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Basal activity of the hypothalamic-pituitary-adrenal axis and cognitive function in anorexia nervosa

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Abstract Anorexia nervosa is associated with abnormalities in neuroendocrine function including sustained hypercortisolism, which has been shown elsewhere to be associated with impairment of function in learning, memory and attention. Cognitive impairment has also been observed in anorexia nervosa. These effects may be mediated in part through cortisol effects on the hippocampus, which is dense with glucocorticoid receptors. We investigated the association between cortisol levels and cognitive function in anorexia nervosa by measuring both 24-hour urinary cortisol counts and performance on tasks of learning, memory and attention in patients suffering from the disorder. Cortisol secretion was shown to be significantly higher in the patient group than in a matched control group and patients were also shown to be impaired in memory and attention. However, no correlations were found between the cognitive deficits and cortisol measures. It is suggested that more sensitive profiling of cortisol levels throughout the circadian cycle may be useful in future studies of cognitive function in anorexia nervosa.

Key Words Anorexia nervosa · Cortisol · Cognition · Neuroendocrine

Background

Anorexia nervosa is a complex psychiatric disorder characterised by a pathological fear of weight gain which results in an extremely disturbed eating pattern. Food intake is severely restricted and patients suffer all the medical effects of starvation. A variety of neuroendocrine abnormalities have been shown to exist in anorexia nervosa, including sustained hypercortisolism (Landon et al. 1966; Warren and Vandeweile 1973; Garfinkel et al. 1975; Vigersky et al. 1976; Boyar et al. 1977; Walsh et al. 1978; Casper et al. 1979; Doerr et al. 1980; Gerner and Gwirtsman 1981; Walsh et al. 1981). This may be severe, with urinary free cortisol excretion reaching levels observed in patients with Cushing's disease or severe depression (Gold et al. 1986). Evidence suggests that cortisol hypersecretion may occur as a consequence of chronic food restriction, rather than being present before the onset of the disorder and as such, amounts to a biological adaptation to starvation (Fichter and Pirke 1990; Kaye et al. 1990).

Previous studies have shown that cognitive function is disturbed in anorexia nervosa (Fox 1981; Hamsher et al. 1981; Maxwell et al. 1984; Witt et al. 1985; Strupp et al. 1986; Palazidou et al. 1990; Pendleton Jones et al. 1991; Szmukler et al. 1992; Kingston et al. 1996). Whilst it is possible that this disturbance arises quite simply as a result of lack of energy availability due to the drastically reduced food intake, it is also possible that the starvation-induced glucocorticoid alterations may play a role. There is evidence that glucocorticoids modulate central nervous system functions involved in stimulus perception and information processing (Carpenter and Gruen 1982; Reus 1984; Rubinow et al. 1984; Wolkowitz et al. 1990; Starkman et al. 1992; Newcomer et al. 1994; Lupien et al. 1994; McEwan and Sapolsky 1995). Recent evidence suggests that these effects may be mediated, in part, through the hippocampus (Diamond et al. 1989, 1992, 1994; Pavlides et al. 1993; McEwan and Sapolsky 1995). This brain structure appears to be particularly sensitive to increased levels of glucocorticoids, possibly because it is dense with glucocorticoid receptors. With high cortisol levels any tasks involving the hippocampus may be impaired. Hence, learning, memory and attentional deficits can be predicted.

One previous study investigated the relationship between cortisol levels and cognitive performance in anorexia ner-

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vosa (Laessle et al. 1992). Patients with anorexia nervosa were found to show an impaired performance in a discrimination task and those patients with higher plasma cortisol levels performed significantly more poorly than patients with lower levels. The authors suggest a possible role of cortisol in the development of attentional deficits in eating disorder patients.

The purpose of the present study was to investigate the relationship between cortisol levels and other aspects of cognitive performance in anorexia nervosa, in addition to attention. The hippocampus is the site of long-term potentiation and elevated levels of glucocorticoids have been shown to disrupt long-term potentiation (Pavlides et al. 1993). It was predicted therefore that impairments of learning and memory, as well as impairments of attention would be shown to exist, and that performance on the tasks assessing these processes would show some relationship with cortisol levels.

Methods

Eighteen female patients satisfying the present Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1995) criteria for a diagnosis of anorexia nervosa (age range 19.3 years to 42.7 years; mean age 27.3 years) and 18 age-matched female control subjects were studied. Patients were all being treated in the Mental Health Unit of the Royal Victoria Infirmary, Newcastle upon Tyne; five as in-patients, the remainder on an out-patient basis. Control subjects were recruited by advertisement from the local population. All control subjects underwent a full psychiatric interview to assess their suitability for taking part. None had any personal or family history of psychiatric or eating disorder. The study received full approval from the local ethics committee.

Cortisol measurement (nmol/24h) was obtained from a 24-hour urine collection, which participants began at 9.00 am on the day preceding testing. Self-report measures of related psychopathology were obtained using the Irritability Depression and Anxiety scale (Snaith et al. 1978). In addition, anorexic attitudes and behaviours were quantified using the Eating Attitudes Test (Garner et al. 1982) and bulimic behaviours (binge/purging) using the Self-Rating Scale for Bulimia (Henderson and Freeman 1987). Pre-morbid IQ was assessed using the National Adult Reading Test (Nelson 1982). Height and weight measurements were also taken to establish body mass index at the time of testing in order to ensure that all patients fulfilled the specified diagnostic criteria for anorexia nervosa.

Cognitive test battery

Cognitive testing consisted of:

- a computer-based vigilance task (Rosvold 1993) which tested the ability of participants to discriminate a target from noise for an eight minute period.
- four subtests of the computerised Cambridge Automated Neuropsychological Test Battery (Park et al. 1994) namely, Pattern Spatial Recognition, Paired Associate Learning, Tower of London and Spatial Working Memory.
- the Auditory Verbal Learning Test (Taylor 1959; Rey 1964). This test assesses both immediate memory for a list of fifteen words, which are presented verbally, and delayed memory for the same words.

Statistical analysis

Clinical ratings were analysed using t-tests. Neuropsychological and urinary free cortisol data were analysed using analysis of variance. The main variable was group (patient or control) and interactions with other variables (e.g. difficulty of test) were examined where appropriate.

Results

Participant characteristics

No significant between-group differences were found with respect to IQ. The patient group however, was found to have significantly elevated levels of irritability, depression and anxiety relative to controls (all p values < 0.0005). Self-report eating disorder symptomatology was also significantly higher in the patient group ($p < 0.0005$).

Cortisol measures

A related samples analysis of variance revealed patients to have significantly elevated levels of urinary cortisol (Patients, Mean (s.d.); 232.28 (105.217): Controls, Mean (s.d.); 149.61 (38.820); $F = 11.99$, *df* 1,17, $p = 0.003$).

Cognitive testing

Patients were shown to be severely impaired on the vigilance task. A two-way, related samples analysis of variance on the number of omissions made by patients and controls in each of the four two-minute periods of the task revealed that patients made significantly more errors of omission than controls throughout the task ($F = 15.52$, *df* 1,17, $p = 0.001$), missing significantly more of the target sequences presented in each two-minute period. A significant interaction effect was also revealed ($F = 5.22$, *df*

Table 1 Mean (and standard deviation) body mass index, IQ and self-report psychopathology measures of patients with anorexia nervosa (N = 18) and matched controls (N = 18)

Dependent measure	Patient	Control	P Value
BMI	15.24 (2.045)	22.133 (1.654)	< 0.0005
IQ	111.50 (9.44)	115.33 (8.07)	0.168
Outward irritability	5.556 (2.955)	3.111 (1.967)	0.003
Inward irritability	7.444 (3.148)	1.000 (1.188)	< 0.0005
Depression	8.0556 (3.152)	2.3889 (1.614)	< 0.0005
Anxiety	8.667 (3.290)	2.611 (1.650)	< 0.0005
EAT-26	37.722 (21.03)	1.667 (1.847)	< 0.0005
BITE	17.611 (8.53)	3.500 (2.333)	< 0.0005

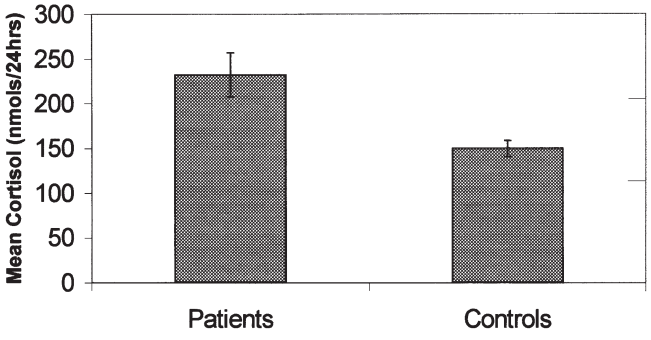

Fig. 1 Mean urinary cortisol level (nmols/24hrs) for patients with anorexia nervosa (N = 18) and matched controls (N = 18)

3,51, p = 0.003) which indicated that the differential performance of patients and controls on the task was particularly pronounced in the first two-minute test period. In order to rule out the possibility of superior performance by controls being attributable to a simple response bias or a patient speed-accuracy trade-off, the number of commissions made by both groups was also analysed, along with mean response latencies. Patients, rather than controls, were shown to make a significantly greater number of commissions, overall (F = 9.99, *df* 1,17, p = 0.006), with the first two minutes again being associated with the greatest difference. No significant between-group differences in response latencies were identified. The data, then reflect an accurate performance by controls on the task and an erratic, poor performance by patients.

There was also evidence of patient impairment on the Auditory Verbal Learning Test. A two-way related samples analysis of variance on the number of items recalled on Trials 1 through to 5 for the patient group and the control group revealed no main effect of group and no interaction effect. Thus, there were no significant differences in the pattern of learning over the five trials shown by patients and controls, as indicated by the immediate free recall scores of participants. However, the analysis did reveal an impaired ability to store the learned material in memory for any period of time. Following the presentation of an "interference" list of a further 15 words and an immediate free recall of those words, a statistical trend was identified (p = 0.08) with patients showing some evidence of forgetting more of the original list than controls. Following a further half-hour delay, this trend reached statistical significance. Patients were able to recall a significantly smaller proportion of the items which they had originally "learned", compared to controls (F = 5.84, *df* 1,17; p = 0.027).

Table 2 Means (and standard deviations) for patients with anorexia nervosa (N = 18) and matched controls (N = 18) on the cognitive tests. Where there is more than one level of difficulty for a particular task, the mean score across all levels or stages is reported (*)
[a] $p < 0.01$; [b] $p < 0.05$ (see text for full details)

	Patient	Control
Vigilance		
Errors of commission[a]	6.944 (7.485)	1.764 (2.153)
Errors of ommission[a]	2.222 (3.716)	0.0556 (0.886)
Latency	456.2 (78.9)	467.8 (91.0)
Auditory Verbal Learning Test		
Immediate (trial 1)	7.667 (2.00)	8.222 (1.957)
Learning (trial 5)	13.611 (2.062)	14.611 (0.979)
AVLT Total (trials 1–5)	58.50 (9.54)	62.61 (6.77)
Interference list (list B)	7.167 (2.662)	8.44 (1.917)
Trial 6	12.278 (2.824)	13.889 (1.367)
Delayed recall (trial 7)[b]	11.50 (3.634)	13.883 (1.618)
Spatial Working Memory		
Between search errors*	7.02 (4.92)	5.444 (4.129)
Within search errors*	0.685 (1.00)	0.4072 (0.3355)
Strategy	32.65 (4.66)	32.71 (4.15)
Tower of London		
Number of excess moves*	0.885 (0.514)	0.6944 (0.3725)
Portion perfect solutions*	67.59 (15.63)	74.54 (12.93)
Motor initiation (ms)*	4150 (1697)	5274 (2354)
Motor execution (ms)*	1472 (1871)	475.3 (404.7)
Paired Associates Learning		
Trials to criterion*	4.019 (2.230)	2.889 (1.279)
Errors	10.15 (9.28)	5.093 (3.768)
Pattern/Spatial Recognition		
Pattern		
Errors	1.611 (1.195)	1.444 (1.294)
Latency	1879.8 (367.0)	2012 (913)
Spatial		
Errors	3.444 (2.121)	2.611 (1.577)

No significant between-group differences in cognitive performance were found on any of the measures arising from the four subtests of the Cambridge Automated Neuropsychological Test Battery.

A series of Pearson correlational analyses revealed no evidence of performance on the cognitive tasks or any of the other measures taken being linearly related to cortisol counts. In order to determine whether a more general trend could be identified, the cortisol measures of the patient group were analysed to determine a median measure for the group, and the performance of the nine patients who had cortisol counts above the median was compared with the performance of the nine patients who had cortisol counts below the median. Using this method, no evidence was found for the higher-cortisol patients being more impaired on the tasks than the lower-cortisol patients.

Discussion

The results of this study show significant impairments in attention and memory in patients with anorexia nervosa when compared to matched, normal controls. In this study, patients with anorexia nervosa had significantly albeit not considerably elevated 24-hour urinary cortisol levels compared to controls. No direct relationship, however, was found between the degree of hypercortisolism and neuropsychological impairment. Previous research has shown similar neuropsychological impairments in this disorder (Fox 1981; Hamsher et al. 1981; Pendleton Jones et al. 1991; Szmukler et al. 1992; Laessle et al. 1992; Kingston et al. 1996) and elevated glucocorticoids are known to be associated with cognitive impairment (Carpenter and Gruen 1982; Reus 1984; Rubinow et al. 1984; Wolkowitz et al. 1990; Starkman et al. 1992; Laessle et al. 1992; Newcomer et al. 1994; Lupien et al. 1994; McEwan and Sapolsky 1995). Hypercortisolism is present in anorexia nervosa and it was therefore predicted that patients suffering from the disorder would show impaired performance on learning, memory and attentional tasks and that some relationship between cortisol levels and cognitive performance in the patient group would be demonstrated.

These results provide partial support for the predictions made. With respect to attention, patients were shown to be severely impaired in their ability to discriminate a target from noise in a vigilance task compared to controls. This finding partially mirrors that of a previous study, in which eating disordered patients (with elevated cortisol levels) were shown to have a significantly lower hit-rate than controls in a similar task of vigilance (Laessle et al. 1992). However, in this previous study, higher morning cortisol levels, measured by serial plasma sampling, were associated with poorer performance on the attentional task in the patient group.

With respect to learning and memory, patients' abilities to learn material for short-term recall did not differ significantly from that of controls. However, an impaired ability to retain material for recall at a later stage was evident. The presentation of a second word list for immediate recall had very little effect upon the ability of control subjects to recall the original word list in the Auditory Verbal Learning Test. Patients, however, showed some evidence of forgetting under these circumstances. Furthermore, following a half-hour delay, patients had forgotten significantly more of the material that they had "learned" compared to controls. This finding may help explain the relative lack of success of re-educative psychotherapeutic packages in patients with anorexia nervosa.

Hippocampal function is altered by corticosteroids (Diamond et al. 1989, 1992, 1994; Pavlides et al. 1993) and this provides a powerful, possible explanation for both the attentional deficit and the selective memory impairment identified in this study. Hippocampal atrophy has been demonstrated in patients with Cushing's disease, and the degree of atrophy correlates with both the degree of cognitive impairment and cortisol levels (Starkman et al. 1992). However, a definite conclusion that the impairments of cognition in anorexia nervosa identified in this study result from hippocampal dysfunction is not yet possible. It is notable that naturally occurring corticosteroids are not necessarily neurotoxic (Hassan et al. 1996). The present study employed 24-hour urine collection as a means of measuring cortisol secretion. This method is crude and somewhat insensitive; future studies should employ more sensitive profiling of cortisol levels throughout the circadian cycle, or ideally the well-established combined dexamethasone/CRH test to investigate the function of the HPA axis in parallel to neuropsychological profiling (von Bardeleben and Holsboer 1989). Furthermore, whilst one previous study (Kingston et al. 1996) has made use of magnetic resonance imaging to investigate the neural basis of cognitive deficits seen in anorexia nervosa, hippocampal volume per se has not been investigated. Disturbed water balance has also been reported in anorexia nervosa (Hannan et al. 1990). This may also contribute to the cognitive deficits we reported although this was not directly examined in this study.

This study constitutes a first attempt at systematically exploring the role of cortisol in a variety of cognitive tasks involving the hippocampus, in patients suffering from anorexia nervosa. Future studies will examine the relationship between circadian cortisol secretion, cognitive function and hippocampal formation volume in this disorder.

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