

REPETITION-SENSITIVE COMPONENTS OF NEURAL ACTIVATION: EVIDENCE  
FROM INTRACRANIAL RECORDINGS FROM THE HUMAN MEDIAL TEMPORAL LOBE

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ABSTRACT

Neuropsychological studies indicate that hippocampal formation in the human medial temporal lobe (MTL) plays a crucial role in the formation and retrieval of memories for recent events. We have found that components of neural activity recorded from the MTL during recognition memory testing discriminate between repeated and nonrepeated words. Such recordings are made possible via intracranial electrodes implanted for the isolation of seizure foci in epileptic patients. Similar activity can be elicited during lexical decision tasks, where it is also sensitive to stimulus repetition. It has been suggested that repetition effects on lexical decision performance measures are a reflection of procedural learning, unlike the type of learning that underlies recognition memory performance, does not involve the MTL. However similar changes in the MTL response during both lexical decision and recognition memory suggests that a common mechanism contributes to repetition effects across tasks. These potentials provide a juncture for studies at both the psychological and synaptic levels of analysis.

INTRODUCTION

Many current biologically inspired models of memory and cognition represent mental states as patterns of activation occurring across a network of processing units (e.g. Hinton & Anderson, 1981). The units are more or less explicitly analogous to neural elements or integrated collections of neural elements. Many of these models share an assumption that the occurrence of a pattern of activation can lead to an event-specific modification of the system. This modification is usually characterized as changes in the weighting of connections between units. Multiple sources of evidence indicate that in the human brain medial temporal lobe (MTL) structures-- in particular the hippocampus --mediate the initial enhancement of connection strength, at least during the acquisition of complex declarative knowledge. In order to explore this learning process we have made intracranial recordings from the hippocampus, parahippocampal gyrus, and emphasis on memory judgments for recognition of recent previous occurrence. In this paper some of our current findings from these studies will be

described.

#### NEUROBIOLOGICAL AND CLINICAL CONTEXT OF RECORDING STUDIES

The MTL is important for the formation and retrieval of memories for recent patterns of activation. Bilateral lesions to this area yield a dense and specific amnesia for recent events (Scoville & Milner, 1957). Unilateral lesions reflect hemispheric specialization for memory functions, thus, lesions to the MTL of the language-dominant hemisphere create a larger deficit on tests for memory for verbal materials than do lesions of the nondominant hemisphere. Stimulation studies indicate that some important MTL contribution to memory is made during the first 500 milliseconds following presentation of a stimulus (Halgren, Wilson, & Stapleton, 1985), both when that item is first presented for learning, and also when it later re-occurs as a recognition probe. Anatomically the MTL is characterized by converging excitatory inputs from both modality specific and transmodal association cortices (coding the results of perceptual and cognitive analyses), and diverging outputs to these same areas, creating a circuit for the cycling of activation between limbic and cortical areas (Van Hoesen, 1982). It is thus well situated to affect changes in the neural activation that presumably underlies experience. Hippocampal synapses are characterized by a plasticity potentially critical for trace formation. That is, activation of hippocampal neurons can result in morphological changes in their connectivity (Lynch & Baudry, 1984) and physiological changes in their conductivity that are specific to the pattern of activated synaptic inputs (McNaughton, 1983; Teyler & Piscenna, 1984).

Formal models of the neural basis of human cognitive memory (e.g. Gardner-Medwin, 1976; Halgren, 1984; Marr, 1971) suggest that the MTL helps retain information about novel juxtapositions of past inputs, functioning in concert with the association cortices and other areas to modify the connectivity of neural elements such that subsequent partial inputs will be sufficient to progressively reconstruct a pattern of activation similar to that of the original experience. In effect, the hippocampus might be viewed as a source of weak randomly wired connections between disparate cortical units. Selective enhancement of these connections might yield dynamic links to support memory until more permanent structural changes in synaptic connectivity are formed (cf. Feldman, 1982). Grossberg (1976) has emphasized the need for a mechanism to stabilize new patterns of activation if subsequent similar input patterns are to be coded into the same recognition category. Halgren (1984) has proposed that new ensembles of cortical elements are stabilized as a result of the emergence of excitatory association cortex-MTL-association cortex feedback loops from these random connections, leading to potentiation of the hippocampal synapses in this circuit.

Unilateral surgical excision of the MTL is a technique often employed in an effort to control medically intractable complex partial epilepsy. In many cases the surgical prognosis can be greatly improved

if the epileptic focus has been previously unambiguously localized to one MTL by monitoring the activity of the MTLs during the onset and spread of seizures (Delgado-Escueta & Walsh, 1983). Such monitoring is made possible by recording from chronically implanted intracranial electrodes. While awaiting the spontaneous occurrence of seizures, the opportunity sometimes exists to record the electrical activity of the MTL while the patient is engaged in controlled cognitive tasks. Such recordings provide a unique window for monitoring neural activity possibly central to memory processes.

A common technique in human electrophysiological studies is to repeatedly sample activity elicited in conjunction with some sharp onset stimulus event, such as the presentation of words in relatively simple judgment tasks. Stimulus-locked recordings can be subjected to signal averaging techniques to produce a representation of the prototypical sequence of neural activity specific to the processing of stimuli of that class. Such representations are referred to as event-related potentials (ERPs). ERP components are typically identified as characteristic task-related peaks on the averaged waveform and referred to by their typical polarity and latency to peak amplitude. Isomorphisms are often made between such components of ERPs, and inferred concomitant cognitive processes. In contrast to recordings of the action-potentials from individual neurons, these field potentials reflect the summation of relatively co-temporal synaptic potentials across a population of neurons. They must then more closely represent gross envelopes of activation that parse or modulate mental events rather than closely reflecting specific information transactions. However even this gross measure is highly sensitive to item specific features such as the intrinsic meaning of a stimulus, its relationship to local context, and whether it has also occurred in the recent past.

#### INTRACRANIAL ERPs DURING RECOGNITION MEMORY TESTING

Scalp-recorded ERPs, inasmuch as they are one of the few measures by which neural activity can be noninvasively monitored in normal humans, have been intensively studied. Among many other things, such recordings have indicated that the waveforms elicited in normal subjects during testing for recognition of previous occurrence discriminate between repeated words and foils (foils in this task are words that are well known in the lexicon, but have not occurred before in the test context, i.e. 'nonrepeated' words). This discrimination is eliminated in subjects who have received surgical lesions that include medial structures in the temporal lobe of the language dominant hemisphere (Smith & Halgren, in preparation). Such an effect underscores a global contribution of the MTL to patterns of neural activation. However scalp-recorded ERPs represent the smearing of activity from multiple intracranial current sources, and thus are seldom informative with respect to the specific activity of any particular brain system. Recording directly from the MTL allows the monitoring of the activity of local neuronal populations. The hippocampus is a laminated structure, with the apical dendrites of its

pyramidal cells arranged in a highly regular parallel fashion. This architecture is appropriate for the summation of synchronous synaptic potentials, and thus potentially for the generation of ERPs. MTL-generated ERPs have been known for some time to be elicited in simple perceptual discrimination tasks (e.g. Halgren, Squires, Wilson, Rohrbaugh, Babb, & Crandall, 1980).

In recent years we have been recording MTL activity during more demanding cognitive tasks, such as the recognition memory (RM) task mentioned above. In this task subjects are presented with a series of 180 common words organized into nine randomly ordered blocks. Ten words are common to all blocks and serve as the target set. The other 90 are presented only once. Following the first block, subjects indicate by a keypress whether each word has also occurred earlier in the test. Words are exposed for 300 msec every 2500 msec, and a feedback tone occurs 1200 msec after word onset. Although this test is very easy for normal subjects, who consistently perform it with a hit rate of well over 90% across blocks and very few false recognitions, it is highly sensitive to MTL dysfunction. Subjects who have received unilateral left-sided MTL lesions score substantially below the normal range in RM, and hit rate approached the chance level in one amnesic patient who was tested.

Intracranial recordings are typically made simultaneously from multiple electrodes and recording contacts, sampling activity from both MTLs across multiple anatomical structures. Such recordings during RM are characterized by long-latency (300-800 msec to peak amplitude) and large amplitude (often 50 to 250 microvolts) ERP components, that often discriminate between repeated and nonrepeated words. The voltage and polarity of these ERP components can vary greatly both within and across MTL structures, with large differences often seen between even closely spaced electrode contacts (for a more detailed explanation of recording method and results, see Smith, Stapleton, & Halgren, 1986). Potentials recorded from the left amygdala of seven patients during RM are illustrated in figure 1. As can be seen in the figure a robust negative component was observed between 300-500 msec after stimulus onset (N460) in response to words on their first presentation. Although the synaptic basis of this component is speculative, it possibly represents the summation of synchronized synaptic activation of hippocampal pyramidal cells in response to diffuse cortical input. The N460 is much attenuated when it is elicited in response to repeated words, suggesting that the MTL (or its input) was modified in some way by the recent experience with the initial patterns of activation elicited by the set of repeated words. This difference is not simply due to a state change or nonspecific habituation, in that repeated and nonrepeated words are intermixed in a random sequence. Following the N460 to correctly recognized repeated words, a broad, typically positive potential (P620) was often observed at many MTL sites. A component with a similar MTL voltage distribution is also elicited by attended infrequent stimuli in simple perceptual discrimination tasks (e.g.

Halgren et al, 1980). Current evidence suggests that it is associated with a decrease in local neuronal firing (Altafullah, Halgren, Stapleton, & Crandall, 1986), possibly as a result of recurrent inhibition of hippocampal pyramidal cells (cf. Andersen, Eccles, & Loynning, 1964).

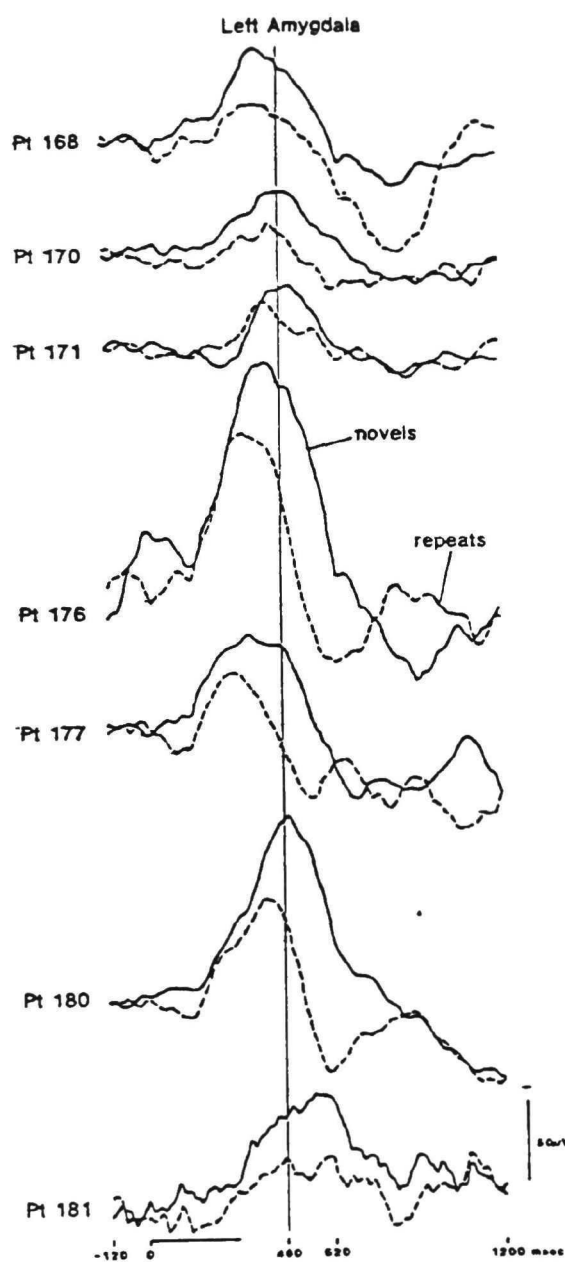


Figure 1. Average waveforms recorded from the left amygdala of 7 patients during recognition memory testing. Negativity is up in this and subsequent traces (from Smith, Stapleton, & Halgren, 1986).

## SMITH, HALGREN, HEIT

Large amplitude, steep voltage gradients, and polarity reversals over short distances, strongly suggest that the N460 and P620 are generated within the MTL. Further evidence for local generation is provided by recordings from multicontact electrodes that allow neural activity to be sampled at regular spatial intervals from the medial temporal lobe sites out to the ipsilateral temporal cortex. Such recordings indicate that these potentials are consistently of largest amplitude at MTL contacts. In addition, in patients with severe MTL pathology, these components are often absent or extremely corrupted, a result that would not be expected if they originated from extra-MTL sources.

Thus, these potentials appear to be generated in a brain structure critical for cognitive memory, at a time when that structure might reasonably be assumed to be making some important contribution to performance. That, and their consistent sensitivity to recent occurrences of similar past inputs, provide strong circumstantial evidence that these potentials directly reflect the neural activity inherent in the early stages of memory formation/retrieval. The N460 might well represent a pattern of activation that results in the enhancement of weak latent connections between cortical elements that is probably central to memory for the novel aspects of recent experience. The P620 might represent a complementary process of dampening that helps prevent the recoding of recently repeated items and promotes context reconstruction. Gardner-Medwin (1976) found that optimal reconstruction of a pattern from memory was obtained when the threshold for neural firing is initially low and then gradually increases over successive iterations in a progressive recall. With a low threshold, a cue such as a recognition probe is able to activate more of its original contextual associates. As the emerging pattern stabilizes, an increase in threshold inhibits the activation of tangential elements. The temporally progressive enhancement of the P620 for repeated words might thus reflect this type of threshold incrementation in the recognition process.

### INTRACRANIAL ERPs RECORDED DURING LEXICAL DECISION

We have attempted to extend our findings by contrasting the components elicited during RM with those obtained from recordings in comparable tasks. Intracranial recordings from the MTL yield waveform records with a distinct voltage distribution across recording sites for each component in each subject. Thus, within individual subject's records it is possible to make systematic comparisons of the depth voltage topography of a component in order to ascertain its identity across different eliciting tasks. By utilizing this strategy we have found that N460 component is also elicited during lexical decision (LD) tasks, where subjects are required to discriminate words from nonsense letter strings (Smith et al, 1986).

Reaction time studies have indicated that repetition of items facilitates performance speed and accuracy in LD. In this task no overt judgment of recent previous experience is required, and learning

of the stimulus set is incidental rather than intentional. To test whether the repetition related decrease in MTL N460 amplitude could be generalized to these conditions, intracranial recordings were obtained during both RM and LD in the same subjects. Individual trial timing and visual stimulus quality was the same in both tasks. In this version of LD stimuli were structured in an initial block of 32 and three subsequent blocks of 64 trials. Order was randomized within blocks. Half of the trials in each block were letter strings that did not form words. The 32 items in the first block were subsequently

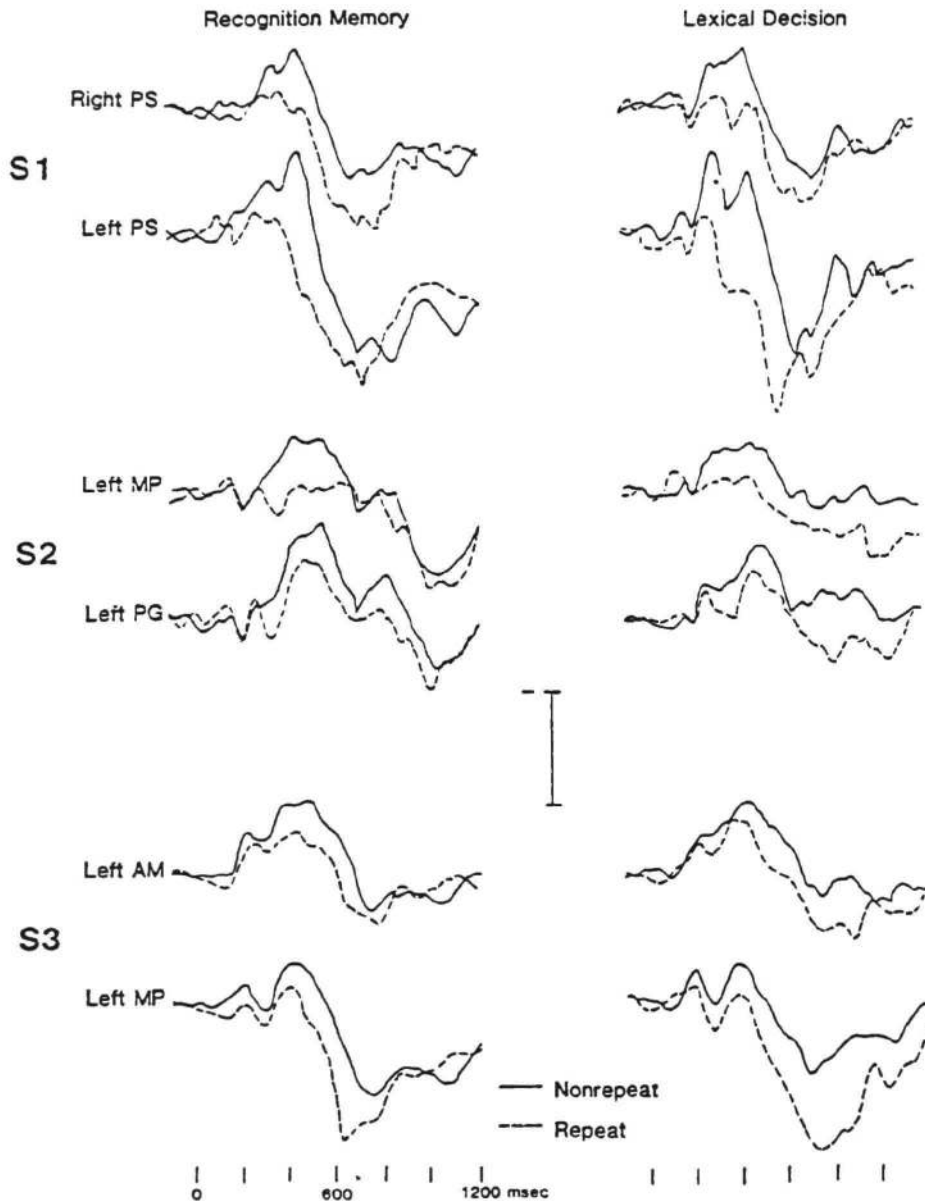


Figure 2. Comparison of repetition related changes in MTL recorded ERPs between recognition memory and lexical decision tasks. Scale is 50 microvolts. Negativity is up. PS=presubiculum, MP= middle pes hippocampus, PG= posterior parahippocampal gyrus, AM= amygdala.

repeated in each of the other three blocks. All other items were presented only once.

We have found that in normal subjects scalp-recorded ERPs elicited during LD discriminate between repeated items and those presented a first time. These differences are very similar to those observed between nonrepeated words and targets in RM (Smith & Halgren, 1986). Intracranial ERPs recorded during RM and LD in three patients are compared in Figure 2. In these three subjects seizure onset was localized to the nondominant MTL. They performed in the normal range on RM and LD, and displayed a substantial enhancement of response speed and accuracy following word repetition in LD. As can be seen in the figure a negativity extending from about 300-500 msec was elicited by words presented for a first time in RM. This potential was followed by a typically positive component that extending between 500-700 msec post-stimulus onset. The first component is analogous to the N460 potential observed in the earlier series of patients, again being smaller in amplitude when elicited by repeated words. A negativity similar in amplitude, MTL voltage distribution, and latency, can also be seen in response to items presented for a first time for lexical judgment. An effect of repetition of similar magnitude to that observed in RM was also observed in the late negative component recorded in LD. Similarly, the second component is analogous to the P620 potential described above, and can also be seen in LD. In both tasks, it is relatively larger in response to repeated items. It is of interest to note that this effect was obtained even though the set of repeated items in LD was much larger than in RM (32 vs 10), they were repeated fewer times (4 vs 9), repetitions were separated by a much longer average lag (over 2 min vs 50 sec, with many more intervening items), subjects were not instructed to remember the items, and no overt judgment of recent occurrence was required.

Parallel voltage distributions and task correlates strongly support the idea that identical populations of neurons are being activated in a similar manner in both tasks. Comparable effects of repetition on ERP components in both RM and LD indicate that these effects are robust and that the MTL makes a general contribution to cognitive processing in both tasks. Moscovitch (1982) found that a group of subjects with memory disorders, including institutionalized elderly subjects and patients in the early stages of Alzheimer's disease, still show repetition related facilitation in LD. He thus proposed that facilitation in LD reflects changes in the 'procedural' system, and were independent of intact MTL function (cf. Cohen, 1984). However the extent of MTL pathology in those subjects was unknown. In contrast, the famous amnesic patient H.M., who suffers from well documented bilateral surgical removal of the MTL, has been reported to show no facilitation in LD when judging repeated words (Gabrielli, Cohen, Huff, Hodgeson, & Corkin, 1984). Further, recent psychological studies have found that 'episodic' sources of priming can have effects on LD performance paralleling priming from other sources (McKoon & Ratcliff, 1986). Thus, in addition to extending the conditions under which repetition effects on the MTL N460 might be obtained, these

results are consistent with the idea that repetition priming effects in lexical decision do not solely reflect procedural learning, but instead share task related components of neural activation with overtly MTL-dependent tasks such as recognition memory (for a similar conclusion derived from an insightful series of behavioral studies, see Ratcliff, Hockley, & McKoon, 1985).

## SUMMARY

We have recorded field potentials from the human hippocampus and associated structures in order to better understand how these brain areas contribute to memory. These recordings have revealed repetition-sensitive components of MTL activation. One component is largest when a stimulus occurs for a first time within a context, and is smaller on subsequent presentations. This component might represent a pattern of activation that results in the enhancement of weak latent connections between cortical processing elements. A second component is instead enhanced to repeated items, possibly reflecting a dampening process that decreases the noise level in the network, or alternatively, that provides a mechanism to reset the system after it reaches a stable point (cf. Anderson & Silverstein, 1978; Grossberg, 1978). These components can be identified in both recognition memory and lexical decision, suggesting that the medial temporal lobe makes a wide-ranging contribution to repetition effects. Analyses of these components at both the synaptic and the psychological levels might provide a juncture for linking these domains of memory.

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SMITH, HALGREN, HEIT

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SMITH, HALGREN, HEIT

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