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Human intracranial high-frequency activity during memory processing: neural oscillations or stochastic volatility?

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Intracranial high-frequency activity (HFA), which refers to fast fluctuations in electrophysiological recordings, increases during memory processing. Two views have emerged to explain this effect: (1) HFA reflects a synchronous signal, related to underlying gamma oscillations, that plays a mechanistic role in human memory and (2) HFA reflects an asynchronous signal that is a non-specific marker of brain activation. We review recent data supporting each of these views and conclude that HFA during memory processing is more consistent with an asynchronous signal. Memory-related HFA is therefore best conceptualized as a biomarker of neural activation that can functionally map memory with high spatial and temporal precision.

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Introduction

The higher intellectual functions of man depend critically on our ability to store memories of past experiences and to retrieve those memories in the service of our current behavior [1]. Achieving an understanding of the neural substrates of memory is not only critical to the noble pursuit of understanding memory itself, but could also help pave the way for therapies aimed at restoring memory function following neurological injury or disease.

The present review focuses on intracranial high frequency activity (HFA), because electrophysiological studies of human memory demonstrate robust increases in HFA power during a wide range of memory tasks [2,3]. For example, HFA in the medial temporal lobe (MTL) increases both during episodic memory retrieval [4] and with increasing memory load [5]. In the posteromedial cortex, HFA increases during the retrieval of autobiographical memories [6]. In the right hemisphere, HFA increases during spatial navigation and spatial learning [7]. These correlations establish that HFA increases during memory processing; it is unclear, however, what aspect of memory HFA represents.

Two representative views have emerged to explain the link between HFA and memory processing. In the first view, HFA reflects gamma oscillations that enhance spike time dependent plasticity and promote inter-regional neuronal communication; previous research links both of these theoretical neural processes to human memory [8,9]. Under this view, phase-synchronous gamma oscillations (PSGOs) play a mechanistic role in memory, coordinating the firing rate of populations of neurons, which in turn fire together to mediate memory encoding and retrieval [10–12].

The second view suggests that HFA represents general neural activation and does not play a specific role in memory processing [13]. This interpretation stems from criticism of the theoretical neural processes attributed to gamma oscillations [14–16]. In the extreme, proponents of this view suggest that HFA reflects an asynchronous increase in spectral power, equivalent to noise caused by large-scale increases in underlying multi-unit activity (MUA) [17]. This activity causes a 'broadband' shift in the frequency spectrum of electrophysiological recordings [18,19]. Because time-varying changes in asynchronous power are equal to fluctuations in the instantaneous variance, the term neural stochastic volatility (NSV) is used to succinctly refer to this asynchronous signal.

Complicating matters, the neural activity giving rise to PSGOs and NSV overlaps, and HFA likely reflects the superposition of both effects [19,20,21•]. Thus, by its very nature, HFA confuses the relation between memory, neural firing rates, and gamma oscillations. However, a practical issue in memory research is determining whether artificially enhancing gamma oscillations using deep brain stimulation will enhance memory function [12,22], as predicted by the PSGO view but not by the NSV view. Thus, it is important to weigh the evidence linking HFA to memory processing, and adjudicate between these two interpretations as best as possible.

Here, we examine recent studies reporting HFA changes in human memory to determine if such changes are more consistent with the NSV or the PSGO view. Using macroelectrode recordings, the PSGO and NSV views can be differentiated based on the shape/morphology of HFA power changes and the amount of HFA phase-synchrony during memory processing. We conclude that HFA during memory processing is more consistent with the NSV view and is probably not mechanistically related to memory. Instead, HFA most likely represents a non-specific metric of neural activation, and the memory-specific information conveyed by this signal is reflected in its spatiotemporal pattern, not its frequency or phase.

Shape/morphology of HFA power during memory processing

Increases in HFA power may reflect narrow-band 'bumps' in the spectrum or broadband increases in power (Figure 1a). Establishing which of these effects shapes HFA power during memory processing is important, because each is associated with a different neural origin [20,23]. Narrow band bumps suggest underlying gamma oscillations (PSGO view) and broadband increases in power suggest asynchronous activity (NSV view) [24].

Unfortunately, memory studies often mask the morphology of the power spectrum by presenting statistics comparing HFA power between memory conditions. As an example, Sederberg *et al.* examined episodic memory formation by comparing spectral power during the presentation of items that were later remembered as compared to those that were later forgotten during a free recall test (subsequent memory effect; SME) [25]. Electrodes that displayed positive SME statistics clustered around 32 Hz, which were interpreted as gamma oscillations (Figure 1b). However, an identical analysis with a larger number of patients revealed that increases in HFA extended to 64 Hz, with no discernible peak [26]. Furthermore, Burke *et al.* showed that the HFA effect was present up to 95 Hz (Figure 1c) [27]. Thus, the statistical changes that initially appeared as an HFA oscillation centered at 32 Hz are actually more consistent with a broadband change (see Figure 1d for an example of broadband changes during memory formation).

Within the memory literature, assessing if increases in HFA reflect bumps or flat increases in power is difficult. To address this issue, Kucewicz *et al.* determined whether band-limited gamma oscillations occur more or less frequently during memory processing [28••]. They found that band limited gamma oscillations predominated in primary visual areas during encoding compared to recall. However, because behavioral performance was not taken into account, these changes may reflect either memory processing or repetition effects. In another study, Lega *et al.* similarly attempted to determine if band-limited gamma oscillations correlate with memory processing [26]. Using a peak detection algorithm, the authors found an increase in the number of oscillatory peaks around 64 Hz during episodic memory encoding, but this result was not statistically verified. More research is needed to determine if band-limited gamma oscillations (bumps) correlate with memory processing.

Another consideration is the anatomical location of HFA. Narrow band bumps are often found in primary sensory cortices [23,29], but memory-related HFA is found throughout the brain, often in association cortices [27]. It is not clear if gamma oscillations in sensory cortex and memory-related HFA in broader brain regions represent the same neural signal. Additionally, even when gamma oscillations are observed, they are often intermixed with broadband activity [30]. In cases where both gamma oscillations and broadband activity occur, recent research suggests that the broadband (asynchronous) features of HFA correlate more strongly with behavior [30,31].

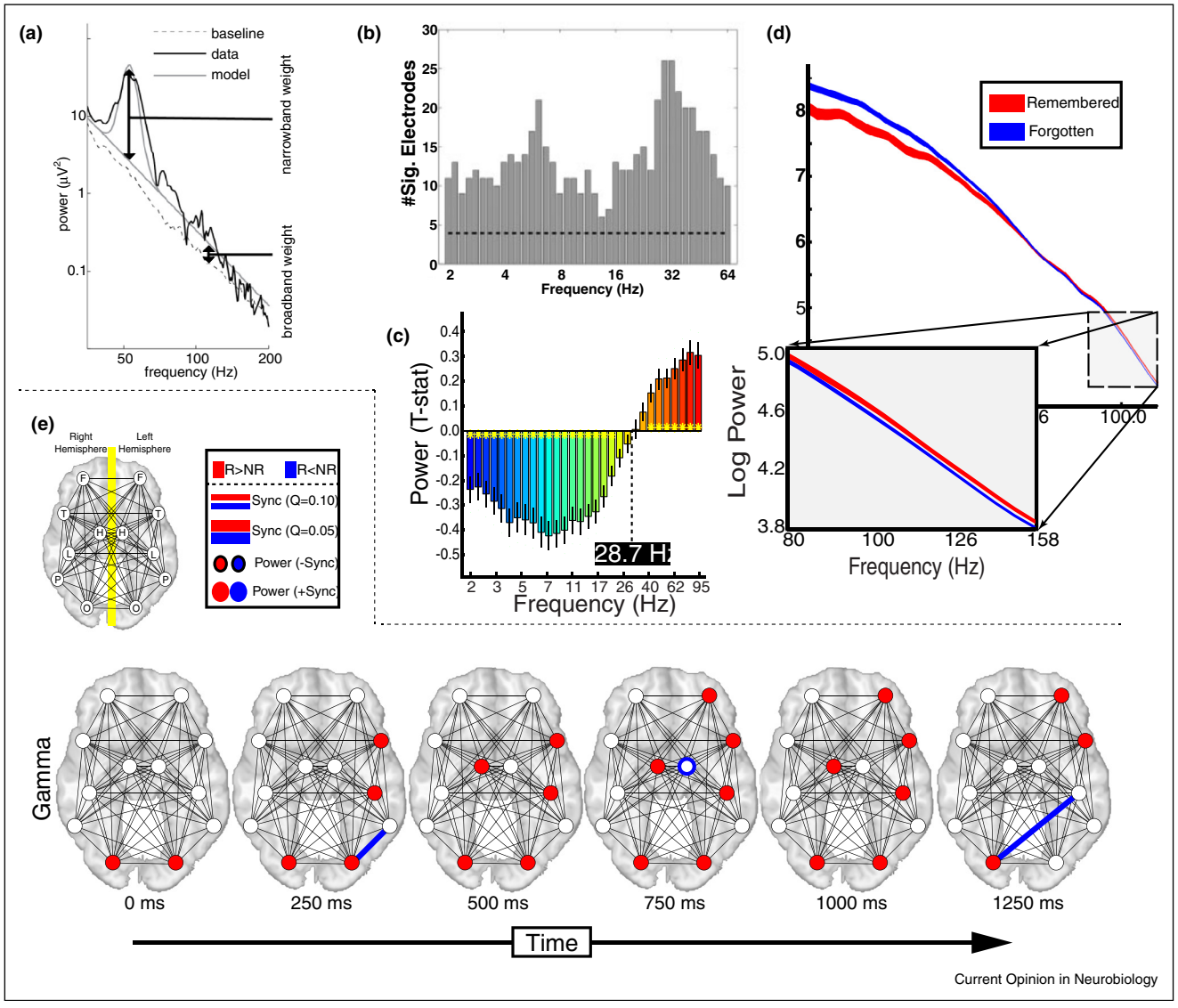
In summary, few studies have systematically shown that HFA during memory reflects narrow band peaks (bumps) in the frequency spectrum. The PSGO theory has largely been informed by studies of selective attention using recordings over sensory cortices where narrow band peaks are readily observed [32]. Whether the PSGO view can be applied to memory-related HFA changes outside of sensory regions and in the absence of these peaks is unclear.

HFA synchrony during memory processing

The PSGO view, at its core, suggests that the phase of gamma oscillations bundles neuronal activity in temporally meaningful packets [8–12]. Thus, although spectral bumps suggest underlying gamma oscillations, they are not by themselves evidence for the PSGO view. This is best intuited from elementary signal processing that reminds us that the power spectrum, by definition, contains no information about the phase of the signal. Demonstrating this point empirically in a neuroscience context, Xing *et al.* showed that narrow-band increases in gamma power could be generated from filtered noise, i.e. they do not *necessarily* represent oscillations with a meaningful phase component [33•] (but see [34]). This study highlights that narrow band gamma oscillations represent data that are consistent with, but not direct evidence for, PSGOs.

The most direct evidence of the PSGO view links phase-synchronization to cognitive processing [35]. In terms of memory, such evidence largely comes from animal models. For example, Igarashi *et al.* found increased phase-synchrony during a rodent odor-place association task in the 20–40 Hz range (slow gamma band; [36]). In this study, phase-synchronization occurred specifically between the distal region of CA1 and the lateral region of entorhinal cortex. Another study found that object

Figure 1



HFA — morphology and synchrony. **(a)** Data from human visual cortex shows the spectral morphology of gamma oscillations ('bumps') as well as broadband increases in asynchronous power. Data courtesy of [30]. **(b)** The number of electrodes, from an early study of episodic memory formation, exhibiting significantly greater spectral power during successful encoding across frequencies from 2 to 64 Hz. Data from [25]. **(c)** Averaged *t*-statistics across 98 patients comparing spectral power for successful versus unsuccessful encoding are shown. Error bars reflect ±1 SEM across patients. Yellow asterisks mark significant increases/decreases in power during encoding (*t*-test; $P < 0.05$; Bonferroni corrected). Data courtesy of [27]. **(d)** Two power spectra during the encoding period of a memory test for items that were later remembered (red) and later forgotten (blue). The shape of the frequency spectrum reveals a flat, asynchronous increase in high frequency power. Data courtesy of Michael J. Kahana. **(e)** During memory formation, large increases in HFA are not accompanied by increases in high-frequency synchrony. In fact, regions showing increases in HFA power display significant decreases in phase synchrony. Data courtesy of [44••].

memory correlates with increased HFA functional coupling between specific cell–cell pairs in the inferior temporal region of non-human primates [37••]. Together these animal studies, among others [38], show that gamma phase-synchronization is involved in memory processing, and such gamma-synchrony occurs on a local anatomical scale, often between classes of functionally related neurons [39]. One caveat is that recent work has challenged the assertion that increased phase-synchronization is sufficient to modulate behavior [40]. Although more research is needed to link high-frequency phase-synchronization to the formation/retrieval of memories, increased phase-synchronization during memory is strong evidence in favor of the PSGO view.

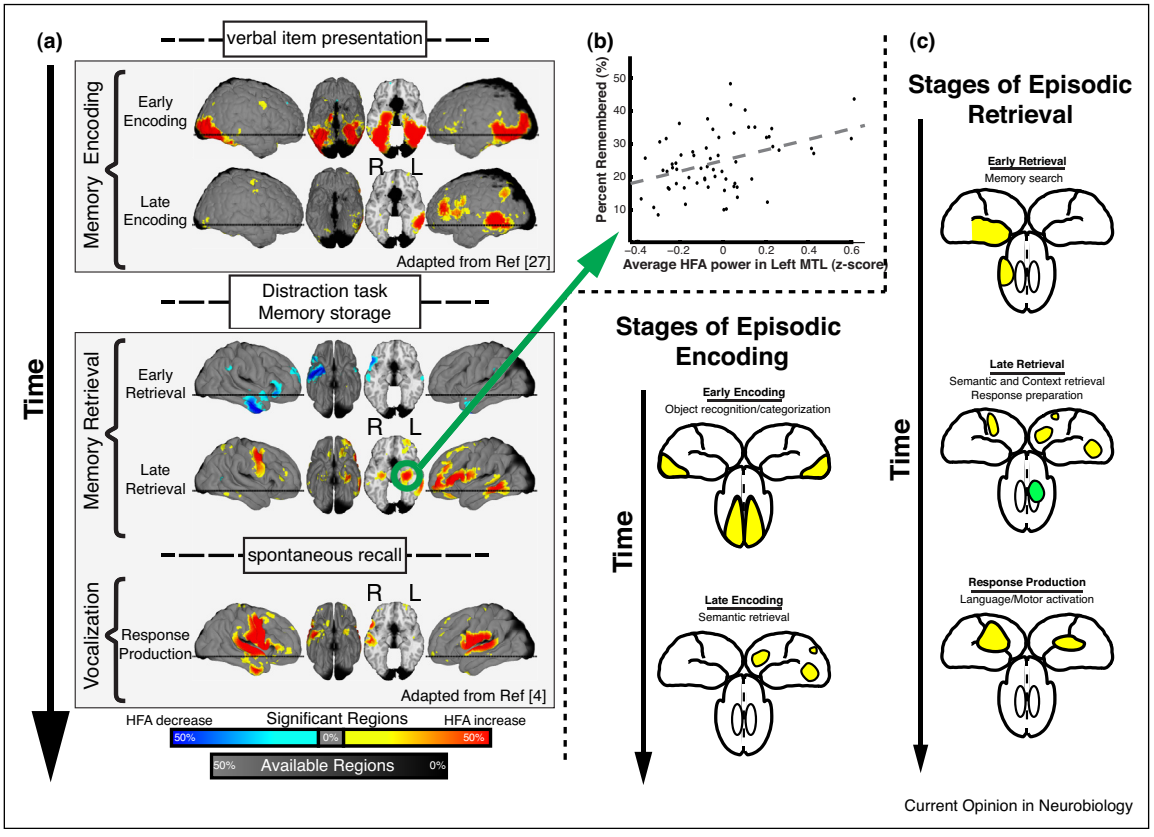
In humans, memory processing elicits increased HFA phase-synchronization between the parahippocampal/rhinal cortex and the hippocampus [41,42]. Most recently, rhinal–hippocampal coupling was shown to occur specifically during source-recognition, as opposed to item-recognition [43••]. These data suggest that spatially localized HFA phase-synchronization, during specific types of tasks, plays a role in memory function and is consistent with the PSGO view. However, whether increases in HFA power during memory processing reflects the PSGO view is less clear. In particular, HFA power increases during many different memory tasks over large regions of the brain [2,3]. If these increases in power reflect the PSGO view, then there should be a massive increase in HFA phase-synchrony during memory processing. Burke *et al.* specifically tested this and found that increases in HFA power during memory formation were accompanied by *decreases* in HFA phase synchrony (Figure 1e) [44••]. These findings may seem surprising, but decreases in phase synchrony during memory processing are actually expected if HFA reflects broadband, asynchronous activity, consistent with the NSV view.

Synthesis: HFA as a functional mapping signal

From this discussion, two points are clear: (1) both phase-synchronous gamma oscillations (PSGOs) and asynchronous activity (NSV) may contribute to human HFA and (2) it is unclear which of these effects is responsible for the increase in HFA observed during memory processing. Future studies are needed to determine the relative contribution of PSGOs and NSV to human memory. Until such evidence is available, it is nonetheless useful to adopt an *a priori* hypothesis when interpreting memory-related HFA. Otherwise, HFA could be used to advance conflicting theories on the neurobiology of human memory.

To this end, given (1) the lack of observed narrow-band peaks in the HFA region of the power spectrum during memory processing (2) the hazards involved in

Figure 2



The neurological stages of episodic encoding and retrieval. **(a)** In each panel, regions that exhibited a significant change in HFA during encoding and recall on a free recall memory task are shown. Color and grayscale renderings represent the percentage of nearby regions exhibiting significant effects and containing more than 5 patients, respectively. Radiological slice view is shown with right (R) and left (L) hemispheres labeled. Data modified from [4] and [27]. **(b)** In the left medial temporal lobe (MTL), HFA correlated with overall memory performance across patients ($r = 0.3911$, $P = 0.0015$). **(c)** Each panel describes a particular stage of neural activity during memory formation and retrieval. The text above each panel provides a putative behavioral/cognitive role of each stage.

extrapolating the cellular scale of PSGOs in animal recordings to human macro-recordings (3) the paucity of evidence linking phase-synchronous oscillatory activity to increases in human HFA power at the macro-recording level and (4) emerging evidence that asynchronous activity correlates well with a variety of behaviors, we posit that memory-related HFA is more appropriately interpreted as asynchronous NSV rather than synchronous gamma oscillations. Given this interpretation, HFA is best used as a spatially and temporally precise metric of neural activation [45,46]. For example, recent studies have shown that the spatiotemporal profile of HFA in the superior temporal gyrus can be used to decode human speech content [47•]. In terms of the neural correlates of human memory, the memory-related information in HFA should be encoded by *when/where* such activations occur, and not *if* such activations occur.

This approach was recently used to map the brain regions responsible for episodic memory encoding [27] and retrieval [4] during verbal free recall (modified in Figure 2a). During successful memory encoding, HFA could be separated into two spatiotemporal distinct stages: an early stage consisting of HFA increases along the ventral visual pathway culminating in hippocampal activation (*Early Encoding*; Figure 2a), and a late stage consisting of HFA increases in discrete areas of the left neocortex (*Late Encoding*; Figure 2a) [27]. Episodic retrieval could be similarly staged into; firstly, early retrieval, consisting of a decrease in HFA in the right temporal cortex (*Early Retrieval*; Figure 2a); secondly, late retrieval, consisting of an increase in HFA in the left neocortex and medial temporal lobe immediately before spontaneous recall (*Late Retrieval*; Figure 2a); and finally motor/language activation during vocalization of the recalled item (*Response Production*; Figure 2A) [4]. Of note, theta oscillations (not shown) occurred simultaneously with decreases in HFA during early retrieval. Also, of all the regions that activated during retrieval, the left MTL predicted memory performance, suggesting that this region represents a final common pathway in recall (Figure 2b).

The spatiotemporal stages outlined in Figure 2a represent a dynamic neural map of verbal episodic memory function. However, how these spatiotemporal stages work together to give rise to memory encoding and retrieval remains to be determined. One possibility is that each stage represents a particular cognitive operation, and the broader behavior of 'memory' emerges from the stereotyped cascade of these operations over time and anatomical space. To that end, in Figure 2c, we suggest a putative cognitive role for each of these spatiotemporal stages based on their timing and anatomical location. Future research should be aimed at confirming, or rejecting, these hypothesized cognitive functions.

The true value of the NSV view is that it emphasizes the functional mapping utility of HFA. Using this approach, HFA is useful to build a dynamic neural map of memory. Further memory research should be geared toward understanding what the components of this map represent and how they work together to create the unique phenomenon of human memory.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Kahana MJ: *Foundations of Human Memory*. New York: Oxford University Press; 2012, .
2. Nyhus E, Curran T: **Functional role of gamma and theta oscillations in episodic memory**. *Neurosci Biobehav Rev* 2010, **34(7)**:1023-1035.
3. Johnson EL, Knight RT: **Intracranial recordings and human memory**. *Curr Opin Neurobiol* 2015, **31(7)**:18-25.
4. Burke JF, Sharan AD, Evans JJ, Healey MK, Sperling MR, Beck EN, Davis KA, Lucas TH, Kahana MJ: **Theta and high-frequency activity mark spontaneous recall of episodic memories**. *J Neurosci* 2014, **34(34)**:11355-11365.
5. van Vugt MK, Schulze-Bonhage A, Litt B, Brandt A, Kahana MJ: **Hippocampal gamma oscillations increase with working memory load**. *J Neurosci* 2010, **30(7)**:2694-2699.
6. Foster BL, Dastjerdi M, Parvizi J: **Neural populations in human posteromedial cortex display opposing responses during memory and numerical processing**. *Proc Natl Acad Sci U S A* 2012, **109(38)**:15514-15519.
7. Jacobs J, Korolev I, Caplan J, Ekstrom A, Litt B, Baltuch G, Fried I, Schulze-Bonhage A, Madsen J, Kahana MJ: **Right-lateralized brain oscillations in human spatial navigation**. *J Cogn Neurosci* 2010, **22(5)**:824-836.
8. Jutras M, Buffalo EA: **Synchronous neural activity and memory formation**. *Curr Opin Neurobiol* 2010, **20(2)**:150-155.
9. Fell J, Axmacher N: **The role of phase synchronization in memory processes**. *Nat Rev Neurosci* 2011, **12(2)**:105-118.
10. Watrous AJ, Fell J, Ekstrom AD, Axmacher N: **More than spikes: common oscillatory mechanisms for content specific neural representations during perception and memory**. *Curr Opin Neurobiol* 2015, **31**:33-39.
11. Lisman JE, Jensen O: **The theta-gamma neural code**. *Neuron* 2013, **77(6)**:1002-1016.
12. Lee H, Fell J, Axmacher N: **Electrical engram: how deep brain stimulation affects memory**. *Trends Cogn Sci* 2013, **17(11)**:574-584.
13. Merker B: **Cortical gamma oscillations: the functional key is activation, not cognition**. *Neurosci Biobehav Rev* 2013, **37(3)**:401-417.

14. Kirschfeld K: **Oscillations in the insect brain: do they correspond to the cortical waves of vertebrates?** *Proc Natl Acad Sci U S A* 1992, **89**:4764-4768.

15. Shadlen M, Movshon J: **Synchrony unbound. A critical evaluation of the temporal binding hypothesis**. *Neuron* 1999, **24**:67-77.

16. Ray S, Maunsell JH: **Differences in gamma frequencies across visual cortex restrict their possible use in computation**. *Neuron* 2010, **67(5)**:885-896.

17. Miller KJ, Honey CJ, Hermes D, Rao RP, den Nijs M, Ojemann JG: **Broadband changes in the cortical surface potential track activation of functionally diverse neuronal populations**. *NeuroImage* 2014, **85**:711-720.

18. Manning JR, Jacobs J, Fried I, Kahana MJ: **Broadband shifts in LFP power spectra are correlated with single-neuron spiking in humans**. *J Neurosci* 2009, **29(43)**:13613-13620.

19. Belluscio MA, Mizuseki K, Schmidt R, Kempter R, Buzsáki G: **Cross-frequency phase-phase coupling between theta and gamma oscillations in the hippocampus**. *J Neurosci* 2012, **32(2)**:423-435.

20. Lachaux JP, Axmacher N, Mormann F, Halgren E, Crone NE: **High-frequency neural activity and human cognition: past, present and possible future of intracranial EEG research**. *Prog Neurobiol* 2012, **98(3)**:279-301.

21. • Scheffer-Teixeira R, Belchior H, Leao RN, Ribeiro S, Tort AB: **On high-frequency field oscillations (>100 Hz) and the spectral leakage of spiking activity**. *J Neurosci* 2013, **33(4)**:1535-1539.
In this study, the authors found that HFA in the rodent hippocampus is composed of two signals: true gamma oscillations as well broadband power. The broadband activity correlated with increased underlying multi-unit activity, consistent with the NSV view. They found that gamma oscillations could be separated from NSV by the detection of circumscribed peaks (bumps) in the power spectrum. Moreover, the authors found that, if gamma oscillations are not present, NSV can influence activity as low as 50 Hz.

22. Fell J, Staresina BP, Do Lam ATA, Widman G, Helmstaedter C, Elger CE, Axmacher N: **Memory modulation by weak synchronous deep brain stimulation: a pilot study**. *Brain Stimul* 2013, **6(3)**:270-273.

23. Sedley W, Cunningham MO: **Do cortical gamma oscillations promote or suppress perception? An under-asked question with an over-assumed answer**. *Front Hum Neurosci* 2013, **7** http://dx.doi.org/10.3389/fnhum.2013.00595.

24. Ray S, Maunsell JH: **Different origins of gamma rhythm and high-gamma activity in macaque visual cortex**. *PLoS Biol* 2011, **9(4)**:e1000610.

25. Sederberg PB, Kahana MJ, Howard MW, Donner EJ, Madsen JR: **Theta and gamma oscillations during encoding predict subsequent recall**. *J Neurosci* 2003, **23(34)**:10809-10814.

26. Lega B, Jacobs J, Kahana MJ: **Human hippocampal theta oscillations and the formation of episodic memories**. *Hippocampus* 2012, **22(4)**:748-761.

27. Burke JF, Long NM, Zaghloul KA, Sharan AD, Sperling MR, Kahana MJ: **Human intracranial high-frequency activity maps episodic memory formation in space and time**. *NeuroImage* 2014, **85**:834-843.

28. •• Kucewicz MT, Cimbalnik J, Matsumoto JY, Brinkmann BH, Bower MR, Vasoli V, Sulc V, Meyer F, Marsh WR, Stead SM, Worrell GA: **High frequency oscillations are associated with cognitive processing in human recognition memory**. *Brain* 2014, **137(8)**:2231-2244.
The authors measured intracranial EEG from 12 patients engaged in a recognition memory task with a 24 hour delay between encoding and recall. Viewing picture stimuli during both encoding and recall correlated with increased spectral 'bumps' in the gamma (50–125 Hz), ripple (125–250 Hz) and fast ripple (250–500 Hz) frequency bands along the ventral visual stream. To test if the HFA bumps reflected memory processing, the authors compared these changes during encoding and recall. HFA bumps clustered in the occipital and parahippocampal cortex during encoding and the temporal and frontal cortex during recall. Of note, memory performance (correct versus incorrect recognition) was not assessed in this study.

29. Winawer J, Miller KJ, Hermes D, Parvizi J, Wandell BA: **Oriented luminance gratings but not noise patterns induce narrow gamma band ECoG responses in human visual cortex**. *J Vis* 2013, **13(9)** 33–33.

30. Hermes D, Miller KJ, Wandell BA, Winawer J: **Stimulus dependence of gamma oscillations in human visual cortex**. *Cereb Cortex* 2014. doi:10.1093/cercor/bhu091.

31. Winawer J, Kay KN, Foster BL, Rauschecker AM, Parvizi J, Wandell BA: **Asynchronous broadband signals are the principal source of the bold response in human visual cortex**. *Curr Biol* 2013, **23(13)**:1145-1153.

32. Fries P, Nikolic D, Singer W: **The gamma cycle**. *Trends Neurosci* 2007, **30(7)**:309-316.

33. • Xing D, Shen Y, Burns S, Yeh CI, Shapley R, Li W: **Stochastic generation of gamma-band activity in primary visual cortex of awake and anesthetized monkeys**. *J Neurosci* 2012, **32(40)**:13873-13880.
Here, the authors tested if HFA from monkey visual cortex (in both awake and anesthetized animals) reflected gamma oscillations. In particular, the authors compared actual LFP spectra to analogous spectra calculated from surrogate LFP data with a random phase component (noise). They found that gamma calculated from the actual LFP was indistinguishable from gamma calculated from the noise signal, indicating that gamma activity is 'temporally unstructured' and incapable of synchronizing.

34. Nikolic D, Fries P, Singer W: **Gamma oscillations: precise temporal coordination without a metronome**. *Trends Cogn Sci* 2013, **17(2)**:54-55.

35. Roberts MJ, Lowet E, Brunet NM, Wal MT, Tiesinga P, Fries P, Weerd PD: **Robust gamma coherence between macaque V1 and V2 by dynamic frequency matching**. *Neuron* 2013, **78(3)**:523-536.

36. Igarashi KM, Lu L, Colgin LL, Moser MB, Moser EI: **Coordination of entorhinal–hippocampal ensemble activity during associative learning**. *Nature* 2014, **510(7503)**:143-147.

37. •• Hirabayashi T, Tamura K, Takeuchi D, Takeda M, Koyano KW, Miyashita Y: **Distinct neuronal interactions in anterior inferotemporal areas of macaque monkeys during retrieval of object association memory**. *J Neurosci* 2014, **34(28)**:9377-9388.
In this study, two monkeys performed a paired associates memory task. The authors recorded from two areas in the anterior inferior temporal region (area TE and 36) during the retrieval portion of the task. They found two classes of functionally distinct neuronal responses: neurons that increased their firing rate when the cue was presented and neurons that increased their firing rate during the retrieval of the association. They found that HFA (gamma) coherence occurred within classes of functionally distinct cell–cell pairs.

38. Colgin LL, Moser EI: **Gamma oscillations in the hippocampus**. *Physiology* 2010, **25**:319-329.

39. Vinck M, Womelsdorf T, Buffalo EA, Desimone R, Fries P: **Attentional modulation of cell class-specific gamma-band synchronization in awake monkey area V4**. *Neuron* 2013, **80(4)**:1077-1089.

40. Histed MH, Maunsell JH: **Cortical neural populations can guide behavior by integrating inputs linearly, independent of synchrony**. *Proc Natl Acad Sci U S A* 2014, **111(1)**:E178-E187.

41. Fell J, Klaver P, Lehnertz K, Grunwald T, Schaller C, Elger CE, Fernandez G: **Human memory formation is accompanied by rhinal–hippocampal coupling and decoupling**. *Nat Neurosci* 2001, **4(12)**:1259-1264.

42. Axmacher N, Schmitz DP, Wagner T, Elger CE, Fell J: **Interactions between medial temporal lobe, prefrontal cortex, and inferior temporal regions during visual working memory: a combined intracranial EEG and functional magnetic resonance imaging study**. *J Neurosci* 2008, **28(29)**:7304-7312.

43. •• Staresina BP, Fell J, Lam ATD, Axmacher N, Henson RN: **Memory signals are temporally dissociated in and across human hippocampus and perirhinal cortex**. *Nat Neurosci* 2012, **15(8)**:1167-1173.
Here, five patients with implanted subdural electrodes performed a recognition memory task in which words were presented during the study period, alongside images of particular scenes/colors. During test, the patients identified previously seen words as 'old' (item memory) and

were also asked to recover the appropriate scene for that word (source memory). The authors found increased HFA phase-synchrony (or coherence) between the rhinal cortex and the hippocampus during the retrieval of source memory compared to item memory. Of note, the authors did not determine if this increase in HFA synchrony was accompanied by an increase in oscillatory power.

44. •• Burke JF, Zaghloul KA, Jacobs J, Williams RB, Sperling MR, Sharan AD, Kahana MJ: **Synchronous and asynchronous theta and gamma activity during episodic memory formation**. *J Neurosci* 2013, **33(1)**:292-304.

In this study of episodic memory formation, 68 patients with subdural electrodes participated in a free recall task. The authors recorded intracranial EEG during the task, and compared HFA power and HFA phase-synchrony for items that were later remembered compared to those that were later forgotten. They found that areas that showed increases in HFA power during memory formation did not show increases in HFA phase-synchrony. Instead, decreases in phase-synchrony were observed in these regions. Using a graph theoretical approach, areas of increased HFA phase-synchrony were observed in the right hemisphere, however increases in HFA power did not localize to this region.

45. Crone NE, Korzeniewska A, Franaszczuk PJ: **Cortical gamma responses: searching high and low**. *Int J Psychophysiol* 2011, **79(1)**:9-15.

46. Su DK, Ojemann JG: **Electrocorticographic sensorimotor mapping**. *Clin Neurophysiol* 2013, **124(6)**:1044.

47. • Mesgarani N, Cheung C, Johnson K, Chang EF: **Phonetic feature encoding in human superior temporal gyrus**. *Science* 2014, **343(6174)**:1006-1010.

In this study, the authors first used HFA to quantify the responsivity of intracranial electrodes to different phonemes in English speech. Using an unsupervised hierarchical clustering algorithm, they found that the spatiotemporal pattern of neural activity across the superior temporal gyrus was selective for speech sounds. This paper is a preeminent example of how interpreting HFA as an asynchronous mapping signal can answer sophisticated questions regarding the neural basis of human cognition.