Structural Changes of the Brain in Relation to Occupational Stress

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Despite mounting reports about the negative effects of chronic occupational stress on cognitive functions, it is still uncertain whether and how this type of stress is associated with cerebral changes. This issue was addressed in the present MRI study, in which cortical thickness (Cth) and subcortical volumes were compared between 40 subjects reporting symptoms of chronic occupational stress (38 ± 6 years) and 40 matched controls (36 ± 6 years). The degree of perceived stress was measured with Maslach Burnout Inventory. In stressed subjects, there was a significant thinning of the mesial frontal cortex. When investigating the correlation between age and Cth, the thinning effect of age was more pronounced in the stressed group in the frontal cortex. Furthermore, their amygdala volumes were bilaterally increased (P = 0.020 and P = 0.003), whereas their caudate volumes were reduced (P = 0.040), and accompanied by impaired fine motor function. The perceived stress correlated positively with the amygdala volumes (r = 0.44, P = 0.04; r = 0.43, P = 0.04). Occupational stress was found to be associated with cortical thinning as well as with selective changes of subcortical volumes, with behavioral correlates. The findings support the hypothesis that stress-related excitotoxicity might be an underlying mechanism, and that the described condition is a stress-related illness.

Keywords: amygdala, caudate, cortical thickness, emotional modulation, stress

Introduction

Western societies are facing increasing reports of stress-related sickness among otherwise healthy and high-performing persons who report that they have not experienced any major negative life events or particular stress in early life (Aholan et al. 2006; Fernandez Torres et al. 2006; Rydmark et al. 2006; Copertaro et al. 2007, 2010). These persons describe having stereotyped symptoms, including memory and concentration problems, sleeplessness, diffuse aches, profound fatigue, irritability, anxiety, and a feeling of being emotionally drained, which they often attribute to occupational stress. Even though many individuals recover from the acute symptoms, the cognitive and emotional dysfunction as well as the increased sensitivity to stress often last for months, or years, forcing the affected individuals to work part-time, change jobs or retire early. The condition is often designated as occupational burnout, a label, which will be used operatively in the article. Its mechanisms are largely unknown, but there is reason to believe (Jovanovic et al. 2011; Backstrom et al. 2013; Blix et al. 2013) that this condition should be primarily investigated in the context of stress pathophysiology.

The predominant conceptual definition of stress, initially defined by Lazarus and Folkman (1987), suggests that stress may be thought of as resulting from an “imbalance between demands and resources.” This interpretation focuses on the transaction between people and their external environment and is known as the transactional model. The transactional model contains several core elements:

- Primary appraisal, which is the evaluation of the significance of a stressor or threatening event.
- Secondary appraisal—defined as evaluation of the controllability of the stressor and a person’s coping resources.
- Coping efforts—actual strategies used to mediate primary and secondary appraisals.

The typical mode of behavior in subjects describing stereotyped symptoms from occupational stress seems to comprise an underestimation of the significance of occupational load, acceptance of high workload, and a feeling that the work situation can be controlled by increasing the working hours. This maladaptive coping effort and strategy results in a drastically reduced recuperation, sleep problems, fatigue, and subsequently to cognitive (Sandstrom et al. 2005; Jovanovic et al. 2011) and emotional dysfunction with impaired ability to modulate emotion (own unpublished data). While initially not appraising work as a stressor, but rather a positive challenge, they end up with a strong demand-control imbalance leading to emotional conflict with a presumable overactivation of the prefrontal networks (Egner et al. 2008) and perception of stress.

The major pathways of the physiological response to stress involve the autonomic nervous system as well as the hypothalamic–pituitary–adrenal (HPA) axis (Ulrich-Lai and Herman 2009). Although an alteration in the reactivity of the HPA system is believed to occur in subjects suffering from symptoms attributed to chronic occupational stress, this does not seem to be a consistent finding (Fries et al. 2009), as various studies have found normal (Mommerteg, Heijnen et al. 2006; Langelaa et al. 2007), reduced (Pruessner et al. 1999; Moch et al. 2003; Mommerteg, Keijsers, et al. 2006; Chida and Steptoe 2009), and elevated (Melamed et al. 1999; Grossi et al. 2003, 2005) cortisol levels after awakening. Because many stressed subjects report anxiety, sleeplessness, and poor initiation, their illness is frequently diagnosed as depression. It seems, however, to represent a separate construct, even if some symptoms (such as anxiety and attention and memory deficits) may overlap with depression. Only a minor portion of those suffering from symptoms related to occupational stress are helped by antidepressants (Asberg et al. 2010) and, in contrast to many patients with major depression (Fries et al. 2008), individuals with occupational stress have shown reduced cortisol and adrenocortico hormone responses to the corticotropin-releasing hormone after dexametason pretreatment (Rydmark et al. 2006; Wahlberg et al. 2009).

The described cognitive and emotional symptoms, as well as fatigue suggest that major limbic and paralimbic networks may be involved, which raises the question of whether
structural changes occurred in these networks. In a recent study using positron emission tomography, we found that patients suffering from chronic occupational stress and burnout symptoms had significant reductions in the 5-HT1A receptor binding in 5 limbic structures: the hippocampus, the anterior cingulate cortex (ACC), and the anterior insular cortex (Jovanovic et al. 2011). In addition, there was a functional disconnection between the amygdala and the medial prefrontal cortex (mPFC), including the ACC, despite an absence of psychiatric comorbidity and major negative life events (Jovanovic et al. 2011). The locations of these changes, in several aspects, corresponded to the locations of structural changes detected through MRI in persons suffering from other stress-related conditions, such as stress in early life, repeated stressful negative life events, and post-traumatic stress disorder (PTSD) (Wang et al. 2000; Cohen et al. 2006; Pavlisa, Papa, Pavic, Pavlisa 2006; Bremner 2007; Bremner et al. 2008; Geuze et al. 2008; Kasai et al. 2008; Porcelli et al. 2008; van Harmelen et al. 2010; Papagni et al. 2011; Kuo et al. 2012; Morey et al. 2012; Pitman et al. 2012). This similarity is of interest for a couple reasons. First, since the pathophysiology of symptoms attributed to occupational stress is highly debated, there is a need for clarification on whether this condition is associated with any cerebral changes. Second, if structural changes similar to those described in other stress-related conditions are also linked to occupational stress, one may hypothesize that chronic psychological stress affects our brains in a rather stereotyped manner, regardless of the underlying cause, and that cerebral changes occur not only in response to exposure to extreme and life threatening situations, but could also be an effect of accumulated everyday stress. Indeed, in a recently published MR study (Blix et al. 2013), we found significant reductions in the relative volume of the caudate and putamen in subjects reporting cognitive impairment attributed to chronic occupational stress; using voxel-based morphometry, we also detected reductions in the gray-matter (GM) volume of the ACC and the mPFC. GM volume is, however, a composite and rather unspecific metric, and several recent studies show that the 2 lower order measures of GM volume, cortical thickness, and surface area are more appropriate to take into account when investigating factors regarding cortical morphology (Kruiggel et al. 2003; Sowell et al. 2003). In the present MRI study, an entirely new group of stressed subjects and controls was investigated specifically with regard to cortical thickness (CTh) and surface area. The study also included an analysis of the structural volumes of the amygdala, the hippocampus, thalamus, and the cerebellum, in addition to the caudate, and putamen. Each of these structures is, according to previous data from animal experiments, involved in the processing of stress stimuli (Ryzhavskii et al. 2003; Ladefoed et al. 2004; Cohen et al. 2006; Filipovic et al. 2011; Yin et al. 2011; Leuner and Shors 2012). Changes in several of these structures have also been found in patients with early life trauma (Cohen et al. 2006; Baker et al. 2013) and in those with PTSD (Sapolsky 2000; Bonne et al. 2001; Pavlisa, Papa, Pavic 2006; Bremner et al. 2008; Filipovic et al. 2011; Papagni et al. 2011; Zhang et al. 2011). Together, these data suggest a direct link to stress that is independent of the specific type of stressor.

On the basis of previous experimental data, it was assumed that repetitive, stress-induced activation could lead to neuronal and dendritic damage in the structures involved. The underlying hypothesis was that subjects suffering from chronic occupational stress would show changes in cortical thickness, primarily in the mPFC and insular cortex. A further hypothesis was that structural volumes would be reduced in the amygdala, hippocampus, caudate, and putamen. Considering our previous observation of reduced basal ganglia volume among subjects suffering from occupational stress, we also specifically investigated fine motor function in this study, since this function reportedly requires that the processes of the basal ganglia are intact (Ciunas et al. 2010).

Materials and Methods

Subjects

Forty right-handed (Oldfield 1971) subjects (15 men, 25 women; age 38 ± 6 years, range 19–46 years; education 17 ± 3 years), who had been diagnosed as having had a “reaction to severe stress and an adjustment disorder” according to the International Classification of Diseases (ICD-10, F43) were recruited. The selection was limited to subjects who attributed their illness to prolonged work-related stress, after working 60–70 h per week continuously over several years prior to the onset of symptoms. Inclusion criteria consisted of a characteristic symptom course of sleeplessness, diffuse aches, palpitations and fatigue, a subsequent onset of irritability, anxiety, memory and concentration problems, feeling of depersonalization, and reduced work capacity (confirmed by the employers) (Sandstrom et al. 2005; Rydermark et al. 2006). All of the subjects attributed their symptoms to chronic stress and had no other known etiology for their distress. All the subjects in the stressed group reported reduced sleep hours and fragmented sleep on the Karolinskas Sleep Questionnaire (Akerstedt et al. 2002). Subjects were also required to have had a symptom duration of at least one year (their histories of stress-related burnout symptoms ranged from 1.5 to 3.5 years), to have been on sick leave (≥50%) for stress-related symptoms for a minimum of 6 months before entering the study, and to have an average stress-burnout score of ≥3.0 on the Maslach Stress-Burnout Inventory—General Survey (MBI-GS) (Schaufeli and Van Dierendonck 1995). This 7-point rating scale, ranging from 0 (never) to 6 (daily), consists of 3 subscales: exhaustion (5 items), cynicism (5 items), and lack of professional efficacy (6 items). When rating perceived stress, subjects were asked to take into consideration the last 6 months, and not only the actual time point. The average scores for Scandinavian populations are around 2 for MBI-GS (Ahola et al. 2006; Stenlund et al. 2007).

Subjects were excluded if they had a previous history of psychosis, personality disorder, major or bipolar depression, alcohol or substance abuse, chronic fatigue, chronic pain, fibromyalgia, or neurological or endocrine disease. Those who had experienced prominent stress factors in their private life or a major traumatic event at any time in their life, including sexual abuse, were also excluded. No daily medication was allowed during the 2 months prior to the study, except contraceptives. According to a review of their pharmacological treatment histories, none of them had taken drugs that are known to affect brain structure (e.g., psychopharmaca).

Forty healthy, right-handed, nonsmoking volunteers (15 females; age 36 ± 6 years, range 25–45 years; education 17 ± 3 years) with no history of chronic stress or heredity for neuropsychiatric disorders comprised the control group. The patient and control groups had similar gender distributions, and both were predominately female to accord with the female-dominated epidemiology of the condition studied (Ahola et al. 2006).

The 2 groups were matched for socioeconomic status assessed on the basis of years of education, type of occupation, and the level of management (employee, middle management responsibility, chief). All were white-collar workers, all were moderate alcohol consumers (on average 3 glasses of wine/week), and they rated similarly on the social support scale (Matsukura et al. 2002). The study was approved by the Ethics Committee at Karolinska Institutet, and written informed consent was received from each participant.
Before the interview, participants completed questionnaires in order to evaluate their stress symptoms and assess their previous life events (Deykin et al. 2001). In addition, the occurrence of major life events among the subjects was assessed through a clinical psychiatric interview based on the nonwork-related items of the Holmes and Rahe (1967) Scale. The participants were asked to answer yes or no to whether they had experienced any nonwork-related stressful life events (e.g., death of a relative or spouse, recent divorce, forced family relocation). They also completed the Karolinska Sleep Questionnaire. Subjects were excluded if they answered positively to having experienced such an event in their lives. Patients also received a medical screening (physical examination, test of thyroid and liver function). The possible presence of psychiatric disorders or personality disturbances were assessed according to the Diagnostic and Statistical Manual of the American Psychiatric Association, 4th Edition (DSM–IV), including the Structured Questionnaire for DSM-IV® Axis I and II (Structural Clinical Interview for DSM-IV®) a shortened version of (SCID-I, and II) (American Psychiatric Publishing, Inc., Arlington, TX, USA, 1997), along with a test for depression using the Montgomery–Asberg Depression scale (Montgomery et al. 1979).

**Salivary Cortisol**

Salivary cortisol was sampled in accordance with a previously established protocol (Karlamangla et al. 2013). Saliva sampling was chosen because the method is simple, noninvasive, and nonstressful; saliva samples have been shown to reflect the levels of the free fraction of cortisol in plasma (Galbois et al. 2010). Subjects were carefully instructed on how to collect the samples, which was done by placing Salivette cotton rolls (Sarstedt, Rommelsdorf, Germany) in their mouths for 2 min. The samples were taken 7 times over the course of a weekday. The first sample (CS1) was collected immediately upon awakening in the morning, irrespective of time. The second sample (CS2) was collected 15 min later, before eating or brushing teeth, and the third sample (CS3) was collected 15 min after that. The fourth sample (CS4) was collected around noontime, before lunch. The fifth sample (CS5) was collected at about 3 PM, the sixth (CS6) at 8:00 PM, and the seventh (CS7) at bedtime, after having been at rest in bed for 15 min and before falling asleep. The samples were frozen (−18°C) until analyzed. The levels of salivary cortisol were measured by radioimmunoassay using the Spectria (125I)-coated tubes radioimmunoassay kit (Orion Diagnostica, FIN-02101 Espoo, Finland).

**Magnetic Resonance Imaging**

**Data Acquisition**

Magnetic resonance imaging data was acquired on a 3-Tesla MRI medical scanner (Discovery 3T GE-MR750, General Electric, Milwaukee, WI, USA) equipped with a 32-channel and/or 8-channel phased array receiving coil. 3D T1-weighted SPGR images were acquired with 1-mm³ isotropic voxel size (TE = 3.1 ms, TR = 7.9 ms, TI = 450 ms, FoV = 24 cm, 176 axial slices, flip angle of 12°). Other MR sequences (not used in the present study) included resting-state functional MRI, performed with a gradient-echo pulse sequence with a voxel size of 3 × 3 mm (TE = 30 ms, TR = 2500 ms, FoV = 28.8 cm, 44 interleaved axial slices, 5 mm thickness, flip angle of 90°). In addition, multislice DTI (not used in the present analyses) was performed using an echo-planar imaging sequence with 2 × 2 mm in plane resolution, [FoV = 23 cm, 60 interleaved axial slices, thickness = 2.9 mm, TE = 83.7 ms, TR = 8000 ms, 60 diffusion gradient directions (0 = 1000), flip angle of 90°]. Finally, there was a clinical sagittal FLAIR: TE/TR = 117/8000, TI = 2255, ETL = 140, ARC accelerator. R = 2 × 2 (slice, phase), FoV: 27 cm, 224 × 224, slice thickness, 1.2 mm.

**Cortical Thickness and Surface Area**

The MR volumes were processed using FreeSurfer software version 5.1 (www.surfer.nmr.mgh.harvard.edu). To calculate the surface-based anatomical measures, models of white-matter (WM) and GM surfaces were reconstructed from MR volumes. The thickness was then measured as the distance between the WM and the GM surfaces at each vertex. The vertices were arranged in ~1 mm spacing, which allows measuring cortical thickness at up to 160 000 vertices in each hemisphere with submillimeter precision. Before the surfaces were reconstructed, several preprocessing steps were done (Fischl and Dale 2000). First, the volume was registered to the Talairach atlas using affine transformation. Second, to bring about intensity normalization, the bias field was computed and used to correct intensity variability across the image caused by radiofrequency field inhomogeneities and susceptibility artifacts. Third, the skull (nonbrain) tissue was removed by deformimg a tessellated ellipsoid template into the shape of the inner surface of the skull. Fourth, the WM hemispheres were constructed; during this procedure, the overlap in intensities between WM and GM was taken into account as well as the fact that the WM/GM borders should be planar due to the laminar structure of the cortex. Fifth, the cutting planes were chosen in such a way as to separate the hemispheres from each other as well as to remove the cerebellum and brain stem. Finally, the WM surface was generated by covering the filled WM hemisphere with triangles (tessellation) and smoothing it to follow the intensity gradients between WM and GM; then, the GM (pial) surface was generated by expanding the WM surface to follow the intensity gradients between the GM and CSF.

The reconstruction of the MRI images was inspected visually at several stages: after the Talairach transformation, after the skull stripping, and, finally, after the surfaces had been built and the volumes labeled. At each of these stages, the necessary corrections were made, including correcting erroneous skull striping by adjusting watershed parameters or by manually editing out the skull tissue, and adding control points to normalize intensity for erroneous WM surface reconstruction.

**Tests of Group Differences in Cortical Thickness and Surface Area**

The study was focused on investigating cortical thickness, but as the FreeSurfer program also calculates surface area, we were able to compare this factor between the 2 populations. All of the possible differences between the groups were evaluated for each vertex, using age as the nuisance variable, and after employing Monte Carlo correction (5000 permutations). This correction method for multiple comparisons generates random noise fields and detects the clusters that appear at specific size and probability thresholds. In our study, after 5000 of such iterations, a frequency of how often a simulated cluster’s value exceeded the value from the true data analysis was computed, and this frequency was used to indicate the results which were significant at the level corrected for multiple comparisons (here set to P < 0.05). Although the groups were age and sex matched, it was, on the basis of previous publications (Sowell et al. 2007), assumed that age could be a factor influencing GM and surface area. We also specifically tested if the 2 groups differed in regard to the effect of age on Gm, by employing age as covariate of interest. A different-offset-different-slope model was used (the slope of the line that represents thickness and surface area as a function of age was set to be different for the groups being compared, and the offset of these 2 lines was allowed to vary during fitting to the data). Within-group analyses were carried out using the same-offset-same-slope model.

**Segmentation of the Subcortical Volumes**

Subcortical segmentation generated with FreeSurfer was used to calculate the volumes of 6 subcortical brain structures: the amygdala, hippocampus, caudate, putamen, thalamus, and cerebellum. When needed, the segmented brain structural masks were modified manually. They were first registered to original gray-scale images, and then refined with 1 pixel erosion to eliminate possible partial volume artifacts and alignment errors. The mean signal intensity (SI) was finally calculated for each of the studied subcortical brain structures by averaging the SI of the voxels extracted from the original gray-scale images based on the segmentation defined volumes of interest (VOIs) using FreeSurfer software (www.surfer.nmr.mgh.harvard.edu), according to the standard procedure (Fischl et al. 2002, 2004). Finally, the structural volumes were labeled based on 3 types of probabilities at each voxel: prior (before observing a volume) probability that a voxel belongs to each of the label classes, probability that a given voxel belongs to the label given the classification of its neighboring points, and probability distribution function of intensity (for volume-based labeling). The
same persons analyzed all the subcortical volumes. Ratios between the respective VOI and the total intracranial volume (TIV) were finally entered into the statistical analyses. After ensuring that the data were normally distributed, group comparisons of relative structural volumes (VOI/TIV) were carried out with a one-way ANOVAs using the individual relative values of the 2 homologous VOIs for each type of structure as input values (P < 0.05, with the Bonferroni correction for the thalamus and cerebellum, but not for the amygdala, hippocampus, and the basal ganglia, for which we had specific hypotheses). The aforementioned analyses were carried out with PASW Statistics 21 (SPSS, Inc., Chicago, IL, USA).

Possible Relationship Between Cth and the MBI-GS and MADRAS Scores
A possible relationship between stress and regional Cth was exploratively assessed using stress score (MBI-GS) as the covariate of interest and age as the nuisance variable (FreeSurfer software, P < 0.05, Monte Carlo correction). The same approach was used to investigate whether there was a relationship between Cth and MADRAS scores. The possible effects of stress on the subcortical volumes that differed between the 2 groups of subjects were investigated using Pearson’s linear regression (P < 0.05) for the MBI-GS scores and the respective VOI/TIV.

Test of the Psychomotor Function
Psychomotor function was investigated using the grooved pegboard test, as described in one of our previous studies (Ciumas et al. 2010).

The Grooved Pegboard test is a fine motor task that requires manipulative dexterity, speed, and complex visual-motor coordination in order to place 25 pegs, one at a time, into 25 keyhole-shaped holes with varying orientations that are randomly positioned on a 5-by-5 matrix. The pegs had to be rotated into position to match the hole before they were inserted, which was to be done as quickly as possible and in a prescribed order. Subjects were required to place the pegs from left to right on the board when using their right hand, and to go in the opposite direction when using their left hand. The criterion variable was the time needed to complete the task.

Results

General Demographics
The majority demographic data are presented in Table 1. The groups were matched for age, sex, and years of education, but differed significantly with respect to stress scores (P < 0.001) and MADRAS scores (P < 0.001). However, none of the stressed subjects were deemed to be depressed according to the MINI questionnaire, and the mean MADRAS score in the stressed group was still within the nondepression range (<20). There was no group difference with respect to cortisol levels, either overall (P = 0.780; F = 0.078) or at any specific time point (Table 1).

Cortical Thickness
In stressed subjects, the mPFC was thinner than in controls (vertex maximum, −log10(P) = −3.6, size 10.0 cm², Talairach’s coordinate −18 36 −16 (Fig. 1). The average difference in Cth in this region was 0.12 cm², the mean F-value according to the F-map was 7.6 (the mean Cth was 2.75 ± 0.22 cm² in stressed subjects and 2.87 ± 0.21 cm² in controls). This difference remained when adding the MADRAS scores as the covariate of no interest. Furthermore, when using MADRAS scores as covariate of interest and merging both study groups, no correlation with Cth was detected in this region. There was an inverse correlation between MADRAS scores and Cth in several other regions, but only one cluster (vertex maximum −log10 (P) = −4.0, size 7.8 cm², Talairach’s coordinate −60 −15 3) survived the multiple comparison correction.

Contrary to our hypothesis, no direct correlation between Cth and MGI-GS scores was detected when using the exploratory analysis and MGS-GI scores as covariate of interest in relation to Cth. When restricting the search space to the mPFC region where significant thinning was found in the stressed group, and applying Person’s correlation analysis, r was −0.2, and P = 0.079. No significant group difference was detected with respect to the surface area.

Post hoc Analyses of Cortical Thickness
Although there was no significant age difference between the groups, the age range was relatively high. It was, therefore, of interest to investigate how Cth covaried with age across the entire study population, and also, if there were any regions in which this covariation differed between the 2 study groups. In a separate FreeSurfer analysis, age was, therefore, employed as covariate of interest using the entire study group, and with the entire brain as search space. There were several clusters

![Figure 1. Clusters showing significant reductions in Cth in stressed subjects.](http://cercor.oxfordjournals.org/)

**Table 1**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Stressed subjects (n = 40)</th>
<th>Controls (n = 40)</th>
<th>P, F values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.9 ± 6.4</td>
<td>36.1 ± 5.9</td>
<td>P = 0.17, F = 1.9</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.6 ± 2.8</td>
<td>16.8 ± 3.1</td>
<td>P = 0.21, F = 1.6</td>
</tr>
<tr>
<td>MBI-GS (score)</td>
<td>3.9 ± 0.6</td>
<td>2.6 ± 0.4</td>
<td>P = 0.00, F = 85.9</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>4.4 ± 1.1</td>
<td>1.3 ± 1.0</td>
<td>P = 0.00, F = 300.4</td>
</tr>
<tr>
<td>Cynicism</td>
<td>3.2 ± 1.3</td>
<td>1.3 ± 0.9</td>
<td>P = 0.00, F = 85.9</td>
</tr>
<tr>
<td>MADRAS (score)</td>
<td>16.8 ± 5.1</td>
<td>3.3 ± 2.9</td>
<td>P = 0.00, F = 213.4</td>
</tr>
<tr>
<td>Cortisol sample 1</td>
<td>13.7 ± 11.0</td>
<td>14.2 ± 6.2</td>
<td>P = 0.3, F = 0.8</td>
</tr>
<tr>
<td>Cortisol sample 2</td>
<td>21.3 ± 13.5</td>
<td>19.3 ± 9.2</td>
<td>P = 0.4, F = 0.7</td>
</tr>
<tr>
<td>Cortisol sample 3</td>
<td>21.3 ± 11.3</td>
<td>22.3 ± 11.6</td>
<td>P = 0.7, F = 0.1</td>
</tr>
<tr>
<td>Cortisol sample 4</td>
<td>8.7 ± 10.8</td>
<td>7.8 ± 4.6</td>
<td>P = 0.8, F = 0.3</td>
</tr>
<tr>
<td>Cortisol sample 5</td>
<td>4.9 ± 2.4</td>
<td>6.6 ± 9.4</td>
<td>P = 0.3, F = 1.0</td>
</tr>
<tr>
<td>Cortisol sample 6</td>
<td>3.6 ± 4.6</td>
<td>3.7 ± 4.7</td>
<td>P = 0.8, F = 0.5</td>
</tr>
<tr>
<td>Cortisol sample 7</td>
<td>2.2 ± 1.9</td>
<td>2.5 ± 3.9</td>
<td>P = 0.7, F = 1.2</td>
</tr>
</tbody>
</table>

Age and education are expressed in years; MBI-GS is a questionnaire to score perceived work-related stress. Raw 3 indicates the mean total score, raw 4–5 the subscores for the exhaustion and cynicism; MADRAS, Montgomery–Asberg Depression Scale. There was no overall group difference in cortisol levels (P = 0.780, F = 0.078, repeated measure ANOVA). Time of the day for cortisol samples: Sample 1: 06:30–07:30; Sample 2: 15 min after; Sample 3: 30 min after sample 1; Sample 4: 12:00–13:00; Sample 5: 15:00–16:00; Sample 6: 20:00–21:00. Sample 7: 22:30–23:30.
showing a significant inverse correlation with age (primarily in the parietal and frontal lobes, and to a minor extent in the occipital lobe, Supplementary Fig. 1 and Table 1). Furthermore, group comparison in regard to this covariation showed a significant difference in a left prefrontal cluster (vertex maximum \(-\log_{10}(P) = 3.6\), size 11.2 cm\(^2\), Talairach's coordinate \(17 37 -15\)). Hence, whereas age was negatively correlated with \(C_{th}\) in several regions this inverse correlation was significantly more pronounced among stressed subjects, possibly suggesting an age-by-stress interaction. There were no regions for which the correlation between age and \(C_{th}\) was more pronounced in controls.

Several more recent studies have shown that functional networks of the brain have an intrinsically cohesive modular structure in that the connections between regions are much denser within each module than between them. The modules are mainly composed of functionally, as well as anatomically, related brain regions and can be identified by maps of covariance. This is of importance for investigations of clinical populations since maps of covariance, such as for \(C_{th}\), may vary as a function of disease processes, and, thus, differ between patients and controls (He et al. 2008). Therefore, it was of particular interest to investigate whether the mPFC region where the cortex was thinner in the burnout group, also had a different pattern of cortico-cortical \(C_{th}\) covariations in this group. Using the left mPFC region with significant group difference in \(C_{th}\) as a seed region of interest, it was found that the covariation was significantly stronger in the stressed group in the primary cortical projections to the mPFC (Petrides and Pandya 1999; the orbitofrontal and rostro-medial frontal cortex, the ACC, and the insular cortex, and on the right side also the supramarginal and fusiform gyri; Table 2, Figure 2). In addition, the covariation in parts of the seed region itself was significantly more pronounced in the stressed group. No regions with greater covariation among controls were detected.

**Subcortical Volumes**

Contrary to the hypothesis, the stressed subjects showed a significantly larger amygdala volume, bilaterally but particularly on the right side, compared with controls (Tables 3 and 4). Furthermore, there was a significant and positive linear correlation between the individual MBI-GS scores and the relative volume of the amygdala on both sides (Pearson's coefficient = 0.435, \(P = 0.038\) for the left amygdala; Pearson's coefficient = 0.427, \(P = 0.044\) for the right amygdala)—thus, the larger the amygdala volume, the higher the stress score. This covariation remained when restricting the correlation analysis to the stressed group; a significant covariation was not found when restricting the analysis to the control group (calculation using mean of the right and left relative amygdala volume; \(r = 0.604, P = 0.000\), and \(r = -0.188, P = 0.122\), respectively), see Supplementary Figure 2. Another structure for which a group difference was found is the caudate, as the stressed group showed a significant volume reduction in this area (Table 3). Notably, the relative caudate volumes were inversely correlated with the MBI-GS exhaustion scores for both sides (Pearson's coefficient = -0.288; \(P = 0.010\) for the left caudate; Pearson's coefficient = -0.237, \(P = 0.036\) for the right caudate; results from the corresponding covariation subanalysis investigating each group separately, failed to reach the significance level). The significance threshold for the aforementioned correlation analyses was 0.05, and no correction for multiple comparisons was applied, as a covariation with the degree of perceived stress was hypothesized in the regions showing altered structural volumes among the stressed subjects. Group differences in the amygdala volumes remained when using the MADRAS scores as the covariate of no interest (\(P = 0.003\), \(F = 6.33\), mean of both sides), whereas the \(P\) value for caudate comparisons was subsignificant (\(P = 0.120\), \(F = 2.09\), mean of both sides). No significant group difference was detected in the relative structural volume of the hippocampus, putamen, thalamus, or cerebellum. The values of structural volumes are presented in Table 3.

Stressed subjects also showed impaired performance for the pegboard task when using the dominant (right) hand, and required significantly longer time to position the pegs (\(P = 0.006\), \(F = 8.1\)). There was a similar trend for the left hand performance, but without passing the significance level (\(P = 0.074\), \(F = 3.3\)) (Table 4). The performance in the pegboard task (time) did not correlate with the relative volume of the caudate or putamen.

**Discussion**

Cognitive impairment is frequently reported among subjects with chronic occupational stress. However, to the best of our knowledge, this is the first study to investigate whether

### Table 2

<table>
<thead>
<tr>
<th>Regions</th>
<th>Left mPFC seed</th>
<th>Cluster size, cm(^2)</th>
<th>Talairach coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Orbitofrontal cortex*</td>
<td>10.7</td>
<td>55.0</td>
<td>-19 17 -17</td>
</tr>
<tr>
<td>L Caudal middle frontal cortex</td>
<td>3.6</td>
<td>10.2</td>
<td>-38 34</td>
</tr>
<tr>
<td>L Superior frontal cortex</td>
<td>3.7</td>
<td>22.9</td>
<td>-7 28 49</td>
</tr>
<tr>
<td>R Superior frontal cortex</td>
<td>6.9</td>
<td>40.1</td>
<td>9 28 33</td>
</tr>
<tr>
<td>L Insular cortex</td>
<td>3.8</td>
<td>9.1</td>
<td>-29 21 4</td>
</tr>
<tr>
<td>R Insular cortex</td>
<td>2.8</td>
<td>12.7</td>
<td>36 -10 4</td>
</tr>
<tr>
<td>R Supramarginal cortex</td>
<td>4.1</td>
<td>8.2</td>
<td>58 -25 27</td>
</tr>
<tr>
<td>R Fusiform gyrus</td>
<td>3.6</td>
<td>12.5</td>
<td>33 59 12</td>
</tr>
</tbody>
</table>

*Significant group difference in cortico-cortical covariations from the left mPFC seed region.

Statistical threshold is \(P < 0.05\), corrected for multiple comparisons (according to Monte Carlo permutations). The individual mean \(C_{th}\) in the left mPFC seed region (where the cortex was significantly thinner in stressed subjects) was used as covariate of interest. The Talairach's coordinates indicate location of maximum vertex for the cluster. Positive Maximum vertex-wise \(-\log_{10}(P)\) values indicate significantly greater covariation in stressed subjects compared with controls. *Covers a portion of the anterior cingulate cortex. R, right; L, left.

Figure 2. Group difference (stressed subjects – controls) in cortico-cortical covariation from the left mPFC (the region showing a significantly thinner cortex in the stressed group), corrected for multiple comparisons (Monte Carlo permutation), and using age as the covariate of no interest. The projection of cerebral hemispheres (MRI images of the Freesurfer atlas) is standardized. Scale is logarithmic and shows \(-\log_{10}(P)\). Warm colors indicate positive contrasts (higher values in stressed subjects), cool colors negative contrasts.
Table 3
Structural volumes

<table>
<thead>
<tr>
<th>Structural volumes (cm$^3$)</th>
<th>Stressed subjects</th>
<th>Controls</th>
<th>$P$, $F$ values</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Caudate volume</td>
<td>3.9 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>$P = 0.04$, $F = 4.5^*$</td>
</tr>
<tr>
<td>R Caudate volume</td>
<td>3.9 ± 0.4</td>
<td>4.2 ± 0.4</td>
<td>$P = 0.04$, $F = 4.3^*$</td>
</tr>
<tr>
<td>L Putamen volume</td>
<td>4.7 ± 0.5</td>
<td>4.6 ± 0.6</td>
<td>$P = 0.51$, $F = 0.44$</td>
</tr>
<tr>
<td>R Putamen volume</td>
<td>4.7 ± 0.5</td>
<td>4.6 ± 0.6</td>
<td>$P = 0.29$, $F = 1.12$</td>
</tr>
<tr>
<td>L Hippocampus volume</td>
<td>4.0 ± 0.3</td>
<td>4.1 ± 0.4</td>
<td>$P = 0.74$, $F = 0.1$</td>
</tr>
<tr>
<td>R Hippocampus volume</td>
<td>4.1 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>$P = 0.31$, $F = 1.0$</td>
</tr>
<tr>
<td>L Amygdala</td>
<td>1.8 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>$P = 0.018$, $F = 5.8^*$</td>
</tr>
<tr>
<td>R Amygdala</td>
<td>2.0 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>$P = 0.003$, $F = 9.5^{**}$</td>
</tr>
<tr>
<td>L Thalamus volume</td>
<td>7.0 ± 0.7</td>
<td>7.2 ± 0.7</td>
<td>$P = 0.58$, $F = 0.30$</td>
</tr>
<tr>
<td>R Thalamus volume</td>
<td>7.0 ± 0.7</td>
<td>7.2 ± 0.8</td>
<td>$P = 0.63$, $F = 0.23$</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>136.1 ± 6.7</td>
<td>136.2 ± 6.6</td>
<td>$P = 0.42$, $F = 0.66$</td>
</tr>
<tr>
<td>TIV volume</td>
<td>1435.1 ± 167.5</td>
<td>1473.4 ± 158.0</td>
<td>$P = 0.325$, $F = 0.96$</td>
</tr>
</tbody>
</table>

*P-values for structural volumes were based on calculations of ratios between the respective structural volume and the TIV.

$^*$ $P < 0.05$; $^{**}$ $P < 0.01$.

TIV: Total Intracranial Volume.

Table 4
Results of the pegboard test

<table>
<thead>
<tr>
<th>Peg scores: time needed to put all the pegs in the pegboard. All the subjects were right handed.</th>
<th>$P$, $F$ values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg right (s) $(n = 40)$</td>
<td>$P = 0.006$, $F = 8.045^{**}$</td>
</tr>
<tr>
<td>Peg left (s) $(n = 40)$</td>
<td>$P = 0.074$, $F = 3.328$</td>
</tr>
</tbody>
</table>

occupational stress may be linked to changes in cortical thickness and structural volumes in regions considered to process psychosocial stress stimuli. It was found that the mPFC was significantly thinner in stressed subjects. Furthermore, the effect of age on cortical thinning in the mPFC was significantly more pronounced among stressed subjects. An additional finding was the increase in amygdala volume and the decrease in caudate volume in the stressed group. Both of these volume changes were related to the degree of perceived stress and caudate changes were accompanied by impaired performance in tests of fine motor function.

All of the aforementioned regions constitute parts of the limbic and paralimbic networks, and the detected changes are in accordance with a large body of animal data suggesting that stress affects this distributed network. The present data are unique in that they show regionally differentiated structural changes within this network in relation to everyday occupational stress. The present study advances the little that is known about the cerebral pathophysiology of this condition in several ways. First of all, it provides measurements of amygdala volume and shows that there is an association between an enlargement of this structure and higher scores of perceived stress. The amygdala is the first relay station in the processing of psychosocial stress stimuli (Koenigs and Grafman 2009), and animal experiments show that severe and/or prolonged stress is associated with a glutamate-induced elevation of brain-derived neurotrophic factor (BDNF), an increased arborization, and dendritic hypertrophy in the basolateral amygdala (Arendt et al. 2012; Boyle 2013). Similar mechanisms may also operate in humans.

Previous structural neuroimaging studies of stress have mainly been restricted to PTSD and early traumas, and seem inconclusive with regard to amygdala volume (Woon and Hedges 2009), with some finding no effect of diagnosis (Gurvits et al. 1996; Lindauer et al. 2004; Chao et al. 2013) and others finding either smaller amygdala volume or enlarged amygdala volume (Lupien et al. 2011; Weber et al. 2013) in patients. One reason for the disparate results is that these studies were often based on small samples and different types of trauma in different studies, which could be different in nature even among the same study group. In contrast, the present data were collected from a population that was homogeneous with respect to stress type and exposure, and that had no comorbid conditions. These characteristics increase the reliability of the finding in this study that amygdala enlargement occurred among stressed persons.

A second finding, which suggests that occupational burnout is a limbic condition is the thinning of the mPFC. Considering that Cth and cortical area are subcomponents of GM volume, this finding advances our recent observation of reduced GM volume in this region (Blix et al. 2013), by helping narrow the number of possible morphological correlates (see next paragraph). The mPFC is a key site for the modulation of stress stimuli (Arnsten 2009), and numerous animal studies (Roozendaal et al. 2004), as well as studies of PTSD patients (Gilboa et al. 2004; Geuze et al. 2008; Koenigs and Grafman 2009; Lyoo et al. 2011) suggest that this structure is affected in individuals with chronic stress. The present observation that cortico-cortical covariation from the mPFC seed region to the insular cortex, the orbitofrontal and rostro-medial frontal cortex was greater in stressed subjects further underlines the limbic involvement of the occupational burnout condition. This observation is of particular interest because the aforementioned regions are axonally connected (Petrides and Pandaya 1988), and the stronger Cth correlation (Lerch et al. 2008) may confer to a mutually trophic effect and modulation/shaping of these connected regions (Pezawas et al. 2004) by an external factor, such as stress.

The detected caudate reduction and its link to perceived stress confirms our recent finding in a different sample of subjects suffering from occupational stress, and adds to it by demonstrating a functional correlate in terms of impaired psychomotor function.

Possible Mechanisms Underlying Changes in Cth and Subcortical Volumes

The exact underpinnings of the described limbic changes can at present only be speculated about. Because the study was cross-sectional, it is difficult to know whether the detected reductions represent neurotoxic effects of stress, effects of other factors, such as nitric oxide, or a pre-existing condition that could have rendered the brain more vulnerable to the development of pathological stress responses. Owing to the strict selection criteria, it is, nevertheless, possible to exclude potential confounding factors such as major life traumas, psychiatric premorbidity, chronic pain, and pharmacological treatment. Considering the congruence with data from animal experiments and some (Lyoo et al. 2011; Papagni et al. 2011), albeit not all (Bonne et al. 2001; De Bellis et al. 2001), reports from longitudinal studies of patients experiencing stressful life events, or PTSD, we find it more likely that the present findings reflect effects of chronic occupational stress. The observed correlation patterns between the stress scores and the relative
amygdalae and caudate volumes support this notion, although the latter correlation was weak.

The study offered no option to directly examine the cellular correlates of the neuroimaging differences identified. Cortical thickness reflects cell-packing density, cell size, the number of cortical neurons, and the dendritic length (Kruggel et al. 2003), factors, which also contribute to subcortical volumes. The molecular underpinnings of the observed morphological changes will primarily be discussed in relation to neuronal modulation by stress. Two mediators of this modulation deserve particular attention—the glutocorticoids and the glutamate. Their effects have been studied in animal models in detail (Conrad 2008; Leuner and Shors 2012) and involve dendritic retraction, neurotoxicity, and, in some cases, even apoptosis (Bremner et al. 2008). Both glutamate and glucocorticoids have neuronal influences on their own, but are also reported to interact (Magarinos and McEwen 1995; Brown et al. 2010). Circulating glucocorticoids interact with various neurotransmitters (McEwen 2000a), and chronic stress in tree shrews is found to reduce the number of dopamine transporter binding sites \( B_{max} \) in the caudate nucleus and the putamen (Isvich et al. 2000). An excess of glucocorticoids is reported to decrease the proliferation of hippocampal and prefrontal neurons, whereas adrenal ectomy is reported to increase it (Wellman 2001; Wong and Herbert 2004). Experiments with betamethasone infusion in fetal sheep show a glucocorticoid-related loss of synaptic density in the frontal neocortex, caudate, putamen, and hippocampus (Conrad et al. 1999; Colberg et al. 2004). However, while a possible impairment in cortisol homeostasis may have had an impact on the presently observed cerebral changes at some intermediate step of the stress-induced chain of events, the present data do not provide direct support for such a mechanism. As in several previous studies of occupational stress, neither the pattern of diurnal cortisol nor the levels at separate time points showed any difference compared with controls (Table 1).

This brings attention to the second stress-associated factor, which could have contributed to the observed changes—glutamate. Data from animal experiments show that stress causes an enhanced release of glutamate, and that a stress-related elevation of extracellular glutamate levels induces retraction in the spines in stress-targeted regions, such as the mPFC, the anterior cingulate, and the basal ganglia (Lowy et al. 1993; Magarinos and McEwen 1995; McEwen et al. 1997; Iijima et al. 2007; Hunter et al. 2009). Interestingly, in the amygdala, stress seems to lead to an increase in neurotrophic factors such as BDNF, and to enhance dendritic outgrowth. In the functional and anatomical projection areas of the amygdala, the stress-related glutamatergic excess is, on the other hand, reported to lead to reduced BDNF and shrinkage of dendrites (Arendt et al. 2012; Boyle 2013). These degenerative events are particularly pronounced in the mPFC (Roozendaal et al. 2004; Brown et al. 2005; Radley et al. 2008; Arnsten 2009; Leuner and Shors 2012). This is of interest because the mPFC exerts a strong negative control over stress pathways. GABAergic signals from the mPFC to the amygdala lead to a repression of the HPA axis. This provides a basis for one possible scenario for the present condition, in which stress-mediated neurotoxic damage to the mPFC, due to high glutamate, cortisol, or the combination of both (see Magarinos and McEwen 1995), has led to impaired prefrontal inhibition of the amygdala (Roozendaal et al. 2004). This would then have provided a context for a vicious circle with a further enhancement of amygdala excitation and subsequent changes along the networks connected to the amygdala (the mPFC, the basal ganglia, the hippocampus, and the insular, anterior cingulate, and orbitofrontal cortices). The presently reported findings among subjects suffering from occupational stress fit into this model, with the increase in amygdala volume and reduction in caudate volume, the thinning of the mPFC, and the more pronounced cortico-cortical covariance between the mPFC and insular cortex (Wang et al. 2007; Liston et al. 2009; Goldstein et al. 2010). It is also compatible with the notion that both the putamen and caudate receive powerful glutamatergic input from the amygdala (McEwen 2000b) and are susceptible to excitotoxicity (Chen et al. 1995; Bernal et al. 2000). This strengthens reiterating the hypothesis presented in our initial stress-related publication (Jovanovic et al. 2011) that repeated stress stimuli could cause excitotoxic, apoptotic, and/or intermediate forms of neuronal death (Bengzon et al. 1997) with atrophy in humans.

One observation worth commenting on is that the hippocampus was seemingly unaffected. Although at odds with animal data showing stress-related dendritic shrinkage and cell death in the hippocampus (McEwen 1994), the finding is congruent with previous volumetric studies among subjects with occupational stress (Sandstrom et al. 2005; Blix et al. 2013), and some (Bonnete et al. 2001; Villarreal et al. 2002; Filipovic et al. 2011; Papagni et al. 2011; Chao et al. 2013), but not all (De Bellis et al. 2001; Landre et al. 2010), studies based on volumetric measurements of patients with PTSD and life traumas. One possible, yet speculative, explanation for this discrepancy is that the effects of stress on the hippocampus could be gender-related. Experimental data suggest that dendritic spine density in the hippocampus may respond in opposite directions to the same stressful event in male and female rats (Shors et al. 2001). A post hoc, within-sex group comparison of the present material failed to show any difference in the hippocampal volume. However, given the relatively limited size of the study group, this does not rule out the possibility that gender may have been a factor affecting the hippocampal changes that occurred in response to stress—a notion which deserves its own, separate study.

**Occupational Stress and Depression**

One important question worth discussing is whether and to what extent the present findings could reflect depression. For several reasons, we find this possibility to be unlikely. First of all, none of the stressed subjects were judged to be depressed according to the psychiatrist in charge and the SCID ratings. Although the depression scores were significantly higher among the stressed group, for those subjects who had high MADRAS scores, the only items, which contributed to these scores were anxiety and poor sleep, which does not necessarily implicate depression. Second, the detected group differences did not show an interaction with the MADRAS scores, and the finding of thinner mPFC in stressed subjects remained when adding the MADRAS scores as the covariate of no interest. Furthermore, the MADRAS scores showed no covariation with thickness of the mPFC. Third, the cortisol levels were normal in our stressed subjects, whereas they have been found to be high in a large portion of patients with genuine depression (Kasckow et al. 2001). We recently also found that women suffering from chronic occupational stress had an elevated...
reaction to allopregnanolone (Backstrom et al. 2013), which differs from the diminished allopregnanolone response that has been reported among depressed women (Girdler and Klatchkin 2007). Emotional reactions to chronic stress and major depression may, thus, represent separate constructs. They share, however, certain symptoms, perhaps due to the affection of similar limbic networks. Indeed, the higher MADRAS scores among the 6 stressed subjects who were not diagnosed as depressed could be an effect of this comorbidity. Given that depression can be triggered by stress, it is also possible that these subjects were developing depression, which was at a subclinical level at the time of investigation.

**Methodological Issues**

The methods used in this study were standard and have been used in several earlier studies yielding comparable results (Fischl et al. 2002; Sowell et al. 2007; Geuze et al. 2008; Lerch et al. 2008; Landre et al. 2010; Lyoo et al. 2011; Bruehl et al. 2013; Dickie et al. 2013). The hippocampal volumes were generally larger than when employing manual delineation (Blix et al. 2013) but were similar to those described in studies using the segmentation method of the FreeSurfer software (Doring et al. 2011; Morey et al. 2012). This systematic difference has been described previously (Tae et al. 2008; Doring et al. 2011) and may partly be attributed to the fact that FreeSurfer segments the entire hippocampus including the tail, which is not always included in the manually delineated hippocampal volumes.

The criteria for subject selection were conservative due to our ambition to optimize the possibility of investigating whether tentative cerebral changes were attributable to occupational stress. Because co-morbid stress factors (such as life traumas, depression, and PTSD) were excluded and the groups were matched for the education, and type of occupation, occupational stress was the major common denominator in the stressed group, and it seems reasonable that the data reliably reflected cerebral changes in relation to this specific factor.

Finally, it is worth mentioning that a more thorough presentation of the neurocognitive performance of these subjects on a detailed battery of neuropsychological tests will be presented in a separate manuscript.

**Conclusion**

In summary, the present findings indicate that chronic occupational stress is associated with morphological cerebral changes that are distributed in a differentiated manner along the limbic and paralimbic brain structures. Although needing longitudinal studies to be validated, the collective data provide reason to believe that the observed changes are more likely to represent effects of stress than causes of it. The changes correlated with the stress scores in a differentiated manner, and were located in regions known to mediate functions that were also shown to be impaired in our stressed subjects. Based on previous animal data and emerging studies of other stress conditions (PTSD), it is hypothesized that an excessive release of glutamate, perhaps in tandem with a dysregulation of HPA, leads to a cascade of events, ultimately leading to the detected changes—a development that hopefully is reversible. This condition needs to be considered as a stress illness, whose sufferers deserve proper and swift treatment.

**Supplementary Material**

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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**Notes**

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