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Minimal changes of thyroid axis activity influence brain functions in young females affected by subclinical hypothyroidism

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ABSTRACT

There is evidence of an association between thyroid hormones (TH) alterations and mental dysfunctions related to procedural and working memory functions, but the physiological link between these domains is still under debate, also for the presence of age as a confounding factor. Thus, we investigated the TH tuning of cerebral functions in young females affected by the borderline condition of subclinical hypothyroidism (SH) and in euthyroid females of the same age.

The experiment consisted in the characterization of the affective state and cognitive abilities of the subjects by means of specific neuropsychological questionnaires, and of brain activity (EEG) in resting state and during the passive viewing of emotional video-clips. We found that SH had i) increased anxiety for Physical Danger; ii) better scores for both Mental Control and no-working-memory-related functions; iii) association between anxiety for Physical Danger and fT4 levels. Thus, in young females, SH increases inward attention and paradoxically improves some cognitive functions. In addition, self-assessed questionnaires showed that SH had a greater susceptibility to unpleasant emotional stimulation. As for EEG data, SH compared to controls showed: i) reduction of alpha activity and of gamma left lateralization in resting state; ii) increased, and lateralized to the right, beta2 activity during stimulations. Both results indicated that SH have higher levels of arousal and greater susceptibility to negative emotion than controls.

In conclusion, our study indicates that minimal changes in TH levels produce subtle but well-defined mental changes, thus encouraging further studies for the prediction of pathology evolution.

Key words

Subclinical hypothyroidism • Cognitive functions • Emotions • EEG

Introduction

The interaction between the endocrine and nervous system plays an important role in the control and maintenance of systemic homeostasis. In this regard, the thyroid hormone system offers a good model of this complex interaction (Smith et al., 2002; for review see Boelaert and Franklyn, 2005). In fact, if on the one hand the hypothalamus-pituitary-thyroid (HPT) axis is influenced by the central nervous system (CNS), on the other hand various cerebral functions including cognitive and affective ones (Baldini et al., 1997; Bernal, 2002; Zhu et al., 2006; Davis and Tremont, 2007) depend on thyroid hormones (THs),

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both during development and adult life. Indeed, T3 receptors are widely distributed in the CNS and THs levels in the brain are maintained within a stable range, independently of their systemic fluctuations due to the balance between the activity of type II-deiodinase (D2) that converts T4 to T3, and type III-deiodinase (D3) that catalyzes the inactivation of THs, thus preventing accumulation of T3 (Santini et al., 2001). An overall analysis of cerebral THs distribution has shown that T3 levels are inversely correlated with D3 activity, and that, among the different brain areas, hippocampus and temporal cortex have the lowest T3 levels associated with elevated D3 activity. This suggests that these regions might be particularly vulnerable to THs decrease. Indeed, most of the mental alterations associated with THs system disorders can be likely attributed to dysfunctions of the temporal lobe structures. In particular, adult patients affected with overt hypothyroidism, typically show deficits in various cognitive abilities (i.e. attention, memory, executive functions etc.), altered mood (depression or anxiety) (Dugbartey, 1998; Bauer and Whybrow, 2001; Bernal, 2002; Simon et al., 2002; Bauer et al., 2003; Davis and Tremont, 2007) and also Alzheimer's disease-like manifestations (memory loss, confusion, slowness, paranoid depression, hallucinations) (Whybrow et al., 1969).

Besides, some studies (Osterweil et al., 1992; Haggerty et al., 1993; Monzani et al., 1993; Baldini et al., 1997; Kalmijn et al., 2000; Zhu et al., 2006; Samuels, 2008) have suggested that subtle deficits in specific cognitive domains as well as affective disorders may exist also in the condition of subclinical hypothyroidism (SH), a peculiar preclinical condition, frequent especially in women, with a prevalence between 2% and 20% in the adult population (Wilson and Curry Jr. 2005; for a review see Biondi and Cooper, 2008). SH increases with age and autoimmune thyroid diseases (goitrous Hashimoto's thyroiditis and atrophic thyroiditis) are its most common causes. Subclinical hypothyroidism offers an interesting model to study the interactions between the THs system and the cerebral functions, since it could represent an early phase of THs system dysfunction in which only TSH levels are mildly elevated (below 10 mIU/ml) while free T4 and T3 are still within the normal ranges.

To date, serum TSH level during overt hypothyroidism has been considered as a marker of the severity of 'brain hypothyroidism' (Schraml et al., 2011). However the association between modest TSH changes and altered mental functions is still under debate.

In fact, recent findings on a community-based sample of middle-aged and older individuals failed to show any associations between mildly elevated TSH levels and reduced cognitive performance in any domain (St. John et al., 2009). Surprisingly, although there was a trend for older individuals with higher levels of TSH to exhibit poor performances on paragraph recall, gender-stratified analyses showed that, in females, TSH levels were positively associated with the scores on word list learning. On the contrary, other studies have shown disorders likely attributable to dysfunctions of the GABAergic system in the dorso-lateral prefrontal cortex, which is involved in the working-memory functions (Zhu et al., 2006; Yin et al., 2012).

The conflicting findings could reflect differences in the study design, sampling population, age-ranges under consideration, thyroid-function indicators, and cognitive domains examined. Among these factors age differences could play a pivotal role, being aging itself a potent cause of cognitive decline and a positive association between TSH levels and cognitive disturbances has been generally found only in older individuals.

Thus, the present study is aimed at providing a close examination of TSH modulation on cognitive and affective functions by using a group of 18-35 years females affected by subclinical hypothyroidism (SH). The young age of our sample has allowed avoiding possible confounding effects of aging on mental functions. For each individual, the cognitive/affective functions and the brain cortical activity were evaluated by means, respectively, of appropriate psychometric scales and EEG recordings. As suggested by different findings of the reported studies, we derived, a novel index from the global memory score, which was not dependent on the working memory components. In addition, cerebral activity was evaluated in conditions of resting state and of cognitive and emotional load, in order to bring out possible latent differences in the patterns of cerebral activity that might otherwise remain masked in the resting condition.

Furthermore, the possible association between THs levels, the measures of the various neuropsychological variables, and the EEG parameters have been evaluated.

Methods

Subjects

Thirty-four right-handed women (18-35 years-old) were enrolled among outpatients of the clinic of the Institute of Clinical Physiology (CNR, Pisa, Italy). Half of them were affected with sub-clinical hypothyroidism (SHs) (mean age, 28 ± 4y) whereas the others were euthyroid control individuals (Controls) (mean age, 28 ± 5y). On account of the high prevalence of SH in the female population only women were enrolled; furthermore, this selection avoids a potential gender bias in the evaluation of the emotional status (Meyers and Smith, 1987). All subjects were selected according to the following inclusion criteria: no history nor evidence of medical diseases, no drug assumption in the last 3 months, Body Mass Index in the normal range, no premenstrual/menstrual phase at the time of testing. The SH group was composed only by novel, asymptomatic and untreated cases (each subject had discovered her subclinical state by chance during a routine check-up within the previous month). Subclinical hypothyroidism was defined by the presence, in two consecutive – time interval less than a month – blood samples, of circulating TSH higher than the upper limit of reference range (i.e. 3.8 microIU/ml) but less than 10 microIU/ml, and free T4 (fT4) and T3 (fT3) in the normal range.

All participants signed an informed consent according to the guidelines of the local Ethical Committee that approved the study. In particular, subjects were told that they would be involved in a study on "brain processing of emotional stress". However, in order to minimize anticipatory anxiety effects, individuals were not informed that they were selected on the basis of the SH condition.

Hormonal assessment

Blood samples were drawn between 8:00 and 9:00 AM, after 20 min of supine rest. Serum TSH, fT3 and fT4 were measured using an AIA-600 analyzer (Eurogenetics-Tosoh, Turin, Italy). Normal ranges for our laboratory were: TSH: 0.3-3.8 mIU/ml; fT3: 2.1-4.2 pg/ml; fT4: 7.1-18.5 pg/ml. Anti-thyroglobulin and anti-microsomal antibodies were determined by a chemoluminescent fully automated technique (Diagnostic Product Corporation, Los Angeles, CA, USA). As stress-related circulating markers, adrenaline, norepinephrine, dopamine, ACTH, and cortisol were also measured as previously described (Emdin et al., 2004).

Psychopathological evaluation

All subjects were submitted to a psychiatric evaluation in order to avoid co morbidity of mood, anxiety and sleep disorders to bias the behavioral changes during the experimental session. This evaluation was carried out by means of proper psychiatric interviews as well as the Hamilton Scales for Anxiety (HAM-A) and Depression (HAM-D) (Horton and Wedding, 2007).

Neuropsychological evaluation

We evaluated the subjects' cognitive and emotional state by means of a set of psychological scales and tests. Between 3:00 PM and 6:00 PM they were randomly administered in order to avoid both circadian variability and order of presentation biases.

To evaluate cognitive functions we administered five tests (Horton and Wedding, 2007): the Wechsler Memory Scale (WMS), a collection of subtests designed to measure different memory functions summarized in a unique global score, named *Memory Quotient*; the Corsi Visuo-Spatial Span, a task to asses non verbal/visuo-spatial short-term memory; the Raven's Progressive Matrices, a non-verbal multiple-choice task to assess general intellectual ability; the Kohs' Cubes test that measures visuo-constructive intelligence; the Category Verbal Fluency, a test to measure executive functions and language, and to evaluate semantic memory.

For the WMS, we concentrated on some subtests as particularly representative of specific functions: the Forward and Backward Digit Span measured passive and active verbal working-memory (WM) function, while the Mental Control subtest reflected executive function control. Besides, we aimed at deriving an index of the not WM-related mnemonic functions from the WMS subtest scores. Since each subtest involved both WM-related and not WM-related components with different proportion, we used a nearly pure WM subtest as a reference to filter out from the Memory Quotient, the WM-related component, and thus deriving a "working-memory-corrected Memory Quotient" (wmc-MQ). As WM reference we used the Backward Digit Span and the wmc-MQ was calculated as the residuals of regressing the global Memory Quotient versus the Backward Digit Span. Indeed, the residuals corresponded to the part of the global score not correlated with the WM reference and thus it was an estimate of the other memory components.

Finally, for the emotional evaluation, we employed the Profile of Mood States (POMS) (McNair et al., 1971) and the Endler Multidimensional Anxiety Scale (EMAS) (Endler et al., 1991) that measure, respectively, mood traits and the degree of anxiety associated with Social Evaluation, Physical Danger, Ambiguous Situation, and Daily Routine.

Experimental protocol

All experiments were performed between 3:00 PM and 6:00 PM. Subjects were sitting on an armchair in a semi-dark and sound-attenuated room, in order to be studied during 2 different conditions. The first condition was a state of minimal sensory perturbation (resting state) in which subjects were instructed to "keep their eyes closed, to relax, to refrain from moving, and to avoid any structured mental activity". The following condition consisted of an audiovisual stimulation performed by means of three randomly presented video clips characterized by different emotional/cognitive content projected on a 19' screen at 1.5 m. Specifically, an arousing but emotionally-neutral video concerning a basic math lesson extracted from an Italian educational TV program ("Consorzio Nettuno") was used as high cognitive load stimulation, while two film sequences, standardized for their aversive (The Blair Witch Project) and pleasant (There's Something About Mary) content, were used as emotional stimulation (Rottenberg et al., 2005). Each video lasted 3 min and was shown in the central visual field of the subject. In order to maintain the attention of the subjects focused on the videos, each video-clip was preceded by 50 s of black background and by 10 s of a countdown over the background.

At the end of each video clip, the subjects were asked to fill out the post-video questionnaire of perceived emotions (Rottenberg et al., 2005). The questionnaire consisted of two scales. The first one required scoring the general valence of the videos (Likert scales from 0 to 8, from unpleasant to pleasant) while the second one required scoring the greatest amount of distinct emotions experienced while watching each video clip. For the analysis of the questionnaires, distinct emotion scores were grouped into four classes: pleasure (happiness, amusement, joy), amazement (astonishment, surprise), apprehension (fear, anxiety), discomfort (sadness, disgust, unhappiness). The class score was derived adding up the scores of its components.

Both during the resting state and the video clips stimulation, EEG was recorded. EEG electrodes were placed according to the 10/20 International System, in frontal (F3, F4), central (C3, C4) and posterior (PO1, PO2) scalp regions and on the ear lobes (A1-A2). EEG signals were referred to the scalp vertex (Cz) and contact impedances were settled below 10 KOhm for all recordings.

During each condition the corrugator frontal muscle activity and electroculogram were also recorded to detect artifacts in EEG signals. All signals were digitally sampled at 250 Hz.

Analysis of EEG signals

From EEG signals we measured two characteristics: 1) the power distribution as a function of the frequency and of the scalp locations; 2) the power lateralization between hemispheres.

The preprocessing of EEG allowed obtaining 50 Hz line-free monopolar signals. Thus, EEG was filtered in the band 0.1-48 Hz and offline re-referenced to the average signal from A1 and A2. In addition, EEG was visual scored and head movement-corrupted epochs were discarded (less than 10% of epochs corrupted by artifacts). Eye movement artifacts were corrected by means of the application of the temporal-constrained ICA (James and Gibson, 2003).

The power related to each electrode was estimated by a periodogram with frequency resolution of 0.25 Hz. According to the IFCN (International Federation of Clinical Neurophysiology) guidelines (Nuwer et al., 1999), we considered six frequency bands: theta (4-8 Hz), alpha (8-12 Hz), beta1 (12-17 Hz), beta2 (17-23 Hz), beta3 (23-35 Hz), and gamma (35-45 Hz). Band-power-content of each EEG signal was normalized to the power in the full frequency range 4-45 Hz and, for each condition the normalized power-band-content characterized the local activity underneath each electrode.

As regards the lateralization of electrical activity, we considered three pairs of electrodes (F3-F4, C3-C4, P3-P4). For each pair, we measured: the imbalance of activity (within each frequency band) as $(P_1-P_2)/$

(P_1+P_2), where P_1 and P_2 are the absolute power for the electrodes 1 and 2.

Statistical procedures

Due to the different statistical properties of the variables (skewed, continuous or discrete, etc.), we applied non-parametric statistical tests instead of single-variable ad hoc transformations aimed at obtaining normal distributions. Thus, blood samples as well as psychiatric and psychometric measures were compared between groups by means of the non-parametric Mann-Whitney test. Also, EEG-related measures obtained in the different conditions (resting state, cognitive, unpleasant and pleasant stimulations) were compared by means of the non-parametric Wilcoxon's rank sum test. For each variable, tables report the group median and its interquartile range, and identify significant differences between groups. Finally, we studied the associations between neuropsychological scores, EEG features and hormonal levels by means of rank-based Spearman correlations.

Results

Hormonal assessment

As shown in Table I, laboratory analysis confirmed that all SHs were affected by autoimmune thyroiditis, as documented by the positive AbTG or AbTPO. They also showed high TSH levels (range, 3.8-9.9 microIU/ml; median + iqr, 5.29 + 1.9) and fT3 and fT4 within the reference range. In SHs the fT4 serum levels, although within the reference range (from 8.6 to 13.5 pg/ml), were slightly lower than in Controls (range from 11.5 to 14.2 pg/ml). Furthermore, at difference with Controls, in SHs a negative correlation was found between TSH and fT4 serum levels ($r = -0.58$, $p < 0.01$).

For the stress-related circulating markers, all subjects had values within the normal range and no differences between groups were found.

Psychometric evaluation

Table II summarized data of the psychiatric and psychometric evaluation. Concerning psychiatric evaluation (Hamilton scales), all subjects showed neither depression nor anxiety pathological scores. Also, no mood alterations were found in either SHs or Controls (POMS).

On psychometric evaluation as well, SHs, similarly to Controls, showed scores within the normal range in all the scales. Nonetheless, the two groups differed in two subtests. In fact, SHs showed significantly higher scores than Controls in Physical Danger (from EMAS) and Mental Control (from WMS) subscales. For SHs, the Physical Danger scale indicated moderate anxiety limited to this situation, while Mental Control highlighted better abilities in automated procedural tasks compared to Controls.

Finally, the wmc-MQ scores were significantly different ($p < 0.01$) between groups, SHs had wmc-MQ scores of 6.5 ± 10 while the Controls had scores of -2.3 ± 4.9 (median ± iqr). In fact, as shown in the scatter plot of Backward Digit Span versus Memory

Table I. - Thyroid- and stress-related circulating markers.

	SH		Controls		prob.	normative reference
	median	iqr	median	iqr		
TSH	5.3	1,.9	1.3	0.5	p < 0.001	0.3-3.80 mU/mL
fT3	2.7	0.5	2.8	0.5	-	2.10-4.20 pg/mL
fT4	10.9	2.0	12.9	1.6	p < 0.05	7-18.5 pg/mL
Adrenaline	31.9	9.5	29.6	10.0	-	< 80 pg/mL
Noradrenaline	244.0	90.0	220.0	105.0	-	< 500 pg/mL
Dopamine	41.0	19.0	30.0	20.0	-	< 100 pg/mL
Cortisol	120.0	40.0	140.0	30.0	-	70-300 ng/mL
ACTH	15.0	5.0	17.0	6.0	-	10-50 pg/mL
AbTG	250.0	200.0	10.0	5.0	p < 0.001	< 40 IU/mL
AbTPO	200.0	350.0	6.0	4.0	p < 0.001	< 25 IU/mL

Table II. - Psichiatric and psychometric evaluations.

		SH		Controls		prob.	normative reference
		median	iqr	median	iqr		
	HAM-Anxiety	8	3	7	2	-	≤ 18
	HAM-Depression	4	2	3	2	-	≤ 7
POMS	Tense/anxious	51	19	54	16	-	51 ± 9
	Depressed/miserable	51	20	54	13	-	55 ± 10
	Aggressive/angry	58	15	53	25	-	58 ± 14
	Vigorous/active	51	21	51	20	-	54 ± 13
	Tired/sluggish	51	16	59	10	-	58 ± 7
	Confused/discouraged	52	31	59	20	-	58 ± 12
EMAS (trait items)	Social Evaluation	49	16	51	14	-	52 ± 9
	Physical Danger	64	12	51	12	< 0.001	49 ± 9
	Ambiguous Situation	52	10	52	12	-	53 ± 10
	Daily Routine	51	18	46	11	-	47 ± 10
WMS (selected items)	Forward Digit Span	6.0	0.8	5.8	0.6	-	7 ± 1.2
	Backward Digit Span	4.4	1.5	4.5	1.2	-	5.3 ± 1.1
	Mental Control	9.0	2.0	7.0	1.0	< 0.001	7.5 ± 2
	Memory Quotient	113	16	108	17	-	68 ± 6
	Corsi Visuo-Spatial Span	4.2	1.5	4.9	0.7	-	4.7 ± 0.8
	Raven Progressive Matrices	20	13	24	10	-	21.8 ± 9.8
	Kohs Cubes Score	123	14	122	20	-	117 ± 16
	Verbal Fluency	26	10	23	6	-	13 ± 4

Interquartile range is shorted iqr. Prob. is the probability that the two group have the same median (Paired Wilcoxon test)

Quotient scores (Fig. 1), keeping the Backward Digit Span fixed, the expected Memory Quotient for SHs was greater than for Controls (see the regression lines).

Links between THs and psychometric features

Analysis of correlation unveiled that some cognitive and emotional functions paralleled the fT4 levels in SHs, while no significant correlations were found in Controls. Among the emotional tests/subtests, Physical Danger was correlated with fT4 levels ($r = 0.55$, $p < 0.05$), whereas, among cognitive tests, both Memory Quotient and wmc-MQ were correlated with fT4 ($r = 0.53$, $p < 0.05$ and $r = 0.54$, $p < 0.05$, respectively). Both Memory Quotient and wmc-MQ were also directly linked with Physical Danger ($r = 0.51$, $p < 0.05$ and $r = 0.49$, $p < 0.05$, respectively); however these correlations were not independent from that with fT4: controlling for fT4, the partial correlations between them were close to zero.

Resting state characterization

As concerns the EEG activity during the resting state, SHs had a reduced alpha rhythm in the right hemisphere and bilaterally in the frontal areas (Table III). Besides, SHs had a general gamma lateralization reduction compared to Controls, which were lateralized to the left. The lateralization difference between groups reached statistical significance ($p < 0.05$) in the parietal areas (Table IV).

Emotional responses to video clips

As regards the self-assessment of emotions experienced during stimulations, cognitive and pleasant video clips had similar general valence scores between groups; while on average the unpleasant one had lower ($p < 0.05$) valence score in SHs (2 ± 3, median ± iqr) with respect to Controls (3 ± 3). In addition, although not significantly different, apprehension and discomfort emotional classes displayed scores notably greater in SHs (7.5 ± 9 and 9 ± 10, respectively) than in Controls (4.5 ± 8 and 5 ± 13, respectively).

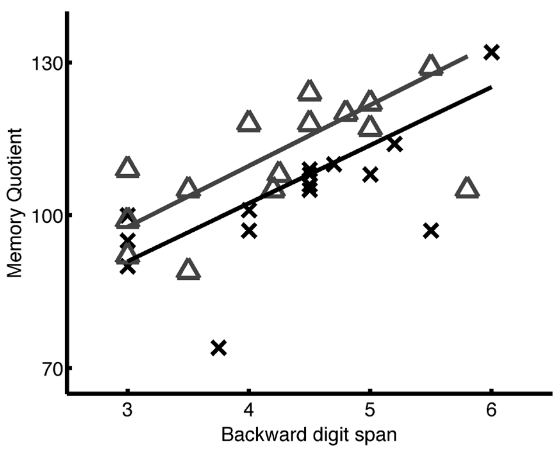

Fig. 1. - Plot of Memory Quotient versus Backward Digit Span scores with linear model fitted for each group. Keeping the Backward Digit Span fixed, the expected Memory Quotient for SHs (light grey triangle) is greater than for Controls (black cross). Namely, controlling for working-memory-related functions, we derived a 'working-memory corrected Memory Quotient' (wmc-MQ) that was significantly greater in SH than in Controls.

The EEG recordings showed that, during all stimulations, both groups exhibited a dominant beta2 activity in the EEG, with a tendency of higher levels for SHs. In addition, this activity in the parietal areas was lateralized toward the right hemisphere in SHs, while toward the left hemisphere in Controls (Table IV).

Discussion

In this work we assessed emotional and cognitive functioning as well as EEG activity in SHs patients compared with euthyroid controls and tested the association between the measures of the different variables and the individual THs levels. EEG activity was evaluated at rest and also during conditions of cognitive and emotional load in order to uncover, possibly otherwise masked, differences in cerebral activity.

Preliminary psychiatric evaluation did not yield any psychopathological criterion for diagnosis of depression and/or anxiety in SHs, thus confirming that mild TSH increases alone are not associated with overt mental disorders. In addition, it also indicated the absence of any biases that could affect the following psychometric and EEG assessment.

Psychometric evaluation, taken as a whole, did not indicate any abnormal values in SHs. However, SHs were significantly more focused about the own Physical Danger than Controls, thus suggesting a greater inward attention for SH. In addition, they did not have any alterations in executive functions or memory but actually they showed better abilities in automated procedural tasks compared to Controls, as indicated by their higher scores in the Mental Control subtest as well as in the working-memory-corrected Memory Quotient (wmc-MQ).

Better memory functions in SHs were an unexpected finding since general cognitive deficit characterizes overt thyroid hypofunction (Davis and Tremont, 2007). However, our finding is in line with a previous epidemiological study over adolescents showing that SHs had, on average, higher reading and block design scores compared to euthyroid subjects (Wu et al., 2006), and with the study of St. John (St. John et al., 2009) that showed, limited to females, a positive association between TSH levels and the scores on word list learning.

The study of the association between THs levels and psychometric traits have highlighted novel links between some cognitive functions and fT4 individual levels in SHs but not in euthyroid controls. In fact in SHs, both Physical Danger and wmc-MQ scores paralleled fT4 levels. Strikingly, although they showed a greater average score than Controls, the SH subjects with the lowest fT4 levels reported the lowest Physical Danger scores, close to the average value of Controls.

In SHs the correlation between wmc-MQ and Physical Danger scores was also statistically significant, but became not significant (actually, close to zero) when removing the fT4 parameter contribute. This result could be interpreted in term of circulating hormone levels influencing arousal, that in turn may favor concentration, and thus enhance performances in procedural tasks.

As concern the EEG assessment of rest and video clip stimulations, to our knowledge, no EEG studies have been previously performed in SHs.

Herein we have found reduction of alpha power activity at rest as well as a tendency of beta2 increase and a significant lateralization toward the right hemisphere during all stimulations and we believe that these results can be interpreted as indicative of higher levels of emotional arousal

Table III. - Resting α activity underneath each electrode.

	SH		Controls		prob.
	Median (n.u.)	iqr	median (n.u.)	iqr	
F3	0.30	0.13	0.38	0.20	< 0.05
F4	0.32	0.15	0.40	0.21	< 0.05
C3	0.33	0.15	0.40	0.13	-
C4	0.33	0.15	0.45	0.17	< 0.05
PO1	0.42	0.26	0.46	0.22	-
PO2	0.44	0.20	0.50	0.30	< 0.05

Interquartile range is shorted iqr. Prob. is the probability that the two groups have the same median (Paired Wilcoxon test)

in SHs. In fact, previous studies demonstrated that anxiety levels parallel right-lateralized beta2 activity (Aftanas and Pavlov, 2005). Accordingly, results concerning the self-assessed questionnaires on stimulation-induced feelings suggested that SHs might have a greater susceptibility to negative emotions. In addition, higher aspecific arousal rhythms associated with an increased anxiety trait, even very specific as Physical Danger, might be explained by taking into consideration that THs depress the GABAergic activity and conversely decreased THs are linked to reinforced GABAergic activity and to enhanced beta2 rhythms as observed with benzodiazepines administration (Wiens and Trudeau, 2006; Romano-Torres et al., 2002). Indeed the involvement of the GABAergic system in working-memory dysfunction, associated with bilateral dorso-lateral prefrontal cortex hypoactivation at fMRI in more advanced SH (TSH levels 14 mIU/ml, on average) has been previously described (Zhu et al., 2006).

Taken as a whole, our data indicate that minimal changes in thyroid hormonal levels produce effects on cognitive and emotional functions, as well as on EEG rhythms: these effects seem to be biphasic. In fact SH increases inward attention and paradoxically improves some cognitive functions provided that THs levels are only slightly changed. On the contrary, within the SH group a more pronounced decrease in fT4 levels is associated with a decrease of inward attention and of no-working-memory-related functions compared to milder SHs.

In conclusion, our study documented subtle but well-defined mental changes in SH compared to healthy controls, encouraging further studies based on the most SH-sensitive parameters indicated by this pilot study. For example, possible future studies would consider the trend of these parameters as a function of the pathology evolution or the introduction in the SH approach of the hormone replacement therapy.

Table IV. - Parietal lateralization (PO1-PO2)

		SH		Controls		prob.
		median	iqr	median	iqr	
β2	Resting	0.02	0.08	0.09	0.13	-
	Cognitive stimulation	-0.03	0.05	0.01	0.06	< 0.05
	Unpleasant stimulation	-0.01	0.06	0.02	0.04	< 0.05
	Pleasant stimulation	-0.01	0.05	0.06	0.11	< 0.05
γ	Resting	0.02	0.18	0.22	0.34	< 0.05
	Cognitive stimulation	-0.02	0.16	0.07	0.21	
	Unpleasant stimulation	-0.07	0.20	0.07	0.20	-
	Pleasant stimulation	-0.05	0.12	0.04	0.15	

Interquartile range is shorted iqr. Prob. is the probability that the two groups have the same median (Paired Wilcoxon test)

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