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Original Articles

Short-term Memory Performance with Magnetic Stimulation of the Motor Cortex

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Summary. Whether transcranial magnetic stimulation of the motor cortex has an influence on memory was investigated. In a first experiment with 21 healthy volunteers six pronounceable nonsense words were visually presented, immediately followed by a magnetic stimulus. There were three blocks of stimulation with field intensities of 60, 80 and 100% (referring to a maximal intensity of 2 Tesla), each block comprising six magnetic stimuli and six nonsense words. After each block there was a free recall test and at the end another free recall trial as well as a multiple-choice recognition test for all 18 words. Eighteen subjects served as controls, undergoing the same procedure, except that the field intensity was zero. A significant but small reduction of short-term memory performance was observed only for 100% field intenisty. In a second experiment with 16 subjects who had not participated in experiment I, the effect of 100% intensity cortical magnetic stimulation was compared with a control stimulation over the cervical spine. There was no difference in free recall or in the multiple-choice test between the sites of stimulation, suggesting that the difference in the 100% intensity block in experiment I was not due to a specific cortical effect of the magnetic field on memory function. With respect to the effect on memory functions, transcranial magnetic stimulation of the motor cortex is thought to be a safe method.

Key words: Transcranial magnetic stimulation – Short-term memory – Side-effect

Introduction

Transcranial magnetic stimulation of the motor cortex for investigation of the descending motor pathways has been recently introduced (Barker et al., 1985). Even though this method causes no serious discomfort when compared with transcranial electrical stimulation, there is still some concern about the safety of the method. In some countries the method is not yet permitted for use with patients.

There seem to be no effects except for the intended short muscle twitch; kindling does not occur with electrial stimuli at frequencies below 10 Hz (Goddard, 1969) and magnetic stimulation is currently carried out with frequencies lower than 1 Hz. There is no influence of magnetic stimulation on cortical electrical activity or cerebral blood flow in the cat (Eyre et al., 1988).

So far, however, no investigation has been carried out that systematically studied the effect of magnetic stimuli on memory. This issue seems to be important, since magnetic stimulation with a large circular coil is less focal than electrical stimulation and one ought to think of remote effects. It is well known that transient disturbances of memory can be induced by brain stimulation (Penfield and Jasper, 1954; Halgren, 1982). The site of stimulation was mostly temporal in these studies.

We tried to answer the question whether transcranial magnetic stimulation with a coil positioned over the motor cortex has any remote effects on short-term memory. In a first experiment (experiment I), cortical magnetic stimulation was compared with dummy (i.e. zero magnetic intensity) stimulation in two independent groups of subjects. A significant effect on memory performance was observed only for the highest (i.e. 100%) intensity of magnetic stimulation. Because most of the subjects experienced some discomfort during magnetic stimulation with this intensity, it could not be decided unequivocally whether the decrease of memory performance reflected a direct cortical effect of magnetic stimulation or was a secondary effect due to discomfort and distraction. Therefore, a second experiment (experiment II) compared the effect of cortical with that of cervical magnetic stimulation in the same subjects. Both types of stimulation induce similar motor reactions with comparable discomfort and distraction.

Subjects and Methods

For experiment I, 21 healthy volunteers (11 females, 10 males; aged 19–29 years) participated as experimental subjects. Another 18 volunteers (8 females, 10 males; aged 21–26 years) served as controls. The controls underwent the same procedure as the experimental group, except that the intensity of magnetic stimulation was set to zero (dummy treatment). All subjects were told that

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they would be exposed to magnetic stimulation of the brain and that they might (or might not) notice muscle twitches after each stimulus. In experiment II, 16 healthy volunteers (8 females, 10 males; aged 21–28 years), none of whom had participated in experiment I, served as subjects. Informed consent was obtained from all subjects.

Experiment I

A Novametrix (Magstim 200, Madaus Medizin Elektronik) magnetic stimulator was used, with the centre of the coil positioned over Cz. Three field intensities were applied (60, 80 and 100%), expressed as percent of the maximal magnetic field intensity which is 2 Tesla at the centre of the coil.

Three consecutive blocks of six magnetic stimuli with intensity increasing from block to block were applied with the experimental subjects. For the control conditions, stimulus intensity was zero throughout. The interstimulus interval was approximately 8 s and each block was separated from the next by about 45 s.

A five-letter pronounceable nonsense word (e.g. RENBAL) printed on a card in upper-case letters was presented. Subjects were asked to read aloud and memorize the word. Immediately after reading, a magnetic stimulus was applied. After each block, the subjects were requested to recall as many of the preceding six words as possible. The answers were tape-recorded. After that, the next block of words and magnetic stimuli was applied.

Following recall of the third block of words, and without prior notice, the subjects were required to recall all 18 words presented before, with a time limit of 120 s. In addition, a multiple-choice recognition test for all 18 words was given. Each of the words was presented together with three other nonsense words. The distractor words were of the same general type as the target words, but close graphemic or phonemic similarities were avoided (e.g. ROFERT, FEIRIG and DONSEN, with RENBAL being the target word).

All nonsense words used for recall and recognition testing were taken from a memory task developed in our department (Recurring Words Test) and were selected with regard to their low association with real words (association values ranging between 5 and 24%).

After the test, the subjects of the experimental group were requested to estimate the degree of subjective discomfort caused by the magnetic stimulation according to a scale with five categories ranging from one (no discomfort) to five (very unpleasant).

Experiment II

The same magnetic stimulator was used as in experiment I. Four blocks of six magnetic stimuli were applied with each subject. In two blocks, we used stimulation with 100% intensity over the vertex, and in the remaining two blocks, we stimulated over the cervical spine with an intensity of 80%. These two stimulation intensities had been found to be comparably "unpleasant" in a pilot study. The sequence of stimulation blocks was cortical/cervical/cervical/cortical for one half of the subjects and cervical/cortical/cortical/cervical for the other half of the subjects.

Six new nonsense words were added to the 18 words used in experiment I. The procedure of word presentation and testing for memory performance was the same as in experiment I (except that four blocks of six words were presented and that the final free recall and recognition trials related to a total of 24 instead of 18 words). Responses given during final free recall and recognition were related to the corresponding blocks of stimuli, that is, performance is given as the number of words correctly recalled or recognized from each of the four blocks.

Each of the 24 stimulus words was followed by a cortical stimulation in half of the subjects and by a cervical-spinal stimulation in the other half of the subjects, and vice versa. This procedure aimed at balancing possible effects of order of magnetic stimulation and of word difficulty.

Results

Experiment I

For statistical analysis, a permutation test (Pyhel, 1980) for the assessment of homogeneity/parallelism of profiles (interaction in a split-plot design), a rank test for monotone trend (Jonckheere, 1954) and the Mann-Whitney U-test for the comparison of two groups were used.

Mean free recall and recognition performances are shown in Figs. 1 and 2. As was to be expected, performance was much lower for free recall than for recognition in both groups of subjects.

The results of the permutation tests showed that the Group × Intensity of stimulation interaction (which was to be predicted on the assumption that magnetic stimula-

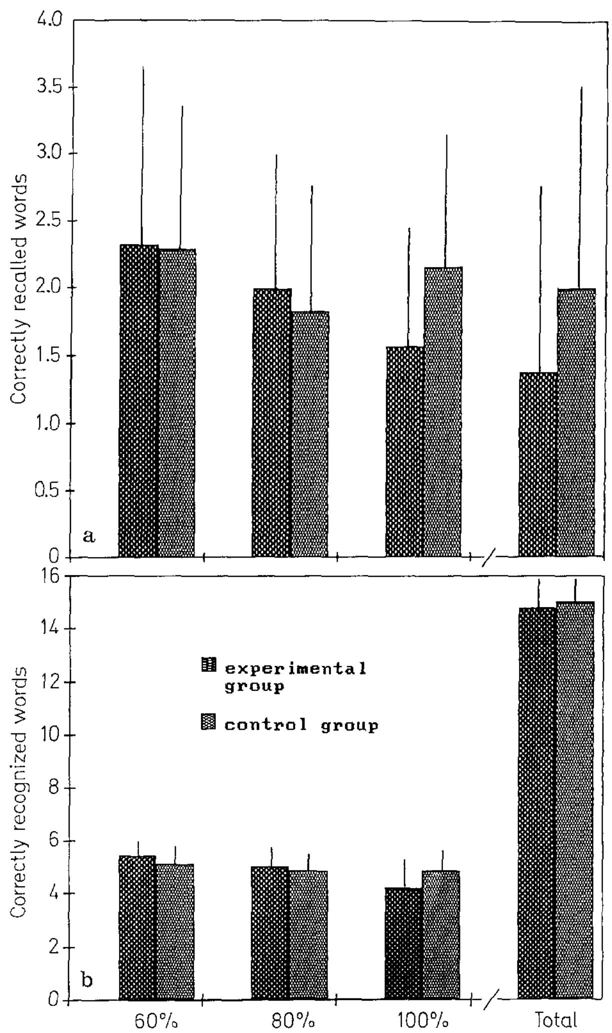

Fig. 1a. Experiment I: Correct answers during free recall of words (mean and standard deviation). 60, 80 and 100% refer to a maximal field intensity of 2 Tesla. There were six test words in each block. Free recall of the six words was requests after each block of stimulation. At the end of the test there was an additional free recall trial of all 18 words ("Total"). **b** Experiment I: Correctly recognized words in the multiple choice test (mean and standard deviation). There was only one multiple choice test after all 18 stimuli ("Total") but the recognition performance related to the 6 words presented in each block is also given

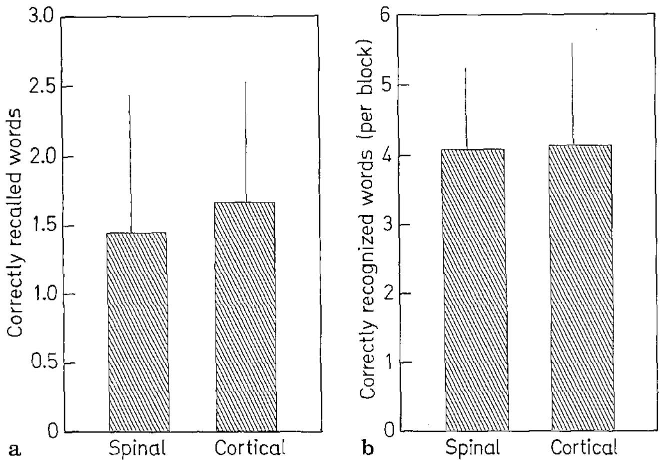

Fig. 2a. Experiment II: Correct answers during immediate free recall after each block of stimuli (mean and standard deviation). Scores are combined for all blocks with spinal respectively cortical stimulation . **b** Experiment II: Correctly recognized words in the final multiple choice test (mean and standard deviation). Recognition performance is related to the six words presented in each block

tion would impair memory performance) approached significance for recognition performance ($P = 0.068$) but fell short of significance for free recall ($P = 0.149$).

Applying the test for monotone trend separately to performance scores for each of the two subject groups, a significant monotone decreasing trend was found in the experimental group for free recall ($P = 0.013$) and for recognition ($P = 0.004$), while there was no monotone trend for either for these measures in the group of controls ($P = 0.500$ and 0.159, respectively). In the experimental group, the monotone trends showed a consistent decline of performance with increasing strength of magnetic stimulation.

Separate comparisons between the two groups by U-tests for each stimulation condition revealed that recognition of the words presented in the last block (100% intensity) was significantly worse in the experimental group (one-tailed $P = 0.044$). A tendency in the same direction was also observed for free recall performance in this block (one-tailed $P = 0.053$). All other comparisons did not approach significance.

Two of the experimental subjects did not report any discomfort during the whole procedure. Ten subjects reported very mild and six subjects moderate discomfort. Two subjects claimed that they had experienced the procedure as unpleasant and one subject reported that the procedure was very unpleasant. This subject stated that he would not like to undergo such a procedure again, whereas the others said they would not mind repeating the procedure. Two subjects complained about some feeling of numbness in the head and mouth at the end of the experiment, which disappeared, however, shortly afterwards. The degree of discomfort reported by the subjects was not substantially related to memory performance.

There was, of course, a major difference between the experimental and the control group: subjects in the latter group did not experience any motor effects. However, when the control subjects were questioned at the end of the whole procedure, they all stated that they had believed to be stimulated without noticing the effect.

Experiment II

A Pitman permutation test for the dependent two-sample problem was carried out for comparison of spinal and cortical stimulation using a personal computer program (Dallal, 1985).

Means and standard deviations for immediate free recall (after each block of stimuli) and for recognition performance (after completion of all four blocks) with cortical and cervical magnetic stimulation are given in Fig. 2a and b. Performance during final free recall, that is after completion of all blocks, was very low ($X = 0.38$; $s = 0.707$ for cortical stimulation and $X = 0.25$, $s = 0.622$ for spinal stimulation). Pitman permutation tests revealed no significant difference between the two modes of stimulation, either for immediate for final free recall ($P = 0.513$ respectively $P = 0.50$, two-tailed) or for recognition performance ($P = 0.855$, two-tailed).

Discussion

In this study, we examined whether transcranial magnetic stimulation with a technique used for investigation of the motor cortex and descending motor pathways may have some influence on memory performance. Magnetic stimuli might have affected two aspects of memory function: as the magnetic stimuli followed immediately after the presentation of the words, memory storage as well as retrieval from short-term memory might be influenced. Because each magnetic stimulus was applied only after the subject had read aloud the visually presented word, the processes of visual perception and linguistic decoding could not have been disturbed by the magnetic stimulation. This is essential to realise, since magnetic stimulation over occipital regions applied 80–120 ms after tachistoscopic presentation of a letter may disturb its visual perception (Amassian et al., 1988).

At first sight, the results of experiment I suggest that free recall and recognition performance steadily decline with increasing magnetic intensity in the experimental group but remain on a more or less constant level in the group of controls.

However, before concluding that it is magnetic stimulation which affects memory performance, several alternative explanations must be considered. First, no strict measures were used to equate the three sets of nonsense words with regard to item difficulty. However, if item difficulty were critical, it should have influenced performance to the same degree in both groups of subjects. Second, the two groups were not matched with respect to prior memory performance. However, the fact that free recall and recognition performance of the experimental subjects were equal to or even slightly better than that of the controls for the first two blocks of magnetic stimulation indicates that the lower performance of the experimental subjects in the last block of experiment I, with highest magnetic intensity, cannot be explained by pre-existing differences in memory performance.

Therefore, it appears that memory performance was indeed adversely affected by stimulation with the highest intensity of the magnetic field i.e. 100%.

The question remains, however, whether this effect was due to a direct influence of magnetic stimulation on the neuroanatomical structures or neuropsychological processes which are critical for memory performance. The experimental paradigm of experiment I does not allow us to exclude the possibility that in the experimental group the experience and expectation of discomfort due to the stimulus-evoked muscle twitches or the proprioceptive effects of the motor reaction itself interfered with the memory storage of the words. This possibility was examined in our second experiment.

The results of experiment II did not show any differential influence of transcranial cortical and cervical-spinal stimulation on memory performance. This strengthens the assumption that the slight impairment of memory performance observed in experiment I can not be interpreted as a direct effect of magnetic stimulation but rather as being due to an interference caused by the experience of discomfort and distraction associated with the induced motor reactions.

Our results are not in conflict with earlier work on disturbance of memory function during brain stimulation using different techniques. Penfield and Jasper (1954) were the first to report memory-like experiences during stimulation of lateral temporal cortex. In later years, the structures critical for memory have been identified in the mesial temporal lobe structures (Chapman et al., 1967) and it has been shown that bilateral stimulation of these structures may lead to an amnesia of short duration (Halgren, 1982). However, with a magnetic coil positioned over the motor cortex, hippocampus and amygdala are about 10 cm away from the focus of stimulation. As the magnetic field is attenuated with increasing distance from the coil, an influence of the magnetic field on these structures might not have been expected. On the other hand, localising memory exclusively to the mesial temporal lobe may be too simplistic. Regardless of its central role for memory functions, a larger part of the cortex is probably involved in memory processes.

When stimulating the motor cortex, an adverse effect on memory function is certainly unwanted. Yet, for investigations such as pre-surgical evaluation of epileptic patients such effects may even be intended. With the use of more focal coils that are centred over the temporal cortex, it might be possible to observe an effect on memory performance. Such experiments may be conducted in the future using a "figure-of-8" coil. An even stronger effect can be expected by using trains of stimuli – a technique that may be available in the near future (Amassian et al. 1990). Double stimulation has recently shown that the first stimulus changes the excitability of the motor cortex (Ferbert et al. 1990).

In future studies concerned with possible neuropsychological side-effects of magnetic stimulation of the motor cortex, it could also prove worthwhile to include parietal lobe functions, as for example perception of spatial orientation.

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