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Hippocampal activations in mesial temporal lobe epilepsy due to hippocampal sclerosis- an observational study on intramural encoding-delayed recall paradigms using task-based memory fMRI

PG Rajesh[a], Bejoy Thomas[b], VS Chandrasekhar Pammi[c], Chandrasekharan Kesavadas[b], Ashalatha Radhakrishnan[d], Aley Alexander[a,d], Sanjeev V Thomas[d], Ramshekhar N Menon[a,d,*]

[a] Cognition and Behavioural Neurology Subsection, Dept. of Neurology, Sree Chitra Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India
[b] Department of Imaging Sciences & Interventional Radiology, Sree Chitra Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India
[c] Centre of Behavioural and Cognitive Sciences (CBCS), University of Allahabad, Allahabad, India
[d] R Madhavan Nayar Centre for Comprehensive Epilepsy Care, Dept of Neurology, Sree Chitra Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India

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ABSTRACT

Objectives: To validate concurrent utility of within-scanner encoding and delayed recognition-memory paradigms to ascertain hippocampal activations during task-based memory fMRI.

Methods: Memory paradigms were designed for faces, word-pairs and abstract designs. A deep-encoding task was designed comprising of a total of 9 cycles run within a 1.5T MRI scanner. A recall session was performed after 1 h within the scanner using an event-related design. Group analysis was done with 'correct-incorrect' responses applied as parametric modulators in Statistical Parametric Mapping version 8 using boot-strap method to enable estimation of laterality indices (LI) using custom anatomical masks involving the medio-basal temporal structures.

Results: Twenty seven subjects with drug-resistant mesial temporal lobe epilepsy due to hippocampal sclerosis (MTLE-HS) [17 patients of left-MTLE and 10 patients of right-MTLE] and 21 right handed age-matched healthy controls (HC) were recruited. For the encoding paradigm blood oxygen level dependent (BOLD) responses in HC demonstrated right laterality for faces, left laterality for word pairs, and bilaterality for design encoding over the regions of interest. Both right and left MTLE-HS groups revealed left lateralisation for word-pair encoding, bilateral activation for face encoding, with design encoding in right MTLE-HS demonstrating a left shift. As opposed to lateralization shown in controls, group analysis of cued-recall BOLD signals acquired within scanner in left MTLE-HS demonstrated right lateralization for word-pairs with bilaterality for faces and designs. The right MTLE-HS group demonstrated bilateral activations for faces, word-pairs and designs.

Conclusion: Recall-based fMRI paradigms indicate hippocampal plasticity in MTLE-HS, maximal for word-pair associate recall tasks.

1. Introduction

Memory functional magnetic resonance imaging (fMRI) has emerged as an important and well validated predictor of material specific memory encoding efficiency post-operatively in patients with refractory temporal lobe epilepsy (TLE) who are planned for anterior temporal lobectomy with amygdalo-hippocampectomy (ATL-AH) (Sidhu et al., 2015). As in neuropsychological studies, fMRI studies have demonstrated ability to lateralize memory encoding with high material specificity, suggesting left lateralization for words, right lateralization for visuospatial stimuli, and bilateral activations for objects (Golby et al., 2001; Kelley et al., 1998; Powell et al., 2005). Memory paradigms are fundamental in analysing blood oxygen level dependent (BOLD) responses in specific anatomical substrates of learning and recall viz. declarative memory systems. During memory fMRI, the hippocampus exhibits a successful memory effect, with stronger activation during encoding of items that will be subsequently remembered compared with items that will be forgotten when tested outside the scanner. (Davachi and Wagner, 2002; Strange et al., 2002) Memory encoding fMRI paradigms that demonstrate lateralized

* Corresponding author at: Epilepsy Office, Department of Neurology, Block 2, Floor 4, Sree Chitra Institute for Medical Sciences and Technology, Thiruvananthapuram, 695011, Kerala, India.
E-mail address: rsnmenon@sctimst.ac.in (M. Ramshekhar N).

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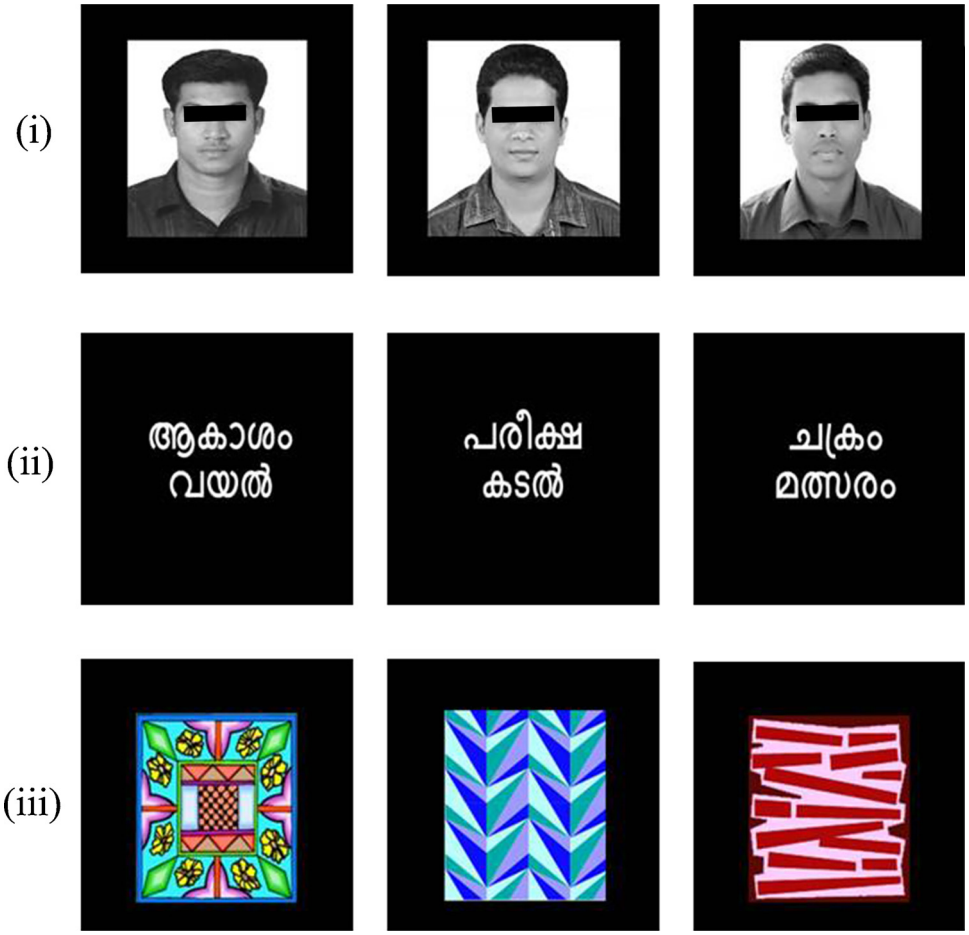

Fig. 1. Examples of stimuli used in memory fMRI paradigm (i) faces (eyes masked for representation purposes in the figure only), (ii) semantically unrelated word-pairs in vernacular language and (iii) abstract designs.

activations of language dominant or language-nondominant hemispheres have shown variable potential to predict post-operative memory decline after ATL-AH (Sidhu et al., 2015; Bonelli et al., 2010; Binder 2011). However individual predictive modelling with regard to postoperative memory performance in unilateral medial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) depends not only on the preoperative functional status of bilateral hippocampal systems but also on the integrity and plasticity of ipsilateral extratemporal structures (Cendes, 2015). These are part of a complex network in verbal memory encoding and retrieval, with its connectivity modulated by widespread structural and electrophysiological dysfunction that accompanies refractory seizures.

Recall efficiency within the scanner has been a subject of debate and few studies have addressed the coherence of BOLD activations while performing free recall/recognition tasks within the MRI scanner (Oztekin et al., 2010). Prior studies incorporated event design paradigms using responses scored outside the scanner included as regressors to encoding task results. Estimating recall efficiency is of paramount importance in detecting hippocampal reserve in patients with medically refractory MTLE-HS. Event-related fMRI, which is validated in encoding studies, is defined as the detection of transient hemodynamic responses to brief stimuli or tasks (Josephs and Henson, 1999). This type of analysis allows the identification of brain regions showing greater activation during the encoding of items that are subsequently remembered compared with items subsequently forgotten(subsequent memory effects), which are then taken as a candidate neural correlates of memory encoding (Wagner et al., 1999).

We present the results of a study using novel indigenously developed yet pragmatic encoding and delayed recall-recognition paradigms implemented within the MRI scanner that minimize scanning time and while retaining scanning efficiency in a group of healthy volunteers and patients with MTLE-HS(who were awaiting ATL) comparing 3 types of stimuli: faces, word-pairs and abstract designs.The primary aims were to develop fMRI paradigms to study task activation and lateralization for memory encoding and recall within the scanner as opposed to out of scanner recognition paradigms detailed in literature and also to evaluate the neural correlates of memory encoding/recall to study paradigm efficacy in localization and lateralization of material specific memory viz. verbal and visual within scanner. We also tested the hypotheses that there will be: (i) evidence of material specific lateralization of memory encoding-recall in controls; (ii) evidence of reorganization of memory encoding-recall in patients with TLE compared to controls, due to the underlying pathology or ongoing epilepsy.

2. Methodlogy

We recruited 21 healthy right-handed volunteers and 27 right-handed patients with unilateral MTLE-HS who had undergone presurgical evaluation with unequivocal demonstration of concordant ictal onset and were awaiting epilepsy surgery. Handedness was ascertained using Edinburgh Handedness Inventory. Their baseline neuropsychology test performances were documented using a standardized vernacular adapted battery of neuropsychological tests as has been detailed previously (Jeyaraj et al., 2013). The tests for verbal memory dysfunction were Weschler Memory Scale Revised (WMS-R) – verbal subsets, WMS-R verbal paired association learning test and Rey Auditory Verbal Learning Test (RAVLT) (Wechsler, 1987; Schmidt, 1996). The tests included for visual memory dysfunction included WMS-R