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Neural response to transcranial magnetic stimulation in adult hypothyroidism and effect of replacement treatment

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Abstract

Purpose: Despite clinical evidences that hypothyroidism is often associated with cognitive dysfunction, affective disorders and psychosis, the effects of thyroid hormone deficiency on the adult brain have been largely unexplored. We investigated the hypothesis that hypothyroidism might affect cortical excitability and modulates inhibitory and excitatory cortical circuits by using Transcranial Magnetic Stimulation.
Materials and methods: Cortical excitability was probed in 10 patients with overt hypothyroidism and 10 age-matched healthy controls. We tested motor thresholds and corticospinal excitability, cortical silent period and peripheral silent period, short interval intracortical inhibition, intracortical facilitation. Patients were evaluated at the time of diagnosis, as well as after 3 and 6 months replacement therapy with L-thyroxin.
Results: At baseline, patients showed decreased cortical excitability, with increased resting and active motor threshold and decreased steepness of the motor evoked potential recruitment curves. These changes were paralleled by longer cortical silent period and decreased short interval intracortical inhibition. After 3 months replacement therapy, all the parameters but short interval intracortical inhibition were restored to normal values. Short interval intracortical inhibition returned to normal values only after 6 months of replacement therapy.
Conclusions: Thyroid hormones are needed to modulate cortical excitability and cortical inhibitory circuits in adults.

Keywords: TMS; Hypothyroidism; Cortical excitability

1. Introduction

Thyroid hormones (THs) are key regulators of metabolism and development and are known to have pleiotropic effects in many different organs including the central nervous system [1]. Their importance for the normal function of the adult brain is substantiated by the frequent association of thyroid dysfunctions with the presence of neurological and psychiatric symptoms. In particular, neuropsychological and affective alterations, such as depression, anxiety, progressive cognitive impairment and memory loss, are often present in both subclinical and overt hypothyroidism

Abbreviations: OH, overt hypothyroidism; TMS, transcranial magnetic stimulation; TH, thyroid hormones; MEP, motor evoked potential; CSP, cortical silent period; PSP, peripheral silent period; SICI, short interval intracortical inhibition; ICF, intracortical facilitation.

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(OH) [2,3]. These symptoms are paralleled by decreased cerebral blood flow in regions involved in the regulation of attention, mood, motor functions, memory and visuo-spatial processing [4].

The relationships between hypothyroidism and cognitive and emotional dysfunctions are complex. It has been reported that patients with subclinical hypothyroidism often display co-morbid major depression and THs have been used both to augment and accelerate the clinical effects of antidepressants [5–8]. In addition, there is evidence that thyroid dysfunction increases the risk of dementia [9–11]. Altogether, these findings suggest that THs might have a profound influence on neurotransmission and synaptic activity in cortical circuits involved in cognitive and emotional regulation [12,13].

Despite the evidence that THs affect brain function in adults, the underlying molecular mechanisms remain poorly understood [14]. It is known that THs action is mediated by nuclear receptors that are widely distributed throughout the brain and influences several neurotransmitters (serotonin, norepinephrine, GABA and glutamate) [15]. Furthermore, studies in rodents showed that hypothyroidism disrupts inhibitory and excitatory neurotransmission , synaptic plasticity and learning and memory [16,17,14].However, these results need to be confirmed in hypothyroid patients.

Transcranial magnetic stimulation (TMS) is a non-invasive technique valuable to investigate cortical physiology. Single and paired-pulse TMS studies have been used to characterize several motor cortex excitability measures and the putative inhibitory and excitatory neurotransmitters which modulate them. These parameters have been employed in several neurological and psychiatric diseases in order to elucidate the underlying neurochemical dysfunctions [18].

Thus, in this study we determined whether OH affects cortical excitability and modulates inhibitory and excitatory intracortical circuitries by using TMS. Given that cognitive and affective abnormalities that accompany hypothyroidism are reversed once euthyroidism is restored, we also investigated whether hormone-replacement treatment can restore physiologic cortical excitability.

2. Methods

2.1. Subjects

Subjects were 10 patients with OH (4 men, 6 women, age: mean±SD 53±8 years) referred to the Endocrinology Unit, University of Messina, Italy, and ten age- and gender-matched normal controls. OH was diagnosed on the basis of elevated serum TSH levels (>4.5 mIU/L (mU/L) and lowered free thyroxine (T4) levels (<12 pmol/L). The causes of OH included Hashimoto's thyroiditis ($n=9$) and radioiodine therapy ($n=1$) for hyperthyroidism treatment. Patients underwent a complete neurological examination and brain MRI and fulfilled the following inclusion criteria: 1) Negative history for depression (score <16 Montgomery–Asberg Depression Rating Scale-MADRS), peripheral neuropathy and myopathy (normal EMG examination); 2) normal Mini-Mental State Exam (MMSE; score >27) [19]; 3) No treatment with psychoactive drugs with psychoactive drugs; 4)negative history for vascular dementia, stroke, epilepsy, convulsions.

Controls were 10 age-matched healthy caregivers. All patients and controls were right-handed according to the Edinburgh Handness Inventory and gave their informed consent for the study, which was approved by the Institutional Ethics Committee. Patients underwent TMS and laboratory testing at the time of diagnosis (baseline) as well as at the end the third and sixth month of replacement therapy with L-thyroxin (range 75–150 μg/die). Control subjects were tested only at baseline.

2.2. Laboratory investigation

TSH and THs were determined in serum samples that were stored at −20 °C until assay. For the purpose of this investigation, each hormone in all 40 sera was assayed in a single run. Serum TSH, fT3 and fT4 are summarized in Table 1.

2.3. TMS stimulation and EMG recordings

Patients and controls underwent a series of tests with TMS. All subjects were seated in a comfortable reclining chair and surface EMG was recorded from the right first dorsal interosseus (FDI) muscle using disposable disc electrodes with a belly-tendon montage. EMG was filtered by Neurolog System supplied by Digitimer with a time constant of 3 ms, and a high pass filter set a 3 kHz. TMS was performed using a Magstim 200 HP magnetic stimulator (Magstim, Whitland, UK), which was connected to one figure of 8 shaped coil. Signals were collected via a CED 1401 laboratory interface (Cambridge Electronic Design, Cambridge, UK) and fed to a personal computer for offline analysis. Stimulation and recording procedures are described in details elsewhere [20–23]. We studied several parameters of cortical excitability including:

1) Resting motor threshold (RMT), defined as the minimal stimulus intensity required to produce MEPs>50 μV in at least 5 out of 10 consecutive trials;
2) Active motor threshold (AMT), defined as the minimum intensity necessary to induce a MEP of at least 200 μV in

Table 1
Thyroid function tests in patients with hypothyroidism at baseline, after 3 and 6 months of replacement therapy

	TSH levels (mU/L)	FT3 levels (pmol/L)	FT4 levels (pmol/L)
Controls	1.86±0.45	4.205±0.15	16.32±0.35
Hypothyroid	24.23±4.98	2.9±0.35	7.72±1.71
Replacement 3 months	2.16±0.35	3.720±0.29	17.07±0.63
Replacement 6 months	1.42±0.51	4.015±0.25	18.21±0.36

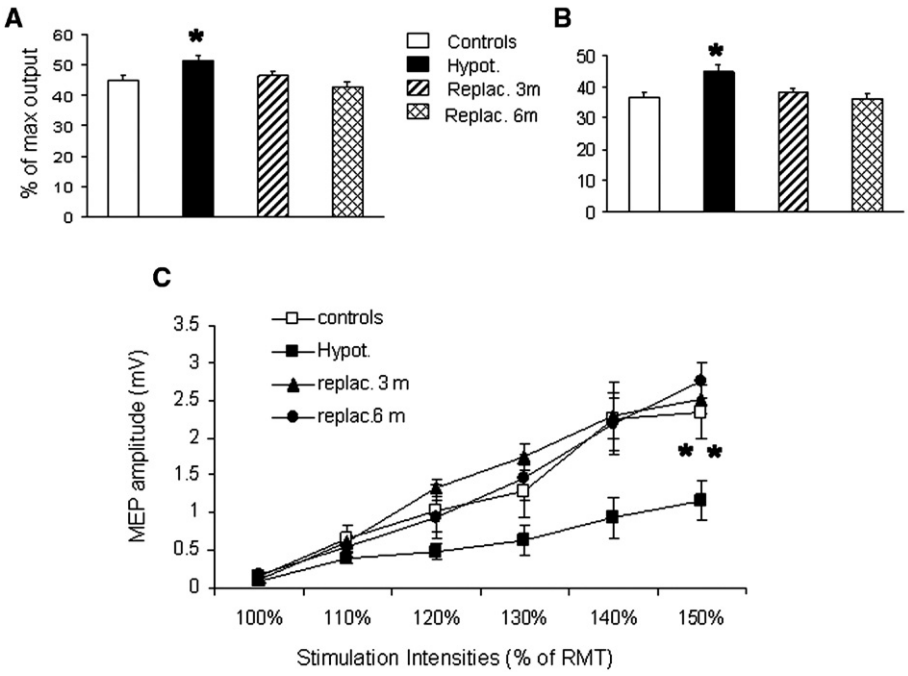

Fig. 1. A, B. RMT and AMT levels in controls and hypothyroid patients at baseline, after 3 and 6 months of replacement therapy. At baseline in patients RMT and AMT were higher then controls (*$p<0.005$). After 3 and 6 months both reached normal values. RMT and AMT are expressed as % of max output. C. Effect of replacement therapy on steepness of MEP recruitment curve: at baseline hypothyroid patients showed a lower steepness then controls (*$p<0.005$). Replacement therapy restored values after 3 months. After 6 months the steepness was still in normal range.

5 out to 10 subsequent trials during 5% of maximum voluntary contraction.

3) MEPs Input–Output recruitment curve at stimulus intensities ranging from 100% to 150% RMT (in steps of 10%). 10 peak-to-peak MEP at each stimulation intensities were averaged.
4) Cortical Silent Period (CSP) at stimulus intensities of 130% RMT during isometric voluntary contraction (30% maximum) of the right FDI muscle. CSP duration was defined in the single trials from the time of the magnetic stimulus to the first reoccurrence of a continuous voluntary EMG activity. For CSP measurements, ten consecutive MEPs were rectified but not averaged.
5) Short interval cortical inhibition (SICI) and intracortical facilitation (ICF), determined by using a conditioning-test paradigm [24]. Briefly, the intensity of the conditioning stimulus was set at 80% AMT. The intensity of the test stimulus was adjusted in order to have a MEP of about 1 mV amplitude. We studied six different inter-stimulus time intervals (ISI). A single block of 70 trials of 10 control trials (test alone) and 60 paired stimulation trials (10 for each condition) was performed. For each ISI, the amplitude ratio of the mean conditioned MEP to the control MEP was determined. SICI and ICF were defined as the averages of the MEP ratios obtained at inhibitory ISI of 2, 3, and 4 ms and facilitatory ISI of 10, 12, and 15 ms, respectively.
6) Peripheral silent period (PSP) was elicited in the right FDI muscle with an electrical stimulation of the ulnar nerve at the wrist at twice intensity to evoke the maximal M wave.

2.4. Statistical analysis

Differences in RMT, AMT, CSP, PSP, SICI and ICF between patients and controls were analyzed with ANOVA. The effect of replacement therapy was evaluated with repeated-measures ANOVA with factors *Group* (2 levels: patients and controls) and *Time* (3 levels: Hypothyroidism, 3 months replacement, 6 months replacement).

To study MEP recruitment curves in patients and in controls, the factors *Group* and *Intensity* (6 levels: 100, 110, 120, 130,140, 150% of MT) were chosen. The effects of replacement treatment on MEP recruitment curve were

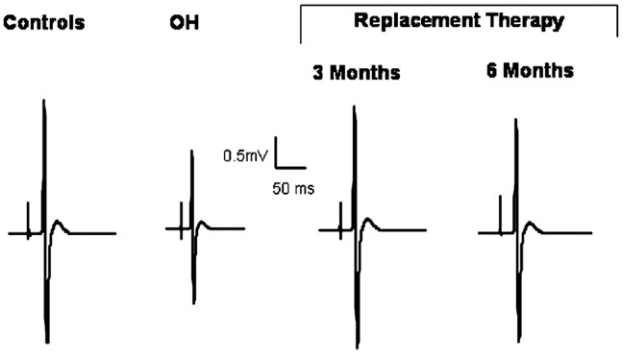

Fig. 2. Representative MEPs at 150% of RMT stimulation intensity from the FDI muscle of a control subject and from an OH patient at baseline and after 3 and 6 months of replacement therapy. MEP amplitude in the hypothyroid patient at baseline was smaller then controls. After 3 months and 6 months L-thyroxine treatment restored normal MEP amplitude.

analyzed with repeated-measures ANOVA with *Time* and *Intensity* as within factors. If appropriate, post hoc *t* tests were performed.

Spearman's correlation coefficient was used to correlate of the TMS parameters with TSH levels. Significance was set at $p<0.05$.

3. Results

TMS did not induce any adverse effects in both controls and patients.

3.1. Motor threshold

At baseline, RMT and AMT were significantly higher in patients than in controls (RMT: $F_{(2,18)}=6.5$, $p=0.019$; AMT: $F_{(2,18)}=10.04$, $p=0.005$ (Fig. 1). A repeated measures ANOVA demonstrated a main effect of treatment in patients (RMT: $F_{(2,9)}=9.149$; $p=0.00018$, AMT: $F_{(2,9)}=6.466$, $p=0.0077$). Both RMT and AMT significantly decreased from baseline values when tested three (RMT $p=0.0005$; AMT: $p=0.001$) and six (RMT $p=0.0002$; AMT: $p=0.003$) months of replacement therapy. After 3 months of replacement therapy both RMT and AMT were not different from those of normal controls (3 months: RMT: $F_{(2,18)}=0.3$, $p=0.5$; AMT: $F_{(2,18)}=0.45$, $p=0.62$; 6 months: RMT: $F_{(2,18)}=0.77$, $p=0.38$; $F_{(2,18)}=0.6$, $p=0.81$) (Fig. 1 A, B).

3.2. MEP recruitment curves

Examples from representative subjects are shown in Fig. 2 and the group data are shown in Fig. 1 and Table 2. MEP amplitudes increased with increasing stimulus intensity in both controls and OH patients. However, at baseline, MEP recruitment curve was significantly less steep in patients compared to controls. ANOVA indicated a significant effect for *Group* ($F_{(1,108)}=26.5$, $p<0.0001$) and *Intensity* ($F_{(1,108)}=15.3$, $p<0.0001$) with a significant interaction between the two factors ($F_{(5,108)}=2.5$, $p<0.02$). Post hoc analysis showed that MEP amplitudes obtained with higher stimulus intensities (130% , 140% and 150% MT) were significantly lower in patients with hypothyroidism (130%: $p=0.03$; 140%: $p=0.008$; 150%: $p=0.01$).

Recruitment curves improved significantly both after three and six month replacement therapy. Repeated measures ANOVA indicated a significant effect of *time* ($F_{(2,18)}=21.7$, $p<0.0001$) and *Intensity* ($F_{(5,45)}=40.4$, $p<0.0001$) with a significant *time*×*intensity* interaction ($F_{(10,90)}=8.1$, $p<0.0001$). Comparison with controls revealed that three months replacement therapy was sufficient to restore MEP recruitment curves to the physiological range (3 months: $F_{(1,18)}=0.215$; $p=0.648$; 6 months: $F_{(1,18)}$ 0.534 $p=0.474$) (Fig. 1C).

3.3. Inhibitory and facilitatory parameters

We first tested inhibitory mechanisms acting at spinal and cortical levels.

The duration of PSP induced by stimulation of the ulnar nerve was similar in controls and patients already at baseline ($p>0.05$), suggesting that spinal excitability tested by PSP is not affected in OH (Table 2).

At baseline, the duration of CSP was significantly longer in patients than in controls ($F_{(1,18)}=13.4$; $p=0.0018$). CSP duration was affected by replacement therapy ($F_{(2,18)}=14.3$; $p=0.002$; post hoc *t* test: 3 months $p=0.0006$; 6 months $p=0.0001$). After 3 months of replacement therapy, CSP of OH patients reached the controls' range ($F_{(1,18)}=0.3$; $p=0.5$) and did not change at the 6 months ($F_{(1,18)}=0.03$; $p=0.8$). These data suggest that cortical inhibitory circuits, possibly $GABA_B$-dependent (Weheran KJ et al, 1999), are impaired reversibly in OH. Another parameter of cortical inhibition, SICI, was reduced in patients compared to controls ($F_{(1,18)}=20.03$; $p=0.0003$). Replacement treatment decreased SICI ($F_{(2,18)}=9.05$; $p=0.001$), but post hoc *t* test demonstrated that this improvement was significant only after 6 months of replacement therapy (3 months: $p=006$; 6 months: $p=0.01$). SICI values in the patient group at 3 months were significantly different than those of controls ($F_{(1,18)}=11.1$; $p=0.00036$), while this difference was not present after six months of treatment ($F_{(1,18)}=2.7$; $p=0.1$) (Table 2).

We then assess the facilitatory intracortical mechanisms with ICF. We found that there was no difference between controls and patients at baseline ($p>0.05$) (Table 2), suggesting that OH does not disrupt intracortical facilitatory circuits.

Finally, we determined whether severity of hypothyroidism, assessed with TSH levels at baseline, could predict the

Table 2
Cortico-spinal excitability in controls and hypothyroid patients, after 3 and 6 months of replacement therapy

Neurophysiological parameters	Controls	OH	Replacement 3 months	Replacement 6 months
CSP(ms)	129.4±6.2	159.7±5.2 **	124.5±6.4 *	127.6±5.8
PSP(ms)	98±10.2	99.25±11.6	96.4±8.4	97.1±10.5
SICI(mV)	0.5±0.03	0.75±0.04 **	0.99±0.15	0.44±0.014 *
ICF(mV)	1.69±0.08	1.53±0.07	1.77±0.18	1.54±0.07

CSP = cortical silent period; PSP = peripheral silent period; SICI = short interval intracortical inhibition; ICF = intracortical facilitation.
* $p<0.001$ difference within patients group after treatment.
** $p<0.001$ difference between patients and controls at baseline.

electrophysiological abnormalities we reported at the time of diagnosis. Indeed, we found that the only significant correlation was between TSH levels and motor thresholds (RMT: $r=0.73$, $p=0.028$; AMT: $r=0.79$, $p=0.019$).

4. Discussion

The main finding of this study is that OH impairs both excitatory and inhibitory cortical mechanisms. Specifically, we found a decrease of cortical excitability with increased motor thresholds and abnormal recruitment curves. Inhibitory cortical circuits were impaired as well, as shown by prolongation of the cortical silent period and reduced intracortical inhibition (SICI). Replacement therapy restored these indexes of cortical function to normal values.

4.1. OH impairs cortical excitability

Motor thresholds and MEP recruitment curves, which were impaired by OH, measure different aspects of cortical excitability [25]. The two parameters are also dependent on different pharmacological mechanisms. It is now accepted that motor thresholds mostly depend upon the activity of voltage-gated Na^+ and Ca^{2+} channels of motor cortical neurons, as they are typically increased by blockers of voltage-gated Na+ channels [26]. Glutamatergic neurotransmission modulates MTs. Specifically, AMPA receptor blockers increases MTs while pharmacological NMDA receptor modulation has no effects on MTs [27,28]. Because hypothyroidism in rodents induces a differential modulation of glutamatergic activity decreasing only NMDA neurotransmission [29], the observed increase MTs is consistent with an effect on cations channels. THs increase intracellular neuronal Na^+ concentration [30–32]. It is thus likely that the increase in motor threshold in OH patients is due to cortical changes in Na+ channels activity. In addition, modulatory effects on cellular Ca^{2+} homeostasis could play a role in the increase MTs [33–35].

MEP recruitment curves are influenced by GABAergic and monoaminergic neurotransmission and by voltage-gated Na^+ and Ca^{2+} channel properties [36,37]. Because of the involvement of multiple systems, recruitment curves represent a sensitive, although non-specific, parameter of corticospinal excitability. Indeed, THs modulates brain adrenergic and serotoninergic neurotransmission [8,15] and intraneuronal Na^+ and Ca^{2+} homeostasis . Pharmacological studies demonstrated that these systems modulate the steepness of recruitment curve [38,36,39,40]: these data may explain our findings.

Another important result in our study is that OH induces CSP prolongation and reduced SICI. CSP represents a GABAergic phenomenon involving both spinal and cortical mechanisms [41]. However, since PSP was within normal limits, CSP prolongation in our OH patients should be due to cortical dysfunctions. CSP duration is modulated by $GABA_B$ [42] while $GABA_A$ system play a prominent role in SICI modulation[43].

THs are involved in the regulation of cortical GABA system, including metabolism, release, reuptake and receptors [44,45]. Increasing and decreasing circulating THs levels experimentally in rodents vivo alter density of GABA receptor-binding sites, but results vary from study to study, which may reflect important regional differences in the brain [46]. Thus, the lack of demonstration of specific GABAergic dysfunctions in motor cortex in OH patients may be in reduced SICI we found .

Interestingly, three months of replacement treatment restored to normal values motor thresholds, recruitment curves, as well as CSP, but not SICI. SICI was normalized only after 6 months of replacement therapy. One possible explanation of this differential effect could be that $GABA_B$ and $GABA_A$ system have a different sensitivity to thyroid status. On the other hand, the decreased excitatory drive on the voluntarily activated muscle could account for the prolonged CSP. This could explain the same time course in the recovery after replacement therapy of MTs, recruitment curves and CSP.

5. Conclusions

In this paper we have shown that THs deficiency affects several cortical excitatory and inhibitory mechanisms. These impairments occur via complex and yet not well-understood modulation of several neurotransmitter systems.

In light of the degree of variability both within- and across-subjects of the parameters we tested [47],our findings may set the stage for future and more probing research on the role of THs in regulating mood and cognitive processes.

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