TITLE: Spatial and episodic memory tasks promote temporal lobe interictal spikes

RUNNING HEAD: Memory tasks promote temporal interictal spikes

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Abstract

Reflex epilepsies have been demonstrated to exploit specific networks that subserve normal physiological function. It is unclear whether more common forms of epilepsy share this particular feature. By measuring interictal spikes in patients with a range of epilepsies, we show that two tasks known to specifically engage the hippocampus and temporal neocortex promote increased interictal spiking within these regions, whilst a non-hippocampal dependent task did not. This indicates that interictal spike frequency may reflect the processing demands being placed on specific functional-anatomical networks in epilepsy.

Introduction

Reflex epilepsies are characterized by seizures that are provoked by well-defined cognitive or sensory stimuli, such as primary reading epilepsy, and musicogenic epilepsy. It is thought that reflex seizures activate pre-existing functional–anatomical networks that subserve specific physiological roles (e.g. the right temporal region in musicogenic epilepsy[1]). Interictal spikes (IIS) are an electrographical feature of epilepsy that are distinct from seizures, but may define the underlying networks that generate those seizures[2]. Hence, we asked whether placing processing demands on specific functional-anatomical networks would increase IIS frequency within that network. To address this, we examined intracranial temporal lobe depth electrode recordings from epilepsy patients performing either a spatial memory[3], episodic memory[4], or attentional bias task.

Methods

Two groups of patients with refractory epilepsy undergoing intracranial EEG monitoring for clinical purposes were asked to perform either a spatial (n=12; 8 with mesial temporal and 4 with extratemporal epilepsy) or episodic memory task (n=12; 6 with mesial temporal and 6 with extratemporal epilepsy), with a subset of the latter group also performing an attentional bias task on a different day (n=6, see Table 1). An orthogonal surgical approach was adopted for all patients, who were on antiepileptic medication - either full dose or 50% reduction - at the time of testing. Prior approval was granted by the NHS Research Ethics Committee, and informed consent was obtained from each subject. Post-implantation review verified that, for the spatial memory / episodic memory / attentional bias task, 9 / 11 / 6 patients had electrode contacts in the hippocampus, 12 / 12 / 6 in the lateral temporal lobe and 9 / 9 / 6 in the amygdala.

Spatial memory was assessed using a desktop virtual reality environment (Fig. 1A; see [3]). Patients first navigated toward and memorized the location of four objects that sequentially appeared in the environment ('encoding'). Patients were then cued with an image of one object ('cue'), placed back in the environment and asked to navigate toward the remembered location of that object and make a button-press response ('response'). The object then appeared in its correct location and the trial ended when they moved to the visible object ('feedback'). The distance error (patient response location versus true location of object) was used as a metric of mnemonic performance.

In the episodic memory task, patients encoded a number of events, each comprising a location, famous person and object (Fig. 2A; see [4]). Each event was encoded across three separate trials where one of the pairwise associations comprising that event - i.e. object-location, person-object, person-location – was presented, interleaved with pairs from other events. In each trial, patients were asked to imagine the pair of items on screen interacting. Following a short delay, memory for the items and associations from each event was tested: first by asking whether each item was old or new (recognition memory); and second by asking patients to make a six-alternative forced choice among potential associates from the same category (associative memory). All associations were tested in both directions on separate retrieval trials, and performance was defined as whether or not the item or association was correctly identified.

In the attentional bias task, patients were repeatedly presented with two faces placed either side of a central fixation cross. Each pair of faces comprised one neutral and one fearful expression performed by the same actor, and patients were simply asked to look towards whichever face captured their attention[5]. Patients completed 2-4 blocks, each of which consisted of 50 trials and lasted ~2 minutes (Fig 3A).

For all patients, interictal spikes (IIS) were manually identified in the hippocampus, lateral temporal lobe, and amygdala throughout the entire recording session including both task (which incorporated both encoding and retrieval periods for the memory tasks, excluding inter-trial intervals) and interleaved non-task periods of approximately equal duration. Spikes were classed as sharply contoured events that met strict criteria: a duration of ≤200ms; amplitude of >100 μV; a subsequent slow wave that disrupted ongoing intracranial EEG activity; and a field distribution consistent with an intracerebral event. In the spatial memory task, retrieval was composed of cue, response and feedback periods; and in the episodic memory task, of recognition and associative memory test periods. A mean IIS frequency was calculated for each period and region, and IIS frequency differences between periods A and B were normalised to account for between subject variance using the formula (A-B) / (A+B).

Finally, to examine the relationship between IIS frequency and performance in the two memory tasks, we performed linear regression across trials separately for each electrode contact. Beta coefficients were then averaged across all electrode contacts in each region for each patient, allowing one-sample t-tests at the second level to be performed.

Results

Hippocampal interictal spike frequency is increased during a spatial memory task

First, we compared normalised interictal spike (IIS) frequency during the spatial memory task with non-task periods immediately before and after (Fig. 1A). To examine the effects of task and recording location, we conducted an ANOVA with those two factors, comparing task versus non-task periods; hippocampal, temporal lobe and amygdala recording locations. We found both a main effect of task ($F(1,43)=8.6$, $p=0.005$) and a task by recording location interaction ($F(2,43)=6.2$, $p=0.02$; Fig. 1B). Subsequent analysis indicated that these results were driven by an increase in IIS frequency in the hippocampus during task versus non-task periods ($t(8)=2.9$, $p=0.005$), but not in the temporal lobe or amygdala (both $p>0.13$). In addition, we compared the task related increase in hippocampal IIS frequency between patients with and without a temporal lobe focus and with electrodes in left and right hemisphere, but did not find a significant difference in either case (both $p>0.13$).

Next, we compared encoding and retrieval periods within the spatial memory task to identify whether either memory operation was primarily responsible for the increase in IIS frequency. However, we found no differences between IIS frequency at encoding or retrieval in the hippocampus ($p>0.29$; Fig. 1C). Similarly, we found no evidence for a relationship between IIS frequency and task performance in any region (all $p>0.53$).

Interictal spike frequency is increased in the hippocampus and temporal lobe during an episodic memory task

Next, we compared normalised IIS frequency during the episodic memory task with non-task periods of approximately equal duration (Fig. 2A). An ANOVA with the same two factors again revealed a main effect of task ($F(1,43)=12.2$, $p<0.001$) and task by recording location interaction ($F(2,43)=5.6$, $p=0.02$; Fig. 2B). Subsequent analysis indicated that these results were driven by an increase in IIS frequency during task versus non-task periods in the hippocampus ($t(10)=3.2$, $p=0.002$) and temporal lobe ($t(11)=2.4$, $p=0.02$), but not the amygdala ($p=0.58$). Again, task related increases in IIS frequency did not differ according to temporal lobe focus or implanted hemisphere (both $p>0.56$).

Next, we asked whether this task-related increase in IIS frequency was driven by encoding or retrieval specifically. Interestingly, an ANOVA with factors of encoding and retrieval, hippocampal and temporal lobe recording site revealed a main effect of task phase ($F(1,44)=21$, $p=0.001$), with increased IIS frequency in both the hippocampus and lateral temporal lobe during encoding, but no effect of recording site or interaction (both $p>0.13$; Fig. 2C). Again, we found no evidence for a relationship between IIS frequency and recognition or associative memory performance during either encoding or retrieval (all $p>0.12$).

Temporal lobe interictal spike frequency is not modulated by an attentional bias task

Finally, we compared normalised IIS frequency during the attentional bias task with non-task periods of approximately equal duration immediately before and after (Fig. 3A). However, an ANOVA with factors of task versus non-task and recording location revealed no main effects or interaction (all $p>0.54$; Fig. 3B). In addition, we made a within-subjects comparison of IIS frequency changes on hippocampal and temporal lobe contacts during the episodic memory and attentional bias task, for those patients that completed both. This revealed a main effect of task ($F(1,23)=6.6$, $p=0.04$), driven by a significantly greater IIS frequency increase during the episodic memory task, but no other main effects or interactions (both p>0.88; Fig. 3C).

Discussion

We have shown that IIS frequency increases in the hippocampus during the performance of a spatial memory task, which is known to engage that region in both rodents[6] and humans[3,7]. Similarly, we have shown that an episodic memory task increases IIS frequency in both hippocampus and lateral temporal lobe. These findings appears to be region specific, as task related changes in IIS frequency were not observed in the amygdala, which is not thought to be engaged by either task[4,8]. Moreover, an attentional bias task – which is not believed to be hippocampal dependent – elicited no significant change in IIS frequency within any temporal lobe region. Nonetheless, we cannot rule out the possibility that task-dependent increases in IIS frequency resulted from other aspects of the memory tasks that were not controlled for, such as the nature of the stimuli used or the level of cognitive effort required.

Although IIS have been proposed to negatively correlate with performance in visual recognition and word recall tasks[9,10], task-related increases in spike activity have not previously been reported. This underlines the importance of removing IIS before analysing task-related changes in oscillatory power, as they could make a strong and task-dependent contribution. It has previously been suggested that suppression of IIS can occur during task execution due to arousal or attention[11], which we controlled for by interleaving task and non-task periods, but we report the opposite pattern of results here.

Within the episodic memory task, IIS frequency was significantly higher during encoding than retrieval within both the hippocampus and lateral temporal lobe, suggesting that memory formation may cause greater engagement of those regions than later recall. Surprisingly, however, we found no relationship between IIS frequency and performance on either task. This may result from task structure, with the spatial memory task being self-paced, and long (>6s) encoding and retrieval epochs used in the episodic memory task, potentially nullifying any effect of IIS. We also found no evidence of laterality in task-related IIS frequency increases, consistent with previous fMRI evidence demonstrating bilateral hippocampal activation during each task[4,8].

Finally, it is important to note that the patient group examined here exhibited a wide range of epilepsies, the majority with a mesial temporal origin. Despite this diversity, abnormal interictal activity was consistently observed in the same hippocampal and temporal neocortical regions, suggesting that the functional networks mediating spatial and episodic memory formation can be appropriated by abnormal epileptiform activity. In summary, spatial and episodic memory function promote regional interictal spiking, suggesting that spike activation can reflect network engagement by cognitive tasks in epilepsy.

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Author Contributions

U.V., D.B., J.A.B., N.B, M.C.W. contributed to the conception and design of the study. U.V, D.B., J.A.B., B.D., A.J., P.N., R.R. contributed to the acquisition and analysis of data. U.V., D.B., J.A.B., A.J., N.B, M.C.W. contributed to drafting a significant portion of the manuscript or figures.

Potential Conflicts of Interest

Nothing to report.

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Figure 1. **IIS frequency is increased in the hippocampus during a spatial memory task.** **(A)** Schematic of the spatial memory paradigm. **(B)** Normalised IIS frequency for task versus non-task periods. Each line represents one patient. **(C)** Normalised IIS frequency for encoding versus retrieval periods

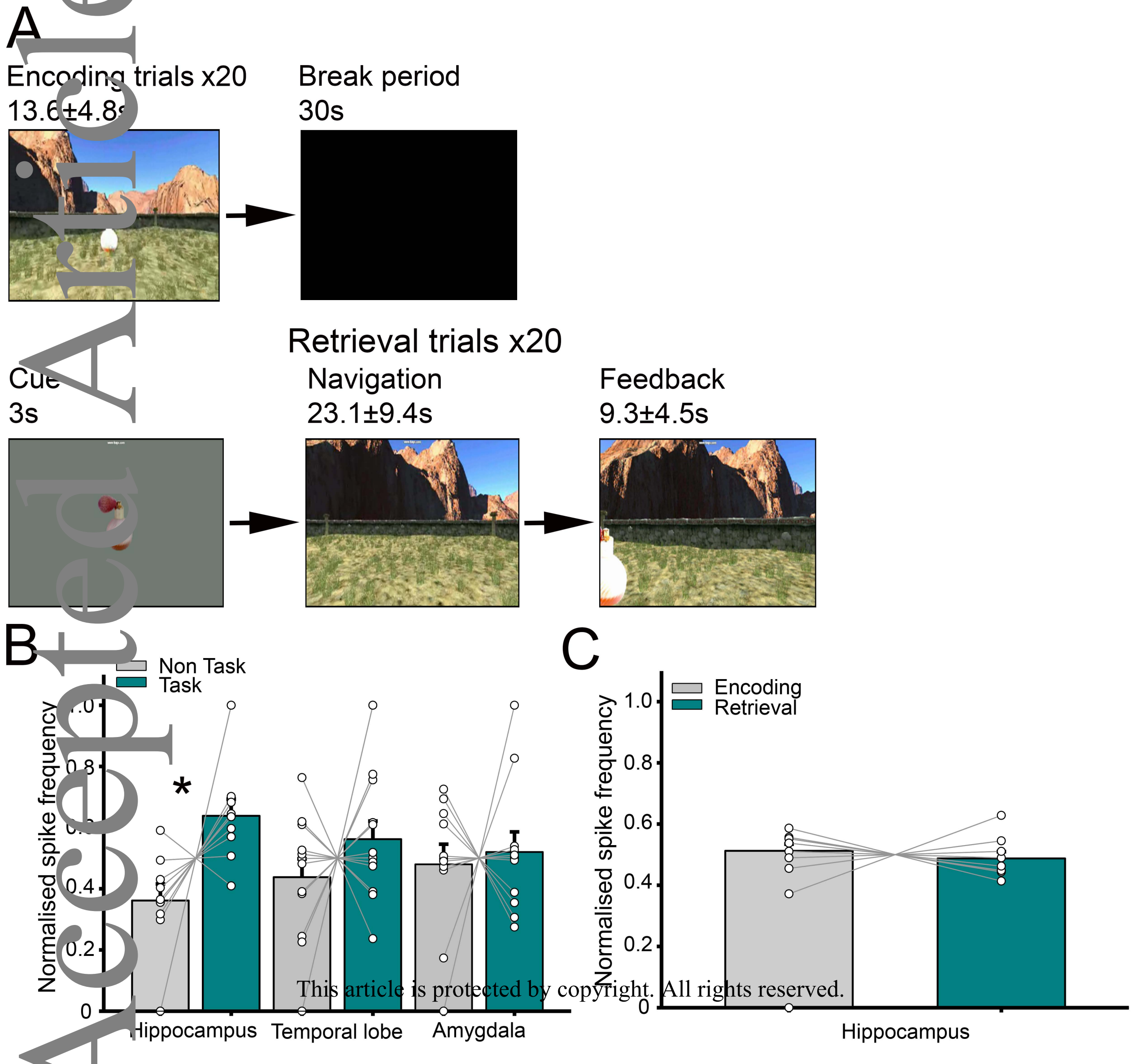
Figure 2. **IIS frequency is increased in the hippocampus during an episodic memory task.** **(A)** Schematic of the episodic memory paradigm. **(B)** Normalised IIS frequency for task versus non-task periods. Each line represents one patient. **(C)** Normalised IIS frequency for encoding versus retrieval periods

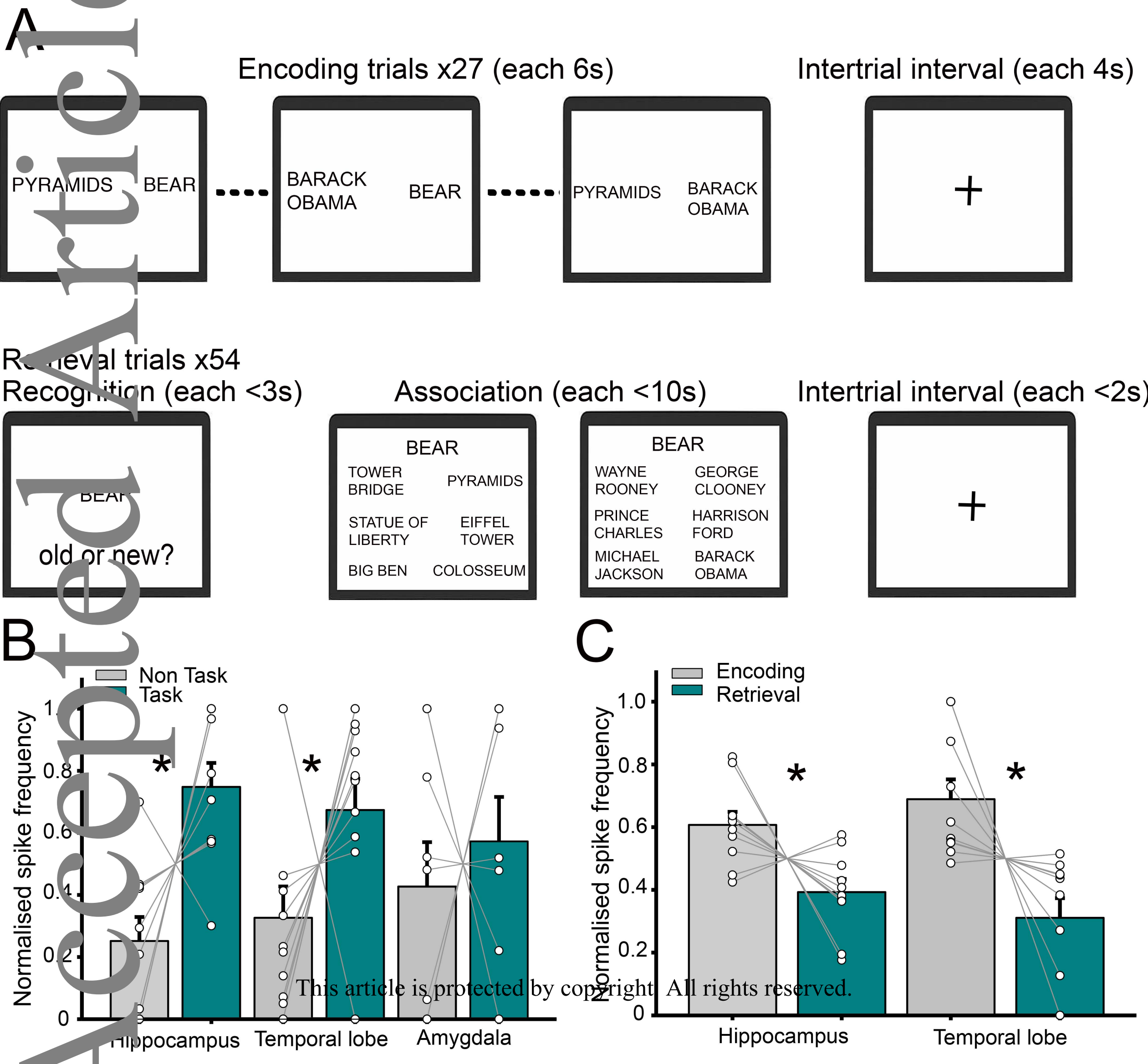
Figure 3. **IIS frequency is not increased in any region during an attentional bias task.** **(A)** Schematic of the attentional bias paradigm. **(B)** Normalised IIS frequency for task versus non-task periods. Each line represents one patient. **(C)** Within-subject task related IIS frequency increase compared between episodic memory task and attention bias task. Each circle represents an individual patient. HPC = hippocampus, TL = temporal lobe

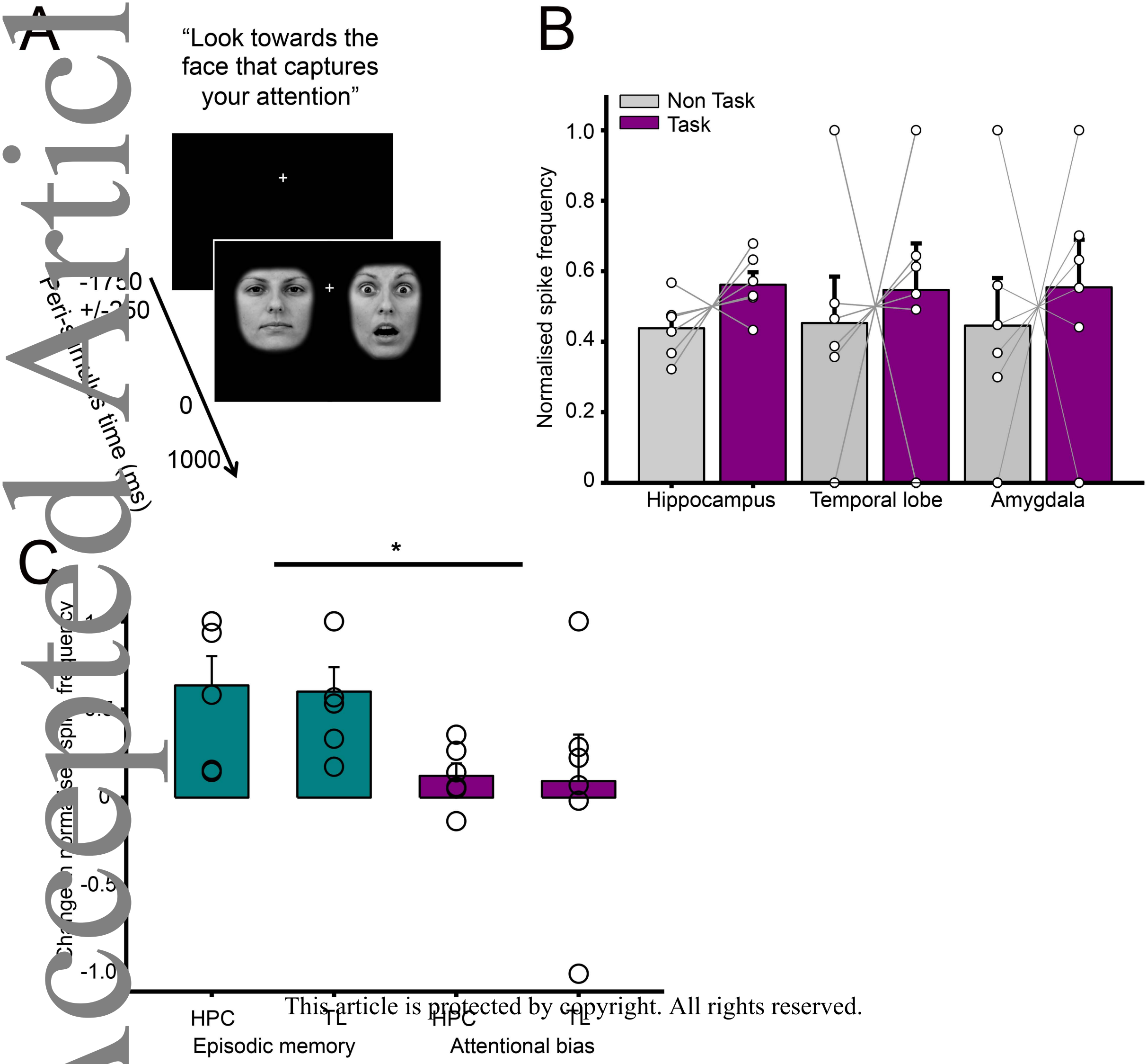
Table 1. Demographics and epilepsy history of patients for spatial memory task and episodic memory task. Asterix denotes patients who also performed the attentional bias task. M=male, F=female, R=right, L=left, B=bilateral

Spatial memory task						
Patient	Age	Gender	Years with epilepsy	Handedness	Side of seizure focus	Region
1	21	F	11	R	R	temporal
2	28	M	6	R	L	temporal
3	44	F	21	R	R	temporal
4	41	M	16	L	R	hippocampus
5	26	M	13	R	R	temporal
6	25	M	24	R	L	occipital
7	22	M	11	R	L	parietal
8	37	F	16	R	R	temporo-occipital
9	30	F	6	R	B	temporal
10	20	F	14	L	R	temporal
11	28	M	20	R	R	temporal
12	29	M	14	R	L	insula
Episodic memory task						
Patient	Age	Gender	Years with epilepsy	Handedness	Side of seizure focus	Region
1	44	F	40	R	R	temporal
2*	22	M	14	R	L	temporo-occipital
3	51	F	33	R	L	temporal
4	23	F	23	A	R	parietal
5*	43	M	39	R	L	unknown

6	41	F	24	R	R	frontal
7	42	M	34	R	R	temporal
8	37	F	10	R	R	frontal
9*	38	M	36	A	L	hippocampus
10*	26	M	20	R	R	frontal
11*	47	F	12	R	R	temporal
12*	38	F	31	R	R	frontal


A
Encoding trials x20
13.6±4.8s
Break period
30s
Retrieval trials x20
Cue
3s
Navigation
23.1±9.4s
Feedback
9.3±4.5s
B
Non Task
Task
Normalised spike frequency
0
0.2
0.4
0.8
Hippocampus
Temporal lobe
Amygdala
*
C
Encoding
Retrieval
Normalised spike frequency
0
0.2
0.4
0.6
0.8
1.0
Hippocampus


A
Encoding trials x27 (each 6s)
Intertrial interval (each 4s)
PYRAMIDS
BEAR
BARACK OBAMA
BEAR
PYRAMIDS
BARACK OBAMA
+
Retrieval trials x54
Recognition (each <3s)
Association (each <10s)
Intertrial interval (each <2s)
BEAR
old or new?
BEAR
TOWER BRIDGE
PYRAMIDS
STATUE OF LIBERTY
EIFFEL TOWER
BIG BEN
COLOSSEUM
BEAR
WAYNE ROONEY
GEORGE CLOONEY
PRINCE CHARLES
HARRISON FORD
MICHAEL JACKSON
BARACK OBAMA
+
B
Non Task
Task
Normalised spike frequency
0
0.2
0.4
0.6
0.8
1
*
*
Hippocampus
Temporal lobe
Amygdala
C
Encoding
Retrieval
Normalised spike frequency
0
0.2
0.4
0.6
0.8
1.0
*
*
Hippocampus
Temporal lobe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"Look towards the face that captures your attention"
-1750
+/-250
0
1000
B
Non Task
Task
1.0
0.8
0.6
0.4
0.2
0
Normalised spike frequency
Hippocampus
Temporal lobe
Amygdala
C
*
-0.5
-1.0
HPC
TL
HPC
TL
Episodic memory
Attentional bias