INDIRECT EVIDENCE: MILD ALZHEIMER'S DISEASE & CANNABIS AFFECT THE SECOND STAGE OF FREE RECALL SUGGESTING LOCALIZATION IN HIPPOCAMPAL CA1

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Recently it was shown explicitly that free recall consists of two stages: the first few recalls empty working memory and a second stage, a reactivation stage, concludes the recall ([20]; for a review of the theoretical prediction see [15]). Here it is shown that the serial position curve changes in mild Alzheimer's disease (AD) and acute cannabis usage — lowered total recall and lessened primacy — are similar to second stage recall and different from working memory recall.

Since cannabis and AD affect the second stage of free recall, the intersection of the two localizes the second stage of free recall to the CA1 area of the hippocampus. Since the second stage of recall uses a retrieval process that is accompanied by a linear rise in the error rate [18] this error generating mechanism should give clues to the structure of the corresponding neural network.

Key words: Mild Alzheimer's disease, marijuana, cannabis, free recall, working memory, short term memory

Introduction. Free recall, in which items in a list are displayed or read to subjects who are then asked to retrieve the items, is one of the simplest ways to probe short term memory. It is used in neuropsychological batteries to test for the presence of Alzheimer's disease, for example, MMSE, ADAS-Cog, FREES, CVLT, DWR, etc (for a review see [7]). The corresponding serial position curve, the probability of recalling an item versus the order in which the item was presented, is u-shaped: items in the beginning of the presented list (primacy) and at the end of the list (recency) are more likely to be recalled than those in the middle of the list.

It was recently shown explicitly that free recall is a well defined two stage process ([20]; this had been suggested before, for a review see [15]). In the first stage working memory is emptied and in the second stage a different retrieval process occurs. Working memory is responsible for recency (and some primacy for short lists) and the second stage recall shows some primacy but no recency. In this paper I use a narrow definition of working memory: the memory that keeps a number of items fully activated.

Let me summarize the relevant results from [20]: In Fig. 1a (Fig. 1b) is shown the sequential serial position curves, one for each recall, of recalls 1-8 from the 10 word (40 word) free recall experiments of [14]. These curves show direct evidence for a two stage process. By definition the first recall comes from working memory, and from the similarity of the 2^{nd} and 3^{rd} recalls these also come from working memory. The last three recalls all appear the same and come from a second stage. Recalls 4 and 5 are a combination of the two. In each recall is plotted a best linear fit which expresses the balance between recency (positive slope) and primacy (negative slope). As we see the slopes go from primacy for the emptying of working memory to recency for the second stage. Working memory can

be seen as responsible for recency (consistent with previous work, see [11; 21]); primacy comes from the secondary process though working memory adds the first items in the shorter 10-2 list; together they create a u-shaped serial position curve.

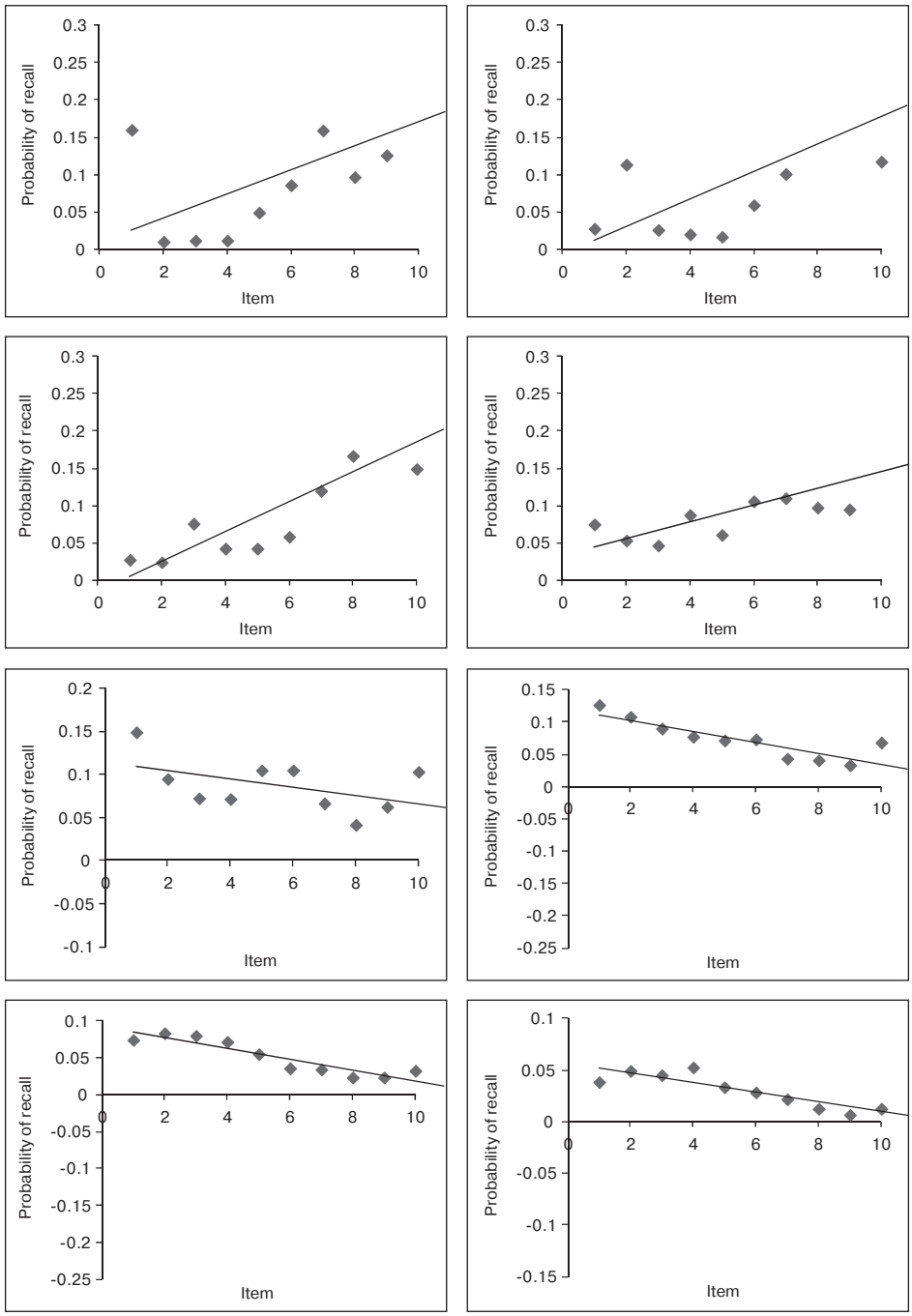

Fig. 1a. Recalls 1-4 (top panel) and 5-8 (bottom panel) for the 10 word list in the dataset [14]. The first three recalls are from working memory, last three recalls from second stage recall, and the 4th and 5th recalls are from a combination of working memory and second stage recall. Figure is taken from [20]

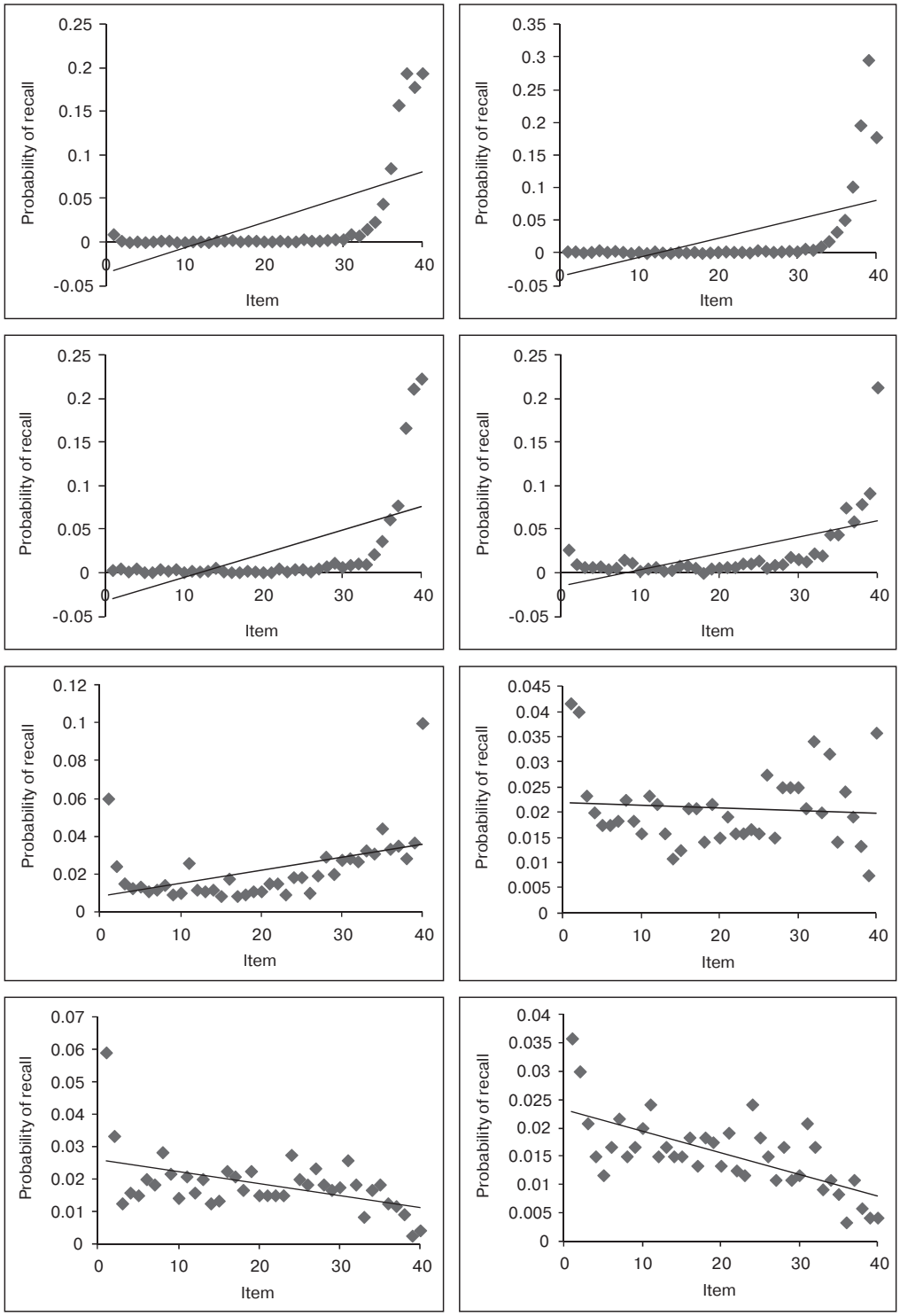

Fig. 1b. Recalls 1-4 (top panel) and 5-8 (bottom panel) for the 40 word list in the dataset of [14]. The first three recalls are from working memory, last three recalls from second stage recall, and the 4th and 5th recalls are from a combination of working memory and second stage recall. Figure is taken from [20]

The slopes as a function of recall are plotted in Fig. 2. The curve is a smoothed step function, which separates the emptying of working memory from the second stage recall. The midpoint of the step function indicates the capacity of working memory and is 4 for the 10 word list and 4.5 for the 40 word list.

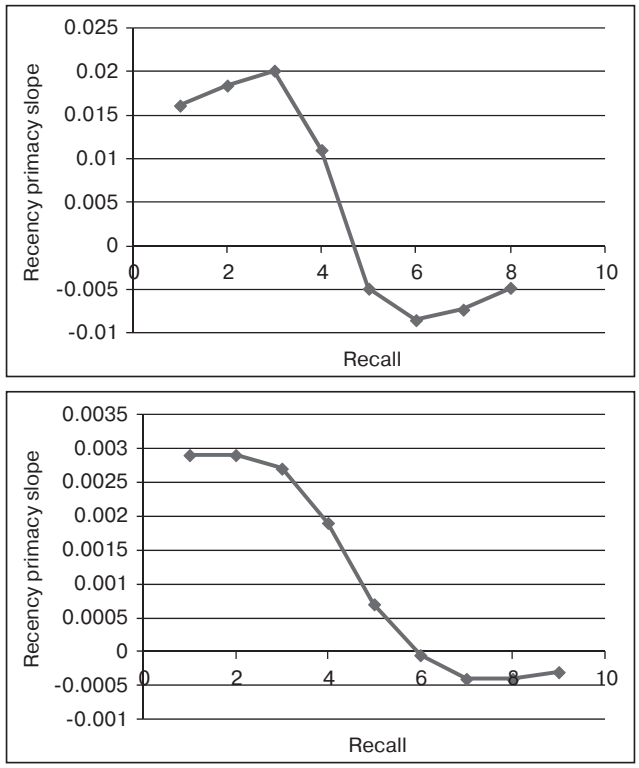

Fig. 2. The slope of a linear fit to the serial position curves for the 10 word list (upper panel) and the 40 word list (lower panel) data. Positive slope indicates recency, negative slope indicates primacy. Note the similarity to a step function. The middle of the step function is a little higher than 4, corresponding to the capacity of working memory. Figure is taken from [20]

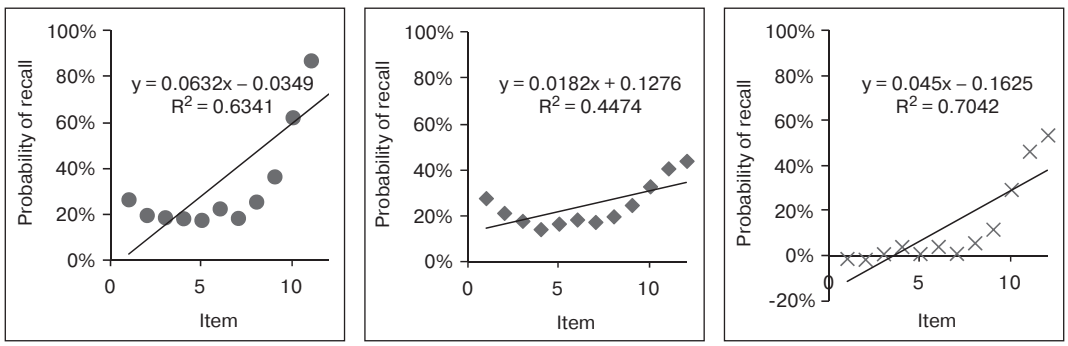

Fig. 3. Serial position curves for immediate free recall (left panel), for delayed free recall (middle panel) and the change in the serial position curves between immediate and delayed free recall (right panel). The total recall difference between immediate and delayed conditions is 1.6 words, much smaller than the working memory capacity indicating an enhanced second stage recall. Figure is taken from [19]

Let me summarize a relevant finding from [19]: If, after the presentation of the word lists, the subjects are distracted by a delay before the free recall begins, this delay almost completely removes the working memory component and somewhat enhances the second stage recall (this had been suggested before [12]). This is shown in Figs. 3 and 4 using word recall data from [13]. Note that the difference in serial position curves looks like the letter "J" indicating that the working memory component is missing.

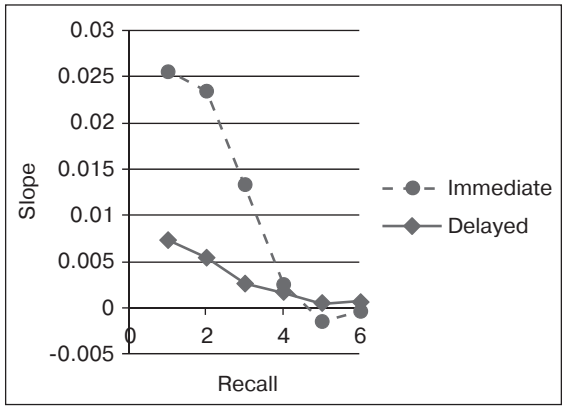

Fig. 4. Slope of linear fit as a function of recall. Note the similarity of the immediate curve to the rounded step function in Figure 2. This characteristic is absent from the delayed curve. This figure is taken from [19]

To summarize: recall from working memory has a large positive slope and looks like the letter "J" while recall from the second stage has a small negative slope and is more similar to a line. If working memory disappears, the difference in the serial position curves looks like a "J" and if the second stage recall disappears, the difference in the serial position curves will look like a line with a negative slope.

Now let us examine the changes to the serial position curves in mild Alzheimer's disease (AD) and acute cannabis usage.

Results & Discussion. Mild Alzheimer's disease changes the serial position curve so that primacy disappears but recency remains the same [3; 6]).

The changes to the serial position curve are linear with a negative slope, indicating that the second stage of free recall is affected the most.

In Fig. 5 is shown the difference in serial position curves between normal and Alzheimer's disease subjects calculated from [6] for a 10 word list. It can be fitted with a line of negative slope and, accordingly, shows that memory from the second stage of recall is missing. In Fig. 6, left panel, is shown the difference in serial position curves between normal and very mild Alzheimer's disease subjects from [3]. This can be fitted with a line with a negative slope and also indicates that memory is missing from the second stage of recall.

In Fig. 6, right panel, is shown the difference in serial position curves between very mild and mild Alzheimer's disease from [3]. This is not well fitted with a line with a negative slope but seems to indicate more of a constant shift. Since the slope is not strongly positive nor looks like a "J", most of the loss presumably still comes from the second stage of recall with a minor component of working memory included.

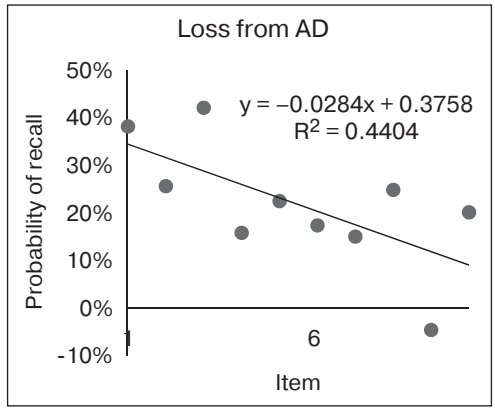

Fig. 5. Change in serial position curve between normal and Alzheimer's disease group in [6]. The negative slope implies that the second stage of recall is affected

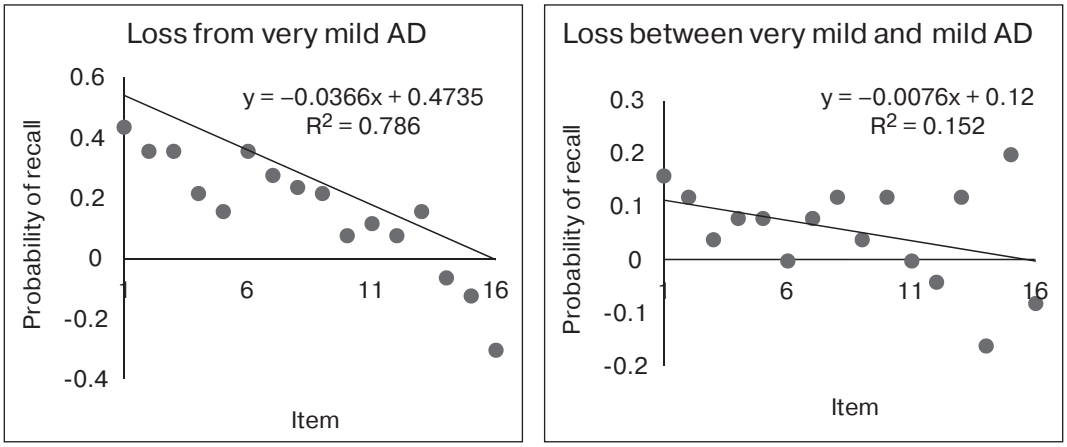

Fig. 6. Change in serial position curve from normal to very mild AD (left panel) and from very mild to mild AD (right panel) using data from [3]. The former shows a line with a negative slope implying that the second stage of recall is affected. The latter shows a line with more spread which presumably implies that the second stage of recall is affected with some losses also occurring in working memory

This finding, that mild Alzheimer's disease damages the second stage of free recall, is consistent with the fact that the delayed free recall test in the MMSE is much more sensitive than the immediate free recall test in which the same items are used [1-2]. Since [19] showed that delayed free recall removes the working memory component of free recall, the delayed test specifically tests the second stage of recall. In addition, since [20] showed that the working memory component takes up the first 3-4.5 items of free recall, the MMSE immediate free recall test only probes the working memory component which, initially, is not damaged by Alzheimer's disease, consistent with [1].

Acute effects of cannabis were reviewed [10; 16]. The effects on free recall occur when the learning of the list takes place while the subject is intoxicated. Typically, the effects on the serial position curve were thought to include depressed recall probabilities for all items but the last. An actual plot of the difference of the free recall data in [8] reveals a

linear dependency with a negative slope (see Fig. 7). This indicates that the loss comes from the second stage of recall.

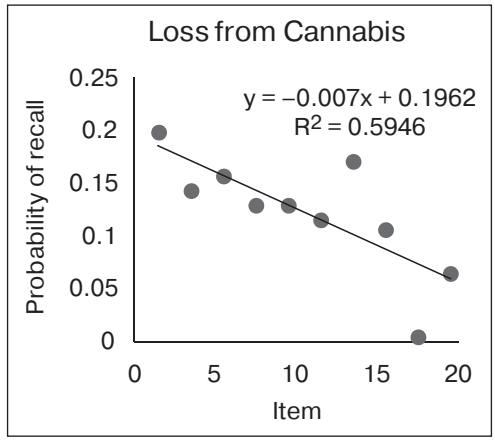

Fig. 7. Change in serial position curve from acute cannabis usage using data from [8]

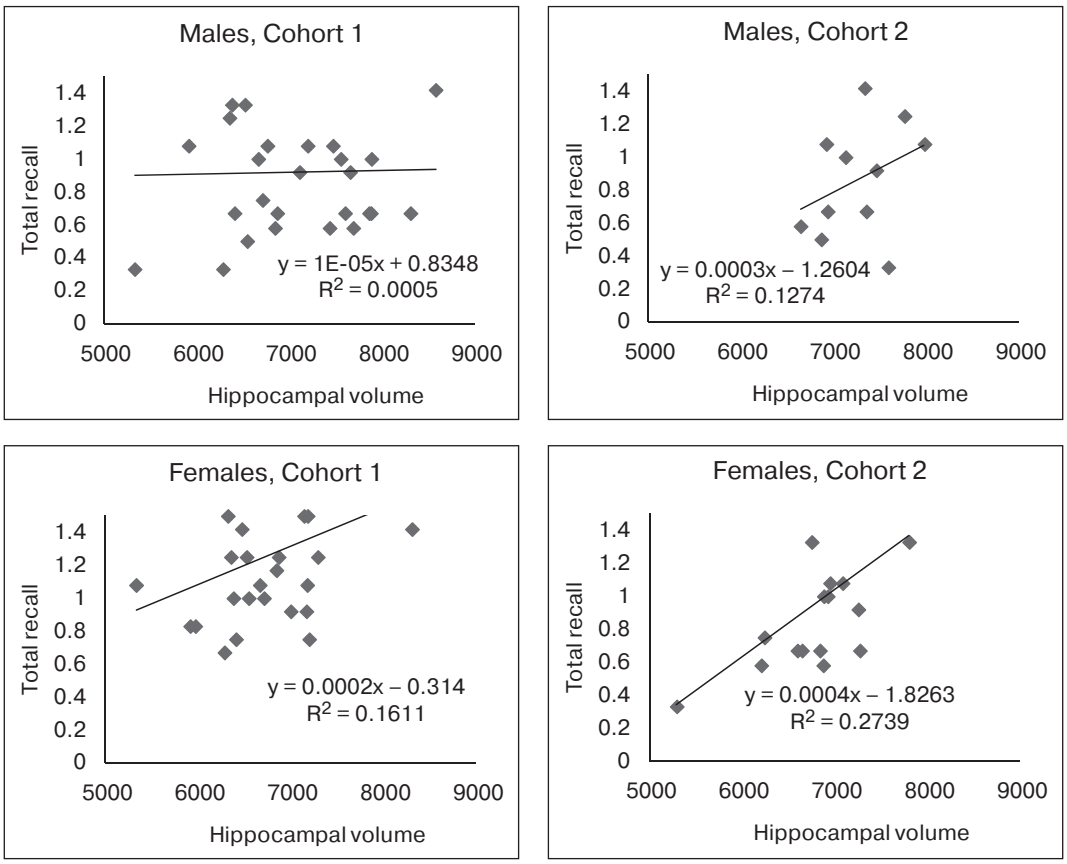

Fig. 8. Delayed total free recall as a function of hippocampal volume using data from [5]. Cohorts 1 and 2 were differently recruited subjects. The volume displayed is the hippocampal grey matter volume in mm^3

The two stages of free recall must have locii in two different structures of the brain since only the second stage is affected by acute cannabis use and by mild AD. The second stage of recall presumably exists at the intersection of locations affected by cannabis and AD. There are two known cannabinoid receptors, CB1 and CB2, and CB1 is particularly highly concentrated in the dentate gyrus, CA1 and CA3 regions of the hippocampus [17]. AD cognitive deficits are thought to originate in the hippocampal region where the CA1 subfield is damaged first [4], thus pointing to hippocampal CA1 as the location of the second stage of free recall. There is a weak positive relationship between hippocampal volume and delayed total free recall in normal subjects (Fig. 8, data from [5]) and a strong positive correlation in subjects with Alzheimer's disease for both immediate and delayed free recall but no such correlation for the parahippocampal gyrus or the temporal neocortex [9].

A testable prediction of this placement would be whether the CA1 area of hippocampus supports a retrieval mechanism that creates errors proportional to the time spent retrieving items [18], this is different from the long term retrieval mechanism which does not include such a rise in the error rate.

REFERENCES

[1] Ashford J.W., Kolm P., Colliver J.A., Bekian C., Hsu L.N. Alzheimer patient evaluation and the mini-mental state: item characteristic curve analysis. *Journal of Gerontology*, 1989, vol. 44, no 5, pp. 139—146.

[2] Ashford J.W., Shan M., Butler S., Rajesekar A., Schmitt F. Temporal quantification of Alzheimer's disease severity: Time index model. *Dementia and Geriatric Cognitive Disorders,* 1995, vol. 6, no 5, pp. 269—280.

[3] Bayley P.J., Salmon D.P., Bondi M.W., Bui B.K., Olichney J., Delis D.C., Thomas R.G., Thal L.J. Comparison of the serial position effect in very mild Alzheimer's disease, mild Alzheimer's disease, and amnesia associated with electroconvulsive therapy. *Journal of the International Neuropsychological Society,* 2000, no 6, pp. 290—298.

[4] Braak H., Braak, E. Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiology of aging*, 1995, vol. 16, no 3, pp. 271—278.

[5] Bruno D., Grothe M.J., Nierenberg J., Zetterberg H., Blennow K., Teipel S.J., Pomara N. A study on the specificity of the association between hippocampal volume and delayed primacy performance in cognitively intact elderly individuals. *Neuropsychologia*, 2015, no 69, pp. 1—8.

[6] Buschke H. *Memory tests using item-specific weighted memory measurements; and uses thereof.* US Patent 6306086. 1999.

[7] Cullen B., O'Neill B., Evans J.J., Coen R.F., Lawlor B.A. A review of screening tests for cognitive impairment. *Journal of Neurology, Neurosurgery & Psychiatry,* 2007, vol. 78, no 8, pp.790-799.

[8] Darley C.F., Tinklenberg J.R., Hollister T.E., Atkinson R.C. Marihuana and Retrieval from Short-Term Memory. *Psychopharmacologia (Berl.)*, 1973, no 29, pp. 231—238.

[9] De Toledo-Morrell L., Dickerson B., Sullivan M.P., Spanovic C., Wilson R., Bennett D.A. Hemispheric differences in hippocampal volume predict verbal and spatial memory performance in patients with Alzheimer's disease. *Hippocampus*, 2000, vol. 10, no 2, pp. 136—142.

[10] Ferraro D.P. Acute effects of marijuana on human memory and cognition. *NIDA Res. Monogr.*, 1980, no 31, pp. 98—119.

[11] Glanzer M. Short-term memory. In Puff R. (Ed.) *Handbook of Research Methods in Human Memory and Cognition*. New York, Academic Press, 1982, pp. 63—98.

[12] Glanzer M., Cunitz A.R. Two storage mechanisms in free recall. *Journal of verbal learning and verbal behavior,* 1966, vol. 5, no 4, pp. 351—360.

[13] Howard M.W., Kahana M.J. Contextual Variability and Serial Position Effects in Free Recall. *Journal of Experimental Psychology: Learning, Memory & Cognition,* 1999, vol. 25, no 4, pp. 923—94.
[14] Murdock B.B., Jr. The serial position effect of free recall. *Journal of experimental psychology*, 1962, vol. 64, no 5, pp. 482.
[15] Murdock B.B. *Human memory: Theory and data*. Lawrence Erlbaum, 1974.
[16] Ranganathan M., D'souza D.C. The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology*, 2006, vol. 188, no 4, pp. 425—444.
[17] Sullivan J.M. Cellular and molecular mechanisms underlying learning and memory impairments produced by cannabinoids. *Learning & Memory*, 2000, vol. 7, no 3, pp. 132—139.
[18] Tarnow E. Free Recall Retrieval Process Creates Errors in Short Term Memory but Not in Long Term Memory. *Bulletin of Peoples' Friendship University of Russia, Series: Psychology and Pedagogy,* 2015, no 2, pp. 54—66.
[19] Tarnow E. Direct Evidence Delay with A Task Decreases Working Memory Content in Free Recall. Submitted for publication, 2015.
[20] Tarnow E. First direct evidence of two stages in free recall. *Bulletin of Peoples' Friendship University of Russia, Series: Psychology and Pedagogy*, 2015, no 4, pp. 15—26.
[21] Watkins M.J. Concept and measurement of primary memory. *Psychological Bulletin*, 1974, vol. 81, no 10, pp. 695—711.

КОСВЕННЫЕ ДОКАЗАТЕЛЬСТВА ЛОКАЛИЗАЦИИ ВТОРОЙ СТУПЕНИ СВОБОДНОГО ВОСПРОИЗВЕДЕНИЯ ИЗ КРАТКОВРЕМЕННОЙ ПАМЯТИ В ОБЛАСТИ CA1 ГИППОКАМПА

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В предыдущих исследованиях [15; 20] было обосновано и показано, что воспроизведение информации из кратковременной памяти включает две ступени: первые единицы воспроизводятся из «опустошающейся» оперативной памяти, вторая ступень воспроизведения имеет характер реактивации. В данной статье показано, что последовательные изменения кривой воспроизведения информации при умеренной болезни Альцгеймера (БА) и значительном употреблении марихуаны — снижение общего количества воспроизведений и уменьшение эффекта первичности — похожи на характер воспроизведения информации на второй ступени и отличаются от воспроизведения из рабочей памяти. Так как употребление марихуаны и БА влияют на вторую ступень свободного воспроизведения, предположительно, эта стадия воспроизведения связана с областью CA1 гиппокампа. Поскольку на втором этапе воспроизведения используется процесс извлечения информации, который сопровождается линейным ростом частоты ошибок [18], этот механизм генерирования ошибки должен помочь понять структуру соответствующей нейронной сети.

Ключевые слова: умеренная болезнь Альцгеймера, марихуана, конопля, свободное воспроизведение из кратковременной памяти, рабочая память, кратковременная память