

Gamma Oscillations Correlate with Working Memory Load in Humans

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Functional imaging of human cortex implicates a diverse network of brain regions supporting working memory — the capacity to hold and manipulate information for short periods of time. Although we are beginning to map out the brain networks supporting working memory, little is known about its physiological basis. We analyzed intracranial recordings from two epileptic patients as they performed a working memory task. Spectral analyses revealed that, in both patients, gamma (30–60 Hz) oscillations increased approximately linearly with memory load, tracking closely with memory load over the course of the trial. This constitutes the first evidence that gamma oscillations, widely implicated in perceptual processes, support the maintenance of multiple items in working memory.

Keywords: gamma oscillations, iEEG, working memory

Introduction

Working memory (Atkinson and Shiffrin, 1968; Baddeley and Hitch, 1974) is a theoretical construct that refers to the set of memory stores and control processes that enable us to keep information 'in mind' after the physical stimuli that gave rise to them are no longer available. A fundamental characteristic of working memory emphasized in the cognitive literature is the ability to maintain several item representations simultaneously. This capacity is essential for many of the functions ascribed to working memory.

The amount of information that must be held in mind at any given time is referred to as memory load. Imaging studies have investigated the anatomical bases of working memory by looking for brain regions where the haemodynamic response is correlated with memory load. These regions typically include prefrontal (Courtney *et al.*, 1997; Rypma and D'Esposito, 1999; de Fockert *et al.*, 2001) and perisylvian cortex (Postle *et al.*, 1999), but can also include medial temporal regions under the proper circumstances (Stern *et al.*, 2001). The electrophysiological correlates of memory load, and hence higher-order working memory function, have been less well explored in humans.

In the Sternberg task (Sternberg, 1966, 1975), a standard test of working memory, a series of stimuli are presented one at a time. After a brief retention interval a probe stimulus is presented. The subject responds to the probe by indicating whether or not the probe was one of the stimuli on the list (see Fig. 1*a*). Subjects can perform this task with near-perfect accuracy. A previous analysis of human brain activity as subjects perform this task revealed prominent theta (4–8 Hz) oscillations that increase sharply at the start of each trial and return to baseline near the time of the subject's response (Raghavachari *et al.*, 2001). In that study, theta power did not vary as a function of memory load, suggesting that working-

memory related theta reflects general task demands that are present during each trial but not between trials.

Gamma (30–60 Hz) oscillations are another candidate for an electrophysiological signature of working memory load. There is considerable evidence, from both human EEG (Tallon-Baudry *et al.*, 1996, 1998; von Stein *et al.*, 2000) and animal recordings (Herculano-Houzel *et al.*, 1999; Friedman-Hill *et al.*, 2000; Fries *et al.*, 2001), that gamma oscillations are involved in perception. The finding of increased gamma power in a wide variety of sensory modalities, and in response to higher-order percepts, has led a growing number of researchers to suggest that gamma is a marker of the more general function of feature binding (Rodriguez *et al.*, 1999; Tallon-Baudry and Bertrand, 1999). There is also evidence that elevated gamma power is associated with the maintenance of detailed item representations over a delay (Tallon-Baudry *et al.*, 1999), indicating a role for gamma in working memory as well as perception. However, until now it has not been known if this elevation in gamma power generalizes to the case in which multiple items must be simultaneously maintained.

Our objective here is to search for electrophysiological markers of working memory load. As shown in Figure 1*b*, memory load changes systematically over the course of each trial of the Sternberg task. Specifically, memory load increases linearly as each additional item is presented but remains constant during the retention interval because no new information is being presented, and because subjects must hold the recently presented items in working memory until the probe item appears. After the response is made, there is no longer any need to keep the list in mind; memory load falls back to baseline levels after the response. Memory load exhibits the following properties:

1. Load increases as items are presented.
2. Load falls to baseline levels after the response is made.
3. Load remains constant during the retention interval at a level that reflects the number of items presented.

Thus, any physiological correlate of memory load should track with item presentation in a similar manner.

Electrophysiological phenomena must meet multiple criteria before we can consider them to be meaningfully correlated with memory load. We looked for such phenomena using intracranial electroencephalography (iEEG). Two patients with medically resistive epilepsy performed the Sternberg task while undergoing invasive monitoring. Brain activity was recorded from subdural grids implanted to localize the regions of seizure onset for the planning of subsequent resective surgery. With a large number of electrodes and a large number of frequencies to examine, we first screened for electrode/

frequencies that exhibited property 1. We subsequently performed additional analyses to test whether these electrode/frequencies were also consistent with properties 2 and 3.

Materials and Methods

Two patients with medically resistive epilepsy participated in behavioral testing while undergoing invasive monitoring for possible epilepsy surgery. By participating in our studies, these patients incurred no additional medical or surgical risk and written informed consent was obtained from the patients and their guardians. The protocol was approved by the Institutional Review Board at Children's Hospital, Boston, MA.

Brain Recordings

Brain activity was recorded from subdural grids implanted to localize the regions of seizure onset for the planning of subsequent resective surgery. Locations of these electrodes were determined from co-

registered computed tomograms and magnetic resonance images by an indirect stereotactic technique (Talairach and Tournoux, 1988). The iEEG signal was amplified, sampled at 256 Hz (Bio-Logic Corp., Mundelein, IL, apparatus; bandpass filter, 0.3–70 Hz).

Recording from patients with epilepsy always brings with it some concern that the observed data are affected by the patients' pathology. To minimize these concerns, we took several precautions. Electrodes overlying seizure onset zones or regions with cortical damage evident on MRI were excluded from our analyses. Patients were not tested during seizures, nor during identifiable clinical epochs preceding seizures. Interictal spikes and sharp waves are signs of pathology in the tissue exhibiting them. Data from sites that showed interictal discharges at any time were excluded from all analyses. Isolated interictal spikes are just that, being limited to a circumscribed region of brain. By definition, they do not affect the electrical response of surrounding brain regions in any detectable way. Interictal discharges are not associated with readily observable cognitive or behavioral correlates in most patients. The locations of cortical electrodes, including those excluded using these criteria, are shown in Figure 2.

Subjects

Subject 1, a 22-year-old female, had subdural grids placed over all four lobes on the left hemisphere. Of 96 electrodes, 18 were excluded from our analyses on the basis of the criteria described above. Subject 2, an 11-year-old male, had subdural grids covering large portions of the left occipital, parietal and temporal cortex. In addition, a strip of electrodes extended over the left frontal lobe and two strips were placed in the interhemispheric space. Of 108 electrodes, 19 were excluded from our analyses. Both patients had normal range personality and intelligence. Patients and their guardians gave informed consent prior to participation.

Behavioral Testing

Behavioral testing was controlled by a personal computer running the Linux operating system that was wheeled to the subjects' bedside. The experiment was administered using a customized software library written in C++.

Each trial began with a fixation cross. A series of uppercase consonants was then presented in the center of a computer monitor (one item each 1400 ms). The retention interval was 1800 ms, meaning that there was a total of 3.2 s between presentation of the last item and the arrival of the probe. These values were chosen to be similar to the parameters used in the original study of Sternberg (1966).

The probe was distinguished from the items in the list by virtue of the longer delay leading to its presentation, a tone presented 400 ms prior to the presentation of the probe, and by the presence of '<NO>' and '<YES>' at the lower left and lower right corners of the screen. Probes were targets (items in the set) and lures (items not in the set) equally often. Subjects pressed the left Ctrl key to indicate that the probe item was not in the list and the right Ctrl key to indicate that the item was in the list. After each response, a text screen indicated both the latency and accuracy of the response. Instructions emphasized the

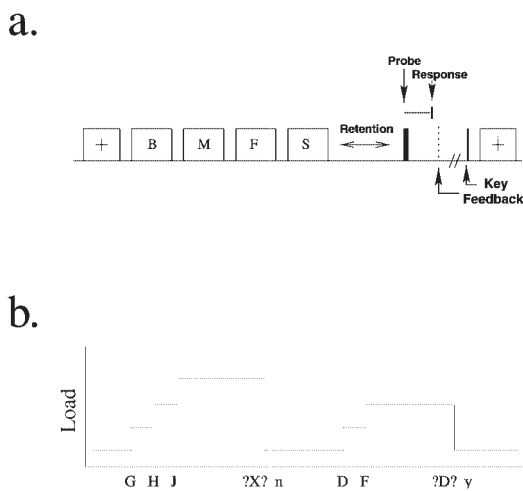


Figure 1. (a) The Sternberg task. This figure illustrates a list length four trial, although the actual list length varied from trial to trial. Items were presented every 1200 ms. An 1800 ms retention interval separated the presentation of the last item and the presentation of the probe item. Following the presentation of the probe, subjects indicated with a button press whether the probe was in the memory set. Adapted from Raghavachari *et al.* (2001). (b) Behavior of the memory load variable across trials. We would expect memory load to increase as each item is presented, and remain constant through the retention interval, because there is no new information to be remembered. It should not decrease, because presumably the function of WM is to maintain information across the delay. Finally, after the response is made, load should decrease back to baseline levels, because the information is no longer required.



Figure 2. Locations of excluded electrodes from the patients with subdural electrodes. Squares indicate sites from subject 1, circles denote sites from subject 2. Open symbols show the location of electrodes that were included in the analyses, whereas filled symbols show the location of electrodes that were excluded from the analyses. The criteria for electrode exclusion are detailed in the text.

importance of making a response both quickly and accurately. Subject 1 was given trials of list length 1–4. Subject 2 was given trials with list length 2–4 and list length 6. Trials of different list lengths were interspersed randomly, so that the subject would not know how many items would be presented in a given trial.

Electrophysiological Analyses

To analyze the time course of various frequency components, we convolved the signal from each trial with a set of Morlet wavelets with a wavenumber of 4 and frequencies $f = 2^{n/4}$ Hz, where n was chosen from the integers from 4 to 24. Using the wavelet-transformed time series, we constructed time-courses for power at 21 different frequencies for 157 different electrodes.

To look for electrode/frequencies whose power increased during list presentation, we computed a linear regression of power to serial position over the first four item presentations for each trial with list length ≥ 4 . Each electrode/frequency yielded a distribution of slopes across trials, which was compared to zero. A significant positive slope for a given electrode/frequency means that at that electrode, power in that frequency tended to *increase* as the list was being presented. We first screened for electrode/frequencies that showed slopes different from zero with $P < 0.001$ (two-tailed t -test). This analysis is potentially beset by issues pertaining to multiple comparisons, non-normal variance and/or across-electrode correlations. To control for these factors, we generated an empirical estimate of the type I error rate by randomizing serial positions for each trial. We used the same randomization across electrodes to control for between-electrode correlations. The analyses were repeated on 10 000 different shuffles of the data. A subsequent set of analyses performed various comparisons of power in the retention interval, the 1.8 s prior to arrival of the probe, at different list lengths for selected electrode/frequencies.

Results

Behavioral

Both subjects performed the Sternberg task with high accuracy and fast reaction times (RTs), as is typical of healthy young adults. For list lengths 2–4, subject 1 was correct on 97% of trials; subject 2 was correct on 93%. Both subjects also exhibited a behavioral effect of memory load on RTs ($P < 0.01$), which increased significantly with increasing list length (see Fig. 3). Importantly, the increase in RT associated with each additional list item was well within the range of those obtained from normals (Sternberg, 1975; the regression lines in Fig. 3 have a slope of 39 ms/item for the targets and 44 ms/item for the lures).

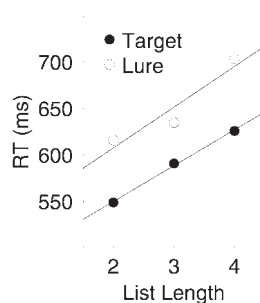


Figure 3. Reaction time increased with list length. Open symbols are mean correct RTs to probe items that were not in the memory set (lures). Filled symbols are mean correct RTs for probe items that were in the set (targets). Both of our patients showed the characteristic increase in RT with list length for both targets and lures. The regression line to the targets has a slope of 39 ms/item and an intercept of 470 ms. The regression line to the lures has a slope of 44 ms/item and an intercept of 520 ms.

Electrophysiological

Figure 4 displays the number of electrodes showing significant changes in power during presentation of the study items in the list length – four trials for each frequency. The distribution of electrodes showing an increase in power (Fig. 4a) revealed prominent peaks in the theta band (peak number of electrodes at 6.73 Hz) and the gamma band (peak number of electrodes at 38 Hz). These electrode/frequencies are of interest as candidates for an electrophysiological correlate of memory load. The distribution of electrodes showing a decrease in power (Fig. 4b) showed a peak in the alpha band (peak number of electrodes at 9.5 Hz) and another peak in the lower theta band (peak at 4.76 Hz).

Nine electrodes across the two subjects showed an increase in theta (6.73 Hz) power during list presentation. Comparable numbers of electrodes showed a decrease in theta power – 12 electrodes showed a significant decrease at 4.76 Hz. The relatively small number of electrodes and an inconsistent pattern of results across electrodes made it impossible to establish any reliable relationship between theta power and memory load using these data.

Twenty-nine electrodes showed a significant ($P < 0.001$) increase in gamma (38 Hz) power during presentation of the list items. These electrodes were distributed across frontal, temporal and parietal cortices in subject 1 and also occipito-temporal locations in subject 2 (the location of these electrodes is shown in Fig. 5).

Figure 6 shows the average time course of gamma power for four of the electrodes showing a significant increase during presentation of the list length four 10 trials, three from subject 1 and one from subject 2. As can be seen in the figure, average gamma power at these sites elevated continuously as the list is

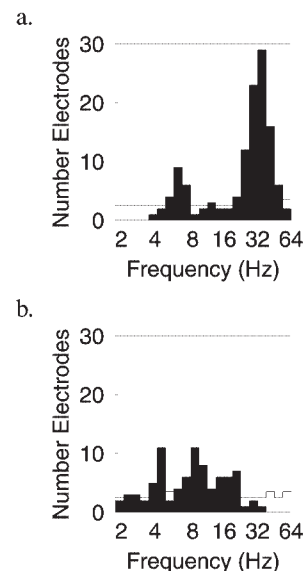


Figure 4. Frequency specificity of load-dependence for list length 4 trials. (a) Number of electrodes, at each frequency, whose power increased over the course of item presentation (positive slopes with $P < 0.001$). To empirically assess the significance of the observed peaks, the data set was repeatedly shuffled, as described in the text. The gray line indicates an estimate of the 0.001 significance level estimated from the shuffled data. That is, no more than 9/10 000 shuffled runs yielded a number of significant electrodes above the gray line for a given frequency. (b) Number of electrodes, at each frequency, whose power decreased over the course of item presentation (negative slopes with $P < 0.001$).

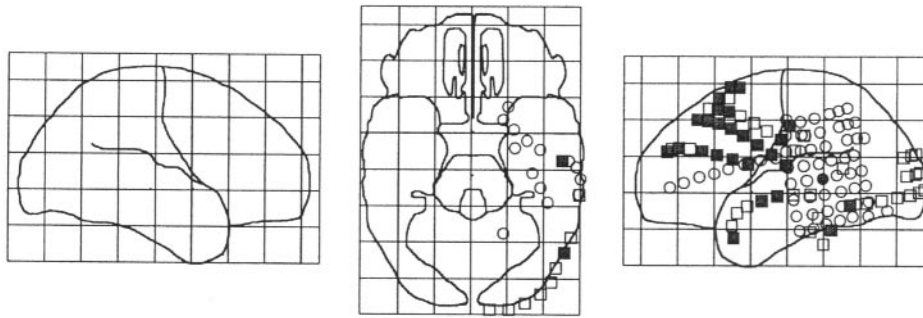


Figure 5. Anatomical distribution of electrodes that showed a positive slope for gamma power during list presentation. Squares represent electrode locations for subject 1. Circles represent electrode locations for subject 2. Filled symbols indicate electrodes that showed a significant ($P < 0.001$) positive slope at 38 Hz. Electrodes that were excluded from the analyses (see Fig. 2) are not included in this figure.

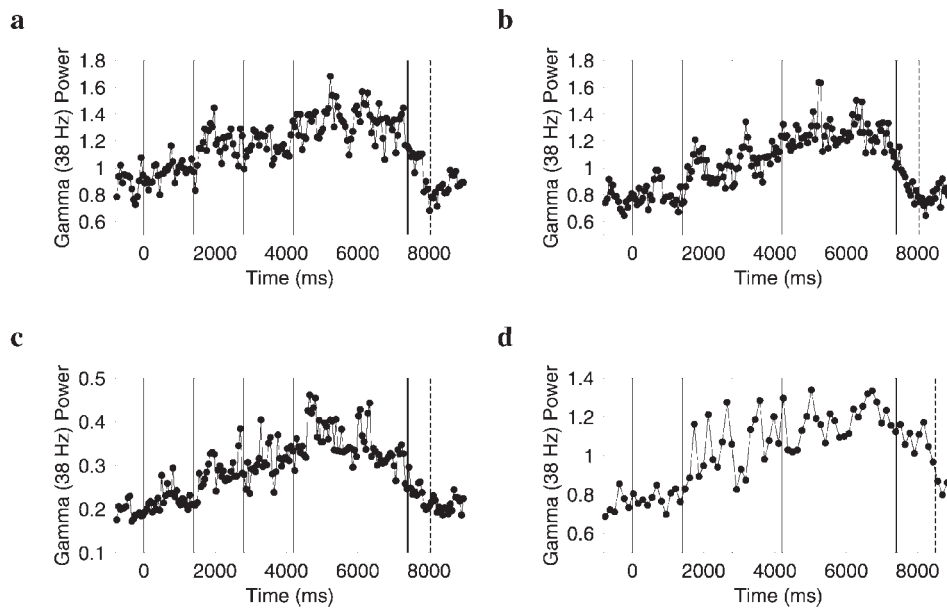


Figure 6. The time course of gamma power tracks with memory load. Power was averaged into bins the size of 10 periods of the corresponding sine wave. A point was plotted every five periods. The first four vertical lines indicate the time of stimulus presentations. The next, heavy vertical lines indicate the arrival of the probe. Dashed vertical lines indicate mean response time. The data show 38 Hz power at selected electrodes. (a–c) These three electrodes lie along a line extending along the left precentral gyrus approaching the collateral sulcus of subject 1. (d) Left superior temporal gyrus, subject 2. Power was averaged over larger time bins for this panel.

presented, remained high throughout the retention interval, and fell precipitously around the time of the response. The drop of gamma power after the response (property 2) is clearly evident from the figure. To quantitatively assess the consistency of gamma power in the retention interval with property 3, we conducted additional analyses.

Comparing gamma power in the retention interval of long lists with the retention interval of short lists offers an additional test of the load-dependence hypothesis. In particular, if gamma power is following memory load, we should observe higher gamma power during the retention interval following longer study lists. Because our earlier analyses relied on lists of four or more items, comparisons with short lists allows for an additional and largely independent appraisal of the load-dependence effect. We found that 26/29 electrodes showed significantly greater gamma power in the retention interval of list length 4 trials than in the retention interval of list length 2 trials (two-tailed t -test, $P < 0.05$). This effect was monotonic,

with gamma power in the retention interval following list length 3 trials being greater than list length 2 for all 29 electrodes (significantly so in 21/29 electrodes) and less than list length 4 for all 29 electrodes (significantly so in 3/29 electrodes). This analysis demonstrates part of property 3, the finding that the level of retention interval power reflects the amount of information held in working memory.

It remains to be shown that gamma power at these electrodes does not increase in the retention interval. Rather than arguing for the null hypothesis, we assessed whether retention interval power following list length N trials is less than power following presentation of item $N + 1$ in other list lengths (see Fig. 7). Consistent with the hypothesis that gamma power at these electrodes is responding to memory load, gamma power was numerically greater following presentation of item $N + 1$ than in the retention interval following list length N in every one of the 29 previously identified load-dependent sites. This increase was statistically significant in 11/29 sites.

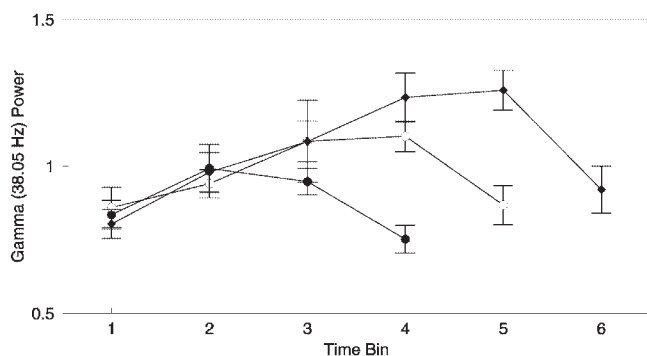


Figure 7. Gamma power across list lengths. Shown is average gamma (38 Hz) power over various task intervals. For each list length N , time bin $i \leq N$ is the interval following presentation of item i , and time bin $N + 1$ is the retention interval. Time bin $N + 2$ refers to the time following arrival of the probe and preceding the response. Average power is remarkably consistent across list lengths following item presentations, increasing roughly linearly with memory load. However, retention interval power 'breaks off', indicating that power is not simply increasing monotonically over the course of the trial. By comparing retention interval power from list length N trials to power following presentation of item $N + 1$ we can assess the dependence of power on memory load *per se* as opposed to the time since initiation of the trial, or anticipation of a motor response. As the probe arrives, power drops off dramatically at each list length. Data are from the electrode shown in Figure 6b. Error bars are 95% confidence intervals.

Discussion

Studies of the neural basis of working memory have revealed that increasing memory load is correlated with increases in the brain's haemodynamic response in a number of regions, especially prefrontal cortex (Courtney *et al.*, 1997; Rypma and D'Esposito, 1999; Bunge *et al.*, 2001; de Fockert *et al.*, 2001). We analyzed electrical recordings from human cortex as patients performed the Sternberg task, a standard assay of working memory. These analyses revealed that at 29 electrodes in two subjects (Fig. 5), oscillations specific to the gamma band increased with memory load over the course of list presentation (Fig. 4a). Gamma power at these electrodes remained constant during the retention interval (Fig. 6), at a level that reflected the amount of information held in working memory (Fig. 7). Gamma power also returned to baseline levels after the information was no longer needed (Fig. 6). Gamma oscillations at these electrodes exhibited all three properties we would expect of a correlate of memory load. Although these results reflect a relatively small sample size, this finding suggests that gamma oscillations support the maintenance of information in multi-item working memory.

Any one of these three properties could be explained by an alternative account. For example, the increase in gamma power during list presentation (property 1) could simply be a correlate of time since initiation of the trial. If this were true we would expect this increase to continue through the retention interval, which was shown not to be the case (Figs 6 and 7). Because we have shown all three of these properties, our findings indicate that changes in gamma power during this task are either a consequence of changes in memory load, or of some factor that is perfectly correlated with memory load in this task. Examples of such factors could be attention and/or arousal.

Our finding of gamma load-dependence in working memory adds to a recent body of work linking theta oscillations with

working memory (Sarnthein *et al.*, 1998; Tesche and Karhu, 2000; Raghavachari *et al.*, 2001). For example, a study using very similar methods (Raghavachari *et al.*, 2001) found that at many cortical sites theta oscillations, which were visible in raw traces, increased (2- to 10-fold) at the beginning of each trial, remained elevated during the trial, then decreased dramatically at the end of each trial. This result suggests that this 'gated' theta activity responds to general task demands but not to the encoding of individual items (Caplan *et al.*, 2001). In contrast to the idea that theta has a non-specific role in working memory, the present results show that gamma activity consistently varied with memory load. These findings support the hypothesis that gamma activity is used to organize and temporally segment the representations of different items in a multi-item working memory system (Lisman and Idiart, 1995; Tallon-Baudry *et al.*, 1996, 1998; Luck and Vogel, 1997; Jensen and Lisman, 1998; Pesaran *et al.*, 2002).

Notes

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