Alterations of Resting State Functional Connectivity Among Resting-State Networks in Thyrotoxicosis.

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Background: Hyperthyroidism or thyrotoxicosis, a clinical condition characterized by elevated free triiodothyronine (FT3), thyroxine (FT4), or both with concomitant suppression of serum thyroid-stimulating hormone (TSH), is associated with a wide range of cognitive and emotional impairments1. Neuropsychiatric symptoms such as nervousness, depression, anxiety, irritability, poor concentration, and memory impairments are often present in hyperthyroid patients. There are various neuroimaging studies which have reported functional, structural and metabolic changes in hyperthyroidism1, 2, 3. Few neuroimaging studies have reported functional changes in thyrotoxicosis4 but the effect on functional connectivity (FC) has not been studied using resting state functional magnetic resonance imaging (rsfMRI). Resting-state fMRI (rsfMRI) is technique to investigate the functional connectivity of the brain which measures coherent spontaneous low-frequency fluctuations in the blood oxygenation level-dependent (BOLD) signal during the resting condition. The primary focus of the present study is to examine whether thyrotoxicosis would impact alteration in resting state networks (RSNs) using rsfMRI.

Materials and Methods: In the present study, 18 healthy controls (mean age ± SD = 34 ± 10.45) and 18 thyrotoxicosis patients (mean age ± SD= 32.92 ± 5.88) were taken. The recruited patients were diagnosed with thyrotoxicosis for the first time and had not been treated earlier. Informed consent was obtained from all the subjects prior to MRI study. Thyroid tests, namely, FT3, FT4 and TSH were carried out in both the groups. In controls the level of thyroid hormones were (FT3 = 2.8-7.1 pmol/l, FT4 =12.0-22.0 pmol/l and TSH = 0.27-4.2 μIU/ml). In thyrotoxicosis group, FT4 level increase from normal range (> 22.0 pmol/l) and TSH level decrease from normal range (< 0.01 μIU/ml) was considered. None of the subject had any history of neurological or psychiatric disorders. The study was approved by the institutional ethics committee. The study was carried out using 3T whole body MR system (Magnetom Skyra; Siemens, Erfurt, Germany). For anatomical reference, a T1- weighted 3D gradient echo sequence (MPRAGE: Magnetization Prepared Rapid Acquisition Gradient Echo, 160 sagittal slices, slice thickness = 1 mm, field of view = 256 mm, TR = 1900 ms, TE = 2.07 ms). Functional brain volumes were acquired using echo-planar T2* -weighted imaging sequence. Each volume consisted of 30 interleaved 5-mm thick slices with no interslice gap (TE = 30 ms, TR = 2000 ms, FOV = 240 mm, flip angle = 90°, voxel size = 3.75 X 3.75 X 5 mm3) image data set was acquired with total scanning time of 410 seconds (205 brain volumes). During rsfMRI the subjects were asked to keep their eyes closed without thinking of anything in particular and not falling asleep. Data analysis was performed using FSL software (http://fsl.fmrib.ox.ac.uk) and independent component and a dual regression approach was used4.

Results: A total nine components were identified as RSNs from group MELODIC output that included right fronto-parietal attention network (RAN), left fronto-parietal attentional network (LAN), default mode network (DMN), medial visual network (MVN) and motor network (MN), anterior DMN (ADNM), posterior DMN (PDNM), auditory network (AN). Out of the 9 components changes were identified in only left fronto-parietal attention and posterior DMN and medial visual RSNs (Fig. 1A, 1B, 1C). Thyrotoxicosis patients showed significantly decreased temporal correlation in the LAN (angular gyrus, lateral occipital gyrus), PDNM (intracalcarine cortex, posterior cingulate gyrus, precuneal cortex, supracalcarine cortex) and MN (lateral occipital cortex) as compared with control subjects (Fig 2A,2B, 2C).

Discussion: To the best of our knowledge, this is the first study to report alterations in resting state functional connectivity in thyrotoxicosis. Our findings showed significantly reduced functional connectivity in LAN, PDNM and MN in hyperthyroid patients. It is reported that the fronto-parietal networks are implicated in working memory and cognitive attention processes, posterior DMN associated with anxiety, depression, higher social inhibitor whereas reduced resting state functional connectivity in the MVN might underlie the attention control deficits in thyrotoxicosis subjects under high perceptual load conditions. There are few functional studies which have shown association of reduced activations in posterior cingulate gyrus, frontal and parietal areas with cognitive functions in thyrotoxicosis patients. Therefore, alterations in the resting state connectivity might be responsible for the cognitive impairments in these patients. These studies support our finding of reduced resting state functional connectivity network related to attention, working memory, anxiety and higher social cognition.

Conclusion: The reduced functional connectivity in left fronto-parietal network, posterior DMN and medial visual network suggests attention, working memory, anxiety and higher social cognition dysfunction in thyrotoxicosis patients. These findings provide an evidence for further studies on cognitive dysfunctions in thyrotoxicosis.

