Inverse Relationship of Peripheral Thyrotropin-Stimulating Hormone Levels to Brain Activity in Mood Disorders

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Objective: *The authors' goal was to investigate relationships between peripheral thyroid hormone levels and cerebral blood flow (CBF) and cerebral glucose metabolism in affectively ill patients.* *Method:* *Medication-free inpatients with major depression or bipolar disorder were studied with oxygen-15 water and positron emission tomography (PET) to measure CBF (N=19) or with [^{18}F]fluorodeoxyglucose and PET to measure cerebral glucose metabolism (N=29). Linear regression was used to correlate global CBF and cerebral glucose metabolism with serum thyrotropin-stimulating hormone (TSH), triiodothyronine (T_3), thyroxine (T_4), and free T_4 concentrations. Statistical parametric mapping was used to correlate regional CBF and cerebral glucose metabolism with these thyroid indexes. Post hoc t tests were used to further explore the relationships between serum TSH and global CBF and cerebral glucose metabolism.* *Results:* *Serum TSH was inversely related to both global and regional CBF and cerebral glucose metabolism. These relationships persisted in the cerebral glucose metabolism analysis and, to a lesser extent, in the CBF analysis after severity of depression had been controlled for. In contrast, no significant relationships were observed between T_3, T_4, or free T_4 and global or regional CBF and cerebral glucose metabolism.* *Conclusions:* *These data suggest that peripheral TSH (putatively the best marker of thyroid status) is inversely related to global and regional CBF and cerebral glucose metabolism. These findings indicate relationships between thyroid and cerebral activity that could provide mechanistic hypotheses for thyroid contributions to primary and secondary mood disorders and the psychotropic effects of thyroid axis manipulations.*

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Thyroid hormones and mood disorders have complex relationships (1–5). Acute depressive exacerbations can be associated with relative hyperthyroxinemia (1) and increased CSF free thyroxine (T_4), which normalizes with recovery (6). This hyperactivity of the thyroid axis, which occurs in at least some depressed patients, may represent an adaptive or compensatory mechanism (7). Thyroid augmentation has been successfully employed in the treatment of mood disorders (8–10). Since thyroid hormones are necessary to maintain normal control of central nervous system (CNS) function, evaluation of the relationship between the brain and thyroid may help clarify the interactions between thyroid activity and mood that are relevant to pathophysiology and therapeutics.

Thyroid function is integrally related to somatic metabolism; increases in basal metabolic rate are associated with increases in thyroid hormones (11). Increased basal metabolic rate entails increased oxygen and glucose utilization, which is induced by thyroid hormones in most peripheral tissues. Several studies in the 1950s sought to determine relationships between brain physiology and thyroid status. Himwich et al. (12) reported increased global cerebral blood flow (CBF) and cerebral oxygen consumption in response to treatment of hypothyroidism. Using quantitative nitrous oxide determination of CBF and cerebral oxygen consumption (13), most investigators failed to demonstrate an increase in cerebral oxygen consumption in hyperthyroid patients (14–17). Although some studies reported that CBF was increased in hyperthyroidism (17, 18) and decreased in hypothyroidism (18–20), these findings were interpreted as most likely being secondary to the changes in vascular resistance that occur in thyroid disease rather

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than caused by changes in brain activity (17, 20). Thus, a consensus emerged that adult brain metabolism is unaltered in thyroid disease, despite clinical disturbances of CNS function in thyroid disorders suggesting the contrary. Subsequent to the initiation of our study, Smith and Ain (21) reported a relatively increased ratio of frontal phosphocreatine to inorganic phosphate in response to treatment of hypothyroidism as assessed by phosphorus-31 nuclear magnetic resonance spectroscopy. To our knowledge, there have been no other human studies using contemporary brain imaging techniques to evaluate relationships between brain and thyroid or to evaluate these relationships in euthyroid patients with affective disorders.

We used positron emission tomography (PET) to measure CBF and cerebral glucose metabolism separately in order to assess relationships between these measures and peripheral thyroid indexes in patients with mood disorders. To our knowledge, this is the first report documenting inverse relationships between peripheral TSH and CBF and cerebral glucose metabolism.

METHOD

Nineteen affectively ill inpatients were studied with oxygen-15 water ($[^{15}O]H_2O$) and PET to measure CBF. Twenty-nine affectively ill inpatients were studied with [^{18}F]fluorodeoxyglucose (FDG) and PET to measure cerebral glucose metabolism. Nine patients had both types of scans. All patients met DSM-III-R criteria for major depression or bipolar disorder, confirmed by a research psychiatrist using the Schedule for Affective Disorders and Schizophrenia (22) and the life charting method (23). Characteristics of the patients in the two studies are summarized in table 1. No patient was manic or psychotic at the time of the procedure, as assessed by Bunney-Hamburg nurse ratings (24). The 17-item Hamilton Depression Rating Scale (25) was used to quantify depression symptoms at the time of study (table 1). Two patients had a history of Hashimoto's thyroiditis; otherwise, patients were free of overt thyroid problems and other medical disorders. In the CBF study, three women were menopausal, seven women were in mean day 12.3 (SD=10.9) of their menstrual cycle on the day of the scan, and for two premenopausal women the day of menstrual cycle on the day of the scan was not obtained. In the cerebral glucose metabolism study, two women were menopausal, 11 women were in mean day 10.1 (SD=7.4) of their menstrual cycle on the day of the scan, and for one premenopausal woman the day of menstrual cycle on the day of the scan was not obtained. Mean day of the menstrual cycle on the day of the scan did not differ significantly between the CBF and cerebral glucose metabolism studies. Patients were studied at the National Institutes of Health (NIH) Clinical Center, and all had been receiving blind treatment with placebo and no active medications for at least 2 weeks prior to the scanning procedures. All patients gave written informed consent after the procedures had been fully explained.

Serum thyroid indexes were measured by the clinical laboratory of the NIH Clinical Center from morning blood samples collected within a mean of 5.5 days (SD=7.2) of the CBF procedure and a mean of 3.3 days (SD=5.2) of the cerebral glucose metabolism procedure. Thyrotropin-stimulating hormone (TSH) was measured with an immunoradiometric assay, which incorporates two high-affinity monoclonal antibodies. The TSH assay used in this study (Serano Diagnostics, Rome, Italy) has a detection limit of 0.02 μU/ml, an interassay coefficient of variation of 4%–5%, an intraassay coefficient of variation of 1.6%–3.1%, and a normal range of 0.4–4.6 μU/ml. Serum triiodothyronine (T_3) and T_4 were measured by radioimmunoassay with detection limits of 15 ng/dl and 1.0 μg/dl, respectively (Quanticoat, Kallestad Diagnostics, Chaska, Minn.). The T_3 assay has an interassay coefficient of variation of 5%–7% and an intraassay coefficient of variation of 2.6%. The T_4 assay has an interassay coefficient of variation of 4.6% and an intraassay coefficient of variation of 2.6%. Free T_4 was measured with radioimmunoassay (GammaCoat, Incstar Corp., Stillwater, Minn.) and has a lower detection limit of 0.08 ng/dl, an interassay coefficient of variation of 3.8%, and an intraassay coefficient of variation of 4.2%. Coefficients of variation for T_3, T_4, and free T_4 represent data from mid-range samples, which are applicable to the patient group used in this study. Interassay coefficients of variation are those of the NIH Clinical Center laboratory.

TABLE 1. Characteristics and Thyroid Indexes of 39 Patients With Major Depression or Bipolar Disorder[a] in Studies of Thyroid Activity in Relation to Cerebral Blood Flow (CBF) and Cerebral Glucose Metabolism

Variable	CBF (N=19)		Metabolism (N=29)	
	N		*N*	
Sex				
Men	7		15	
Women	12		14	
DSM-III-R diagnosis				
Bipolar disorder type I	2		8	
Bipolar disorder type II	10		12	
Major depression	7		9	
Rating on 17-item Hamilton depression scale at time of scan				
Depressed (score ≥10)	14		27	
Euthymic (score <10)	5		2	
	Mean	*SD*	*Mean*	*SD*
Age (years)	41.1	9.4	40.0	11.5
Score on 17-item Hamilton depression scale	17.4	11.2	19.4	8.9
Time between scan and thyroid function tests (days)	5.5	7.4	3.3	5.2
Thyroid index				
TSH (μU/ml)	2.86	2.33	2.92	2.39
T_3 (ng/dl)	125.95	27.97	121.59	15.8
T_4 (μg/dl)	7.53	1.42	7.36	1.26
Free T_4 (ng/dl)	1.27	0.22	1.33	0.23

[a]Nine patients had both CBF and cerebral glucose metabolism studies. All patients had been medication free for at least 2 weeks.

Scanning Procedures

CBF images were obtained by using a Scanditronix PC2048-15B PET scanner (Scanditronix, Uppsala, Sweden) with an in-plane resolution of 7 mm and axial resolution of 5–6.5 mm. Data were collected in 15 planes parallel to the canthomeatal line and spaced 6.5 mm apart. Patients were at rest with their eyes closed in a darkened room and asked to focus on their emotional and sensory experience during the scans; eye movements were not otherwise restricted. Thirty mCi of $[^{15}O]H_2O$ was injected intravenously, and tomographic image acquisition began when the bolus of radiotracer arrived in the head. The time course of regional cerebral radioactivity was recorded by collecting 16 scan frames (12×10 seconds, 4×30 seconds) over 4 minutes following the arrival of radiotracer in the brain. The arterial time-activity curve was measured with an automated arterial blood sampling and counting system and was used with a pixel-by-pixel rapid least squares method to produce quantitative images of regional CBF (26).

Cerebral glucose metabolism images were obtained by using a Scanditronix PC1024-7B PET scanner with an in-plane resolution of 5.2 mm and an axial resolution of 10 mm. Data were collected in four sets of seven slices spaced 13.5 mm apart to yield 28 interleaved slices parallel to the canthomeatal line, spaced 3.4 mm apart. Patients' eyes were covered and headphones were used while 4–5 mCi of FDG was

TABLE 2. Correlations of Thyroid Indexes With Global Cerebral Blood Flow (CBF) and Cerebral Glucose Metabolism

	Global CBF (N=19)		Metabolism (N=29)	
Thyroid Index	r (df=17)	p (one-tailed)	r (df=27)	p (one-tailed)
TSH	–0.41	0.04	–0.35	0.03
T_3	0.03	0.46	0.02	0.46
T_4	–0.09	0.36	0.13	0.26
Free T_4	0.31	0.10	–0.00	0.49

administered and subjects performed a continuous auditory discrimination task for 30 minutes (27). At the end of this 30-minute period, the headphones were removed and four interleaved emission scans of seven slices each were acquired. The conversion of image pixel values from nanocuries per cubic centimeter to milligrams of glucose per 100 mg of tissue per minute (ml/100 g per minute) was performed by using methods described elsewhere (28–31).

For both $[^{15}O]H_2O$ and FDG scans, head movement was restricted with a thermoplastic mask. Transmission scans were obtained with a Ge68/Ga68 source rotated around the subject's head and were used to correct the emission data for photon attenuation. Intravenous lines were placed for administration of the tracer, and radial arterial lines were placed for serial arterial blood sampling during image acquisition to allow quantification of CBF and cerebral glucose metabolism.

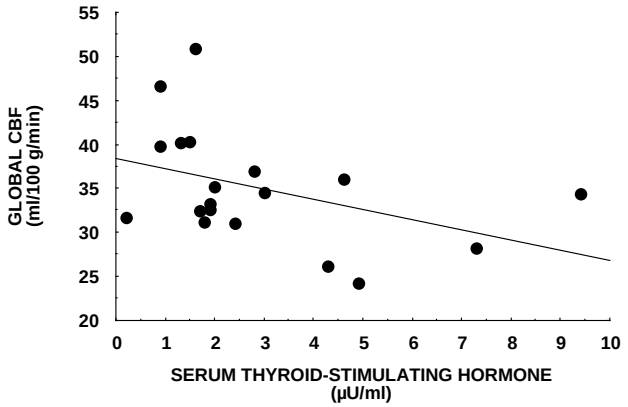
Data Analysis

Image analysis was performed by using PROMATLAB (Mathworks, Sherborn, Mass.) on a SUN SPARCstation 2 (Sun Microsystems, Mountain View, Calif.) with software for image display (32). Data were analyzed by using Statistical Parametric Mapping software (MRC Cyclotron Unit, Hammersmith Hospital, London). Each scan was individually inspected for image quality and possible artifacts, interpolated to 43 slices, and roll and yaw corrected. The intercommissural line was identified on the PET images, and the images were reoriented along this line (33). The images were then resized, rescaled, and resliced (i.e., stereotactically normalized) to correspond to the human brain atlas of Talairach and Tournoux (34).

Global CBF and cerebral glucose metabolism were calculated from the mean value in the stereotactically normalized images after application of masks to exclude pixels with values less than one-third of the maximum voxel for each image. Both Pearson and Spearman correlation coefficients were used to correlate global CBF and global cerebral glucose metabolism with plasma TSH, T_3, T_4, and free T_4. Based on relationships between somatic metabolism and thyroid indexes (11), we adopted the hypothesis that global CBF and cerebral glucose metabolism would be directly related to serum T_3, T_4, and free T_4 and inversely related to serum TSH; hence, the criterion for significance was set at 0.05 (one-tailed). For each global analysis, four correlations were performed (global CBF or cerebral glucose metabolism versus TSH, T_3, T_4, and free T_4). Post hoc t tests were used to further explore the relationship between serum TSH and CBF and cerebral glucose metabolism.

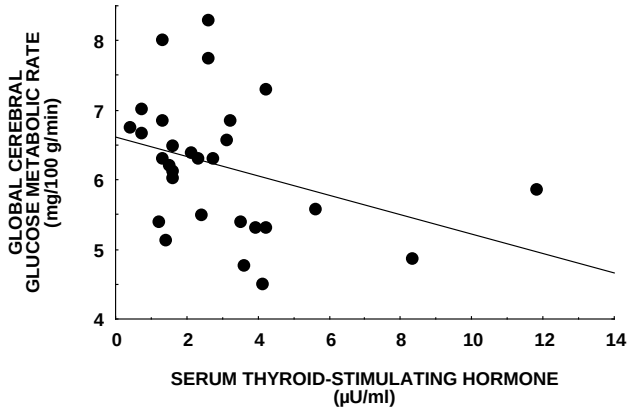
Additionally, voxel-by-voxel Pearson correlation analyses (35, 36) were performed between the stereotactically normalized, absolute (not adjusted with analysis of covariance) CBF and cerebral glucose metabolism PET images and each of the thyroid indexes. Results were displayed as statistical parametric maps with r value thresholds corresponding to p<0.05 (one-tailed, not corrected for multiple comparisons). There were 4×50,000 significance tests, each tested at a p value of 0.05 (one-tailed). If independence is assumed, up to 10,000 voxels (4×50,000×0.05) might attain significance by chance. However, chance correlations should arise equally in both the predicted and opposite direction. To protect against possible type I errors, the number of voxels correlating in the predicted direction are noted along with the number of correlations attaining significance in the opposite direction.

FIGURE 1. Negative Correlation Between Serum Thyroid-Stimulating Hormone and Global Cerebral Blood Flow in 19 Patients With Major Depression or Bipolar Disorder[a]



[a]r=–0.41, df=17, one-tailed p<0.04; r_s corrected for ties=–0.50, one-tailed p<0.02.

FIGURE 2. Negative Correlation Between Serum Thyroid-Stimulating Hormone and Global Cerebral Glucose Metabolic Rate in 29 Patients With Major Depression or Bipolar Disorder[a]



[a]r=–0.35, df=27, one-tailed p<0.03; r_s corrected for ties=–0.41, one-tailed p<0.02.

RESULTS

Serum TSH (table 2) correlated inversely with both global CBF (figure 1) and cerebral glucose metabolism (figure 2). Similar relationships between global cerebral activity and TSH were obtained when the three patients with serum TSH values outside the normal range (0.4–4.6 µU/ml) were excluded in a post hoc analysis.

In the CBF analysis (threshold r <–0.39, df=17, one-tailed p<0.05, not corrected for multiple comparisons), 30,461 of 50,000 cerebral voxels (2×2×4 mm) were inversely correlated with TSH; no voxels had positive correlations. Similarly, 26,651 voxels had inverse correlations between serum TSH and cerebral glucose metabolism, and no voxels had positive correlations (threshold r<–0.31, df=27, one-tailed p<0.05, not corrected for multiple comparisons). As shown in tables 2

and 3, global and regional CBF and cerebral glucose metabolism did not significantly correlate with either T_3 or T_4. Although positive correlations occurred between free T_4 and global and regional CBF, this was not replicated in the cerebral glucose metabolism analysis.

Left dorsolateral prefrontal cortex (Talairach –52,8,28) and mesial prefrontal regional CBF had maximal inverse correlations with TSH (figures 3 and 4). Right cuneus (Talairach 6,–94,8) regional cerebral glucose metabolism had maximal inverse correlations with TSH (r=–0.57, df=27, one-tailed p<0.001, not corrected for multiple comparisons, r_s corrected for ties=–0.38, one-tailed p<0.03, not illustrated), but the maximal inverse correlation between regional cerebral glucose metabolism and TSH in the cuneus appeared to be driven by two patients with high TSH levels.

Mean TSH, T_3, T_4, free T_4, Hamilton depression ratings, global CBF, and global cerebral glucose metabolism did not differ significantly between men and women in either analysis. Additionally, gender and diagnosis did not differ significantly between the CBF and cerebral glucose metabolism study subjects. Day of menstrual cycle did not significantly correlate with Hamilton depression scores, thyroid indexes, or global CBF or cerebral glucose metabolism. In the CBF study, Hamilton depression score (table 1) correlated significantly with TSH (r=0.61, df=17, one-tailed p=0.003) and to a lesser degree with global CBF (r=–0.33, df=17, one-tailed p=0.08). The partial correlation between global CBF and TSH (with Hamilton depression score held constant) was reduced (r=–0.28, df=16, one-tailed p=0.14), and the partial correlation between global CBF and Hamilton depression score (with TSH held constant) was even less (r=–0.11, df=16, one-tailed p>0.25). In the cerebral glucose metabolism study, Hamilton depression score (table 1) did not correlate significantly with either TSH (r=0.05, df=27, one-tailed p=0.41) or global cerebral glucose metabolism (r=–0.10, df=27, one-tailed p=0.31). The partial correlation between global cerebral glucose metabolism and TSH (with Hamilton depression score held constant) remained significant (r=–0.35, df=26, one-tailed p<0.04), and the partial correlation between global cerebral glucose metabolism and Hamilton depression score (with TSH held constant) remained nonsignificant (r= –0.09, df=26, one-tailed p>0.32).

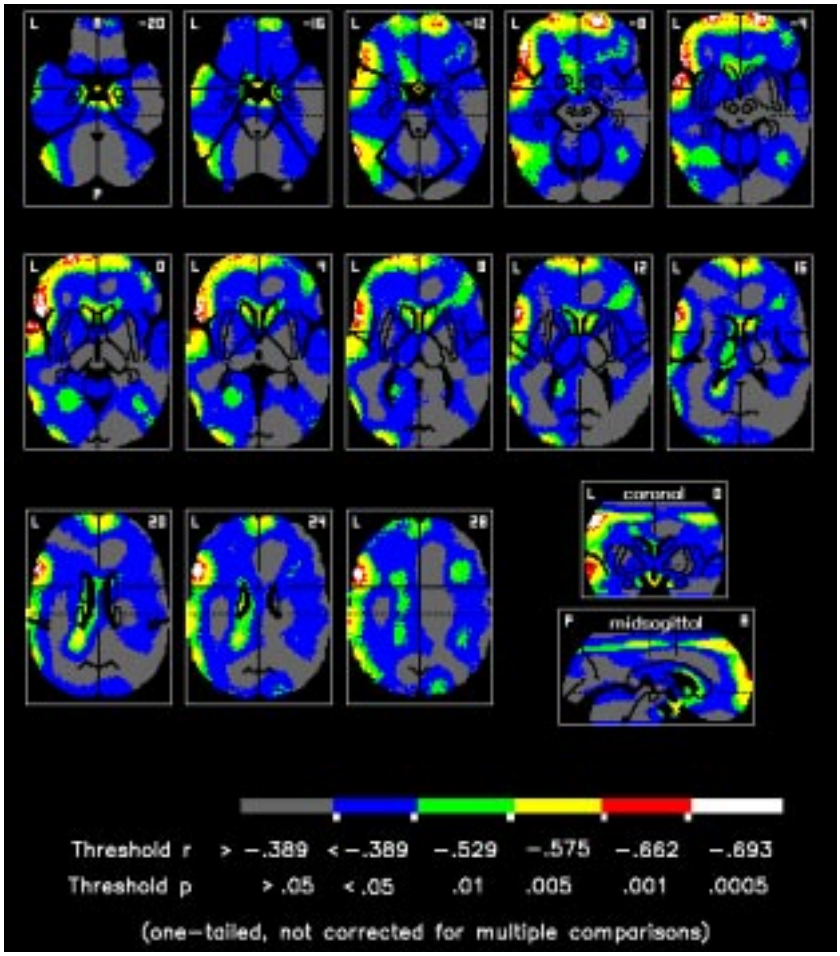
During post hoc visual inspection of the correlations between TSH and cerebral activity (figures 1–3) we noted that the samples could be divided into low (<3.5 μU/ml) and high

TABLE 3. Number of Voxels With Significant[a] Correlations Between Thyroid Indexes and Measure of Cerebral Blood Flow (CBF) or Cerebral Glucose Metabolism

Thyroid Index and Direction of Correlation	Number of Voxels: Absolute Regional CBF	Number of Voxels: Metabolism
TSH		
Negative	30,461	26,651
Positive	0	0
T_3		
Negative	0	11
Positive	0	78
T_4		
Negative	0	0
Positive	0	61
Free T_4		
Negative	0	22
Positive	7,790	42

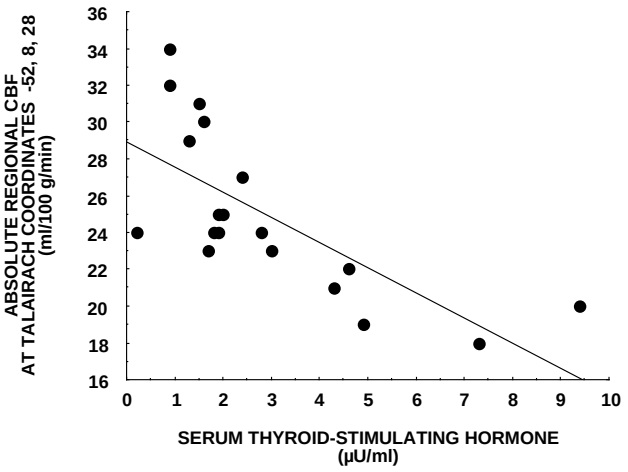
[a]p<0.05 (one-tailed) not corrected for multiple comparisons. To protect against possible type I errors, the number of voxels correlating in the predicted direction was noted along with the number of correlations attaining significance in the opposite direction. The image consists of 50,000 voxels. A random distribution predicts equal numbers of positive and negative voxels.

FIGURE 3. Negative Correlations Between Serum Thyroid-Stimulating Hormone and Absolute Regional Cerebral Blood Flow in 19 Patients With Major Depression or Bipolar Disorder[a]



[a]30,461 voxels with r<–0.39 (r minimum=–0.71), no voxels with r>0.39 (r maximum=–0.04).

FIGURE 4. Maximal Inverse Correlation Between Serum Thyroid-Stimulating Hormone and Absolute Regional Cerebral Blood Flow in Left Dorsolateral Prefrontal Cortex in 29 Patients With Major Depression or Bipolar Disorder[a]



[a]r=–0.71, df=17, one-tailed p<0.0002; r_s corrected for ties=–0.81 one-tailed p<0.0003.

(≥3.5 µU/ml) TSH subgroups. Global CBF was higher in the subgroup with low TSH (N=14) than in the subgroup with high TSH (N=5) (t=2.33, df=17, one-tailed p<0.02), and this difference was even more evident in dorsolateral prefrontal regional CBF (t=3.91, df=17, one-tailed p<0.001). Similarly, global cerebral glucose metabolism was higher in the subgroup with low TSH (N=20) than in the subgroup with high TSH (N=9) (t=3.44, df=27, one-tailed p<0.001), and this difference was even more evident in precuneus regional cerebral glucose metabolism (t=3.85, df=27, one-tailed p<0.0004). For both the CBF and cerebral glucose metabolism studies the low and high TSH subgroups did not differ significantly from each other in age, gender, diagnosis, or Hamilton depression scores.

DISCUSSION

Data from this study group of affectively ill patients suggest that serum TSH levels are inversely related to global CBF and cerebral glucose metabolism. Since serum TSH is the putative best overall marker of peripheral thyroid hormone availability (higher TSH levels are associated with lower thyroid hormone availability and hence lower somatic metabolism), the inverse relationship between TSH and cerebral activity is consistent with a positive relationship between both global and regional cerebral activity and overall thyroid function. If replicated, these data support the clinical observation that, in some instances, the adult CNS may be sensitive to thyroid status, even within the putative normal range or in the absence of classical clinical somatic signs and symptoms of thyroid dysfunction.

These data include several reassuring internal consistencies. Inverse correlations between TSH and brain activity were observed with both CBF and cerebral glucose metabolism and in both the global and regional analyses. The correlation between TSH and regional CBF involved 30,461 negatively correlated voxels (out of 50,000) and no voxels with positive correlations. The correlation between TSH and regional cerebral glucose metabolism involved 26,651 negatively correlated pixels and again no voxels with positive correlations. Therefore, given the threshold correlations with more than half of the cerebral voxels in both analyses, the inverse relationship between serum TSH and brain activity appears unlikely to be due to chance, despite the lack of correction for multiple correlations. These findings are unlikely to be random because we found that all correlations were negative rather than finding a random distribution of positive and negative correlations.

In contrast to previous studies of patients with primary thyroid disease, it is unlikely that there were significant changes in vascular resistance in our patients, all of whom were medically well except for their mood disorders, medication free, and clinically euthyroid. Although female subjects were at various points in their menstrual cycle, it is unlikely that the relationships between TSH and CBF or between TSH and cerebral glucose metabolism are an artifact of menses because the day of menstrual cycle did not correlate with CBF or cerebral glucose metabolism or thyroid indexes, and there were no significant differences between male and female subjects in the relationships between serum TSH and cerebral activity.

The known relationship between depression and CBF and cerebral glucose metabolism must also be considered when interpreting these data. The dorsolateral prefrontal and mesial prefrontal cortices have been shown to have decreased regional CBF (37–39) and decreased regional cerebral glucose metabolism (40–44) in depressed patients, often related to the severity of depression as rated on the Hamilton depression scale (40–45). In the cerebral glucose metabolism analysis, Hamilton depression ratings were not significantly correlated with either TSH or global cerebral glucose metabolism, although there was a relationship in the CBF analysis. The relationship between Hamilton depression scores and TSH observed in the CBF but not the cerebral glucose metabolism analysis could be related to the slight, statistically nonsignificant differences in the study subjects. Partial correlations, with depression controlled for, did not affect the significance of the correlation between TSH and global cerebral glucose metabolism but did attenuate the correlation between TSH and global CBF. Therefore, the inverse relationship between TSH and CBF and cerebral glucose metabolism may have a component related to the degree of depression, which needs to be further assessed in future studies. However, the lack of a significant relationship between serum TSH and Hamilton depression ratings in the cerebral glucose metabolism data set suggests that the associations between TSH and brain activity are unlikely to be wholly driven by associations with severity of depression.

It is of interest that dorsolateral prefrontal and mesial prefrontal cortices were the areas of maximal negative correlation between regional CBF and TSH. This finding of a regional relationship must be considered preliminary because it was derived from multiple correlations, could be at least partially confounded by the association between serum TSH and Hamilton depression ratings in the CBF analysis, and differed from the cerebral glucose metabolism analysis. However, there are several possible explanations for the difference in the location of the maximal inverse relationships with regional CBF and cerebral glucose metabolism. The auditory cognitive performance task, which patients performed during the cerebral glucose metabolism but not the CBF scans, activates the dorsolateral prefrontal cortex (46) and thus would tend to attenuate negative correlations in this region in the cerebral glucose metabolism study. Additionally, the passive introspection task performed during the CBF scans is similar to the "REST" condition described by Andreasen et al. (47), which activates the precuneus and thus may attenuate negative correlations in this area in the CBF study. This task difference might also explain why Hamilton depression scores correlated with global CBF but not global cerebral glucose metabolism. It is less likely but also possible that CBF may be disassociated from cerebral glucose metabolism in the dorsolateral prefrontal cortex of patients with mood disorders.

It is noteworthy that we found a relationship between brain activity and TSH but not T_3, T_4, or free T_4. Total serum T_4 is strongly influenced by thyroid binding proteins, and as such is the measure least reflective of overall thyroid status. T_3 is generally considered the active hormone, but total T_3 is subject to the same protein binding considerations as is total T_4. It would be of interest to investigate the relationship between free T_3 and brain activity. Free T_4 tended to have direct relationships with global and regional CBF, but this finding must be viewed with particular caution because it was not as robust as the TSH correlation and was not replicated with cerebral glucose metabolism. In both the CBF and cerebral glucose metabolism studies, blood samples were not all drawn immediately before the scan. We are currently replicating this study with thyroid indexes obtained immediately before the PET scans.

If confirmed, these findings indicate a relationship between thyroid and cerebral activity that could be of mechanistic and therapeutic interest. Our current findings are consistent with observations that sleep deprivation in depressed patients increases serum TSH (48–51) while decreasing cerebral metabolism (52) and improving mood. We are currently extending our study of relationships between brain activity and thyroid indexes (particularly TSH) to healthy volunteers in order to ascertain to what degree these relationships are unique to affective disorders or reflect normal physiology. Similarly, additional studies are needed to better ascertain if these relationships are best expressed as a continuum or a categorical (low versus high TSH) split. Such data should shed more light on the intricate relationships between mood and thyroid and cerebral activity.

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