Cortical activation during finger tapping in thyroid dysfunction: A functional magnetic resonance imaging study

S Khushu[1,*], S Senthil Kumaran[1], T Sekhri[2], R P Tripathi[1], P C Jain[3] and V Jain[1]

[1]*NMR Research Centre,* [2]*Thyroid Research Centre, Institute of Nuclear Medicine and Allied sciences, Brig. S K Majumdar Road, Delhi 110 054, India*

[3]*Department of Physics and Astrophysics, University of Delhi, Delhi 110 007, India*

**Corresponding author (Fax, 91-11-23919509; Email, skhushu@yahoo.com)*

Thyroid dysfunction is associated with attention deficit and impairment of the motor system (muscle weakness and fatigue). This paper investigates possible motor function deficit in thyroid patients, compared to the controls. Functional MRI studies (fMRI) were carried out in five hypo and five hyperthyroid patients and six healthy volunteers. Whole brain imaging was performed using echo planar imaging (EPI) technique, on a 1.5T whole body MR system (Siemens Magnetom Vision). The task paradigm consisted of 8 cycles of active and reference phases of 6 measurements each, with right index finger tapping at a rate of 120 taps/min. Post-processing was performed using statistical parametric mapping on a voxel-by-voxel basis using SPM99. Clusters of activation were found in the contralateral hemisphere in primary somatomotor area (M1), supplementary motor area (SMA), somatosensory, auditory receptive and integration areas, inferior temporal lobe, thalamus and cerebellum. Increased clusters of activation were observed in M1 in thyroid subjects as compared to controls and with bilateral activation of the primary motor cortex in two hyperthyroid patients. The results are explained in terms of increased functional demands in thyroid patients compared to volunteers for the execution of the same task.

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1. Introduction

The initial functional magnetic resonance imaging (fMRI) experiments (Belliveau *et al* 1990) used an exogenous gadolinium-based contrast agent. The discovery that deoxyhaemoglobin could be used as an endogenous contrast agent made repetitive experiments possible (Ogawa *et al* 1990). The development of high-performance gradient systems and ultra fast imaging techniques, such as echo planar imaging (EPI) (Stehling *et al* 1991) and turbo gradient echo (FLASH), are highly sensitive to magnetic susceptibility variations (T_2^*), particularly at long echo times. These have facilitated dynamic studies involving the non-invasive mapping of the human brain functions and dysfunctions. Since the early experiments (Belliveau *et al* 1991), EPI and FLASH (Kleinschmidt *et al* 1997) are used extensively to detect changes in the cerebral blood flow (CBF) and oxygenation levels elicited by the neuronal activity. Though signal intensity is found to be higher in FLASH, EPI is still widely used and is considered to be a reliable technique (Fellner *et al* 1998) due to the reduced imaging time and increased slice coverage.

BOLD fMRI has evolved into a widely accepted methodology for neural mapping of the cortical areas corresponding to vision, motor, language, memory, emotion, and pain (Tootell *et al* 1998; Ashe and Ugurbil 1994; Binder 1997, Fletcher *et al* 1997; Philips 1997; Davis *et al* 1997). Also, fMRI studies have been performed in the diseased

Keywords. fMRI; hypothyroid; hyperthyroid; motor task

Abbreviations used: BA, Brodmann's areas; EPI, echo planar imaging; FLASH, turbo gradient echo; fMRI, functional magnetic resource imaging; M1, primary somatomotor cortex; SMA, supplementary motor area; TSH, thyroid stimulating hormone.

conditions, like stroke (Leifer *et al* 1998), amputation and phantom limbs (Lotze *et al* 1998), epilepsy (Graveline *et al* 1998) and schizophrenia (Wenz *et al* 1994) to look for the functional impairment. Thus fMRI is used to understand brain organization, assessing of neurological status, and involved neurosurgical risk in diseased conditions.

Four major regions in the frontal lobes control motor function: namely, the primary somatomotor cortex (M1), supplementary motor area (SMA), lateral premotor cortex and the cingulate motor area. The primary somatomotor cortex is responsible for the direct production of movements via its outputs to the pyramidal tract. Any damage to these areas, resulting from diseases like stroke, produces a weakness in the corresponding parts of the body. Patients with dysfunction of the thyroid gland show disorders of the motor system (muscle weakness, fatigue), poor performance on neuro-psychological test requiring complex visual discrimination, conceptualization, mental flexibility or organization (Whybrow *et al* 1969; Wallace *et al* 1980; Trzepacz *et al* 1988; Stern *et al* 1996). Thyroid hormone levels can influence the mitochondrial enzyme activities in muscle to cause fatigue and exercise-intolerance in both hypo and hyperthyroidism (Rulf 1986). Muscle bioenergetic impairment has been reported in human hypothyroid suggesting mitochondrial defect (Argov *et al* 1988; Kaminsky *et al* 1992). Since the energy metabolism and cell function are closely linked, it may be expected that the motor cortex (involving the motor functional areas in the brain and the skeletal muscle) function may be impaired in thyroid patient and may differ from that of healthy volunteers. The present study was to look for the functional status in these patients, as it has not been investigated so far.

2. Materials and methods

2.1 *Subjects*

Three groups of subjects, namely, healthy volunteers (controls), frank hypo and hyperthyroid were considered. Six right-handed subjects in the age range 20–45 years were recruited in each group. There was no previous history of neurological disorders or any muscle weakness in the control group. Thyroid function tests, namely, free tri-iodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) were carried out in all the subjects. The thyroid function tests were in the normal range for the volunteers (FT3 = 2.5–5.8 pmol/l, FT4 =11.5–23.0 pmol/l and TSH = 0.17–5.2 μIU/ml). In hypothyroid group, patients with FT4 below normal and TSH of atleast 100 μIU/ml or above and in hyperthyroid group, patients with FT4 >23 pmol/l and TSH of less than 0.01 μIU/ml were recruited for the study.

2.2 *Study details*

All these subjects were studied by BOLD technique using multi-slice gradient echo EPI sequence. Thirty-nine axial slices parallel to the bicommissural plane through the fronto-parietal cortex covering the whole brain were acquired using single shot EPI sequences (TE = 64 ms; flip angle = 90°; slice thickness = 3 mm; matrix 64 x 64; number of measurements = 96). The in plane resolution was 3.28 mm x 3.28 mm with a total field of view (FOV) of 210 mm. Prior to the acquisition of EPI images, multi-angle projection (MAP) shim was performed to optimise the magnetic field homogeneity. Corresponding T_1 weighted high-resolution images with parameters history matched with that of EPI were acquired for co-registration of the anatomy with functional information. The images were acquired using 1.5 Tesla whole-body MRI system (Siemens Magnetom Vision, Erlangen, Germany) using a circularly polarized head coil and 25mT/m actively shielded gradient system.

2.3 *Task paradigm*

The subjects were requested to perform the motor task, by tapping the right index finger, at a rate of 120 taps/min (in tune with an auditory cue from the Metronome), at a constant force using a tapping device fabricated in-house. Block design paradigm with eight cycles of activation and baseline phases was used. Each cycle consisted of six measurements for activation and six for reference phase. The same experimental conditions were maintained in all the experiments. Verbal commands were given to start and stop the motor task. The subjects were visually monitored during the examination to confirm adherence to the experimental design.

2.4 *Data post-processing*

The fMRI data sets were subjected to image pre-processing steps, mainly, image realignment, image normalization and image smoothing. The datasets with motion parameters more than 1.5 mm (translation) and 1° (rotational) were discarded. The image volumes were normalized with EPI template provided by Montreal Neurological Institute (MNI). Smoothing was carried out using Gaussinan kernel with FWHM of 6 mm. The model chosen was delayed boxcar response function. The functional maps based on student's '*t*' test were generated using the SPM 99 software (*www.fil.ion.ac.uk*), in Matlab environment (The MathWorks, Inc., USA) on a stand-alone SUN – SPARC 10/40 workstation.

To make the subjects acclimatized to the EPI gradient noise and the task paradigm, and also to suppress T_1

saturation effects, the first 12 studies (acquisitions) were discarded. Hence, 84 studies were considered for post-processing, which constitute 7 cycles of resting and activation phases of 6 measurements each, with inter-scan interval of 7.06 s. Using this model, the fMRI data sets were post-processed using *t*-contrast, with a threshold of P=0.001 (corrected) and voxel threshold of 10. Activated brain areas were classified into Brodmann's areas (BA) according to their corresponding stereotaxic co-ordinates (x,y,z) (Talairach and Tournoux 1988).

3. Results

The control group performed right index finger tapping at 120 (SD ± 10) taps/min and adhered to the experimental requirements. Hypothyroid patients could tap at only 90 (SD ± 8) taps/min and hyperthyroid patients had a mean tapping rate of 120 (SD ± 8) taps/min. Due to non adherence to the experimental requirements one patient each of hypo and hyperthyroid were not included in the data so only five subjects from each category were considered for the final analysis.

The areas of activation were the primary somatomotor area (BA 4), supplementary motor area (BA 6), somatosensory area (BA 1,2,3), auditory receptive and integration region (BA 22,37,38,41,42). From the individual subject analysis, clusters were estimated in different BA of the brain. Average cluster volumes in terms of number of voxels (mean ± SD) in the individual groups of healthy, hypo and hyperthyroid subjects is given in table 1. In hypothyroid subjects, additional activation in cerebellum was also observed, compared to control group (table 1). Apart from the areas recruited for normal subjects, cerebellum and thalamus were also activated in hyperthyroid group (table 1). The grey scale activation maps (Glass brain view) and pseudo colour maps (red – yellow - white) in schematic orthogonal planes for representative subjects in the three groups are shown in figure 1. The cluster summary at the M1 (BA 4) shows an increased area of activation in the hyperthyroid group and almost equal number of voxels in the hypothyroid group (table 1). The plots of the fitted BOLD signal response as a function of scan during the resting and motor task in primary motor area and supplementary areas of a healthy volunteer are shown in figure 2. The BOLD signal change was observed to be 6.8% ± 1.5% at the M1 location and 2.6% ± 1.7% at the SMA with respect to the baseline condition (figure 2). In two out of five hyperthyroid patients, bilateral activation was observed in the primary motor cortex, with dominance on the contralateral hemisphere (figure 1f). The activation signal rendered onto the 3D brain surface of a hyperthyroid subject is shown in figure 3.

4. Discussion

Activation of a brain area is accompanied by a depolarization of neuron membrane potentials. Maintaining and re-establishing this potential require an increased supply of energy, which causes increase in the supply of blood flow and oxygen use in these activated regions. The execution of a motor task demands the recruitment of a number of

Table 1. Cluster volume summary for healthy, hypo and hyperthyroid subjects.

Area	Brodmann area (BA)	Number of clusters (mean ± SD)		
		Healthy	Hypo	Hyper
Primary somotomotor area precentral gyrus - left cerebrum	BA 4	1060 ± 80	965 ± 55	1600 ± 180
Primary somotomotor area precentral gyrus - right cerebrum	BA 4			28 ± 10*
Supplementary motor area medial frontal gyrus, superior frontal gyrus - left cerebrum	BA 6	255 ± 75	288± 72	130 ± 20
Somatosensory area postcentral gyrus - right Cerebrum	BA 1,2,3			22 ±8
Auditory receptive, integrative area superior temporal gyrus (left cerebrum)	BA 22,37,38,41,42	49 ± 14	56 ± 20	82 ± 11
Auditory receptive, integrative area superior temporal gyrus (right cerebrum)	BA 22			13 ± 6
Right cerebellum			17 ± 9	10 ± 11
Thalamus	Medial dorsal nucleus			56 ± 10

* In two subjects.

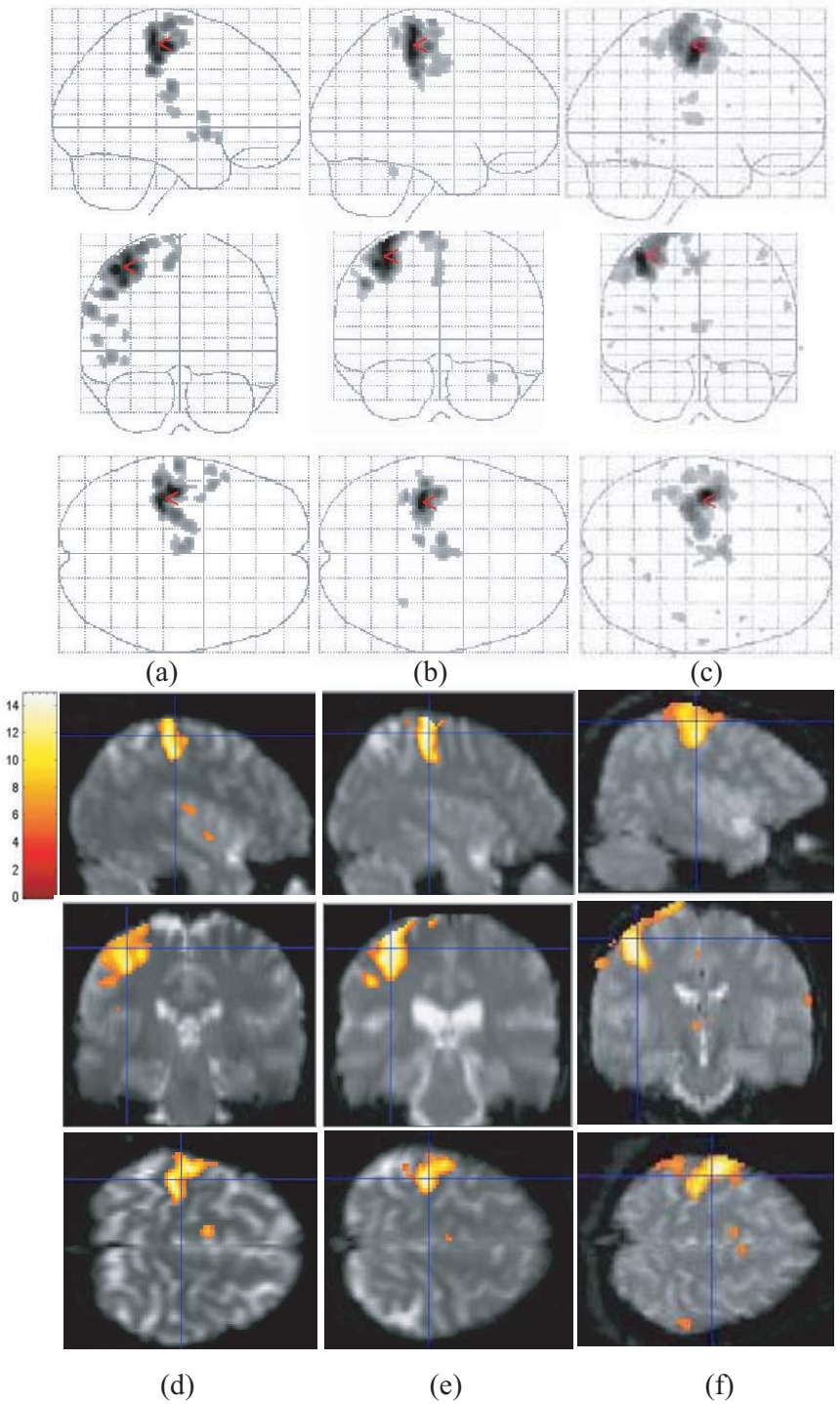

Figure 1. The BOLD activation pattern in the brain represented in Glass Brain View (**a,b,c**) and pseudo colour maps rendered on orthogonal slices (**d,e,f**) in representative healthy (**a,d**), hypothyroid (**b,e**) and hyperthyroid (**c,f**) subjects.

cortical areas necessary for the translation of the intention to accomplish a voluntary movement into motor action. In movements confined to intrapersonal space (which do not depend on the external environment), the passage from intention to action requires the activation of preMA, M1 and SMA for the programming of the voluntary movement

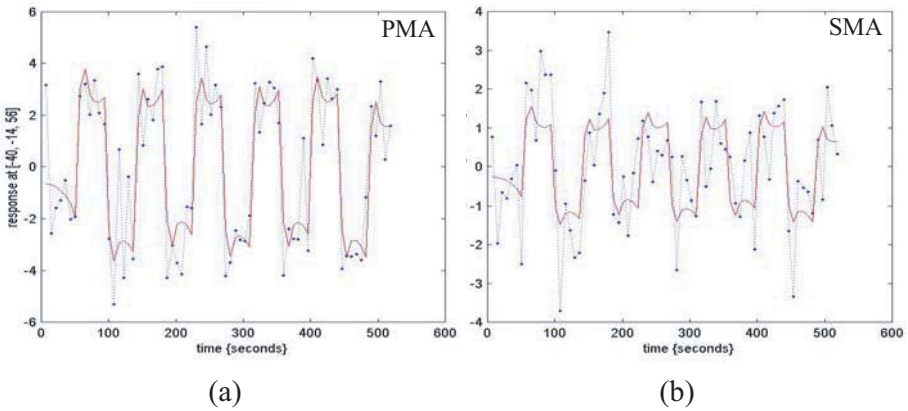

Figure 2. The signal intensity plotted against the scans (temporal characteristics) at the M1 and SMA area in a volunteer.

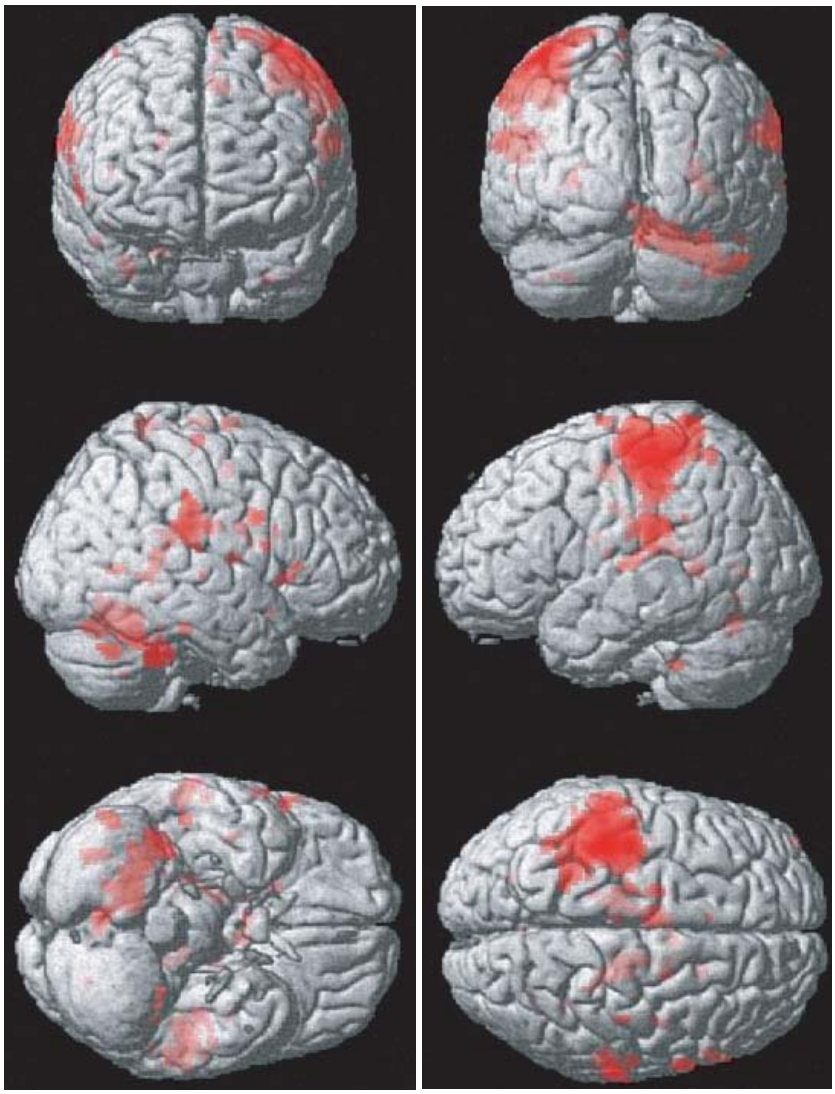

Figure 3. Surface rendering on the whole brain volume showing different activated clusters in a finger tapping experiment on a hyperthyroid subject.

and their execution. The location of the hand representation is in an omega-shaped region of the central sulcus (Yousry *et al* 1997).

A precise and consistent activation pattern in healthy volunteers was observed in the primary somatomotor area, supplementary motor area, somatosensory area, auditory receptive and integration region and inferior temporal lobe. The activation pattern of the M1 and SMA in healthy subjects in the present study is in agreement with the literature (Rao *et al* 1995; Khushu *et al* 2001). The number of clusters activated in M1 is higher than that observed in the SMA (Khushu *et al* 2003). Also, the BOLD signal change is 6.8% ± 1.5% at the M1 location and 2.6% ± 1.7% at the SMA. The increase in signal percentage and activation area could be due to the increased recruitment of the neurons.

Activation in the transverse temporal convolutions representing the primary auditory receptive cortex (BA-41), auditory integration region (BA-42) and other auditory association areas (BA-21, 22, 38) could be due to the attention of the subjects to the verbal instructions (start and stop of the finger task) or due to the concentration while listening to the external cue (listening to the sound of Metronome) for matching the tapping rate. The primary somatosensory cortex (BA 1, 2, 3) sends efferent fibers to the red nucleus and more particularly to area 2, to the substantia nigra, the pontine nuclei and central gray nuclei. Hence, activation in this area could be due to the touching of fingers during tapping. Similar fMRI activation maps were obtained in finger tapping tasks, either when subjects were required to touch fingertips with the thumb or to perform similar opposition movements without touching fingers (Jansma *et al* 1998, Khushu *et al* 2001). Activation in two adjacent gyri, presumably corresponding to the contralateral primary sensory and motor cortices, was found during continuous tactile stimulation of the palm (Yetkin *et al* 1995), suggesting that exteroceptive information may induce significant fMRI signal changes in M1.

Hypothyroid subjects presented motor activation in the primary motor area of the contralateral hemisphere like normal subjects. The cluster level activation in the M1 was in the range 965 ± 55 and in the SMA, it was in the range of 288 ± 72 voxels. Inspite of a much lower tapping rate, the number of voxels is comparable to those of volunteers in the M1. In healthy subjects, a linear increase in the area of activation up to 120 taps/min has been observed (Sadato *et al* 1996, 1997; Khushu *et al* 2001). Assuming a similar trend (of our earlier results), the area of activation at 90 taps/min would be lower than that at 120 taps/min in controls. The area of activation observed in hypothyroid in the present case is hence higher or comparable to that of controls at 90 taps/min. Low phosphocreatine to inorganic phosphate ratio observed in hypothyroid subjects indicates secondary mitochondrial myopathy, which has also been observed at rest (Argov *et al* 1988, Kaminsky *et al* 1992). This impairment may be causing additional energy demands, resulting in additional recruitment of neurons. In volunteers, as the functional demands increase, there is an increased area of activity and percent signal change (Khushu *et al* 2001), indicating the recruitment of additional neurons to carry out the motor task. Hence, one may expect more neuronal recruitment in hypothyroid subjects as compared to the control subjects for performance of a same level of task (Khushu *et al* 2003). Whole brain fMRI studies require activation for a longer time (40–50 s) during the active phase (six measurements). Hypothyroid patients could not keep pace with the requisite tapping rate for such a long period, and could tap at an average rate of 90–95 taps/min in the present study. In addition, activation is observed in the cerebellar cortex in hypothyroid subjects, which was absent in the control group. This could be due to the higher motor co-ordination, since the patients tried to put in more concentration to comply with the task.

Two out of five hyperthyroid patients showed bilateral activation in the primary motor cortex with dominance in the contralateral hemisphere, as compared to volunteers where activation was seen only in the contralateral hemisphere. Activation was also observed in the ipsilateral somatosensory area in these patients. In the other three hyperthyroid patients, activation in the contralateral M1 was observed and the area of activation was much larger as compared to the healthy subjects. The cluster level activation was in the range 1600 ± 180 in the M1 and 130 ± 20 voxels in the SMA. The number of voxels on the ipsilateral hemisphere was 22 ± 8 voxels only, showing very minimal area of activation compared to the contralateral hemisphere.

At 1.5 T, bilateral activation in the M1 and SMA has been observed for complex movements in healthy volunteers (Kim *et al* 1993a; Rao *et al* 1993; Shibasaki *et al* 1993; Li *et al* 1996; Sadato *et al* 1996). In fMRI investigations performed on a 4T system in right handed volunteers, it was found that both peak intensity changes and the surface area of activation were less in the right precentral gyrus during ipsilateral rather than contralateral finger tapping (Kim *et al* 1993a, b). PET has shown considerable bilateral M1 activation in relation to unilateral complex movements (shoulder movement), but not to finger movements (Colebatch *et al* 1991). In patients with unwanted mirror movements, a significant increase in the mean volume of activation was found around the ipsilateral central sulcus relative to healthy controls for hand movements (Leinsinger *et al* 1997). Ipsilateral neuronal recruitment is found to occur in complex motor movements in patients with hemiplegia (Jones *et al* 1989). There is anatomical evidence that 10–15% of fibers in the lateral cortical spinal tracts of humans are uncrossed (Nyberg and Rinvik 1963). The above studies suggest that these uncrossed fibers may play a role either during complex

motor tasks or when the contra-lateral brain is affected by some pathology. In the present case, all the subjects were closely monitored throughout the study for adherence to the experimental design and any movement in the non-tested hand was not observed. Two hyperthyroid subjects in their feedback session conveyed that they were trying to control the tremors during the study, as they were aware of such tremors in the non-tested hand during movement of tested hand. So the ipsilateral activation in these subjects may be attributed to the thought (consciousness) of suppression of such tremors or may be due to the severity of the disease.

The motor task paradigm in all the subjects presented in this paper was a simple, unidirectional finger tapping with no complexity. While performing simple finger tapping task, bilateral activation was not observed in any of the healthy volunteers in this study. The previous studies also did not show any bilateral activation in healthy volunteers, even at high tapping rates, though there was an increase in the area of activation (Khushu *et al* 2001). The neurobehavioural and psychological changes associated with thyrotoxicosis are multiple and varied (Wayne 1954; Wallace *et al* 1980), with concentration, in particular, impaired. Indeed this may be the earliest subjective disturbance, associated with a growing restlessness and tremulousness. It has long been known that hyperthyroidism is characterized by symptoms and signs which closely resemble an acute anxiety state: symptoms such as palpitations, sweating, tremor and faintness on the one hand, and irritability, restlessness, over-activity and lack of concentration on the other (MacCrimmon *et al* 1979). A substantial proportion of patients are affected by more straightforward psychological symptoms of anxiety, including 'nervousness', tension and frank paranoia.

The present study shows that in thyroid dysfunction, functional demands are higher in patients compared to the healthy subjects for the execution of the same motor task. This is attributed to motor function deficit associated with metabolic impairment in these patients.

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