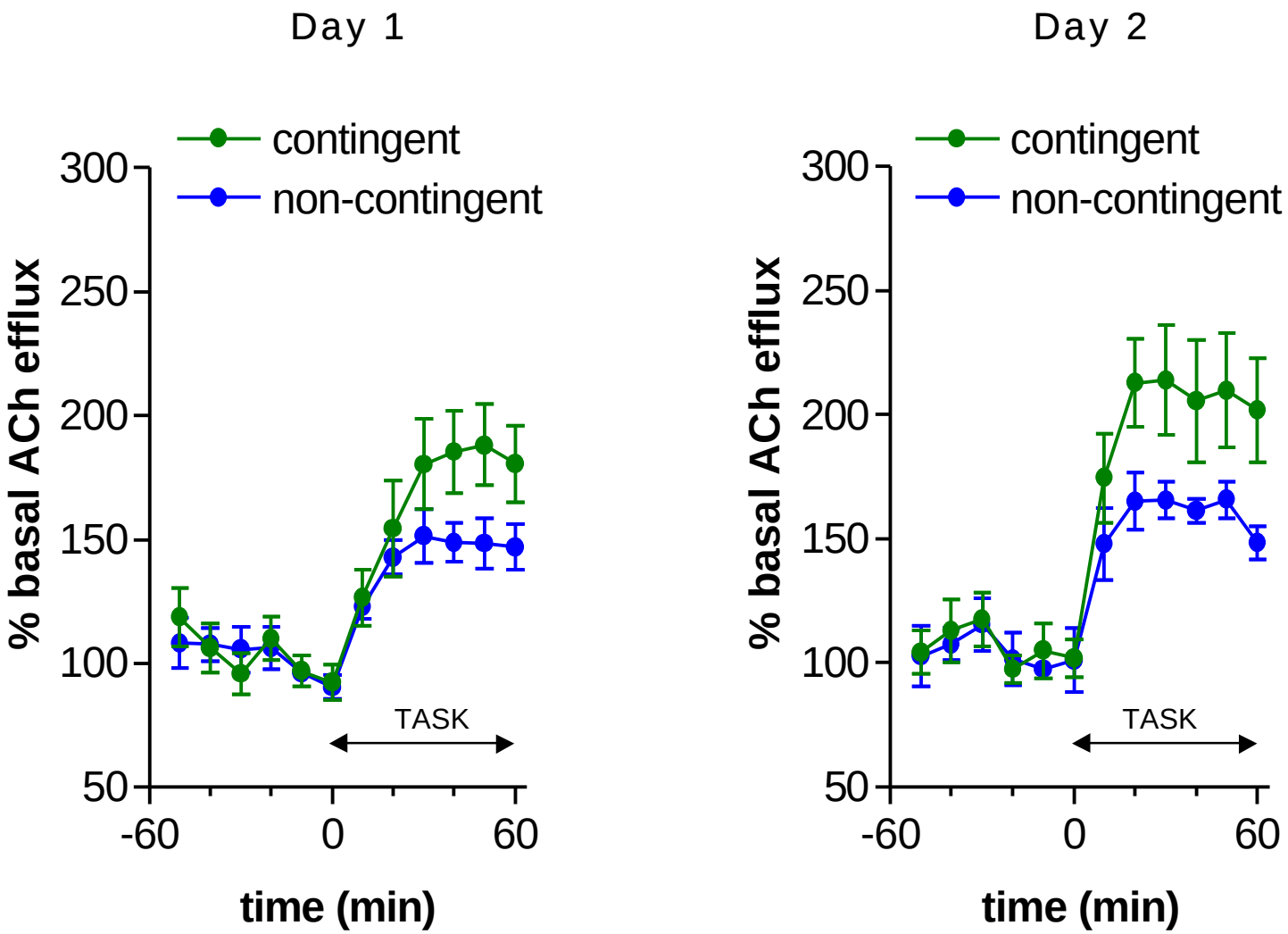
5-choice performance (12x5-min bins)



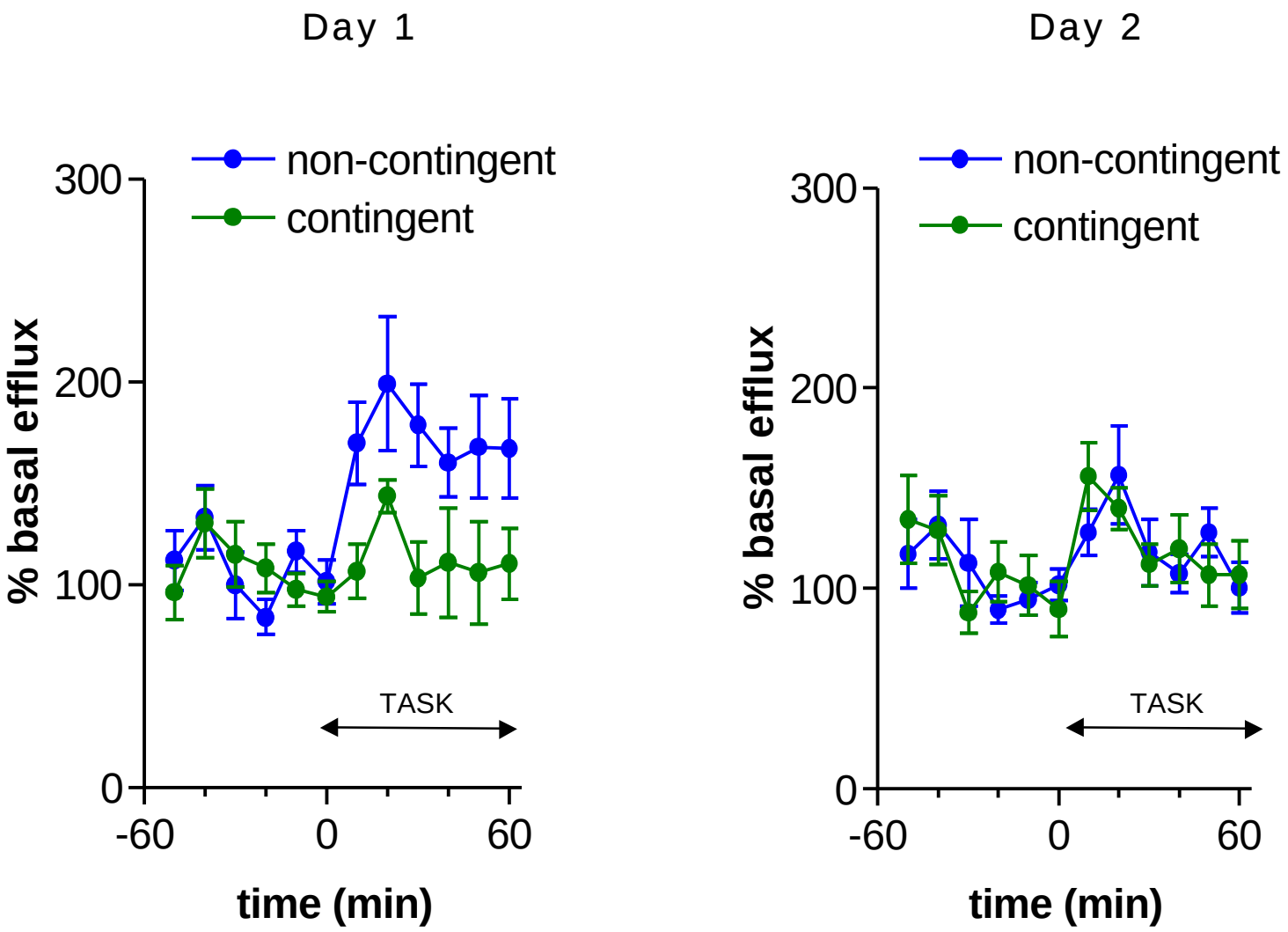
Contingent performance (3x20-min bins)

	Day 1			Day 2		
Total trials	121 ± 3	125 ± 3	118 ± 4	122 ± 5	123 ± 6	125 ± 4
Correct trials	69 ± 7	74 ± 7	66 ± 6	70 ± 8	76 ± 10	77 ± 8
Accuracy (%)	80 ± 2	81 ± 2	79 ± 1	78 ± 2	81 ± 3	83 ± 2
Omission Rate	19 ± 3	19 ± 3	26 ± 5	19 ± 4	20 ± 6	23 ± 4
Correct Latency	66 ± 3	65 ± 3	69 ± 4	67 ± 5	62 ± 3	68 ± 5

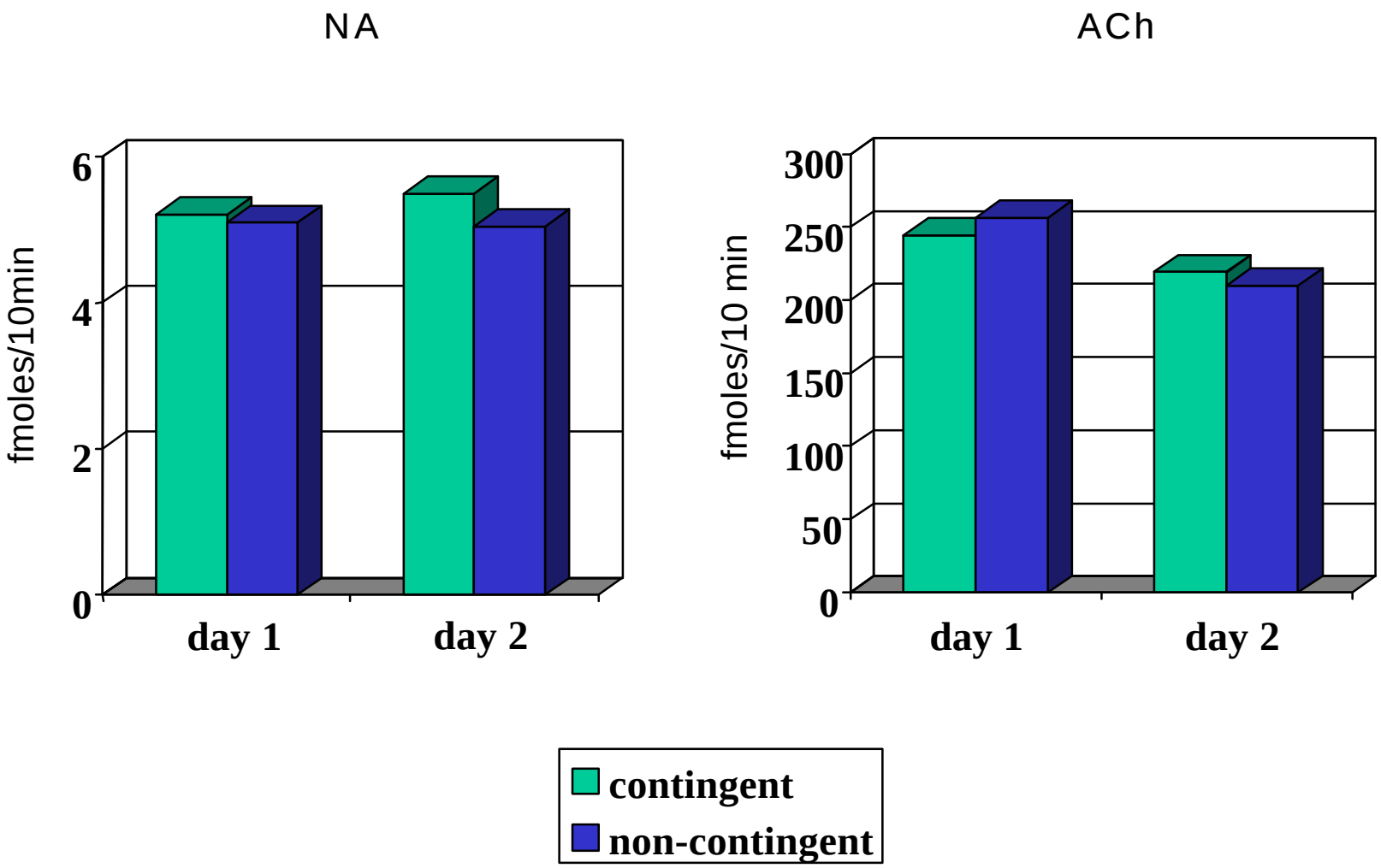
Acetylcholine efflux



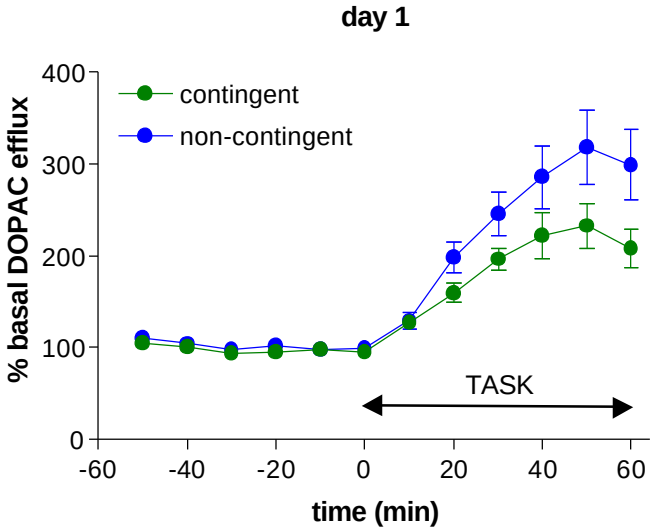
Noradrenaline efflux

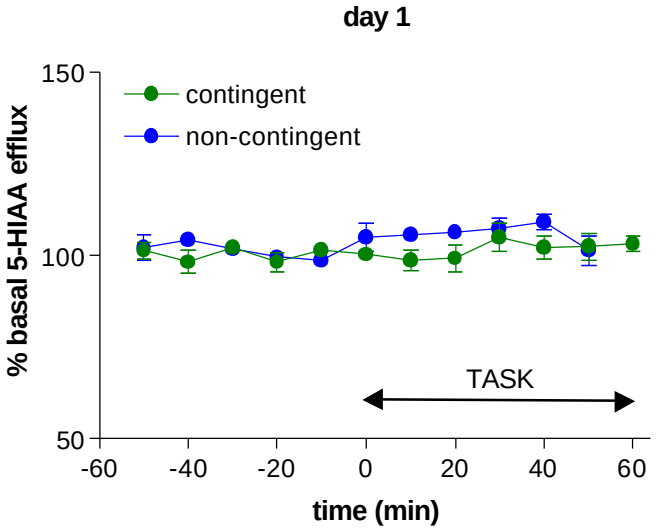


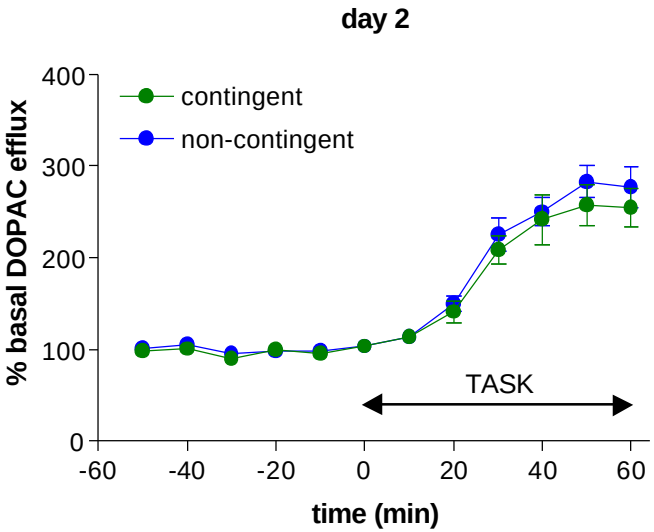
Basal efflux

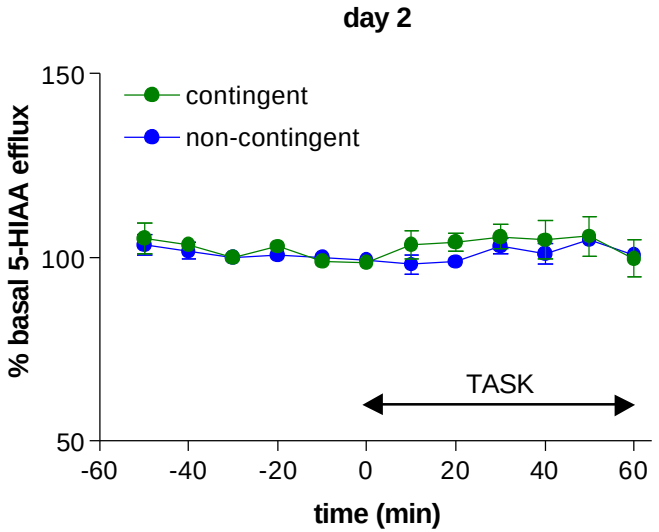


Monoamine metabolite data









Conclusions

- Extracellular levels of ACh in the medial prefrontal cortex of the rat increase during sustained attention performance on the 5-choice serial reaction time task.

- The coeruleo-cortical noradrenergic system is not activated during stable performance on this task (as assessed by changes in neurotransmitter levels).

- Shifting the instrumental contingency of the task to non-contingent (response-independent) reinforcement specifically increases cortical noradrenaline efflux.

- Increased cortical ACh efflux associated with sustained attention performance is reduced during extinction of instrumental (action-outcome) actions.

- These data are consistent with the hypothesis that the coeruleo-cortical system contributes to an upper arousal mechanism that serves to optimize performance in novel situations where processing resources are limited and new behavioral strategies are required.

- The observed dependency of cortical cholinergic transmission on instrumental performance further implicates cortical ACh function in attentional processing.

References and acknowledgements

- Aston-Jones G and Bloom FE (1981) Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. J Neurosci., Aug 1(8): 887-900.

- Dalley JW and Stanford SC (1995) Incremental changes in extracellular noradrenaline availability in the frontal cortex induced by naturalistic environmental stimuli: a microdialysis study in the freely moving rat. J Neurochem., 65(6): 2644-2651.

- Himmelheber AM, Sarter M and Bruno JP (2000) Increases in cortical acetylcholine release during sustained attention performance in rats. Cog Brain Res., 9(3): 313-325.

- Haung T, Yang L, Gitzen J, Kissinger PT, Vreeke M and Heller A (1995) Detection of basal acetylcholine in rat brain microdialysate. J Chromatography B 670: 323-327.

- Passetti F, Dalley JW, O'Connell MT, Everitt BJ and Robbins TW (2000) Increased acetylcholine release in the rat medial prefrontal cortex during performance of a visual attentional task. Eur J Neurosci., 12(8): 3051-3058.

- Sarter M and Bruno JP (2000) Cortical cholinergic inputs mediating arousal, attentional processing and dreaming: differential afferent regulation of the basal forebrain by telencephalic and brainstem afferents. Neuroscience 95(4): 933-952.

This work was supported by the Wellcome Trust and by an MRC Cooperative in Brain, Behavior and Neuropsychiatry.