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Human intracranial high-frequency activity maps episodic memory formation in space and time

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ABSTRACT

Noninvasive neuroimaging studies have revealed a network of brain regions that activate during human memory encoding; however, the relative timing of such activations remains unknown. Here we used intracranially recorded high-frequency activity (HFA) to first identify regions that activate during successful encoding. Then, we leveraged the high-temporal precision of HFA to investigate the timing of such activations. We found that memory encoding invokes two spatiotemporally distinct activations: early increases in HFA that involve the ventral visual pathway as well as the medial temporal lobe and late increases in HFA that involve the left inferior frontal gyrus, left posterior parietal cortex, and left ventrolateral temporal cortex. We speculate that these activations reflect higher-order visual processing and top-down modulation of attention/semantic information, respectively.

Introduction

Among those experiences that enter the focus of our attention, some are encoded in a manner that can easily support subsequent recollection while others are not. This variability in goodness of memory encoding has been the subject of considerable psychological research over the last century (Kahana, 2012), yet only in the last decade or so have we begun to uncover its physiological basis. In the laboratory, one can investigate the neural basis of goodness of encoding by recording brain signals from participants while they engage in a learning task and then correlating specific features in the signal with subsequent memory performance (Paller and Wagner, 2002).

Using this approach, often referred to as the subsequent memory (SM) paradigm, functional magnetic resonance imaging (fMRI) studies have identified several brain regions involved in memory encoding; the left prefrontal cortex (Blumenfeld and Ranganath, 2007), posterior parietal cortex (Uncapher and Wagner, 2009), medial temporal lobe (Henson, 2005), and fusiform cortex are among those areas most consistently activated during successful encoding (Kim, 2011; Spaniol et al., 2009). However, fMRI studies lack the temporal resolution required to identify the temporal sequence of activations underlying memory encoding. This, in turn, has limited our understanding of how these regional activations interact to form functional memory encoding networks (Rugg et al., 2002).

To investigate the spatiotemporal properties of this memory encoding network, it is necessary to use a brain signal with millisecond temporal resolution, such as intracranially recorded high-frequency activity (HFA). HFA refers to fast fluctuations in neuro-electrophysiological recordings that manifest as increases in spectral power at frequencies above 60–70 Hz. The neural mechanism that gives rise to such fast activity is a topic of on-going research: HFA has been linked to asynchronous signals related to increased multi-unit activity (Manning et al., 2009; Miller et al., 2009; Milstein et al., 2009; Ray and Maunsell, 2011), the superposition of multiple high-frequency oscillations (Crone et al., 2011; Gaona et al., 2011), as well as a combination of these two processes (Scheffer-Teixeira et al., 2013). Despite its unclear neural origin, however, an increasing number of studies have leveraged HFA as a marker of underlying neural activation (Crone et al., 2011; Lachaux et al., 2012), similar to the blood-oxygen-level-dependent (BOLD) signal. Indeed, HFA has been directly correlated with BOLD activity (Conner et al., 2011; Mukamel et al., 2005), further suggesting that HFA represents a marker of general neural activation.

As a marker of general activation, HFA has been used to functionally map areas involved in motor activity (Leuthardt et al., 2007), auditory perception (Crone et al., 2001), language processing (Sinai et al., 2005), tactile sensation (Chang and Cheung, 2012), among others. Here, using

Abbreviations: HFA, High-frequency activity; SM, Subsequent memory; LFA, Low-frequency activity; IFG, Inferior frontal gyrus; VLTC, Ventrolateral temporal cortex; PPC, Posterior parietal cortex.

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intracranial recordings from neurosurgical patients in the SM paradigm, we leverage HFA to functionally map areas of the brain responsible for episodic memory formation. Whereas previous work has established that HFA increases during successful memory encoding in the SM paradigm (Sederberg et al., 2007a, 2007b), such work has interpreted HFA strictly through an oscillatory framework. However, if HFA instead represents a more general metric of neural activation, the information conveyed by this signal should be reflected in the exact time and spatial location in which it is active. By collecting data from a very large number of patients (ninety-eight), we were able to overcome the limited spatial sampling of human intracranial electrophysiology and use HFA to map memory encoding in both space and time. This approach revealed a dynamic spatiotemporal activation of functional networks that mediate encoding, as described in this report.

Material and methods

Participants

Participants with medication-resistant epilepsy underwent a surgical procedure in which grid, strip, and depth electrodes were implanted so as to localize epileptogenic regions. Data were collected over a 14 year period as part of a multi-center collaboration with neurology and neurosurgery departments across the country. Our research protocol was approved by the institutional review board at each hospital and informed consent was obtained from the participants and their guardians. Our final participant pool consisted of 98 patients (86 left-language dominant patients; see Supplementary Table S1).

Free recall task

Each patient participated in a delayed free-recall task. In each trial of this task, participants are instructed to study a list of 15 or 20 words and are then asked to freely recall as many words as possible. Words were presented sequentially and remained on the screen for 1600 ms, followed by a randomly jittered 800–1200 ms blank inter-stimulus interval (ISI). Immediately following the final word in each list, participants were given a distraction task (arithmetic problems; minimum 20 s) and were then given 45 s to recall as many words as possible from the list in any order. Words that were presented during the encoding period and successfully retrieved during the recall period are considered successfully encoded (Paller and Wagner, 2002).

iEEG recordings

Clinical circumstances alone determined electrode number and placement. Subdural (grids and strips) and depth contacts were spaced 10 mm and 8 mm apart, respectively. iEEG was recorded using a Bio-Logic, DeltaMed (Natus), Nicolet, Grass Telefactor, or Nihon-Kohden EEG system. Depending on the amplifier and the discretion of the clinical team, the signals were sampled at 200, 256, 400, 500, 512, 1000, 1024, or 2000 Hz. Signals were converted to a bipolar montage by differencing the signals between each pair of immediately adjacent contacts on grid, strip, and depth electrodes; 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 (Burke et al., 2013). Signals were re-sampled at 256 Hz; a notch filter was applied at 60 Hz or 50 Hz. Analog pulses synchronized the electrophysiological recordings with behavioral events. Contact localization was accomplished by co-registering the post-op CTs with the MRIs using FSL Brain Extraction Tool (BET) and FLIRT software packages. The resulting contact locations were mapped to both MNI space and Talairach space using an indirect stereotactic technique. To identify whether a particular anatomical area exhibited task-related changes in power, we grouped spatially similar electrodes from different participants by segregating Talairach space into 53,471 overlapping 12.5 mm radius spheres spaced every 3 mm. Only spherical regions that had electrodes from 5 or more patients were included in analyses.

Spectral power

We convolved clips of iEEG (1000 ms before item onset to 2900 ms after onset, plus a 1000 ms flanking buffer) with 30 complex valued Morlet wavelets (wave number 10) with center frequencies logarithmically spaced from 2 to 95 Hz (Addison, 2002). We squared and log-transformed the wavelet convolutions, and then averaged the resulting log-power traces into 500 ms epochs with 490 ms overlap, yielding 341 total temporal epochs surrounding each word presentation. For the low-temporal resolution analysis in Figs. 1 and 2, we averaged the continuous time power trace into a single time epoch from 0 to 2000 ms after word presentation. Power was then averaged into a high-frequency activity (HFA) band (64 to 95 Hz), which was used to create the topographic activation maps. We *z*-transformed power values separately for each session (Burke et al., 2013). For every electrode and for every temporal epoch, we assessed the difference in spectral power during memory formation by calculating a parametric *t*-statistic on the distributions of average power values during successful and unsuccessful encoding. In Figs. 1B-D and 4A, *t*-statistics comparing power during successfully and unsuccessfully encoded words were averaged across all electrodes from each patient in a particular region.

Statistical procedure

For the anatomical plots in Figs. 2 and 3, we assessed whether changes in spectral power were significant across participants for a given ROI or spherical voxel using a non-parametric permutation procedure. We calculated a *t*-statistic on the distribution of log-power values during successful and unsuccessful encoding during a single temporal epoch for every electrode and from each participant. We then permuted the labels for the conditions 10,000 times to generate a distribution of 10,000 shuffled *t*-statistics. We averaged the true and permuted *t*-statistics across all electrodes within each spherical region for each participant. For each region, we then summed the true and permuted averaged values across all participants (Burke et al., 2013; Sederberg et al., 2007a). To generate a *p*-value for changes in spectral power for a given region, we determined the position of the summed true *t*-statistics in the distribution of summed permuted values. To correct for multiple comparisons across space (Fig. 2) and time (Fig. 3), we used a false discovery rate (FDR) procedure (Genovese et al., 2002, $q = 0.05$).

Topographic plots

To plot spatial changes in spectral power, we identified spherical regions that exhibited a statistically significant (FDR corrected) increase or decrease in power across participants. At each spherical region, we calculated the percentage of other regions within 12.5 mm that exhibited identical encoding-related effects. We translated these percentages to color saturation and rendered these values onto cortical and subcortical topographical plots using a standard MNI brain with information from the WFU PickAtlas toolbox (Maldjian et al., 2003). Colored values were smoothed using a three-dimensional Gaussian kernel (radius = 12.5 mm; $\sigma = 3$ mm). The maximal color saturation in either direction corresponded to 50% of adjacent spherical regions. All regions with fewer than five patients were colored black and were not analyzed. Grayscale rendering in other regions represented the percentage of spherical regions surrounding a given location with at least five patients, and thus represented regions that were analyzed but that did not exhibit significant effects. For anatomical plots collapsed across time (Figs. 2 and 5), only contiguously statistically significant regions (spherical regions flanked by other significant regions in all