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Human Temporal Cortical Single Neuron Activity During Working Memory Maintenance

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Abstract

The Working Memory model of human memory, first introduced by Baddeley and Hitch (1974), has been one of the most influential psychological constructs in cognitive psychology and human neuroscience. However the neuronal correlates of core components of this model have yet to be fully elucidated. Here we present data from two studies where human temporal cortical single neuron activity was recorded during tasks differentially affecting the maintenance component of verbal working memory. In Study One we vary the presence or absence of distracting items for the entire period of memory storage. In Study Two we vary the duration of storage so that distractors filled all, or only one-third of the time the memory was stored. Extracellular single neuron recordings were obtained from 36 subjects undergoing awake temporal lobe resections for epilepsy, 25 in Study one, 11 in Study two. Recordings were obtained from a total of 166 lateral temporal cortex neurons during performance of one of these two tasks, 86 study one, 80 study two. Significant changes in activity with distractor manipulation were present in 74 of these neurons (45%), 38 Study one, 36 Study two. In 48 (65%) of those there was increased activity during the period when distracting items were absent, 26 Study One, 22 Study Two. The magnitude of this increase was greater for Study One, 47.6%, than Study Two, 8.1%, paralleling the reduction in memory errors in the absence of distractors, for Study One of 70.3%, Study Two 26.3% These findings establish that human lateral temporal cortex is part of the neural system for working memory, with activity during maintenance of that memory that parallels performance, suggesting it represents active rehearsal. In 31 of these neurons (65%) this activity was an extension of that during working memory encoding that differed significantly from the neural processes recorded during overt and silent language tasks without a recent memory component, 17 Study one, 14 Study two. Contrary to the Baddeley model, that activity during verbal working memory maintenance often represented activity specific to working memory rather than speech or language.

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Keywords

temporal cortex; single neurons; human; working memory

1. INTRODUCTION

The Working Memory model of human memory, first introduced by Baddeley and Hitch (1974), has been an influential psychological construct in cognitive psychology and human neuroscience. The model postulates brain systems involved with the temporary storage and manipulation of information (Baddeley, 1992), with what was previously called “immediate” or “short-term memory” as one of its components. It has many features that separate it from long-term memory. (Baddeley, 1992; Shallice and Warrington, 1970; Squire and Wixted, 2011). It is labile, dependent on ongoing brain activity, and disrupted by competing distracting tasks. It deteriorates over time intervals of seconds and minutes and has a limited capacity.

The model includes a central executive involved with the coordination of resources and two “slave” systems, a visuospatial sketch pad and a phonological loop, the former involved with manipulating visual images, the latter storage of verbal (“speech-based”) information (Baddeley, 1992). The phonological loop is composed of a short-term memory store and an articulatory rehearsal mechanism, which is often characterized as a subvocal rehearsal process.

Investigation of the neurobiological substrate for working memory based on the effects of brain lesions suggest that it is related to neocortical activity. Lesions in parietal and lateral temporal lobes have been shown to disrupt working memory processes (Shallice and Warrington, 1970), while medial temporal lesions associated with disruption of long-term memory do not (Squire and Wixted, 2011). The central executive of the Baddeley model for working memory has been arguably related to function of lateral frontal cortex, although the details of this relationship remain controversial. The part of the phonological loop related to articulatory subvocal rehearsal in the model has been related to inferior frontal areas involved in speech production, while the short-term memory store has been related to inferior parietal cortex (Muller and Knight, 2006).

Functional magnetic resonance imaging (fMRI) changes with working memory have been particularly prominent in lateral prefrontal cortex (Underleider, Courtney *et al* 1998). However, the fMRI signal during working memory retention is increased in many other regions, particularly those involved with the representation of the specific retained information. For verbal material this includes frontal and temporal cortical language regions involved in language representations (D’Esposito, 2007).

Both physiologic and lesion findings have related the temporal lobe of nonhuman primates to working memory. Neuronal activity correlates of working memory have been identified in lateral frontal and inferior temporal cortex of nonhuman primates as sustained increases in activity during the delay period of delayed match-to-sample paradigms (Jacobson 1936, Fuster and Alexander, 1971; Fuster and Jervey, 1982; Goldman-Rakic, 1988; Miyashita and

Chang, 1988). The frontal and temporal components could be dissociated by the effects of a distracting task, which interfered with the temporal but not frontal neuronal activity (Miller, Erickson, *et al.*, 1996). Effects of frontal and anterior temporal lesions in nonhuman primates also dissociate the frontal and temporal components of working memory, with increasing delay impairing performance after temporal lesions, and increasing load after frontal, which was interpreted as indicating that the temporal component was involved in memory maintenance and the frontal executive processes (Petrides 2000).

Previous work in our laboratory has examined changes in neuronal activity in human lateral temporal cortex during working memory, utilizing the opportunity afforded during awake neurosurgery for the treatment of medically intractable epilepsy. These investigations have utilized an encoding-storage-retrieval measure of the short-term memory component of working memory (Peterson and Peterson, 1959). Previous neuropsychological investigations using this paradigm have demonstrated the hallmarks of working memory function, including limited capacity and interference by distracting stimuli (Melton, 1963). Performance on this paradigm is impaired by human lateral temporal lesions (Ojemann and Dodrill, 1987) and temporal cortical electrical stimulation mapping (Ojemann, 1978, Ojemann and Dodrill, 1985, Perrine, Devinsky *et al.*, 1994). We have previously reported unique changes in neuronal activity associated with memory encoding for verbal material, by contrasting the neural activity that occurs when subjects identify targets (i.e. names a pictured object, or reads a written word), with the neural activity that occurs when the subject is asked to identify and remember this information for later recall. Significant changes in activity were present in 57% of the 243 neurons recorded from 136 sites in 86 subjects (Ojemann, Creutzfeldt *et al.*, 1988; Haglund *et al.*, 1994; Weber and Ojemann, 1995; Ojemann and Schenfield-McNeill, 1998;1999; Ojemann, Schoenfield-McNeill *et al.*, 2002, 2009). Increased activity represented 65% of these encoding changes.

Here we report the changes during the storage period, comparing activity in the presence or absence of distracting stimuli. These observations are reported for two different patient series. In Study One, activity is compared between the presence or absence of distractors for the entire storage period. In Study Two, distractors are always present, but the duration of the storage is varied so that they occupy only a portion of the storage period on longer storage trials. An abstract of a portion of Study One was previously presented (Zamora, Corina *et al.*, 2001).

The goal of these studies is the identification of neuronal populations with changes in activity that reflect the effect of distractors on working memory. The following questions are addressed: 1. Does the presence or absence of a distractor task during working memory storage modulate the firing patterns of neurons in lateral temporal cortex? 2. What is the relationship between that neural activity and memory performance? 3. What is the relationship of that activity to that of the same neurons during memory encoding and overt speech production?

These data establish the role of the lateral temporal cortex in the maintenance of memory and provide evidence of a direct neural correlate of the active rehearsal process proposed in the Baddeley model of working memory. However, our data indicate that temporal cortical

activity during working memory storage differs significantly from that during language. Additionally these data allow us to draw parallels between human and nonhuman primate studies of working memory under conditions of distraction.

2. METHODS

Many of the same methods were used across both studies. Those are described first, followed by methods that differ between them.

2.1 Methods shared by both studies

Subjects—All subjects were undergoing neurological surgery for the treatment of intractable temporal lobe epilepsy at the University of Washington Medical Center with a technique where they were awake under local anesthesia for a portion of the operation, so that physiologic information unperturbed by general anesthesia could be obtained to plan the resection (Ojemann, 1995). Once this information was obtained and prior to any resection, the microelectrode recordings reported here were obtained. At that time, subjects were fully awake under local anesthesia, having awakened from the propofol intravenous anesthesia used for placement of the local anesthetic field block and craniotomy at least an hour earlier. Surgeries were performed on either the left or right temporal lobe, depending on the origin of the epileptic seizures. Language dominance had been determined preoperatively with intracarotid amobarbital perfusion testing (Wada and Rasmussen 1960). All these studies and the procedures for obtaining informed consent were approved annually by the University of Washington Institutional Review Board and informed consent obtained from each subject.

Behavioral Design—Both studies were conducted across sessions consisting of blocks of memory or identification trials. A memory trial consisted of three phases: *encoding*, *storage*, *retrieval*. During the *encoding phase*, subjects were asked to identify aloud the target stimulus on the screen. During the *storage phase*, subjects maintained the target information in memory. The presence or absence of distracting items and the duration of this phase differ between the two studies. Distracting items, when present, were identified aloud. During the *retrieval phase*, a blank screen with the text “RECALL” was presented, cueing subjects to indicate aloud the target stimulus presented during the encoding phase. All stimuli used were nouns balanced for frequency and concreteness. No target or distracting items were repeated. Figure 1 is an example of a typical memory trial with distractors during memory storage.

An identification trial consisted of a target stimulus on the screen. The subject’s task was to identify aloud the item but without the instruction to remember the item. Stimulus items were the same modality as those used during memory trials. For both studies, 72 items were presented at a 6s interval. The order of the blocks of memory or identification trials was pseudorandomly varied between subjects. Also for both studies, only memory and identification trials with correct performance were included.

Intraoperative Microelectrode Recording—The sites of microelectrode recording were in cortex that was free of interictal epileptiform discharges but were to be subsequently resected as part of the surgical therapy of the subject’s epilepsy. Two commercial tungsten microelectrodes were back loaded through a translucent 1 cm diameter footplate into each of

two hydraulic microdrives, with tips separated by 1–1.5mm. The footplate was used to dampen cortical pulsations. Care was taken to avoid blanching pial vessels. Two microdrives placed in lateral temporal cortex were used in all subjects; however, usable recordings from both drives were not always obtained. The sites of these recordings were identified by numbered tags and their location recorded photographically. Figure 2 indicates the location of the recording sites in Study Two.

The location of the recording sites in Study One were similarly in anterior temporal cortex; their location has been previously published (Ojemann, Schoenfield-McNeill et al 2002). Once stable neuronal activity free from evidence of injury or epileptiform burst activity (Calvin, Ojemann *et al.*, 1973) was identified in at least one microelectrode, the behavioral task was initiated. The archived record for each subject included microelectrode channels along with separate channels for markers indicating when test items were presented and patient's responses. Subsequent analysis was done off line, with initial analysis directed at excluding recordings with artifact or where neuronal activity was lost during behavioral testing. Supplemental Figures S1 and S2 are plots of the firing rates of the individual neurons of each study, comparing activity during the different experimental conditions, but during the encoding phase of the memory measure, before any of those experimental manipulations of distractors had occurred. The high correlations of this encoding activity across the randomly interspersed trials that subsequently will have the different experimental conditions is an indication of this recording stability.

Statistical Evaluation—Each item that required a verbal response was divided into time epochs that were based on the subject's verbal output. Epoch 1 began at the item's presentation onset and continued until 300ms before the subject's overt verbal output. The average duration of this epoch across all items was 1251ms. Epoch 2 began 300ms before overt output and continued for 1500ms. Epoch 2 included activity related to speech motor output. Epoch 3 began at the termination of epoch 2 and continued until the onset of the next stimulus item. Figure 1 illustrates these epochs. Normalized frequency of activity was determined for each epoch of each neuron. All statistical comparisons were between activity during each epoch of one condition to the same epoch from the other condition. Encoding activity was also compared to that during identification of items of the same modality.

For each study the magnitude of the difference in activity between the two conditions was evaluated across the entire population of recorded neurons (Cohen's *d*). The mean change in firing rate across the two conditions for both studies (Distractor vs Non-Distractor, Long-Short Delay) was calculated and histograms were constructed to show the average mean change in firing rate activity in spikes/s of each neuron for each phase of the memory measure, separated by epoch and modality of trial items. In histograms showing activity during the storage phase, activity across the three distractors was averaged for each epoch, as there were no significant differences between first, second or third distractors. On those histograms a value of zero indicates no difference in mean firing rates between the experimental conditions for that neuron. The difference in population mean firing rates overall effect size (the "D" value on each histogram) was then calculated with significance set a $p < 0.05$, calculations performed in Matlab.

Significance of a change in individual neuron activity was determined with Mann-Whitney U tests using StatView (SAS) software. The use of non-parametric statistics for individual neuron analyses was necessary because data do not meet normal distribution assumptions or sample size requirements for parametric analysis. Significance was set at $p < 0.05$, with Bonferroni correction when there were multiple comparisons for the same neuron, such as with the multiple epochs. Differences between groups of neurons were assessed with Chi square statistics.

2.2 Study One

Subjects—The effect of the presence or absence of distracters during memory storage was examined in 25 subjects. They were a subset of the patients reported in Ojemann, Schoenfield-McNeill et al 2002, where firing rates changes with the difference phases of the memory test *with distractors* during storage, and the comparison of that activity during encoding to that during identification was reported. They represent all the patients who performed the distractor manipulation paradigm. The characteristics of those subjects is presented in Table 1.

Behavioral Measures—Data were collected across two testing sessions: one memory and one identification. The presentation order of the sessions was randomly assigned across subjects. The timing of the phases of the individual trials of the memory measure, and the identification trials is also presented in Table 1. The ten second storage phase of the memory session was either filled with three intervening distractor items (*Distractor* task) or with no distractor items (*No-distractor* task). Distractor items in each trial were the same modality as the stimuli to be remembered. Data were collected across seven blocks, each containing six trials. Trials were quasi-randomized within blocks, ensuring that three Distractor trials and three No-distractor trials were presented. Items to be remembered included nameable object pictures, text words and auditory words, pseudorandomly presented in equal numbers.

Neuronal Analysis—Intraoperatively recordings were archived on FM tape. Subsequently, each channel on the FM tape was digitized at 10 KHz on a MacIntosh IIfx computer using a proprietary program designed for the Ojemann lab. Activity of each microelectrode channel was divided into individual neurons using a window discriminator and visual separation of the resulting amplitude-frequency histograms (Schwartz, Haglund *et al.*, 1996). Activity during the storage phase of the memory measure was compared between distracted and non-distracted trials, dividing each distractor into the three temporal epochs and non-distractor trials into epochs based on their average duration for distractor trials. Figure 1 illustrates a typical distractor trial of this study.

2.3 Study Two

Subjects—Characteristics of this separate series of patients are presented in Table 1

Behavioral Measures—The subject engaged in a series of tasks designed to measure memory with different durations of storage. Data were collected across three testing sessions: two memory and one identification. The presentation order of the sessions was randomly assigned across subjects.

Memory sessions contained fourteen trials that were randomly interleaved between Long Delay and Short Delay conditions. During the Storage phase, the subject maintained target item information for either 10s (Short Delay condition) or 30s (Long Delay condition). In either case the storage phase contained three equally spaced overtly identified text distractors, each presented for 3.3s. Figure 1 illustrates a short delay trial, Figure 3 a long delay trial.

The timing of the phases of the individual trials of the memory measure and the identification trials is also presented in Table 1. Because of the extra time required for the long delay trial, and the limited amount of time available in the operating room for this research study, only text word items were presented.

Neuronal Analysis—Intraoperatively each microelectrode channel was digitized at 10 KHz using PowerLab (AD Instruments) software on a Mac G4 system (Apple). Neuronal separation was done offline using the PowerLab spike histogram program. Only neurons whose recordings were consistent throughout each block were used for spike frequency analysis with a proprietary frequency analysis program using MatLab (MathWorks). Normalized firing frequencies for each temporal epoch of the storage phase distractors were compared for each neuron. The difference between long and short storage duration trials was the duration of epoch 3 (cross hatched storage areas in Figure 3).

3. RESULTS

3.1.1 Study One

This study examined the effect of the presence or absence of distracting items during the memory storage. Behavioral data showed that recall error rates averaged 32.7% for Distractor trials and 9.7% for No-distractor trials ($\chi^2 = 12.1$; $p < 0.001$).

Table 2 presents the number of neurons recorded, their distribution across temporal cortex and overall average firing rate. Histograms of the average difference in firing rate between distracted and non distracted trials in each of the 86 neurons were constructed for each phase of the memory test, separately for items of each modality and overall. The histogram for the encoding phase showed no evidence of nonrandom distributions of those changes, as would be expected since there was no indication yet as to the distractor condition on that trial (Supplementary Fig S3). The histogram for the storage phase, when distractor manipulation occurred, is shown in Figure 4

Nonrandom distribution of overall activity changes is evident for each modality considered separately and all modalities together. Additionally, there is nonrandom distribution of changes during epoch 1 for text and auditory words and all items. Inspection of these histograms indicates an excess of neurons with greater activity for nondistracted than distracted trials.

Thirty-six of the 86 neurons had significant changes between distractor and non-distractor trials. In 33 neurons this change was only during storage, 1 only during retrieval, and 3 across more than one memory phase (1 during encoding and storage, 2 during storage and

retrieval). Of these 36 neurons, 26, recorded from 13 patients, had increased firing only during No-distractor trials, 10 (5 patients) only during distractor trials. ($\chi^2=7.111$, $p=0.008$). For the 26 neurons that exhibited *increased firing during No-distractor trials*, average firing rate during the storage phase was 8.25 spikes per second for No-distractor trials and 5.59 for Distractor trials. Activity of a typical neuron with these features is shown in Figure 5. These neurons were recorded from 4 of 17 superior temporal gyrus neurons sampled, and 22 of 69 from middle gyrus, with no significant difference between hemispheres (13 of 49 dominant, 13 of 37 nondominant).

Twenty-one of these neurons had changes for only a single modality, 8 with auditory items, 7 text and 6, objects. The remaining 5 neurons had changes with multiple modalities, 3 with auditory and object items, 1 for auditory and text, and 1 for all three modalities.

This difference in activity was most prominent in overall activity and in epoch 1, the period from distractor item presentation to 300ms before the overt identification of that distractor. Ten neurons had this combination of significant changes (Example in Figure 5), 5 others only in epoch 1 and 4 others only in overall activity. Activity of the remaining 7 neurons was divided between only epoch 2 (3) and only epoch 3 (4). The distribution across phases and epochs of the task is illustrated in Figure 6.

The 10 neurons with *increased firing during Distractor trials* had a storage phase average firing rate of 3.12 spikes per second for Distractor trials and 2.89 for the No-distractor trials. These were identified slightly more often in middle than superior temporal gyrus recordings (9 of 69 neurons sample from middle gyrus, 1 of 17, superior gyrus), and more often from dominant hemisphere (8 of 10). However none of these differences are statistically significant. This change was somewhat more frequent in epoch 2 (7), the period of overt speech, and was present only for single modalities, 5 auditory, 2 text, 3 objects.

3.1.2 Relation to encoding effect—The encoding phase of the memory task and identification of items of the same modality both require the same speech behavior, differing only on the instruction to remember the item, or not. This direct comparison of neuron activity during encoding compared to identification nullifies contributions of speech which is common to each of these tasks, highlighting the contribution of memory processes. In that comparison, 48 of 86 neurons had significant differential firing rates, most with increased firing during encoding. Of the 26 neurons with *increased activity during the storage phase in the No-distractor trials*, 17 (65%) had increased activity during encoding. These neurons have a change in encoding activity that is significantly different from that during an identification task that requires the same speech processes. That activity continues from memory encoding into memory storage in the Non Distracted trials. This sustained activity is not related to overt language processes. Moreover, the increased activity during the storage phase of the No-distractor trials occurs when no overt articulation is taking place. Indeed it is reduced with overt language processes (Figure 5).

The timing of the onset of that encoding activity has been previously reported for the neurons of this study (Ojemann et al, 2009). Those data were available for 14 of the 17 neurons with significant increased activity for the nondistracted condition, and significantly

increased encoding activity. Seven had onset of this activity in the first epoch, some very early, peaking within 50–100ms of item presentation.

Of the neurons with *increased activity for the distracted condition*, three had greater activity for identification than encoding, two the reverse and the remainder no significant differences on that comparison. Four of the five encoding changes appeared in the first epoch.

3.2.1 Study Two

This separate study examined the effect of lengthening memory storage from 10s (Short Delay condition) to 30s (Long Delay condition) while including three equally spaced distractors, each lasting 3.3s, during the storage phase of both conditions. All presentation items were text words. The error rate for short delay trials averaged 38%, similar to that for the distracted trials of Study One, which is the identical task. However, the error rate was still 28% for Long Delay trials, a difference that is not statistically significant. Table 2 indicates the number of neurons recorded, their distribution across temporal cortex and average firing rate. As in Study One, the histogram of changes in activity of all neurons between trials with long and short delays during the encoding phase, when the patient did not know if it would be a long or short delay trial, had no significant differences (Supplementary Figure S4)

Figure 7 shows the histogram for the storage phase. Significant non random distributions of changes are evident for epochs 1 and 3. However inspection of them indicates that in epoch 1 there is an over representation of activity that is greater for short delay trials, and in epoch 3 neurons with greater activity during long delay trials are overrepresented. The experimental manipulation, between long and short delay trials was confined to this epoch.

Thirty-six of the 80 neurons showed a significant difference in firing rate between these two conditions. Figure 8A shows the distribution of these between the phases of the memory test.

As in Study One, most (29 of 36) of these firing differences occurred during the storage phase ($\chi^2 = 16.125$, $p < 0.001$). Three neurons exhibited increased firing only during encoding, 18 only during storage, 4 only during retrieval, and 11 across more than one memory phase (4 during encoding and storage, 6 during storage and retrieval, 1 across all memory phases). Since the experimental manipulation occurred during the storage phase, our subsequent analyses focused on these 29 neurons.

Of these 29 neurons, 23 had *increased firing during Long Delay trials* and 6 had increased firing during the Short Delay trials ($\chi^2 = 7.111$, $p = 0.008$). For those 23 neurons with increased activity, average firing during the storage phase of the Long Delay trials was 3.46 spikes per second and 3.20 for the Short Delay trials. These neurons were recorded from 8 patients. Figure 9 illustrates the average activity of one of these neurons during the two conditions.

Nine were among the 51 neurons recorded in language-dominant hemisphere, 14 from 39 neurons from non-dominant hemisphere. ($p = .056$, Fishers exact, 2 tail). They represented 3 of the 4 neurons recorded from superior temporal gyrus and 20 of the 77 neurons from middle or inferior temporal gyri ($\chi^2 = 4.182$, $p = 0.04$). When the activity of these neurons was

divided by the temporal epochs, 4 neurons exhibited these differences during epoch 1 (two only then), six during epoch 2 (five only then), 22 during epoch 3 (15 only then), and 10 during overall activity (2 only then) ($\chi^2=18.24$ $p < 0.001$). Figure 8B illustrates this for the different epochs.

Of the 22 neurons showing a significant effect during epoch 3, all 22 neurons had higher firing rates during the Long Delay trials compared to the Short Delay trials ($\chi^2=22.00$, $p < 0.001$). Average firing rate for these neurons was 3.52 spikes per second in Long Delay trials and 2.59 for the Short Delay trials. Epoch 3 of the storage phase is the period between 1200ms after initiating the overt identification of a distractor, until the presentation of the next distractor. In this interval the patient is silent but activity of these neurons increases, as can be seen for the neuron in Figure 9. This is similar to the increased activity during the silent No Distractor trials of Study One.

For the 6 neurons that had *increased firing during the Short Delay trials*, average firing rate was 11.86 spikes per second for the Short Delay trials and 10.11 for the Long Delay trials. Half were located in middle temporal and half in inferior temporal gyri. The three neurons in middle temporal came from language-dominant hemisphere and the three in the inferior gyrus non-dominant hemisphere.

3.2.2 Relation to encoding effect—As in Study One, we compare firing rates from the identification trials to the firing rates during the encoding phase of the memory trials, which allow us to factor out all of the language effects and associate any differential changes in neuronal activity to memory processes. A significant difference between these two tasks was observed for 45 of the 80 neurons in Study Two. Of those 45 neurons, 21 also had a significant difference in the Study Two experimental manipulation in the storage phase of the memory task, in 14 of these increased activity during epoch 3, the silent period between distractors. Those neurons represent 64% of the 22 neurons with that change. As was shown in the previous study, there is a change in activity in these neurons that is independent of identification processes that continues from memory encoding into memory storage.

4. DISCUSSION

This study examined the effects of distracting tasks on human lateral temporal single neuron activity during the storage phase of an encoding-storage-retrieval measure of verbal working memory. Behaviorally, distractors impair working memory performance (Baddeley *et al.*, 1975) including specifically on the short-term verbal memory measure assessed in our study (Melton 1963). Our subjects demonstrated a similar impairment of performance when the distracting task occupied the entire storage period (Study One) with 3.3 times as many errors on trials with distractors as without.

In that study we identified a population of human lateral temporal cortical neurons with activity that was significantly different between the presence or absence of distractors, representing 42% of the 86 recorded neurons. In 73% this was increased activity in the absence of distractors, an increase that averaged 48%. This activity thus reflects an active

neuronal process in the short term store component of working memory, reduction of which by distracters is associated with poorer memory performance.

Study Two provides additional insight into this. That study compared activity when the 10s storage period was filled with 3.3s distractors, to a storage period three times longer (30s) where the 3.3s distractors occupied only a third of the storage period, the remaining part of the storage period on those trials represented the undistracted condition. Forty-five percent of the 80 single neurons recorded in that study demonstrated a significant difference between the short and long storage periods, with 79% having increased activity for the Long Delay trials, though averaging only an 8.1% increase. Previous experience with our paradigm indicated that increasing the storage period should increase errors (Melton, 1963); however, this was not the case in our eleven subjects. Rather there was no significant effect on performance in either direction, with the average error rate slightly but not significantly less for our Long Delay storage period trials compared to the Short Delay trials. At best the small increase in neuronal activity during the undistracted period may have counteracted the expected effect of the longer storage period. Studies One and Two are readily compared. The “baseline” conditions of the two studies, the distracted trials of Study One and the short delay trials of Study Two, are behaviorally identical. Memory retention for those trials is very similar (32.7% errors in Study One, 38% Study Two). However the effect of the different distractor manipulations had different effects on both neuronal activity and performance in the two studies, with Study One having a large increase in neuronal activity in the absence of distracters and a large improvement in memory performance, while in Study Two there is a small increase in activity and no significant improvement. The degree of memory retention is related to the level of the increased activity during memory maintenance. In both studies most of this increased activity was confined to a silent interval, in Study Two from the end of the epoch containing overt identification of a distractor to the presentation of the next distractor. For 15 neurons, it was specific to that time period.

These findings provide affirmative answers to the first two questions we posed. Human lateral temporal cortex exhibits increased activity in the storage phase of undistracted working memory that is reduced by distractors, similar to findings in nonhuman primates (Miller, Erickson *et al.*, 1996). In addition, the level of that activity is related to performance, as expected if it represents the active storage process. The neurobiologic substrate of the short-term memory store has been generally considered to be parietal cortex (Shallice and Warrington, 1970; Mueller and Knight, 2006). Our findings extend this to lateral temporal cortex.

In the Baddeley model, the active storage process is often conceived as a speech-based rehearsal for verbal material that refreshes the phonological store. Much of the neural activity we identified in lateral temporal cortex during memory storage is dissociable from that with overt speech. We have previously described the changes in single temporal cortical neuron activity during overt language (see Ojemann 2013 for review). The encoding phase of our short term memory measure includes overt language. To remove any effect of activity related to overt language, we compared activity during encoding to that during an identification task of the same modality, where the only behavioral difference was the presence or absence of the instruction to retain the item in memory. Of the neurons recorded

in the present studies with significantly increased activity during memory storage, 65% in Study One and 64% in Study Two had a significant difference with this encoding comparison, indicating that for a substantial portion of these neurons, this activity during encoding is not equivalent to that with overt speech production, but rather specific to the memory process. Although the encoding comparison was to overt speech, there is evidence that this difference between the activity during verbal memory and that during language extends to covert (silent) language. The significant change in left temporal lobe single neuron activity during language measures is a reduction in activity, an effect that is evident in the temporal epoch immediately after item presentation, before any overt speech (Schwartz, Haglund *et al.*, 1996; 2000). In that same epoch, memory encoding activity is increased. Moreover, the increased activity during memory storage in the present study occurs in those periods when there is an absence of overt speech. Indeed it is suppressed by overt speech distractors. This non-speech related increased activity is sustained from encoding to memory storage. We have previously published examples of individual neurons with sustained activity extending from encoding into storage (Ojemann, Schoenfeld-McNeill *et al.*, 2002), and when viewed by individual trial activity across the entire recording session as a significant task specific sustained increase in firing rate for the block of trials of the memory test, compared to the preceding and following control tasks (Ojemann and Schoenfeld-McNeill, 1999).

There is additional evidence of the importance of this temporal cortical sustained activity to working memory maintenance. Only correctly performed trials were included in both studies reported here. However, we have previously reported the differences in single neuronal activity between trials with correct or incorrect working memory performance, when the storage period was filled with distractors and identification during encoding was intact (Ojemann, Schoenfeldt-McNeill *et al.*, 2004). In all cases, activity significantly differentiating correct from incorrect memory performance could be detected during encoding, with both increases and decreases in activity for trials with errors compared to those without. Half of these neurons had similar differential activity persisting into the storage period of those trials.

Previous findings for the neurobiologic correlates of the phonological loop subsystem derived with other methods for assessing cortical function have shown a link to parietal rather than temporal cortex (Paulesu, Firth *et al.*, 1993; Awh, Jonides *et al.*, 1996; Becker, Mintun *et al.*, 1996; Smith and Jonides, 1999; Muller and Knight, 2006). Some of the more recent reconceptualizations of this subsystem discuss verbal working memory as a process that emerges from activity across the entire neural network underlying perception and language production (Fiebach, Rissman *et al.*, 2006; Buschbaum and D'Esposito, 2008). Moreover, it has been suggested that working memory maintenance can be supported by either an overt, speech-based rehearsal or by an alternative covert process (Cowan, 1999; Chein, Ravizza *et al.*, 2003). Our findings indicate that in temporal cortex the neurobiologic substrates for recent verbal memory and language are at least in part separate. Additional evidence for this separation of speech from working memory comes from the effects of high frequency electrical stimulation of anterior temporal cortical sites. Stimulation there interferes with working memory performance, particularly when the current is applied during encoding or storage, rather than at retrieval. Similar to our single neuron findings,

this effect on working memory is separate from effects on language, as stimulation of these sites generally does not interfere with language measures (Ojemann, 1978; Ojemann and Dodrill, 1985).

The present studies provide some insights into the role of this non-speech activity in working memory. Several features suggest that it reflects attentional mechanisms: its sustained “tonic” nature and the abrupt shift in the level of this tonic activity with the introduction and removal of the distractors. Speculatively, this activity may provide a necessary increase in gain on the activity of the working memory neural network rather than conveying specific item information. Attention selection and monitoring during working memory has been considered to be the role of prefrontal cortex (Muller and Knight, 2006). Other features of our study seem compatible with providing item specific information. These features include the modality specificity of Study One, and the very early onset of the peak increase (the first 50–100ms of exposure to the item during encoding) in some of the activity sustained into memory storage. There is even evidence of neurons that have both this early peak phasic activity and the tonic sustained activity changes during working memory (Ojemann et al 2009).

Combining the findings from the present studies with our previous investigations of single neuronal activity during this paradigm provides the basis for a model of one of the common patterns of lateral temporal cortical neuronal activity during the verbal short term memory store of “working memory”. With encoding, there is activation of a large neuronal pool, 50% or more of the various samples in our different series of patients. This activity differs significantly from that during verbal identification of the encoded material. (Ojemann, Creutzfeldt *et al.*, 1988; Haglund, *et al.*, 1994; Weber and Ojemann, 1995; Ojemann and Schoenfeld-McNeill, 1998, 1999; Ojemann, Schoenfeld-McNeill *et al.* 2002; 2009). This encoding activity occurs very early in superior temporal gyrus, and somewhat later in middle gyrus (Ojemann, Schoenfeld-McNeill *et al.*, 2009). Working memory errors occur in the absence of this activity (Ojemann, Schoenfeld-McNeill *et al.*, 2004). The studies of the present paper indicate that about 30% (35% Study One, 31% Study Two) of this encoding activity is sustained into the period when the memory is stored, and influenced by distractors. The level of this activity is related to working memory performance, suggesting that it reflects active rehearsal. Neurons with these properties account for about 60% of those with increased activity during non-distracted periods of memory storage (65% Study One, 61% Study Two). How long this activity is sustained is unknown. The longest period assessed in the present studies was the third epoch of the retrieval phase, from approximately 39–41s after item presentation. Figure 10 demonstrates that an effect of distractor manipulation can still be demonstrated at that time, but in many fewer neurons that had this effect during memory maintenance (Figure 8B).

Supportive evidence for this observation comes from an earlier study of serial retrieval of the same item after ten second distractor storage periods, when activity steadily diminishes. (Haglund, Ojemann *et al.*, 1994). Presumably in the period when these cortical neurons have been active, the information has been transmitted to medial temporal structures, where the earliest evidence for increased neural activity in humans is about 400ms (Rutishauser U, Schuman et al 2014), for eventual long term memory consolidation.

This pattern of neuronal activity, increased activity during encoding extending into memory storage, has been reported in recordings from temporal cortex of nonhuman primates during working memory, despite the differences in homology between monkey and human temporal lobes (with more gyri and a substantial anterior expansion in the latter) and the differences in experimental design with verbal items and cued recall in our studies and colors and figures and recognition memory in the monkey. About 25% of monkey inferior temporal gyrus neurons have this pattern, as shown by differential responses to different stimuli depending on whether the item is to be remembered, differences that are sustained into the delay period (Fuster and Jervey 1982; Miyashita and Chang, 1988). As in the human, this effect is largely lost, with activity no longer related to performance when distractors are introduced (Miller, Lin *et al.*, 1993). Although the samples of neuronal activity during working memory paradigms are small for both monkey and human, it would appear that in the human there is a higher proportion of neurons with these properties present over a wider area of anterior lateral temporal cortex including superior and middle temporal gyri.

The changes in human temporal cortical neuronal activity with episodic working memory have a number of parallels with the changes identified there with associative learning (Weber and Ojemann, 1995; Ojemann and Schoenfield-McNeill, 1998). Neurons with activity that differentiated learned from unlearned items were those with reduced activity during overt identification, but increased activity during working memory (assessed as in the present study). In those neurons, the activity that differentiated associations learned or not learned on the first encoding trial was that sustained throughout encoding for the learned associations, compared to the rapid deterioration of activity when the associations were not learned. Sustained non-speech activation seems to be a common feature of human temporal cortical neuronal activity during episodic memory and associative learning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Human single neuron activity was recorded in lateral temporal cortex,
- Effects of manipulating distractors during working memory maintenance was observed
- There were significant changes in activity in 39% of 166 neurons recorded
- In 74% of those neurons there was increased activity in the absence of distractors
- Magnitude of this activity parallels memory performance, suggesting active rehearsal
- That activity differs significantly from that during overt and silent speech.

Figure 1.

Typical distracted trial of Study One and short delay trial of Study Two. There is no delay between distractors, so the entire storage phase is 10s long.

Figure 2.
Location of recording sites in Study Two.

Figure 3.

Typical long delay trial of Study Two. The total duration of the storage phase is 30s, with each distractor lasting 3.3s, separated from the next distractor by 3.7s (those intervals indicated by the cross-hatching during storage).

Figure 4.

Histogram of differences in firing rate between trials with distractors during memory storage and those without (D-Non-D) for each neuron recorded in Study One. Firing rate difference in action potentials/s indicated on x-axis, number of neurons with each different firing rate difference on the y-axis. Presentation is by different modality of items (Text, Audio or Object and All modalities together), for the different temporal epochs (E1–3, defined in 2.1) as well as overall activity (EA). As there were no significant differences between changes in activity after first, second or third distractors on each trial those changes were averaged together for that trial. Epochs with statistically significant nonrandom distribution of the differences are indicated by crosses.

Figure 5.

Study One. Activity of a typical neuron during trials with and without distractors. This neuron demonstrated significantly increased activity in the absence of distractors for auditory items ($p < 0.05$), most evident in epoch 1. **a.** Raster of activity summed for all auditory trials by each phase of a trial, separately for the experimental conditions. Bars on time line indicate onset of distractors. **b.** Activity during the storage phase aligned to the onset of each of the three 3.3s distracting item when present, or average time of onset when absent. Below that activity is shown summed across all three distractors, in 50msec bins. Bars delineate the onset of the three temporal epochs described in 2.1. Vertical axis is firing rate in discharges /second. Neuron 9828 4.2, Left superior middle temporal gyrus, 41mm from temporal lip, 1mm deep

Figure 6. Study One. Distribution of neurons with *increased activity during nondistractor trials*, by phase of the task (A) and temporal epoch (B).

Figure 7.

Study Two. Distribution of average long-short firing rate difference for storage phase in each neuron by epoch and all epochs combined. Analysis and presentation as in Figure 4.

Figure 8.

Study Two. Number of neurons with significantly greater firing for long vs short delay condition, by paradigm phase (A) and epoch (B)

Figure 9.

Average activity of a single human temporal cortical neuron during the storage phase of the recent memory measure described for Study Two in the text, with the duration of that storage phase 10s (short delay) or 30s (long delay). a. Raster of activity summed for all trials of the entire storage phase, aligned to onset of first distractor. Onset of each 3.3s distractor indicated by vertical bar on time line. These are spaced 3.3s apart with storage phase of 10s duration, 10s apart with storage phase of 30s duration. b. Above: rasters of summed activity for all trials separately aligned to onset of each of the three distractors. Below: peristimulus time histograms in 50msec bins of that activity summed for all three distractors, aligned to each distractor's onset. Bars on the time line delineate the three temporal epochs described in 2.1. Vertical axis is firing rate in discharges/second. Horizontal axis is in seconds. This neuron demonstrates significantly increased firing in epoch 3 of long duration storage phase, the time between the distracting items ($p < 0.05$). Neuron 0223 2.1 Right superior middle temporal gyrus, 38mm from temporal tip, 2mm deep.

Figure 10.

Study Two. Histogram of long-short difference in all neuron by epoch for retrieval. Note nonrandom excess of greater firing for long delay in epoch 3. This epoch would start about 39s after item presentation

Table 1

Subject characteristics and Behavioral measures parameters for the two studies.

	Study 1	Study2
Subjects: number	25, 16 female	11, 3 female
Age (range)	36years (20–61)	38years (26–52)
Age at seizure onset (range)	17 (4m–35)	28 (12–45)
Preoperative VIQ	94 (72–115) 21 subjects	88 (72–119)
Side of operation: Left/Dominant hemisphere	15/12	7/7
Right/Dominant hemisphere	10/1	4/0
Behavioral measures: memory trial timing:		
Encoding	6s	6s
Storage	10s, with or without 3 3.3s distractors	10 or 30s, all with 3 3.3s distractors
Recall	6s	6s
Modalities tested:	Auditory words, text words, object names	Text words
Identification timing	6s	6s

Table 2

Number of neurons recorded in the two studies, their distribution across lateral temporal cortex, number with significant differences between the presence or absence of distracting stimuli during memory storage, as well as the number of those neurons with significant differences between memory encoding and identification of the same material.

	Study 1	Study 2
Number of neurons	86, 49 dominant hemisphere	80, 51 dominant hemisphere
Temporal cortex distribution:		
Superior temporal gyrus	17	4
Middle temporal gyrus:	69	57
Inferior temporal gyrus:	0	19
Overall firing rate	6.24 discharges/s	5.43 discharges/s
Number of neurons with significant difference with the distractor experimental manipulation, presence or absence (Study 1), interval between (Study 2) *	38 (44%) ***	36 (45%) ***
Number that occurred in memory storage phase **	36(42%)	29 (36%)
Number of those memory storage neurons with increased activity for the non-distractor condition (Study One) or epoch 3 long delay (Study Two)	26 (30%)	22 (27.5%)
Number of neurons in the row above that also had significantly greater activity for encoding than identification for items of the same modality (the two conditions differing only by the instruction to retain the item in memory for encoding)	17 (19.8%)	14 (17.5%)
Performance (% memory errors)	32.7% Distractor trials, 9.7% No-distractor trials **	38% Short Delay trials, 28% Long Delay trials

* $p < 0.05$, Mann-Whitney test with Bonferroni correction for multiple comparisons

** $\chi^2 p < 0.05$

*** Per cent of total number of neurons recorded in that study.