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Research Report

Impaired visual discrimination learning in anorexia nervosa

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Abstract

The primate dopamine system is involved in appetitively motivated behaviours, including certain forms of learning, for example, visual discrimination learning. Furthermore, food restriction in animals and anorexia in humans is associated with impaired dopamine signaling. Based on this, we hypothesized that patients with anorexia nervosa (AN) would show a deficit in visual discrimination learning. In a dynamic categorization task involving the learning of a series of two-alternative forced-choice visual discriminations, conceptually identical to one shown to activate dopamine neurons in primates, and sensitive to dopaminergic manipulations in humans, patients with AN showed a deficit in learning that was most pronounced in the early stages of acquisition. In contrast, AN showed spared performance on a pattern recognition memory test sensitive to medial temporal lobe lesions, but insensitive to dopaminergic manipulations. We conclude that impaired appetitive function in patients with AN extends to include deficits in visual discrimination learning, and that this deficit represents indirect evidence for altered dopaminergic neurotransmission in AN.

Keywords: Dopamine; Appetitive behaviour; Reward; Affective neuroscience

1. Introduction

The dopamine system has long been implicated in appetitive behaviour, including the processing of food and stimuli that reliably predict the presentation of food (Wise and Rompre, 1989; Robbins and Everitt, 1996; Hoebel et al., 1999; Ikemoto and Panksepp, 1999; Berridge, 2001). Recent experiments have helped to refine this role, indicating a specific role for dopamine in coding reward prediction errors, critical for certain forms of learning (Schultz et al., 1997; Berridge, 2001). For example, Hollerman and Schultz (1998) have shown that during visual discrimination learning, dopamine neurons reflect the changes in reward (or more generally, outcome) prediction during individual learning episodes; they are activated by rewards during early trials, when errors are frequent and rewards unpredictable, but activation progressively reduces as performance is consolidated and rewards become predictable (i.e. as a learning set develops). These, and other findings have lead to the hypothesis that dopamine mediates activity in a 'behavioural approach' (Gray, 1987; Pickering and Gray, 2001); 'behavioural facilitation' (Depue and Collins, 1999) or 'Seeking' (Panksepp, 1982, 1998) system involved in exploratory/investigative behaviors critical for the acquisition of valued biological resources.

Dopamine lesions lead to weight loss and anorexia in animals (Zigmond and Stricker, 1972; Baez et al., 1977; Szczypka et al., 2001) and food restriction leads to altered dopamine system function (Pothos et al., 1995; Kosta et al., 1999). In humans, patients with anorexia nervosa (AN) have impaired dopamine function, as indexed for example by reduced CSF concentrations of the dopamine metabolite homovanillic acid, and altered growth hormone response to apomorphine stimulation (Barry and Klawans, 1976; Gillberg, 1983; Owen et al., 1983; Kaye et al., 1999; Brambilla et al., 2001). We hypothesized that, if dopamine is critical for error-driven learning, and anorexia is associated with impaired dopamine signaling, then individuals with AN should show an impairment in such learning.

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In the current study, we examined the performance of patients with AN and healthy controls on a task comprising a suite of two-alternative forced-choice visual discriminations and reversals (Roberts, Robbins and Everitt, 1988). This task is sensitive to manipulations of dopaminergic neurotransmission, including L-dopa treatment in Parkinson's disease (Lange et al., 1992), and is analogous to discrimination learning tasks shown to activate dopamine neurons in primates (Hollerman and Schultz, 1998). Given our hypothesis, we predicted that patients with AN would be impaired in such learning, perhaps especially during the early stages of the task, when dopaminergic activity should be at a maximum (Hollerman and Schultz, 1998). As a control task, we included a test of pattern recognition memory requiring the detection of stimulus repetitions. This task is sensitive to damage to medial temporal lobe structures (Owen et al., 1995), but is insensitive to dopaminergic manipulations (Lange et al., 1992; Mehta et al., 1999). We predicted no deficit on this task in AN.

2. Method

The participants were 12 female patients meeting DSM-IV criteria (American Psychiatric Association, 1994) for AN and 12 healthy female volunteers. The groups were well matched for both age ($Z = 0.83$, $P = 0.44$) and reading-estimated IQ ($Z = 1.23$, $P = 0.22$) as measured by the National Adult Reading Test (Nelson, 1982), but differed significantly in body mass index (BMI) ($Z = 4.16$, $P < 0.001$), depression as assessed by the Beck Depression Inventory (Beck et al., 1961) ($Z = 3.22$, $P = 0.001$), and state ($Z = 3.61$, $P < 0.001$) and trait ($Z = 3.62$, $P < 0.001$) anxiety as measured by the Spielberger Anxiety Inventory (Spielberger, 1983). Demographic and clinical data are presented in Table 1. Addenbrooke's NHS Trust Research Ethics Committee approved the study and, after the procedure had been fully explained, participants gave written informed consent.

2.1. Visual discrimination learning suite

This test (Roberts, Robbins and Everitt, 1988) comprises a suite of 2-alternative forced choice visual discriminations and their reversals, progressing through an intra-dimensional shift and culminating in an extra-dimensional shift and its reversal.

The task is composed of nine stages presented in the same fixed order, starting with a simple discrimination (SD) and its reversal (SDR) for stimuli varying in just one dimension (e.g. two different white-line configurations) (see Garner (1978) for a discussion of stimulus features and dimensions). A second, alternative dimension is then introduced (purple filled shapes) and compound discrimination (C_P, CP) and reversal (CPR) are tested. To succeed, participants must continue to respond to the previously relevant dimension whilst ignoring the presence of the new, irrelevant dimension. At the intradimensional shift (IDS) stage, novel exemplars of each of the two dimensions are introduced and participants must continue to respond to one of the two exemplars from the previously relevant dimension. Following another reversal (IDR), the extra-dimensional shift (EDS) and its reversal (EDR) are presented, again using novel exemplars of each stimulus dimension. In order to succeed at this stage, participants must shift responding to the previously irrelevant stimulus dimension, whilst ignoring the previously relevant dimension.

At each stage, criterion is six consecutive correct responses. Participants are rewarded with a high-pitch pleasant tone and 'correct' feedback, and punished with a low-pitch tone and 'wrong' feedback.

2.2. Pattern recognition memory

In this task (Sahakian et al., 1988), participants are presented with a series of 12 abstract patterns and their task is to remember them. Following a delay of 5 s, each pattern is re-presented in reverse order paired with a novel pattern and participants are asked to touch the pattern they have seen previously. This procedure is then repeated with a further 12 patterns.

Table 1
Demographic and clinical information on study participants

Group	Age	NART	BMI	BDI	SAI	TAI
AN	25.7 (7.2)	116 (7.4)	15.8 (1.4)	27 (14.0)	55 (14.0)	64 (11.2)
CS	26.7 (6.2)	113 (5.4)	24.4 (4.0)	5 (4.7)	29 (6.4)	36 (10.2)

NB Data represent mean (SD) values. NART, national adult reading test estimated IQ; BMI, body mass index; BDI, beck depression inventory; SAI, Spielberger state anxiety inventory; TAI, Spielberger trait anxiety inventory. AN, anorexia nerrosa patients; CS, healthy controls.

3. Results

The data for the discrimination learning task did not follow a Gaussian distribution (Kolmogorov-Smirnov test, $P < 0.05$), and so errors at each stage were analyzed separately using the non-parametric Mann-Whitney test. A Bonferroni correction was applied, with a significance level P of $(0.05/9) = 0.0056$. The only stage where group differences reached this level was the initial SD learning stage ($Z = 2.87$, $P = 0.004$), with AN making significantly more errors than controls. No significant differences occurred at any other stage (all $Z < 1$, all $P > 0.3$), although AN generally made more errors than controls on most stages of the task (see Fig. 1).

On the pattern recognition memory test, there was no significant group difference ($Z = 0.70$, $P = 0.51$). The mean