Human gamma-frequency oscillations associated with attention and memory

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Both theoretical and experimental animal work supports the hypothesis that transient oscillatory synchronization of neuronal assemblies at gamma frequencies (30–100 Hz) is closely associated with sensory processing. Recent data from recordings in animals and humans have suggested that gamma-frequency activity also has an important role in attention and both working and long-term memory. The involvement of gamma-band synchronization in various cognitive paradigms in humans is currently being investigated using intracranial and high-density electro- and magnetoencephalography recordings. Here, we discuss recent findings demonstrating human gamma-frequency activity associated with attention and memory in both sensory and non-sensory areas. Because oscillatory gamma-frequency activity has an important role in neuronal communication and synaptic plasticity, it could provide a key for understanding neuronal processing in both local and distributed cortical networks engaged in complex cognitive functions. This review is part of the INMED/TINS special issue Physiogenic and pathogenic oscillations: the beauty and the beast, based on presentations at the annual INMED/TINS symposium (http://inmednet.com).

Introduction

In recent years, fast cortical oscillatory activity in the gamma-frequency band (30–100 Hz), as recorded in humans using electro- or magnetoencephalography (EEG or MEG, respectively), has received increasing interest because of its association with various cognitive functions in healthy humans [1–3] and a possible role in psychiatric and neurological dysfunctions [4,5]. Although the coordinated activity of large numbers of neurons is required to produce oscillatory gamma-frequency activity in EEG and MEG recordings, its functional role remains unclear. The current understanding of fast oscillations is that they reflect synchronous activity of large ensembles of rhythmically firing neurons, which can be observed at multiple spatial scales, from single-unit recordings to the scalp EEG (Box 1).

From a physiological perspective, there are strong arguments for synchronization in the gamma-frequency band being important for neuronal communication. If a neuron receives input from several other neurons, this drive is enhanced if the spiking inputs are coincident because the synchronization enables the postsynaptic potentials to integrate [6] (Box 2, Figure 1a). The duration of an excitatory postsynaptic potential (PSP) is approximately \( \tau_{\text{PSP}} \sim 10 \text{ ms} \) [7], which defines the timeframe of temporal integration. Thus, gamma-frequency oscillations with a duration of 10–30 ms will provide a ‘tighter’ synchronization than will oscillations in lower frequency bands (Box 2, Figure 1a). Because this principle enables a group of neurons to exert a stronger drive when synchronized on downstream networks, it has been proposed that long-distance neuronal communication is reflected by phase synchronization [6,8–10].

The hypothesis that synchronous firing of a group of cells increases their functional impact has been the cornerstone of various theories of the role of oscillatory gamma-frequency activity. For instance, the ‘binding problem’ addresses the physiological mechanisms responsible for combining different features in a visual scene to form a coherent percept. It has been proposed that the binding problem can be solved by synchronous firing of neurons encoding the features to be combined [11]. The synchronized neurons will additionally provide a stronger drive to downstream visual areas, enabling a coherent percept to propagate. Electrophysiological recordings in both humans and animals have provided experimental support for feature binding being achieved by neuronal synchronization in the gamma-frequency band [12–20]. Furthermore, in the locust, odour discrimination is impaired if oscillatory synchronization is blocked pharmacologically [21].

In agreement with the hypothesis that synchronization is important for neuronal communication, it has been proposed that gamma-frequency synchronization serves as a mechanism for gain control [6]. Because an increase in neuronal synchronization results in amplification of the drive exerted on downstream areas, the gain with respect to neuronal firing increases too (Box 2, Figure 1b). As addressed below, gain control by neuronal synchronization might provide the neuronal substrate for directed attention. Finally, it has been proposed that sustained neuronal
firing in the gamma-frequency range is responsible for active maintenance of representations in working memory. This hypothesis has received support from animal recordings [22] and, as reviewed below, also human research [23–28]. All of the mechanisms addressed above pertain to dynamic changes in the pattern of neuronal firing. However, stable, long-lasting modifications of synaptic connections are another essential component of neuronal processing. Experimental work has demonstrated an intricate connection between neuronal firing and the phase of ongoing gamma-frequency oscillations in relation to synaptic plasticity (Box 1, Figure Id) [29]. As discussed below, oscillatory gamma-band activity has also been associated with encoding and recall of long-term memory.

In summary, there are several theories suggesting that gamma-band synchronization has a pivotal role in attention and memory. These theories have received partial support from animal research; however, it remains to be determined whether the same mechanisms are present in humans when complex cognitive tasks are applied. Recent technical developments in human electrophysiological research have provided the tools for addressing this question. Beyond advances in recording techniques, these developments include better source-modelling methods for localizing oscillatory brain activity from EEG and MEG signals and the application of novel signal-processing techniques for detection of transient neural oscillations. Using these techniques, it has become possible to study human gamma-band neural synchronization in various cortical regions, such as the primary visual cortex, Broca’s area and pars opercularis. This emerging line of research is reviewed here to better understand the role of gamma-frequency synchronization in human attention and memory.

**Gamma-frequency activity during attentional selection and stimulus encoding**

Because of the limited processing capacities of human sensory systems, attention helps to select stimulus features relevant for behavioural goals from a rich and noisy environment. At the physiological level, attention appears to operate by increasing the relative ability of neurons to respond to the presence of stimuli.

### Box 1. Detecting gamma-frequency activity: from pairs of neurons to cortical lobes

The lowest level at which oscillatory gamma-frequency activity can be detected is in the firing pattern of individual neurons. This can be achieved by intracranial single- or multi-unit recordings in animals and, in rare cases, humans. Typically, the gamma-frequency activity is observed as spiking patterns that repeat every 10–30 ms. A group of neurons is said to have ‘oscillatory synchronous activity’ if their spiking co-occurs periodically. From single-unit recordings, oscillatory synchrony can be characterized from the spiking activity by simple analysis techniques, such as auto- and cross-correlograms. The example in Figure 1a (reprinted, with permission, from Ref. [59]) shows the cross-correlogram for two neurons with overlapping receptive fields ~3–4 mm apart recorded in the primary visual cortex of the cat. The repeated correlations, each of ~20 ms, are indicative of oscillatory synchronization at ~50 Hz. The cross-correlogram is estimated between pairs of cells by calculating the histogram of the number of spikes fired by the second neuron as a function of time relative to spikes of the first neuron.

Intracranially recorded local field potentials (LFPs) reflect the joint activity of a larger group of neurons. The LFP is thought to measure postsynaptic potentials resulting from neuronal spiking. Oscillatory gamma-frequency activity is observed as a periodic modulation of the ongoing LFP trace. The example in Figure 1b (adapted, with permission, from Ref. [60]. Copyright 2003 by the Society for Neuroscience) shows the relationship between neuronal firing, recorded as multi-unit activity, and the LFP, recorded simultaneously at the same site in cat area 18. The 200 ms epoch marked by the horizontal bar is expanded below. The vertical broken line indicates the onset of the stimulus (sinewave gratings) presented to the cat. The spiking of the neurons (multi-unit activity) was phase-locked to the gamma-frequency oscillations in the LFP. Phase-locking between neuronal firing and the LFP implies that the LFP is produced by larger ensembles of neurons firing in synchrony.

Often, oscillatory activity in the LFP is characterized by time-frequency representations of power. The time-frequency representation in Figure 1c (adapted, with permission, from Ref. [60]. Copyright 2003 by the Society for Neuroscience) is calculated from the LFP signals in Figure 1b. Approximately 50 ms after the onset of the sinewave gratings, the power in the gamma-frequency band (50–70 Hz) increased and it is sustained while the stimulus is presented. Because the power is constrained to the gamma-frequency band it reflects sustained oscillations in the LFP. Time-frequency representations of power were calculated using spectral analysis (Welch’s method), applying a sliding 100 ms Hanning-tapered time window.

In humans, activity can be measured using iEEG recordings, by placing subdural electrodes directly at the brain surface. This is typically carried out in epileptic patients undergoing presurgical evaluations. The iEEG is related to LFP recordings; however, the spatial scale over which the two techniques integrate neuronal activity is different. The iEEG records the average electrical activity of patches of cortical tissue ~1 cm² in diameter (for a review, see Ref. [61]). The example in Figure 1d (adapted, with permission, from Ref. [62]) shows the time-frequency representation of the gamma-band response recorded by iEEG in the human lateral occipital sulcus in response to face stimuli (Morlet wavelet analysis; units are in standard deviations of a prestimulus baseline).

Finally, oscillatory gamma-frequency activity can be detected in healthy subjects using scalp EEG or MEG recordings. The signals measured by MEG and EEG represent the sum of activity from large ensembles of cells on a fairly crude spatial scale. Although the EEG and MEG signals are highly spatially smeared at the sensor level, they might still reflect local changes in neuronal synchronization, to be distinguished from changes in long-range synchronization visible in signals measured by two distant sensors. Evidence of this was obtained by recent simultaneous iEEG and MEG recordings in an epileptic patient performing cognitive tasks [63] and the comparison of iEEG, EEG and MEG studies of different subjects performing identical tasks [16,62]. The example in Figure 1e (adapted, with permission, from Ref. [64]) shows time-frequency representations of changes in power in response to visual stimulation measured by MEG (using an average of 28 axial gradiometers over the visual cortex). Changes are determined relative to the 1 s prestimulus baseline. The brain areas responsible for producing the gamma-frequency activity can be identified using source analysis and mapped onto the subject’s magnetic resonance imaging (MRI) scan (Figure 1f; Adapted, with permission, from Ref. [64]). Consistent with animal findings, the sources of the gamma-frequency activity were identified in the primary visual cortex.

In summary, those comparisons using different recording techniques have revealed strong similarities between the gamma-band responses recorded at different spatial scales, with respect to both timing and the response to experimental manipulation. The gap between micro- and macroscopic recordings is further bridged by recent methodological developments, for instance the ability to localize the neuronal sources of the gamma-frequency band responses. This suggests that gamma-band modulations recorded at the scalp level in humans probably reflect local changes in oscillatory synchronization, although definitive experimental and theoretical evidence is still partially lacking.
representing attended stimuli in sensory cortices to influence downstream cortical areas [30]. One proposed mechanism involves neural synchronization: as already mentioned, a neuron receiving multiple synaptic inputs is more likely to fire if these inputs are synchronized [6]. Thus, a group of neurons representing a visually attended object has a stronger effect on receiving neurons in downstream areas if it fires synchronously (Box 2, Figure Ia,b). Indeed, several studies in monkeys have directly observed this phenomenon: visual or somatosensory neurons responding to a visual and somatosensory stimulus fire in synchrony if their target stimulus is attended [31–33]. In humans, several EEG and MEG studies have found similar effects. Attended visual and somatosensory stimuli trigger stronger gamma-band responses than unattended stimuli [34,35] (Figure 1). A MEG study demonstrated that shifts of selective attention between visual and auditory modalities were accompanied by enhancements of the gamma-band responses towards cortical areas, which were specific to the attended modality [36]. The amplification of gamma-band activity by attention is not unique to sensory cortices, because intracranial EEG (iEEG) recordings have revealed similar effects in the premotor cortex in subjects shifting their visual attention towards the location of an upcoming target [37]. Those results complement the hypothesis that neural synchrony mediates feature binding and, in addition, underlies attentional mechanisms for encoding feature conjunctions [38]. In combination, these results suggest that attention relies on gamma-band synchronization to integrate neural activities related to a specific sensory object into a stable, salient and coherent representation, which would then be available for further maintenance in short-term memory or encoding into long-term memory.

**Gamma-frequency activity during maintenance of working and short-term memory**

Short-term memory is defined as the capacity to retain and manipulate information that is no longer accessible in the environment. Following the hypothesis that the representation of a specific stimulus relies on a synchronously oscillating assembly of neurons, a memory trace could be established by sustained oscillations in the absence of external stimulation (Box 2, Figure Ic). This provides a putative mechanism for maintenance of short-term or working memory of neuronal representations in agreement with Hebb’s [39] proposal that neuronal representations can be sustained by persistent firing of recurrently connected neurons.

Studies of gamma-band activity during short-term or working memory tasks have yielded crucial support for this model. For instance, Tallon-Baudry et al. [26] found that active maintenance of abstract visual shapes in short-term memory was characterized by enhanced gamma-frequency power at occipital and bilateral temporal EEG electrode sites. Furthermore, the time course of this activity varied according to the duration of the retention interval [27]. However, the spatial resolution of the EEG was insufficient to tell whether the same neural populations were underlying both perception and memory. A recent MEG study identified sustained gamma-frequency activity in a spatial, delayed match-to-sample task [28]. Subjects were required to maintain the orientation of presented faces during a 3-s retention period. The sources accounting for the gamma-frequency activity during the retention period were identified in occipital areas. The model and data presented above suggest that the memory trace of a visual stimulus is maintained by the neuronal representations in visual
Box 2. The functional role of neuronal gamma-frequency synchronization

Because oscillatory gamma-frequency activity reflects the spike timing of a large ensemble of neurons, it is bound to have a profound effect on neuronal processing. Consider a neuron receiving input from a set of neurons in a network (red traces; Figure 1a). When the firing of the neurons in the network is synchronized, their effect on the receiving neuron increases because their inputs will add up. In particular, oscillations at gamma frequencies provide a mechanism for synchronizing the input with high temporal precision relative to the time course of postsynaptic potentials (PSPs). Synchronization at lower frequencies (e.g. alpha-frequency oscillations) is more temporally smeared, resulting in a less-pronounced summation of the PSPs. Thus, neurons synchronized by alpha-frequency oscillations probably have a smaller effect on target cells. As a consequence, neuronal synchronization in the gamma-frequency band provides an important mechanism for neuronal communication.

Gamma-frequency synchronization can be a physiological mechanism for directed attention (Figure 1b). According to the principle of binding by neuronal synchronization, groups of neurons encoding the red and blue faces, respectively, will fire synchronously. However, there will be little synchronization between the cells encoding the red and blue faces. When attention is directed to the red face, the synchronization of the respective cells will increase. Thus, this group of neurons (red cells) will provide a stronger drive to downstream targets compared with less-synchronized cells (blue cells). During working memory operations, a set of cells encoding a specific sample stimulus will fire in synchrony during presentation (Figure 1c). When the object disappears, the synchronous oscillatory firing is maintained during the retention interval, thus providing a mechanism for the maintenance of working memory. Note that this principle might also apply to extrastriate visual areas and association cortices because representations in working memory are not necessarily maintained in early sensory areas. Phase-specific synaptic input, with respect to the gamma rhythm, can facilitate synaptic plasticity and thus encoding of long-term memory (Figure 1d) [29]. Consider a cell driven by subthreshold gamma-frequency oscillations. If incoming spikes are timed to the phase of the oscillations, this is likely to result in a stronger synaptic strengthening (top traces) compared with when the spikes are arriving independent of the phase (bottom trace).

Figure 1.

Several iEEG studies in patients have provided evidence for sustained gamma-frequency activity outside early sensory cortices. Two studies, in which patients were asked to memorize short, visual-letter sequences, reported a parametric increase in gamma-frequency activity, with memory load (the number of memorized letters) in non-a parametric increase in gamma-frequency activity, with

Several iEEG studies in patients have provided evidence for sustained gamma-frequency activity outside early sensory cortices. Two studies, in which patients were asked to memorize short, visual-letter sequences, reported a parametric increase in gamma-frequency activity, with memory load (the number of memorized letters) in non-visual cortical areas (Figure 2a,b) [23,25]. Mainy et al. [25] found sustained gamma-frequency oscillations in regions associated with phonological processing, including Broca’s area and auditory and prefrontal cortices. Modulations of gamma-frequency activity in areas along the visual ventral stream were also observed in intracranial recordings during encoding in a working-memory task, in which objects had to be either ignored or attended [40]. Pronounced differences were found between the lateral occipital cortex and the fusiform gyrus, reflecting enhancement of anticipation and stimulus-induced gamma-frequency activity, respectively. These studies indicate that synchronously oscillating neural assemblies in extrastriate visual cortex, and even nonvisual areas, are engaged in maintenance of the memory traces of visual stimuli. This suggests a mechanism of transmission or transformation between synchronous neural assemblies, from sensory cortices to higher-order cortical regions. Mainy et al. [25] have further demonstrated that such a transmission might start during stimulus presentation, because gamma-band responses to letter presentation occurred simultaneously in Broca’s area and visual regions.

Studies of other modalities have also suggested that the locus of oscillatory activity underlying short-term memory depends on the type of information that must be retained. Recordings using iEEG during maintenance of olfactory identity information revealed sustained gamma-frequency oscillations in the amygdala [41]. Gamma-frequency activity in auditory, short-term memory tasks was found in regions containing the putative auditory dorsal and ventral processing streams during maintenance of spatial, versus nonspatial, sound features [22,41]. An auditory, spatial, delayed match-to-sample task, in which subjects were asked to compare specific auditory features of sounds presented 800 ms apart, was associated with posterior temporoparietal gamma-frequency activity during the delay phase [42], suggesting involvement of the auditory dorsal stream in encoding and maintenance of auditory spatial information (Figure 2c–e). Conversely, memory-related increases in gamma-frequency power were
From a physiological perspective, there are several reasons why gamma-frequency activity and long-term memory can be transferred into long-term memory. The next question is how representations in working memory do not necessarily belong to the same brain regions. Apparently, in several situations, it is not the precise physical aspects of the stimulus being reflected in the gamma-frequency band but rather higher-level representations of relevant information. These higher-level representations could, for instance, represent a 'label', enabling retrieval of the actual stimuli. The next question is how representations in working memory can be transferred into long-term memory.

**Gamma-frequency activity and long-term memory**

From a physiological perspective, there are several reasons to believe that synchronized activity in the gamma-frequency band should have a role in encoding long-term memory through the modification of synaptic connections. First, it has been argued that the neuronal synchronization of representations in sensory areas results in a stronger synaptic drive to downstream areas [6]. As a consequence, the stronger drive results in stronger neuronal firing, promoting synaptic plasticity. Second, it has been demonstrated that the timing of synaptic discharges, with respect to the phase of ongoing gamma-frequency oscillation, modulates synaptic plasticity [29]. This could be explained by an increase in plasticity when a synaptic discharge coincides with depolarization provided by a peak in the gamma-frequency cycle (Box 2, Figure Id). Where there are few animal studies exploring gamma-frequency activity in paradigms of long-term memory, the relationship between long-term memory and gamma-frequency activity has been supported by several experimental studies in humans. Subsequent memory paradigms using EEG, MEG and iEEG recordings have shown that gamma-frequency activity during encoding predicts successful formation of long-term memory [43–46]. The gamma-frequency sources, reflecting the subsequent memory effect, were identified in early visual areas from MEG data [44] (Figure 3). It was argued that the gamma-frequency synchronization in visual areas results in a stronger drive, promoting synaptic changes in downstream association areas responsible for encoding long-term memory. Intracranial depth-electrode recordings in epileptic patients have demonstrated that local gamma-frequency activity in the hippocampus and synchronization between rhinal and hippocampal areas was correlated with successful encoding of long-term memory [47]. Furthermore, gamma-band activity has been shown to reflect successful retrieval of long-term memory too. Recognition of previously encoded items resulted in increased gamma-frequency activity compared with rejection of novel items [43,44]. Because the primary gamma-frequency sources have been identified in the occipital cortex, it was proposed that retrieval from long-term memory involves a top-down drive, reactivating the actual visual representations [44].

Long-term memory effects are also evident in models investigating stimulus repetitions. Initial presentations of line drawings of common objects, but not novel stimuli, were shown to elicit increases of induced gamma-frequency activity and phase synchronization between distant electrode sites [48], probably reflecting the activation of an existing memory trace [1]. Whereas gamma-frequency activity was reduced following repeated presentations of familiar stimuli, possibly reflecting a more sparse representation by a 'sharpened' network [49], novel objects elicited increases of gamma-frequency power and inter-electrode phase-locking to repeated presentations, which would be consistent with the formation of a new object representation in the cortex.

These studies demonstrate that successful encoding and recall of long-term memory are associated with increased gamma-frequency activity. During encoding, the increased gamma-frequency activity provides a phasic drive to neurons that are already active. This might serve to entrain the gamma activity in the receiving network and thus adjust the timing of neuronal firing to be optimal for observed in the left inferior frontal and anterior temporal cortex during maintenance of short-term memory of auditory patterns [24].

In summary, these studies support the proposed model that maintenance of short-term and working memory involves sustained neural synchronization in the gamma-frequency band. However, it seems evident that the synchronous assemblies mediating perception and the maintenance of memory do not necessarily belong to the same brain regions. Apparently, in several situations, it is not the precise physical aspects of the stimulus being reflected in the gamma-frequency band but rather higher-level representations of relevant information. These higher-level representations could, for instance, represent a 'label', enabling retrieval of the actual stimuli.

**Figure 1.** Selective attention results in increased gamma-frequency activity in the somatosensory system. Specific tactile stimuli were presented simultaneously to both index fingers and subjects were asked to identify, and thereby attend to, stimuli on either the left or the right finger. Short-lasting stimuli were delivered every 1 s using a Braille device. Brain activity was recorded using a whole-head MEG system. (a) The time-frequency representations of power show that gamma-band activity in sensors over left-brain areas increased when attention was directed to the right finger compared to when attention was directed to the left finger. (b) The sensors showing this effect were located over left sensorimotor areas. (c) The regions accounting for the allocation of attention were identified in the left primary sensorimotor cortex using a source-modelling approach. Similar effects were identified in the right somatosensory system when attention was directed to the left finger. Adapted, with permission, from Ref. [34]. Copyright 2006 by the Society for Neuroscience.

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synaptic plasticity (Box 2, Figure Id). During recall, the increased gamma-frequency activity might reflect reactivation of synaptically encoded representations. These hypotheses are consistent with the suggestion that gamma-frequency activity supports maintenance of working memory. It has been proposed that sustained representation in a working-memory buffer facilitates synaptic encoding in long-term memory [50].

**Concluding remarks**

Although the studies reviewed here point to an important role of activity in the gamma band, it should be emphasized that oscillatory brain activity is produced in other frequency bands too. In particular, theta-band activity is modulated by both working [51,52] and long-term memory tasks [44,45,53]. Interestingly, recent iEEG studies reported that gamma-frequency power is modulated by the phase of theta-frequency oscillations [54,55]. This finding is consistent with theoretical work proposing that nested theta- and gamma-frequency oscillations have an important role in memory processing [50,56,57]. Extensive empirical work is required in the future to better understand the interactions between brain oscillations in various frequency bands. Another issue is that gamma-band modulations from 30–100 Hz are considered here. This is a broad frequency range and future work might reveal that specific cognitive effects are reflected in more well-defined sub-bands in the gamma-frequency range.

Several conclusions can be drawn from this review. First, the hypothesis that oscillatory activity in the gamma-frequency band is related to object representations in humans is supported by a range of studies using EEG and MEG recordings. The human studies go beyond object representation and have demonstrated that directed attention and maintenance of working memory are reflected by increases in gamma-band synchronizations. These modulations are observed not only in early sensory areas, but also in association areas and the medial temporal lobe.
Whereas most studies have employed visual paradigms, somatosensory and auditory tasks have also been shown to modulate gamma-band activity during directed attention and maintenance of working memory. Although human studies have typically applied more complex paradigms than those used in animals, there seem to be no obvious contradictions between human and animal findings. Thus, it seems justified to use the knowledge of single-cell firing in relation to the gamma-frequency activity obtained from animal recordings to interpret the human findings. The main advantage of studying gamma-frequency activity in humans is the possibility of employing complex paradigms. This is exemplified by the paradigms of long-term memory addressed above; similar experiments could only be performed in animals with great difficulty. Finally, gamma-frequency activity in humans provides physiological markers of human attention and memory processes that can be applied to the diagnosis of neurological and psychiatric disorders [5,58]. Animal studies and human research should go hand-in-hand in the future to further elucidate the precise neural basis of those functions. In particular, human findings could guide microelectrode explorations in animals to investigate the neural basis of functional gamma-band effects observed at the macroscopic level.

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