CLINICAL STUDY

Functional magnetic resource imaging assessment of altered brain function in hypothyroidism during working memory processing

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Abstract

Context: Hypothyroidism is related to multiple cognitive deficits including working memory dysfunction, of which the underlying neural correlates were rarely studied. In this study, the impact of hypothyroidism on neural circuits involved in working memory processing was explored by functional magnetic resource imaging (fMRI).

Design: Using fMRI, we conducted a longitudinal study investigating alterations of brain function during a working memory task, the four-digit backward recall (BR) and forward recall (FR), in hypothyroid patients and controls.

Methods: fMRI scan was used in 13 female patients at two time points: before and after having been treated with levothyroxine (L-T₄) for ~6 months, and 12 matched euthyroid controls were also scanned. Wechsler Memory Scale–Chinese Revision was used to assess the memory states of each participant.

Results: The hypothyroid patients showed poorer memory states than that in controls. Furthermore, significant differences of task-induced deactivation (TID, task-dependent decreases in neural activity relative to rest) between patients and controls were found in the bilateral medial prefrontal cortices, posterior cingulate cortices, and left inferior parietal lobule ($P < 0.05$). These regions were considered as parts of a task-negative network, namely the default mode network (DMN). Concretely, relative to controls, patients showed diminished TID during BR in contrast to FR. After the L-T₄ treatment, neither the poor memory states nor the alteration of TID was detectable in patients.

Conclusion: Hypothyroidism is related to alterations of TID within DMN regions during working memory processing. These exploratory findings may imply potential neural correlates in hypothyroidism-related cognitive deficits and their recoveries.

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Introduction

Thyroid hormone plays a critical role in adult brain, influencing both mood and cognition (1, 2). It is well accepted that hypothyroidism is related to pathological alterations of thyroid hormone distributions and functioning in both hippocampus and cerebral cortex (1, 3, 4). There are various adverse effects of hypothyroidism on cerebral-dependent neurocognitive functions (1, 2, 5–7) including working memory (8, 9), which is the executive and attentional control of short-term memory providing for temporal storage and online manipulation of information (10). Working memory is considered to be the core of many other cognitive functions and vital for general human

intelligence (10, 11). Furthermore, specific deficit in working memory was found even at the mild stage of the disease (subclinical hypothyroidism) (9, 12). Therefore, working memory may be one of the primarily affected cerebral-dependent functions in hypothyroidism. However, the underlying neural substrate of such dysfunction remains to be explored.

Within decades, a new perspective on investigating the disease–brain interaction has been provided through neuroimaging approaches, such as functional magnetic resource imaging (fMRI) (13–15). It is a noninvasive technique that evaluates neural activity by measuring changes in the magnetic field associated with the deoxygenation of hemoglobin, namely the blood oxygen-level dependence (BOLD) signal. fMRI

scanning during certain conditions, such as performing a cognitive task, is used to reveal regional brain function and its disease-related alteration. Using fMRI, former studies had demonstrated two separate brain networks involved in working memory. Of the two networks, one is the task-positive network, including a series of frontal–partial brain regions showing raised BOLD signal, or the so-called task-induced activation (TIA, task-dependent increases in neural activity) (16, 17). The other is the task-negative network, including a series of medial frontal–partial brain regions showing reduced BOLD signal, or the so-called task-induced deactivation (TID, task-dependent decreases in neural activity) (18–20).

Accordingly, in order to investigate the impact of hypothyroidism on neural circuits involved in working memory, we conducted an fMRI study in newly diagnosed hypothyroid adults performing a working memory task, the four-digit backward recall (BR) and forward recall (FR) paradigm. Both TIA and TID during the task were compared between patients and controls to explore the potential hypothyroidism-related alteration in brain function. Post-scan psychometric evaluation using Wechsler Memory Scale–Chinese Revision (WMS–CR) was also employed to assess general memory function, including working memory function (21, 22). Moreover, all patients were investigated after having been treated with levothyroxine (L-T₄) for ~6 months, again, to examine the restoration of the altered brain functions.

Patients and methods

Participants

A total of 25 right-handed women, 13 patients with adult-onset hypothyroidism due to Hashimoto's thyroiditis and 12 voluntary euthyroid controls (age- and education-matched controls, Table 1), participated in this study. All patients were newly diagnosed with elevated TSH and abnormally low free T₄ (fT₄) and free triiodothyronine (fT₃) levels, and were recruited from the Division of Endocrinology in The First Affiliated Hospital of Anhui Medical University during 2007–2009. No participant was post-menopausal. During the entire study, neither of them was under pregnancy nor using oral contraceptives or other medications that were known to affect cognition. No one has reported any previous history of ischemic heart disease, stroke, diabetes, head injury, epilepsy, psychiatric illness, significant visual impairment, or endocrine diseases other than hypothyroidism. This study was approved by the human subjects review committee of The First Affiliated Hospital of Anhui Medical University. Written informed consents were obtained from all participants at recruiting.

Table 1 Comparison of clinical information and psychometric evaluations for hypothyroid and control participants (mean $\pm$ S.D.). Serum hormone levels distributed range: euthyroid controls, TSH (0.9–3.1 mIU/l); fT₄ (12.6–21.9 pmol/l); fT₃ (3.8–5.8 pmol/l). Pre-treatment patients, TSH (20.7–>150 mIU/l); fT₄ (3.5–9.7 pmol/l); fT₃ (0.4–3.3 pmol/l). Post-treatment patients, TSH (0.5–4.1 mIU/l); fT₄ (15.6–22.5 pmol/l); fT₃ (3.7–5.8 pmol/l).

	Euthyroid controls (n=12)	Hypothyroid patients (n=13)	
		Pre-treatment	Post-treatment
Age (years)	29.3 $\pm$ 6.7	29.4 $\pm$ 6.3	
Education (years)	12.8 $\pm$ 3.0	12.0 $\pm$ 3.2	
TSH (mIU/l)	1.7 $\pm$ 0.7	102.6 $\pm$ 57.8 [†]	1.8 $\pm$ 1.0 [¶]
fT ₄ (pmol/l)	16.9 $\pm$ 2.8	7.2 $\pm$ 1.9 [†]	18.3 $\pm$ 2.5 [¶]
fT ₃ (pmol/l)	4.6 $\pm$ 0.7	2.3 $\pm$ 0.9 [†]	4.6 $\pm$ 0.6 [¶]
MQ	124.4 $\pm$ 14.1	100.2 $\pm$ 25.1 [*]	121.0 $\pm$ 13.6 [¶]
Numeric span	14.4 $\pm$ 3.2	12.3 $\pm$ 2.7 [‡]	13.5 $\pm$ 3.0 [§]

fT₄, free thyroxine; fT₃, free triiodothyronine; MQ, memory quotient. Significant differences revealed by independent *t*-test between patients and controls, ^{*}*P* < 0.01, [†]*P* < 0.001; [‡]marginal significant, *P* = 0.090. Significant differences revealed by paired *t*-test between pre- and post-treatment patients, [§]*P* < 0.05, [¶]*P* < 0.01, [‡]*P* < 0.001.

Experimental design

We conducted a longitudinal study that included two identical experimental sessions of fMRI scan and psychometric evaluation for each patient. Of the two sessions, one was performed before treatment. All patients were then treated with L-T₄ immediately, and became euthyroid after 1 month. After that, they were treated continuously to maintain the euthyroid states. The second session was performed after 6 months of the replacement therapy to investigate a stabilized treating effect. Between the two sessions, no treatment other than L-T₄ was employed for any patient. All the controls participated only in one experimental session. Each participant took part in her experimental session during the first 10–15 days after onset of menstrual bleeding.

Hormone level assessment and psychometric evaluation

Serum hormone levels were measured for each participant 1-day before each session. Serum fT₃, fT₄, and TSH levels were measured by immunoassay using direct, chemiluminometric technology (ADVIA Centaur FT3, FrT4, and TSH-3, respectively, Siemens Healthcare Diagnostics Inc., New York, NY, USA) with a sensitivity of 0.3 pmol/l, 1.3 pmol/l and 0.004 mIU/l respectively. The normal reference ranges were 3.5–6.5 pmol/l for fT₃, 11.5–22.7 pmol/l for fT₄, and 0.35–5.5 mIU/l for TSH.

General memory states were assessed with the WMS–CR, a neurocognitive battery designed for the assessment of memory function by providing an overall memory quotient (MQ) (21, 22). A subtest of the

WMS-CR, the numeric span, which stands for the age-adjusted score of the sum of digital forward and backward span, was particularly evaluated between the groups to assess working memory function (23).

fMRI four-digit BR and FR task

All participants performed four-digit BR and FR trials (24) during the fMRI scan (Fig. 1). Every trial started with a fixation point displayed for 1 s in the center of the screen. Subsequently, four digits (selected from 1 to 9 without repetition, 1 s/digit) were presented sequentially at the location of fixation. After the last digit, a cue was presented to instruct the participants to recall the digits either in a forward or in a backward order by writing them on a sheet of paper. The participants were instructed to keep their heads still and not to watch while writing. An author stood near the scanner and made the recording paper available after each trial. The cue lasted for 1 s. Then, the screen remained blank until the onset of the next trial's fixation point. The total time allocated to recall and rest was 30 s. Because participants were able to finish the BR or FR task within 14 s, there was enough time (more than 16 s) for the BOLD signal to recover to the baseline level. Using a video projector, stimuli were presented on a translucent screen placed near the scanner bed, so that the participants could view the stimuli through a mirror placed above their eyes. The fixation-point, the digits, and the cue to instruct participants to recall extended at $2^\circ \times 2^\circ$, $2^\circ \times 2^\circ$, and $2^\circ \times 3^\circ$ visual angles on the screen respectively. Each participant completed two scans, one including ten BR trials and the other including ten FR trials. Before each scan, the type of task was told to participants. The order of the scans was counter-balanced among the participants.

MRI data acquisition and processing

Imaging data were collected on a 1.5 T Philips Infinion MR System (12). A circularly polarized head coil was used, with foam padding to restrict head motion. Functional images were acquired with a T2*-weighted

echo-planar imaging sequence (repetition time (TR)=2 s, echo time (TE)=40 ms, field of view (FOV)= 24×24 cm², matrix= 64×64 , flip angle= 90°) with 21 axial slices (slice gap=1.2 mm, voxel size= $3.75 \times 3.75 \times 4$ mm³) covering the whole cerebrum. Corresponding high-resolution T1-weighted imaging data were also obtained with a spin echo sequence (for anatomical overlay) and a spoiled gradient-recalled echo sequence (for stereotaxic transformation).

MRI data were analyzed using the Analysis of Functional NeuroImages (AFNI) (12, 24–26). For each run, the first three time points were discarded to account for the approach to steady state in the BOLD signal. The raw data were corrected for temporal shifts between slices and head motion, spatially smoothed with a Gaussian kernel (full width at half maximum=4 mm), and temporally normalized (for each voxel, the signal of each image was divided by the temporally averaged signal). Realignment parameters for each participant were carefully examined to ensure that the participant's head movement did not exceed 2 mm.

For each participant, the functional data set of each task (BR or FR) was correlated with a box-car time series (Task vs rest. Twenty different time series were contained. These time series started from the second, third, fourth, and fifth TR of each trial, with widths of one to five TRs, and all convolved with a gamma haemodynamic response function) to generate the individual correlation maps (27). Voxels that were positively/negatively correlated with the determined box-car time series were defined as activated (TIA)/deactivated (TID) voxels during the task respectively. The fit coefficients, which represented the scaling value required to best fit the reference time series to the observed BOLD signal, were used as a measure of the magnitude of TIA/TID (27). Very large fit coefficients (absolute value >15) were assumed to correspond to large draining veins and were ignored in the analyses (27).

All individual correlation maps were transformed to the Talairach space (re-sampled voxel size: $3 \times 3 \times 3$ mm³) according to the spatial transformation between the anatomic data and the Talairach space (28). Totally, six maps (controls, pre-treatment patients, and post-treatment patients, during BR or FR respectively) were generated by voxel-wise one-sample *t*-test. The survived clusters were determined by combining individual voxel threshold of $P < 0.001$ with a spatial cluster (cluster size from 40 to 49 voxels among the six maps), which yielded a false-positive level of 0.05 over the whole cerebrum according to Monte Carlo simulations conducted with AFNI (26). Clusters that did not reach this significant level were discarded.

The six maps of survived clusters were combined together with a logical 'OR' to locate the regions of interest (ROIs) (24). The ROIs of task-positive network were defined as clusters showing TIA, including the bilateral dorsolateral prefrontal cortices (dlPFC, BA 9), bilateral middle/inferior frontal gyri (M/IFG, BA

Figure 1 The sample paradigm of the four-digit backward (BR) and forward recall (FR) task. The reaction cues in actual experiments were displayed in Chinese.

6/9/44), supplementary motor areas (SMAs, BA 6/24, including part of dorsal anterior cingulate cortex), premotor areas (PMA, BA 6), and parietal areas (PA, BA 7/39/40). The ROIs of task-negative network were defined as clusters showing TID, including the bilateral medial prefrontal cortices (mPFC, BA 32/24, including part of rostral anterior cingulate cortex), posterior cingulate cortices (PCC, BA 31/7, including part of precuneus), and inferior parietal lobules (IPL, BA 39). The Talairach's coordinate and voxel size for each ROI were shown in [Supplementary Table 1](#), (see section on [supplementary data](#) given at the end of this article). For each task of every participant, fit coefficients of all voxels within each ROI were averaged and dropped into further group level analyses.

Statistical analysis

Student's *t*-tests for independent or paired samples in this study were used to evaluate the significance of group differences in age, education, serum hormone levels, psychometric evaluation, and fMRI data (described in detail below) with SPSS version 13.0 (SPSS, Chicago, IL, USA). Statistical significance for these analyses was set at $\alpha=0.05$ (all tests were two tailed).

A subtraction method (29) was applied in the group level analysis of fMRI data. In this study, FR was considered as a reference task in which mainly short-term memory was involved, whereas BR was considered as the true working memory task because it needs more attention and executive processes to generate the reverse sequence (24, 30). Because global effects of multiple non-neural factors, such as age-, mood-, disease-, and medication-related changes in neurovascular coupling, may confound the interpretation of differences in the BOLD signal (31, 32), systematic differences between conditions in one group versus another are considered to better reflect the specific differences in underlying neural activity (31). Therefore, either TIA or TID during FR was subtracted from that during BR within each ROI to generate the magnitude of BR–FR contrast (brain function contrast during BR and FR), which was used as the index of magnitude of working memory component (the additional attention and executive function involved in BR relative to FR). This index was then compared among the groups (patients (pre-treatment, or post-treatment) versus controls) using independent sample *t*-test or among the patient conditions (pre-treatment versus post-treatment) using paired *t*-test.

Results

Clinical and psychometric evaluation

All hypothyroid patients were diagnosed with elevated TSH and abnormally low fT₄ and fT₃ levels, while all of

which were restored within normal ranges after the L-T₄ treatment. The pre-treatment differences between patients and controls in these serum hormone levels were eliminated after treatment ([Table 1](#)). Pre-treatment patients showed significantly lower MQ ($P=0.007$) and marginally significant lower numeric span ($P=0.090$) than controls, which indicated poor memory states and slight working memory deficit. After treatment, the patients' memory states (including working memory) were significantly ameliorated (pre-treatment versus post-treatment, $P<0.016$) and reached comparable levels as those of controls (post-treatment patients versus controls, $P>0.483$) ([Table 1](#)).

Neuroimaging

The recall accuracies for fMRI four-digit BR and FR task were very high in all three groups (controls (BR: 97.50% $\pm$ 4.52; FR: 100% $\pm$ 0), pre-treatment (BR: 99.23% $\pm$ 2.77; FR: 100% $\pm$ 0), post-treatment (BR: 99.23% $\pm$ 2.77; FR: 99.23% $\pm$ 2.77)), with no significant differences between groups or patient conditions ($P>0.05$).

Comparisons of working memory component (BR–FR contrast)

TIA within task-positive network regions TIA was observed during both BR and FR in both patients and controls within the bilateral dlPFC, M/IFG, SMA, PMA and PA (detailed data shown in [Supplementary Table 2](#), see section on [supplementary data](#) given at the end of this article).

However, no significant difference in the magnitude of BR–FR contrast of TIA was found within any region between groups (patients versus controls), neither before, nor after treatment. There were no significant differences between the patient conditions (either pre-treatment or post-treatment; $P>0.05$).

TID within task-negative network regions TID was observed during both BR and FR in both patients and controls within the bilateral mPFC, PCC, and IPL (detailed data shown in [Supplementary Table 2](#), see section on [supplementary data](#) given at the end of this article).

Before treatment, significant differences of the magnitude of BR–FR contrast of TID between pre-treatment patients and controls were found in the bilateral mPFC (left, $t(1,23)=2.340$, $P=0.028$; right, $t(1,23)=2.202$, $P=0.038$), PCC (left, $t(1,23)=3.038$, $P=0.006$; right, $t(1,23)=2.326$, $P=0.029$), and left IPL ($t(1,23)=2.813$, $P=0.010$; [Fig. 2](#), [Table 2](#)). As a deactivation, the change in TID magnitude is opposite to common activations. Enhanced TID would result in more negative fMRI signals, vice versa. In order to better demonstrate the differences in TID among the groups,

we intentionally reversed the y axis in Fig. 2. In these regions, an enhanced TID was found during BR relative to FR in controls, whereas a diminished TID was found during BR relative to FR in pre-treatment patients (find detailed demonstrations in [Supplementary Figure 1](#), see section on [supplementary data](#) given at the end of this article).

After treatment, the pre-treatment differences of the magnitude of BR–FR contrast of TID were no longer detected within the same regions ($P > 0.05$; Fig. 2, Table 2). The TID of post-treatment patients had resumed to a similar pattern as that of controls, whilst enhanced TID was found during BR relative to FR (find detailed demonstrations in [Supplementary Figure 1](#), see section on [supplementary data](#) given at the end of this article). Furthermore, significant differences between pre-treatment and post-treatment patients were found in the bilateral PCC (left, $t(1,12) = 2.484$, $P = 0.029$; right, $t(1,12) = 2.219$, $P = 0.047$), and left IPL ($t(1,12) = 2.209$, $P = 0.047$) (Fig. 2, Table 2).

Discussion

This study intended to explore potential alteration of brain function in hypothyroid patients during working memory processing. Brain function related to working memory was evaluated between groups (patients (pre-treatment and post-treatment) versus controls) and patient conditions (pre-treatment versus post-treatment), using BR–FR contrast as an index. Before treatment, the results from WMS–CR revealed significant worse memory states (including slightly working memory deficit) in patients. During the fMRI scanning, the patients (pre-treatment and post-treatment) performed comparably well as controls in the four-digit BR and FR task. No significant difference of BR–FR contrast of TIA between pre-treatment patients and controls was found. However, significant differences of BR–FR contrast of TID between pre-treatment patients and controls were found in the bilateral mPFC, PCC, and left IPL. In these brain areas, the patients showed diminished TID during BR in contrast to FR relative to

Figure 2 Comparisons of working memory component (BR–FR contrast) related TID within task-negative network between patients with controls. Regions showing TID during the four-digit BR and FR task are demonstrated. mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; IPL, inferior partial lobule. Only comparisons within the left side of brain regions were shown, whereas those within the right side of brain regions were similar except for the right IPL. Detailed data for both sides could be found in [Table 2](#). In order to better demonstrate the deactivation, y axes were reversed. At diagnosis, significant differences between pre-treatment patients with controls were found in the mPFC, PCC, and IPL. After treatment, no significant difference between post-treatment patients with controls was found in all these brain regions. Significant differences between pre-treatment and post-treatment patients were found in the PCC and IPL. TID magnitude, average fit coefficient. Full colour version of this figure available via <http://dx.doi.org/10.1530/EJE-11-0046>.

Table 2 Working memory component (BR–FR) related TID within task-negative network. Significant differences revealed by student's *t*-tests are shown in bold.

ROIs	Patients (mean ± s.d.)		Controls (mean ± s.d.)	Student's <i>t</i> -tests (<i>P</i> value)		
	Pre	Post		Pre vs Controls	Post vs Controls	Pre vs Post
L-mPFC	0.06 ± 0.31	−0.16 ± 0.41	−0.28 ± 0.41	0.028	0.452	0.154
R-mPFC	0.08 ± 0.42	−0.12 ± 0.34	−0.29 ± 0.43	0.038	0.280	0.177
L-PCC	0.12 ± 0.18	−0.05 ± 0.18	−0.10 ± 0.18	0.006	0.476	0.029
R-PCC	0.14 ± 0.22	−0.02 ± 0.19	−0.06 ± 0.21	0.029	0.570	0.047
L-IPL	0.07 ± 0.21	−0.06 ± 0.13	−0.17 ± 0.22	0.010	0.129	0.047

ROI, region of interest; pre, pre-treatment hypothyroid patients; post, post-treatment hypothyroid patients; L, left; R, right; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; IPL, inferior parietal lobule.

controls. After having been treated with L-T₄ for ~6 months, the patients showed significantly ameliorated memory states (including working memory), which reached comparable levels as those of controls. In particular, all pre-treatment statistical differences of BR–FR contrast of TID between the two groups were no longer detected, implying a restoring progress of brain functioning within these regions of patients.

Both TIA and TID were observed in both patients and controls performing the four-digit BR and FR task. TIA was found in the task-positive network, including the bilateral dlPFC, M/IFG, SMA, PMA, and PA. These brain areas play a role in the attentional, executive, and mnemonic processes involved in generating and maintaining original/reverse digit sequences (24). Correspondingly, TID was found in the task-negative network, including the bilateral mPFC, PCC, and IPL. These brain areas play a role in the reallocation of mental resources by suppressing less task-relevant cognitive processes (that is how the deactivation comes from) (18–20).

To our knowledge, it is the first time that the alteration of TID has been revealed in patients with thyroid hormone deficiency. Former studies on euthyroid subjects had found that increase of cognitive load was related to enhancement of TID (19, 27, 33). In particular, TID of bilateral mPFC and left IPL was more sensitive to attention load, whereas the TID of bilateral PCC was sensitive to both attention and mnemonic loads involved in working memory tasks (34). In this study, we found consistent results in controls, although the pre-treatment hypothyroid patients showed diminished TID during BR (high load) contrast to FR (low load) relative to controls. Similar diminishment of TID was also found in several brain diseases and mental disorders, such as age-related cognitive impairment (20), Alzheimer's disease (35), and major depression (36), etc.

The regions showing altered TID in this study, including the bilateral mPFC, PCC, and left IPL, were also considered as parts of the default mode network (DMN) (18, 37), which were frequently found activated during rest for their role in 'stimulus-independent thoughts', ranging from internal and external

monitoring to mind wandering (38, 39). The DMN plays an important role in the pathophysiology of many brain diseases and mental disorders (39, 40). However, there is no direct evidence for the mechanism of hypothyroidism-related alteration of TID within DMN regions. Several possibilities should be considered. An interpretation may be that hypothyroidism affects TID through regulating neurotransmitters, such as dopamine. Animal studies showed that hypothyroidism was related to decreased accumulation rate of dopamine (41), and downregulation of dopamine was related to diminished TID (42). Another possibility may be that hypothyroidism alters regional brain perfusion (43) or metabolism (44) within these DMN regions, which results in alteration of TID. Additionally, pathological changes in thyroid autoimmunity (45, 46), genetic polymorphisms of deiodinase enzymes and thyroid hormone transporters (45, 47), as well as mood disorders associated with hypothyroidism (7, 48–50), etc. could also be potential explanations. Further investigations with corresponding approaches are required to test all these possibilities.

In this study, we did not find significant alteration of TIA in pre-treatment patients underlying comparable task performance. However, this result did not suggest that the task-positive network was intact in hypothyroid patients. Altered TIA within task-positive network regions, including the bilateral dlPFC, M/IFG, and SMA were found combining with worse task performance in subclinical hypothyroid patients when they were asked to perform a harder working memory task (two-back) during fMRI scanning (12). Therefore, there could have been potential alteration of TIA beyond our present observation, which may be concealed by a potential ceiling effect due to the relatively easy task condition (average accuracies over 95% were achieved in all groups).

Interestingly, differences in TID were not concealed at the same easy task condition within the same subjects, which may be of potential implications. A necessary precondition for fMRI application is that the participants should perform the task acceptably well during scanning, because they may disengage from the task if it is too hard (51), which would render the corresponding

fMRI data meaningless. For example, in our previous study, hypothyroid patients were excluded from fMRI investigation because they could not perform the two-back task at an acceptable level (12), although this task was considered to be more sensitive (9). Comparing with hard tasks, easy tasks, i.e. digit span, are more practicable and less restricted by the wide range of cognitive deficit severity in hypothyroid patients (5, 52), and could be performed even by patients with relatively severe hypothyroidism. Accordingly, TID during easy task conditions may play a promising role in clinical applications in exploring the pathological cognitive processes in hypothyroidism.

The L-T₄ treatment was useful for restoration of both behavior performance and brain function. After the treatment, the memory states (including working memory function) of patients were significantly ameliorated to comparable levels of controls, which were consistent with some previous behavior studies (23, 53). Meanwhile, no significant difference in brain function was detected either in TIA or in TID, which was also in line with former neuroimaging studies (44). Significant differences of TID between pre- and post-treatment patients were found in the bilateral PCC and left IPL, suggesting an overt treatment-related restoration of brain function within these regions.

Hypothyroidism is also frequently associated with mood disorders, mostly depression and anxiety (48–50). Cognitive deficits in hypothyroidism were found in both studies in which mood disturbances were controlled (9, 54) or not (1, 2). Meanwhile, during working memory processing, both similarity and differences between current findings with those from mood disorder studies were revealed. Depression would result in diminished TID within the mPFC, which is similar to our results, but not within the PCC or IPL (36). In the contrary, anxiety would result in elevated TID within the DMN regions (55). Nevertheless, as the neuropsychological symptoms were not specifically evaluated in this study, the potential role of hypothyroidism-related mood disorders in altered brain function remains to be explored.

Further limitations of the study design should be considered, such as training effect. Previous evidence (56, 57) showed that the training-related cerebral activation was found after about 2 weeks of daily working memory practices (over ten times of practices in total) and changed following an inverse U-shaped quadratic function within 4 weeks (56). Accordingly, our findings may not be mainly accounted for the training effects due to both the lack of practices (no specific training between the two experimental sessions) and the relatively long time interval (over 6 months). However, the sample size of this study is relatively limited. Therefore, our results should be viewed as exploratory and the association of thyroid hormone or thyroid autoimmunity with brain function remains to be explored in the future.

In summary, this study provides novel evidence for alteration of brain function in hypothyroid patients during working memory processing. Altered TID within DMN regions was found before treatment but no longer detectable after the L-T₄ treatment. These findings implied potential clinical applications of TID in investigating the pathological cognitive processes in hypothyroidism.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-11-0046>.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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