Original Article

Lower Intelligence Quotient and Larger Brain Volume in the Precuneus among Patients with Graves' Disease

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Abstract

Objectives: Neuropsychiatric symptoms are related to hyperthyroidism. Whether global cognitive function is impaired is unclear. In this study, we intended to investigate whether patients with Graves' disease (GD) are characterized by a lower intelligence quotient (IQ) and gray matter volume loss. **Methods:** We enrolled 36 patients with GD and 36 healthy controls. Intelligence quotient and other cognitive functions, such as memory and attention, were assessed. Magnetic resonance imaging (MRI) study was used to measure the gray matter volume for those study participants. **Results:** Significantly lower IQ scores ($p < 0.001$) and poor memory function ($p < 0.05$) were found among the patients with GD. We also found that patients with GD had a nonsignificant larger gray matter volume in the precuneus compared with that in healthy controls. **Conclusion:** The deficits on global and complex cognitive testing among patients with GD should be noted. We speculate that the larger gray matter volume in the precuneus might be due to compensation.

Key words: continuous performance test, executive function, hyperthyroidism, magnetic resonance imaging study
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Introduction

Anxiety and depression are the most predominant neuropsychiatric symptoms of Graves' disease (GD), an autoimmune disease leading to hyperthyroidism. Other neuropsychiatric symptoms have also been found. Impairment of cognitive function [1], such as attention and working memory [2], has been reported. Cognitive impairment in patients with GD is improved after hyperthyroidism is managed [3, 4]. Whether there remains a deficit in intelligence quotient (IQ), which is a standardized index covering global cognitive function in patients with GD is unclear.

As the evidence on this topic is scarce, we did a study to examine IQ, memory, and attention among treated and stable patients with GD. Furthermore, whether potential cognitive deficits in GD patients have a structure-based mechanism is unclear. A recent study indicated that volume loss in the medial temporal lobe is present in both the hyperthyroid state and after treatment [5]. This mechanism may reflect the decline of both attention and working memory [6]. But evidence regarding the altered brain volume among patients with GD is scarce. In the present study, we intended to study whether patients with GD are characterized by a lower IQ, poor memory function, poor attention, and reduced gray matter volume. We also did other tests for specific cognitive domains in these study patients.

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Methods

Study patients

The institutional review board at National Cheng Kung University Hospital approved the study (IRB protocol number = A-BR-105-096 and date of approval = May 19, 2017) with the need that all study participants provided written informed consent.

We enrolled 36 patients with GD and 36 healthy controls. The inclusion criteria were patients who were (a) aged between 20 and 60 years; (b) a diagnosis of GD. The diagnosis can often be established based on clinical features with history, in which elevated blood levels of thyroxine (T4) and triiodothyronine (T3) and undetectable levels of thyroid-stimulating hormone (TSH) were noted or recorded. If the diagnosis is uncertain, additional testing may include measuring TSH receptor antibodies (TRAbs), radioactive iodine (RAI) uptake, or thyroid ultrasound with Doppler, each of which can confirm the diagnosis of GD [7]. A senior endocrinologist treated these patients with GD and referred them to this study; (c) psychiatric diagnosis.

A senior psychiatrist did the diagnostic interview based on the Mini International Neuropsychiatric Interview (MINI) [8]. Some of the GD participants were in the remitted or residual phase of mental disorders including major depressive disorder, generalized anxiety disorder or anxiety disorder not otherwise specified (NOS), or depressive disorder NOS. The Young Mania Rating Scale (YMRS) and Hamilton Rating Scale for Depression (HAM-D) were also used.

The exclusion criteria were patients who were (a) pregnant women (or those suspected to be pregnant) or nursing women; (b) subjects with other major physical and mental illnesses within six months before screening; (c) those with drug or alcohol dependence or abuse in the past six months according to *the DSM-IV* criteria; and (d) any other risks as judged by the physician.

Because the protocol of this study was designed to probe the effect of mindfulness and neural imaging, the clinical history was collected with a retrospective telephone interview. According to the available data, the duration of illness was 10.08 ± 10.90 years (n = 24). Most of the patients (17/19) received pharmacological treatment within one year after diagnosis with GD. Only two patients received the treatment after 7 and 29 years. Totally, 32% of patients (9/28) received the surgery at 7.35 ± 10.91 years after diagnosis.

Study tools

Wechsler Adult Intelligence Scale-Revised

The Wechsler Adult Intelligence Scale-Revised [9] was used to evaluate individual intelligence. The six-subtest short-form combination was composed of digit symbol, block design, object assembly (these were used to estimate performance IQ and PIQ), digit span, similarity, and arithmetic tests (these were used to estimate verbal IQ and VIQ).

Wechsler Memory Scale-Revised

Wechsler Memory Scale-Revised [10] was used as we did in our previous study [10]. This evaluation tool comprises 13 brief subtests and is derived to five indexes, namely verbal memory, visual memory, general memory, attention/concentration, and delayed recall.

Continuous performance test

The continuous performance test (CPT) is an evaluation instrument for attention [11]. Only the AX task (subjects were asked to respond whenever the number "9" was preceded by the number "1") was used in the present study. Each test session began with a 2-min practice period (repeated if the subjects required it) to ensure that the subjects knew how to press the button correctly. During the test, numbers from 0 to 9 were randomly presented for 50 miliseconds (ms) each at a rate of one per second. A total of 331 trials, 34 (10%) of which were target stimuli, were presented over five minutes. Each participant completed two sections of the CPT: the unmasked task and the masked task. During the unmasked session, participants were instructed to respond to the target stimulus by pressing a button. In the masked session, a snow pattern was used to change the background for ground dots, rendering the image indistinct. The d' was measured to assess participants' signal differentiation ability from background noise. A higher d' value indicates better processing performance. In this study, subject responses were recorded with the CPT machine (Sunrise Systems, version 2.20, Pembroke, Massachusetts, USA) [12].

Imaging studies

Imaging acquisition

Magnetic resonance imaging (MRI) images were acquired using a 3.0 Tesla MRI scanner (MR750, GE Medical Systems, Milwaukee, Wisconsin, USA) with an eight-channel head coil in the Mind Research and Imaging Center of National Cheng Kung University. All study participants received T1-weighted images. The imaging acquisition is identical to that of our previous study [13].

Data processing and voxel-based morphometry analysis

The data were preprocessed using the Computational Anatomy Toolbox 12 (CAT12, http://www.neuro.uni-jena.de/cat/) toolbox to evaluate the volumes of various whole brain areas. In this study, we segmented the images, and only the data for gray matter were analyzed. A high-dimensional nonlinear approach with the diffeomorphic anatomical registration through an exponentiated lie algebra algorithm (DARTEL) was used to normalize the segmented scans into standard MNI space. The images were then modulated using an affine transformation. Finally, the images were smoothed using eight-mm full-width-half-maximum Gaussian smoothing. We calculated the total intracranial volumes (TIVs) and later entered as a regressor of noninterest in the statistical model.

Statistical analysis

The group difference in the gray matter volume was presented using Statistical Parametric Mapping 12 (SPM12, Wellcome Institute of Neurology, University College London,

United Kingdom) and xjView 8.0 (Human Neuroimaging Lab, Baylor College of Medicine, Houston, Texas, USA) running under MATLAB R2016a (MathWorks Inc., Natick, Massachusetts, USA).

To avoid false-positive finding due to multiple comparisons, the type I error was controlled as follows: with the cluster-based inference, the cluster-forming height threshold was set at $p = 0.001$ uncorrected, and the family-wise error (FWE) rate was set at $p = 0.05$ for the cluster level.

To further analyze the correlations between gray matter volume and scores on cognition tests, we extracted the gray matter volume raw values from the significant clusters in the above-mentioned analyses using the MarsBaR toolbox (http://marsbar.sourceforge.net). Partial correlation, controlling for age and TIVs, was used to test the relationships.

The study data were analyzed using the Statistical Package for the Social Science software version 22 for Windows (SPSS Inc., Chicago, Illinois, USA). The independent *t*-test was used to test the differences between the groups. The differences between the groups were considered significant if *p*-values were smaller than 0.05.

Table 1. Comparison of demographic characteristics, memory, fine motor skill, ability to display flexibility, attention, and intelligence quotient between patients with Graves' disease and healthy controls

	Patients with GD	Healthy controls
Sex, male/female	5/31	5/31
Age, years	40.92 ± 11.35	40.56 ± 11.65
Education duration, years	14.14 ± 2.75	14.47 ± 2.57
HAM-D	4.57 ± 0.77***	1.78 ± 0.30
YMRS	1.97 ± 0.35***	1.77 ± 0.32
Duration of illness, years, (*n*=24)	10.08 ± 10.90	
Episode time, *n* (%), *n*=28		
0	2 (7.1)	
1	17 (60.7)	
2	9 (32.1)	
T3 (ng/dL)	132.05 ± 85.96	
T4 (μg/dL)	8.53 ± 3.82	
TSH (μg/dL)	0.79 ± 0.91	
FSH (mIU/mL)	19.34 ± 23.46	
WAIS-R		
Performance IQ	97.72 ± 12.16**	107.17 ± 14.56
Verbal IQ	99.00 ± 10.39**	106.31 ± 11.67
Full IQ	98.25 ± 9.71***	107.08 ± 11.80
WMS-R		
Verbal memory index	94.69 ± 16.95*	102.69 ± 16.43
Visual memory index	105.44 ± 16.83	109.92 ± 14.25
General memory index	95.83 ± 23.06*	105.67 ± 15.77
Attention/concentration index	107.92 ± 12.92	111.31 ± 11.98
Delayed recall index	102.72 ± 17.31*	111.22 ± 15.15
CPT		
Unmasked d'	4.48 ± 0.50	4.45 ± 0.52
Masked d'	3.48 ± 1.01	3.41 ± 1.13

*$p < 0.05$, **$p < 0.01$; ***$p < 0.001$ significantly different tested using *t*-test
GD, Graves' disease; HAM-D, Hamilton Rating Scale for Depression; YMSR, Young Mania Rating Scale; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; WAIS-R, Wechsler Adult Intelligence Scale-Revised; IQ, intelligence quotient; WMS-R, Wechsler Memory Scale-Revised; CPT, continuous performance test

Results

As shown in Table 1, no significant differences between two groups were found in the demographic characteristics

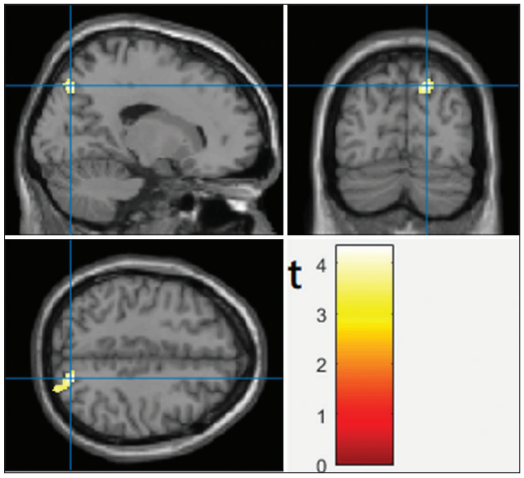

Figure 1. Size of magnetic resonance imaging scan of the study patients (MNI coordinates: 18, −78, 45, cluster size 301). The gray matter volume of the right precuneus was not significantly correlated with the scores on cognition tests in the patients with Graves' disease.

Table 2. Past psychiatric history and psychotropic medications of the patients with Graves' disease

	n (%)
Past psychiatric history	
Anxiety disorder	1 (2.8)
Dysthymic disorder	1 (2.8)
Major depressive disorder	5 (13.9)
Minor depressive disorder	1 (2.8)
Obsessive-compulsive disorder	1 (2.8)
Antidepressants	
Fluoxetine	1 (2.8)
Duloxetine	1 (2.8)
Trazodone	3 (8.3)
Escitalopram	1 (2.8)
Agomelatine	4 (11.1)
Vortioxetine	4 (11.1)
Sertraline	2 (5.6)
Benzodiazepines	
Clonazepam	1 (2.8)
Lorazepam	4 (11.2)
Dormiicum	1 (2.8)
Alprazolam and estazolam	3 (5.6)
Benzodiazepine receptor agonists	
Zolpidem	1 (2.8)
Zopiclone	1 (2.8)

between the patients with GD and the controls (sex, age, or educational years). There were significant differences in IQ ($p < 0.01$) and several important domains of memory ($p < 0.05$), but no difference in attention was observed between the patients with GD and the controls. The duration of illness was not correlated with these cognitive functions after controlling for age, sex, and educational years. In total, 25 patients with GD completed the MRI scan, and 18 were matched with controls who completed MRI. No significant differences were found in sex, age, and education. There was no group difference between the participants who undertook gray matter volume comparison and those who did not in the patients with GD (data not shown). Table 2 lists the past psychiatric history and psychotropic medications of the GD.

Figure 1 shows that the gray matter volume of the right precuneus in the patients with GD was larger than that in the controls but that the gray matter volume of the right precuneus was not significantly correlated with the scores on cognition tests in the patients with GD.

Discussion

In the present study, we reconfirmed the poor cognitive function among patients with GD. Although the attention function was not different from the healthy controls, poor memory function ($p < 0.05$) and poor IQ ($p < 0.01$) were found (Table 1). But to our surprise, a larger gray matter volume in the right precuneus was observed.

Anxiety and depression are present in patients with GD [14]. In this study, we also had the same findings of anxiety and depression in nine patients who received various antidepressants and various benzodiazepine or various benzodiazepine receptor agonists (Table 2). Mild deficits in complex attention are also found in patients with GD. Also, the patients with GD with major depressive disorder and generalized anxiety disorder are more likely to present a cognition deficit [15]. Whether the mechanism of complex attention deficits in GD patients with anxiety and depression is similar to that in patients with major depressive disorder and generalized anxiety disorder, but without GD or other similar disorders, is unknown.

Furthermore, an increased thyroid hormone level may be related to the anxiety and depressive symptoms of GD, as these psychiatric symptoms improve after antithyroid pharmacological treatment. A anxiety and depression are related to increased blood levels of thyroid peroxidase antibodies [16], and anxiety is also associated with increased blood levels of TSH receptor antibodies [17]. To our surprise, our study was unable to confirm the previous finding regarding brain volume loss [5], but we found a nonsignificant larger volume in the right precuneus (Figure 1).

Currently, the mechanism of this controversial phenomenon is unclear. It was proposed that altered cingulate-precuneus homogeneity is a marker for anxiety and depression [18], which are the important characteristics for patients with GD. A study using functional connectivity indicated more functional connectivity in the precuneus among unmedicated patients with depression [19]. As the precuneus is related to several domains of cognitive function, such as certain aspects of memory [20], we speculate that patients with GD would expend extra effort on cognitive function in their daily life, resulting in a larger precuneus as compensation. Although evidence supporting this speculation is scarce, a study has shown higher activation in the precuneus in the cognition connectivity network among patients with depression [21]. A recent study has also revealed a similar mechanism among individuals with a tendency toward agoraphobia [22]. But the evidence for this compensation is not clear yet. Furthermore, in our analysis, the gray matter volume of the right precuneus was not correlated with cognition tests. We speculate that this could be due to a small sample size and the right precuneus may not play a dominant rôle in cognitive function.

Study limitations

The readers are warned not to overinterpret the study results because the study has two major limitations:

- As the sample size was small, the statistical power with regard to specific cognitive function and gray matter volume was limited.
- The only global function assessment in this study was the IQ test, and whether this result could be replicated on other cognitive assessments is unclear.

Summary

Deficit in global and complex cognitive functions among patients with GD should be noted in this study. Whether this phenomenon is related to daily function is unclear.

Data Availability Statement

Original study data used in this study can be shared if contact with one of the corresponding authors is made.

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Conflicts of Interest

The authors report no financial relationships with commercial interests. The funding institutions had no further rôle in the study design, the collection, analysis, and interpretation of data, the writing of this paper, or the decision to submit it for publication.

Yen Kung Yang is an associate editor of *the Taiwanese Journal of Psychiatry*. Yang was not involved in the peer review process of the manuscript, and he did not participate in the decision on publishing this original article.

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