Technetium-99m ethyl cysteinate dimer (ECD) cerebral accumulation and symptom and sign severity during hypothyroidism

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Submitted: 2009-10-28 Accepted: 2010-01-01 Published online: 2010-02-17

Key words: **hypothyroidism; brain; single photon emission computed tomography (SPECT); neuropsychological; depression; thyroid stimulating hormone (TSH)**

Neuroendocrinol Lett 2010; **31**(1):161–167 **PMID:** NEL310110A02 NEL310110A02

Abstract

OBJECTIVE: The purpose of this study was to correlate hypothyroid-related symptomatology with regional cerebral blood flow (rCBF) during hypothyroidism.
MATERIALS AND METHODS: Nine thyroidectomized patients underwent neuropsychological testing and single photon emission computed tomography (SPECT) of their brains with technetium-99m (Tc-99m) ethyl cysteinate dimer (ECD), a lipophilic cerebral blood flow radiotracer, while hypothyroid, and again following thyroid hormone replacement. Neuropsychological test scores and TSH levels while hypothyroid were correlated with rCBF in hypothyroid-affected areas of the brain.
RESULTS: Correlations were found during hypothyroidism between the noted parameters and ECD radiotracer accumulation in the following respective regions, all of which demonstrated hypothyroid-related cerebral blood flow (CBF) aberrations: TSH and left middle occipital gyrus; psychomotor performance speed and left precentral gyrus; and depression and right middle frontal gyrus, left middle frontal gyrus, right insula, and left thalamus.
CONCLUSIONS: Severity of psychomotor impairment and depression, and TSH level during hypothyroidism appeared to correlate with CBF to brain regions associated with motor activity, mood and vision, respectively; and previously shown to manifest significantly altered rCBF during hypothyroidism.

ORIGINAL ARTICLE

INTRODUCTION

Numerous investigators have documented depression, anxiety, psychomotor slowing and cognitive impairment in individuals when hypothyroid which are not present when euthyroid (Denicoff *et al.* 1990; Constant *et al.* 2005). Moreover, hypothyroidism-related aberrations in both regional cerebral blood flow (rCBF) and cerebral metabolic rate of glucose utilization (CMRGlc) have been demonstrated using nuclear medicine techniques (Constant *et al.* 2001; Krausz *et al.* 2004; Nagamachi *et al.* 2004; Kaya *et al.* 2007). Although findings have been somewhat inconsistent, we and several other investigators have found similarities in rCBF in the brains of patients with hypothyroidism and those with major depressive disorder (Nagamachi *et al.* 2004; Schraml *et al.* 2006; Krausz *et al.* 2007). In a previous publication, we described regional cerebral decreases and increases of technetium 99m (Tc-99m) ethyl cysteinate dimer (ECD) accumulation, representing differences in rCBF, in a cohort of patients during severe, transient hypothyroidism relative to the thyroid hormone-replaced state (Schraml *et al.* 2006). We also found this group of patients to be significantly more depressed, anxious and psychomotorically-slowed during the hypothyroid state, and we commented on the significance of the particular brain regions in which these differences were observed in light of their functional neuroanatomic implications in our subject's symptomatology. In the present study, we took the further step of correlating degree/severity of symptoms and signs of hypothyroidism (as well as TSH level) with the previously defined hypothyroid-related regional changes in CBF/Tc-99m ECD accumulation. In light of the symptomatology in our cohort and the results from similar correlative analyses in major depressive disorder (Marangell *et al.* 1997; Graff-Guerrero *et al.* 2004; Beauregard *et al.* 2006), we expected to find overlap between the cerebral ECD accumulation patterns related to neuropsychological measurement scores and thyroid stimulating hormone (TSH) levels, and those previously shown to be related to the hypothyroid condition in our cohort.

MATERIALS AND METHODS

Subjects

Nine patients, each status post thyroidectomy for treatment of thyroid carcinoma who were presenting for a radioiodine thyroid cancer survey, participated in the study. These subjects included four women and five men with a mean age of 33.3 (± 8.7 SD) years who, with the exception of thyroid cancer, were free of current or past significant medical problems; including no history of neurological or psychiatric illness. None of the subjects had evidence of brain metastases, and no subject was taking psychotropic medication. Each subject was right handed and, educationally, each had at least a high school diploma.

The study was approved by the Institutional Review Board of the National Naval Medical Center, the procedures followed were in accordance with the ethical standards of the Institutional Review Board, and all of the subjects demonstrated understanding of the experiment and provided written informed consent.

Study Design

Subject evaluations were performed at two points in time: when each subject was markedly hypothyroid and after each subject had received appropriate thyroid hormone replacement. When initially evaluated, each subject had been without thyroxine for at least 7 weeks and without triiodothyronine for at least 3 weeks to achieve their markedly hypothyroid condition. At the time of the second evaluation, each subject had received thyroxine for at least seven weeks. The initial and follow-up evaluations consisted of thyroid function tests; assessments of mood, anxiety level, and psychomotor function; and single photon emission computed tomography (SPECT) of the brain.

Neuropsychological Testing

Testing was performed 4 (± 2.6 SD) days after the hypothyroid scan and 2 (± 6.3 SD) days after the thyroid hormone replacement scan. Mood and anxiety assessments included the Beck Depression Inventory (BDI) and the state portion of the Spielberger State-Trait Anxiety Inventory (STAI), respectively. The measures of interest in this study were the total scores on the mood and anxiety scales, with the scores being directly related to the degree of depression and anxiety, respectively (Beck *et al.* 1961; Spielberger 1983). A psychomotor assessment was performed using the Grooved Pegboard Test (GPT) in which subjects are required to insert metal pegs into a pegboard containing slotted holes. Scores are determined for each hand (PegD=dominant hand; PegND=non-dominant hand) and are based on time to complete the task. This is a sensitive measure of general psychomotor slowing, and can also aid in identifying lateralized impairment (Matthews *et al.* 1995). The scores for each of these measures at the two points in time were compared using paired samples t-tests.

Single Photon Emission Computed Tomography (SPECT) of the Brain

The first scan was performed during hypothyroidism and the other after at least 7 weeks of thyroxine replacement. There was a time separation range of 7 to 11 weeks between the scans with a mean of 58.4 (± 8.2 SD) days apart. In preparation for the SPECT scan, each subject was placed in a dimly lighted room in a supine position with his or her eyes open. A catheter was then inserted into an antecubital vein and normal saline was infused at a 'KVO' rate. 30 minutes following the catheter insertion, approximately 1110 MBq (± 10%) of Tc-99m ECD was administered. SPECT imaging of each subject's brain was begun 45 minutes after admin-

istration of the radiopharmaceutical. All acquisitions were performed on a triple-headed rotating SPECT camera (PICKER PRISM 3000) with low-energy/high-resolution collimators and a system spatial resolution (CFOV at 10 cm) of 8.7 mm full-width at half maximum (FWHM). A total of 40 projections were acquired per camera head (3 degrees per stop in 'step and shoot' mode) in a 128 × 128 matrix. These data were reconstructed using a 360 degree filtered back projection algorithm with attenuation and motion correction. Attenuation correction was performed using the Chang algorithm (Chang 1978). A Weiner filter was then used for post-reconstruction 3D filtering.

Data Analysis

The SPECT scans for all subjects were realigned and spatially normalized into standard stereotactic space and smoothed to a FWHM of 10, 10, and 10 mm in the x, y, and z planes. To control for variability in global flow, rCBF values at each voxel were ratio adjusted to the mean global flow of 50 ml/100 g/min for each image. The image data were analyzed using Statistical Parametric Mapping (*SPM2; Wellcome Department of Cognitive Neurology, London, England*), where restricted voxel by voxel comparisons were performed within regions previously shown to have altered rCBF patterns in hypothyroidism (Schraml *et al.* 2006).

Separate analyses were performed for each neuropsychological test score (BDI, STAI, and GPT PegD and PegND) and the TSH level during the hypothyroid state. Analyses could not be performed on measures of free T3 and free T4 because these values fell below the threshold level of detectability during the hypothyroid state.

In each analysis, the score (or serum level) of interest was correlated with patterns of ECD signal intensity for the thyroid-hormone-replaced and hypothyroid states separately using a simple regression model. Significant effects for each contrast were based on $p \leq 0.01$. To control for multiple comparisons, cluster analyses were performed on each contrast to determine the significance of correlated voxels based on the magnitude ($p \leq 0.01$) and spatial extent (≥ 80 mm^3) (Poline *et al.* 1997). The results from this step then were used in a second level conjunction analysis to determine differences between the thyroid-hormone-replaced and hypothyroid states (threshold $p \leq 0.05$, magnitude $p \leq 0.01$, spatial extent ≥ 80 mm^3).

RESULTS

During the hypothyroid condition, the thyroid stimulating hormone (TSH) level ranged from 55.3 to 297.0 μIU/mL. These and other thyroid function test results are displayed in Table 1.

The neuropsychological testing results indicated that the subjects were significantly more depressed ($p<0.005$), anxious ($p<0.05$), and psychomotorically slowed ($p<0.05$) during hypothyroidism than when thyroid hormone replaced. These results are shown in Table 1. No significant correlations between psychomotor speed and depression or anxiety were observed in this group.

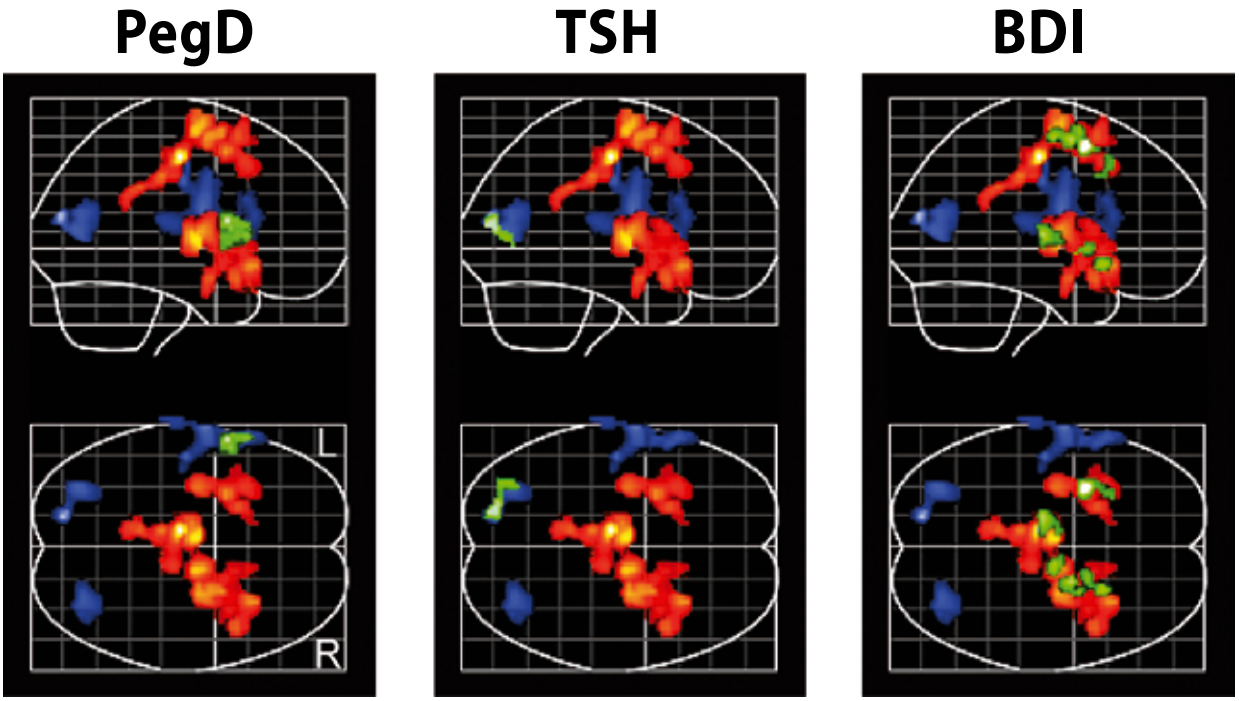

Fig. 1. Lateral and horizontal views of the brain show regional cerebral blood flow patterns during hypothyroidism relative to the thyroid hormone- replaced condition (red = increased ECD; blue = decreased ECD). Regions related to psychomotor speed (PegD), thyroid-stimulating hormone (TSH) levels and depression (BDI) that overlap the compromised pattern of ECD accumulation during hypothyroidism are shown in green.

Tab. 1. Thyroid function test values and psychological assessment values showing mean (standard deviation).

Measure	Hypothyroid	Thyroid Hormone Replaced	Paired sample t-test
Free T4 (0.71 to 1.85 ng/dL)	<0.40 (NA)*	1.47 (0.41)	0.00002
TSH (0.49 to 4.67 μIU/mL)	157.14 (93.77)	1.23 (1.65)	0.0005
Free T3 (230 to 420 pg/dL)	<160 (NA)*	335.22 (61.26)	0.00001
Beck Depression Inventory (BDI)**	13.6 (8.7)	3.4 (2.5)	0.003
State Anxiety Inventory (STAI)**	36.7(12.7)	30.5 (6.6)	0.03
Pegboard Dominant/non-Dominant (hand)***	37.7 (10.1)/36.7 (7.3)	48.6 (11.2)/43.7 (8.3)	0.01/0.01

* Denotes that all measured values were below threshold of assay detectability.
** Score is directly proportional to the degree of depression and anxiety, respectfully.
*** Score listed is a T score and is directly proportional to the rapidity with which the subject completed the task.

Tab. 2. Areas of significant correlations between ECD accumulation and scores/levels during the hypothyroid condition relative to the thyroid hormone-replaced state.

		COORDINATE						
MEASURE	**Hem**	**x**	**y**	**z**	**t-value**	***p*-value**	**Size (mm³)**	**REGION**
PegD	L	–60	2	16	7.16	<0.001	458	Precentral Gyrus (6)
TSH	L	–20	–82	12	9.97	<0.001	76*	Mid Occipital Gyrus (18)
	L	–36	–76	6	4.68	0.005	76*	Mid Occipital Gyrus (19)
BDI	R	22	0	60	3.92	0.004	48	Mid Frontal Gyrus (6)
	L	–30	8	56	6.18	<0.001	98	Mid Frontal Gyrus (6)
	R	26	16	–8	3.65	0.005	22	Insula
	L	–14	–16	8	4.06	0.003	130	Thalamus

Stereotactic coordinates are listed. Brodmann areas are indicated in parentheses.
* Local maxima contained within one cluster.

Significant relationships were found between three of the variables examined and ECD accumulation within regions of the brain previously shown to be affected by hypothyroidism (Figures 1 and 2, and Table 2). No significant associations were found between ECD accumulation and the state scores on the State-Trait Anxiety Inventory (STAI) or the non-dominant hand performance speed on the Grooved Pegboard Test (GPT).

Associations were seen for both Grooved Pegboard Dominant hand (PegD) performance speed and TSH levels during hypothyroidism in regions of hypothyroid-related decreased rCBF. An inverse relationship between speed of completion of the psychomotor task with the dominant (right) hand and tracer accumulation was seen in the left precentral gyrus (Brodmann Area (BA) 6) during the hypothyroid condition, suggesting that faster speed (i.e. less time to completion) was associated with decreased rCBF. An inverse relationship was also demonstrated between TSH level and ECD accumulation in the left middle occipital gyrus (BA 19) during hypothyroidism relative to the thyroid hormone replaced state, suggesting that higher TSH levels were associated with decreased rCBF in this area. Both positive and negative associations were seen between Beck Depression Inventory (BDI) score and ECD levels; all of these in regions of hypothyroid-related increased rCBF. Hypothyroid individuals with higher BDI scores, indicating higher levels of depression, showed greater ECD accumulation in the right insular cortex and the left thalamus, but also showed *less increased* ECD accumulation in bilateral middle frontal cortices (BA 6).

DISCUSSION

Our findings suggest that there is a relationship between psychomotor speed, depression and TSH level, and alterations in rCBF in the hypothyroid brain.

Hypothyroidism and psychomotor performance

As we reported previously, decreased tracer accumulation was seen in our subjects during hypothyroidism in the left precentral gyrus or primary motor cortex (Schraml *et al.* 2006). This is reflective of the motor slowing observed in many hypothyroid patients, including ours. In our current analysis, we found that the left precentral gyrus accumulated ECD to an extent inversely related to the speed of completion of the psychomotor task with the subject's dominant hand during hypothyroidism,

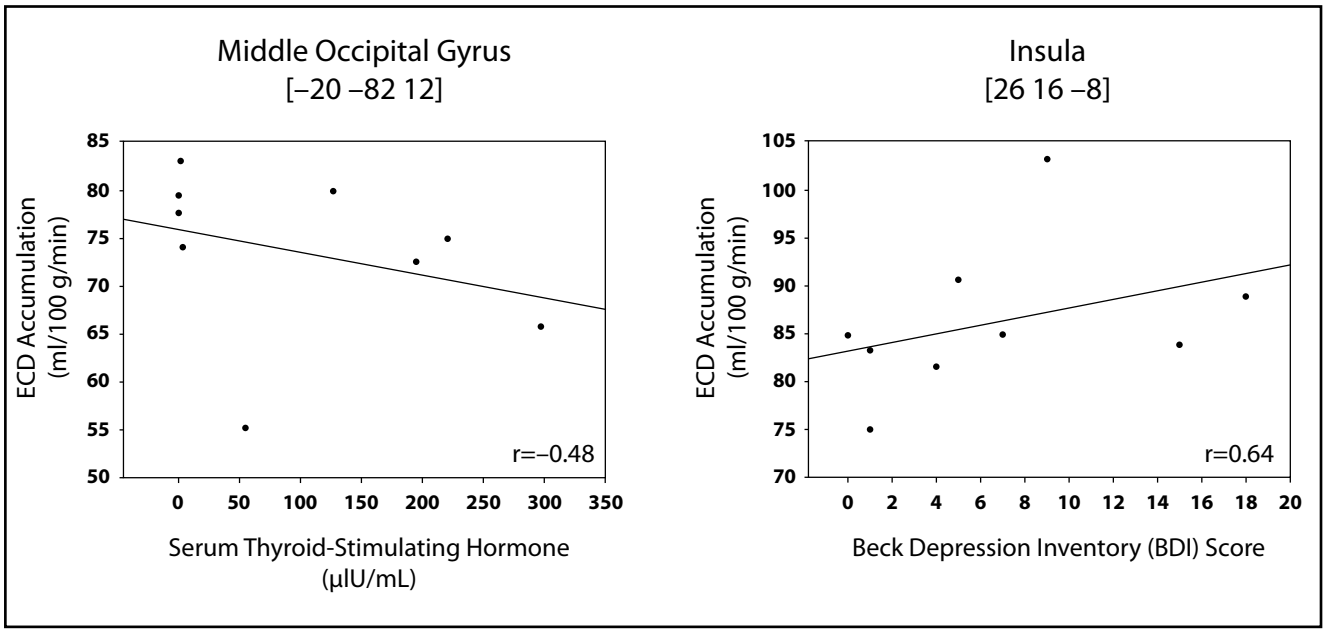

Fig. 2. A negative correlation between ECD accumulation and thyroid-stimulating hormone (TSH) was seen in the middle occipital gyrus (p<0.001); a positive correlation between ECD accumulation and level of depression (BDI) was seen in the insular cortex (p=0.005).

suggesting that the faster the speed of task completion while hypothyroid, the less the regional activity.

Hypothyroidism affects not only the central nervous system as manifested by hypometabolism and hypoperfusion (Constant *et al.* 2001; Krausz *et al.* 2004; Nagamachi *et al.* 2004; Kaya *et al.* 2007), it also causes a peripheral neuropathy (Khedr *et al.* 2000), and disturbs skeletal muscle motor function by producing a secondary mitochondrial myopathy (Argov *et al.* 1988; Khushu *et al.* 2006). This impairment could be expected to result in additional energy demands and neuronal recruitment during many motoric activities of daily living. In fact, Khushu *et al.* (2006) recorded an increase in contralateral primary motor cortex brain activation as measured by functional MRI in hypothyroid subjects compared to euthyroid controls during performance of a psychomotor task, despite the hypothyroid subject's slower speed. Our data would appear to support a similar phenomenon: We would expect that the more psychomotorically impaired the subject, the greater the compensatory effort necessary during motor tasks. It would not be unexpected for this effort to result, in turn, in relatively greater cerebral motor neuronal activation responsible for perfusion and trapping of ECD; thus, those that are more impaired show *less of a decrease* in radiotracer accumulation in the primary motor cortex.

Hypothyroidism and TSH level

Thyroid stimulating hormone (TSH) level correlated inversely with ECD accumulation in the left middle occipital gyrus of the visual association cortex (BA 19), previously observed to have decreased rCBF during hypothyroidism relative to the thyroid hormone replaced state. Of the multiple areas of decreased rCBF observed in our subjects during hypothyroidism (Schraml *et al.* 2006), the degree of relative hypoperfusion was most marked in this region of the brain. Decreased activity in the occipital lobes during hypothyroidism has also been observed by other investigators (Krausz *et al.* 2004; Nagamachi *et al.* 2004; Krausz *et al.* 2007); and Marangell *et al.* (1997) demonstrated an inverse correlation between occipital blood flow and TSH in a cohort of depressed patients, with the caveat that this correlation was driven primarily by the few patients in the cohort with elevated TSH levels. These occipital finding are particularly interesting in that the scientific literature fails to reveal any specific visual manifestations of hypothyroidism. Perhaps careful neuro-opthalmalogic evaluations would reveal signs in hypothyroid patients which are not associated with typically reported symptoms.

Hypothyroidism and depression

Cerebral ECD accumulation and level of depression were related to blood flow within areas of the brain showing relatively increased rCBF during the hypothyroid condition. A greater degree of depression was associated with greater tracer accumulation in the right insula and left thalamus. Concordant with our previously reported findings, other investigators have demonstrated mood and/or mood disorder-related increases in blood flow and cellular metabolism in the right insula and the left thalamus (Mayberg *et al.* 1999; Deicken *et al.* 2001).

A greater degree of depression was also related to *less increased* accumulation in bilateral middle frontal cortical regions. Depression-related increases in rCBF and metabolism have been observed in Brodmann Area 6, part of the supplemental motor area (Osuch *et al.* 2000); a region in which we observed increased ECD activity during hypothyroidism relative to the thyroid hormone replaced state. Our additional finding of an inverse correlation between degree of depression (as reflected by BDI score) and CBF to the right middle frontal gyrus, suggesting that the greater the degree of depression, the *less the increase* in rCBF, also has literature-based corroboration (Kim *et al.* 2008).

It seems reasonable to expect a process with as many neuropsychiatric dimensions as hypothyroidism to manifest multiple effects on regional brain physiology. For example, affective flattening or a dulling of emotional expression (as was observed in our subjects when hypothyroid but not thyroid hormone replaced) is common in hypothyroidism (Constant *et al.* 2001), and Brodmann Area 6 plays a critical role in the expression of emotions (DeLong 1996; Boswell *et al.* 2002). No attempt was made to specifically assess this finding and to correlate the degree of affective flattening with rCBF. This or some other unmeasured symptom or sign related to, or not related to, the hypothyroid-associated depressed mood state may have accounted for the significant relative increase in rCBF during the hypothyroid condition, despite the inverse relationship with the aspect(s) of depression measured by the BDI. Graff-Guerrero and colleagues found, for example, that in a group of depressed patients, rCBF to the right medial frontal gyrus correlated both positively and negatively depending on the particular symptom of depression with which CBF was correlated (Graff-Guerrero *et al.* 2004).

CONCLUSIONS

Other imaging studies have investigated the effects of hypothyroidism on the brain (Nagamachi *et al.* 2004; Kaya *et al.* 2007), yet none have fully assessed the relationship between neuropsychological manifestations of hypothyroidism (or TSH) and hypothyroid-related CBF aberrations. Our results suggest that significant correlations exist between the severity of two of the most common manifestations of hypothyroidism and rCBF during the hypothyroid state, and are consistent from neuroanatomic and functional imaging perspectives with related scientific literature. The etiology and significance of the correlation between decreased occipital lobe activity and TSH vis-à-vis the potential influence of TSH itself or the impact of a related factor (e.g. the availability of thyroid hormone) on cerebral activity in the occipital lobes are unknown. These findings could prompt further exploration for potential neuro-opthalmologic manifestations of hypothyroidism.

We believe that imaging studies such as ours may help to further elucidate the effect of thyroid function on the brain. However, the small number of subjects, the iatrogenic and relatively abrupt induction and reversal of thyroid function abnormalities, and the profound degree of hypothyroidism, makes the applicability of these findings to the understanding of brain activity in more typical clinical hypothyroidism somewhat unclear. Longer term, prospective investigations involving larger cohorts of subjects, perhaps with less severe hypothyroidism, and with data collection at more points in time (including during a prolonged state of euthyroidism), would likely shed greater light on this subject. Additionally, further investigation of the potential effect of hypothyroidism on mechanism(s) of uptake and retention of ECD and other cerebral blood flow tracers could lead to a greater understanding of the molecular aspects of thyroid physiology as it pertains to the brain.

ACKNOWLEDGEMENTS

This study was supported in part by a grant from Dupont Industries. Dr. Beason-Held's work was supported by the Intramural Research Program of the NIH, National Institute on Aging. The opinions expressed in this work are those of the authors, and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. government.

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