

Short Term Memory May Be the Depletion of the Readily Releasable Pool of Presynaptic Neurotransmitter Vesicles

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Abstract:

The Tagging/Retagging model of short term memory was introduced earlier (1) to explain the linear relationship that exists between response time and correct response probability for word recall and recognition: At the initial stimulus presentation words tag the corresponding long term memory locations. The tagging process is linear in time and takes about one second to reach a tagging level of 100%. After stimulus presentation the tagging level decays logarithmically with time to 50% after 14 seconds and to 20% after 220 seconds. If a probe word is reintroduced the tagging level has to go back to 100% for the word to be properly identified, which leads to a delay in response time. This delay is proportional to the tagging loss which is in turn directly related to the decrease in probability of correct word recall and recognition.

Evidence suggests that the tagging level is the level of depletion of the Readily Releasable Pool (RRP) of neurotransmitter vesicles at presynaptic terminals. The evidence includes the initial linear relationship between tagging level and time as well as the subsequent logarithmic decay of the tagging level. The activation of a short term memory may thus be the depletion of RRP (exocytosis) and short term memory decay may be the ensuing recycling of the neurotransmitter vesicles (endocytosis).

1. Introduction

Cognitive psychologists attempt to quantify the properties of short term memory (for a review see (2)). Unfortunately this work has not led to a theoretical convergence. Various models of memory stores have been introduced and survive in text books even though they have been disproven(3). Presumably the lack of an accepted theory is due, in part, to a lack of connection of the cognitive literature to the details of the underlying biochemistry. Without this “harder science” connection it may be difficult to convince various parts of the community of the supremacy of one theoretical model over another.

One way to make a connection from cognitive psychology to the underlying biochemistry is to look at functional forms and see whether a particular process may decay, for example, exponentially with a time constant that corresponds to a particular biochemical reaction. In a recent contribution (1) the current author showed that short term memory correct recall and recognition probabilities are linearly related to response times over a large time range (from 6 to 600 seconds). I interpreted this observation according to a new tagging model of short term memory in which long term memory locations are tagged linearly in time. When the tagging level is 100% the subject has identified the word. As time passes the tagging level decays. For a subject to identify the word again the tagging level has to increase to 100% leading to a delay in response time. The tagging level decay function is the same as for recall and recognition probabilities and is logarithmic with time.

The current paper addresses what might be the biochemical underpinning of the tagging model. I start by describing the tagging model and the evidence for the active tagging process being linear in time and the subsequent tagging decay being logarithmic in time. The biochemical process needs the same two properties: (a) an active process linear in time with (b) a logarithmic decay time. I suggest that exocytosis, the process of depletion of presynaptic neurotransmitter vesicles corresponds to the tagging process and endocytosis, the process of rebuilding presynaptic neurotransmitter vesicles corresponds to the tagging level decay. A brief summary concludes the paper.

2. The Tagging Model

The Tagging/Retagging model was introduced (1) to explain the linear relationship between the probability of recall/recognition and response time in experiments testing recall/recognition of words (4),(5) (see linear relationships in Figure 1, Figure 2 and Figure 3). A recent item requires

a short response time and an item almost forgotten requires a longer response time.

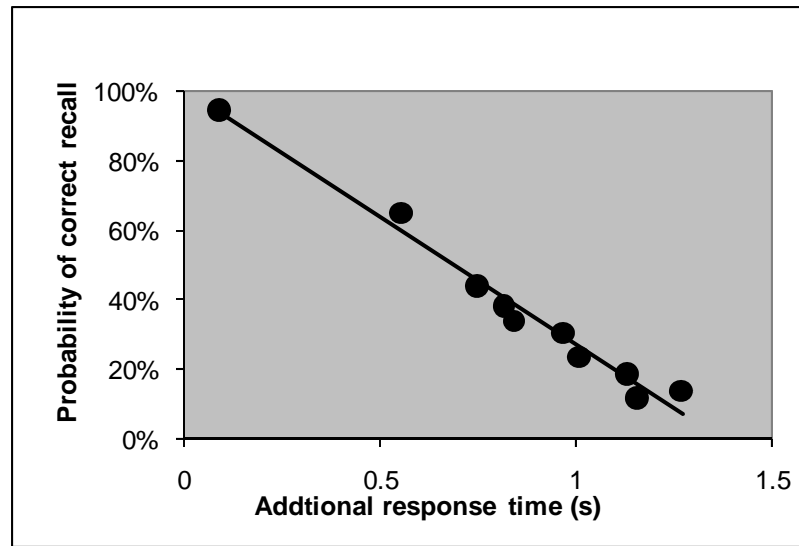


Figure 1 Response time as a function of the probability of correct recall (1). The time after stimulus presentation is not shown but short times (from 0 seconds) correspond to high probability of recall and long times (up to 594 seconds) correspond to low probability of recall.

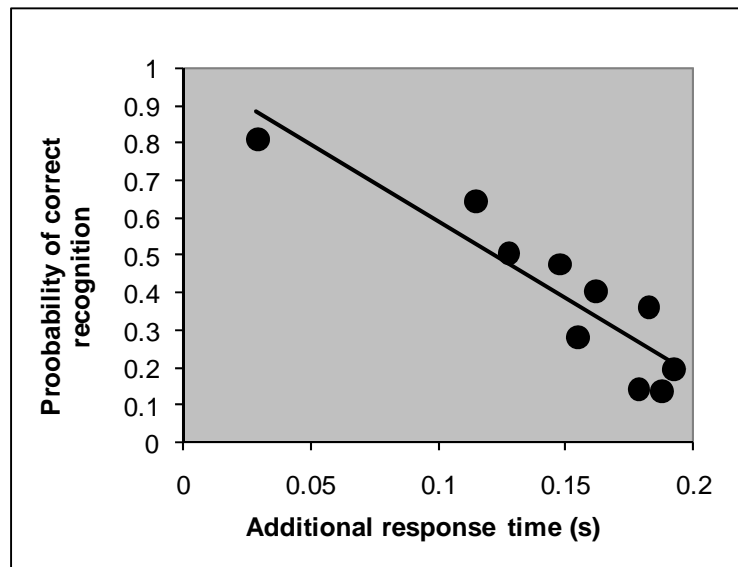


Figure 2 Response time as a function of the probability of recognition(1). The time after stimulus presentation is not shown but short times (from 0 seconds) correspond to high probability of recognition and long times (up to 594 seconds) correspond to low probability of recognition. The time scale is smaller than the time scale in Figure 1 so the experimental noise accounts for a larger amount of R^2 .

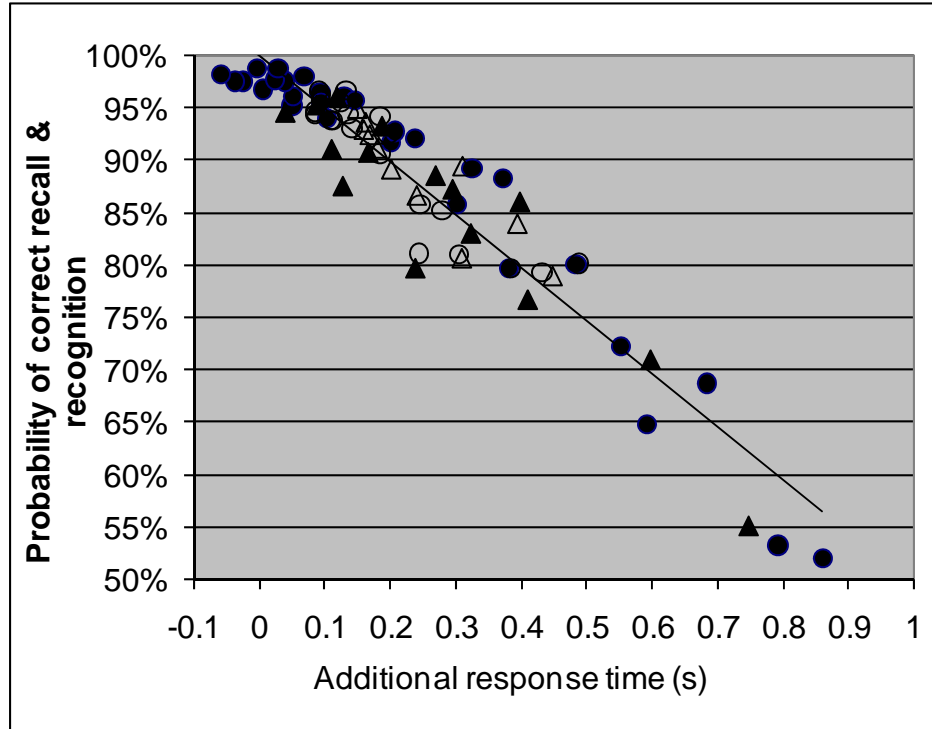


Figure 3 Response time as a function of the probability of recognition (unfilled symbols) and recall (filled symbols) from experiments on repeated learning(5) (see (1) for details). The triangles represent the data with interference, the circles data without interference.

The linear curves found are the central findings of the earlier paper. Their simplicity suggests that they describe a core property of short term memory. I explained the relationships by introducing the Tagging/Retagging model of short term memory:

When presented with a word, a subject tags that word by marking long term memory locations (Figure 4 and Figure 5). The tagging level, defined as the probability of a correct identification, then slowly decays (Figure 6) until the word is reintroduced, at which point the tagging level goes back up (the same word is read again and subjected to the same procedure as the first time it was presented see Figure 7). The retagging time can be inferred from the delay in the response and is found to be proportional to the tagging level drop from the linear relationship between response time and probability of recall and recognition. When the tagging level of the probe word drops to x%, the tagging level of the reference to the initial list (for recognition) and of the word association (for recall) also drops to x%. As the exposure to the probe word retags the probe word, the tagging levels of the list reference and word association are not increased and the subject only responds correctly x% of the time.

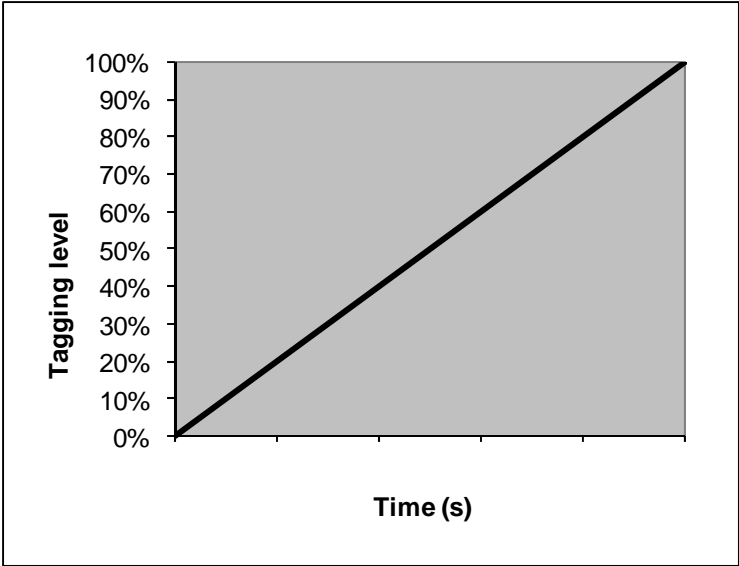


Figure 4. Tagging increases linearly with time.

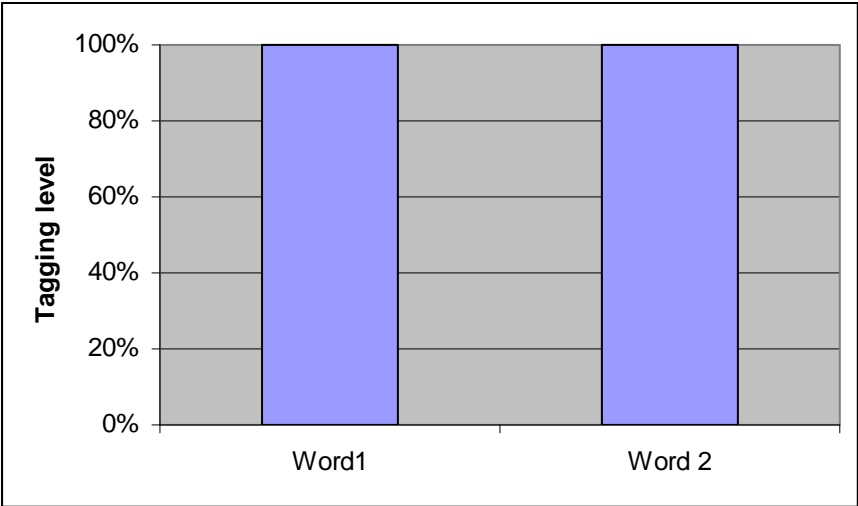


Figure 5: Initial tagging levels for recall experiment. A word pair is read in and forms a joint memory. Right after stimulus presentation both words are fully tagged.

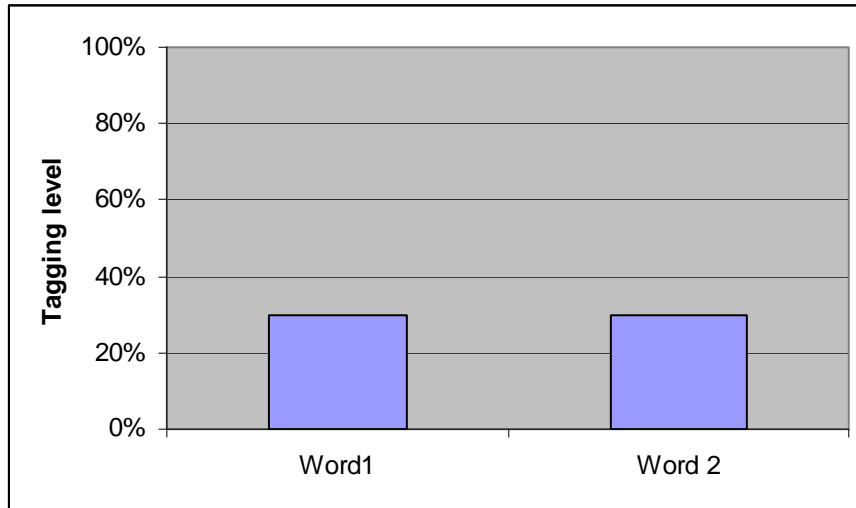


Figure 6 After 90 seconds the two words 1 lost 70% of the tagging. Probability of finding either is the current tagging level of 30%.

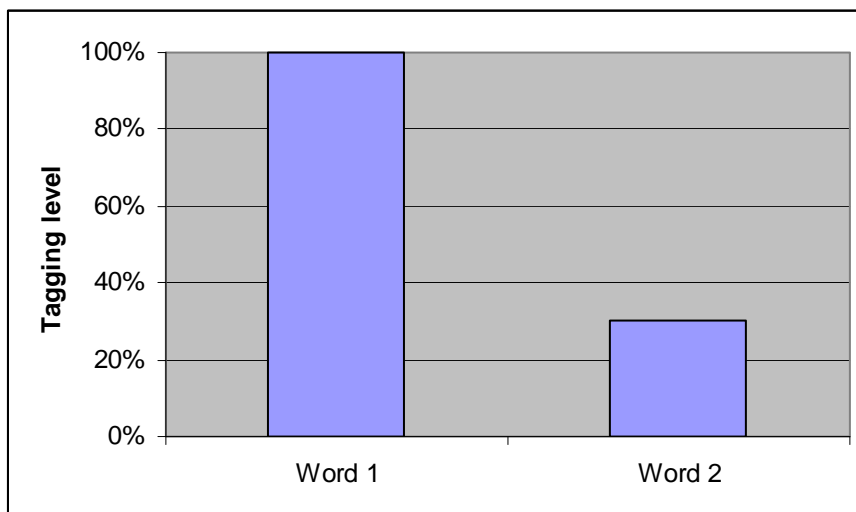


Figure 7. The display of recall prompt word 1 takes place at 90 seconds after stimulus presentation. Word 1 is now retagged. Word 2 is not retagged and the probability of finding it is still 30%.

The tagging level (the probability of correct response) decays equally fast for recognition and recall (see Figure 8). The tagging level decay with time for the average of the two data sets calculated from (4) is shown in Figure 9 ((5) did not test memory as a function of time but as a function of repeated learning so it is not included). It fits a logarithmic curve. The time for the tagging to decay to 50% is about 14 seconds but because of the logarithmic decay the time to drop to 20% is much longer - 220 seconds.

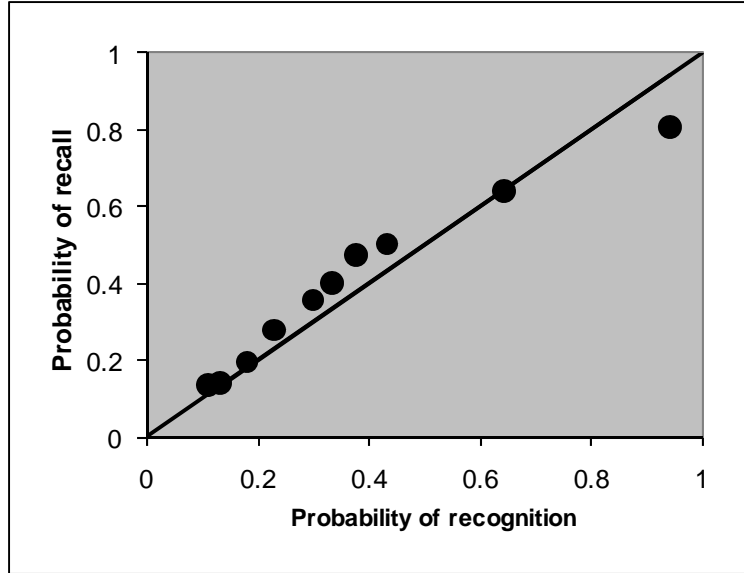


Figure 8. Probability of recognition and recall for the same delay times in (4). The line is the $x=y$ function.

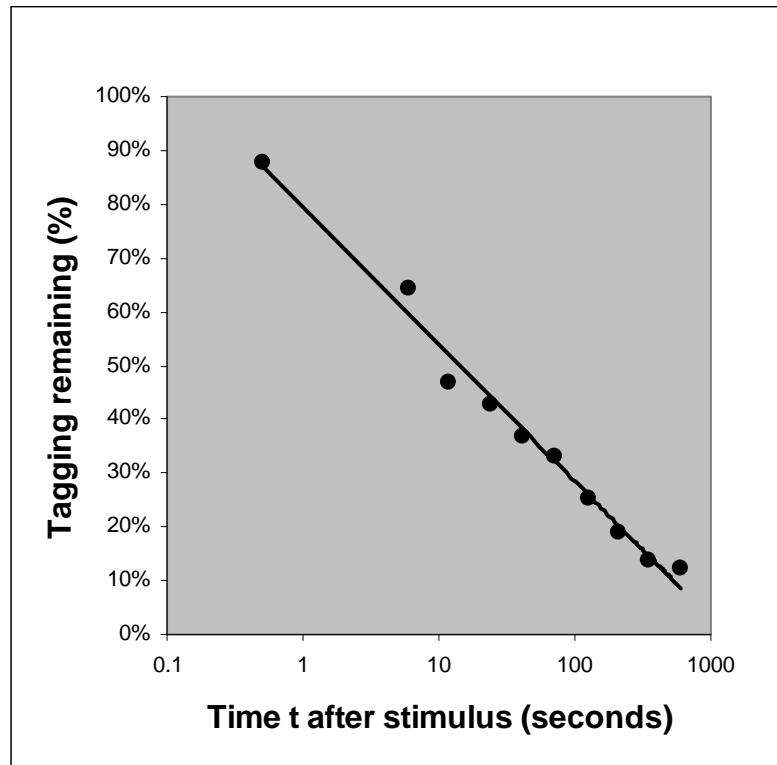


Figure 9. Tagging remaining averaged over recall and recognition memory items from (4). The curve represents a two parameter logarithmic fit, moving $t=0$ seconds to $t=0.5$ seconds to avoid a divergence.

The strikingly linear relationship between response probability and response time is likely a fundamental property of our short term memory. The tagging model is a compelling explanation of the data. But any memory process is one of biochemistry. What could possibly be a biochemical mechanism explaining the tagging model? We know that long term memory is related to long term synaptic changes presumably via protein synthesis (6). Short term behavior in aplysia can also be related to changes in the synapses: “serotonin leads to an increase in presynaptic cAMP, which activates PKA and leads to synaptic strengthening through enhanced transmitter release produced by a combination of mechanisms”(6). Thus it is tempting to search for something that quickly tags synapses and more slowly untags them and does so in a reversible fashion (if the changes are not reversible, it would be long term memory rather than short term). Such a system is the cycle of exocytosis and endocytosis of neurotransmitter vesicles in the presynaptic terminal.

3. The Cycle of Exocytosis and Endocytosis

Neurotransmitter is stored in small vesicles in the presynaptic terminal (for an introduction please see (7) pp. 105-7 and the introduction in (8)) and one can surmise that “all presynaptic functions, directly or indirectly, involve synaptic vesicles” (9) (exocytosis and endocytosis has been reviewed elsewhere ((9) and (10)).

When an action potential occurs in the presynaptic neuron, the Ca²⁺ channels open and in 10-20% of cases (11),(12) cause one (12) vesicle to fuse to the plasma membrane of the presynaptic terminal and open up a pore into the synaptic cleft and release neurotransmitter into the synaptic cleft (exocytosis). After repeated stimulation available vesicles in what is called the Readily Releasable Pool of vesicles (RRP, for reviews of the RRP see (13) and (9)) can be completely depleted. Exocytosis results in neurotransmitters crossing over to the receptors in the postsynaptic terminal and they are quickly broken down by enzymes in the synaptic cleft.

Exocytosis is a possible candidate for the tagging process. In *Figure 10* is shown the average time course for exocytosis (depletion of the Readily Releasable Pool (RRP) of neurotransmitter vesicles) in a rat hippocampal culture (12). It is quasi-linear and the overall time is a little over 1 second, consistent with the tagging time in the experiments quoted (calculated in (1) to range from 0.2 to 1.8 seconds). Full tagging corresponds to a state of the synapse in which the presynaptic neurons are no longer actively influencing the postsynaptic neuron, in effect, limiting the size of the overall neural excitation corresponding to the recalled or recognized word.

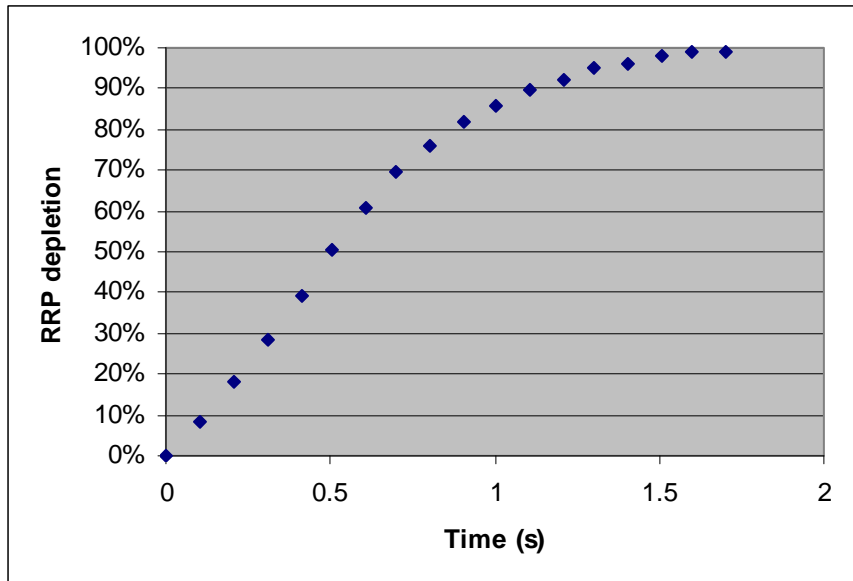


Figure 10. Average time course of depletion of the RRP for the 16 synapses, each normalized to its initial RRP size (12). NEED MORE OF THESE TO GET THE SPREAD

Endocytosis, the reversal of the RRP depletion, is a possible candidate for the tagging decay. *Figure 11* displays the endocytosis of synaptic vesicles from a variety of paired pulse experiments on hippocampal mouse synapses and one on rat calyx of Held synapse together with the memory decay curve from above. Experiments not included on this graph which do not fit straight lines were those on chromaffin (14) and mossy-fiber-CA3 synapses (15). All other data sets investigated show a straight line (logarithmic decay – please see Appendix I for a further discussion) and the slope is remarkably similar to the memory decay (0.11-0.14/sec for endocytosis experiments versus 0.11/sec for the memory curve). There is a spread in the experimental offset though this spread does not seem to overlap with the memory curve. The experimental curves are each averages over several synapses and it could be that the memory curve is determined by the synapses with the slowest response perhaps explaining the discrepancy in offset (see difference between a collection of fast and slow cells from (16) in *Figure 12*) or that human synapses have a different offset than those of mice (the author is not aware of data on short term memory decay in mice or on endocytosis in human synapses).

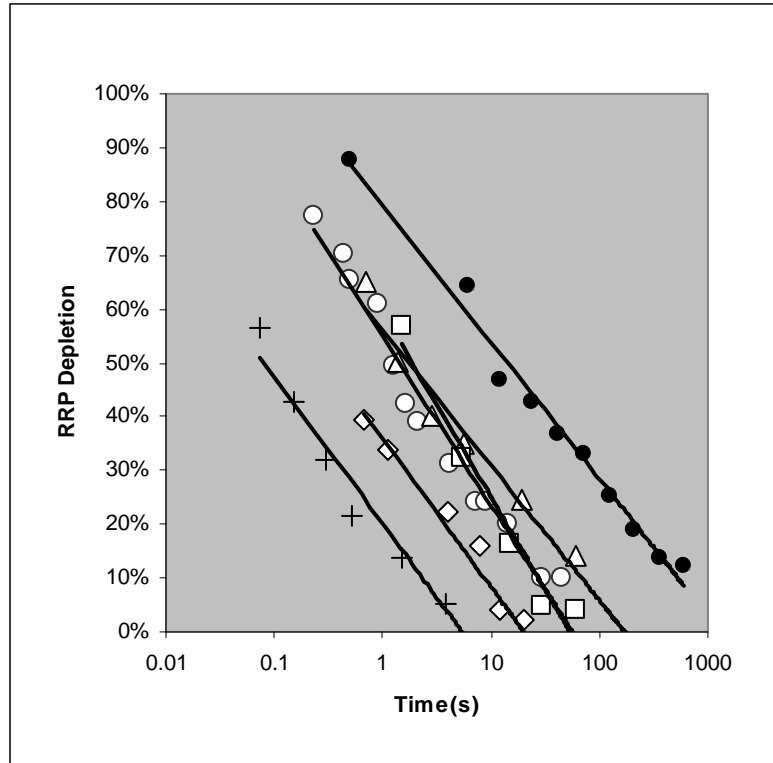


Figure 11. Reversal of RRP depletion (endocytosis) from a variety of paired-pulse experiments. Filled circles indicate the memory decay from Figure 9.

Plus symbols shows data from mouse inner hair cell, normalized by the author to a total number of vesicles of 10, from Fig. 5 in (17)

Unfilled circles shows data from autaptic synapses from a culture of mouse hippocampal CA1 and CA3 cells from Fig. 4C in (16)

Unfilled diamonds shows data from rat calyx of Held from Fig. 7D in (18)

Unfilled triangles shows data from hippocampal neurons from mouse fetuses according to Fig. 9A in (19)

Unfilled squares shows data from a culture of hippocampal synapses from newborn mice from Fig. 2A in (20)

All curves can be well fitted with a line and have similar slopes but there is a spread in offsets.

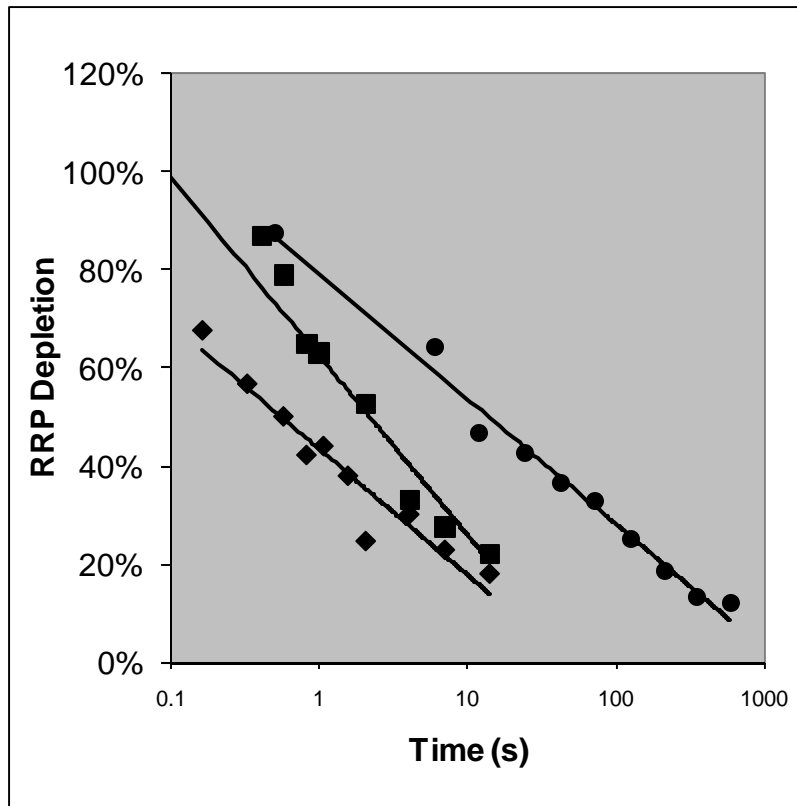


Figure 12. Vesicle recovery from slow cells (filled squares) and fast cells (filled diamonds) from (16) (the average over the two is shown in Figure 11) with the memory curve in filled circles.

4. Summary

Exocytosis in a presynaptic terminal occurs until the action potentials have stopped or all the vesicles in the RRP have released their transmitter under prolonged firing of the action potentials. In our model, a word is read causing prolonged firing which in turns depletes the RRP of the presynaptic terminals. The short term memory trace of a word is the particular pattern of RRP depleted presynaptic terminals. The particular pattern should be related to the long term memory version of the word. After the action potential firing has slowed down, endocytosis causes the word to decay from short term memory. If the endocytosis is allowed to finish (the word is not read again), the pattern of exhausted postsynaptic terminals is gone and, in our model, the short term memory of the word is gone.

The evidence presented includes corresponding qualitative and quantitative functional forms for tagging (exocytosis) and tagging decay (endocytosis). Two more fact supports our finding. First, the failure to effect human memory using subliminal stimulation has a parallel in the endocytosis. The time course of endocytosis of a variety of synapse (including hippocampal

cultured synapses) is stimulus-dependent – the longer the stimulation the much longer the endocytosis takes (21), (22) (the experimental results plotted in *Figure 11* result from complete depletion of the RRP). The authors in (22) found that the time for endocytosis was 56 ms after single-vesicle exocytosis but could increase to 8.3 seconds after longer stimulation suggesting that subliminal stimulation may only lead to an incomplete tagging that lasts a tenth of a second. Second, this split in short and long time scales of endocytosis may also correspond to the two phases of short term memory (3).

5. Appendix I

Typically the endocytosis curves are fit with two exponentials that each has an associated time constant presumably with the hope in mind that there are one or perhaps two unknown biochemical reactions with a corresponding energy barrier. To check whether the customary double exponential fit is an appropriate fit, I tabulated some of the exponential fitting time constants for the experiments of Figure 10 in Table 1. There seems to be little correlation of the time constants suggesting that a double exponential fit is inappropriate. In contrast, the logarithmic fits of **Figure 11** give slopes that are very similar and thus seem more appropriate.

<u>Source</u>	<u>Short time constant</u>	<u>Long time constant</u>
(17)	0.14 seconds	3 seconds
(16)	0.84 seconds	23 seconds
(18) 30Hz data	0.28 seconds	4.8 seconds
(18) 100Hz data	0.51 seconds	6.7 seconds
(19)	1.28 seconds	56.8 seconds
(20)	6.7 seconds	N/A

Table 1. Time constants used to fit the RRP endocytosis curves of the various articles.

The correct functional form of the endocytosis curve can presumably be derived from the findings of (22). They found that single vesicle endocytosis occurs with a decaying exponential with the time constant of 56 ms (in young rat calyx of Held). When three or more vesicle were fused per active zone (with roughly 600 active zones in the calyx) then each vesicle added about 1900 ms to the time constant (22) fitted 1700 ms). If each active zone releases the same number of vesicles then the ensuing endocytosis is a sum of two exponentials – the fast 56 ms for the first two vesicles and then a slow $1900 \times (\text{number of vesicles})$ ms time constant for the subsequent vesicles. In *Figure 13* I show the experimental data from (18) and compare it with the predicted data from a normal distribution causing an average of two vesicles to release per active zone with a standard deviation of 1 vesicle per active zone. The overlap is excellent. I inquired into what change in parameters would cause the calyx curve to coincide with the memory decay curve from *Figure 9*. One possibility is to increase the 1.9 second multiplicative time constant to 100 seconds*(number of vesicles), another one is to increase the number of vesicles per active zone or increasing the average number of vesicles released after an action potential train.

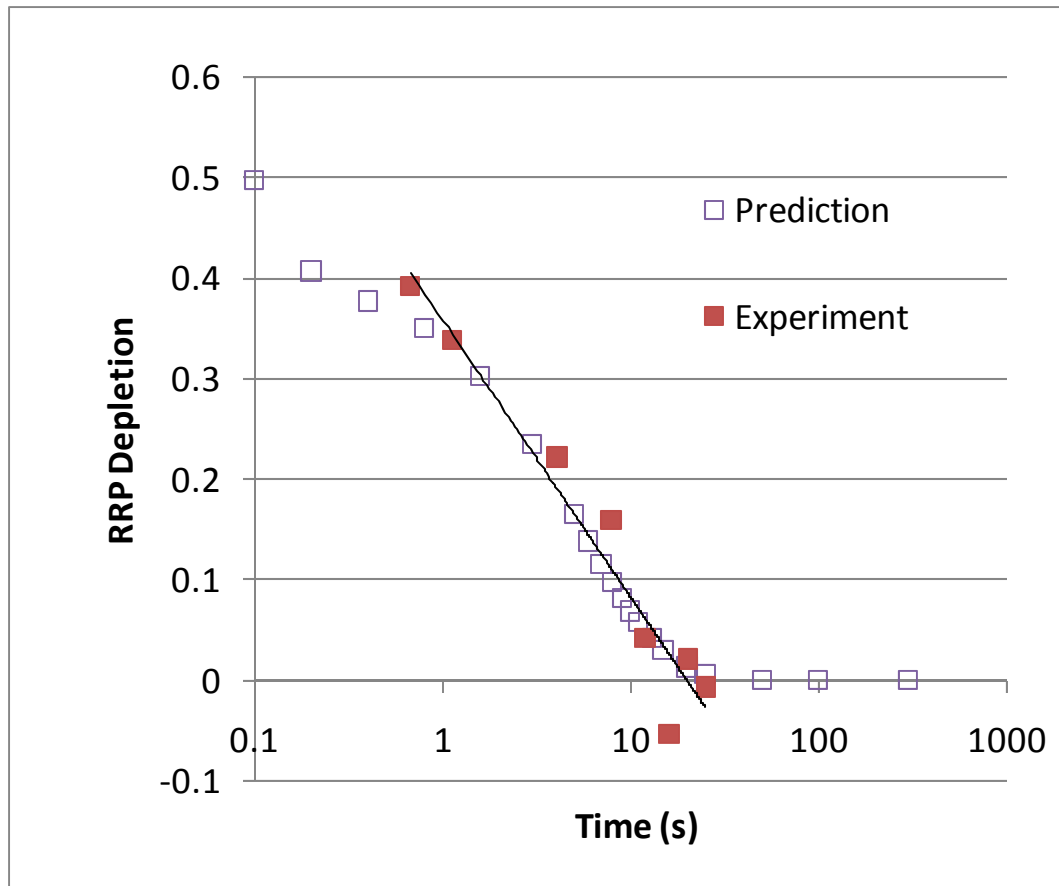


Figure 13. Comparison between data on rat Calyx (18) and prediction based on a normal distribution of depleted RRP vesicles with average of 2 depleted vesicles and a standard deviation of 1. The prediction used the constants fit from the data in (22).

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