Altered resting state functional connectivity in hypothyroidism

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Target audience: Researchers working in the field of endocrine disorders.

Purpose: It is reported that hypothyroidism has been associated with cognitive dysfunction, disturbed attention and depressed moods[1]. There are various neuroimaging studies which have reported functional, structural and metabolic changes in hypothyroidism[2-4]. But there is no study which has shown brain functional connectivity due to hypothyroidism in adult population using resting state functional magnetic resonance imaging (rsfMRI). Resting-state fMRI (rsfMRI) is an fMRI technique to investigate the functional connectivity of the brain which measures spontaneous low-frequency fluctuations in the blood oxygenation level-dependent (BOLD) signal during the resting condition[5]. Therefore, the present study was aimed to investigate functional brain connectivity changes associated with hypothyroidism in all the resting state networks as identified using independent component analysis approach.

Materials and Methods: 22 healthy subjects (mean age± SD = 28.5±5.82 years) and 22 hypothyroid patients (mean age± SD =28.8±5.52 years) were chosen for the study. The informed consent was obtained from all the subjects prior to MRI study. All the patients recruited for the study were diagnosed with hypothyroidism for the first time and had not been treated earlier. Thyroid function tests, namely, free tri-iodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) were carried out in all hypothyroid patients and control subjects. The thyroid function tests were in the normal range for controls (FT3 = 2.8-7.1 pmol/l, FT4 =12.0-22.0 pmol/l and TSH = 0.27-4.2 μIU/ml). In hypothyroid group, patients with FT4 below normal and TSH of atleast 20 μIU/ml or above were recruited for the study. None of the subject had any history of neurological or psychiatric disorders. The study was approved by the Institutional ethics committee.

Imaging was performed on a 3-Tesla MRI scanner (Magnetom, Skyra, Siemens) with a 16 channel head coil and 25 mT/m actively shielded gradient system. The conventional MR imaging was done prior to MRS to rule out any structural abnormality using routine T2-weighted turbo spin-echo sequence. Functional brain volumes were acquired using echo-planar T2* -weighted imaging sequence. Each volume consisted of 30 interleaved 5-mm thick slices without interslice gap (TE = 30 ms, TR = 2000 ms, FOV = 240 mm, flip angle = 90°, voxel size = 3.75 X 3.75 X 5 mm^3). 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) image data set was acquired Total scanning time was 410 seconds (205 brain volumes), during which the subjects were asked to keep their eyes closed without thinking of anything in particular and not falling asleep.

Pre-processing and post-processing of the resting state functional data were performed using the FMRI Expert Analysis Tool (FEAT), which is a part of FSL (FMRIB's Software Library, www.fmrib. ox.ac.uk/fsl.

Results: Total five components were identified as RSNs from group MELODIC output that included right fronto-parietal network, left fronto-parietal network, default mode network (DMN), medial visual network and motor network (Fig 1). Hypothyroid patients showed significantly decreased temporal correlation in the right fronto-parietal network as compared with control subjects in frontal pole (Fig 2a). Significantly decreased functional connectivity was also observed within the medial visual network in hypothyroid patients relative to healthy controls which include lateral occipital gyrus, precuneus cortex and cuneal cortex areas (Fig 2b). Motor network also showed a decreased connectivity in precentral gyrus, postcentral gyrus, precuneus cortex, paracingulate gyrus, cingulate gyrus and supramarginal gyrus (Fig 2c). No significant differences between control and hypothyroid subjects were found in the left fronto-parietal network and DMN connectivity.

Discussion: To the best of our knowledge, this is the first study to report alterations in resting state functional connectivity in hypothyroidism. Our findings showed significantly reduced functional connectivity in right frontoparietal network, medial visual network and motor network in hypothyroid patients. It is reported that the fronto-parietal networks are implicated in working memory and cognitive attentional processes[6] whereas medial visual network is associated with early visuospatial processing task[7].There are few functional and structural studies which have shown association of reduced activations in frontal and parietal areas with cognitive functions in hypothyroid patients[2,4,8]. Therefore, alterations in the resting state connectivity might be responsible for the cognitive impairments in these patients. Alongwith it, motor network also showed reduced connectivity in hypothyroid patients. A previous fMRI study has shown motor deficits in thyroid patients[3] whereas a VBM study has reported grey and white matter loss in motor areas[4]. These studies support our findings which showed a reduction in resting state functional connectivity in the somato-sensory information processing centres of the brain in hypothyroid patients.

Conclusion: The reduced functional connectivity in right fronto-parietal network, medial visual network and motor network suggests cognitive and motor dysfunction in hypothyroid patients. These findings provide an evidence for future studies on the impact of changes in thyroid hormones on brain circuit organization and function.

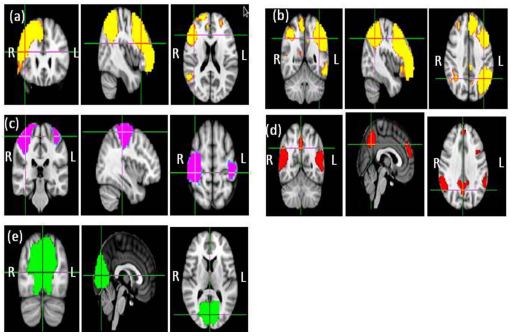

Fig 1: Resting state networks identified using ICA which were used for the dual regression analysis: (a) Right fronto-parietal attention network, (b) Left fronto-parietal attention network, (c) Somato-motor network, (d) Default-mode network (DMN) & (e) Medial visual network

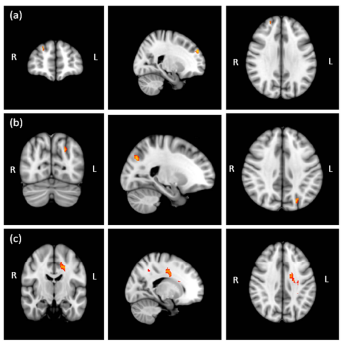

Fig 2: Randomise output for the control vs hypothyroid patient group contrast threshold at p<0.05 (FWE corrected). Reduced connectivity was observed in regions of (a) Right fronto-parietal network, (b) Medial visual network & (c) Motor network. Results are shown on MNI 1 mm standard Atlas.

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