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Decreases in theta and increases in high frequency activity underlie associative memory encoding

Jeffrey A. Greenberg [a,1], John F. Burke [a,1], Rafi Haque [b], Michael J. Kahana [a], Kareem A. Zaghloul [b,*]

[a] Department of Psychology, University of Pennsylvania, 19104, USA
[b] Surgical Neurology Branch, NINDS, National Institutes of Health, 20892, USA

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ABSTRACT

Episodic memory encoding refers to the cognitive process by which items and their associated contexts are stored in memory. To investigate changes directly attributed to the formation of explicit associations, we examined oscillatory power captured through intracranial electroencephalography (iEEG) as 27 neurosurgical patients receiving subdural and depth electrodes for seizure monitoring participated in a paired associates memory task. We examined low (3–8 Hz) and high (45–95 Hz) frequency activity, and found that the successful formation of new associations was accompanied by broad decreases in low frequency activity and a posterior to anterior progression of increases in high frequency activity in the left hemisphere. These data suggest that the observed patterns of activity may reflect the neural mechanisms underlying the formation of novel item-item associations.

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Introduction

When searching our memory for previously experienced episodes, we rely on retrieval cues established during memory encoding to target the desired memory. These retrieval cues can be shaped by environmental context, internal mental states, or by associations formed between items or events. For example, one may associate a given restaurant with an important conversation with a colleague; subsequent visits to the same restaurant may easily prompt recollection of that same conversation. Several theories of memory encoding posit computational correlates underlying the formation of such associations (Norman and O'Reilly, 2003; McClelland et al., 1995), and associative memory encoding appears to occupy a specific type of processing in the human memory system (Kahana, 2012). Functional MRI studies provide empiric evidence for the anatomic locations where these processes take place. These studies implicate the hippocampus and the perirhinal cortex in binding conceptual representations across distal and closely interacting cortical regions, respectively (Davachi et al., 2003; Mayes et al., 2007; Dalton et al., 2013). Despite theoretical and experimental work, however, understanding the specific neural mechanisms that underlie how associative memory encoding is mediated by the brain still remains an unresolved question.

Direct intracranial recordings during paired associates memory tasks offer an experimental paradigm well suited to directly explore this issue (Caplan, 2005). Participants in paired associates tasks are instructed to form explicit associations between items and then attempt to recall one member of each pair when the other is provided as a cue. Combining paired associates tasks with subsequent memory effect (SME) analyses, in which neural activity is compared between successful and unsuccessful encoding (Paller and Wagner, 2002; Sederberg et al., 2003), can isolate the neural mechanisms responsible for forming associations (Caplan and Glaholt, 2007; Molle et al., 2002). Intracranial electroencephalography (iEEG) recordings offer a range of benefits when compared to fMRI in investigating the precise spatiotemporal changes underlying this process (Jacobs and Kahana, 2010), but SME analyses using human iEEG have not been previously performed during a paired associates task.

We address this here by investigating the changes in neural activity underlying the successful formation of explicit associations using iEEG recordings captured from subdural and depth electrodes as 27 patients with medically refractory epilepsy participated in a paired associates memory task. Previous studies investigating changes in episodic memory related changes in iEEG activity have linked successful encoding with both increases and decreases in oscillatory power in multiple frequency bands (Nyhus and Curran, 2010). Most episodic memory tasks require encoding of both items and associations, however, and it is unclear whether these discrepancies may be related to the cognitive demands specific to the encoding task (Hanslmayr and Staudigl, 2013). Here, we directly compared changes in low (3–8 Hz; theta) and high (45–95 Hz; high gamma) frequency oscillatory power during the successful and unsuccessful encoding of explicit associations in order to investigate the neural mechanisms that specifically underlie associative memory encoding.

Materials and methods

Twenty seven participants with medication-resistant epilepsy underwent a surgical procedure in which platinum recording contacts

* Corresponding author at: Surgical Neurology Branch, NINDS, National Institutes of Health, Building 10, Room 3D20, 10 Center Drive, Bethesda, MD 20892-1414, USA.
E-mail address: kareem.zaghloul@nih.gov (K.A. Zaghloul).
[1] Denotes equal contribution.

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Table 1
Patient demographics, behavioral performance, and electrode counts. The table shows the gender, age, the number of items seen during the paired associates task (# items), the percent recall, and the number of bipolar pairs of electrodes for each patient (#BPD). In addition, a hospital code for each patient indicates where data were collected: Thomas Jefferson University Hospital (T), the University of Pennsylvania (U), and the National Institutes of Health (N).

Patient	Gender	Age	# items	% correct	# BPD
T1	M	33	300	44.0	105
T2	M	23	148	39.2	109
T3	F	48	100	39.0	84
T4	M	33	200	72.0	46
T5	M	45	200	31.0	86
T6	M	23	200	75.5	78
T7	M	29	200	65.0	63
T8	F	20	700	77.9	126
T9	M	20	500	31.6	140
T10	M	50	200	26.5	105
T11	M	18	200	25.5	91
T12	M	57	100	12.0	50
U1	M	20	200	35.5	130
U2	M	37	200	18.5	123
U3	M	40	100	11.0	46
U4	F	25	100	13.0	160
N1	M	13	180	40.6	51
N2	F	52	300	26.3	54
N3	M	22	180	21.7	84
N4	M	49	360	14.4	52
N5	F	44	276	14.5	94
N6	M	31	120	83.3	151
N7	F	54	240	25.0	104
N8	F	25	240	24.6	71
N9	F	33	300	38.0	90
N10	M	40	240	25.42	91
N11	F	30	434	58.3	79

were implanted subdurally on the cortical surface, as well as deep within the brain parenchyma. In each case, the clinical team determined the placement of the contacts so as to best localize epileptogenic regions. Data were collected at three different facilities: Hospital of the University of Pennsylvania (UP; Philadelphia, PA), Thomas Jefferson University Hospital (TJ; Philadelphia, PA), and the Clinical Center of the National Institute of Health (NIH; Bethesda, MD). The research protocol was approved by the institutional review board at each hospital, and informed consent was obtained from the participants and their guardians. All patients participated in the paired associates task during their stay at these hospitals (see Table 1).

Paired associates task

In each trial of the paired associates task, patients were first shown a list of study word pairs, and then later cued with one word from each pair selected at random. Patients were instructed to recall each cue word's partner from the corresponding study word pair list. Lists were composed of four pairs of common nouns, chosen at random and without replacement from a pool of high-frequency nouns (http://memory.psych.upenn.edu/WordPools). Words were presented sequentially and appeared in capital letters at the center of the screen. During the study period (encoding), each word pair was preceded by an orientation stimulus (a row of capital X's) that appeared on the screen for 300 ms, followed by a blank interstimulus interval (ISI) of 750 ms with a jitter of 75 ms. Word pairs were then presented on the screen for 2500 ms, followed by a blank ISI of 1500 ms with a jitter of 75 ms. During the test period (retrieval), one randomly chosen word from each study pair was shown, and the participant was asked to recall the other word from the pair by vocalizing a response into a microphone. The length, in items, between the pair of words presented during study and the cue word given at retrieval varied and is termed the study-test lag.

Each cue word was preceded by an orientation stimulus (a row of question marks) that appeared on the screen for 300 ms, followed by a blank ISI of 750 ms with a 75 ms jitter. Cue words were then presented on the screen for 3000 ms, followed by a blank ISI of 4000 ms. Participants could vocalize their response any time during the recall period after cue presentation. Vocalizations were digitally recorded and then manually scored for analysis. Responses were designated as correct (and considered successfully encoded) if the correct word was retrieved following the cue. Participants could also respond with a word that was not paired with the cue (intrusions) or with the word 'pass' or with no vocalization (pass).

In the main analyses, we compared EEG power during the presentation of items between correct and pass trials, excluding all intrusions. See Fig. 1a for a visual representation of the paradigm. The primary contrast of interest is the comparison of correct recalls and incorrect recalls. However, because there are many ways in which the participant can make an

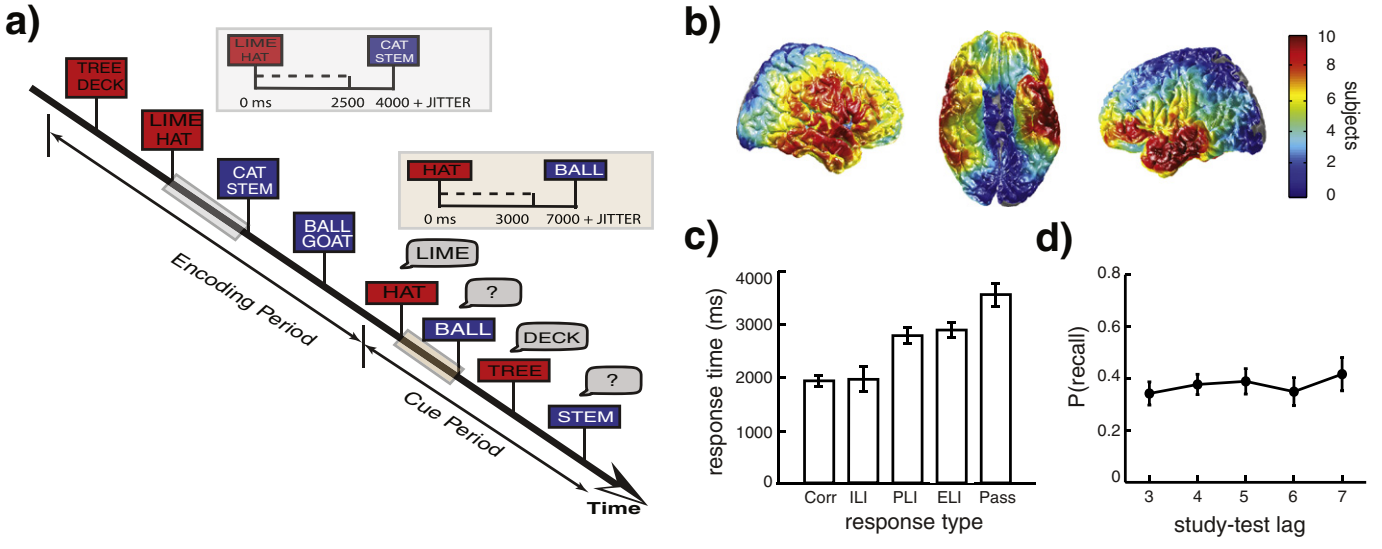

Fig. 1. a) Paired associates episodic memory task. In each trial, pairs of words are presented on the screen during encoding. Subsequently during retrieval, one word from each pair is randomly chosen and presented, and participants are instructed to vocalize the associated word. Timing of word and cue presentation are shown in the inset. b) Electrode coverage across all 27 participants. Colors correspond to the number of participants with electrodes contributing to each spatial region. Only anatomic regions with electrode contributions from at least five participants were included for group analyses. c) Mean response times in milliseconds, for each response type, across all participants. Error bars represent standard error of the mean. Bars represent response times for correct (Corr), intra-list intrusions (ILI), prior-list intrusions (PLI), extra-list intrusions (ELI), and pass trials. d) Probability of correct recall for all study-test lags averaged across all participants. Error bars represent standard error of the mean.