Annexure-IX

PROJECT COMPLETION REPORT

1. Title of the project:

   Validation of Memory Functional Magnetic Resonance Imaging (fMRI) paradigms and its utility in pre-surgical evaluation of patients with refractory temporal lobe epilepsy (TLE)

2. Principal Investigator(s) and Co-Investigator(s):

   Dr. Ramshekhar N Menon
   Associate Professor, CBNS,
   Department of Neurology
   SCTIMST, Thiruvananthapuram-695011

   Dr. Bejoy Thomas, Additional Professor,
   Department of IS & IR, SCTIMST,
   Thiruvananthapuram - 695011

3. Implementing Institution(s) and other collaborating Institution(s):

   Sree Chitra Tirunal Institute for Medical Science and Technology, Thiruvananthapuram

4. Date of commencement: 19/09/2013

5. Planned date of completion: 19/09/2016

6. Actual date of completion: 19/03/2017

7. Objectives as stated in the project proposal:
   i. Development of Functional MRI paradigms for standardizing Memory task activations and evaluation in the assessment of postoperative memory in patients with Temporal lobe epilepsy(TLE) .
   ii. Analyze whether preoperative memory performances based on fMRI, correlates with better postoperative memory outcome.

8. Deviation made from original objectives if any, while implementing the project and reasons thereof: Nil

9. Experimental work giving full details of experimental set up, methods adopted, data collected supported by necessary table, charts, diagrams & photographs:

The project started on 30/09/2013after approval from the SCTIMST - Institute Ethics Committee and receipt of funds from SERB.
The selection of Healthy volunteers and Temporal lobe Epilepsy (TLE)patients was based on the assessment of the Neurologist after ascertaining clinical and neuropsychological performance. Functional MRI- Memory sessions are being conducted on patients as well as the healthy volunteers recruited for the study. Memory encoding and memory recall paradigms are administered as fMRI tasks. The acquired image data is processed using SPM image processing software and results are analyzed to study whether preoperative memory correlates with better postoperative memory outcome along with residual activations suggesting re-organization following temporal lobectomy.

- Memory fMRI Paradigm development:

The Memory paradigm used 3 types of stimuli - faces, word pairs and designs. They are visually presented to the subjects while they are supine inside the scanner. The scanning

procedure involves two tasks and among that, the initial one is the Memory Encoding session. The encoding task is followed by a delayed recall session which is performed after one hour within scanner, which is the novel aspect of this study. The faces are black and white photographs of Indian faces unfamiliar to the subjects, the word pairs are semantically unrelated nouns and the designs are pictures of coloured patterns. A set of 10 selected target stimuli is used for each material type is visually presented to the subjects with an fMRI block paradigm during a single scanning session in the Memory Encoding task. The active phase of the block design has duration 20 seconds in which, each of the target stimuli is presented for 2 seconds. The rest phase is presented with a cross hair fixation which last for 20 seconds. Each stimuli types (Faces, Word-pairs and Designs) is presented in 3 cycles and thus the entire encoding paradigm has nine cycles. The total duration of the encoding paradigm is 6 minutes. The encoding task will be followed by a recall sessions which is done after one hour and the number of stimuli will be increased in this session by adding certain set of distracters (15 distracter images). Here each of the jitter stimuli is presented for 1.5 seconds and followed by cross hair till the next stimuli is presented. And as used in event related designs, here the inter stimulus interval will vary from 7.5 second to 13.5 seconds. During the inter stimulus interval, the subjects can specify whether they remember each stimuli and can indicate it by pressing the button response pad.

The volunteers of the study is given detailed instruction and a test task run before they move to the MRI machine for the investigation. Inside the scanner, the subjects are specifically instructed to concentrate on the images that are displayed and to 'memorize' it for a recognition test following the scan. During the encoding session, subjects are taught to perform a deep memory encoding task which involved making a judgment on whether each faces, word pairs, designs were pleasant/unpleasant, semantic association exist and symmetrical/asymmetrical respectively. After encoding session, memory performances are evaluated from their choice of yes–no in identifying the encoded stimuli.

The memory fMRI paradigms were administered using stimulus delivery/control software called Presentation (Neurobehavioural Systems INC, USA) . Presentation is an effective tool

for implementing psychological and neurobehavioral experiments with good precision in stimulus delivery. It can records responses from various input device and support the control of parallel and serial port, thereby, it enables smooth communication to and from fMRI devices, response devices and brain imaging equipment.

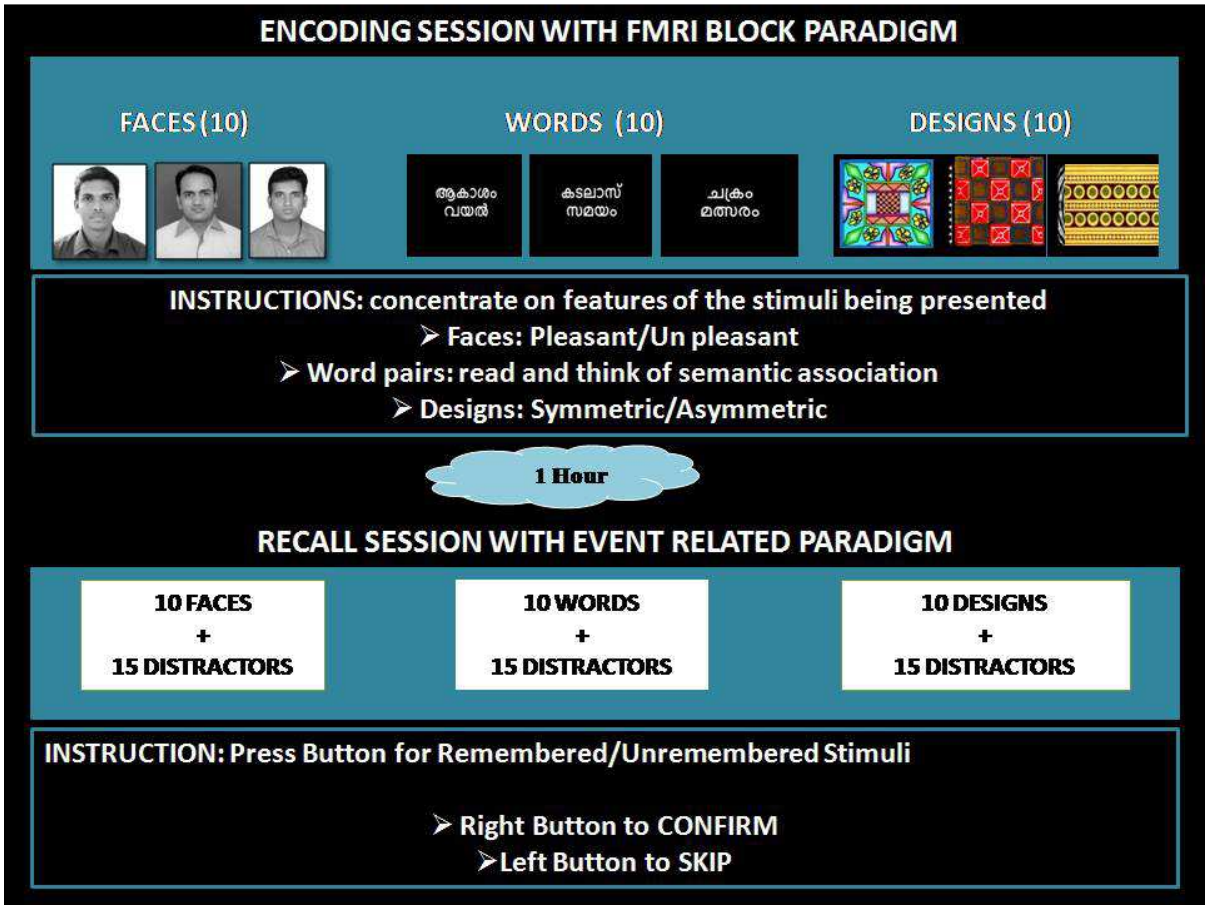


Figure: The schema of memory encoding and recall paradigm

- MRI acquisition protocol and post-processing

All the subjects were imaged by using a 1.5T MR imaging scanner (Siemens Magnetom Avanto Erlangen, Germany) equipped with a 12-channel head coil. Gradient- echo EPI was used for functional acquisitions with the following parameters: TR/TE/flip angle, 2000 ms/33

ms/90°, 22 contiguous sections of 4 mm, FOV of 256x 256mm2, and an acquisition matrix of 64 x 64; 180 scans were acquired for encoding session and 530 volumes for recall run.

Functional MRI scans were acquired throughout the task. The statistical processing of the acquired fMRI images are done with the help of SPM (statistical parameter mapping), which is an image processing toolbox of Matlab software. SPM uses statistical techniques to extract significant change in brain activity associated with the process under investigation. In order to improve the statistical significance of the results, certain pre-processing steps are applied to the raw EPI data prior to the statistical analysis. The three main steps in the pre-processing include (i) realignment, (ii) normalization and (iii) smoothing. The data analysis employs a mass-univariate approach based on General Linear Modeling (GLM). It involves the specification of GLM design matrix, fMRI data files and filtering, evaluation of GLM parameters using classical or Bayesian approaches and cross-examination of results using contrast vectors to generate Statistical Parametric Maps. The graphical representation of the analysis can be viewed as a map displaying coordinates that show sustained activations with respect to cognitive tasks. The memory indices and the BOLD activations of its neural correlates form the bases of comparison between the healthy volunteers and patients with Temporal Lobe Epilepsy.

10. Detailed analysis of results indicating contributions made towards increasing the state of knowledge in the subject:

Face-Encoding & Recall

The maximal BOLD activation was noted over right hippocampus in healthy controls, Left fusiform for left MTLE patients and Right fusiform for Right MTLE patients (figure 1a) . The laterality index calculated based on the SPM group analysis results points to right dominance for healthy controls (LI **-0.42)**, bilateral with left dominance for left MTLE patients (LI **0.081**) and right dominance for right MTLE (figure 1b) with LI **-0.37**

In the face-recall paradigm, group activation patterns depicted maximal activation in right hippocampus for both healthy controls and left MTLE patients and left parahippocampus for right MTLE patients (figure 1c). The laterality index (figure 1d) favored right dominance for healthy controls and Left MTLE patients with LI values -0.45 and -0.49 respectively whereas left dominance for right MTLE patients with LI 0.25

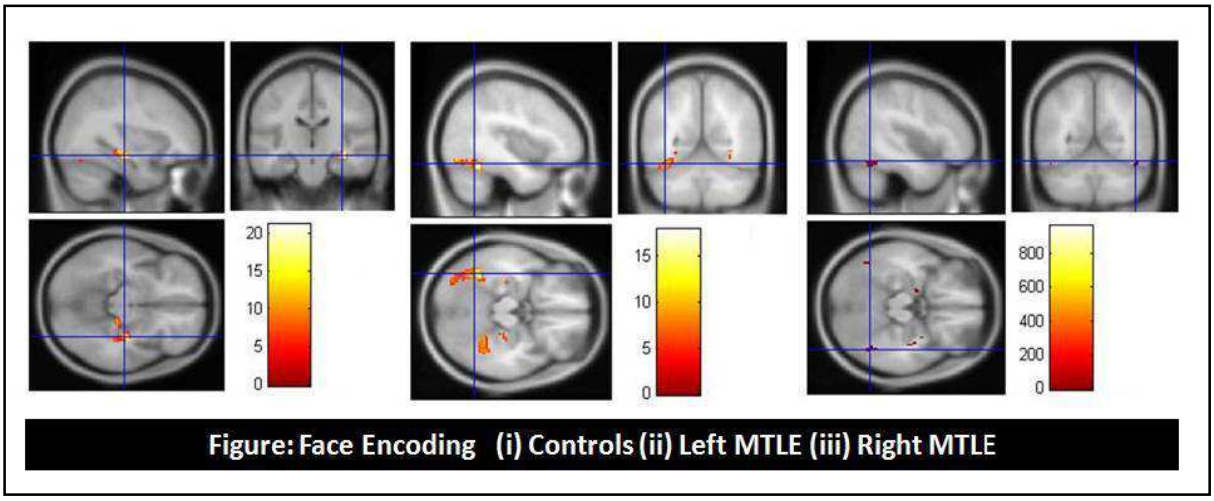


Figure 1a

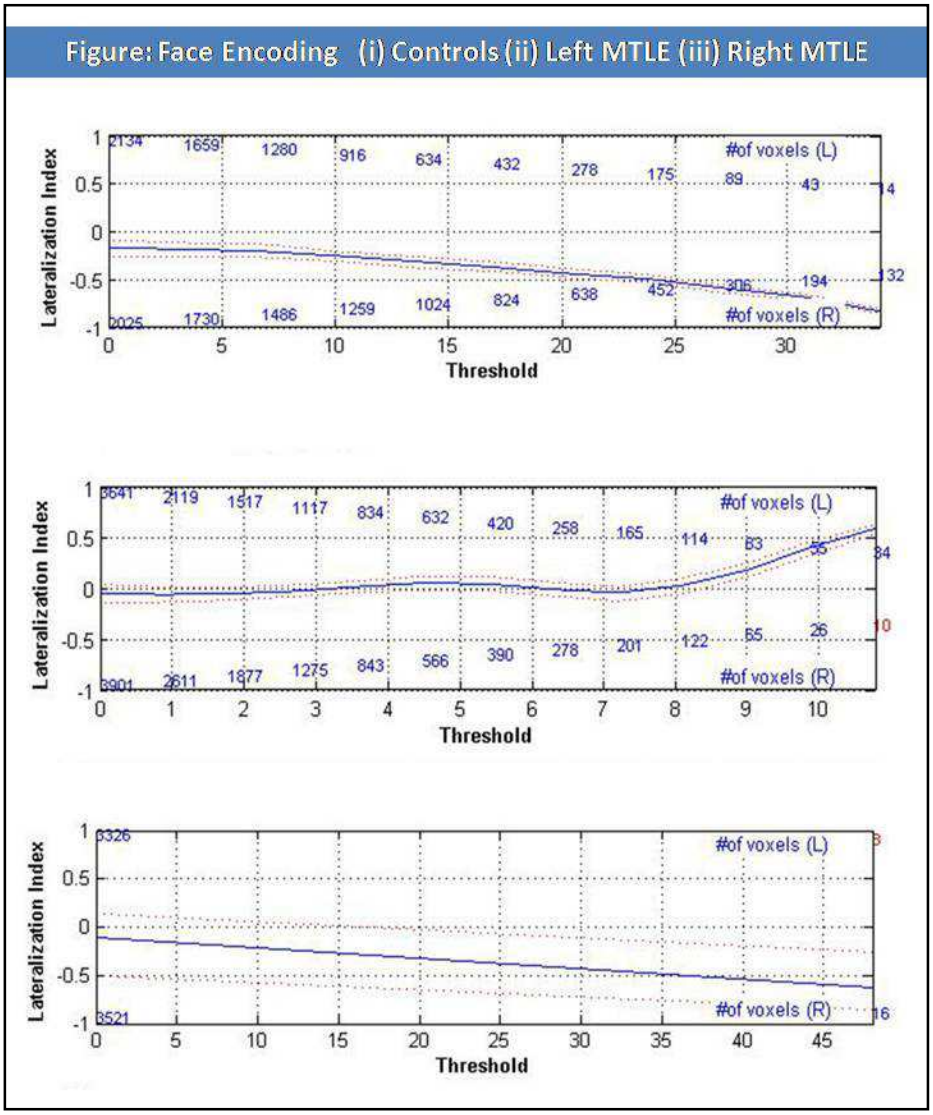


Figure 1b

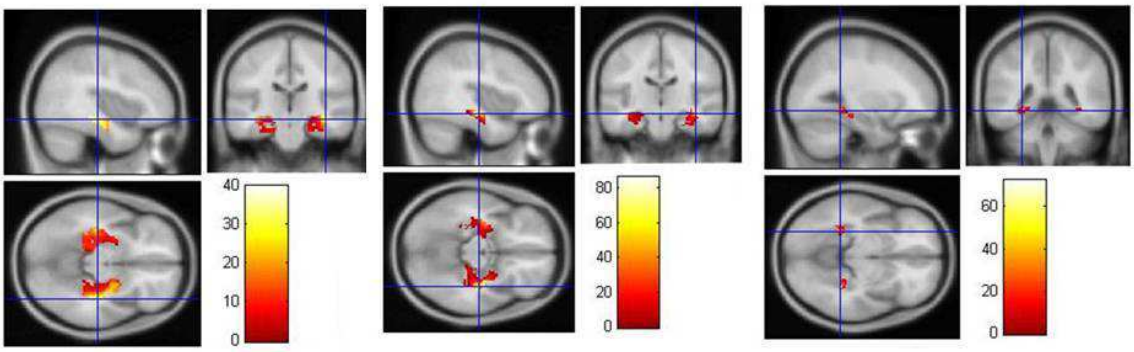


Figure: Face Recall (i) Controls (ii) Left MTLE (iii) Right MTLE

Figure 1c

Figure: Face Recall (i) Controls (ii) Left MTLE (iii) Right MTLE

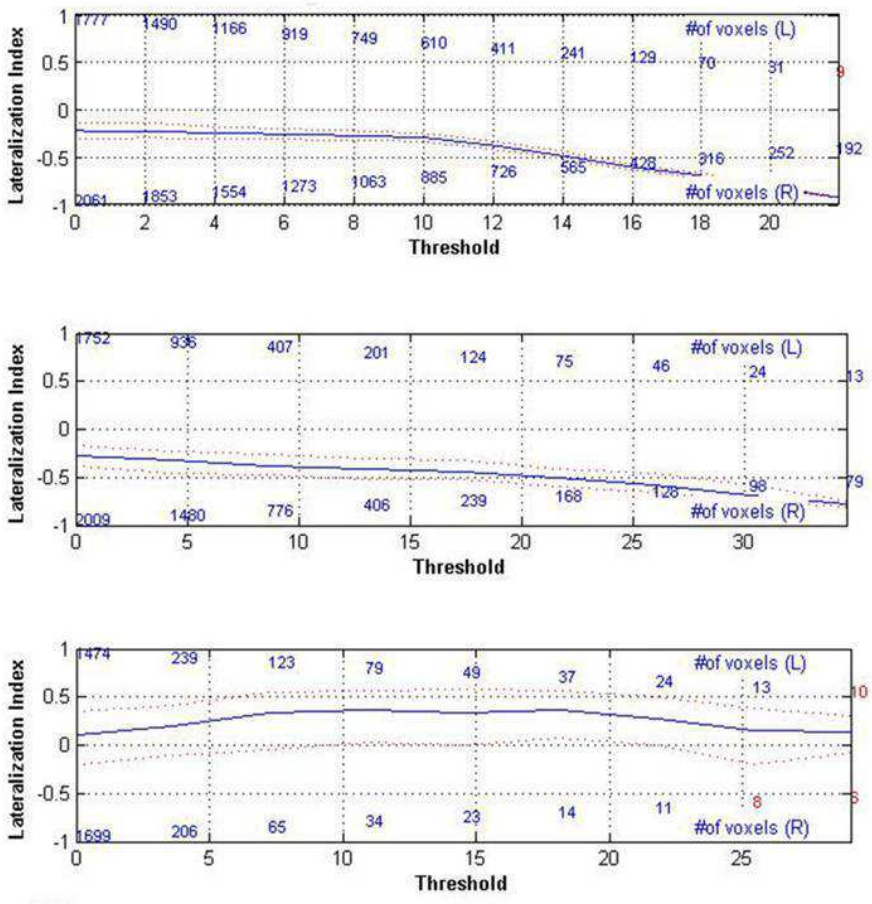


Figure 1d

Word-pair Encoding & Recall

For the word-pair encoding task, the maximal BOLD activations were observed in Left parahippocampus for healthy contols , Right fusiform for left MTLE group and left fusiform for right MTLE group(figure 2a)

The laterality index of SPM group analysis of wordpair encoding task (figure 2b) reported right dominance for healthy controls and left MTLE patients with LI's -0.25 and -0.31 respectively whereas for the right MTLE the LI is 0.42left lateralised and no significant number of clusters to generate the graph.

For the word-pair recall task, the overall activation pattern appears as bilateral, but maximal activation were seen in right hippocampus for controls and left MTLE group and left hippocampus for right MTLE group(figure 2c) . Each group's laterality (figure 2d), revealed, strong right dominance for healthy controls and left MTLE, as evident from LI values -0.6, -0.54 respectively and strong left lateralization for right MTLE group with LI of 0.51

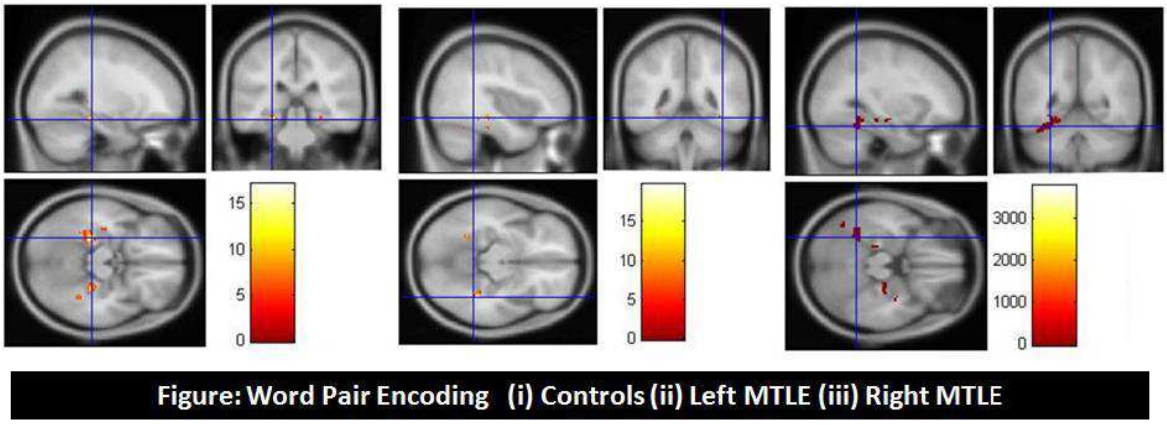


Figure: Word Pair Encoding (i) Controls (ii) Left MTLE (iii) Right MTLE

Figure 2a

Figure: Word Encoding (i) Controls (ii) Left MTLE

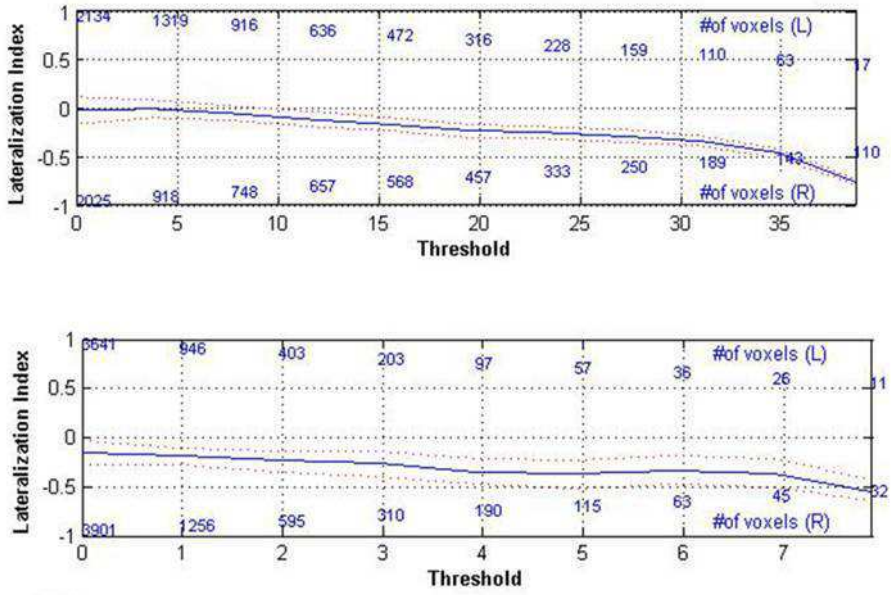


Figure 2b

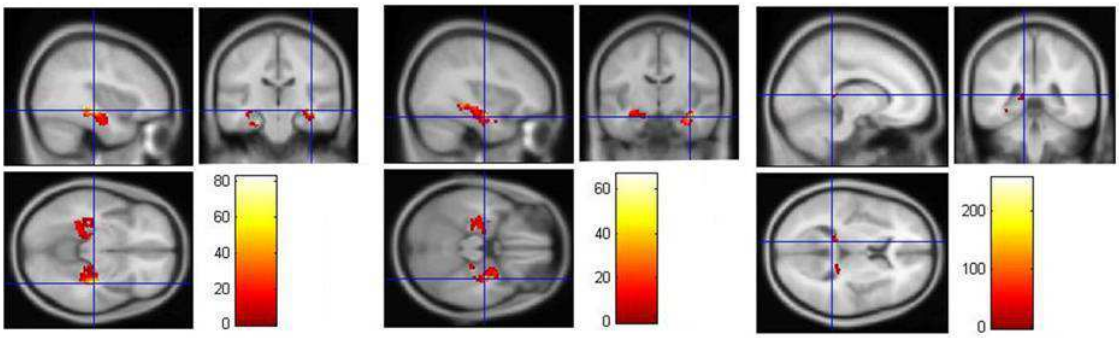
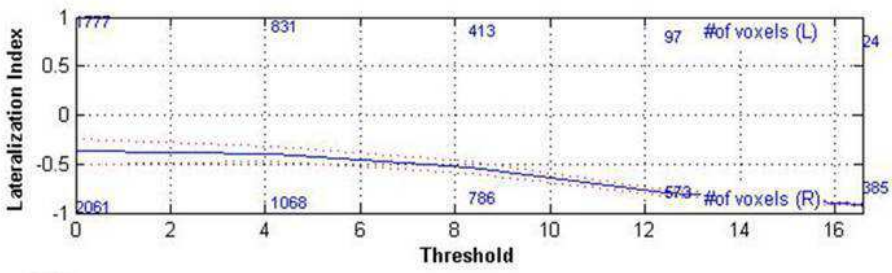
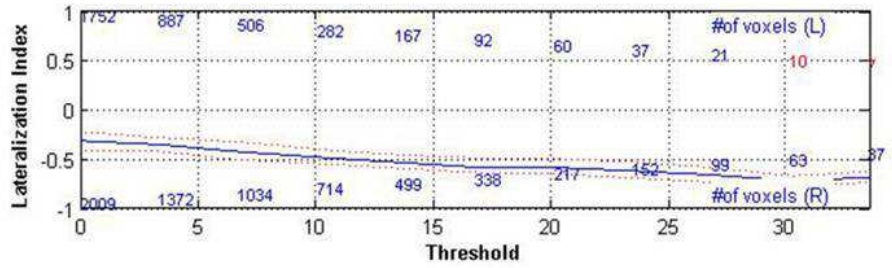


Figure: Word Pair Recall (i) Controls (ii) Left MTLE (iii) Right MTLE

Figure 2c

Figure: Word Recall (i) Controls (ii) Left MTLE (iii) Right MTLE





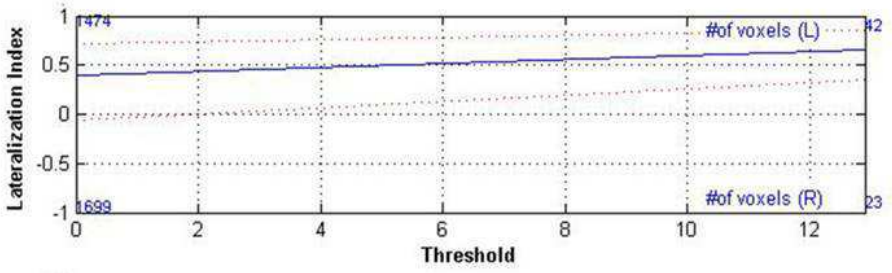


Figure 2d

Design-encoding and recall.

Design-encoding task indicated right hippocampal activation for healthy controls and left MTLE group, whereas left fusiform activation for right MTLE group(figure 3a).The laterality index calculation (figure 3b) reported, right dominance for healthy and left MTLE group with LI values -0.47 and -0.16 and left dominance for right MTLE groupwith LI 0.43.

Design recall paradigm revealed right hippocampal activation for healthy contol and left MTLE group and left parahippocampal activation for right ATL group(figure 3c). The laterality index (figure 3d) points to right dominance for healthy controls and left MTLE group and bilateral for right MTLE group with LI values -0.3, -0.21, -0.035 respectively.

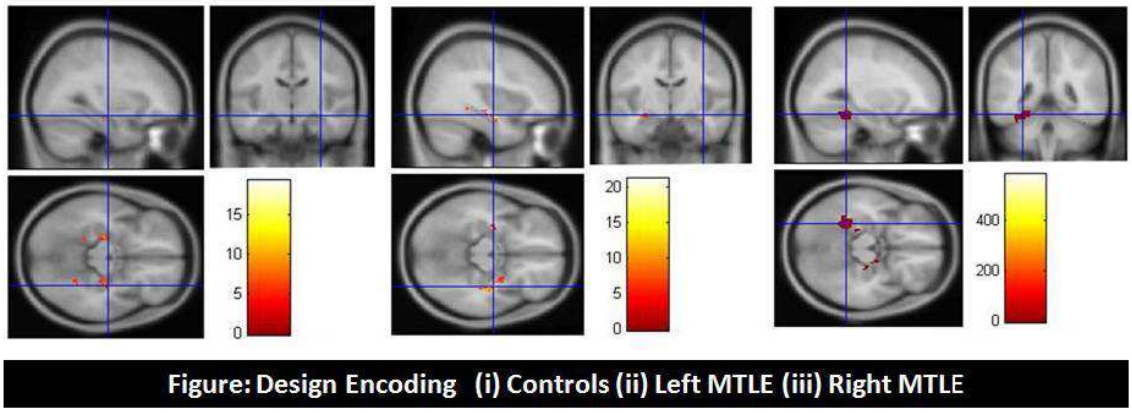


Figure 3a

Figure: Design Encoding (i) Controls (ii) Left MTLE (iii) Right MTLE

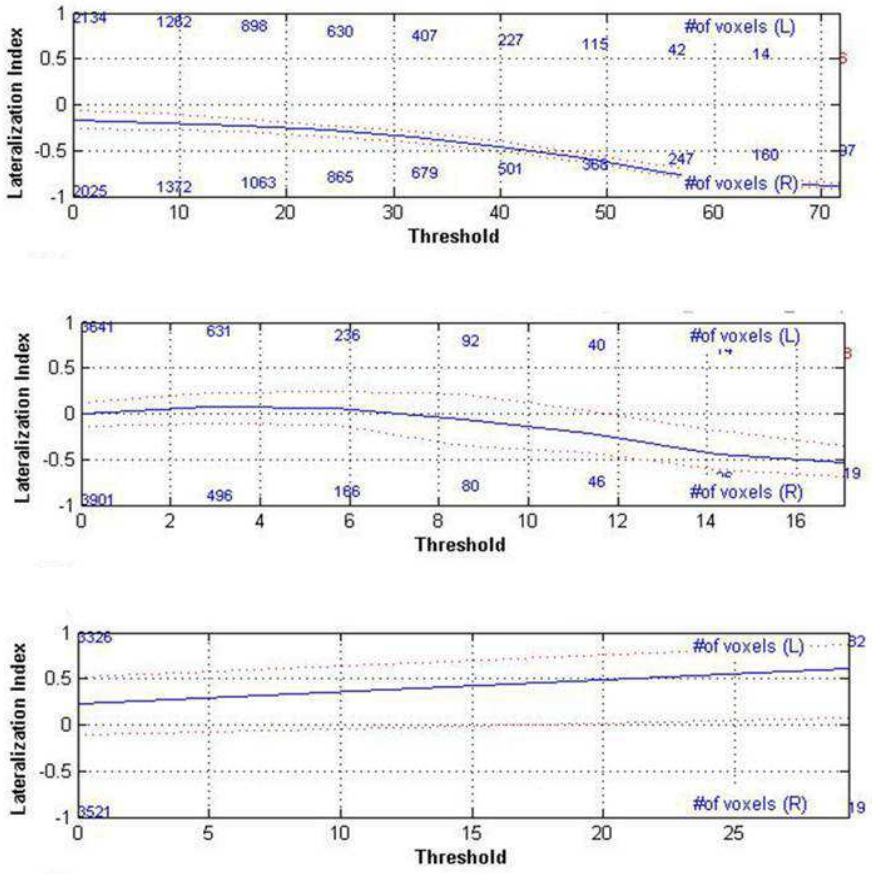


Figure 3b

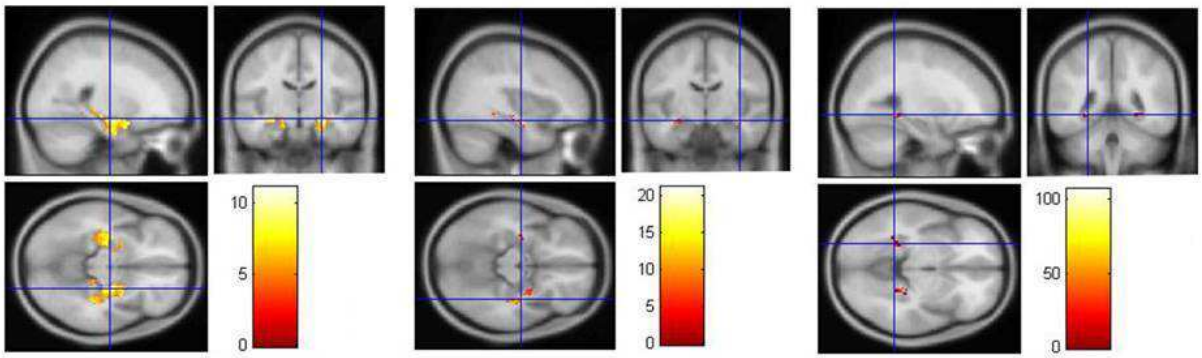


Figure: Design Recall (i) Controls (ii) Left MTLE (iii) Right MTLE

Figure 3c

Figure: Design Recall (i) Controls (ii) Left MTLE (iii) Right MTLE

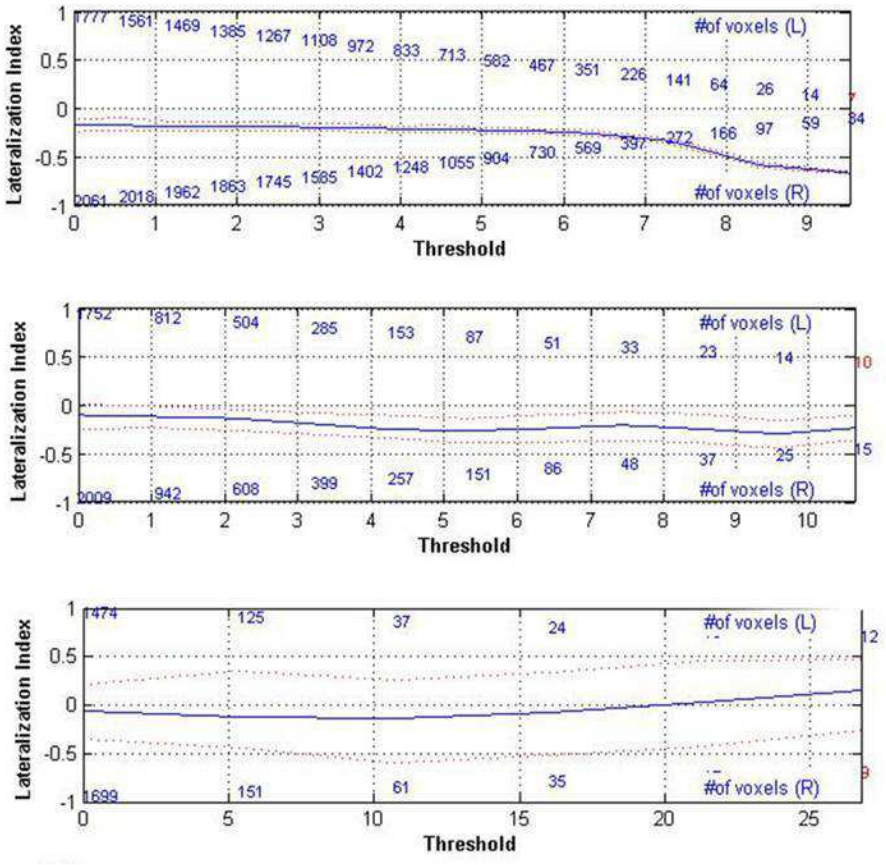


Figure 3d

11. Conclusions summarizing the achievements and indication of scope for future work:

- Research Fellow was recruited in the project.

- Siemens Avanto 1.5T MRI scanner operating software has been studied and examined to test capabilities for carrying out memory fMRI task.

- A Memory test based fMRI system, incorporating memory encoding and memory recall has been operated successfully and acquired BOLD images.

- Carried out extensive literature review to design block and event related paradigms for the for administering fMRI Task.

- The Neurobehavioural Systems Presentation software is one of the best stimulus delivery/control software which can record stimulus and button responses with high accuracy. This software was used to present the memory fMRI paradigm. Training of this software and its synchronization with scanner pulses has been accomplished. Training of image post processing software tools were also carried out.

- Collaboration with Neuropsychologists for task designing as well as neuropsychological evaluation of patient volunteers.

- A test study with 5 healthy volunteers was designed and established initially to regularize paradigm and to acquire images to verify resultant BOLD activations. This was done to assess the reliability of the study and to ensure the adaptation of task by the participants and to collect feedback.

- Volunteer Recruitment & memory-fMRI session completed :
  Group (i) : 20 Healthy Volunteers &
  Group (ii) : 26 Patient (Patients with Mesial Temporal Lobe Epilepsy)

- Credible results of memory performances in healthy volunteers and patient population were obtained and the corresponding neural correlates were identified.

- Identified a potential collaborator and initiated collaboration with Centre for Behavioral and Cognitive Sciences (CBCS), University of Allahabad, for advanced data processing.

- Regular online meetings and discussions were conducted to streamline the image post processing pipeline.

- Organized a visit by Dr.Chandrasekhar Pammi, Professor, CBCS, University of Allahabad to SCTIMST, Trivandrum for standardizing steps for Image post processing, Regressor based analysis, Group level analysis and a lecture on fMRI image processing.

- Work Presented: (i) At International conference on Cognition, Brain and Computation, December 2015 at IIT Gandhinagar. (ii) Abstract accepted for the 32nd International Epilepsy Congress (IEC), Barcelona, 2017, which is an esteemed scientific meeting organized by International Bureau for Epilepsy (IBE) and the International League Against Epilepsy (ILAE).

- Two publications - one based on the pilot study (15 healthy volunteers and 15 patients) and the other on the final complete validation study are under preparation for submission to prestigious international journals.

- The Current study is only one of its kind in the country, equipped with memory fMRI employing the combination of boxcar and event related paradigm to effectively invoke memory encoding and memory recall.

12. S&T benefits accrued:

i. List of Research publications

S No	Authors	Title of paper	Name of the Journal	Volume	Pages	Year
1	P.G. Rajesh, J.Sunitha, Ramshekhar N.Menon, Bejoy Thomas , Ashalatha Radhakrishnan	An Encounter with Memory - Functional MRI Paradigm development and implementation for evaluating Memory Encoding & Recall.	International conference on Cognition, Brain & Computation, IIT Gandhinagar	-	Page 100	December 2015
2	Ramshekhar N.Menon, P.G. Rajesh, Bejoy Thomas	Imaging memory in temporal lobe epilepsy- validation of 'within-scanner' material specific encoding-recall paradigms during memory task-based functional magnetic resonance imaging (fMRI)"	32nd International Epilepsy Congress (IEC), Barcelona, 2017			2017

ii. Manpower trained on the project

a) Research Scientists or Research Associates

Research Fellow -1

b) No. of Ph.D. produced

Nil

c) Other Technical Personnel trained

Nil

iii. Patents taken, if any

Nil

13. Financial Position:

No	Financial Position/ Budget Head	Funds Sanctioned	Expenditure	% of Total cost
I	Salaries/ Manpower costs	11,00,000 /-	5,85,979	53.27%
II	Equipment		--	--
III	Consumables		1,44,050	13.09%
IV	Contingencies		75,229	6.83%
V	Travel		27,363	2.48%
VI	Overhead Expenses		2,53,400	23.03%
VII	Others, if any		--	--
	Total	11,00,000 /-	10,86,021 /-	98.71%

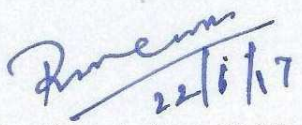
14. Procurement/ Usage of

Equipment a) Nil

S No	Name of Equipment	Make/Model	Cost (FE/ Rs)	Date of Installation	Utilization Rate (%)	Remarks regarding maintenance/

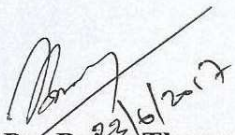
b) Plans for utilizing the equipment facilities in future Nil

Name and Signature with Date:



a. **Dr. Ramshekhar N Menon**

(Principal Investigator)



b.**Dr. Bejoy Thomas**

(Co-Investigator)