The HPA axis in depression/HPA-aksen ved depression

Abstract

The HPA axis is hyperactive in depressed patients, possibly leading to enlarged adrenal glands, pituitary gland and hypothalamus compared to healthy controls. The aim of this study was to review studies that have measured adrenal or pituitary gland or hypothalamus volume in depressed patients and healthy controls. 5 studies have examined adrenal glands, 9 have examined the pituitary gland, but no studies on hypothalamus were found. 3 out of 5 studies found a statistically significant increase in adrenal volume in patients and 4 out of 9 studies found a statistically significant increase in pituitary volume in patients. Different methodological problems were identified: small populations, different subtypes of depression and insufficient matching of patients and controls make it necessary with more studies to provide sufficient data.

Resume

HPA-aksen er hyperaktiv hos deprimerede patienter, hvilket muligvis fører til forstørrede binyrer, hypofyse og hypothalamus i forhold til raske kontrolpersoner. Målet med dette studie var at lave en oversigt over studier, der har undersøgt binyre- hypofyse- eller hypothalamusvolumen hos deprimerede patienter og raske kontrolpersoner. 5 studier har undersøgt binyrer, 9 har undersøgt hypofyse, men der blev ikke fundet studier der har undersøgt hypothalamusvolumen. 3 ud af 5 studier fandt signifikant forøget binyre volumen hos patienter og 4 ud af 9 studier fandt signifikant forøget hypofyse volumen hos patienter. Forskellige metodeproblemer blev identificeret: små populationer, forskellige subtyper af depression og insufficient matching af patienter og kontrolpersoner gør det nødvendigt med flere undersøgelser.
Introduction

The HPA axis

Acute and chronic stress leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis. Hypothalamus integrates signals from the thalamus, the reticular-activating substance, the limbic system, the eyes and the neocortex. In the hypothalamus, neurons in the paraventricular nucleus secrete corticotropin-releasing hormone (CRH). CRH is released into the capillary plexus of the superior hypophyseal artery and reaches the pituitary through the long portal vein and the secondary capillary plexus. CRH stimulates the synthesis and release of adrenocorticotropin (ACTH) from the corticotrophs in the pituitary. ACTH reaches the adrenal glands through the systemic circulation and stimulates growth of the cortisol-secreting cells of the adrenal cortex and the synthesis and release of cortisol from the adrenal cortex. Cortisol exerts negative feedback via glucocorticoid receptors (GR) of the pituitary and hypothalamus, by inhibiting secretion of ACTH from the pituitary and CRH from hypothalamus. Thus the secretion of ACTH from the pituitary is controlled by a balance between stimulation from CRH and inhibition from cortisol.

Hyperactivity of the HPA axis in major depression

Many studies, reviewed by Pariante (1) have shown hyperactivity of the HPA axis in depressed patients. This has been shown by hypersecretion of cortisol: increased 24-hour urinary free cortisol, elevated plasma and CSF concentrations of cortisol (reviewed by Nemeroff (2)). Normal levels of ACTH and CRH in spite of hypercortisolism have also been shown (3). This is not seen in normal controls where hypercortisolism leads to decreased levels of ACTH and CRH because of negative feedback. It is believed that the lack of negative feedback in depressed patients is caused by impaired GR function (4). Non-suppression of cortisol and ACTH after dexamethasone administration and blunted ACTH-response after injection of CRH has also been described (5). Both indicating impaired feedback and down regulation of glucocorticoid receptors.

Hyperactivity of HPA axis could lead to enlargement of the organs included: hypothalamus, pituitary gland and adrenal glands; and due to the tropic effect of CRH on the corticotrophs in
the pituitary and ACTH on the adrenal cortex, it is possible that they will be enlarged in depression. Lack of negative feedback on CRH-secreting neurons might have an effect on the size of hypothalamus.

The aim of this study was to do a systematic review of case-control studies of adrenal, pituitary and hypothalamus volume in major depression compared to healthy controls. Due to the limited size of this paper, post mortem studies were not included.
The aim was to study unipolar depression, but it is still not possible to completely distinguish between unipolar and bipolar depression (6).

**Methods**

The method used was to search the PubMed database and the following search profile was used:

((("Hypothalamus"[Mesh] OR "Pituitary Gland"[Mesh]) OR "Adrenal Glands"[Mesh])) AND ("Diagnostic Imaging"[Mesh]))) AND ("Depression"[Mesh] OR "Depressive Disorder"[Mesh]))

To make sure that all relevant studies were included in this review, related articles and references were looked through and “MRI hypothalamic depressive disorder” was used as an extra search profile.

Selection criteria: Original papers that measured volumes of adrenals, pituitary and hypothalamus in depressed patients and healthy controls by CT or MR imaging. Studies that only included bipolar patients were excluded whereas studies with a mix of bipolar and unipolar patients were included.

**Results**

In the systematic search 50 articles were found of which 13 met the criteria for this study. The extra search gave one article that also fit the criteria. No articles on the volume of hypothalamus were found.
Adrenal glands

5 studies on the volume of the adrenal glands were found in the PubMed search. The studies comprised a total of 110 patients and 80 controls. Summarized in table 1.

As the table shows, 3 out of 5 studies show significant increase of adrenal volume in depressed patients compared to healthy controls.

In most studies there were more women than men (50-100% women), and they had mean ages between 36 and 51. Most patients were outpatients and they were classified according to DSM-III, except for the study by Ludescher (7) where the patients were classified according to DSM-IV.

Amsterdam et al (8) examined 16 patients and found that there is not significant increase in adrenal volume in depressed patients. Nemeroff et al (9) examined 38 patients and found that there is a significant increase in adrenal volume; this was also concluded from one study done by Rubin (10) with 11 patients. Another study by Rubin (11), which comprised 35 patients again found that there was increased adrenal volume in depressed patients, whereas Ludescher et al (7) who examined 10 patients, all female, did not find significant adrenal volume increase in patients. In this study the patients were not medication free.

The study by Amsterdam (8) had 13 female and 5 male outpatients with a mean age of 36, all unipolar, major depressive disorder, some first episode, some recurrent. The patients had a minimum score of 20 on the 21-item Hamilton Scale (mean score 23), the length of the present episode varied from 4 to 42 months and patients were drug free for at least 2 weeks before the test. 11 healthy controls, matched by age, height and weight, were also examined. All scans, done with CT Scanner, were analysed by the same person and the status of the subjects was blinded.

The study by Nemeroff (9) had 19 female and 19 male inpatients, all diagnosed with major depression. Length and number of depressive episodes are not mentioned or whether the patients had received any medication. Subjects were physically examined and had a laboratory evaluation and were excluded if findings were known to influence the HPA axis.
Healthy controls, 4 women and 7 men, were recruited by advertisement. Two radiologists graded the CT scans and completely agreed on presence or absence of enlarged adrenals.

One study by Rubin (10) was part of a larger study and had 9 (8 female and 1 male) adult and 2 male adolescent patients and similar individually matched controls. The adults had a median age of 46 and the adolescents were aged 14 and 15. 10 patients had unipolar and 1 had bipolar depression. Patients were only included if they had a primary major depression with a Hamilton score of 17 (21 item) or greater. Some patients had received medication before the study; they underwent a 2- to 3-week drug washout period before testing. They were recruited from the hospital psychiatric emergency, different clinics and practices and through public service announcements. Control subjects were recruited from hospital employees, their family and friends and newspaper announcements. The adrenal gland volume was measured by MR imaging and it was the same technician that obtained all scans. The radiologist that examined the scans was unaware of subject status and patients and controls were assessed in random order.

It is unclear if the patients examined in the study mentioned above are included in the study mentioned below.

The next study by Rubin (11) had 35 patients with major depression, aged 18 to 64 with a mean age of 41, and 35 healthy controls individually matched to the patients for age, sex, race, height, weight and menstrual status for the women. The patients were recruited from the hospital psychiatric emergency, different clinics and practices and through public service announcements. 3 patients had bipolar and 32 had unipolar depression. Only subjects with a primary major depression with a Hamilton score of 17 (21 item) or greater were included. The mean score on the Hamilton scale was 28 with a range from 22-31. All patients had a physical exam and laboratory analysis, and were excluded if they had any psychiatric illness, drug or alcohol abuse or medical illness. A few of the patients had received medication and they were held medication free for 2 to 3 weeks before testing. Control subjects were recruited from hospital employees, their family and friends and newspaper announcements. The adrenal volumes were measured by MR imaging and as for the first study by Rubin the same technician performed all scans and the radiologist was blind to diagnosis and patients and controls were assessed in random order.
Ludescher et al (7) examined 10 female patients, mean age 50, with a depressive syndrome: major depressive episode in unipolar or bipolar disorder (it is not mentioned how many of each), and 12 healthy age-matched women. The Hamilton score was 15 (21 item) or more, mean score 22, the mean number of depressive episodes was 3, and the median duration of the current episode was 9 months. Only subjects without medical or neurological disorder or any addictions were included in the study. The patients received several different kinds of medication. The adrenal volumes were measured by MR imaging.

Pituitary

A total of 9 studies were on the volume of the pituitary gland were found in the Pub Med search. The studies comprised a total of 188 patients and 218 controls. Summarized in table 2. As the table shows, 3 studies by MacMaster et al (12-14) were done with children and adolescents. One study had 17, one had 35 and one had 10 patients, between 53 and 60% were girls. Of these three studies, two showed significant pituitary volume increase in patients, whereas one showed volume increase only in boys. The study by Krishnan et al (15) with 19 patients showed significant increase. The last five studies by Schwartz (16), Sassi (17), Miranda-Scippa (18), Eker (19) and Lorenzetti (20), with 19, 13, 12, 34 and 29 patients respectively, did not show significant increase. All scans were performed by MR imaging. In all studies except Schwartz and Miranda-Scippa the patients were diagnosed according to DSM-IV, in the study by Krishnan DSM-III.

In the study by Krishnan (15) 18 inpatients and 1 outpatient (of which 14 were females) were compared to 19 healthy controls matched by age and sex. The patients had a mean age of 55 and were classified with major depression, 16 had unipolar and 3 had bipolar depression. Only patients who did not receive medication and who did not have any other medical condition that might influence the HPA axis were included in the study. The controls were community volunteers. Two physicians, blinded to the clinical diagnosis, obtained all measurements independently and one neuroradiologist evaluated all the scans.

Schwartz et al (16) examined 19 (13 female, 6 male) patients, mean age 39 years, diagnosed with winter-SAD and 19 sex-, age-, height-, and weight-matched controls. Both groups were recruited
through the local media and all had normal physical exams and routine laboratory tests and were medication free. The severity of depression was measured by The Structured Interview Guide for the Hamilton Depression-SAD version (SIGH-SAD), and patients had a mean score of 27. Two scorers who were blind to status of the subjects measured the scans independently.

Sassi et al (17) studied 23 patients with bipolar disorder, 13 patients with unipolar disorder and 34 healthy controls. Only the patients with unipolar disorder and the healthy controls are considered in this paper. The unipolar group had 12 females and one male and the mean age was 41 years. They had been free of psychotropic medication for at least 4 weeks and had normal physical exams, no history of neurological problems, no comorbid psychiatric disorder and no abuse of alcohol or substances. The patient and the control group had no significant difference in education level, but the unipolar group had a significantly larger number of women than the control group. A trained evaluator blind to status of the subjects obtained the measurements of the pituitary.

In the first study by MacMaster (12) 17 patients, 8 male and 9 female, with a mean age of 17 were compared with 17 matching controls. Controls were recruited through advertisement. All patients had major depressive disorder and the mean duration of illness were 36 months. The Childhood Depression Rating Scale (CDRS) was used to measure severity of the depression and the mean score was 65. Subjects were excluded if they had a history of physical illness. Two patients had a comorbid diagnosis of Substance Abuse and one of Oppositional Defiant Disorder. 3 subjects had started medication within 2 weeks before the test; the others were treatment naïve. One rater made all measurements and was blind to identities of subjects.

The next study by MacMaster (13) comprised 35 patients (15 male, 20 female) with a mean age of 14 years and 35 controls matched by age and sex. All participants had an IQ of 80 or greater. The patients had unipolar major depressive disorder; mean duration of illness was 23 months and mean CDRS-R score was 56. All patients were medication free and had no medical, neurological or other psychiatric illness. One rater made all measurements and was blind to identities of subjects.
The last study by Macmaster (14) had 10 healthy controls, 10 patients with unipolar depression and 10 patients with bipolar depression. Each group had 4 males and 6 females, and the mean age was 16 for the controls and 17 years for the patient groups. This paper only considers the control and the unipolar group. Patients in the unipolar group had a mean score of 71 on the CDRS and patients with neurological or medical illness were excluded. One person made all measurements and was blind to subject identity.

Miranda-Scippa et al (18) studied 12 (5 male and 7 female) patients with depression with a seasonal winter pattern and 12 controls matched for sex, age and phase of menstrual cycle. The patients were selected in a previous study and the controls were recruited by advertisement at a school of medicine. Patients had a mean SIGH-SAD score of 25; 7 patients had a bipolar depression and 5 had a unipolar depression. One patient had used clonazepam; the others had been medication free for at least 3 weeks. One neuroradiologist, who was blind to status of the subjects, calculated the measurements.

Eker et al (19) examined 34 (8 male, 26 female) depressed patients, mean age 32 years. Patients met DSM-IV criteria for MDD and had a minimum of 18 on the 17-item Hamilton Depression Scale. Patients had a mean of 1.4 episodes, the last episode had lasted on average 8 months and all patients had been medication free for at least 4 weeks. Patients were compared to 39 healthy controls matched by age and sex. A well-trained rater who was blind to status of the subjects did all volume tracings.

Lorenzetti et al (20) studied 29 currently depressed patients, 27 remitted depressed patients and 33 healthy controls. The aim of this paper is to look at depressed patients, so the remitted group is ignored here. The depressed group had 22 females and 7 males and they had a mean age of 33 and a mean IQ of 105, the control group was matched for age, sex and IQ. Patients were recruited through advertisement in the local media and via outpatient clinics and all had a diagnosis of MDD. Only 6 patients were medication free. Each pituitary was measured by the same investigator who was blind to the status of the subject.
Discussion

Publication Bias

There may be a tendency that only studies with a positive result are published. In this case it could mean that there might be more studies that do not show a difference, but that have not been published. If this is the case this study may show a tendency in the direction of a difference that is stronger than it is in reality.

Selection Bias

When patients and controls are not selected the same way there is a risk that they come from different social groups who live under different circumstances. For example: if healthy controls who work in the hospital are compared to patients from a lower socio-economic class, the difference in adrenal or pituitary volume might be a result of the patients having lived under stressful circumstances all their lives, and this in itself might give rise to enlarged adrenals or pituitary even if the patients did not suffer from depression.

Adrenal: In the studies by Amsterdam (8) and Ludescher (7) it is not mentioned how the controls were recruited, the study by Nemeroff (9) has recruited controls by advertisement and Rubin (10;11) uses controls recruited from hospital employees, their family and friends and newspaper announcements. Both the study by Nemeroff and the studies by Rubin show an increase in adrenal volume in patients. If the majority of controls in the studies by Rubin come from a higher social class than the patients this could be part of the explanation for the enlarged adrenals in patients found in these studies.

Pituitary: In the studies by Sassi (17) and Lorenzetti (20) controls are matched to patients by education level and IQ respectively and in the study by Schwartz (16) both patients and controls are recruited through local media, which increases the probability that they come from similar circumstances.
In the other studies it is either not mentioned how controls were recruited or they are not recruited the same way as patients. This increases the risk that patients and controls come from different social groups leading to a false result of the comparison.

There seems to be little correlation between negative result and matching of controls, though all studies with well-matched controls do not find a significant volume difference between patients and controls.

**Confounders**

**Substance or alcohol Abuse:**

**Adrenal:** Patients were excluded from the studies if they had alcohol or substance abuse.  
**Pituitary:** In the studies by Krishnan (15), Schwartz (16), MacMaster (14) and Miranda-Scippa (18) it is not mentioned if subjects with alcohol or substance abuse were excluded; in one study by MacMaster (12) there were two subjects with substance abuse, whereas subjects with abuse were excluded in the studies by Sassi (17), Eker (19) and Lorenzetti (20). Abuse of alcohol or substances could alter the HPA axis function, so that abuse would lead to false results, therefore it would be a better strategy to exclude patients with addictions.

**Other illness:**

In all studies except the ones by Miranda-Scippa (18) and Lorenzetti (20) it is mentioned that patients with medical or neurological illness were excluded. This could influence the results since these disorders might alter the HPA axis function. On the other hand patients with the above mentioned disorders might have been excluded from the studies even though it is not mentioned.

**Blinding**

Except for the study by Ludescher (7), all studies mention that the radiologist or rater was blind to the status of the subject, to avoid that measurements or conclusions are coloured by expectations. The radiologist in the study by Ludescher could have been blinded even though it is not mentioned, but if this is not the case it could have influenced the results.
Size of the studies

Adrenal: The studies by Amsterdam (8) and Ludescher (7), with 16 and 10 patients respectively, both showed increased adrenal volume in patients, but the increase was not significant. If the patient populations had been larger, the same increase could have been significant, given that it was a true increase. If that was the case all studies would have shown significant adrenal volume increase in depressed patients. But because of the small sizes of the populations the increases found in the two studies could also be a coincidence and larger populations might have revealed that there was not a true increase in depressed patients.

Pituitary: Most of the studies were very small; only 3 studies had more than 20 patients. Small populations give low statistical force, which means there is a risk that the results do not reflect reality.

Medication

Adrenal: In the study by Ludescher (7) the patients received different kinds of medication, in the studies by Amsterdam (8) and Rubin (10;11) the patients had been medication free for at least 2 weeks, and Nemeroff (9) does not mention anything about medication. Medication could normalize the HPA axis function explaining the negative result found by Ludescher (7), but Amsterdam (8) does not find a significant increase even though the patients are medication free.

Pituitary: In the studies by Krishnan (15), Schwartz (16), Sassi (17), one study by MacMaster (13) and Eker (19) all the patients were medication free, but in the other 4 studies a varying proportion of the patients were receiving medication. This may have an effect on the results since the medication is known to influence the HPA axis but it does not seem to correlate with the results since 3 out of 5 studies with medication free patients found no significant increase, one study did find significant increase and one study found significant increase in boys but not in girls. Of the 4 studies where some patients received medication 2 found a significant increase and 2 did not.
Rubin’s critique of Nemeroff’s study

Rubin states in a comment in Archives of General Psychiatry (21) that there is problems with Nemeroff’s study (9). He finds that the measured adrenal volumes are too large and more like Cushing’s syndrome size, and therefore it must be a measuring problem rather than real enlarged volumes. He concludes that it is likely that there is a calibration problem with the CT scan rather than increased adrenal volume in the depressed patients. Nemeroff answers that there are other studies of adrenal volume that have found adrenals the same size as what they find in his study. This discussion suggests that the measuring methods are different and therefore the studies are not adequately comparable.

Different subtypes of depression

Some studies specifically excluded patients with a bipolar disorder whereas other included them and put unipolar and bipolar depression in the same group. It has been shown that patients with bipolar disorder have smaller pituitaries than normal controls (17).

The study by Ludescher (7) with a patient group consisting of women with unipolar or bipolar depression and the study by Miranda-Scippa (18), which had 7 bipolar out of 12 patients, did not show increased pituitary volume in depressed patients. As mentioned above patients with a bipolar disorder may have smaller pituitaries than healthy controls and if one assumes that patients with a unipolar disorder have larger pituitaries than healthy controls, the mix of unipolar and bipolar patients could result in a mean pituitary volume equal to healthy controls and therefore it is not surprising that these studies do not find a volume difference between patients and controls.

The studies by Schwartz (16) and Miranda-Scippa (18) both examined patients with a seasonal depression and did not find a significant increase in pituitary volume, and this is in line with previous reports that states that seasonal depression is not associated with HPA-axis hyperactivity (22;23).
General discussion and conclusion

Adrenal: Inappropriate matching of patients and controls in the two studies by Rubin (10;11) questions the increase found in these studies. Too small populations question the negative results in the studies by Amsterdam (8) and Ludescher (7). The negative result in the study by Ludescher is further questioned by the fact that the patients were not medication free. One could argue that the results from the studies that find a significant volume increase in patients are false negative due to selection bias, but one could also argue that the studies that find no significant volume increase in patients could be false negative due to too small populations. This review shows that there seems to be a correlation between depression and enlarged adrenal glands, but the small sizes of the studies and the methodological problems questions the correlation and calls for larger studies and stricter methodology.

Pituitary: The studies that have measured pituitary volumes are very different and therefore difficult to compare. There are 3 studies with children and adolescents (12-14), one study with inpatients (15), two studies with patients with a seasonal depression (16;18), one study where most patients were on medication (20) and studies with adults with no specific marks (17;19). 4 studies show increased pituitary volume in patients but 3 of these are the studies with children and adolescents (12-14) and might reflect that their bodies and brains are still developing. Further studies with clear methodology are required in order to clarify the correlation between depression and pituitary volume.

Perspectives

Studies with larger populations, medication free patients and better matching between patients and controls would be required to make a conclusion. To avoid bias, patients and controls must be matched for age, sex, premorbid IQ and education level.
Reference List


(4) Pariante CM. The glucocorticoid receptor: part of the solution or part of the problem? J Psychopharmacol 2006 Jul;20(4 Suppl):79-84.


