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Structural brain correlates of burnout severity in medical professionals: A voxel-based morphometric study

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**ABSTRACT**

Occupational burnout has become a pervasive problem, especially among medical professionals who are highly vulnerable to burnout. Since the beginning of the COVID-19 pandemic, medical professionals have faced greater levels of stress. It is critical to increase our understanding of the neurobiological mechanisms of burnout among medical professionals for the benefit of healthcare systems. Therefore, in this study, we investigated structural brain correlates of burnout severity in medical professionals using a voxel-based morphometric technique. Nurses in active service underwent structural magnetic resonance imaging. Two core dimensions of burnout, namely, emotional exhaustion and depersonalization, were assessed using self-reported psychological questionnaires. Levels of emotional exhaustion were found to be negatively correlated with gray matter (GM) volumes in the bilateral ventromedial prefrontal cortex (vmPFC) and left insula. Moreover, levels of depersonalization were negatively correlated with GM volumes in the left vmPFC and left thalamus. Altogether, these findings contribute to a better understanding of the neural mechanisms of burnout and may provide helpful insights for developing effective interventions for medical professionals.

1. Introduction

Burnout is the emotional depletion and loss of motivation resulting from chronic emotional and interpersonal work-related stressors [1–6]. Medical professionals are particularly vulnerable to burnout, which may lead to reduced motivation, medical errors, and voluntary absenteeism [7–10]. Moreover, recurrent stressful interactions with patients are known to cause high emotional exhaustion and depersonalization [10–13]. To ensure the efficiency of healthcare systems, a better understanding of burnout among medical professionals is needed.

Several functional magnetic resonance imaging (fMRI) studies have shown that the function of several brain areas is associated with burnout severity in medical professionals. For example, de Andrade et al. (2016) reported that the prefrontal cortex activity during the execution of an attentional task was positively correlated with high burnout scores in pediatric residents [11]. Moreover, reduced empathy-related brain activity has been found to predict higher burnout severity in nurses [10].

In addition to influencing brain function, various types of stress are known to influence regional brain structural volumes [14–16]. Recent studies have revealed that chronic stress is significantly associated with gray matter (GM) volumes in multiple brain areas [15,17–19], such as the ventromedial prefrontal cortex (vmPFC), insula, and caudate. Savic et al. (2015) found a significant thinning of the mesial frontal cortex in occupationally stressed subjects compared to healthy controls [18]. Moreover, a recent study found that patients with high levels of mental fatigue had smaller caudate and putamen volumes compared to those with low-moderate levels of mental fatigue [2]. These findings suggest that burnout severity is associated with individual differences in

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region of GM volumes in medical professionals. Investigation of this issue can add to our understanding of the underlying neural mechanisms of burnout in this population and may provide helpful information for the development of effective interventions. However, to the best of our knowledge, no study has directly investigated the relationship between the regional GM volumes and burnout severity in medical professionals.

In the present study, we investigated the structural brain correlates of burnout severity among medical professionals using voxel-based morphometry (VBM). VBM is an automated and unbiased imaging-analysis method for exploring changes in regional GM [20,21]. This technique has been widely used in the study of anatomical differences and psychiatric conditions [22–24]. Previous studies suggest that neurotoxic effects of stress cause negative changes (i.e., a decrease) in GM volumes [18,24]. However, positive changes (i.e., an increase) can be observed during improvement after therapeutic intervention [25,26]. We predicted that regional GM volumes in the above-mentioned brain areas associated with chronic occupational stress will be negatively correlated with higher burnout severity in medical professionals.

2. Methods

2.1. Participants

A total of 43 nurses in active service were enrolled in this study (32 females, 41 right-handed, age range: 22–39 years, mean ± standard deviation (SD) = 27.2 ± 4.0 years). Participants were recruited via advertising from hospitals in Kyoto. They practiced nursing for at least 1 year. No participants met the criteria for any psychiatric disorder according to the evaluation of experienced psychiatrists using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I). In addition, no participants had a history of head trauma, serious medical or surgical illness, or substance abuse. Average IQ was estimated to be 98.0 ± 8.4 using the Japanese Version of the National Adult Reading Test short form [27].

This study was approved by the Committee on Medical Ethics of Kyoto University and was conducted in accordance with the Code of Ethics of the World Medical Association. After they received a complete description of the study, written informed consent was obtained from all participants. This study is a part of a larger project aimed at investigating individual differences among medical professionals, and participants completed a range of measures, not all of which are reported here.

2.2. Burnout severity

Burnout severity was assessed using the Japanese version of the Maslach Burnout Inventory [5,6,9,10], which includes two core dimensions: (1) “emotional exhaustion” and (2) “depersonalization.” The “emotional exhaustion” dimension assesses feelings of being emotionally over-extended and exhausted by one’s work (5 items), while the “depersonalization” dimension assesses emotional detachment toward the recipients of one’s care (6 items). Higher scores indicate higher levels of emotional exhaustion and depersonalization. In line with previous studies [9,10], the “personal accomplishment” subscale was excluded.

2.3. MRI data acquisition and pre-processing

All participants underwent MRI scanning by a 3 T whole-body scanner equipped with an 8-channel phased-array head coil (Trio, Siemens, Erlangen, Germany). The scanning parameters of the T1-weighted three-dimensional magnetization-prepared rapid gradient-echo (3D-MPRAGE) sequence were as follows: TR = 2000 ms, TE = 4.38 ms, TI = 990 ms, FOV = 225 × 240 mm, matrix = 240 × 256, resolution = 0.9375 × 0.9375 × 1.0 mm³, and 208 total axial sections without intersection gaps.

MRI data were processed using SPM8 (Wellcome Trust Center for Neuroimaging, London, UK) and the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) running on MATLAB (MathWorks, Natick, MA, USA). Briefly, all images were tissue classified and spatially normalized to the same stereotaxic space using the diffeomorphic anatomical registration through exponentiated Lie algebra (DARTEL) algorithm [28]. The voxel values of segmented and normalized GM images were modulated by the Jacobian determinants obtained from non-linear normalization steps. We used the default parameters of the VBM8 toolbox. The resultant GM images were smoothed with a Gaussian kernel of 8 mm full width at half maximum. All further analyses were performed using these images.

2.4. Data analyses

To explore the brain regions correlated with levels of emotional exhaustion and depersonalization, we performed multiple regression analysis separately using the general linear model framework in SPM. Age and gender were entered into the model as covariates of no interest. Because the images were modulated for non-linear warping only, intracranial volume was not included as nuisance covariate [21,22]. Based on previous neuroimaging studies of burnout and mental stress [e.g., 2,15,17–19], we focused on the following regions of interest (ROIs): vmPFC, middle frontal gyrus (MFG), anterior cingulate cortex, insula, amygdala, caudate, putamen, thalamus, and hippocampus. Anatomical masks of these ROIs were made using the Automated Anatomical Labeling atlas [29] in the WFU pickatlas toolbox [30]. The statistical threshold was set at a cluster-level family-wise error (FWE) corrected p < 0.05 for each ROI (at voxel-level, uncorrected p < 0.005), based on previous studies [e.g., 31,32]. With respect to brain regions outside these ROIs, the statistical threshold was set at the voxel-level p < 0.05 (FWE corrected), with a minimum cluster extent of 100 contiguous voxels after whole-brain correction for multiple comparisons.

3. Results

Participants’ emotional exhaustion and depersonalization subscale scores ranged from 5 to 24 (mean ± SD = 16.6 ± 4.6) and from 6 to 20 (11.8 ± 3.6), respectively. The results reflected considerable individual differences in burnout severity in our sample.

Fig. 1, Supplementary Fig. S1 and Table 1 present the brain regions for which the GM volumes correlated with the emotional exhaustion subscale scores. Emotional exhaustion scores were negatively correlated with GM volumes in the bilateral vmPFC and left insula. In other words, participants with lower GM volumes in these brain areas showed higher levels of emotional exhaustion.

Fig. 2, Supplementary Fig. S2 and Table 2 present the brain regions for which GM volumes correlated with the depersonalization subscale scores. Depersonalization scores were negatively correlated with GM volumes in the left vmPFC and left thalamus. When using a more lenient threshold (p < 0.005, uncorrected, k = 100), emotional exhaustion scores were negatively correlated with GM volumes in the left MFG. Additionally, depersonalization scores were negatively correlated with GM volumes in the right vmPFC. Please see Supplementary Fig. S3 for details.

Our analysis did not identify any brain areas where GM volumes were positively correlated with emotional exhaustion or depersonalization subscale scores.

3.1. Additional analyses

We performed further analysis to examine data in greater detail. We further divided the participants according to burnout severity into high and low groups, based on the emotional exhaustion and depersonalization subscale scores. Following this, we compared regional GM volumes between the groups. Using the same threshold in the main analyses as mentioned above, we observed no significant differences in regional GM volumes between the groups. However, when we used a more
Fig. 1. Brain regions significantly correlated with emotional exhaustion. Emotional exhaustion subscale scores were negatively correlated with GM volumes in the bilateral vmPFC and left insula. The statistical threshold was set at cluster-level FWE corrected \( p < 0.05 \). Abbreviations: FWE = family-wise error, \( GM = \) gray matter, \( vmPFC = \) ventromedial prefrontal cortex.

Table 1

| Brain Region | Coordinates (mm) | \( T \) | Cluster (voxels) |
|--------------|------------------|--------|-----------------|
| Positive     |                  |        |                 |
| Negative     |                  |        |                 |
| L vmPFC      | \(-2\) \(\Leftrightarrow\) \(26\) \(\Leftrightarrow\) \(-17\) | 4.17   | 574             |
| R vmPFC      | \(2\) \(\Leftrightarrow\) \(58\) \(\Leftrightarrow\) \(-18\) | 4.20   | 485             |
| L insula     | \(-33\) \(\Leftrightarrow\) \(17\) \(\Leftrightarrow\) \(-9\) | 3.74   | 393             |

\( p < 0.05 \), cluster-level FWE corrected (at voxel-level, uncorrected \( p < 0.005 \)). MNI coordinates and \( T \)-values are provided for the local voxel maximum of each respective cluster.

Abbreviations: FWE = family-wise error, L = left, MNI = Montreal Neurological Institute, R = right, \( vmPFC = \) ventromedial prefrontal cortex.

Fig. 2. Brain regions significantly correlated with depersonalization. Depersonalization subscale scores were negatively correlated with GM volumes in the left vmPFC and left thalamus. The statistical threshold was set at cluster-level FWE corrected \( p < 0.05 \). Abbreviations: FWE = family-wise error, \( GM = \) gray matter, \( vmPFC = \) ventromedial prefrontal cortex.

Table 2

| Brain Region | Coordinates (mm) | \( T \) | Cluster (voxels) |
|--------------|------------------|--------|-----------------|
| Positive     |                  |        |                 |
| Negative     |                  |        |                 |
| L vmPFC      | \(0\) \(\Leftrightarrow\) \(56\) \(\Leftrightarrow\) \(-18\) | 3.76   | 305             |
| L thalamus   | \(-10\) \(\Leftrightarrow\) \(-10\) \(\Leftrightarrow\) \(18\) | 4.11   | 224             |

\( p < 0.05 \), cluster-level FWE corrected (at voxel-level, uncorrected \( p < 0.005 \)). MNI coordinates and \( T \)-values are provided for the local voxel maximum of each respective cluster.

Abbreviations: FWE = family-wise error, L = left, MNI = Montreal Neurological Institute, \( vmPFC = \) ventromedial prefrontal cortex.

4. Discussion

In the present study, we investigated the structural brain correlates of burnout severity in medical professionals using the VBM technique. These results can provide significant insights into the neurobiological mechanisms of burnout in medical professionals.

Our results revealed that the GM volume of the vmPFC was negatively correlated with both emotional exhaustion and depersonalization scores. The vmPFC is a key region in the modulation of stress-related stimuli [33–35]. Previous studies of patients with post-traumatic stress disorder [36–38] have repeatedly found alterations in this brain region. Similarly, Savic et al. (2015) reported that the mPFC was significantly thinner in occupationally stressed subjects compared with the controls, and proposed that cerebral changes occur not only in response to the exposure to extreme and life-threatening situations but also as a consequence of accumulated everyday stress [18]. Since this study was cross-sectional, it is difficult to say whether the detected associations represent neurotoxic effects of occupational stress or a pre-existing condition that may have rendered the brain more vulnerable to the effects of stress responses. Furthermore, some sources of stress can contribute to eustress, which is a level of stress that enhances performance in medical professionals [39,40]. Our results may also partly reflect compensatory neuroanatomical changes associated with coping responses of an individual. Nevertheless, our results conform to previous studies and highlight that the vmPFC is crucial for studying the mechanisms of burnout.

Interestingly, the GM volume in the left insula was also significantly associated with emotional exhaustion. The insula is known to be involved in olfaction, gustation, somatosensory, and in the processing of negative emotions [41–48]. The left insula, which was specifically analyzed in this paper, is known to play an essential role in executive set-switching and language attainment [49,50], which is crucial in complex medical situations. Moreover, a previous study has showed that lower activity in the insula during empathy was associated with a higher severity of emotional exhaustion in medical professionals [10]. This...
suggessteds that medical professionals who struggle to identify their own emotional reactions experience stronger emotional dissonance, emotional exhaustion, and burnout. Similar to previous studies, our findings suggest that the insula plays a key role in the individual differences in burnout severity among medical professionals.

We also found that the GM volume in the left thalamus was significantly associated with depersonalization scores. The thalamus has many functions, acting as a sensory hub between other subcortical nuclei and the cortices as well as contributing to sleep and wakefulness, awareness, motor control, and cognition [51–53]. Abnormalities in thalamic functioning are thought to contribute to dysregulation of sensory filtering, circadian rhythms, alertness, and consciousness [51–53]. A previous animal study revealed that severe stress induces atrophy of the thalamus [54]. Furthermore, Gavriel et al. (2017) found that the activation of the left side of thalamus, identified in this study, was increased after a training in participants suffering from stress-related exhaustion [55]. Combined with the findings of previous studies, our results may provide useful information for developing effective interventions for burnout.

There are several limitations to this study. First, various factors have been reported to influence burnout severity and central nervous system morphology [5,6,15,19]. In particular, the fields of specialization, working hours, and sleep conditions of participants are important when investigating the effect of burnout on regional GM volumes. However, these factors were not controlled in this study, and this could be a source of bias. Thus, our findings should be interpreted cautiously and need to be confirmed by future studies with more detailed designs. Second, the sample size was relatively small for the study of individual differences. Third, only self-reported measures were used to assess the severity of burnout. Moreover, our simplistic categorization of burnout (i.e., emotional exhaustion and depersonalization) limits the interpretation of the findings. Fourth, this study was conducted using a cross-sectional design. Longitudinal studies applying various measurement tools to assess burnout symptoms are needed to strengthen our current findings. Since the outbreak of the COVID-19 pandemic [7,11,12], medical professionals have faced even greater stress. We hope that our findings will contribute to a better understanding of the mechanisms of burnout and offer useful insights for developing effective interventions to manage stress and burnout.

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