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Two components of long-term memory

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Abstract. The existence of two independent components of long-term memory has been demonstrated by the authors. The evidence has been derived from the authors' findings related to the optimum spacing of repetitions in paired-associate learning. The two components are sufficient to explain the optimum spacing of repetitions as well as the spacing effect. Although the molecular counterparts of the two components of memory are not known, the authors provide a collection of guidelines that might facilitate identification of such counterparts.

Short communication

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It has been found in earlier research that the optimum spacing of repetitions in paired-associate learning, understood as the spacing which takes a minimum number of repetitions to indefinitely maintain a constant level of knowledge retention (e.g. 95%), can roughly be expressed using the following formulae (Woźniak and Gorzelańczyk 1994).

$$I_1 = C_1 \qquad (1)$$

$$I_i = I_{i-1} * C_2 \qquad (2)$$

where:

I_i - inter-repetition interval after the i-th repetition

C_1 - length of the first interval (dependent on the chosen knowledge retention, and usually equal to several days)

C_2 - constant that denotes the increase of inter--repetition intervals in subsequent repetitions (dependent on the chosen knowledge retention, and the difficulty of the remembered item)

The above formulae have been found for human subjects using computer optimization procedures employed to supervise the process of self-paced learning of word-pairs using the active recall dropout technique.

The length of an optimum inter-repetition interval computed using Eqns. (1) and (2) is determined by the following factors:

- interval must be short enough to prevent forgetting
- interval must be long enough to prevent the negative impact of the spacing effect (Hintzman 1974, Glenberg 1977).

The evolutionary value of forgetting and the spacing effect may be to optimize the use of limited memory storage for preserving the most relevant and useful engrams. Forgetting probably serves as a garbage collection mechanism that is used to remove the least relevant memory traces and to prevent storage overflow. On the other hand, the spacing effect might prevent conserving memories that are relevant only in a limited period of time. Without the spacing effect, a large number of repetitions in a very short period of time might increase the optimum inter-repetition interval to an excessive value, far beyond the period in which the learned association is important for the conditioned individual.

Because of a deeply-rooted evolutionary significance of the increasing interval paradigm in consolidating long-term memories, the authors postulate the universal applicability of their findings on optimum spacing of repetition to a wide range of learning tasks in mammals, and probably beyond.

The molecular correlates underlying the regular nature of the optimum spacing of repetitions have not yet been identified.

The majority of publications on mechanisms of memory introduce the ill-defined term "strength of memory", which at the molecular level is used synonymously with the term "synaptic potentiation". Strength of memory is usually understood as the parameter of the memory system whose value, which determines the ease of recall, increases with repetitive actions accompanying learning.

It has been widely assumed that the study of long-term potentiation (LTP) in CA1 cells of the hippocampus may shed light on at least some mechanisms underlying consolidation of memory in humans (Aronica et al. 1991, Bliss and Collingridge 1993). This area of study has recently abounded in identifying molecular factors correlated with strength of memory or synaptic potentiation in the wake of conditioning. At different points in time, these include: activation of glutamate NMDA receptors (Bliss and Lynch 1988), elevation of cytosolic calcium (Lisman and Goldring 1988), activation of metabotropic glutamate receptor (Bashir et al. 1993), activation of phospholipase C, increased levels of diacylglycerol (DAG) and inositol triphosphate (IP_3) (Nahizaka 1989), increased levels of nitric oxide (NO) (Bruchwyler et al. 1993), increased levels of arachidonic acid (AA) (Bliss and Collingridge 1993), increased levels of pre- and postsynaptic cAMP and cGMP (Mork and Geisler 1989, Wood et al. 1990), increased activity of membrane-bound protein kinase C (Alkon 1989, Olds et al. 1989, Spieler et al. 1993), etc. Also, after a longer period of time, the following changes can be observed: synthesis of some transcription factors (Kaczmarek 1993), gene expression (Matthies 1989), increased number of various glutamate receptors (Lynch 1984), etc.

As it will be shown below, however, the widely investigated strength of memory (or synaptic potentiation) does not suffice to account for the regular pattern of optimum repetition spacing.

Consider the following illustrative example, if (1) the probability of recalling a piece of information from memory is 97% at a given point in time following the first repetition, and (2) the same probability is equal to 97% at another moment after the second repetition, then (3) the state of memory in these two moments of time must be different. On one hand, there must be a mechanism that determines that the probability of recall is 97% and not otherwise. On the other, the memory system after the point in time following the first repetition will manifest a much faster decline in the recall probability than in the moment following the second repetition (note, that optimum inter-repetition intervals increase with each successive repetition). In other words, though the recall probability is 97% in both cases, the stability of memories is higher in the latter case. The conclusion is that more than one independent memory process must underlie the regularities implied by Eqns. (1) and (2).

Let us have a slightly more formal look at the above observation.

1. We want to determine the set of (molecular) variables involved in storing memory traces that will suffice to account for the optimum spacing of repetitions. Let us, initially, assume two correlates of these variables in learning that is subject to optimum spacing as expressed by Eqns. (1) and (2):

r - time which remains from the present moment until the end of the current optimum interval (optimum interval is the interval at the end of which the retention drops to the previously defined level, e.g. 95%)

s - length of the current optimum interval.

2. Just at the onset of the i-th repetition, $r=0$, while $s_i > s_{i-1} > 0$ (s_i denotes s right at the onset of the i-th repetition). This indicates that there is no function g_1 such that $s=g_1(r)$, i.e. s cannot be a function of r only.

3. During the inter-repetition interval, $r(t_1)<>r(t_2)$ if $t_1<>t_2$ (t denotes time and $r(t)$ denotes r at the moment t). On the other hand, $s(t_1)=s(t_2)$ ($s(t)$ denotes s at the moment t). This shows that there is no function g_2 such that $r=g_2(s)$, or we would have: $r(t_1)=g_2(s(t_1))=g_2(s(t_2))=r(t_2)$, which leads to a contradiction. r cannot be a function of s only.

4. In Steps 2 and 3 we have shown that r and s are independent, as there are no functions g_1 and g_2 such that $s=g_1(r)$ or $r=g_2(s)$. This obviously does not mean that there exists no parameter x and functions y_s and y_r such that $s=y_s(x)$ and $r=y_r(x)$.

5. It can be shown that r and s suffice to compute the optimum spacing of repetitions (cf. Eqns. (1) and (2)). Let us first assume that the two following functions f_r and f_s are known in the system involved in memory storage: $r_i=f_r(s_i)$ and $s_i=f_s(s_{i-1})$. In our case, these functions have a trivial form f_r: $r_i=s_i$ and f_s: $s_i=s_{i-1}*C_2$ (where C_2 is the constant from Eqn. (2)). In such a case, the variables r and s are sufficient to represent memory at any moment t in optimum spacing of repetitions. Here is a repetition spacing algorithm which shows this to be true:

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1. assume that the variables $r_i$ and $s_i$ describe the state of memory after the i-th repetition
2. let there elapse $r_i$ time
3. let there be a repetition
4. let the function $f_s$ be used to compute the new value of $s_{i+1}$ from $s_i$
5. let the function $f_r$ be used to compute the new value of $r_{i+1}$ from $s_{i+1}$
6. i:=i+1
7. goto 2
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The above reasoning shows that variables r and s form a sufficient set of independent variables needed to compute the optimum spacing of repetitions. Obviously, using a set of transformation functions of the form $r=Tr(r)$ and $s=Ts(s)$, one can conceive an infinite family of variable pairs r-s that could describe the status of the memory system. A difficult choice remains to choose such a pair *r-s* that will most conveniently correspond with molecular phenomena occurring at the level of the synapse.

The following terminology and interpretation is proposed by the authors in a memory system involving the existence of the *r-s* pair of variables: the variable R, retrievability, determines the probability with which a given memory trace can be invoked at a given moment, while the variable S, stability of memory, determines the rate of decline of retrievability as a result of forgetting, and consequently the length of inter-repetition intervals in the optimum spacing of repetitions.

Assuming the negatively exponential decrease of retrievability, and the interpretation of stability as an inverse of the retrievability decay constant, we might conveniently represent the relationship between R and S using the following formula (t denotes time):

$$R=e^{-t/S} \qquad (3)$$

The transformation functions from the pair *r-s* used in Steps 1-5 of the reasoning, to the proposed interpretation R-S will look as follows (assuming the definition of the optimum inter-repetition interval as the interval that produces retention of knowledge K=0.95):

$$S=-s/\ln(K) \qquad (4)$$

$$R=e^{-(s-r)/S} \qquad (5)$$

The relationship between the stability after the i-th repetition (S_i) and the constants C_1 and C_2 determining the optimum spacing of repetitions as defined by Eqns. (1) and (2) can therefore be written as:

$$S_i=-(C_1*C_2^{i-1})/\ln(K) \qquad (6)$$

and finally, retrievability in the optimum spacing of repetitions can be expressed as:

$$R_i(t)=e^{t*\ln(K)/(C_1*C_2^{i-1})} \qquad (7)$$

where:

i - number of the repetition in question

t - time since the i-th repetition

$R_i(t)$ - retrievability after the time t passing since the i-th repetition in optimum spacing of repetitions

C_1 and C_2 - constants from Eqns. (1) and (2)

K - retention of knowledge equal to 0.95 (it is important to notice that the relationship expressed by Eqn. (7) may not be true for retention higher than 0.95 due to spacing effect resulting from shorter intervals)

For the proposed interpretation of variables R and S, they should exhibit the following set of properties in accordance with the known properties of memory:

1. R should be related to the probability of recalling a given memory engram; forgetting should be understood as the decrease in R
2. R should reach a high value as early as after the first repetition, and decline rapidly in the matter of days (the average optimum inter-repetition interval for retention 95% equals several days)
3. S determines the rate of decline of R (the higher the stability of memories, the slower the decrease of retrievability)
4. with each repetition, as S gets higher, R declines at a slower rate (stability of memory increases with successive repetitions)
5. S should assume a high value only after a larger number of repetitions (stability of memories is positively correlated with the amount of training)
6. S should not change (significantly) during the inter-repetition interval
7. if the value of R is high, repetitions do not affect S significantly (spacing effect)
8. R and S increase only as a result of an effective repetition (i.e. repetition that takes place after a sufficiently long interval)

As shown above, if high levels of retrievability prevent the increase in stability, the two presented components of long-term memory suffice to account not only for the optimum spacing of repetition, but for the spacing effect as well.

The above properties of R and S can be used in the search for their molecular counterparts. Most importantly, retrievability should be correlated with changes that are immediately observable in the wake of learning (properties 1 and 2). This suggests that it might perhaps be correlated with some of the molecular phenomena associated with LTP (as listed earlier).

The existence of the second component of long-term memory, stability, has not been reported prior to the presented paper. The probable reason is that stability might manifest itself only after a number of training sessions, while a vast majority of molecular research has been done on memory processes spanning from minutes to days at the very most.

The most striking property of stability is its long-term sustainability (properties 4, 5, 6, and 8). This might perhaps indicate a potential involvement of gene expression and protein synthesis (Crick 1984).

Though little is known regarding which molecular factors might indeed correspond to the presented two-component model of long-term memory, extending the hypothesis of universal applicability of the increasing interval paradigm in optimum repetition spacing, the authors postulate that the existence of retrievability and stability of memories is likely to appear in a wide range of learning tasks across a broad spectrum of taxonomic categories in the living world.

Alberini C.M. Ghirardi M., Metz R., Kandel E. R. (1994) C/EBP is an immediate-early gene required for the consolidation of long-term facilitation in Aplysia. Cell. 25: 76: 1099-114

Alkon D. L. (1989) Memory storage and neural systems. Sci. Am. 7: 42-50.

Aronica E., Frey U., Wagner M., Schroeder H., Krug M., Ruthtich H., Catania M. V., Nicoletti E., Reymann K. G..(1991) Enhanced sensitivity of metabotropic glutamate receptors after induction of long-term potentiation in rat hippocampus. J. Neurochem. 57: 376-383.

Bashir Z.I., Bortolotto Z.A., Davies C.H., Berretta N., Irving A.J., Seal A.J., Henley J.M, Jane D.E, Watkins J.C., Collingridge G.L. (1993) Induction of LTP in the hippocampus needs synaptic activation of glutamate metabotropic receptors. Nature 363: 347-350.

Bliss T.V.P., Collingridge G.L. (1993) A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361: 31-39.

Bliss T. V. P, Lynch M. A.(1988) Long term potentiation of synaptic transmission in the hippocampus: Properties and mechanisms. In: Neurology and neurobiology (Eds. Landfield P. W. and Deadwwyler S. A). Allan R. Liss Inc., New York, 35: 3-72.

Bruchwyler J., Chleide E., Liégeois J. F., Carrer F. (1993) Nitric oxide: a new messenger in the brain. Neur. Behav. Rev. 17: 273-384.

Crick F. (1984) Memory and molecular turnover. Nature 312: 101.

Glenberg, A.M. (1977) Influences of the retrieval processes on the spacing effect in free recall. J. Exp. Psychol.: Hum. Learn. Mem. 3: 282-294.

Hintzman D. L. (1974) Theories in cognitive psychology. The Loyola Symposium p. 77-99.

Kaczmarek L. (1993) Glutamate receptor-driven gene expression in learning. Acta Neurobiol. Exp. 53: 187-196.

Lisman J. E., Goldring M. A., (1988) Feasibility of long term storage of graded information by the calcium/calmodulin-dependent protein kinase molecules of the postsynaptic density. Proc. Natl. Acad. Sci. 85::5320-5324

Lynch G. (1984) Hypothetical model of the cellular basis of long-term potentiation. Science 224: 1057-1063

Matthis H. (1989) Neurobiological aspects of learning and memory. Ann. Rev. Psychol. 40: 381-404.

Mork A., Geisler A. (1989) The effects of lithium in vitro and ex vivo on adenylate cyclase in brain are excreted by distinct mechanisms. Neuropharmacology 28: 307-311.

Nahizaka Y.(1989) The role of protein kinase C in cell surface signal transduction and tumor promotion. JAMA 262: 1826-1833.

Qu M., Lu Z., Zilles K. (1994) Aging of nucleolar organizer region in rat basal forebrain neurons related to learning and memory. Anat. Anz. 176:39-43

Olds J. L., Anderson M. L., McPhie D. L., Staten D., Alkon D. L. Imaging of memory-specific changes in the distribution of PKC in the hippocampus. Science 245: 866-869

Spieler K., Schoch P., Martin J. R., Haefely W. (1993) Environmental stimulation promotes changes in the distribution of phorbol ester receptors. Pharmacol. Biochem. Behav. 46: 553-600.

Wood P. L., Emmett M. R., Rao T. S., Cler J., Mick S., Iynger S. (1990) Inhibition of nitric oxide synthetase blocks N-methyl-D-aspartate-, quisqualate-, kainate-, and pentylometetrazole-dependent increases in cerebellar cyclic GMP in vivo. J. Neurochem. 53: 979-981.

Woźniak P. A., Gorzelańczyk E. J. (1994) Optimization of repetition spacing in the practice of learning. Acta Neurobiol. Exp. 54: 59-69.

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