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Dual origins of measured phase-amplitude coupling reveal distinct neural mechanisms underlying episodic memory in the human cortex

Alex P. Vaz[a,b], Robert B. Yaffe[a,c], John H. Wittig Jr[a], Sara K. Inati[d], Kareem A. Zaghloul[a,*]

[a] *Surgical Neurology Branch, NINDS, National Institutes of Health, Bethesda, MD 20892, USA*
[b] *Medical Scientist Training Program, Duke University School of Medicine, Durham, NC 27710, USA*
[c] *Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD 21218, USA*
[d] *Office of the Clinical Director, NINDS, National Institutes of Health, Bethesda, MD 20892, USA*

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ABSTRACT

Phase-amplitude coupling (PAC) is hypothesized to coordinate neural activity, but its role in successful memory formation in the human cortex is unknown. Measures of PAC are difficult to interpret, however. Both increases and decreases in PAC have been linked to memory encoding, and PAC may arise due to different neural mechanisms. Here, we use a waveform analysis to examine PAC in the human cortex as participants with intracranial electrodes performed a paired associates memory task. We found that successful memory formation exhibited significant decreases in left temporal lobe and prefrontal cortical PAC, and these two regions exhibited changes in PAC within different frequency bands. Two underlying neural mechanisms, nested oscillations and sharp waveforms, were responsible for the changes in these regions. Our data therefore suggest that decreases in measured cortical PAC during episodic memory reflect two distinct underlying mechanisms that are anatomically segregated in the human brain.

Introduction

Interactions between oscillations in the brain remain poorly understood, though they are hypothesized to temporally coordinate information between local neuronal populations (Lisman and Idiart, 1995; Lisman, 2005; Jensen and Colgin, 2007; Canolty and Knight, 2010; Lisman and Jensen, 2013). One such interaction, phase-amplitude coupling (PAC), occurs when the phase of a low frequency oscillation modulates the amplitude of a high frequency oscillation (Canolty et al., 2006; Canolty and Knight, 2010). In the context of memory, this may provide a mechanism for embedding, and retrieving, individual memory representations within a broader context (Hasselmo and Eichenbaum, 2005; Buzsáki, 2005; Canolty and Knight, 2010). Indeed, evidence that PAC may play a role in memory formation has emerged in studies of the hippocampus in both animals and humans (Tort, Komorowski, Manns, Kopell, and Eichenbaum, 2009; Axmacher et al., 2010; Lisman and Jensen, 2013; Lega, Burke, Jacobs, and Kahana, 2014; Heusser, Poeppel, Ezzyat, and Davachi, 2016).

Despite empiric support for the role of PAC in memory, however, successful memory encoding has also been linked with decreases, rather than just increases, in PAC (Lega et al., 2014; Axmacher et al., 2010; Leszczynski, Fell, and Axmacher, 2015). This raises the question as to whether, in some cases, PAC limits effective neural processing. This may be the case in the cortex, where PAC has been observed in pathologic conditions such as Parkinson's disease (de Hemptinne et al., 2013, 2015). Hence, although PAC is ubiquitous throughout the cortex (Canolty et al., 2006; He, Zempel, Snyder and Raichle, 2010; Canolty and Knight, 2010), it is unclear whether cortical PAC is beneficial for memory encoding. One possibility is that increases in cortical PAC may improve memory encoding, lending support to the hypothesis that cortical PAC coordinates information just as in the hippocampus. Conversely, if PAC actually limits information processing in the cortex, then successful memory formation should be accompanied by decreases in PAC.

We examine this question here using intracranial EEG (iEEG) in participants with subdural electrodes placed for seizure monitoring as they engaged in a paired associates verbal memory task. Importantly, properly interpreting these data must account for the fact that measured PAC may arise due to two different underlying neural mechanisms - true interactions between low and high frequency oscillations that may help coordinate local neural populations (Jensen and Colgin, 2007; Lisman and Jensen, 2013), or repeated sharp or non-sinusoidal deflections in the iEEG signal that may be related to changes in synchrony of synaptic bursts (Sherman et al.,

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[*] Corresponding author.
E-mail address: kareem.zaghloul@nih.gov (K.A. Zaghloul).

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2016; Burke, Ramayya, and Kahana, 2015; Lozano-Soldevilla, ter Huurne, and Oostenveld, 2016; Cole et al., 2016). As such, we used a waveform analysis to investigate the electrophysiological contributions to any changes in PAC. We were motivated to understand whether any changes in cortical PAC related to successful memory encoding could be attributed to these distinct neural mechanisms.

Methods

Participants

33 participants with medication-resistant epilepsy underwent a surgical procedure in which platinum recording contacts 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 to localize epileptogenic regions. The Institutional Review Board (IRB) approved the research protocol, and informed consent was obtained from the participants and their guardians. These data were initially collected and analyzed for changes in spectral power in separate studies (Yaffe et al., 2014; Greenberg et al., 2015).

Paired associates task

Each patient participated in a paired associates task (Fig. 1a). Participants were asked to study a list of word pairs and then later cued with one word from each of the pairs, selected at random. Participants were instructed to vocalize each cue word's partner from the corresponding word pair. Lists were composed of four pairs of common nouns, chosen at random and without replacement from a pool of high-frequency nouns. Words were presented sequentially and appeared in capital letters at the center of the screen. Word pairs were separated from their corresponding recall cue by a minimum lag of two study or test items. 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), a randomly chosen word from each of the four study pairs was shown, and the participant was asked to recall the other word from each pair by vocalizing a response into a microphone. 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 4500 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, as intrusions, or as passes when no vocalization was made or when the participant vocalized the word ‘pass’. Intrusion and pass trials were designated as incorrect trials. A single experimental session contained up to 25 lists. For analysis, we designated a single trial as the encoding period for a study word pair and the retrieval period during testing of its corresponding cue.

Intracranial EEG (iEEG) recordings

Depending on the amplifier and the discretion of the clinical team, intracranial EEG (iEEG) signals were sampled at 1000 or 2000 Hz. Signals were referenced to a common contact placed subcutaneously, on the scalp, or on the mastoid process. All recorded traces were resampled at 1000 Hz, and a fourth order 2 Hz stopband butterworth notch filter was applied at 60 Hz to eliminate electrical line noise. The testing laptop sent +/−5 V digital pulses via an optical isolator into a pair of open lines on the clinical recording system to synchronize the electrophysiological recordings with behavioral events.

We collected electrophysiological data from a total of 2750 subdural and depth recording contacts (83.3 ± 5.5 per subject; PMT Corporation, Chanhassen, MN; AdTech, Racine, WI). Subdural contacts were arranged in both grid and strip configurations with an intercontact spacing of 10 mm. Hippocampal depth electrodes (6–8 linearly arranged contacts) were placed in four patients. Contact localization was accomplished by co-registering the post-op CTs with the post-op MRIs using both FSL Brain Extraction Tool (BET) and FLIRT software packages and mapped to both MNI and Talairach space using an indirect stereotactic technique and OsiriX Imaging Software DICOM viewer package. The resulting contact locations were subsequently projected to the cortical surface of a Montreal Neurological Institute N27 standard brain (Dykstra et al., 2011). Pre-operative MRIs were used when post-operative MR images were not available.

We analyzed iEEG data using bipolar referencing to reduce volume conduction and confounding interactions between adjacent electrodes (Nunez and Srinivasan, 2006). Bipolar referencing is routinely used for subdural electrode recordings, and has been noted be superior to the average reference montage in reducing muscular artifacts in iEEG (Kovach et al., 2011). We defined the bipolar montage in our data-set based on the geometry of iEEG electrode arrangements. For every grid, strip, and depth probe, we isolated all pairs of contacts that were positioned immediately adjacent to one another; bipolar signals were then found by finding the difference in the signal between each pair of immediately adjacent contacts. The resulting bipolar signals were treated as new virtual electrodes (henceforth referred to as electrodes throughout the text), originating from the midpoint between each contact pair. All subsequent analyses were performed using these derived bipolar signals. Importantly, we excluded all electrodes exhibiting ictal or interictal activity at the seizure focus and at sites of generalization as identified by a team of trained epileptologists in order to avoid confounding any memory effects with concurrent seizure activity. In total, our dataset consisted of 2292 electrodes (1048 left hemispheric, 1244 right hemispheric). Additionally, we excluded any trials displaying excessive variance or kurtosis (defined as greater than 2.3 times the interquartile range away from the third quartile) in order to provide the most conservative assessment of normal human electrophysiology in the context of noise and transient epileptiform activity.

Spectral power and phase

We quantified spectral power and phase by convolving the bipolar iEEG signals with complex valued Morlet wavelets (wavelet number 6) (Addison, 2002). To quantify phase-amplitude coupling (PAC) and to generate corresponding comodulograms, we calculated spectral power and phase using 15 linearly spaced wavelets between 2 and 16 Hz for the phase frequencies and 25 linearly spaced wavelets between 5 and 250 Hz for the amplitude frequencies. The encoding period was 0 to 4500ms from the onset of pair presentation, and the retrieval period was from the onset of cue presentation to the time of vocalization. The omission of any data after the start of vocalization was intended to minimize any potential confounding effects associated with speech generation. We convolved the above wavelets with the iEEG data from each of these periods in order to generate continuous measures of instantaneous amplitude and phase. During pass trials where no vocalization was present, we assigned a response time by randomly drawing from the distribution of correct reaction times. One participant was instructed to vocalize her response only after the cue word disappeared from the screen. In all trials, we included a 1000 ms buffer on both sides of the clipped data.

To examine PAC between frequency bands, we also quantified spectral power and phase for each frequency band by first bandpass filtering the iEEG signal into four predefined frequency bands using a second order Butterworth filter: theta (3–8 Hz), alpha (8–12 Hz), low gamma (30–58 Hz), and high gamma (70–180 Hz). We then calculated