Hypothalamus and pituitary volume in schizophrenia: a structural MRI study

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Abstract
Volumetric differences of the hypothalamus and/or the pituitary gland tend to support involvement of the HPA axis in psychotic disorders. These structures were manually outlined in 154 schizophrenia patients and 156 matched healthy comparison subjects by MRI brain images. Linear regression analyses were performed to investigate differences in volume between groups. Moreover, the effects of illness duration and type of medication were investigated. No significant differences were found between patients and healthy controls in volumes of the hypothalamus and pituitary gland. In addition, there were no differences in volumes between patients with short and long illness duration. There was a trend towards patients receiving typical antipsychotic medication at the time of scanning having larger pituitary volumes than patients receiving atypical medication. These findings indicate that volume decreases in brain structures important for the normal functioning of the HPA axis are not present, either in recent-onset or chronically ill patients.

Key words: Hypothalamus, pituitary gland, schizophrenia, structural magnetic resonance imaging.

Introduction
There is convincing evidence that stressful life events can trigger psychosis in individuals with a genetic predisposition to be vulnerable for stress (Corcoran et al. 2003; Gispen-de Wied & Jansen, 2002). An important model aiming to explain the underlying (neuro)biological mechanisms is the neural diathesis-stress model for schizophrenia (Walker & Diforio, 1997). The hypothalamic–pituitary–adrenal (HPA) axis plays a leading role in this model. In response to psychological and/or physiological stressors, neural signals are converted into an endocrine response at the level of the hypothalamus, which results in activation of the pituitary gland and finally release of the stress hormone cortisol by the adrenal gland. A prominent role for the HPA axis in the development of psychotic disorders like schizophrenia has been suggested (Walker et al. 2008).

Volumetric differences of the hypothalamus and/or the pituitary gland tend to support involvement of the HPA axis in psychotic disorders. As reviewed by Pariante (2008), the most notable findings so far are: (1) increases in pituitary volume during the prodromal phase and shortly after psychosis onset; (2) decreases in volume in chronically ill patients; and (3) additional enlarging effects as a result of antipsychotic medication intake, particularly for typical antipsychotics (Nicolo et al. 2010). Smaller (Goldstein et al. 2007) as well as larger (Hulshoff Pol et al. 2005; Koolschijn et al. 2008) hypothalamus volumes have been reported. However, these studies consisted only of small samples of patients and the latter two studies differed notably from the Goldstein et al. study in segmentation procedures and boundaries that were used. The aim of the current study is to compare the volumes of the pituitary gland and the hypothalamus between patients with schizophrenia and healthy comparison subjects by means of structural magnetic resonance brain images. To our knowledge, this is the first study to investigate the volumes of both these structures in the same group of subjects and to include a relatively large sample. Since it has been suggested that disease duration and medication intake (typical/atypical and
prolactin enhancing/sparing) might affect pituitary volume (Pariante, 2008), these variables were taken into account.

Method

Subjects

A total of 159 patients with schizophrenia and 158 healthy comparison subjects were included. All subjects received a magnetic resonance imaging (MRI) scan of the brain as part of a study investigating structural brain abnormalities in schizophrenia (Hulshoff Pol et al. 2002). For the current study, 154 patients and 156 controls were included (some data were lost because the quality of scans was too poor to perform manual segmentation).

The presence or absence of psychopathology was established for all subjects using the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al. 1992) and was assessed by two independent raters; diagnostic consensus was achieved in the presence of a psychiatrist. Age at onset of illness was defined as the first time a patient experienced psychotic symptoms, as obtained from the CASH interview. Duration of illness was defined as the time between age of onset and age at scan acquisition. Details of recruitment have been described previously (Hulshoff Pol et al. 2002). All patients were receiving antipsychotic medication at the time of their scan. (See Table 1 for the demographic characteristics.) This study was approved by the medical ethics committee for research in humans of the University Medical Center Utrecht, The Netherlands. Written informed consent was obtained from all subjects.

Imaging

All images were acquired on a Philips NT scanner operating at 1.5 T. T1-weighted three-dimensional fast-field echo (3D-FFE) scans with 160–180 contiguous coronal slices [echo time (TE) = 4.6 ms, repetition time (TR) = 30 ms, flip angle = 30°, 1 × 1 × 1.2 mm³ voxels], and T2-weighted dual echo–turbo spin echo (DE-TSE) scans with 120 contiguous coronal slices (TE1 = 14 ms, TE2 = 80 ms, TR = 6350 ms, flip angle = 90°, 1 × 1 × 1.6 mm³ voxels) of the whole head were used for quantitative measurements. MRI processing methods have been described previously (Hulshoff Pol et al. 2002). Images were coded to ensure investigator blindness to subject identification and diagnosis; scans were placed into Talairach frames without scaling and corrected for inhomogeneities in the magnetic field. Segmentation of the hypothalamus, its mamillary bodies and the pituitary gland were performed following protocols developed at our institute, using Display (http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC). A segmentation protocol for the hypothalamus had been developed previously (Hulshoff Pol et al. 2006), but was changed to include the separate segmentation of the mamillary bodies. For 119 subjects a hypothalamus segment was already present; these were adjusted according to the new protocol. Tracing was performed slice by slice on T1-weighed images in coronal orientation. Axial and sagittal orientations were used for reference when the segmentation boundaries in the coronal view were unclear.

Mamillary bodies (Fig. 1a, b):

Anterior: first coronal slice in which the mamillary bodies ‘pop up’ as part of the hypothalamus.
Lateral: darker grey of the hypothalamus or the bundles of white matter that surrounds it.
Dorsal: floor of the 3rd ventricle.
Ventral: CSF-filled suprasellar cistern.
Posterior: very last slice in which the mamillary bodies are still visible.
This resulted in an average of five slices in which the mamillary bodies could be traced.

Hypothalamus (Fig. 1a, b):

Anterior: first coronal slice after the anterior commissure (AC).
Posterior: mamillary bodies.
Dorsal: AC–PC (posterior commissure) plane in transversal section, which approximates the hypothalamic sulcus.
Ventral: where the optic chiasm, infundibular stalk or the mamillary bodies begin.
Lateral: bundles of white matter.
This resulted in an average of 10 slices in which the hypothalamus could be traced. The third ventricle is removed from the segments by multiplying the segment with the whole brain mask.

Pituitary gland (Fig. 1c, d):

Anterior and ventral: sphenoid sinus.
Lateral: cavernous sinuses.
Posterior: dorsum sellae.
Dorsal: diaphragma sellae.
The infundibular stalk was excluded from the segment. This resulted in an average of 10 slices in which the pituitary gland could be traced.

All segmentations were performed by A.K. The intra-rater reliability of the volume measurements
determined by the intra-class correlation coefficient (ICC) in 10 brains was as follows: hypothalamus (ICC = 0.96), mamillary bodies (ICC = 0.86), and pituitary gland (ICC = 0.96).

**Statistical analysis**

Groups were compared on demographic variables, using an independent-samples t test for continuous variables and Pearson’s χ² for categorical variables. Group differences in the volumes of the hypothalamus (including and excluding the mamillary bodies), the mamillary bodies, and pituitary gland were examined using linear regression analysis with the volume of interest as dependent variable, and group, age, sex, and intracranial (IC) volume as independent variables. For significant group differences the analyses were repeated adding total brain (TB) volume instead of IC volume as an independent variable. In addition, main effects of age and sex and their interaction with group were investigated.

The patient group was divided in two subgroups based on the type of medication used at the time of scan (typical or atypical antipsychotic medication) or on illness duration (<2 yr or ≥2 yr). For a subsample of patients (n = 106), detailed information about medication intake was available making it possible to investigate the effect of using prolactin-enhancing (all typical medication and the atypicals risperidone and amisulpiride) or prolactin-sparing (all other atypicals) antipsychotic medication. Volumes of interest were compared between groups using linear regression analyses with volume of interest as dependent variable, group [typical/atypical or prolactin-enhancing/prolactin-sparing or illness duration (<2 yr or ≥2 yr)],

### Table 1. Demographic, clinical and volumetric information for both groups

<table>
<thead>
<tr>
<th>Characteristic or measure</th>
<th>Schizophrenia patients (N = 154)</th>
<th>Healthy control subjects (N = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>109/45</td>
<td>34.8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>16.9–67.5</td>
<td>10.8</td>
</tr>
<tr>
<td>Handedness (right/left)</td>
<td>132/22</td>
<td>10.8</td>
</tr>
<tr>
<td>Level of educationa (yr)</td>
<td>10.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Age of first symptoms (yr)</td>
<td>21.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Illness duration (yr)</td>
<td>(0.4–51.5)</td>
<td>14.0</td>
</tr>
<tr>
<td>Medication at time of scan (typical/atypical/unknown)</td>
<td>74/62/18</td>
<td>1410.4</td>
</tr>
<tr>
<td>Patients with extended information on (lifetime)</td>
<td>58</td>
<td>(11.0–3401.3)</td>
</tr>
<tr>
<td>medication intake</td>
<td>21</td>
<td>0.138</td>
</tr>
<tr>
<td>Prolactin-enhancingb</td>
<td>26</td>
<td>0.037</td>
</tr>
<tr>
<td>Prolactin-sparring</td>
<td>11</td>
<td>0.139</td>
</tr>
<tr>
<td>Medication freec or unknown</td>
<td>11</td>
<td>156</td>
</tr>
<tr>
<td>Cumulative medication intake (HEQ)d (range)</td>
<td>38</td>
<td>1096.0</td>
</tr>
<tr>
<td>Hypothalamus (no mamillary bodies)e</td>
<td>153</td>
<td>1.042</td>
</tr>
<tr>
<td>Mamillary bodies</td>
<td>154</td>
<td>0.227</td>
</tr>
<tr>
<td>Pituitary gland</td>
<td>149</td>
<td>0.636</td>
</tr>
</tbody>
</table>

N gives the total number of reliable segments per structure in each group.

a Not matched for subject’s level of education.
b Prolactin-enhancing: typical antipsychotics, risperidone, and amisulpiride. Prolactin-sparring: any of the other atypical antipsychotics.
c Medication free: no medication for at least 1 month at the time of scan acquisition.
d Cumulative antipsychotic medication intake: the total amount of medication (lifetime) used at the time of scan acquisition in haloperidol equivalents (HEQ).
e Due to segmentation difficulties (e.g. blood vessels blocking view of the structure, poor quality scans, borders indefinable, etc.), it was not possible to obtain a reliable segment of all three structures in every participating subject.
age, sex and IC as independent variables. Finally, within each illness-duration group those on typical antipsychotic medication were compared to those on atypical medication, and those with prolactin-enhancing medication were compared to those without for all volumes (for numbers per group see Table 2. The SPSS 17.0 statistical package for Windows (SPSS Inc., USA) was used for all statistical analyses. All linear regression analyses were performed with a two-tailed alpha level of 0.05.

### Results

Uncorrected mean volumes of the hypothalamus, mamillary bodies and pituitary gland for both groups are shown in Table 1. There were no significant differences between patients with schizophrenia and healthy control subjects for the hypothalamus \([b = -0.01\ (s.e. = 0.01) \text{ ml}, p = 0.49]\), mamillary bodies \([b = -0.002\ (s.e. = 0.004) \text{ ml}, p = 0.53]\), and the pituitary gland \([b = 0.02\ (s.e. = 0.01) \text{ ml}, p = 0.26]\).

Main effects for sex were found for the hypothalamus [including the mamillary bodies; \(b = 0.05\ (s.e. = 0.02) \text{ ml}, p = 0.01\]; larger volumes in males compared to females] and the pituitary gland [\(b = -0.09\ (s.e. = 0.02) \text{ ml}, p < 0.001\]; larger volumes in females compared to males]. For the mamillary bodies separately a main effect for sex was significant at trend level \((p = 0.065)\). No group \times sex interaction effects were found.

A main effect for age was found for hypothalamus \([b = -0.004\ (s.e. = 0.001) \text{ ml}, p < 0.001]\). While no significant main effect for age was found in the mamillary bodies, there was a significant interaction effect

### Table 2. Number of patients on typical/atypical or prolactin-enhancing/sparing medication for both recent-onset (illness duration < 2 yr) and chronically ill (illness duration \(\geq 2\) yr) patients

<table>
<thead>
<tr>
<th>Illness duration</th>
<th>&lt; 2 yr</th>
<th>(\geq 2) yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin-enhancing</td>
<td>10</td>
<td>68</td>
</tr>
<tr>
<td>Prolactin sparing</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Typical</td>
<td>9</td>
<td>65</td>
</tr>
<tr>
<td>Atypical</td>
<td>12</td>
<td>18</td>
</tr>
</tbody>
</table>

Five patients did not receive medication at the time of scan (i.e. they were not medication-naive). One patient received both typical and atypical antipsychotic medication at the time of scan.

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![Fig. 1. The hypothalamus, mamillary bodies and pituitary gland by magnetic resonance imaging (MRI). The hypothalamus (red) and the mamillary bodies (green) in a coronal T1-weighed MR image, (a) without and (b) with segment. The pituitary gland (red) in (c) coronal-oriented and (d) sagittal-oriented T1-weighed MR image.](https://academic.oup.com/ijnp/article-abstract/15/2/281/656340)
between group and age \( [b = 0.001 \text{ (s.e. = 0.001) ml, } p = 0.02] \) representing an larger increase of 0.001 ml/yr (0.4\%) in patients compared to controls. Controls showed only a very subtle decrease with increasing age. No main effects of age or group \( \times \) age interaction were found for the pituitary gland.

No significant differences in hypothalamic or pituitary volumes were found between patients with short-duration of illness \( (< 2 \text{ yr, } n = 26) \) and long-duration of illness \( (\geq 2 \text{ yr, } n = 127) \). The patient group with an illness duration of < 2 yr \( [\text{mean } 1.19 \text{ yr (s.d. = 0.43)}] \) represents a recent-onset sample. The two patient groups that resulted after dividing on illness duration were, due to the high correlation between illness duration and age (Spearman’s \( \rho = 0.87 \) \( p < 0.001 \)) not matched for age.

Patients receiving typical antipsychotic medication at time of scanning \( (n = 75) \) had larger pituitary volumes than patients receiving atypical medication \( (n = 67) \) \( [b = -0.04 \text{ (s.e. = 0.02) ml, } p = 0.05] \). No differences in hypothalamic or pituitary volumes were found between patients taking prolactin-enhancing medication \( (n = 80) \) and patients taking medication that did not affect prolactin levels \( (n = 26) \).

In recent-onset or chronically ill patients no significant differences were found in any of the brain volumes between patients on typical or atypical medication. In recent-onset patients, pituitary volume was significantly smaller in those taking prolactin-sparing medication \( (n = 10) \) compared to those taking prolactin-enhancing medication \( (n = 12) \) \( [b = -0.11 \text{ (s.e. = 0.05) ml, } p = 0.05] \). No further significant differences were found for any of the volumes in either of the illness-duration groups between those patients taking typical vs. atypical or prolactin-enhancing vs. prolactin-sparing medication.

**Discussion**

Findings of abnormal HPA axis functioning in schizophrenia have suggested an important role for the biological stress system. Volumetric abnormalities in hypothalamus and/or pituitary gland in patients would strengthen this theory. No significant volumetric differences between patients with schizophrenia and healthy controls were found in these structures.

Presuming abnormal HPA activity in this sample of schizophrenia patients, our findings suggest that this does not necessarily influence the size of some of the crucial structures involved. This brings us to an important limitation of this and previous studies: none of the studies that looked at volumetric differences of the pituitary or hypothalamus in schizophrenia have looked at hormonal levels at the time of scan acquisition. Therefore, it cannot be verified whether HPA axis activity was indeed abnormal in these patient groups; this can only be presumed on the basis of the available literature (for reviews see Walker & Diforio, 1997; Walker et al. 2008).

Previous studies of our group (Hulshoff Pol et al. 2005; Koolschijn et al. 2008) excluded the mamillary bodies from the hypothalamus segment, because of their distinct morphology and origin in relation to other hypothalamic nuclei (Keyser, 1979). However, the study of Goldstein et al. (2007) included the mamillary bodies and suggested that the increase they found in hypothalamic volume could, at least partially, be explained by enlargement of these nuclei. This is in line with post-mortem findings of enlarged mamillary bodies in schizophrenia (Briess et al. 1998). Therefore, we changed our segmentation protocol to include the mamillary bodies but we were unable to replicate their findings.

Considering the HPA axis and the role of the hypothalamus, the main focus should probably not be on the mamillary bodies, but on the paraventricular nucleus (PVN). The PVN lies adjacent to the third ventricle in the periventricular zone of the front half of the hypothalamus. The PVN is functionally associated with the posterior lobe of the pituitary gland. It is the hypothalamic nucleus that produces the precursor of cortisol, corticotropin-releasing hormone (CRH). The PVN is, however, a small nucleus and is difficult to detect on the T1-weighted images that are acquired at 1.5 T. Whether changes in the volume of this nucleus alone affects the volume of the entire hypothalamus is unknown.

The pituitary gland is not part of the brain but it is a hormonal gland and is known to vary in size when activated (e.g. in pregnancy). We found no effect of disease or illness duration on pituitary volume. It has been suggested that effects of illness duration and medication use influence pituitary volume in schizophrenia (for review see Pariante, 2008). Indeed, volumetric increase has been found in high-risk individuals that made the transition to psychosis, in the prodromal phase, during early psychosis and in schizotypal patients (Buschlen et al. 2011; Garner et al. 2005; Takahashi et al. 2009). It is not clear yet if this is an effect of HPA axis activation caused by the upcoming disease or that there is a genetic predisposition to heightened HPA axis activity, since enlarged pituitary volumes were also found in family members of psychosis patients (Mondelli et al. 2008). The effects on pituitary volume in chronically ill...
patients remain unclear, as both smaller (Pariante et al. 2004; Upadhyaya et al. 2007) and normal volumes (Tournikioti et al. 2007) have been reported. It has been suggested that chronic activation of the HPA axis will lead to a decrease in pituitary volume in those that have been ill for a long time, but that this can be masked by an increase in volume due to chronic prolactin-enhancing medication use (MacMaster et al. 2007; Pariante, 2008). Longitudinal studies showed excessive volume increases in the pituitary gland over time during the early course of the schizophrenia spectrum (MacMaster et al. 2007; Takahashi et al. 2011), but a non-significant loss has also been reported (Nicolo et al. 2010). Recently, reviews of the literature concluded that there is an association between intake of antipsychotic medication and brain volume (change) in patients with schizophrenia.

Most likely, effects of medication are dependent on type of medication as well as location in the brain (Moncrieff & Leo, 2010; Navari & Dazzan, 2009; Smieskova et al. 2009). Indeed, in a large longitudinal study it was shown that typical antipsychotics appear to be associated with larger brain volume loss over time while atypical antipsychotics tend to ameliorate the tissue loss (Van Haren et al. 2007, 2008). This is in line with findings from a randomized control trial showing greater loss of grey-matter volume in those patients who were taking haloperidol compared to those on olanzapine (Lieberman et al. 2005). In contrast, there are both human and animal studies that provide evidence for volume loss being associated with higher dose of atypical antipsychotic medication (Dorph-Petersen et al. 2005; Ho et al. 2011; Vernon et al. 2011). Relevant for the current study are the findings from Nicolo et al. (2010) and Pariante et al. (2005). Using a cross-sectional design, little volume differences were found between medication-free patients and those receiving atypical antipsychotics. However, those patients that received typical antipsychotics had the largest pituitary volumes. Interestingly, Nicolo et al. (2010) showed a negative correlation between change in pituitary volume dose of atypical antipsychotic, indicating a larger tissue loss in the pituitary gland in the presence of a higher dose of atypical antipsychotics. In addition, MacMaster et al. (2007) found a pituitary volume increase over time in patients that were neuroleptic-naive at baseline. This increased seemed driven by the prolactin-enhancing antipsychotic risperidone.

Our findings on the effects of medication use support this notion. We see a trend towards an enlarging effect of typical medication use on pituitary volume in the total sample. Moreover, in recent-onset patients only, those who were taking prolactin-sparing medication had smaller pituitary volumes relative to those on prolactin-enhancing medication, which is in line with previous findings (MacMaster et al. 2007). However, the groups were rather small to reliably investigate the effects of type of medication, cumulative dose of antipsychotic medication or illness duration. Next to including hormonal levels, all future studies should therefore control for conditions that could enhance neuroendocrine activity, such as (antipsychotic) medication use.

In the patient group, mamillary body volume increase was more pronounced with age compared to the control group (on average 0.4%/yr). Since age had almost no effect on mamillary body volume in healthy subjects and because age and disease duration are highly correlated, the excessive increase could be an effect of disease duration. However, age-related decreases of the mamillary bodies have also been described (Raz et al. 1992; Sheedy et al. 1999). In the total sample, hypothalamic volume decreased with age, with an average decrease of 0.004 ml/yr. As far as we know, no studies have looked into the effects of ageing in the volume of this structure.

Pituitary volume was significantly increased in females compared to males; their pituitary volume was on average 0.09 ml higher (~14%). Males were found to have significantly greater hypothalamus volumes than females (on average 0.05 ml; ~4%). These sex effects are in line with previous findings (Hulshoff Pol et al. 2005; Koolschijn et al. 2008; Pariante et al. 2004, 2005; Upadhyaya et al. 2007).

In conclusion, our findings indicate that volume decreases in the hypothalamus and pituitary gland, which are important brain structures for normal functioning of the HPA axis, are not present, either in recent-onset or chronically ill patients.

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None.

Statement of Interest

None.

References


