NeuroImage: Clinical 17 (2018) 354–358

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Voxel-based comparison of brain glucose metabolism between patients with Cushing's disease and healthy subjects

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ARTICLE INFO

Keywords:
Cushing's disease
Positron emission tomography
Cortisol
Voxel-based analysis

ABSTRACT

Cognitive impairment and psychiatric symptoms are common in patients with Cushing's disease (CD) owing to elevated levels of glucocorticoids. Molecular neuroimaging methods may help to detect changes in the brain of patients with CD. The aim of this study was to investigate the characteristics of brain metabolism and its association with serum cortisol level in CD. We compared brain metabolism, as measured using [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG PET), between 92 patients with CD and 118 normal subjects on a voxel-wise basis. Pearson correlation was performed to evaluate the association between cerebral FDG uptake and serum cortisol level in patients with CD. We demonstrated that certain brain regions in patients with CD showed significantly increased FDG uptake, including the basal ganglia, anteromedial temporal lobe, thalamus, precentral cortex, and cerebellum. The clusters that demonstrated significantly decreased uptake were mainly located in the medial and lateral frontal cortex, superior and inferior parietal lobule, medial occipital cortex, and insular cortex. The metabolic rate of the majority of these regions was found to be significantly correlated with the serum cortisol level. Our findings may help to explain the underlying mechanisms of cognitive impairment and psychiatric symptoms in patients exposed to excessive glucocorticoids and evaluate the efficacy of treatments during follow-up.

1. Introduction

Cushing's disease (CD), which was first described by Harvey Cushing (Cushing, 1969), is the most common cause of endogenous hypercortisolism. Excess cortisol is associated with numerous general and endocrine symptoms, and in particular, may result in cognitive impairments and psychiatric symptoms ranging from anxiety to frank psychosis (Newell-Price et al., 2006). Despite advances in diagnosis and therapy, the treatment of CD is frequently a challenge. Moreover, some cognitive impairments and psychiatric symptoms can persist for a long time after treatment (Forget et al., 2002), which cause prolonged impaired quality of life (Heald et al., 2004; Lindsay et al., 2006). Therefore, the neurotoxic effects caused by excessive cortisol warrants investigation.

Radiological imaging is a reliable and noninvasive method to investigate changes within the brain when exposed to excessive cortisol. Decreased total brain volume (Bourdeau et al., 2002; Momose et al., 1971) can be observed in patients with CD and Cushing's syndrome. Regions of the brain known to be associated with the regulation and activity of cortisol, including the hippocampus (Herman et al., 2005; Jacobson and Sapolsky, 1991), amygdala (Gray et al., 1989), and cerebellum (Hawrylycz et al., 2012), have shown structural and functional changes in these patients (Maheu et al., 2008; Santos et al., 2014; Starkman et al., 1992). Furthermore, some studies have used imaging to examine white matter integrity (van der Werff et al., 2014) and changes in the brain's biochemical composition (Resmini et al., 2013) in patients exposed to elevated cortisol levels. Radiological imaging findings help to establish the mechanisms underlying cognitive disorders in patients with elevated cortisol levels.

[^{18}F]-Fluorodeoxyglucose positron emission tomography (FDG PET)

Abbreviations: CD, Cushing's disease; FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography; ACTH, adrenocorticotropic hormone; FWE, family-wise error

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http://dx.doi.org/10.1016/j.nicl.2017.10.038
Received 27 June 2017; Received in revised form 30 October 2017; Accepted 31 October 2017

is a noninvasive radiological imaging technique for detecting and measuring cellular activity. FDG PET provides information regarding FDG metabolism in the brain in vivo, and has been widely used to evaluate functional changes in the brain that are known to be associated with cognitive disorders (Nasrallah and Wolk, 2014). In the current study, we aimed to investigate the changes in brain metabolism associated with serum cortisol level by using FDG PET. We first performed a voxel-based statistical comparison of brain metabolism between patients with CD and heathy subjects, and then screened for an association between metabolic changes and elevated serum cortisol level in the patients with CD.

2. Materials and methods

2.1. Participants

In this retrospective study, data for a total of 210 participants were obtained. The experimental group comprised 92 consecutive CD patients treated at Peking Union Medical College Hospital between January 2010 and January 2015. The inclusion criteria for the experimental group were as follows: 1) adults with newly diagnosed CD, 2) presurgical PET scan of the brain, 3) presurgical laboratory tests of serum cortisol and serum adrenocorticotropic hormone (ACTH), and 4) no prior craniotomy or stereotactic biopsy. The diagnosis of CD had been confirmed at the endocrinology and/or neurosurgery division of our hospital on the basis of internationally established guidelines. Blood samples for the serum cortisol and ACTH level measurements were obtained at 8 AM using standard procedures.

The control group comprised 118 healthy participants matched for age and sex. The inclusion criteria for healthy controls were: 1) age between 18 and 70 years, 2) no history of craniotomy or stereotactic biopsy, 3) no current medication, 4) and no history of psychiatric or neurological disorders.

The study design and protocol were approved by the Ethics Committee of our hospital and conformed to the tenets of the Declaration of Helsinki, and all patients provided informed consent.

2.2. FDG-PET acquisition

The participants were required to fast for at least 4 h before undergoing FDG PET. The blood glucose level of each patient was confirmed to be within normal limits (< 6.4 mmol/L). A dose of 5.55 MBq (0.15 mCi) FDG per kilogram of body weight was administered intravenously. The FDG was produced on-site using RDS-111 Cyclotron (CTI, Knoxville, TN, USA). The scans were obtained on a Biograph 64 TruePoint TrueV PET/CT system (Siemens Medical Solutions, Erlangen, Germany).

2.3. FDG-PET data processing and voxel-based analysis

The FDG PET images of all participants were first processed in three steps: 1) registration with the Montreal Neurological Institute space (voxel size $= 3 \times 3 \times 3$ mm^3, 0.027 ml) by using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8), 2) spatial smoothing with a 6-mm full width at half maximum Gaussian kernel, and 3) global normalization. Then, the intensity normalized images were entered into two-sample *t*-tests with age and sex as covariates. The Bonferroni correction was applied to the one-tailed T-map to maintain the family-wise error (FWE) level within 0.05 with a threshold of a cluster size > 50 to exclude suspicious voxels.

2.4. Correlation between voxel-based findings and cortisol levels

After regressing age and sex of each cluster, the metabolism value was extracted and averaged for each subject. The Pearson's correlation between the averaged metabolism value and the serum cortisol level was calculated.

Table 1
Clinical characteristics of patients with Cushing's disease ($n = 210$).

Variables	Patients	Controls	*p*-Value
Number	92	118	
Age			0.177*
Median (range)	35 (18–65)	39 (20–60)	
Gender			0.238#
Male (%)	26 (28)	43 (36)	
Female (%)	66 (72)	75 (64)	
Cortisone (μg/dl) (mean ± S.D.)	28.3 ± 10.4		
ACTH (pg/ml) (mean ± S.D.)	98.3 ± 80.8		

ACTH = adrenocorticotropic hormone.
* Student's *t*-test.
# Chi-square test.

2.5. Statistical analysis

Voxel-based comparisons of FDG PET data between patients and normal subjects were conducted by using Matlab (R2014a, MathWorks, Natick, MA, USA). Pearson correlation was performed by using R language (https://www.r-project.org/). Differences were considered significant when $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics

We evaluated clinical data for 210 participants, of whom 92 had a confirmed diagnosis of CD and 118 were healthy controls. Demographic and clinical characteristics, including age, sex, and hormone levels, are summarized in Table 1. No significant differences were observed between groups in terms of age and sex.

3.2. Voxel-based analysis

The voxel-based comparison between groups showed that certain brain regions in patients with CD demonstrated significantly increased FDG uptake, including the basal ganglia, anteromedial temporal lobe, thalamus, precentral cortex, and cerebellum (Fig. 1A & C). Meanwhile, the clusters showing significantly decreased uptake were mainly located in the medial and lateral frontal cortex, superior and inferior parietal lobule, medial occipital cortex, and insular cortex (Fig. 1B & C).

3.3. Correlations between brain metabolism and hormone level

A total of 11 clusters were chosen to calculate the mean normalized metabolism value for each patient. Specifically, 5 clusters showed a higher metabolic rate in patients with CD than in normal subjects, and 6 clusters showed a lower metabolic rate in patients with CD. Details regarding the brain regions that involved these clusters are demonstrated in Table 2. The findings indicated that the cortisol level was significantly correlated with 6 of the 11 clusters (Fig. 2 and Fig. 3).

4. Discussion

The current study examined the voxel-wise differences in brain metabolism between 92 patients with CD and 118 normal subjects by using FDG PET data. To our knowledge, this is the largest study to have attempted characterization of brain metabolic changes in patients with CD. The findings demonstrated, when compared with the healthy subjects, significantly increased metabolism mainly localized to the hippocampus, amygdala, basal ganglia, and cerebellum in patients with CD; moreover, significantly decreased metabolism was mainly localized

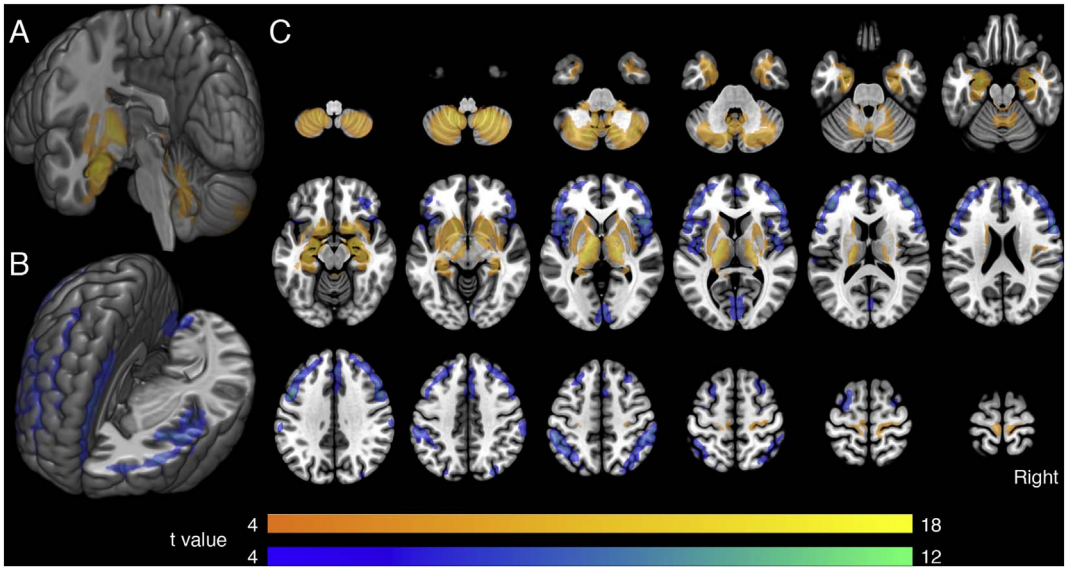

Fig. 1. Voxel-wise comparison between patients with CD and healthy subjects. Brain regions with higher metabolic rates in the CD patients than in healthy controls are shown in yellow, and regions with lower metabolic rates in CD patients than in healthy controls are shown in blue. Rendered images are shown in (A) and (B), and axial slices in (C). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Main clusters with significant differences between patients with Cushing's disease and normal subjects.

Clusters	Brain regions (voxel size)
Clusters of higher metabolism in CD patients	
Cluster 1R/L	Precentral gyrus, Paracentral lobule (130/87)
Cluster 2R/L	Limbic lobe, Parahippocampa gyrus, Putamen, Hippocampus, Amygdala, Thalamus (1332/1574)
Cluster 3	Cerebellum (2626)
Clusters of lower metabolism in CD patients	
Cluster 4R/L	Lateral frontal cortex, Insular lobe (1375/1386)
Cluster 5	Medial frontal gyrus, Cingulate gyrus (420)
Cluster 6R/L	Lateral parietal cortex (361/332)
Cluster 7	Medial occipital cortex (226)

CD = Cushing's disease.

to the cerebral cortex. More importantly, we found significant correlations between FDG uptake in these brain regions and serum cortisol level. These findings provide direct evidence that patients with CD experience changes in energy metabolism in the central nervous system, which is correlated with elevated serum cortisol levels.

One of our main findings was the metabolic changes in the limbic system observed in CD patients when compared to the healthy control group. The limbic system expresses high levels of glucocorticoid receptors and is involved in the response to and regulation of glucocorticoids (Herman et al., 2005). Numerous studies have investigated the association between the limbic system and glucocorticoids in both normal subjects and patients with stress, Cushing syndrome, psychosis, and other diseases associated with elevated glucocorticoid levels. However, the specific role of the limbic system in these diseases is far from clear. The advances in neuroimaging technologies have allowed for obtaining more information from living animals and humans. In studies based on structural imaging, volume reduction was found in the hippocampus (Starkman et al., 1992) and prefrontal cortex (MacLullich

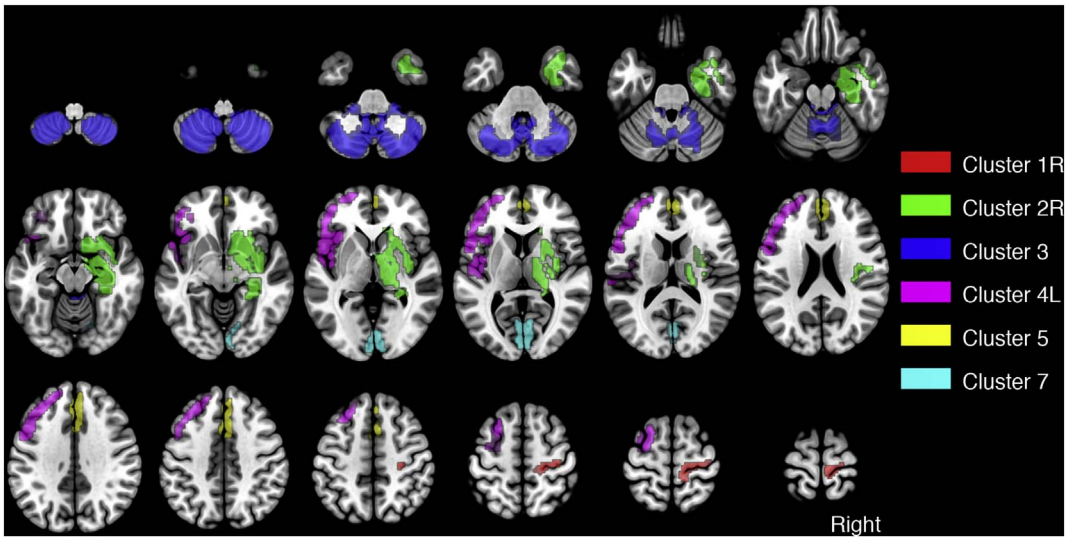

Fig. 2. Significant brain regions that correlated with cortisol level are shown in different colors. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

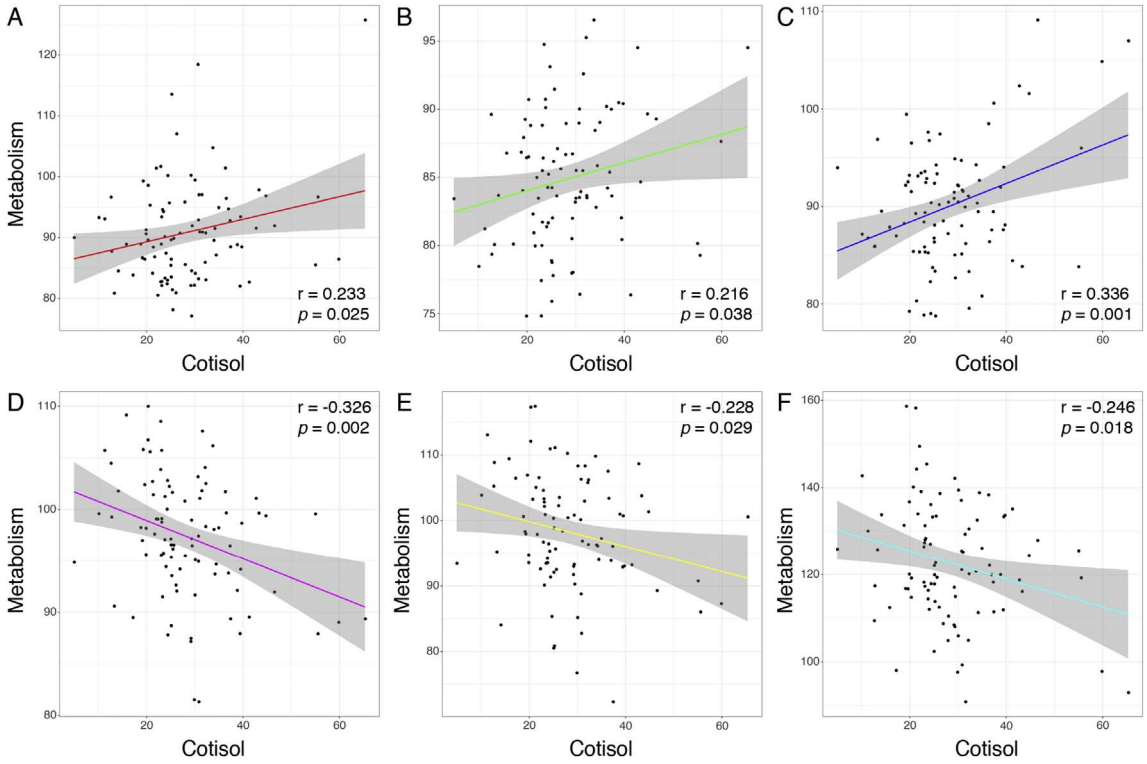

Fig. 3. Correlation between metabolism of significant brain regions and cortisol level. Cluster 1R, Cluster 2R, Cluster 3, Cluster 4L, Cluster 5 and Cluster 7 are sequentially shown in (A) to (F). The color of the six clusters is same as shown in Fig. 2. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

et al., 2006) when the patients were exposed to excessive glucocorticoid. Functional neuroimaging studies conducted in healthy subjects have demonstrated positive relationships between medial, temporal, and frontal lobe activation and glucocorticoid concentrations (Pruessner et al., 2008; Tessner et al., 2007; van Stegeren et al., 2007). In the present study, we found that patients with CD patients had higher metabolic rates than the controls in the medial temporal lobe including the hippocampus and amygdala, and lower metabolic rates in the prefrontal cortex. This indicates that a functional disorder of the limbic system exists in patients with CD, which may explain why these patients develop cognitive impairments and psychiatric symptoms.

In addition, we found higher FDG uptake in the thalamus among CD patients. The thalamus possesses connections with the limbic system in terms of the synthesis of cognition, memory, and emotion (Barbas, 2000). Previous studies also found higher metabolic rates in the thalamus in patients with major depression (Brody et al., 2001), and decreased Cho/H_2O ratios in those with Cushing's syndrome (Khiat et al., 2001). Thus, the thalamus is vulnerable to excess cortisol.

The role of the basal ganglia in emotion and cognition is clearly defined in diseases involving hypercortisolism; therefore, radiological changes observed in patients with CD may help to extend our understanding. In our study, we found that the metabolic rate of the basal ganglia in CD patients was higher than that in normal subjects. A previous study described structural changes in the basal ganglia in patients with CD, and an increase in caudate volume was found after treatment (Starkman et al., 2007). Another study investigated patients with depression using functional magnetic resonance imaging (MRI) and demonstrated increased blood flow in the basal ganglia after treatment (Martin et al., 2001). Interestingly, the studies mentioned above both found radiological changes in the basal ganglia in the right side. An FDG PET-based study investigated subjects with major depression and showed that these patients possessed higher metabolic rates in the caudate than did the controls. This result was in accordance with ours, which did not show obvious lateralization. An investigation that combines MRI and PET may better illustrate changes in the basal ganglia related to hypercortisolism.

The cerebellum is also susceptible to increased cortisol levels. A reduction in cerebellar volumes has been observed in diseases such as major depression and bipolar disorder (Brambilla et al., 2002), with hypercortisolism playing an important role in this process. In addition, reduced cerebellar cortex volume is observed in patients with active Cushing's syndrome (Santos et al., 2014). After achieving long-term remission from CD, an increase is the volume of the left posterior lobe of the cerebellum has been observed (Andela et al., 2013). Studies using functional imaging to investigate how hypercortisolism affects the cerebellum are rare. Our results demonstrate that the cerebellum shows a higher energy metabolic rate in patients with CD than that in controls. Considering that the cerebellum plays a key role in a variety of cognitive and emotional processes and is involved in many psychiatric disorders (Phillips et al., 2015), its metabolic changes warrant additional investigation in patients with CD.

We observed a neurotoxic effect at the cortex in patients with CD. Specifically, a widespread reduction in FDG uptake was observed in the frontal, parietal, and insular lobes, and higher FDG uptake was detected in the cortex near the central sulcus. These brain regions are involved in motor, cognition, and emotion functions, and possess connections with the limbic system and the cerebellum. Previous findings also support the notion that glucocorticoids are involved in regulating motor functions (Metz, 2007). Moreover, it is interesting that the precentral gyrus shows higher rather than lower metabolic rates than in other regions of the cortex. Our results in terms of higher metabolic rates in the precentral gyrus, basal ganglia, and cerebellum, which participate in motor functions, may help to explain movement disorders in patients with CD.

In addition, we found correlations between cortisol level and metabolism of brain regions including the limbic system, cerebellum and parts of cortex in CD patients. This indicated that the neurotoxic effects induced by cortisol was associated with its elevation. Especially, the metabolism of the limbic system, which involved in regulating the activity of the hypothalamic-pituitary-adrenal axis for cortisol secretion through a negative feedback loop was positively correlated with

cortisol level (Herman et al., 2005; Jacobson and Sapolsky, 1991). Maybe the condition of hypercortisolism activated the limbic system for the process of suppression of cortisol secretion. We need more evidences from fundamental experiments.

In our previous work (Liu et al., 2016), we investigated the association between brain metabolism and elevated cortisol level in CD patients. We found the metabolism of some brain regions was correlated with the cortisol level of patients, especially for the hippocampus, amygdala, and cerebellum which were involved in the regulation and action of cortisol. To further examine these brain regions that correlated with cortisol level, we made comparison between CD patients and normal subjects in the current study. As described above, the metabolism of hippocampus, amygdala, and cerebellum possessed significant differences from normal subjects, and was correlated with the cortisol level of CD patients. In addition, the metabolic characteristics of some brain regions in the cortex were also in line with our previous findings. These results indicated that the brain metabolism was affected by elevated cortisol and possessed a strong association with the cortisol level.

There are some limitations in this study, such as its retrospective nature and caveats of registration and normalization procedures. In addition, we did not have sufficient whole brain MRI data for the study cohort. We hope future studies will collect both FDG PET and MRI data to investigate whether metabolic changes in the brain correlate with structural changes in patients with CD. Lastly, the comparison of preoperative and post-operative metabolism of the brain in CD patients would be interesting. We would examine the metabolic changes when the cortisol level decreased after operation in future study.

In conclusion, we demonstrated that certain brain regions in patients with CD present significantly different metabolism than that observed in healthy controls, which were found to correlate with serum cortisol levels. Our findings may help to explain the underlying mechanisms of cognitive impairments and psychiatric symptoms in patients exposed to excessive glucocorticoids, and evaluate the efficacy of treatments during follow-up.

Acknowledgments

None of the authors have conflicts of interest relevant to this article.

Our research is supported by the National Natural Science Foundation of China (No. 81201121) and the Beijing Postdoctoral Research Foundation (2017-ZZ-116).

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