

1 REVIEW ARTICLE

2 **High frequency oscillations in human memory and** 3 **cognition: a neurophysiological substrate of engrams?**

4 Michal T. Kucewicz,^{1,2} Jan Cimbalnik,^{1,3,4} Jesus S. S. Garcia,¹ Milan Brazdil^{1,4,5} and Gregory A.
5 Worrell^{1,2}

6 **Abstract**

7 Despite advances in understanding the cellular and molecular processes underlying memory and
8 cognition, and recent successful modulation of cognitive performance in brain disorders, the
9 neurophysiological mechanisms remain underexplored. High frequency oscillations beyond the
10 classic electroencephalogram spectrum have emerged as a potential neural correlate of
11 fundamental cognitive processes. High frequency oscillations are detected in the human mesial
12 temporal lobe and neocortical intracranial recordings spanning gamma/epsilon (60-150 Hz),
13 ripple (80-250 Hz) and higher frequency ranges. Separate from other non-oscillatory activities,
14 these brief electrophysiological oscillations of distinct duration, frequency and amplitude are
15 thought to be generated by coordinated spiking of neuronal ensembles within volumes as small
16 as a single cortical column. Although the exact origins, mechanisms, and physiological roles in
17 health and disease remain elusive, they have been associated with human memory consolidation
18 and cognitive processing. Recent studies suggest their involvement in encoding and recall of
19 episodic memory with a possible role in the formation and reactivation of memory traces. High
20 frequency oscillations are detected during encoding, throughout maintenance, and right before
21 recall of remembered items, meeting a basic definition for an engram activity. The temporal
22 coordination of high frequency oscillations reactivated across cortical and subcortical neural
23 networks is ideally suited for integrating multimodal memory representations, which can be
24 replayed and consolidated during states of wakefulness and sleep. High frequency oscillations
25 have been shown to reflect coordinated bursts of neuronal assembly firing and offer a promising
26 substrate for tracking and modulation of the hypothetical electrophysiological engram.

27

1 **Author affiliations:**

2 1 BioTechMed Center, Brain & Mind Electrophysiology laboratory, Department of Multimedia
3 Systems, Faculty of Electronics, Telecommunications and Informatics, Gdansk University of
4 Technology, Gdansk, 80-233, Poland

5 2 Bioelectronics, Neurophysiology and Engineering Laboratory, Mayo Clinic, Departments of
6 Neurology and Biomedical Engineering & Physiology, Mayo Clinic, Rochester MN, 55902,
7 USA

8 3 Department of Biomedical Engineering, St. Anne's University Hospital in Brno & International
9 Clinical Research Center, Brno, 602 00, Czech Republic

10 4 Brno Epilepsy Center, 1th Department of Neurology, St. Anne's University Hospital and
11 Medical Faculty of Masaryk University, member of the ERN-EpiCARE, Brno, 602 00, Czech
12 Republic

13 5 Behavioural and Social Neuroscience Research Group, CEITEC - Central European Institute of
14 Technology, Masaryk University, Brno, 625 00, Czech Republic

15

16 Correspondence to: Michal T. Kucewicz

17 BioTechMed Center, Brain & Mind Electrophysiology laboratory, Department of Multimedia
18 Systems, Faculty of Electronics, Telecommunications and Informatics, Gdansk University of
19 Technology, ul. Narutowicza 11/12, 80-8233 Gdansk, Poland

20 E-mail: michal.kucewicz@pg.edu.pl

21

22 **Running title:** High frequency oscillations in human memory

23

24 **Keywords:** network oscillations; intracranial EEG; local field potential; cognition; sharp-wave
25 ripples; memory consolidation

26 **Abbreviations:** iEEG = intracranial electroencephalogram; HFO = high frequency oscillation

27



1 Neurophysiological activities bridging neural oscillations 2 and neuronal spiking as a window into memory and 3 cognition

4 Intracranial electrophysiological recordings and stimulation have provided unprecedented access
5 to study the neural activities that underlie the most complex and abstract functions of the human
6 brain ^{1-4,5,6,7,8}. Local field potential (LFP) recordings reflecting the activity of neural populations
7 associated with memory and cognitive functions can be either oscillatory or non-oscillatory. The
8 emergence of high-density macro-, meso-, and micro-electrode arrays now enables recording the
9 wide range of various LFP activities ⁹⁻¹². Still, probing specific electrophysiological activity
10 recorded at various scales to determine their origins remains a major challenge ¹³⁻¹⁵, as is
11 mapping these to particular processes underlying our cognition.

12 At the high resolution end of the electrophysiological activity spectrum, neuronal action potential
13 spiking, also known as the single unit activity, has been linked to mental representations of
14 abstract concepts and proposed as a building block for our thinking and declarative memory ^{8,16-}
15 ¹⁸. These single neuron spiking activities are confined to extracellular field potentials sampled on
16 a micrometer scale from electrode contacts in the immediate vicinity of a spiking cell ¹⁹. On the
17 other end of the spectrum (Fig. 1 top), there are LFP oscillations in the classic EEG spectrum
18 generated by coordinated synaptic currents of large neural populations. The oscillations are
19 traditionally classified into distinct frequency bands, commonly referred to as brain waves or
20 rhythms, which are thought to be generated at different scales of neural organization. Low
21 frequency oscillations of the delta or theta bands engage larger volumes and spatially extended
22 neural networks, whereas higher frequency rhythms in the gamma bands are more local and
23 confined to more specific neuronal ensembles ^{20,21}. Between the two ends of this spectrum,
24 linking the low ranges of the classic EEG bands (<60 Hz) and the high ranges of detecting the
25 neuronal action potentials (>600 Hz), there is a wide frequency span of electrophysiological
26 activities, including high frequency oscillations (HFOs) and other non-oscillatory sources of
27 spectral power (Fig. 1 bottom). The HFOs may serve as a bridge to link the ‘building blocks’ of
28 single neuron spiking with large-scale LFP activities reflected in neural network oscillations ²².



1 In this review, we will first define the terms for various types of electrophysiological activities
2 captured by extracellular LFP recordings and the vast frequency spectrum between EEG
3 oscillations and the neuronal spiking. Various terms that are used for similar LFP activities in
4 overlapping frequency ranges have been a matter of recent controversy in dissociating sharp-
5 wave ripples from high frequency oscillations or broadband power increases^{23,24}. These previous
6 reviews were focused on the lower ranges of the high gamma and ripple frequency spectrum,
7 treating HFOs in the ranges beyond 250 Hz as predominantly related to the pathophysiology of
8 epilepsy. Here, we focus on the HFOs across the wide frequency range between the EEG
9 oscillations and neuronal single unit activity. We will review the basic physiology of HFOs with
10 reference to the other high frequency LFP activities with particular focus on human studies to
11 support the proposed terms and definitions and to provide background for the
12 neuropsychological theories of neuronal assemblies and engrams posed in the title question.

13 This will set the scene for discussing what is known about the roles of HFOs in memory and
14 cognition. Several recent studies have reported HFOs in the ripple frequency and beyond to be
15 associated with memory encoding, reactivation, recall and consolidation across hippocampal-
16 cortical networks^{25–33}. We will conclude by discussing the title proposal that HFOs can provide
17 electrophysiological substrates of engrams, reconciling the single neuron research of abstract
18 concept representations, spatiotemporal dynamics of high frequency LFP activities across the
19 brain, and the most recent advancements in the engram research. Finally, we will conclude with a
20 prospective use of HFOs to track large-scale dynamics across widespread networks of connected
21 neural assemblies during memory and cognitive functions.

23 **Classification and definitions of electrophysiological** 24 **activities in the high frequency spectrum**

25 **HFOs are classified across overlapping frequency ranges based on** 26 **physiological properties**

27 Given the wide variety of LFP activities recorded in the high frequency range between the classic
28 EEG bands on one end and the neuronal spiking on the other (Fig. 1), it has been a major



1 challenge to determine distinct boundaries and names in this previously uncharted territory. Over
2 three decades of animal and human studies, describing both physiological and pathological,
3 oscillatory, non-oscillatory, induced/evoked and spontaneous phenomena, have produced
4 nomenclature and definitions that are not fully consistent and standardized in one unified view. A
5 consensus statement recently published by a representative group of researchers defining sharp-
6 wave ripples in the context of other high frequency LFP activities in humans, non-human
7 primates and rodents ²³. The statement addresses the key problems in the field related to signal
8 processing and exclusion of artifacts, methods for detection and analysis of LFP ripples,
9 anatomical localization in the hippocampus and neocortex, and relationship to other
10 physiological and pathological discharges in the spectrum. Some of these problems were also
11 discussed in a special volume of reviews dedicated to the high frequency oscillations ^{24,34,35}. Both
12 the recent statement and the previous reviews pertained mainly to the high gamma and ripple
13 frequency ranges, aiming to separate them from other pathological discharges and non-
14 physiological artifacts. Oscillations beyond these ranges were mostly treated as related to the
15 pathophysiology of epilepsy ³⁶.

16 Bottom panel of Figure 1 summarizes the proposed classes of distinct high frequency activities,
17 including both oscillatory and non-oscillatory sources of LFP spectral power. The lower end of
18 the HFO spectrum is dominated by several classes of gamma and ripple frequency ranges, which
19 are highly overlapping within a span extending from 60 to 150 Hz. On the higher end, the
20 frequency boundaries for fast and ultra-fast ripples and their relationship with and influence from
21 neuronal spiking activities ^{37,38} have not been clearly defined.

22 There has been more in-depth research into the contribution of neuronal spiking to spectral LFP
23 activities recorded in the gamma and ripple frequency ranges ^{39,40}. The lower frequency ranges
24 (> 60 – 250 Hz) are more clearly charted and classified on the spectrum based on their
25 physiological phase coupling with oscillations in the classic EEG bands like the theta rhythm ^{41–}
26 ⁴³. Hence, three frequency subbands were proposed within a wider gamma range: low (30–90
27 Hz) and fast/epsilon band (~90–150 Hz), which are separate from the overlapping ripple range
28 (~140–220 Hz) ³⁵.

29 Focusing on the oscillations, distinct classes have been separated based on the underlying neural
30 mechanisms of their generation. One of the first such distinctions was made in rodent



1 hippocampus between ripples occurring at 140-200 Hz range, which were associated with sharp-
2 wave bursts of neuronal spiking and relatively high amplitude of oscillations visible in the raw
3 signal, compared to fast gamma/epsilon oscillations of lower frequencies (100-130 Hz), which
4 were not associated with the sharp-wave bursts but shared common neuronal mechanisms with
5 the ripples⁴⁴. A later study confirmed that these two classes of HFO are quantitatively distinct
6 but share similar neuronal networks and mechanisms⁴⁵. Both studies found that the ripples (140-
7 220 Hz) and fast gamma/epsilon (90-140 Hz) oscillations had different anatomical localizations
8 in the hippocampal subfields and the connected neocortical areas.

9 In general, there is ample evidence for different types or classes of HFOs based on their
10 anatomical locations, neural substrates and mechanisms of generation³⁵. Separating these based
11 on frequency boundaries into distinct gamma, ripple and higher frequency ranges appears
12 challenging and cumbersome because the boundaries are highly overlapping (Fig. 1).

13 **Defining human HFO types in specific frequency ranges and** 14 **anatomical localization.**

15 It would seem from these original studies in the rodent hippocampus and mesial temporal
16 neocortex that ripples and gamma HFOs should be easily distinguishable based on either the
17 frequency range (higher for ripples), mechanism of generation (e.g. presence of a LFP sharp-
18 wave) or anatomical location (e.g. hippocampal subfields). In the human hippocampus, however,
19 ripples with the greatest amplitude were detected in 80-140 Hz frequency range^{31,46-48}, which is
20 overlapping with the high gamma range (70-150 Hz). Sharp-wave bursts have not been
21 commonly used for detection of ripples or separation from high gamma LFP activities in these
22 original or subsequent studies since they were conducted in people with epilepsy, who have
23 epileptiform sharp-waves (a.k.a. interictal epileptiform spikes) often accompanied by a high
24 frequency oscillation. Differentiating pathological epileptiform sharp-wave transients and
25 physiological sharp-waves and the associated HFOs is a challenge^{25-28,31-33}. In these cognitive
26 studies, therefore, the only criterion used to distinguish ripples from high gamma or epsilon
27 oscillations is the anatomical localization in the hippocampus or, more recently, in its CA1
28 subfield. But since gamma and ripple HFOs share common cellular mechanisms^{44,45}, they are
29 virtually impossible to separate without the main distinguishing sharp-wave feature.



1 Ripples are also recorded outside of the hippocampus proper or the connected mesial temporal
2 lobe structures. One of the first reports of neocortical ripples in rats described them as ‘spike-
3 and-wave discharges’ with oscillations in the fast ripple frequency range ⁴⁹. Neocortical ripple
4 oscillations were later found to be synchronized with the hippocampal ripples especially during
5 sleep following learning ⁵⁰, congruent with their proposed roles in hippocampal-cortical transfer
6 of information related to memory consolidation ⁵¹⁻⁵³. Recent studies in humans report similar co-
7 occurrence of hippocampal and cortical ripples during sleep and cognitive tasks ^{26,29,30}.

8 Furthermore, ripples are commonly recorded both in the epileptic and non-epileptic hippocampus
9 and neocortex ^{32,46,48,54-58} and it remains a matter of controversy whether distinct classes of
10 physiological and pathological HFOs can be separated by frequency, amplitude or any other
11 characteristic. The same term ‘ripples’ and especially ‘fast-ripple’ has thus been used to describe
12 a pathological class of events in the hippocampus and the neocortex without a clearly established
13 relationship to the physiological hippocampal-cortical interactions.

14 Altogether, classifying various gamma, ripple and fast ripple HFOs types based on anatomical
15 location, states of sleep or wakefulness, physiological or pathological roles is an even more
16 cumbersome task in human studies, where there is less mechanistic insight than in the animal
17 models.

18 **Using frequency range instead of a definite class is a more replicable** 19 **alternative**

20 What we are left with is a general category of high frequency oscillations with specific labels
21 used for approximate frequency ranges, as presented in Figure 1. Naming frequency ranges with
22 explicitly specified low- and high-end boundaries provides a more replicable and robust
23 approach than attempting to identify a distinct class of events across animal and human studies.

24 For instance, instead of labeling a given class of oscillations like ripples in humans based on the
25 sharp-wave ripple complexes in rodents, one can objectively define the ripple frequency range
26 that was used. For instance, stating that: ‘oscillations were detected in a ripple frequency range
27 (80-150 Hz)’ would be a more objective and replicable alternative to: ‘ripples were detected
28 between 80-150 Hz frequency range’. The former only claims that the detected events were
29 actual oscillations as opposed to other non-oscillatory sources of spectral power in this frequency



1 range but claims no particular class of LFP activity. The latter explicitly claims that the detected
2 events were ripples, presumably corresponding to the sharp-wave ripples in rodents, as opposed
3 to other high gamma/epsilon oscillations.

4 Definite statements about an HFO type like ripples should only be made if supported with
5 enough evidence ^{23,24,35}, e.g. concurrent detection of sharp-wave transients and micro-electrode
6 recordings of single unit spiking ^{25,34,59,60} that would correspond to the patterns reported in rodent
7 electrophysiology. For this reason, we suggest using the general term HFOs without making
8 connotations to any specific class or frequency range of oscillations - pathological or
9 physiological, unless explicitly stated. Since the gamma, ripple, and fast ripple oscillations share
10 common neuronal mechanisms of generation, it seems appropriate to refer to them with the
11 general term HFOs in particular frequency ranges. Emerging computational tools ^{61,62} and
12 analysis methods ⁶³ for automated and objective classification of various HFO types offer a
13 promising future direction for defining and differentiating distinct types of HFOs.

14 Having established the basic definitions, we will now turn to the neural correlates of HFOs and
15 set the scene for addressing the title question about their role in human engram processes.

17 **Neuronal assembly origins and mechanisms of HFO** 18 **generation**

19 **HFOs are generated by coordinated spiking of local neuronal** 20 **assemblies**

21 Early studies of HFOs in epilepsy patients using macro- and micro-contact electrodes showed
22 that oscillations recorded in the ripple and fast ripple frequency ranges are very local. Given that
23 an individual 'fast ripple' HFO (250-600 Hz) can be detected on a single micro-wire but not on
24 any of the neighboring ones in the same bundle, it was estimated that these are generated within
25 1 cubic millimeter of neural tissue ^{47,64}. The origins of these fast ripple HFOs would thus be
26 confined to a volume as small as a single cortical column, as in the case of other micro-scale
27 electrophysiological discharges recorded both in people with epilepsy and in some cases patients
28 with chronic pain and no history of epilepsy ⁶⁵.



1 HFOs are thought to be generated by neural ensembles coordinated together at a range of local
2 anatomical scales and network architectures, and detected in the field potentials sampled with
3 micro-, meso-, or macro-electrode contacts (Fig. 2). A smaller and more local ensemble confined
4 to a single cortical column would generate an HFO in the higher frequencies of, e.g., the fast
5 ripple range, detected only on a single micro-contact, whereas a gamma-frequency HFO
6 originating from a larger ensemble more widely spread across cortical columns (Fig. 3A) would
7 be detected on several micro- and on macro-contacts⁶⁶⁻⁶⁸. This gradation of anatomical scale
8 along the frequency range of HFOs, starting from ‘macro’ oscillations on the low end through to
9 ‘micro’ electrophysiological activity on the high end, fits into the picture of bridging network
10 oscillations and single unit activities (Fig. 1).

11 On the micro-scale of single neurons, it is known that HFO generation is associated with distinct
12 firing patterns of inhibitory interneurons that gate firing of the excitatory pyramidal cells. The
13 original studies of ripple and fast ripple HFOs in epilepsy patients showed synchronized firing of
14 neurons around the amplitude peaks^{47,59,69} that were found to be phase-locked to the cycle of the
15 HFO. This coordinated firing to the phase of a given ripple HFO was observed among a large
16 proportion of excitatory pyramidal cells^{25,29,60}, which was preceded by bursts of interneuron
17 firing⁵⁹. Analogous pattern of firing was reported in rodents⁷⁰ - pyramidal cells were spiking at
18 the negative phase of the oscillation with the preceding inhibitory cell rhythmic firing matching
19 the ripple frequency.

20 In addition to this ‘in-phase’ mechanism of generation, HFOs in the ripple and fast ripple
21 frequency ranges can be generated through ‘out-of-phase’ population firing^{71,72}, which explains
22 the emergent HFO frequencies beyond the limits of the refractory periods of individual neurons.
23 Separating these different mechanisms may not be possible using spectral methods, but should be
24 feasible with high-density microelectrode recordings of the underlying neuronal spiking, like in
25 case of laminar multielectrode arrays across the superficial and deep cortical layers⁷³.

26 Rodent studies using optogenetic activation or silencing of specific types of cells showed that
27 local activation of a small group of excitatory cells is sufficient to induce ripple HFOs artificially
28⁷⁴. A similar HFO induction was achieved by locally activating parvalbumin-positive
29 interneurons, which resulted in the phase-locking of neuronal spiking and induction of gamma
30 oscillations^{75,76}. Hence, even though the original human studies were performed in people with



1 epilepsy, the cellular mechanisms agree with the physiological origins unveiled in these rodent
2 studies. Recent investigations of physiological firing patterns underlying ripple HFOs during
3 human memory and cognitive processes ^{25,29,30,60} confirm this coordinated neuronal spiking to
4 specific phases of the oscillation.

5 The origins of any one HFO can, therefore, be traced to coordinated firing of a subset of neurons.
6 In contrast to the sharp-wave bursts, which are driven by synchronized firing across a large
7 number of neurons in a given population, the ripple oscillation itself involves only a
8 subpopulation of cells ^{44,45,77}. The coordinated firing of the cells underlying HFOs, aka the neural
9 ensembles or assemblies, can be sampled in the extracellular field potential at various spatial
10 scales, depending on the electrode contact type used (Fig. 3A). For example, HFOs in the fast
11 ripple range were found to be more local and confined to even a single micro-contact compared
12 to the equivalent events detected in the ripple frequencies on two or more contacts ⁶⁴. On the
13 other side of the scale, oscillations in the gamma and ripple frequency ranges are commonly
14 detected simultaneously on several micro- and macro-contacts sampling from much wider
15 volumes of neural tissue compared to more local fast ripples ^{64,66}.

16 **HFOs are detected as bursts of spectral power in discrete frequency** 17 **range and duration**

18 Several distinct HFOs are typically detected on an electrode contact in different frequency
19 ranges. An example is presented in Fig. 3B with four HFO detections in the gamma and
20 epsilon/ripple frequencies. Each has a discrete duration, lasting typically between 20-50 ms and
21 centered around a particular peak-amplitude frequency (marked in blue), with exception of non-
22 oscillatory detections that span a broad range of frequencies (red). The former (oscillations) can
23 be observed in the unfiltered raw signal, whereas the latter are associated with a sharp transition
24 in the filtered signals (Fig. 3B). Such broadband increases of high-frequency power can result
25 not only from the sharp transitions in the signal (e.g. interictal epileptiform spikes) but also from
26 other sources, including muscle, eye-movement and blinking artifacts ⁷⁸⁻⁸², or neuronal firing
27 ^{39,40,83}. Individual HFO detections, on the other hand, result in a confined increase in power
28 around a narrow span of the peak-amplitude frequency. They can be described as discrete bursts
29 of oscillation lasting at least 4 cycles ^{46,66,84} that occur spontaneously or in response to, e.g.,
30 cognitive stimulation.



1 The HFO bursts were first shown in the human cortex in response to presentation of visual
2 stimuli ^{32,85}. Analogous bursts were associated with working memory performance in non-human
3 primates ^{86,87}. Most of the physiological HFO detections were found to have the same properties
4 of discrete bursts, which were distinct from the ones with a broad frequency span ^{32,33} like the
5 example in red from Fig. 3B.

6 **Bursts of HFO power are physiologically distinct from broadband** 7 **power increase**

8 It is important, however, to distinguish the actual bursts of physiological oscillations from other
9 sources of increased power in the high-frequency ranges mentioned above ^{23,24,34}. Spectral power
10 across these ranges is known to generally correlate with neuronal firing ^{37-40,60,81,82,88}. This firing
11 may not necessarily be related to an actual oscillation like in the case of phase-locking of action
12 potentials to ripple HFOs. Spikes of action potentials in a signal can result in an increase of
13 spectral power across a wide range of frequencies, including gamma and even lower EEG bands
14 ⁸³. Although micro-contact recordings of the local field potential are especially affected by this
15 phenomenon, given that the sharp waveforms of action potential spikes are recorded in these
16 high-impedance signals, this so-called ‘spike-bleeding’ can also affect macro-contact recordings
17 but may be removed by detecting broad frequency spans of increased spectral power or phase-
18 coupling to slower oscillations ^{33,83,89}.

19 A recent study in the macaque visual cortex identified two distinct sources of increased power in
20 the high gamma frequency range in response to light flash stimulation⁹⁰: initial ‘early’ neuronal
21 firing in deep cortical layers and ‘late’ dendritic field potentials in the superficial layers. This
22 finding in non-human primates is reminiscent of the findings in the human visual cortex using
23 word names displayed on the screen for memory encoding ³³. Even though the human study was
24 limited to macro-contact recordings, it could still separate an early increase in detections with a
25 broad frequency span on individual trials, which could correspond to enhanced neuronal firing in
26 response to stimulus presentation. This early response was followed by a later more gradual
27 increase in HFO detections with a confined frequency span centered around the peak power of
28 each detection. The latter oscillatory detections outnumbered the former non-oscillatory power
29 increases in the low gamma band. This disproportion was gradually decreasing with more events
30 of broad frequency span detected in the high gamma and epsilon ranges ³³. Ripple and fast ripple



1 frequency ranges would contain proportionally more non-oscillatory power increases, which is
2 expected as the frequencies approach the ranges used for detecting single unit action potentials
3 (> 600 Hz). The oscillatory and non-oscillatory components can be separated based on the
4 spectrogram characteristics of each detection^{33,83}.

5 It does not mean, however, that action potential firing is not contributing to the oscillatory
6 events. Both local dendritic currents and action potentials from cells as far from the recording
7 micro-contact as >0.1 mm were found to contribute to the power of ripple oscillations in rodents
8⁹¹. In humans, a recent careful examination of power increases in 80-120 Hz range recorded on
9 macro-contacts in the temporal cortex confirmed that these comprise several individual HFO
10 bursts detected on micro-contacts, which, in turn, are related to bursts of coordinated action
11 potential firing⁶⁰. On the micro-scale, these results are congruent with the original studies in
12 human epilepsy, concluding that subsets of excitatory pyramidal cells would synchronize their
13 spiking at specific windows of inhibitory cell firing^{47,59}, locking to a particular phase of the
14 oscillation.

15 **Individual HFO bursts can be used to trace specific neural** 16 **assemblies?**

17 The results by Tong et al.⁶⁰ reconcile the previous observations that increased power across a
18 broad range of frequencies is composed of multiple HFO bursts detected at discrete frequencies
19^{32,33,85}. In Figs 2 and 3 we summarize the general mechanism from micro-scale ensembles of
20 firing neurons, through bursts of individual HFOs detected in particular trials at specific
21 frequencies, to the resultant trial-averaged enhanced power across a broad frequency range.
22 Coordinated firing in response to a stimulus presentation gives rise to HFOs at particular
23 frequencies depending on the size and spread of the underlying neural ensemble (Fig. 3A, C).
24 Other ensembles generate HFOs at particular frequencies in response to stimuli on subsequent
25 trials. Eventually, multiple trials result in a uniform shift in power across a broad frequency
26 range of the spectrum relative to a pre-stimulus baseline (Fig. 3C). Detections from specific trials
27 can be displayed together as points at their corresponding peak-amplitude on a cumulative time-
28 frequency plot, producing a pattern closely overlapping with the trial-averaged power
29 spectrogram (Fig. 3D).



1 This is an explanation for the resultant broadband shift in power across the high-frequency
2 spectrum associated with cognitive and motor tasks and increased neural firing ^{92–95}, which
3 argued against oscillations at particular frequency bands. If the intermediate step of detecting
4 individual bursts of oscillations on a trial-by-trial basis is skipped, the overall trial-averaged
5 power will be most highly correlated with general firing rates in the entire neural population
6 without any common temporal pattern or coordination to oscillations. If, however, independent
7 constituent bursts of oscillations and the underlying firing in subsets of neural ensembles are first
8 resolved one-by-one, then multiple patterns of coordinated activity emerge. In this large-scale
9 mechanism, coordinated electrical activity from multiple neural sources generating oscillations at
10 distinct frequencies could explain the broadband shifts in power across the spectrum ²⁴. Separate
11 sources of HFO bursts detected at various frequencies remain to be demonstrated on the macro-
12 and micro-recording scales.

13 Assuming that individual HFOs can indeed be separated based on their spectral features ^{96–98}
14 and thus identify particular sources of LFP activities, it should be possible to resolve the
15 neurophysiological substrates of memory and cognition proposed in our title question. High
16 frequency LFP activities were suggested to track particular neuronal assemblies on the level of
17 micro-contact local field potential in rodents ⁹¹. Intracranial recordings in non-human primates
18 ^{86,87} and in human patients ^{22,32,85} can also resolve distinct bursts in the frequency-time space of
19 individual trials, which could hypothetically be the features of particular neuronal assemblies ²⁴.
20 HFO bursts beyond the ripple frequency range, which were shown to be generated very locally
21 on the scale of a single cortical column ⁶⁴, would correspond to arguably the fundamental level of
22 neural organization and information processing ⁹⁹. In the next section, we will review the roles of
23 temporal coordination in gamma and higher frequencies in supporting processes of memory and
24 cognition.

25

1 **A fundamental role of high frequency oscillations in memory** 2 **and cognitive processing**

3 **Synchrony and oscillations in high frequency ranges are pivotal to** 4 **the neuropsychological models of neuronal assemblies**

5 The temporal coordination of neuronal firing was originally proposed to explain cognitive
6 processing in neuropsychological theories developed by Jerzy Konorski¹⁰⁰ and Donald Hebb¹⁰¹.
7 They envisioned that neurons that are active at the same time will develop connections and form
8 assemblies, which inspired the famous phrase: ‘cells that fire together, wire together’ and
9 introduced the concept of synaptic plasticity. Thus, assemblies would synaptically connect
10 together cells that encode the same stimulus like in case of the concept cells^{8,16–18}. One of the
11 first pieces of experimental evidence for such temporal coordination was reported in the cat
12 visual cortex, where neurons responding to the same visual features of the presented stimulus
13 would synchronize their firing to provide a unified representation of the attended stimulus,
14 leading to the idea of binding various sensory features by synchrony or temporal correlation^{102–}
15¹⁰⁴. In other words, neurons that encode features of the same stimulus correlate their firing in
16 time and form distinct assemblies, which were shown to oscillate at gamma frequencies in these
17 pioneering experiments. The assemblies of neurons co-firing with gamma rhythmicity would
18 also be organized into cortical columns⁹⁹ that were particularly well mapped in the visual cortex.
19 These seminal research studies led to several hypotheses about the role of oscillations in the
20 gamma frequencies that have remained a topic of interest and some controversy^{105,106}.

21 We already mentioned the role in sensory object representation, which was also described as
22 perceptual binding¹⁰⁷. Since these oscillations are not limited to sensory cortical areas, a more
23 general role in integration and communication of information processing across the brain was
24 proposed^{108–110}. Integrating information processing across the sensory and higher order
25 association areas is especially important for cognitive functions like attention or working
26 memory¹¹¹, where interplay with low frequency oscillations particularly in the theta frequency
27 band is pivotal^{112–115}.



1 Taken together, these hypotheses point to a fundamental role in cortical computations ¹¹⁶ that
2 presents a tangible substrate for the information processing and synaptic plasticity foreseen in the
3 original neuropsychological theories of Konorski and Hebb. This fundamental role may extend to
4 high frequency oscillations in general. The HFO bursts in the gamma ranges of the spectrum last
5 approx. 50-200 ms of temporally coordinated firing activities among the underlying neural
6 assemblies, which was proposed to constitute the basic units or ‘packets’ of cortical information
7 encoding ^{117,118} and a sufficient pattern for inducing synaptic plasticity ^{119,120}. Hence, an
8 individual HFO burst may provide a viable unitary event for cognitive processing, congruent
9 with the proposed anatomical substrate of neuronal assemblies ¹²¹ at the scale of a cortical
10 column.

11 **Synchronous and asynchronous high frequency LFP activities need** 12 **to be considered and reconciled**

13 This fundamental role may only apply to the actual oscillatory events as opposed to other non-
14 oscillatory sources of high-frequency power. There has been an on-going debate whether the
15 electrophysiological signals recorded in the gamma frequency range and above comprise
16 temporally coordinated ‘synchronous’ or stochastic ‘asynchronous’ LFP activities ^{95,97}. In the
17 light of the above-mentioned explanation of multiple discrete oscillations and their underlying
18 distinct assemblies that together give rise to a broadband increase in power across entire neural
19 populations (see Figure 3), the seemingly opposite views can be reconciled within the proposed
20 large-scale frame of reference. At the micro-scale of neuronal assemblies generating individual
21 HFO bursts, as measured in the cat visual cortex or in people with epilepsy, the temporal
22 coordination of firing to specific phases of one oscillation can easily be detected and quantified.
23 On the other hand, this can be much harder on the macro-scale with a multitude of assemblies
24 each coordinated to a different oscillation. A plausible explanation proposed that there is no one
25 global ‘clock’ or ‘metronome’ at the macro-scale of LFP activities that comprise various distinct
26 assembly units each synchronized locally¹²². Hence, the scale at which a given signal is recorded
27 needs to be considered and caution applied when dissociating HFO bursts from other LFP
28 activities.

29 Evoked responses to stimulus presentation are one example of non-oscillatory
30 electrophysiological activity. Although neural mechanisms of the evoked and induced responses



1 were shown to be related ¹²³, the former is known to occur first with short latencies and ‘locked’
2 in time to stimulus presentation and the latter occurs at longer latencies not ‘locked’ to the
3 stimulus. Induced responses in the EEG gamma frequency range were demonstrated by Tallon-
4 Baudry and colleagues at around 280 ms latency from stimulus presentation and were modulated
5 by perceptual binding of its visual features into coherent representations of illusory or real
6 triangles, which was not observed for the evoked responses around the same latencies ¹²⁴. A
7 similar study was conducted with intracranial EEG recordings showing that the evoked responses
8 were more stereotypical with a constant latency of approx. 100 ms from stimulus onset, in
9 contrast to the induced responses in the gamma frequencies that varied from 200 to 500 ms on a
10 trial-by-trial basis ⁸⁵. Compared to the evoked response, the induced bursts of gamma oscillations
11 were detected at various latencies, frequencies and amplitudes on a given trial, as shown in this
12 and subsequent studies ^{32,33,86,87}. One of these subsequent studies dissociated the actual HFO
13 bursts from other non-oscillatory detections with a broad frequency span and found that only the
14 latter were phase-locked to the evoked response ³³, even though both correlated with amplitude
15 of the evoked response potential. This confirms that the two response types are related to
16 common neural mechanisms but are qualitatively different and separable ¹²³. In contrast to the
17 evoked response, the HFO bursts are induced at various magnitudes (related to the total number
18 and amplitude of each detection), at a range of frequencies (around the peak amplitude of each
19 burst), and at different latencies on any one trial depending on a given brain region.

20 **Spatiotemporal dynamics of high frequency power tracks cognitive** 21 **processing across the brain**

22 Across the brain, there is a temporal pattern of the induced responses following an anatomical
23 order of brain regions, where HFO bursts are induced along a hierarchical sequence of
24 information processing. In response to visual stimuli, they are first induced in the primary visual
25 areas of the occipital cortex, followed by higher order sensory processing areas in the ventral
26 visual stream, hippocampus and amygdala, and finally induced with the longest latencies in the
27 association areas of the temporal and prefrontal cortex ³². Studies that used broadband gamma
28 power as a general index of neural activation confirmed this hierarchical sequence of induced
29 LFP activities in the gamma frequency range ^{125–128}, proceeding from an early sensory stages in
30 the posterior anatomical areas through to late association stages all the way to the most anterior



1 areas of the frontal pole (Fig. 4). When this broadband, trial-averaged response is visualized on a
2 universal brain surface it gives an impression of a ‘wave’ of information processing sweeping
3 through the cortical surface in a posterior-to-anterior direction⁹⁸. This ‘wave’ of high-gamma
4 spectral power was found to be induced independent from similar waves observed earlier in the
5 lower frequency bands^{98,129} and showed characteristic properties along the processing stream. Its
6 amplitude was the highest in the beginning of the stream, where the latencies were the shortest
7 with small variance, and decreased gradually toward the most anterior ends, where the latencies
8 were the longest with a greater variance (Fig. 4B). Overall, the high-gamma power responses
9 become less stereotypical proceeding from early to late processing in the stream, which is
10 explained by the greater trial-by-trial variance in latencies of behavioral responses in a task.

11 Not all cortical areas show these induced responses - the exact localization depends on stimuli
12 and tasks applied. The example in Fig. 4 used visually presented words as stimuli, in a task for
13 subsequent memory recall - the identified areas with the greatest response on trials with
14 successfully remembered words relative to the forgotten ones were localized in the visual areas
15 processing word shapes, like the lingual gyrus of Brodmann areas 19 and 20 (Fig. 4c-d); even
16 greater magnitude of the induced responses predicting successful memory performance were
17 found in the language processing areas of the left lateral prefrontal cortex anterior to the Broca’s
18 field^{98,127,130}. Therefore, even this broadband power signal averaged across a wide range of high
19 frequency LFP activities (typically 60-150 Hz) can accurately track and localize cognitive
20 processing across the brain. It has been one of the main signals for mapping not only cognitive
21 but also other sensory and motor processes^{24,131–133}, being highly correlated with blood
22 oxygenation in active brain regions detected by neuroimaging methods^{134–137}. Hence, the high
23 frequency power has been used as a general index of neuronal firing to map discrete regions
24 involved in sensory, cognitive or motor functions.

25 **What cognitive processes are reflected by the high frequency LFP** 26 **activities?**

27 High frequency LFP activities can tell us more than just map areas of increased neuronal firing
28 and blood oxygenation when processing stimuli or executing motor commands. For instance,
29 broadband power in the high gamma frequency range induced in distinct areas of the association
30 cortex reflects higher-order cognitive processes. It was associated with conscious visual



1 awareness of stimuli presented in a perception task, in contrast to the same LFP activities
2 recorded in the sensory visual areas ¹³⁸. A similar example is perception of the dreaming contents
3 during sleep ¹³⁹. Hence, it is not only a general spectral feature of neural activation or
4 information processing in each brain area, but a signal of actual cognitive processes related to
5 ongoing mental states.

6 Even in the sensory areas this signal is well known to be modulated by attention, visual
7 awareness, and vigilance states. At its fundamental level of the individual HFO bursts, a recent
8 study in the primate visual cortex showed that the rate of bursting was modulated by the stimulus
9 properties and attention to a given receptive field ¹⁴⁰, linking ripple-frequency HFOs with goal-
10 directed perceptual processes. The original studies in humans showed that the rate of induced
11 HFOs was different in response to emotionally charged versus neutral or familiar versus new
12 stimuli ^{22,32} across all cortical areas. There are also more HFO bursts induced in the visual cortex
13 on trials with stimuli that were subsequently remembered compared to the ones that were
14 forgotten ³³ - a phenomenon known as the ‘subsequent memory effect’ ¹⁴¹. The occurrence and
15 number of HFO bursts is therefore associated with memory and cognitive processes and may
16 explain the effects observed on the level of averaged broadband power.

17 What process then does an individual HFO burst reflect? So far, we have established that they
18 are generated at a microscale of coordinated local neural assemblies, which in case of the
19 frequencies beyond the ripple range could be contained within volumes of a single cortical
20 column. The bursts are induced with activation of particular brain regions in response to, e.g.,
21 sensory stimulation at various latencies and peak-amplitude frequencies. On the macroscale of
22 brain regions, they follow a hierarchical order or sequence of information processing and are
23 associated with memory and cognitive functions, which modulate the rates of their occurrence.
24 In the final part of this article, we will address the title hypothesis that the bursts reflect a basic
25 engram process.

26



1 **A neurophysiological substrate of engram processing?**

2 **HFOs are associated with encoding and recall of human memories**

3 Engram is defined as a neural substrate responsible for storing and recalling a memory trace ¹⁴².
4 Then, the basic requirement for an engram activity is to manifest at the time of encoding and
5 recalling memory - there are multiple activities engaged during encoding or recall of a memory
6 but only the ones that are consistently present in both can be specific to engram processing. If we
7 thus follow assumptions of the Konorski-Hebb theories that neural assemblies provide feasible
8 substrates for engrams, then their coordinated electrophysiological activities, emerging from
9 coincident neural firing, could be traced as a feature of an engram process. HFO bursts would be
10 a suitable candidate for such a spectral feature of coordinated firing as engrams are formed and
11 reactivated when memories are encoded and recalled.

12 Our original studies in epilepsy patients ^{32,33} showed that bursts of HFOs in the gamma and
13 higher ranges are induced during encoding and recall of memorized stimuli. The studies in
14 primates ^{86,87} detected them also throughout delay phases of a working memory task, suggesting
15 that memory traces for memorized stimuli are maintained in the form of such discrete
16 synchronous events rather than continuous neuronal firing ¹⁴³. Still, this is not enough to claim
17 that an HFO burst underlies an engram activity for a specific stimulus.

18 A series of recent studies in epilepsy patients shed light on the hypothetical engram activity.
19 Inspired by the role that sharp-wave ripples in rodents play in forming and retrieving memories
20 for places ^{52,53,144,145}, Norman and colleagues showed that ripple HFOs, which are induced in the
21 hippocampus in response to presentation of images, are then re-occurring immediately preceding
22 spontaneous recall of the remembered ones ²⁸. This spontaneous (not stimulus-induced) increase
23 in the HFO rate before recollecting a memory was specific to images that induced more bursts
24 during encoding - only those images that were presumably 'well' encoded or attended were
25 subsequently freely recalled (the subsequent memory effect) heralded by an increased rate of
26 bursting. Although the authors did not resolve individual HFO bursts in the neocortex, they
27 found that broadband power in the high gamma range coincided with the ripple bursts in the
28 hippocampus and used them to match the encoding and recall patterns for specific images
29 remembered.



1 Vaz and colleagues found in a similar study with epilepsy patients that neocortical HFOs in the
2 anterior temporal lobe are underpinned by sequences of neuronal spiking, which are repeatedly
3 detected during encoding, throughout delay, and before recall of word stimuli²⁵. The sequences
4 of spiking, which was locked to phases of the burst oscillation, were specific to the word stimuli
5 remembered and predicted failed memory performance when the order of a sequence was
6 disrupted. This is the first study to show in humans that HFO bursts of sequential neuronal firing
7 are replayed in the neocortex with encoding, maintenance and retrieval of remembered stimuli,
8 like in case of the rodent hippocampal sharp-wave ripple recordings¹⁴⁶⁻¹⁵⁰. The authors found
9 that these neocortical bursts of coordinated sequential firing are preceded by HFOs in the
10 hippocampus, which explains at a finer resolution the coupling between hippocampal HFOs and
11 neocortical high gamma power reported in the study by Norman *et al.*^{27,28} Strength of this
12 hippocampal- neocortical HFO coupling predicted successful memory retrieval. Taken together,
13 during memory performance HFO bursts reflect phase-locked sequential neural firing
14 coordinated in time between hippocampus and neocortex that is specific to particular memory
15 items and indicative of their successful retrieval.

16 **Memory-related HFOs are observed across widespread cortical** 17 **areas during wakefulness and sleep**

18 Since engrams are formed not only ‘online’ during memory performance but also ‘offline’ when
19 memories are stored and consolidated, an engram activity should be detected also during resting
20 wakefulness or sleep when they are reactivated as we think or dream about a particular memory.
21 Coordinated hippocampal-cortical HFO bursting has now been reported also outside of task
22 performance throughout states of wakefulness and sleep^{29,30}. Dickey and colleagues first
23 characterized ripple HFOs detected during non-REM sleep in terms of their anatomical location
24 in the neocortex and their detection rates, as well as the duration, peak frequency and amplitude
25 of each detected burst²⁹. Their findings were in agreement with the previously reported detection
26 rates and general properties like amplitude, duration, and oscillation frequency of individual
27 cortical HFO bursts during memory performance^{32,85}.

28 More importantly, the study provided more in-depth and detailed insight into their neuronal
29 mechanisms and possible roles in memory consolidation. The authors detected the ripple bursts
30 and the underlying neuronal firing during sleep and wakefulness across all cortical areas, though



1 less densely in the association cortex. One of the previous studies showed that these general rates
2 can be modulated by cognitive states with more bursts detected in the sensory areas during
3 encoding of stimuli than during recall and, *vice versa*, more in the association areas during recall
4 than during encoding³². Dickey and colleagues did not focus their study as much on the state
5 modulation but rather provided exquisite detail of the neurophysiological mechanisms of each
6 burst, demonstrating phase-locking of putative pyramidal and interneuron spiking to the high-
7 frequency oscillation, which is consistent with the previously proposed mechanism of HFO
8 generation^{47,64,151}. This coordinated timing of neuronal firing was concluded to be ‘optimal’ for
9 facilitating neuronal plasticity, as reported for the hippocampal sharp-wave ripples^{119,120}, and
10 thus ideally suited to support memory and cognitive functions required for an engram activity
11 during both ‘online’ encoding and recall, and ‘offline’ storage and consolidation of memorized
12 information.

13 In a parallel study, Dickey and colleagues reported more evidence for the essential role of the
14 hippocampal-cortical ripple bursts in the hypothetical engram processes³⁰. They report that the
15 ripple bursts detected across multiple cortical areas or even hemispheres co-occur together,
16 phase-locking with a consistent lag. Interestingly, the neocortical bursts co-occurred with the
17 hippocampal ripple HFOs as well but were not phase-locked to these oscillations, suggesting that
18 the phase-locking is mediated by more direct cortico-cortical connections. This precisely
19 synchronized bursts of neural co-firing was increased preceding memory recall, making the
20 authors suggest that their observations support the hypothesis for the role of synchrony in
21 retrieval of particular memories and, more generally, the role in binding perceptual and
22 mnemonic representations^{102–104}. All in all, the burst co-firing was detected both during ‘online’
23 retrieval of memories and ‘offline’ during wakefulness outside of any task and in sleep, making a
24 compelling case for a viable engram activity reflecting encoding, retrieval, as well as the storage
25 and consolidation processes.

26 **The role of HFOs in consolidation of human memories remains to be** 27 **directly tested**

28 The studies by Dickey et al.^{29,30} and Vaz et al.^{25,26} contributed unprecedented detail to the neural
29 mechanisms for possible roles that HFO bursts could play in ‘online’ and ‘offline’ memory
30 processing. However, none of these have directly tested their roles in the engram storage and



1 consolidation. One of the first studies to investigate the ‘online’ and ‘offline’ role of ripple HFOs
2 in human memory consolidation found that the hippocampal and cortical HFO bursts predicted
3 post-sleep recall of memory items, which were encoded before sleep ³¹. This and subsequent
4 studies confirmed that the hippocampal-cortical HFO bursts are not only coordinated to each
5 other but are also coupled to delta slow-wave oscillations and cortical sleep spindles ^{29,31,152,153}.
6 This temporal coupling provides mechanistic evidence for the classic theories of how memories
7 are transferred, stored and consolidated between the two structures in sleep and quiet
8 wakefulness ^{154–157}. In rodents, the hippocampal and neocortical coupling of HFO bursts was
9 shown to be strengthened during post-learning sleep and suggested to mediate transfer of
10 memory traces across the two structures ⁵⁰. Disrupting this transfer process ‘online’ or ‘offline’
11 with optogenetic or electrical stimulation is known to slow down learning and interfere with
12 retrieval and consolidation processes ^{51–53}. Comparable causal evidence remains to be
13 demonstrated in humans with direct electrical stimulation to either interfere or enhance memory
14 processing ^{4,158,159}. So far, the engram processes proposed for the HFO bursts have not been
15 directly tested in humans.

16 **Hypothetical neurophysiological correlates of engrams await further** 17 **verification**

18 In the animal models, the engram research has predominantly focused on the cellular and
19 molecular substrates and mechanisms of synaptic plasticity ^{160–162} with very impressive
20 demonstrations of manipulating, silencing or even *de novo* generation of ‘artificial’ memories.
21 Pharmacological and imaging experiments in humans corroborate similar dynamics and
22 manipulation of engram formation and consolidation ^{163,164} but evidence for analogous cellular
23 and molecular substrates remains to be provided. How these basic cellular mechanisms relate to
24 the electrophysiology of LFP activities remains elusive. One problem in linking the cellular
25 mechanisms with the electrophysiological activities is that the former are spread across large
26 neural populations distributed throughout the entire brain whereas the latter are sampled only in
27 selected spatially confined areas of electrode contact implantation. A recent study in mice
28 showed that almost half of all cortical and subcortical brain regions studied revealed molecular
29 markers related to encoding of one memory trace, which were then reactivated during recall in
30 another half of these ¹⁶⁵. Hence, a quarter of the studied regions participated in the formation and



1 reactivation of a single engram. The other quarter that was originally activated was not specific
2 to the engram processes but related to non-specific sensory and other processes. Hence, the
3 molecular activity was not specific to the engram processes selectively. In the same manner,
4 HFOs can serve as a non-specific electrophysiological activity to track engram processes under
5 particular definitions of memory encoding and recall.

6 Another problem is that within any one of these regions the configuration of engram cells may
7 differ between memory encoding and recall. Electrophysiological recordings in rat hippocampus
8 and prefrontal cortex performing a spatial working memory task showed that neural assemblies
9 of cells firing together during encoding of either left or right lever are not the same as the
10 assemblies reactivated during delay or recall of the lever position ¹⁴³. Nevertheless, the large-
11 scale recordings of HFOs can potentially provide a less variable engram signal in time and space
12 than the molecular or the electrophysiological activity of single cells.

13 In an ideal scenario, there would be one assembly of engram cells that is first active during
14 encoding of a memory and then reactivated during its maintenance and recall. That assembly
15 would generate HFOs detected at a consistent frequency and amplitude by a recording electrode
16 contact. However, the engram activities appear highly dynamic in terms of their spatial
17 localization in the brain, distance from the recording contacts, and across time of memory
18 processing. The emerging neurotechnologies are only now making it possible to investigate
19 engram stability over longer periods of time as new cells join and leave particular neural
20 assemblies ¹²¹. HFO localization was also shown to be dynamically changing with time even in
21 the case of mapping epileptic discharges in the brain ¹⁶⁶. Memory and cognitive processes would
22 arguably turn out to be much more dynamic and distributed across the brain. Tracking these
23 highly dynamic bursts at a large-scale of LFP activities across anatomical space of the brain and
24 chronically over time holds promise for capturing the underlying aberrant engram assemblies.

25 **Conclusions, outstanding questions and future perspective**

26 **Global sequences of HFO bursting are analogous to synfire chains of** 27 **single unit spiking**

28 In this review we have summarized the current evidence for HFOs supporting engram processes.
29 Oscillations in these high frequency ranges meet the basic requirements for a fundamental



1 unitary activity that would coordinate assemblies of connected cells underlying the remembered
2 information. They can be detected within a micro-scale of single cortical columns or on a macro-
3 scale of multiple neighboring electrode contacts in case of the fast ripple and gamma frequency
4 bursts, respectively. On the micro-scale, these oscillations are aligned with spiking of neuronal
5 assemblies that underlie encoding and recall of specific memorized stimuli. On the macro-scale,
6 the bursts contribute to the spectral power induced across sensory and higher order association
7 areas as the visual, semantic or affective features of the remembered stimuli are processed.

8 This large-scale mechanism is summarized in Figure 5A, starting with a macro-scale view of the
9 spectral power from multiple underlying meso-scale sources, which is propagated across
10 occipital, temporal and frontal lobes. Each of these sources can theoretically be traced to neural
11 assemblies connected on a micro-scale of individual cells that participate in processing (and
12 binding?) sensory, semantic and affective features of an engram. The latest HFO studies show
13 concurrent detection of ripple frequency bursts between multiple sensory and higher order
14 association areas in the neocortex and the hippocampus^{29,30}. These brief bursts of firing with
15 coordinated timing across multiple areas provide an ideal substrate for supporting multisensory,
16 abstract engram representations in the human brain and mind.

17 Exactly how such large-scale HFO burst dynamics would operate is an open question. One
18 possibility is that they would form synfire chains analogous to the ones described for neuronal
19 spiking¹⁶⁷. In this scenario, each burst could be treated like a point process analogous to an
20 action potential²² but viewed on a macro scale like in Figure 5. HFOs detected at the same time
21 on selected contacts from multiple cortical areas as memories are recalled (Fig. 5) would reflect
22 sequences of spike firing observed on micro-scale of a single area²⁵. We are now positioned to
23 test these hypothetical mechanisms in the new large-scale, high-density, human brain recordings
24 with combined macro-, meso- and micro-electrode contacts during memory tasks. These
25 recordings present a unique opportunity to track such basic electrophysiological activities and
26 ascribe them to the mental processes engaged in the formation and retrieval of memory items.



1 **Are pathological and physiological HFOs reflecting the same** 2 **underlying processes?**

3 One challenge is that the human recordings are mostly performed in people with epilepsy, which
4 are known to generate pathological HFOs. Distinguishing the pathological and physiological
5 bursts has been an on-going quest with various states of sleep, quiet wakefulness and cognitive
6 performance proposed as viable approaches to separate them^{55–57,168–170}. Another approach is to
7 treat both as the same process that has been ‘hi-jacked’ in epilepsy pathophysiology but,
8 otherwise, involves common neural substrates and mechanisms. For example, we proposed that
9 the mechanisms of memory consolidation ascribed to ripple HFOs are engaged in the process of
10 developing neural assemblies that underlie seizure generation¹⁷¹. Whether such ‘seizure
11 engrams’ utilize common electrophysiological and synaptic mechanisms as those involved in
12 memory processing remains to be established. There may be some HFO discharges that are
13 specific only to epilepsy pathophysiology like the ultra-fast high frequency oscillations¹⁷²,
14 which were found almost exclusively in the areas associated with seizure generation. Where is
15 the upper frequency boundary for the memory-related HFOs is another outstanding question with
16 no clear answer so far.

17 **One HFO burst: one memory trace?**

18 Finally, a key question for the engram hypothesis is whether a given HFO could track a
19 particular memory? Would it be specific to an engram or other non-specific process? Would it be
20 one or more neural assemblies encoding a memory or several supporting multiple related
21 memory traces? Would concept cells participate in the assemblies and their HFO generation and
22 make them more specific? Would each assembly generate bursts at the same frequency
23 consistently in time and anatomical location? An assembly of a given size could in theory
24 oscillate together at a consistent resonant frequency, providing a signature frequency for the
25 encoded information. In practice, however, the highly dynamic nature of neural assemblies with
26 some cells joining and some leaving¹²¹, as memories are consolidated and reconsolidated over
27 time¹⁷³, makes it virtually impossible to track particular engrams with HFOs. They are, arguably,
28 still a better feature than individual spiking cells in terms of their accessibility to record over a

1 large scale of electrophysiological signals, which are more stable and resistant to chronic
2 biophysical changes at the recording site of an electrode contact.

3 Such considerations are critical for a potential use as features in brain-computer interfaces ¹⁷⁴ to
4 track and modulate memory processing. Our knowledge of how a given HFO can be traced to
5 remembered stimuli is very limited compared to neuronal spiking. For example, it is known that
6 individual concept cells can specifically encode an abstract representation ¹⁷ or that neural
7 populations can sparsely encode specific stimulus features ^{5,16} but less is known about HFOs ²².
8 Would there be a ‘core’ neural assembly that participates in encoding most stimuli of the same
9 type, e.g., words, or would there be separate assemblies for each word with some or no overlap
10 between assemblies? These questions present testable predictions about the anatomical
11 localization of HFOs detected on micro- or macro-scale, about their consistency of detection
12 across words, and maybe even their characteristic frequencies. Predictions like that can be
13 directly tested with brain stimulation to impair or enhance particular engrams as performed in the
14 rodent cellular studies. The currently available experimental evidence is yet to show whether
15 HFOs could be the neurophysiological substrate to track the human engrams.

16 **Acknowledgements**

17 Sathwik Prathapagiri provided material from his doctoral studies at the Gdansk University of
18 Technology for plotting the final rasterplot example in Figure 5. The authors would like to thank
19 Prof. Joshua Jacobs from Columbia University for providing comments for this manuscript.
20

21 **Funding**

22 This research was funded in part by the National Science Centre, Poland, grant Opus LAP
23 number: 2020/39/I/NZ4/02070 and by the Gdansk University of Technology IDUB grant
24 ARGENTIUM. J. C., M. B. and G.A.W. were additionally supported by the Gdansk University
25 of Technology IDUB grant AURUM.
26

27 **Competing interests**

28 The authors report no competing interests.



References

1. Jacobs J, Kahana MJ. Direct brain recordings fuel advances in cognitive electrophysiology. *Trends Cogn Sci.* 2010;14(4):162-171.
2. Engel AK, Moll CKE, Fried I, Ojemann GA. Invasive recordings from the human brain: clinical insights and beyond. *Nat Rev Neurosci.* 2005;6(1):35-47.
3. Johnson EL, Knight RT. Intracranial recordings and human memory. *Current Opinion in Neurobiology.* 2015;31:18-25. doi:10.1016/j.conb.2014.07.021
4. Johnson EL, Kam JWY, Tzovara A, Knight RT. Insights into human cognition from intracranial EEG: A review of audition, memory, internal cognition, and causality. *J Neural Eng.* 2020;17(5):051001.
5. Fried I, Rutishauser U, Cerf M, Kreiman G. *Single Neuron Studies of the Human Brain: Probing Cognition.* MIT Press; 2014.
6. Lhatoo SD, Kahane P, Luders HO. *Invasive Studies of the Human Epileptic Brain: Principles and Practice.* Oxford University Press, USA; 2019.
7. Axmacher N. *Intracranial EEG: A Practice-Oriented Guide for Cognitive Neuroscientists.* Springer; 2023.
8. Suthana N, Fried I. Percepts to recollections: insights from single neuron recordings in the human brain. *Trends Cogn Sci.* 2012;16(8):427-436.
9. Kucewicz MT, Michael Berry B, Worrell GA. Simultaneous Macro- and Microrecordings. *Invasive Studies of the Human Epileptic Brain.* Published online 2018:489-499. doi:10.1093/med/9780198714668.003.0036
10. Chang EF. Towards large-scale, human-based, mesoscopic neurotechnologies. *Neuron.* 2015;86(1):68-78.
11. Chiang CH, Lee J, Wang C, et al. A modular high-density μ ECoG system on macaque vIPFC for auditory cognitive decoding. *J Neural Eng.* 2020;17(4):046008.
12. Viventi J, Kim DH, Vigeland L, et al. Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. *Nat Neurosci.* 2011;14(12):1599-1605.

- 1 13. Buzsáki G, Anastassiou CA, Koch C. The origin of extracellular fields and currents--EEG,
2 ECoG, LFP and spikes. *Nat Rev Neurosci*. 2012;13(6):407-420.
- 3 14. Parvizi J, Kastner S. Promises and limitations of human intracranial electroencephalography.
4 *Nat Neurosci*. 2018;21(4):474-483.
- 5 15. Nunez PL, Srinivasan R. *Electric Fields of the Brain: The Neurophysics of EEG*. Oxford
6 University Press, USA; 2006.
- 7 16. Rutishauser U, Reddy L, Mormann F, Sarnthein J. The Architecture of Human Memory:
8 Insights from Human Single-Neuron Recordings. *The Journal of Neuroscience*.
9 2021;41(5):883-890. doi:10.1523/jneurosci.1648-20.2020
- 10 17. Quiroga RQ. Concept cells: the building blocks of declarative memory functions. *Nature*
11 *Reviews Neuroscience*. 2012;13(8):587-597. doi:10.1038/nrn3251
- 12 18. Kamiński J, Rutishauser U. Between persistently active and activity-silent frameworks:
13 novel vistas on the cellular basis of working memory. *Ann N Y Acad Sci*. 2020;1464(1):64-
14 75.
- 15 19. Buzsáki G. Large-scale recording of neuronal ensembles. *Nat Neurosci*. 2004;7(5):446-451.
- 16 20. Buzsáki G. Rhythms of the Brain. Published online 2006.
17 doi:10.1093/acprof:oso/9780195301069.001.0001
- 18 21. McCarty MJ, Woolnough O, Mosher JC, Seymour J, Tandon N. The Listening Zone of
19 Human Electrographic Field Potential Recordings. *eNeuro*. 2022;9(2).
20 doi:10.1523/ENEURO.0492-21.2022
- 21 22. Kucewicz MT, Michael Berry B, Bower MR, et al. Combined Single Neuron Unit Activity
22 and Local Field Potential Oscillations in a Human Visual Recognition Memory Task. *IEEE*
23 *Transactions on Biomedical Engineering*. 2016;63(1):67-75.
24 doi:10.1109/tbme.2015.2451596
- 25 23. Liu AA, Henin S, Abbaspoor S, et al. A consensus statement on detection of hippocampal
26 sharp wave ripples and differentiation from other fast oscillations. *Nat Commun*.
27 2022;13(1):6000.
- 28 24. Lachaux JP, Axmacher N, Mormann F, Halgren E, Crone NE. High-frequency neural



- 1 activity and human cognition: past, present and possible future of intracranial EEG research.
2 *Prog Neurobiol.* 2012;98(3):279-301.
- 3 25. Vaz AP, Wittig JH Jr, Inati SK, Zaghoul KA. Replay of cortical spiking sequences during
4 human memory retrieval. *Science.* 2020;367(6482):1131-1134.
- 5 26. Vaz AP, Inati SK, Brunel N, Zaghoul KA. Coupled ripple oscillations between the medial
6 temporal lobe and neocortex retrieve human memory. *Science.* 2019;363(6430):975-978.
- 7 27. Norman Y, Raccach O, Liu S, Parvizi J, Malach R. Hippocampal ripples and their
8 coordinated dialogue with the default mode network during recent and remote recollection.
9 *Neuron.* 2021;109(17):2767-2780.e5.
- 10 28. Norman Y, Yeagle EM, Khuvis S, Harel M, Mehta AD, Malach R. Hippocampal sharp-wave
11 ripples linked to visual episodic recollection in humans. *Science.* 2019;365(6454).
12 doi:10.1126/science.aax1030
- 13 29. Dickey CW, Verzhbinsky IA, Jiang X, et al. Cortical Ripples during NREM Sleep and
14 Waking in Humans. *J Neurosci.* 2022;42(42):7931-7946.
- 15 30. Dickey CW, Verzhbinsky IA, Jiang X, et al. Widespread ripples synchronize human cortical
16 activity during sleep, waking, and memory recall. *Proc Natl Acad Sci U S A.*
17 2022;119(28):e2107797119.
- 18 31. Axmacher N, Elger CE, Fell J. Ripples in the medial temporal lobe are relevant for human
19 memory consolidation. *Brain.* 2008;131(Pt 7):1806-1817.
- 20 32. Kucewicz MT, Cimbalnik J, Matsumoto JY, et al. High frequency oscillations are associated
21 with cognitive processing in human recognition memory. *Brain.* 2014;137(Pt 8):2231-2244.
- 22 33. Kucewicz MT, Berry BM, Kremen V, et al. Dissecting gamma frequency activity during
23 human memory processing. *Brain.* 2017;140(5):1337-1350.
- 24 34. Worrell GA, Jerbi K, Kobayashi K, Lina JM, Zelmann R, Le Van Quyen M. Recording and
25 analysis techniques for high-frequency oscillations. *Prog Neurobiol.* 2012;98(3):265-278.
- 26 35. Buzsáki G, Silva FL da. High frequency oscillations in the intact brain. *Prog Neurobiol.*
27 2012;98(3):241-249.
- 28 36. Staba RJ, Frigetto L, Behnke EJ, et al. Increased fast ripple to ripple ratios correlate with



- 1 reduced hippocampal volumes and neuron loss in temporal lobe epilepsy patients. *Epilepsia*.
2 2007;48(11):2130-2138.
- 3 37. Baker SN, Curio G, Lemon RN. EEG oscillations at 600 Hz are macroscopic markers for
4 cortical spike bursts. *J Physiol*. 2003;550(Pt 2):529-534.
- 5 38. Telenczuk B, Baker SN, Herz AVM, Curio G. High-frequency EEG covaries with spike
6 burst patterns detected in cortical neurons. *J Neurophysiol*. 2011;105(6):2951-2959.
- 7 39. Ray S, Crone NE, Niebur E, Franaszczuk PJ, Hsiao SS. Neural correlates of high-gamma
8 oscillations (60-200 Hz) in macaque local field potentials and their potential implications in
9 electrocorticography. *J Neurosci*. 2008;28(45):11526-11536.
- 10 40. Ray S, Maunsell JHR. Different origins of gamma rhythm and high-gamma activity in
11 macaque visual cortex. *PLoS Biol*. 2011;9(4):e1000610.
- 12 41. Colgin LL, Denninger T, Fyhn M, et al. Frequency of gamma oscillations routes flow of
13 information in the hippocampus. *Nature*. 2009;462(7271):353-357.
- 14 42. Belluscio MA, Mizuseki K, Schmidt R, Kempter R, Buzsáki G. Cross-frequency phase-
15 phase coupling between θ and γ oscillations in the hippocampus. *J Neurosci*.
16 2012;32(2):423-435.
- 17 43. Canolty RT, Edwards E, Dalal SS, et al. High gamma power is phase-locked to theta
18 oscillations in human neocortex. *Science*. 2006;313(5793):1626-1628.
- 19 44. Csicsvari J, Hirase H, Czurkó A, Mamiya A, Buzsáki G. Fast network oscillations in the
20 hippocampal CA1 region of the behaving rat. *J Neurosci*. 1999;19(16):RC20.
- 21 45. Sullivan D, Csicsvari J, Mizuseki K, Montgomery S, Diba K, Buzsáki G. Relationships
22 between hippocampal sharp waves, ripples, and fast gamma oscillation: influence of dentate
23 and entorhinal cortical activity. *J Neurosci*. 2011;31(23):8605-8616.
- 24 46. Staba RJ, Wilson CL, Bragin A, Fried I, Engel J. Quantitative Analysis of High-Frequency
25 Oscillations (80–500 Hz) Recorded in Human Epileptic Hippocampus and Entorhinal
26 Cortex. *Journal of Neurophysiology*. 2002;88(4):1743-1752. doi:10.1152/jn.2002.88.4.1743
- 27 47. Bragin A, Wilson CL, Staba RJ, Reddick M, Fried I, Engel J. Interictal high-frequency
28 oscillations (80-500Hz) in the human epileptic brain: Entorhinal cortex. *Annals of*



- 1 *Neurology*. 2002;52(4):407-415. doi:10.1002/ana.10291
- 2 48. Bragin A, Engel J, Wilson CL, Fried I, Mathern GW. Hippocampal and Entorhinal Cortex
3 High-Frequency Oscillations (100-500 Hz) in Human Epileptic Brain and in Kainic Acid-
4 Treated Rats with Chronic Seizures. *Epilepsia*. 1999;40(2):127-137. doi:10.1111/j.1528-
5 1157.1999.tb02065.x
- 6 49. Kandel A, Buzsáki G. Cellular-synaptic generation of sleep spindles, spike-and-wave
7 discharges, and evoked thalamocortical responses in the neocortex of the rat. *J Neurosci*.
8 1997;17(17):6783-6797.
- 9 50. Khodagholy D, Gelinek JN, Buzsáki G. Learning-enhanced coupling between ripple
10 oscillations in association cortices and hippocampus. *Science*. 2017;358(6361):369-372.
- 11 51. Buzsáki G. Memory consolidation during sleep: a neurophysiological perspective. *J Sleep*
12 *Res*. 1998;7 Suppl 1:17-23.
- 13 52. Joo HR, Frank LM. The hippocampal sharp wave-ripple in memory retrieval for immediate
14 use and consolidation. *Nat Rev Neurosci*. 2018;19(12):744-757.
- 15 53. Carr MF, Jadhav SP, Frank LM. Hippocampal replay in the awake state: a potential substrate
16 for memory consolidation and retrieval. *Nat Neurosci*. 2011;14(2):147-153.
- 17 54. Bragin A, Engel J, Wilson CL, Fried I, Buzsáki G. High-frequency oscillations in human
18 brain. *Hippocampus*. 1999;9(2):137-142. doi:10.1002/(sici)1098-1063(1999)9:2<137::aid-
19 hipo5>3.0.co;2-0
- 20 55. Staba RJ. Normal and pathologic high-frequency oscillations. *Epilepsia*. 2010;51:21-21.
21 doi:10.1111/j.1528-1167.2010.02807.x
- 22 56. Matsumoto A, Brinkmann BH, Matthew Stead S, et al. Pathological and physiological high-
23 frequency oscillations in focal human epilepsy. *J Neurophysiol*. 2013;110(8):1958-1964.
- 24 57. Pail M, Cimbáľník J, Roman R, et al. High frequency oscillations in epileptic and non-
25 epileptic human hippocampus during a cognitive task. *Sci Rep*. 2020;10(1):18147.
- 26 58. Frauscher B, von Ellenrieder N, Zelmann R, et al. High-Frequency Oscillations in the
27 Normal Human Brain. *Annals of Neurology*. 2018;84(3):374-385. doi:10.1002/ana.25304
- 28 59. Le Van Quyen M, Bragin A, Staba R, Crépon B, Wilson CL, Engel J Jr. Cell type-specific

- 1 firing during ripple oscillations in the hippocampal formation of humans. *J Neurosci.*
2 2008;28(24):6104-6110.
- 3 60. Tong APS, Vaz AP, Wittig JH, Inati SK, Zaghoul KA. Ripples reflect a spectrum of
4 synchronous spiking activity in human anterior temporal lobe. *Elife.* 2021;10.
5 doi:10.7554/eLife.68401
- 6 61. Navas-Olive A, Rubio A, Abbaspoor S, Hoffman KL, de la Prida LM. A machine learning
7 toolbox for the analysis of sharp-wave ripples reveals common waveform features across
8 species. *Commun Biol.* 2024;7(1):211.
- 9 62. Blanco JA, Stead M, Krieger A, et al. Unsupervised classification of high-frequency
10 oscillations in human neocortical epilepsy and control patients. *J Neurophysiol.*
11 2010;104(5):2900-2912.
- 12 63. Sebastian ER, Quintanilla JP, Sánchez-Aguilera A, Esparza J, Cid E, de la Prida LM.
13 Topological analysis of sharp-wave ripple waveforms reveals input mechanisms behind
14 feature variations. *Nat Neurosci.* 2023;26(12):2171-2181.
- 15 64. Bragin A, Mody I, Wilson CL, Engel J Jr. Local generation of fast ripples in epileptic brain.
16 *J Neurosci.* 2002;22(5):2012-2021.
- 17 65. Stead M, Bower M, Brinkmann BH, et al. Microseizures and the spatiotemporal scales of
18 human partial epilepsy. *Brain.* 2010;133(9):2789-2797.
- 19 66. Worrell GA, Gardner AB, Matt Stead S, et al. High-frequency oscillations in human
20 temporal lobe: simultaneous microwire and clinical macroelectrode recordings. *Brain.*
21 2008;131(4):928-937. doi:10.1093/brain/awn006
- 22 67. Crépon B, Navarro V, Hasboun D, et al. Mapping interictal oscillations greater than 200 Hz
23 recorded with intracranial macroelectrodes in human epilepsy. *Brain.* 2010;133(Pt 1):33-45.
- 24 68. Schevon CA, Trevelyan AJ, Schroeder CE, Goodman RR, McKhann G Jr, Emerson RG.
25 Spatial characterization of interictal high frequency oscillations in epileptic neocortex.
26 *Brain.* 2009;132(Pt 11):3047-3059.
- 27 69. Curot J, Barbeau E, Despouy E, et al. Local neuronal excitation and global inhibition during
28 epileptic fast ripples in humans. *Brain.* 2023;146(2):561-575.



- 1 70. Buzsáki G, Horvath Z, Urioste R, Hetke J, Wise K. High-frequency network oscillation in
2 the hippocampus. *Science*. 1992;256(5059):1025-1027. doi:10.1126/science.1589772
- 3 71. Ibarz JM, Foffani G, Cid E, Inostroza M, Menendez de la Prida L. Emergent dynamics of
4 fast ripples in the epileptic hippocampus. *J Neurosci*. 2010;30(48):16249-16261.
- 5 72. Alvarado-Rojas C, Huberfeld G, Baulac M, et al. Different mechanisms of ripple-like
6 oscillations in the human epileptic subiculum. *Ann Neurol*. 2015;77(2):281-290.
- 7 73. Fabo D, Bokodi V, Szabó JP, et al. The role of superficial and deep layers in the generation
8 of high frequency oscillations and interictal epileptiform discharges in the human cortex. *Sci*
9 *Rep*. 2023;13(1):9620.
- 10 74. Stark E, Roux L, Eichler R, Sensai Y, Royer S, Buzsáki G. Pyramidal cell-interneuron
11 interactions underlie hippocampal ripple oscillations. *Neuron*. 2014;83(2):467-480.
- 12 75. Cardin JA, Carlén M, Meletis K, et al. Driving fast-spiking cells induces gamma rhythm and
13 controls sensory responses. *Nature*. 2009;459(7247):663-667.
- 14 76. Sohal VS, Zhang F, Yizhar O, Deisseroth K. Parvalbumin neurons and gamma rhythms
15 enhance cortical circuit performance. *Nature*. 2009;459(7247):698-702.
- 16 77. Chrobak JJ, Buzsáki G. High-frequency oscillations in the output networks of the
17 hippocampal-entorhinal axis of the freely behaving rat. *J Neurosci*. 1996;16(9):3056-3066.
- 18 78. Ball T, Kern M, Mutschler I, Aertsen A, Schulze-Bonhage A. Signal quality of
19 simultaneously recorded invasive and non-invasive EEG. *Neuroimage*. 2009;46(3):708-716.
- 20 79. Kovach CK, Tsuchiya N, Kawasaki H, Oya H, Howard MA 3rd, Adolphs R. Manifestation
21 of ocular-muscle EMG contamination in human intracranial recordings. *Neuroimage*.
22 2011;54(1):213-233.
- 23 80. Yuval-Greenberg S, Tomer O, Keren AS, Nelken I, Deouell LY. Transient induced gamma-
24 band response in EEG as a manifestation of miniature saccades. *Neuron*. 2008;58(3):429-
25 441.
- 26 81. Kern M, Ball T, Lahr J, Mutschler I, Aertsen A, Schulze-Bonhage A. Signal Quality of
27 Simultaneously Recorded ECoG and Non-Invasive EEG: Results from Analysis of
28 Spontaneous Eye Blinks and Saccades. *NeuroImage*. 2009;47:S126. doi:10.1016/s1053-



- 1 8119(09)71211-x
- 2 82. Jerbi K, Freyermuth S, Dalal S, et al. Saccade related gamma-band activity in intracerebral
3 EEG: dissociating neural from ocular muscle activity. *Brain Topogr.* 2009;22(1):18-23.
- 4 83. Waldert S, Lemon RN, Kraskov A. Influence of spiking activity on cortical local field
5 potentials. *The Journal of Physiology.* 2013;591(21):5291-5303.
6 doi:10.1113/jphysiol.2013.258228
- 7 84. Cimbálník J, Hewitt A, Worrell G, Stead M. The CS algorithm: A novel method for high
8 frequency oscillation detection in EEG. *J Neurosci Methods.* 2018;293:6-16.
- 9 85. Lachaux JP, Rodriguez E, Martinerie J, Adam C, Hasboun D, Varela FJ. A quantitative study
10 of gamma-band activity in human intracranial recordings triggered by visual stimuli. *Eur J*
11 *Neurosci.* 2000;12(7):2608-2622.
- 12 86. Lundqvist M, Rose J, Herman P, Brincat SL, Buschman TJ, Miller EK. Gamma and Beta
13 Bursts Underlie Working Memory. *Neuron.* 2016;90(1):152-164.
- 14 87. Lundqvist M, Herman P, Warden MR, Brincat SL, Miller EK. Gamma and beta bursts
15 during working memory readout suggest roles in its volitional control. *Nat Commun.*
16 2018;9(1):394.
- 17 88. Rich EL, Wallis JD. Spatiotemporal dynamics of information encoding revealed in
18 orbitofrontal high-gamma. *Nat Commun.* 2017;8(1):1139.
- 19 89. Scheffer-Teixeira R, Belchior H, Leão RN, Ribeiro S, Tort ABL. On high-frequency field
20 oscillations (>100 Hz) and the spectral leakage of spiking activity. *J Neurosci.*
21 2013;33(4):1535-1539.
- 22 90. Leszczyński M, Barczak A, Kajikawa Y, et al. Dissociation of broadband high-frequency
23 activity and neuronal firing in the neocortex. *Sci Adv.* 2020;6(33):eabb0977.
- 24 91. Schomburg EW, Anastassiou CA, Buzsáki G, Koch C. The spiking component of oscillatory
25 extracellular potentials in the rat hippocampus. *J Neurosci.* 2012;32(34):11798-11811.
- 26 92. Miller KJ, Honey CJ, Hermes D, Rao RPN, denNijs M, Ojemann JG. Broadband changes in
27 the cortical surface potential track activation of functionally diverse neuronal populations.
28 *Neuroimage.* 2014;85 Pt 2(0 2):711-720.



- 1 93. Miller KJ, Sorensen LB, Ojemann JG, den Nijs M. Power-law scaling in the brain surface
2 electric potential. *PLoS Comput Biol*. 2009;5(12):e1000609.
- 3 94. Manning JR, Jacobs J, Fried I, Kahana MJ. Broadband shifts in local field potential power
4 spectra are correlated with single-neuron spiking in humans. *J Neurosci*.
5 2009;29(43):13613-13620.
- 6 95. Burke JF, Ramayya AG, Kahana MJ. Human intracranial high-frequency activity during
7 memory processing: neural oscillations or stochastic volatility? *Current Opinion in*
8 *Neurobiology*. 2015;31:104-110. doi:10.1016/j.conb.2014.09.003
- 9 96. Fellner MC, Gollwitzer S, Rampp S, et al. Spectral fingerprints or spectral tilt? Evidence for
10 distinct oscillatory signatures of memory formation. *PLoS Biol*. 2019;17(7):e3000403.
- 11 97. Siegel M, Donner TH, Engel AK. Spectral fingerprints of large-scale neuronal interactions.
12 *Nat Rev Neurosci*. 2012;13(2):121-134.
- 13 98. Marks VS, Saboo KV, Topçu Ç, et al. Independent dynamics of low, intermediate, and high
14 frequency spectral intracranial EEG activities during human memory formation.
15 *Neuroimage*. 2021;245:118637.
- 16 99. Hubel DH, Wiesel TN. Anatomical demonstration of columns in the monkey striate cortex.
17 *Nature*. 1969;221(5182):747-750.
- 18 100. Konorski J. *Conditioned Reflexes and Neuros Organizations.*; 1948.
- 19 101. Hebb DDO. *Organization of Behavior: A Neuropsychological Theory*. Wiley; 1949.
- 20 102. Singer W, Gray CM. Visual feature integration and the temporal correlation hypothesis.
21 *Annu Rev Neurosci*. 1995;18:555-586.
- 22 103. Singer W. Neuronal synchrony: a versatile code for the definition of relations? *Neuron*.
23 1999;24(1):49-65, 111-125.
- 24 104. Singer W. Temporal Coherence: A Versatile Code for the Definition of Relations. *The*
25 *Senses: A Comprehensive Reference*. Published online 2008:1-9. doi:10.1016/b978-
26 012370880-9.00287-5
- 27 105. Treisman A. Solutions to the binding problem: progress through controversy and
28 convergence. *Neuron*. 1999;24(1):105-110, 111-125.



- 1 106. Roelfsema PR. Solving the binding problem: Assemblies form when neurons enhance their
2 firing rate—they don't need to oscillate or synchronize. *Neuron*. 2023;111(7):1003-1019.
- 3 107. Tallon-Baudry C. Oscillatory gamma activity in humans and its role in object representation.
4 *Trends in Cognitive Sciences*. 1999;3(4):151-162. doi:10.1016/s1364-6613(99)01299-1
- 5 108. Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: Phase synchronization and
6 large-scale integration. *Nature Reviews Neuroscience*. 2001;2(4):229-239.
7 doi:10.1038/35067550
- 8 109. Buzsáki G, Wang XJ. Mechanisms of gamma oscillations. *Annu Rev Neurosci*. 2012;35:203-
9 225.
- 10 110. Fries P. Rhythms for Cognition: Communication through Coherence. *Neuron*.
11 2015;88(1):220-235.
- 12 111. Jensen O, Kaiser J, Lachaux JP. Human gamma-frequency oscillations associated with
13 attention and memory. *Trends Neurosci*. 2007;30(7):317-324.
- 14 112. Düzel E, Penny WD, Burgess N. Brain oscillations and memory. *Curr Opin Neurobiol*.
15 2010;20(2):143-149.
- 16 113. Lisman JE, Jensen O. The Theta-Gamma Neural Code. *Neuron*. 2013;77(6):1002-1016.
- 17 114. Lisman JE, Idiart MA. Storage of 7 +/- 2 short-term memories in oscillatory subcycles.
18 *Science*. 1995;267(5203):1512-1515.
- 19 115. Jensen O, Lisman JE. Hippocampal sequence-encoding driven by a cortical multi-item
20 working memory buffer. *Trends Neurosci*. 2005;28(2):67-72.
- 21 116. Fries P. Neuronal gamma-band synchronization as a fundamental process in cortical
22 computation. *Annu Rev Neurosci*. 2009;32:209-224.
- 23 117. Luczak A, McNaughton BL, Harris KD. Packet-based communication in the cortex. *Nat Rev*
24 *Neurosci*. 2015;16(12):745-755.
- 25 118. Luczak A, Barthó P, Harris KD. Spontaneous events outline the realm of possible sensory
26 responses in neocortical populations. *Neuron*. 2009;62(3):413-425.
- 27 119. Sadowski JHLP, Jones MW, Mellor JR. Ripples make waves: binding structured activity and



- 1 plasticity in hippocampal networks. *Neural Plast.* 2011;2011:960389.
- 2 120. Sadowski JHLP, Sadowski JHL, Jones MW, Mellor JR. Sharp-Wave Ripples Orchestrate the
3 Induction of Synaptic Plasticity during Reactivation of Place Cell Firing Patterns in the
4 Hippocampus. *Cell Reports.* 2016;14(8):1916-1929. doi:10.1016/j.celrep.2016.01.061
- 5 121. Yuste R, Cossart R, Yaksi E. Neuronal ensembles: Building blocks of neural circuits.
6 *Neuron.* Published online January 22, 2024. doi:10.1016/j.neuron.2023.12.008
- 7 122. Nikolić D, Fries P, Singer W. Gamma oscillations: precise temporal coordination without a
8 metronome. *Trends Cogn Sci.* 2013;17(2):54-55.
- 9 123. David O, Kilner JM, Friston KJ. Mechanisms of evoked and induced responses in
10 MEG/EEG. *Neuroimage.* 2006;31(4):1580-1591.
- 11 124. Tallon-Baudry C, Bertrand O, Delpuech C, Pernier J. Stimulus specificity of phase-locked
12 and non-phase-locked 40 Hz visual responses in human. *J Neurosci.* 1996;16(13):4240-
13 4249.
- 14 125. Burke JF, Zaghoul KA, Jacobs J, et al. Synchronous and asynchronous theta and gamma
15 activity during episodic memory formation. *J Neurosci.* 2013;33(1):292-304.
- 16 126. Burke JF, Long NM, Zaghoul KA, Sharan AD, Sperling MR, Kahana MJ. Human
17 intracranial high-frequency activity maps episodic memory formation in space and time.
18 *Neuroimage.* 2014;85 Pt 2(0 2):834-843.
- 19 127. Kucewicz MT, Saboo K, Berry BM, et al. Human Verbal Memory Encoding Is
20 Hierarchically Distributed in a Continuous Processing Stream. *eNeuro.* 2019;6(1).
21 doi:10.1523/ENEURO.0214-18.2018
- 22 128. Gaona CM, Sharma M, Freudenburg ZV, et al. Nonuniform high-gamma (60-500 Hz) power
23 changes dissociate cognitive task and anatomy in human cortex. *J Neurosci.*
24 2011;31(6):2091-2100.
- 25 129. Brázdil M, Janeček J, Klimeš P, et al. On the time course of synchronization patterns of
26 neuronal discharges in the human brain during cognitive tasks. *PLoS One.*
27 2013;8(5):e63293.
- 28 130. Topçu Ç, Marks VS, Saboo KV, et al. Hotspot of human verbal memory encoding in the left



- 1 anterior prefrontal cortex. *EBioMedicine*. 2022;82:104135.
- 2 131. Wu HC, Nagasawa T, Brown EC, et al. γ -oscillations modulated by picture naming and
3 word reading: intracranial recording in epileptic patients. *Clin Neurophysiol*.
4 2011;122(10):1929-1942.
- 5 132. Crone NE, Sinai A, Korzeniewska A. High-frequency gamma oscillations and human brain
6 mapping with electrocorticography. *Prog Brain Res*. 2006;159:275-295.
- 7 133. Jerbi K, Ossandón T, Hamamé CM, et al. Task-related gamma-band dynamics from an
8 intracerebral perspective: review and implications for surface EEG and MEG. *Hum Brain*
9 *Mapp*. 2009;30(6):1758-1771.
- 10 134. Brovelli A, Lachaux JP, Kahane P, Boussaoud D. High gamma frequency oscillatory activity
11 dissociates attention from intention in the human premotor cortex. *Neuroimage*.
12 2005;28(1):154-164.
- 13 135. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological
14 investigation of the basis of the fMRI signal. *Nature*. 2001;412(6843):150-157.
15 doi:10.1038/35084005
- 16 136. Niessing J, Ebisch B, Schmidt KE, Niessing M, Singer W, Galuske RAW. Hemodynamic
17 signals correlate tightly with synchronized gamma oscillations. *Science*.
18 2005;309(5736):948-951. doi:10.1126/science.1110948
- 19 137. Lachaux JP, Fonlupt P, Kahane P, et al. Relationship between task-related gamma
20 oscillations and BOLD signal: new insights from combined fMRI and intracranial EEG.
21 *Hum Brain Mapp*. 2007;28(12):1368-1375.
- 22 138. Panagiotaropoulos TI, Deco G, Kapoor V, Logothetis NK. Neuronal discharges and gamma
23 oscillations explicitly reflect visual consciousness in the lateral prefrontal cortex. *Neuron*.
24 2012;74(5):924-935.
- 25 139. Siclari F, Baird B, Perogamvros L, et al. The neural correlates of dreaming. *Nat Neurosci*.
26 2017;20(6):872-878.
- 27 140. Doostmohammadi J, Gieselmann MA, van Kempen J, Lashgari R, Yoonessi A, Thiele A.
28 Ripples in macaque V1 and V4 are modulated by top-down visual attention. *Proc Natl Acad*

- 1 *Sci U S A*. 2023;120(5):e2210698120.
- 2 141. Long NM, Burke JF, Kahana MJ. Subsequent memory effect in intracranial and scalp EEG.
3 *NeuroImage*. 2014;84:488-494. doi:10.1016/j.neuroimage.2013.08.052
- 4 142. Josselyn SA, Köhler S, Frankland PW. Heroes of the Engram. *J Neurosci*.
5 2017;37(18):4647-4657.
- 6 143. Domanski APF, Kucewicz MT, Russo E, et al. Distinct hippocampal-prefrontal neural
7 assemblies coordinate memory encoding, maintenance, and recall. *Curr Biol*.
8 2023;33(7):1220-1236.e4.
- 9 144. Buzsáki G. Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory
10 and planning. *Hippocampus*. 2015;25(10):1073-1188.
- 11 145. Wilson MA, McNaughton BL. Reactivation of Hippocampal Ensemble Memories During
12 Sleep. *Science*. 1994;265(5172):676-679. doi:10.1126/science.8036517
- 13 146. Harris KD, Csicsvari J, Hirase H, Dragoi G, Buzsáki G. Organization of cell assemblies in
14 the hippocampus. *Nature*. 2003;424(6948):552-556.
- 15 147. Dragoi G, Buzsáki G. Temporal encoding of place sequences by hippocampal cell
16 assemblies. *Neuron*. 2006;50(1):145-157.
- 17 148. Pastalkova E, Itskov V, Amarasingham A, Buzsáki G. Internally generated cell assembly
18 sequences in the rat hippocampus. *Science*. 2008;321(5894):1322-1327.
- 19 149. Lee AK, Wilson MA. Memory of sequential experience in the hippocampus during slow
20 wave sleep. *Neuron*. 2002;36(6):1183-1194.
- 21 150. Skaggs WE, McNaughton BL. Replay of neuronal firing sequences in rat hippocampus
22 during sleep following spatial experience. *Science*. 1996;271(5257):1870-1873.
- 23 151. Van Quyen ML, Bragin A, Staba R, Crepon B, Wilson CL, Engel J. Cell Type-Specific
24 Firing during Ripple Oscillations in the Hippocampal Formation of Humans. *Journal of*
25 *Neuroscience*. 2008;28(24):6104-6110. doi:10.1523/jneurosci.0437-08.2008
- 26 152. Staresina BP, Bergmann TO, Bonnefond M, et al. Hierarchical nesting of slow oscillations,
27 spindles and ripples in the human hippocampus during sleep. *Nat Neurosci*.
28 2015;18(11):1679-1686.

- 1 153. Ngo HV, Fell J, Staerens B. Sleep spindles mediate hippocampal-neocortical coupling
2 during long-duration ripples. *Elife*. 2020;9. doi:10.7554/eLife.57011
- 3 154. McGaugh JL. Memory--a century of consolidation. *Science*. 2000;287(5451):248-251.
- 4 155. Stickgold R. Sleep-dependent memory consolidation. *Nature*. 2005;437(7063):1272-1278.
- 5 156. Born J, Wilhelm I. System consolidation of memory during sleep. *Psychol Res*.
6 2012;76(2):192-203.
- 7 157. Rothschild G, Eban E, Frank LM. A cortical-hippocampal-cortical loop of information
8 processing during memory consolidation. *Nat Neurosci*. 2017;20(2):251-259.
- 9 158. Lee H, Fell J, Axmacher N. Electrical engram: how deep brain stimulation affects memory.
10 *Trends Cogn Sci*. 2013;17(11):574-584.
- 11 159. Kucewicz MT, Worrell GA, Axmacher N. Direct electrical brain stimulation of human
12 memory: lessons learnt and future perspectives. *Brain*. Published online November 21,
13 2022. doi:10.1093/brain/awac435
- 14 160. Josselyn SA, Tonegawa S. Memory engrams: Recalling the past and imagining the future.
15 *Science*. 2020;367(6473). doi:10.1126/science.aaw4325
- 16 161. Tonegawa S, Liu X, Ramirez S, Redondo R. Memory Engram Cells Have Come of Age.
17 *Neuron*. 2015;87(5):918-931.
- 18 162. Tonegawa S, Morrissey MD, Kitamura T. The role of engram cells in the systems
19 consolidation of memory. *Nat Rev Neurosci*. 2018;19(8):485-498.
- 20 163. Brodt S, Gais S, Beck J, Erb M, Scheffler K, Schönauer M. Fast track to the neocortex: A
21 memory engram in the posterior parietal cortex. *Science*. 2018;362(6418):1045-1048.
- 22 164. Kindt M, Soeter M, Vervliet B. Beyond extinction: erasing human fear responses and
23 preventing the return of fear. *Nat Neurosci*. 2009;12(3):256-258.
- 24 165. Roy DS, Park YG, Kim ME, et al. Brain-wide mapping reveals that engrams for a single
25 memory are distributed across multiple brain regions. *Nat Commun*. 2022;13(1):1799.
- 26 166. Gliske SV, Irwin ZT, Chestek C, et al. Variability in the location of high frequency
27 oscillations during prolonged intracranial EEG recordings. *Nat Commun*. 2018;9(1):2155.



- 1 167. Abeles M. *Local Cortical Circuits: An Electrophysiological Study*. Springer Science &
2 Business Media; 2012.
- 3 168. Stacey W. Abby...Normal? a New Gold Standard for Identifying Normal High Frequency
4 Oscillations. *Epilepsy Currents*. 2015;15(4):211-212. doi:10.5698/1535-7511-15.4.211
- 5 169. Cimbalnik J, Pail M, Klimes P, et al. Cognitive Processing Impacts High Frequency
6 Intracranial EEG Activity of Human Hippocampus in Patients With Pharmacoresistant Focal
7 Epilepsy. *Front Neurol*. 2020;11:578571.
- 8 170. Jiang X, Gonzalez-Martinez J, Cash SS, Chauvel P, Gale J, Halgren E. Improved
9 identification and differentiation from epileptiform activity of human hippocampal sharp
10 wave ripples during NREM sleep. *Hippocampus*. 2020;30(6):610-622.
- 11 171. Bower MR, Stead M, Bower RS, et al. Evidence for consolidation of neuronal assemblies
12 after seizures in humans. *J Neurosci*. 2015;35(3):999-1010.
- 13 172. Brázdil M, Pail M, Halánek J, et al. Very high-frequency oscillations: Novel biomarkers of
14 the epileptogenic zone. *Ann Neurol*. 2017;82(2):299-310.
- 15 173. Hupbach A, Gomez R, Hardt O, Nadel L. Reconsolidation of episodic memories: a subtle
16 reminder triggers integration of new information. *Learn Mem*. 2007;14(1-2):47-53.
- 17 174. Kawala-Sterniuk A, Browarska N, Al-Bakri A, et al. Summary of over Fifty Years with
18 Brain-Computer Interfaces—A Review. *Brain Sciences*. 2021;11(1):43.
- 19 175. Kucewicz MT, Michael Berry B, Bower MR, et al. Combined Single Neuron Unit Activity
20 and Local Field Potential Oscillations in a Human Visual Recognition Memory Task. *IEEE*
21 *Trans Biomed Eng*. 2016;63(1):67-75.
- 22 176. Topçu Ç, Marks VS, Saboo KV, et al. Hotspot of human verbal memory encoding in the left
23 anterior prefrontal cortex. *EBioMedicine*. 2022;82:104135.
- 24

1 **Figure legends**

2
3 **Figure 1 High frequency LFP activities bridge neural oscillations with neuronal spiking**
4 **across the large scale of brain electrophysiology.** (A) Four examples of electrophysiological
5 activities recorded across a range of anatomical scales show gradually increasing focality and
6 spatiotemporal granularity of the source neural populations, assemblies and single cells. (B) Span
7 of LFP activities extends from slow rhythms to fast oscillations and waveforms of individual
8 action potentials. (C) High frequency activities comprise a variety of overlapping frequency
9 subranges used to classify physiologically HFOs and other LFP activities.

11 **Figure 2 Simplified model of generation and detection of high frequency oscillation bursts.**

12 Individual bursts of oscillations in the LFP signal are recorded from electrode contacts that are
13 proximal to the source generator of a neuronal assembly. The assembly is composed of a network
14 of connected neurons, which in case of fast ripple HFOs can be organized within a volume and
15 cytoarchitecture of a single cortical column. Individual assembly neurons fire action potentials -
16 measures as single unit activity (SUA) - with more or less coordinated timing of their spiking. If
17 the spiking is temporally aligned it drives deflections in the LFP signal, compared to the periods
18 when it is not coordinated in time and the LFP signal is flat. Repeated discharge of this
19 coordinated assembly firing results in a burst of an oscillation with deflections corresponding to
20 cycles associated with the temporally aligned spiking (arrows). Frequency of the emergent
21 oscillation depends on the interval period between the coordinated spiking. If a given unit fires a
22 burst of action potentials at intervals as small as the refractory period limit (approx. 2.5 ms), then
23 the emergent oscillation can reach a peak frequency of 400 Hz. Notice that individual units in a
24 given assembly can skip cycles of an oscillation because other units are firing at that time.
25 Hence, the emergent frequency of an HFO can exceed the limit of maximum burst spiking
26 frequency of any one unit, which explains the 'in-phase' and 'out-of-phase' mechanisms of HFO
27 generation^{71,72}. The outcome of this coordinated SUA is detected in the LFP signal as an
28 oscillation upon crossing of an arbitrary amplitude threshold of detection (dashed line), which is
29 usually set above 3 standard deviations from the signal mean. Duration of a given burst can thus
30 be determined between the detection thresholds of a given burst with at least four cycles, lasting



1 approximately between 50-100 ms³³. Hence, these bursts can be treated as discrete binary
2 events, much like the spiking activity¹⁷⁵, centered around the peak amplitude at a given frequency.

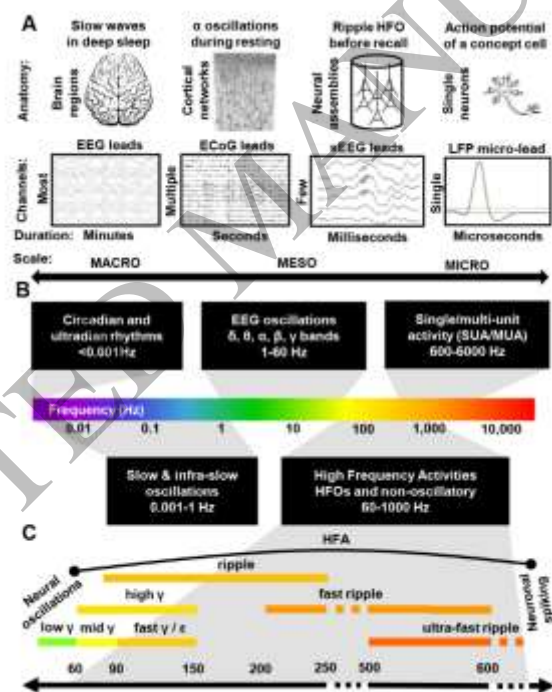
3
4 **Figure 3 Discrete bursts of HFOs constitute spectral power responses across high frequency**
5 **ranges.** (A) Electrode contact type determines cortical volume of the recorded neural ensemble
6 generating a particular HFO. (B) Example macro-contact detections of three example HFO
7 detections (zoomed in red) in distinct frequency ranges. (C) Diagram explains a broadband
8 increase in average high frequency power by pooling constituent HFO bursts from the
9 underlying neural assemblies. (D) Spectrogram of trial-averaged high frequency power induced
10 by cognitive stimulation closely overlaps with the cumulative plot of HFO detections (black
11 dots) from all trials on the right. In case of this prefrontal macro-electrode contact the highest
12 frequencies of the induced power were observed up to 1000 Hz (black arrow) and the rate of
13 induced HFO detections remained elevated even after the stimulus presentation time (white
14 arrow). Adapted from Kucewicz *et al.*^{32,33}

15
16 **Figure 4 Spectral power in the high frequency range tracks memory processing.** (A)
17 Normalized high gamma/ripple frequency responses averaged from over 100 subjects around
18 encoding of word stimuli shows a continuous wave of induced power across Brodmann cortical
19 areas, which were sorted according to peak latency. (B) The earliest induction of power in the
20 visual sensory areas (warm colors) reveals gradually sharper responses of greater peak power
21 than the higher order association areas (colder colors) with more widely distributed and thus
22 lower peak responses. (C) A wave of the induced high frequency power propagates in the
23 posterior to anterior direction of the hierarchical processing stream of the early and late encoding
24 phases. (D) The greatest differences between the power induced during encoding of the
25 subsequently remembered and forgotten words were localized in the occipitotemporal areas of
26 the ventral visual processing stream and in the left anterior prefrontal cortex rostral to the
27 language-processing Broca's area. Adapted from Kucewicz *et al.*,¹²⁷ Marks *et al.*⁹⁸ and Topcu *et*
28 *al.*¹⁷⁶

29



1 **Figure 5 Large-scale dynamics reconciles local and global spatiotemporal coordination of**
 2 **HFO bursts across the brain.** (A) Schematic model of high frequency power induced in the
 3 occipital, temporal and frontal lobes that proposes a simplified mechanism of temporally
 4 coordinated HFO bursting between locally and globally connected neural assemblies. (B)
 5 Rasterplot shows coordinated HFO bursting between macro-contacts (rows) implanted across
 6 cortical lobes (color-coded as in 'a') of an example patient, which were sorted in descending
 7 order of temporal correlation during free recall of one word from memory (vertical line indicates
 8 start of uttering the recalled word). Notice temporally coordinated bursting between the three
 9 cortical areas within approx. 1 second from the recall utterance followed by diminished bursting
 10 activity.
 11



12
 13
 14
 15
 Figure 1
 79x95 mm (x DPI)

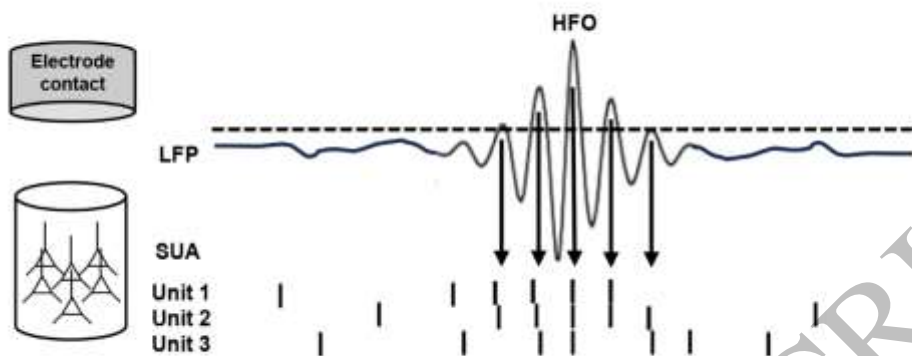


Figure 2
143x69 mm (x DPI)

1
2
3
4

ACCEPTED MANUSCRIPT

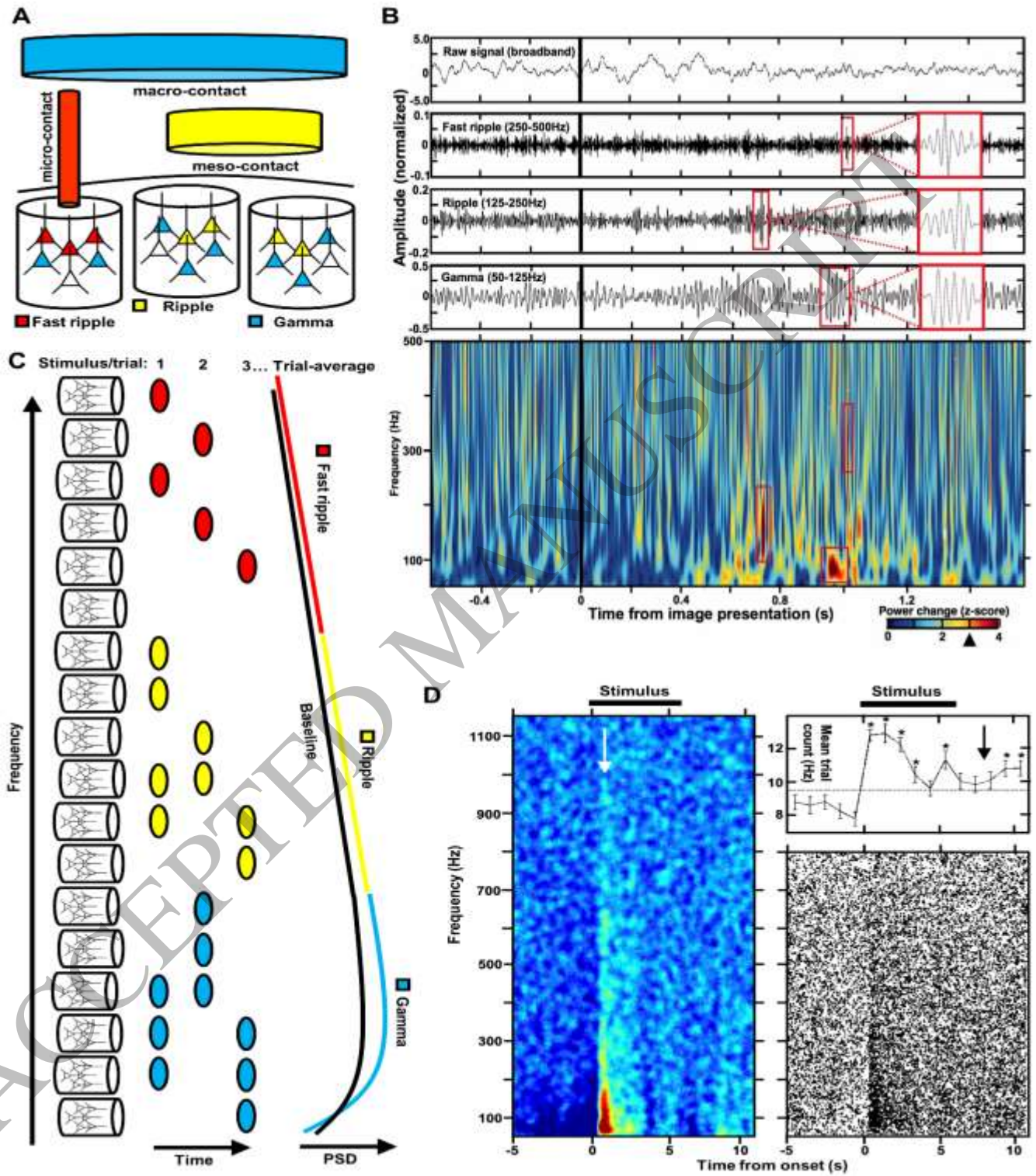


Figure 3
180x242 mm (x DPI)

1
2
3
4

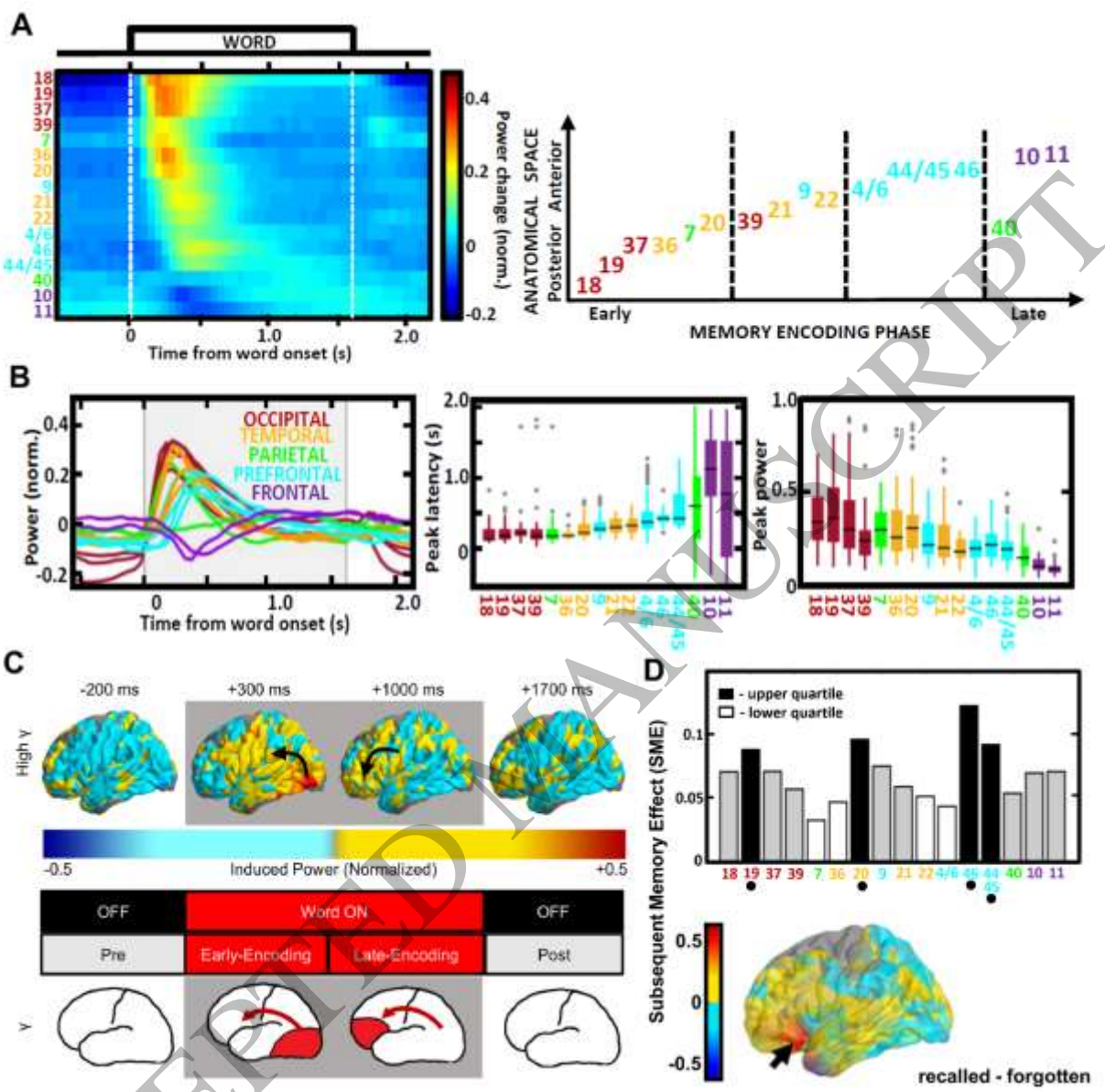


Figure 4
192x187 mm (x DPI)

1
2
3
4

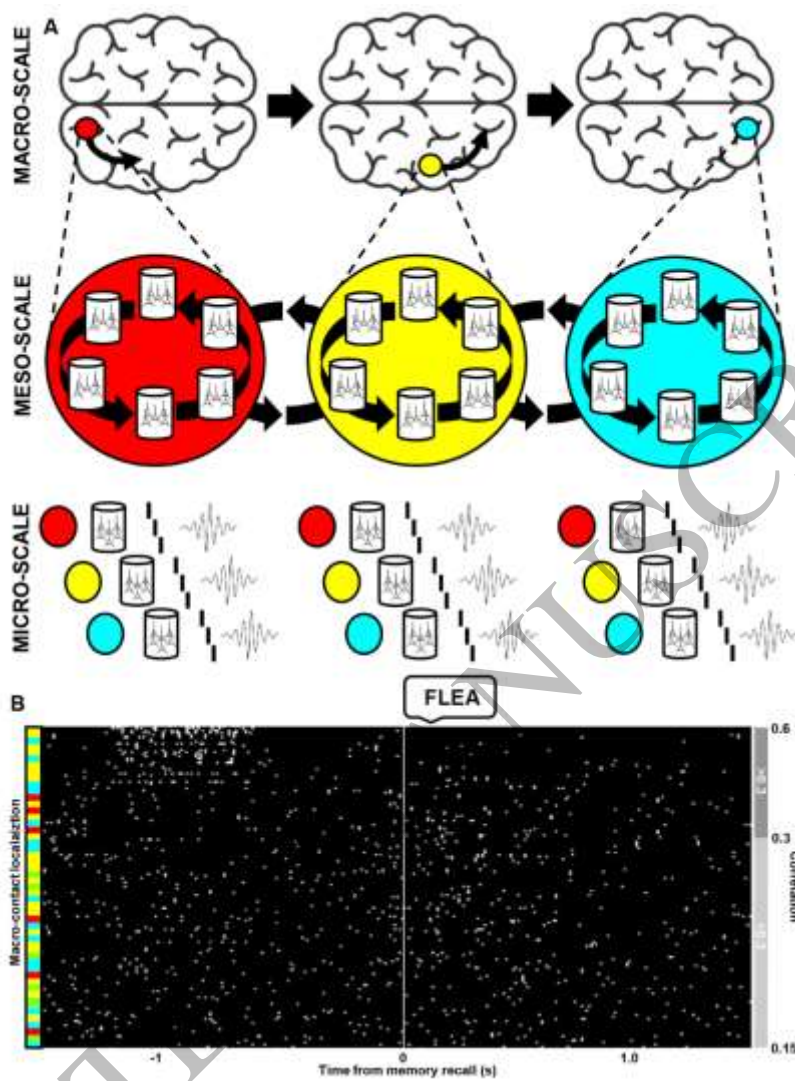


Figure 5
112x144 mm (x DPI)

1
2
3