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Cerebral blood flow in transient hypothyroidism after thyroidectomy: Arterial spin labeling magnetic resonance study

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Abstract

OBJECTIVE: Our purpose was to apply arterial spin labeling (ASL) magnetic resonance imaging (MRI) to characterize regional cerebral blood flow (rCBF: the CBF values at each voxel / the subject's mean global flow) in patients with transient hypothyroidism after thyroidectomy.

METHODS: Our study included 27 patients who had undergone total thyroidectomy due to thyroid cancer and pre-^{131}I therapy and 24 controls. Patients were evaluated at two points in time: before and after thyroxine replacement. The assessments for the patients and controls consisted of evaluation of ASL of the brain and the severity of depression using 21-question Beck Depression Inventory (BDI). The assessments for the patients also included thyroid hormone lebel. We performed the comparison of rCBF between patients and controls, and investigated the association between rCBF in hypothyroid patients and thyroid hormone level and BDI score.

RESULTS: Hypothyroid patients showed a significantly lower rCBF in the cerebellum, the left thalamus and some regions, and showed a significantly higher rCBF in the bilateral frontal gyri and some regions. After thyroxine replacement, patients showed a significantly lower rCBF mostly in the right frontal lobe, and showed a significantly higher rCBF in the left frontal and parietal lobes, although the degree of rCBF changes was lower after thyroxine replacement. In the hypothyroid patients, significant positive relationships were found between free T3 and the rCBF ($p<0.05$ corrected for FDR).

CONCLUSIONS: This study revealed alterations of rCBF in patients with transient hypothyroidism. ASL is helpful for understanding of the effects of hypothyroidism on the brain.

ORIGINAL ARTICLE

INTRODUCTION

Hypothyroidism is a contributor to psychiatric morbidity such as inattentiveness, inability to concentrate, deficits in memory, psychomotor slowing but also depressive mood state, anxiety and persecutory delusion (Constant *et al.* 2001). Positron emission tomography- and single photon emission computed tomography studies have shown changes in the regional cerebral blood flow (rCBF) of patients with hypothyroidism (Schraml *et al.* 2006; Krausz *et al.* 2007; Nagamachi *et al.* 2004). Patients whose thyroid cancer is addressed by total thyroidectomy may develop hypothyroidism, rCBF changes, and psychiatric disturbances, especially depression, because there is a close relationship between hypothyroidism and rCBF changes (Nagamachi *et al.* 2004; Whybrow, 1994; O'Brien & Harris, 1968) although the underlying pathogenesis has not been elucidated. According to some studies, adequate thyroid hormone replacement therapy alleviated or reversed such rCBF changes (Sensenbach *et al.* 1954; Scheinberg, 1950) while according to others it did not (Krausz *et al.* 2007; Nagamachi *et al.* 2004). Changes in rCBF may be a biomarker for the effect of thyroid hormone replacement therapy in patients who had undergone total thyroidectomy for thyroid cancer.

Arterial spin labeling (ASL) magnetic resonance imaging (MRI), a technique for quantifying regional brain perfusion, does not require the use of radioactive sources or contrast agents. This is important if rCBF is to be used for tracking therapeutic effects. Furthermore, the measurement reliability and reproducibility of three-dimensional (3D) pseudo-continuous ASL (pCASL) perfusion imaging (Wu *et al.* 2007) is sufficiently high for the assessment of the rCBF (Wu *et al.* 2014). In our search of the literature we found no studies that used ASL to investigate rCBF in hypothyroid patients. We examined the feasibility of using 3D pCASL MRI to characterize the rCBF in patients with transient hypothyroidism.

MATERIALS AND METHODS

Subjects

This study was approved by the Ethics Committee of Hiroshima University, Japan; written informed consent was obtained from all participants.

We initially enrolled 37 thyroid cancer patients who had undergone thyroidectomy and ^{131}I therapy between December 2012 and September 2014. All were older than 20 and younger than 75 years. None had undergone thyroxine replacement therapy for at least four weeks for the purpose of increasing ^{131}I uptake until ^{131}I therapy started. The diagnosis of hypothyroidism was based on the level of serum free tri-iodothyronine (free T3, normal range 2.3–4.7 pg/mL), free thyroxine (free T4, normal range 1.1–1.9 ng/dL), and thyroid-stimulating hormone (TSH, normal range 0.48–4.82 μU/mL) within a week before the start of ^{131}I therapy. On the day of the assessment of thyroid function all patients underwent brain MRI studies and were quantified the severity of depression using the 21-question Beck Depression Inventory (BDI) where higher scores indicate more severe depressive symptoms.

We excluded 10 patients from our study because the image quality was inadequate due to susceptibility artifacts induced by dental metals (n=2) or metals used for posterior cervical spinal fusion (n=1), or due to machine trouble (n=1), venous malformation (n=3), brain infarcts (n=2), or brain metastasis (n=1). Thus, the final study population consisted of 27 patients (9 men, 18 women; median age 50 years, range 22–74 years). For 16 of the 27 patients, this was the first use of ^{131}I therapy after thyroidectomy. For six patients, it was the second time, for three, it was the third time, for one, it was the fourth time, and for one, it was the seventh time. Thyroxine replacement therapy was immediately resumed after the ^{131}I therapy.

At the second assessment each patient had been receiving thyroxine for at least 12 weeks (median 16 weeks, range 12–34 weeks) from recommencement of the thyroxine replacement therapy. All patients underwent brain MRI studies and the 21-question BDI again on the same day. The diagnosis of euthyroidism was based on the latest level of serum free T3, free T4 and TSH being available around the second assessment.

Our controls were 24 healthy volunteers (8 men, 16 women; median age 44 years, range 32–66 years). We found no significant difference in age between the patients and the controls (p=0.19, Mann-Whiteney test). Again, we found no significant difference in gender between the two groups (p=1.00, chi-square test). The controls had no neurological or psychiatric disorders including alcoholism, substance abuse, atypical headache, head trauma, or asymptomatic cerebral infarction detected by MRI. They underwent brain MRI studies and the 21-question BDI only once.

MRI

All studies were performed on a 3T magnetic resonance (MR) system (Signa HDxt, GE Healthcare, Milwaukee, WI) using a dedicated eight-channel phased-array head coil (USA Instruments, Aurora, OH). During the MR examination, all subjects were instructed to relax with their eyes closed but without falling asleep. All patients underwent three-dimensional (3D) pseudo-continuous ASL (pCASL) perfusion imaging (Wu *et al.* 2007) covering the whole brain using a 3D background suppressed fast-spin-echo stack-of-spiral readout module with 8 in-plane spiral interleaves (TR/TE = 4463/10.2 ms, labeling duration = 1500 ms, post-labeling delay = 1525 ms, no flow-crushing gradients, in-plane matrix = 128×128, flip angle = 155°, NEX = 4, slice thickness = 4 mm, FOV = 240 mm, voxel size = 1.8×1.8×4 mm), and an echo train length of 1 to obtain 30 consecutive axial slices. A 10-mm-thick labeling plane was placed 20 mm

inferior to the lower edge of the cerebellum. The total scan time was 335 seconds. For each of the 30 volumes unlabeled- were subtracted from labeled images and M0 map correction was performed using vendor-supplied software. For voxel-based analysis, axial 3D fast spoiled gradient-recalled echo (3D-FSPGR) images covering the whole brain were acquired for image registration and normalization (TR/TE = 6.8 ms/1.9 ms, TI = 450 ms, matrix = 256×256, flip angle = 20°, slice thickness = 1 mm, spacing = 0 mm, acquisition time = 359 seconds, FOV = 256×256 mm).

Image analysis

For each subject we converted the image files from the proprietary format to Analyze. The rest of the analysis was conducted using both the FMRIB Software Library (FSL, v5.0.2.2, http://fsl.fmrib.ox.ac.uk) and Statistical Parametric Mapping 8 (SPM8, Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk) software. We combined both geometric transformations (normalization and co-registration with removal of non-brain tissue) to express all ASL images of all subjects in the Montreal Neurological Institute (MNI) T1 template in SPM8 using the ASL toolbox (Institute of Psychiatry at King's College London, Reina Sofia Foundation and Rey Juan Carlos University, http://www.fundacioncien.es). Then, the parameters were applied to the corresponding perfusion maps and each voxel was resampled to 2×2×2 mm (Kandel *et al.* 2015). Finally, the images were spatially smoothed using an isotropic Gaussian filter (8-mm full-width at half-maximum).

Statistical analysis

Group analysis was performed using SPM8. For voxel-based comparisons of the perfusion maps of hypothyroid and control subjects, and of euthyroid and control subjects we applied the two-sample *t*-test that uses the age and sex as covariates to detect hyper- and hypoperfusion. To reduce the potential inter-individual variability in CBF, the CBF values at each voxel were divided by the subject's mean global flow. We defined this as rCBF.

To analyze the possible association between the pretreatment rCBF in hypothyroid subjects and the serum level of free T3 and free T4 we subjected the BDI score obtained in the hypothyroid state and the reduction in the BDI score [(baseline score – follow-up score) / baseline score] to multiple regression analysis using the age and sex as covariates.

For each analysis the initial voxel threshold was set at $p<0.001$; it was corrected for multiple comparisons by using the false discovery rate (FDR) ($p<0.05$) with cluster size threshold k. All locations are reported in MNI coordinates.

RESULTS

In the hypothyroid state, the mean value of free T3 was 1.5±1.3 (standard deviation, SD) pg/mL; it was 0.3±0.2 ng/dL for free T4, and 79.5±67.3 μU/mL for TSH. In the euthyroid state, the mean value of free T3 was 3.0±0.7 pg/mL; it was 1.6±0.3 ng/dL for free T4, and 0.9±1.7 μU/mL for TSH (Table 1).

Compared with the controls, the rCBF was significantly lower in the posterior parts of the brain, including parts of the cerebellum, the left fusiform gyrus, the left thalamus, and the left red nucleus in patients who manifested hypothyroidism before treatment. All clusters exceeding the statistical threshold ($p<0.05$ corrected for FDR; k≥1052) supplied by the SPM8 software are listed in Table 2. The rCBF was significantly greater in the left superior-, medial-, and inferior frontal gyri, the right superior and middle frontal gyrus, the right orbital gyrus, the left superior and middle temporal

Tab. 1. Results of post-thyroidectomy thyroid function tests.

Measure	Hypothyroid	Thyroid hormone replaced
Free T3 (pg/mL)	1.5±1.3	3.0±0.7
Free T4 (ng/dL)	0.3±0.2	1.6±0.3
TSH (μU/mL)	79.5±67.3	0.9±1.7
BDI score	7.9±7.3	6.5±3.6

Data are the mean ± standard deviation; T3 = tri-iodothyronine, T4 = thyroxine; TSH = thyroid-stimulating hormone; BDI = 21-question Beck Depression Inventory

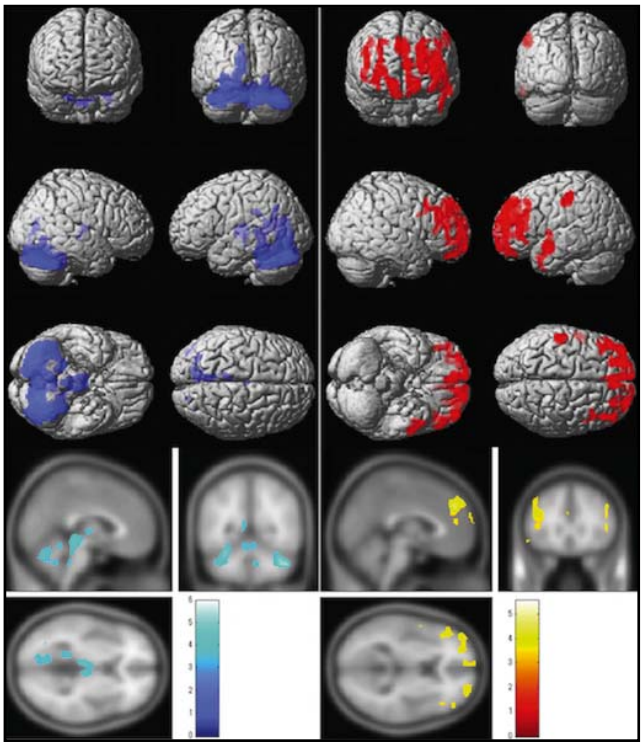

Fig. 1. rCBF in hypothyroid patients and the controls. The color bars represent the *t*-value of the rCBF changes. (a) Regions with significantly lower rCBF in hypothyroid patients than the controls. (b) Regions of significantly higher rCBF in hypothyroid patients than the controls ($p<0.05$ corrected for FDR), see Table 2 for details.

Tab. 2. Analysis of statistical parametric mapping in patients with hypothyroidism.

rCBF	Location of clusters	Cluster size	Maximal *t* score	MNI coordinates of maximal *t* score		
				x	y	z
Decreased	Right cerebellum (culmen)	8471*	5.96	38	–58	–34
	Left fusiform gyrus (BA19)	8471*	5.22	–28	–58	–12
	Left thalamus	1052*	4.71	–6	–20	6
	Left red nucleus	1052*	4.47	–5	–22	–4
Increased	Left medial frontal gyrus (BA 9)	807*	5.54	–4	44	36
	Left medial frontal gyrus (BA 10)	807*	4.71	5	44	35
	Left superior frontal gyrus (BA 9)	2072*	4.99	–20	56	34
	Left inferior frontal gyrus (BA 46)	2072*	4.77	–46	35	14
	Left superior frontal gyrus (BA 10)	701*	4.89	–6	68	20
	Left superior frontal gyrus (BA 11)	701*	4.8	–16	54	–14
	Right superior frontal gyrus (BA 11)	1583*	4.81	14	68	–10
	Right orbital gyrus (BA11)	1583*	4.81	5	48	–22
	Right middle frontal gyrus (BA9)	1583*	4.52	48	34	34
	Left postcentral gyrus (BA2)	261*	4.59	–52	–26	46
	Left middle temporal gyrus (BA21)	458*	4.58	–54	2	–14
	Left superior temporal gyrus (BA38)	458*	4.42	–45	2	–12

MNI = Montreal Neurological Institute; BA = Brodmann's area; Cluster size refers to the number of voxels; All maximal *t* scores are reported by using MNI coordinates; * Local maxima within one cluster.

Tab. 3. Analysis of statistical parametric mapping after thyroxine replacement therapy.

rCBF	Location of clusters	cluster size	maximal *t* score	MNI coordinates of maximal *t* score		
				x	y	z
Decreased	Right inferiorl frontal gyrus (BA 45)	902*	5.76	58	20	4
	Right inferiorl frontal gyrus (BA 47)	902*	5.57	38	15	–10
	Right medial frontal gyrus (BA 25)	348*	4.99	6	10	–20
	Right hypothalamus	348*	3.99	5	–2	–12
	Left cerebellum (culmen)	351*	3.96	–6	–32	–16
	Left red nucleus	351*	3.77	–6	–22	–5
	Right thalamus	351*	3.55	8	–12	10
Increased	Left postcentral gyrus (BA 2)	1625*	5.07	–54	–28	48
	Left precentral gyrus (BA 6)	1625*	4.91	–50	–2	38
	Left precentral gyrus (BA 4)	1625*	4.84	–56	–14	40
	Left superior frontal gyrus(BA10)	1877*	5.06	–20	50	18
	Left medial frontal gyrus (BA 8)	1877*	4.77	–42	30	46

MNI = Montreal Neurological Institute; BA = Brodmann's area; Cluster size refers to the number of voxels; All maximal *t* scores are reported by using MNI coordinates; * Local maxima within one cluster.

gyrus, and the left precentral gyrus of patients with pre-treatment hypothyroidism. All clusters exceeding the statistical threshold (p<0.05 corrected for FDR; k≥261) supplied by the SPM8 software are listed in Table 2. These results are also shown in Figure 1.

Patients after thyroxine replacement therapy showed a significant decrease in the rCBF in the right inferior and medial frontal gyrus, the right hypothalamus, left cerebellum, left red nucleus, and right thalamus. All clusters exceeding the statistical threshold (p<0.05 corrected for FDR; k≥348) supplied by the SPM8 software are listed in Table 3. The post-treatment patients also showed a significant increase in the global CBF. Regions exhibiting increased rCBF included the left precentral

and postcentral gyrus, the left superior frontal gyrus, and the left medial frontal gyrus. All clusters exceeding the statistical threshold (p<0.05 corrected for FDR; k≥325) supplied by the SPM8 software are listed in Table 3. These results are also shown in Figure 2.

There was a significant relationship between free T3 and the rCBF in the right fusiform gyrus and the right cerebellum of hypothyroid patients before treatment (p<0.05 corrected for FDR; k≥340) (Table 4, Figure 3) but not between free T4, the BDI score, the BDI reduction rate, and rCBF in the hypothyroid brain.

DISCUSSION

To our knowledge, this is the first study that used ASL to evaluate the rCBF during thyroidectomy-induced transient hypothyroidism. We document that in hypothyroid patients the rCBF in the posterior parts of the brain was significantly decreased and that it was increased primarily in the frontal and temporal regions and there was a significant positive relationship between their free T3 value and the rCBF. After thyroxine replacement therapy rCBF changes in some regions persisted.

We also found a significant reduction in the rCBF in the cerebellum, the left fusiform gyrus, the left thalamus, and the left red nucleus in the hypothyroid patients. Our findings coincide with nuclear medicine studies that reported a decrease in the rCBF in hypothyroidism (Constant *et al.* 2001; Schraml *et al.* 2006; Nagamachi *et al.* 2004; Krausz *et al.* 2004) and raise questions regarding mechanisms by which thyroid hormones might affect the rCBF. In the amygdala and hippocampi, regions rich in nuclear thyroid hormone receptors, the rCBF was not reduced, suggesting that they do not mediate thyroid regulation of the rCBF but that extranuclear processes are involved. The thyroid status influences baroreflex function and autonomic contributions to the arterial pressure and heart rate (Foley *et al.* 2001) and a decrease in CBF has been attributed to increased vascular resistance (O'Brien & Harris, 1968; Sensenbach *et al.* 1954). While the cerebral vasculature is richly innervated by autonomic nerves (Edvinsson, 1987; Heistad & Marcus, 1978), the vessels of the vertebrobasilar system manifest less sympathetic innervation than the vessels of the carotid system (Garg, 2001). We posit that an autonomic imbalance due to hypothyroidism may result in insufficiency for maintaining adequate CBF in the posterior cerebral areas.

We also document a relatively increased rCBF in the left superior-, medial-, and inferior frontal gyri, the right superior and middle frontal gyrus, the right orbital gyrus, the left superior and middle temporal gyrus, and the left precentral gyrus in hypothyroid patients. Schraml *et al.* (Schraml *et al.* 2006). showed that rCBF was increased in the bilateral medial frontal gyri during hypothyroidism. However, most nuclear medicine studies demonstrated no areas of increased rCBF. This discrepancy may be due to the use of dif-

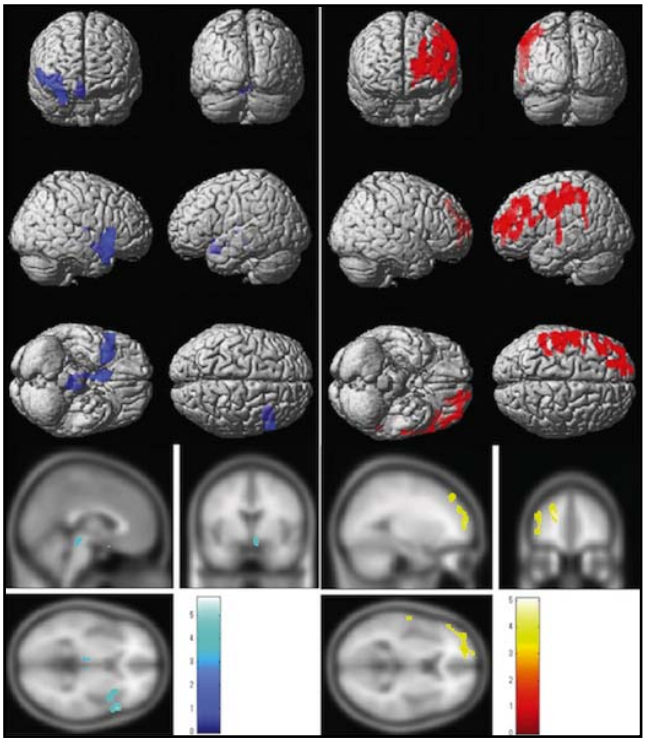

Fig. 2. rCBF in patients after thyroxine replacement therapy and in the controls. Color bars represent the t-value of the rCBF changes. (a) Regions displaying significantly lower rCBF in patients than the controls. (b) Regions of significantly higher rCBF than in the controls (p<0.05 corrected for FDR), see Table 3 for details.

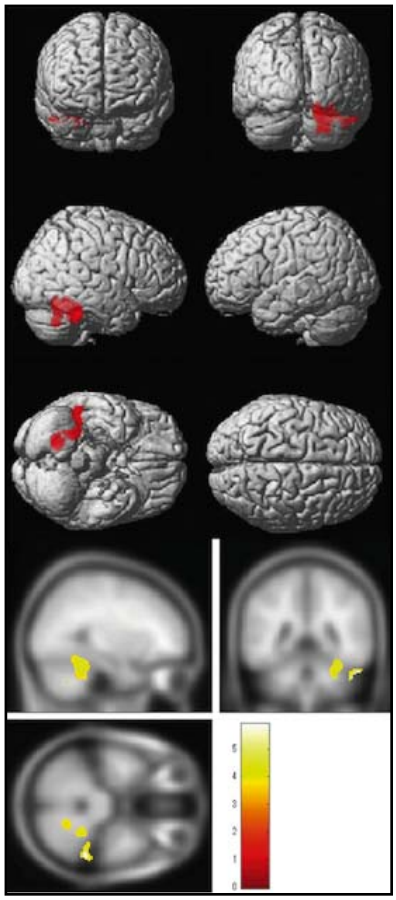

Fig. 3. Clusters showing a significant positive correlation between rCBF and the serum free T3 level in hypothyroid patients (p<0.05 corrected for FDR), see Table 4 for details.

Table 4 Clusters showing a significant positive correlation between rCBF and serum free T3 in patients with hypothyroidism

Measure	correlated cluster	cluster size	maximal *t* score	MNI coordinates of maximal *t* score		
				x	y	z
Free T3	Right fusiform gyrus (BA20)	403*	5.91	52	–40	–30
	Right cerebellum (culmen)	403*	5.47	46	–42	–36
	Right cerebellum (declive)	340*	5.21	18	–60	–22
	Right cerebellum (pyramis)	340*	4.07	22	–64	–40

MNI = Montreal Neurological Institute; BA = Brodmann's area; Cluster size refers to the number of voxels; All maximal *t* scores are reported by using MNI coordinates; * Local maxima within one cluster.

ferent radiotracers and modalities; Schraml *et al.* used a ^{99m}Tc ethyl cysteinate dimer (ECD) while ^{99m}Tc hexamethylpropylene amine oxime (HMPAO) was used in the other studies (Nagamachi *et al.* 2004; Krausz *et al.* 2004). ASL CBF measures reflect delivery of blood to the capillary bed (Luh *et al.* 2000), so we think that the discrepancy between our study and the others may be due to the differene of modalities.

The frontal areas and left thalamus with altered rCBF in our study are parts of the limbic-thalamo-cortical circuit. As it is implicated in depressive disorders (Drevets, 2003), rCBF changes in these areas may contribute to depression in hypothyroid patients.

Although the degree of rCBF changes was lower after thyroxine replacement therapy, we found that rCBF deficits persisted in our patients. Some studies reported the normalization of decreased rCBF upon return to the euthyroid state (Constant *et al.* 2001; Sensenbach *et al.* 1954; Scheinberg, 1950), however, as they did not compare patients with controls, it remained unknown whether rCBF in either the hypothyroid or the euthyroid condition is similar to the rCBF of controls. Our results suggest this may not be so and earlier studies support our findings (Nagamachi *et al.* 2004; Krausz *et al.* 2004). For example, Nagamachi *et al.* (2004) reported that an area with significantly low rCBF persisted in 7 of 16 of their patient treated with thyroxine replacement therapy. Moreover, they found no statistically significant difference between improved rCBF and the patient age, the serum level of T4, T3, and TSH, and the severity of depression. As we also detected no significant relationship between the BDI reduction rate and rCBF in our patients we are unable to identify the factor(s) that led to rCBF improvements. Regional perfusion deficits may require a longer time to normalize or they may reflect an abnormal trait pattern typical of hypothyroidism.

The free T3 level correlated with rCBF in the right fusiform gyrus, involved in the recognition of faces and words (Radua *et al.* 2010; Acheson & Hagoort, 2013), and with rCBF in the right cerebellum. The cerebellum plays an important role in motor control and it may also be involved in some cognitive functions such as attention and language (Wolf *et al.* 2009). Changes in the rCBF in these areas may contribute to the cognitive deficits recognized in hypothyroid patients. We found no regions in the hypothyroid brain in which there was a significant association between the serum free T4 level and rCBF. This may explain why T4 was less active than T3.

We detected no significant relationship between the BDI score and rCBF in the hypothyroid brain. Schraml & Beason-Held (2010) who used EDC reported that hypothyroid patients with higher BDI scores, indicative of higher levels of depression, manifested increased rCBF in the right insular cortex and left thalamus and Nagamachi *et al.* (2004) who used HMPAO showed that an area with significantly decreased rCBF extended to the prefrontal area as the severity of depression increased.

Our study has some limitations. First, as the number of hypothyroid patients was small, the significance of our findings is unclear. Long-term prospective studies on larger cohorts are underway to confirm our results and to investigate the effects of prolonged thyroxine treatment. Second, we didn't eliminate some factors that could affect CBF quantification such as diurnal imaging time and caffeine administration. Third, we did not investigate the influence of hypothyroidism on cardiac contractility (Forfar *et al.* 1982; Foldes *et al.* 1987). Because the rCBF is affected by cardiac function (Gruhn *et al.* 2001; Wu *et al.* 2009, Fushimi *et al.* 2013) we cannot exclude the influence of impaired cardiac contractility. We are planning future studies that categorize hypothyroid patients based on their myocardial function.

CONCLUSION

Our ASL findings suggest that widespread rCBF changes occur in patients with transient hypothyroidism and that they persist after thyroxine replacement therapy. There was a significant positive relationship between the serum free T3 level and rCBF in some brain regions. These ASL findings may help to elucidate the effects of hypothyroidism on the brain.

Conflict of interest

We declare that we have no conflict of interest.

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