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Memory performance under varying cueing conditions in patients with Parkinson's disease

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Abstract—The present study is a continuation of a previous study in memory performance which showed that Parkinson's disease (PD) patients increasingly relied on explicit cues which prompt the external strategy of serial clustering, in comparison to control subjects (CS), who profited increasingly from implicit cues which prompt the internal and more effective strategy of semantic clustering. In this study, we investigated whether the recall of PD patients can be affected by adding or removing explicit cues. We manipulated the California Verbal Learning Test in two ways. First, we told the subjects under study in advance from which categories the items to be recalled were derived, thus making the implicit cue to cluster semantically explicit (explicit condition). Next, we permuted the sequence of the items in each trial, thus preventing the subjects from adhering to the serial order, i.e. to explicit cues (permuted condition). We included the data of our previous study (mixed condition) in the analysis of memory and learning performance in the three conditions. Learning of PD patients, as reflected in the semantic ratio, proved to be more affected by the cueing conditions than that of CS. Total performance and the serial ratios did not show a significant interaction between group and cueing condition. The results are discussed in terms of external and internal generation of problem-solving strategies. Copyright © 1996 Elsevier Science Ltd

Key Words: memory; Parkinson's disease; cue.

Introduction

In many studies [2, 5, 15, 22, 23], it is established that patients with Parkinson's disease (PD) perform problem-solving tasks as well as control subjects (CS), when cues are available. The performance of PD patients seriously decreases when cues are absent. However, it is unclear whether or not a response of PD patients is dependent on certain qualities of a cue.

In a recent study [3], we made the distinction between explicit and implicit cues. We investigated whether PD patients responded differentially to explicit or implicit cues in a memory task. Responding to explicit cues means that the subject utilizes the information of the cue just as it is, i.e. as an external guideline. Responding to implicit cues means that the subject processes the information

internally in such a way that surplus information is derived from the cue before utilizing it. We selected the California Verbal Learning Test [7], a test in which items of four semantic categories have to be learned in five consecutive trials. Since the semantic organization of the items was not divulged in advance, it is an implicit cue requiring internal processing, which results in semantic clustering. Recall, in terms of spontaneous grouping of the items in semantic categories, implicates an internal, self-directed strategy. Adhering to the sequence in which the words are read by the experimenter reflects responding to explicit cues, this being an external strategy. We found that PD patients gradually adhered to the externally imposed serial strategy, in contrast to CS, who increasingly recalled items in semantic clusters, this being a result of internally generated strategy. These findings showed that PD patients increasingly responded to explicit cues, i.e. moved on to the externally prompted strategy in a verbal memory task.

In the present study, we continued our research in this

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field. First, we investigated whether PD patients can be activated to cluster semantically when the implicit cue to do so is made explicit, thus making internal processing of implicit information redundant. To this end, we presented the CVLT to PD patients and CS, but we told the subjects under study in advance from which semantic categories the items were derived, thus making the implicit semantic organization of the items explicit. We refer to this manipulation of the CVLT format as the explicit condition, in contrast to the mixed condition of our previous study, in which explicit and implicit cues were simultaneously presented. If the performance of PD patients equals that of CS, and if the profiles of the semantic ratios of PD patients and CS across the trials are similar, this indicates that—just like CS—PD are able to utilize semantic cues in a recalling task, when these are explicitly presented.

Next, we examined whether PD patients resort to semantic clustering when explicit cues, which prompt external strategies, are removed, and consequently only the implicit cue to internal processing is left. Sagar *et al.* [19] found evidence that PD patients showed a similar build-up and release of proactive interference (PI) on the basis of implicit semantic categories as CS. These authors correctly point out that such a normal PI build-up and release presuppose the ability to use implicit semantic information spontaneously. This is fully in line with the results of our previous study which showed that PD patients were able to use the implicit cues of the test items, which indicates the internal strategy of semantic clustering, although at a reduced level compared with CS. In fact, in the first trial, the PD patients showed even a slightly higher semantic ratio than CS. In the subsequent trials, the semantic ratio of the PD patients remained constant, whereas that of CS substantially increased. These findings suggest that the presence of explicit cues prevents PD patients from profiting from the more effective, but internal, strategy, i.e. semantic clustering. We presented the CVLT to PD patients and CS, but this time, we permuted the sequence of the items in each trial. In this 'permuted condition', subjects are prevented from adhering to the serial order, i.e. to explicit cues, which were present in both the mixed and the explicit condition. If the semantic ratio of PD patients across the trials increases in the same way as that of CS, it is plausible that, in the absence of strong and explicit cues, PD resort to the only cue which is left, and which implicitly prompts semantic clustering. Moreover, if the total performance of PD patients equals that of CS in the permuted condition, PD patients benefit from the more effective strategy of clustering to the same extent as CS. However, if their total performance is poorer, it is plausible that PD patients are impaired in profiting from implicit cues, even when explicit cues are removed.

Since both experiments are the continuation of our previous study in memory performance in PD, the data of that study will be included in the analyses of the present data.

Materials and methods

Subjects

Fifty-four PD patients (42 men and 12 women) and 11 CS (four men and seven women) participated in the study of the explicit condition. Among them, 23 were untreated. Thirty PD patients were on L-DOPA, six were on anticholinergic therapy, and five were on both therapies.

The patient group of the permuted condition consisted of 17 patients (10 men and seven women) and 27 CS (eight men and 19 women). Seven PD patients were untreated. Ten patients were on L-DOPA, and one was also on anticholinergic therapy. All gave informed consent. The diagnosis of idiopathic PD was based on the presence of at least two of the following symptoms: tremor, rigidity, bradykinesia and postural disturbances. The symptoms were evaluated by a neurologist (M. H.) a week before psychological testing. Patients with non-PD symptoms, EEG and CT scan abnormalities, cerebrovascular disease and psychiatric illness, according to DSM III-R criteria, or clinical evidence of dementia, based on the MMSE [10], were excluded. The severity of PD was rated by means of the motor examination part of the Unified Parkinson's Disease Rating Scale [8].

As far as CS are concerned, most of them were patients' spouses, which explains the large number of female CS. Subjects with CNS disease, psychiatric illness according to DSM III-R criteria, head injury, clinical evidence of dementia based on the MMSE or taking centrally active drugs were excluded from the study.

Methods

In order to compare the groups and to control for intelligence, attention and depression, we used the same reference tests as in the previous study: four tests of the Dutch adaptation of the WAIS-R, the Stroop Color Word Test [13] and the Zung Depression Scale [26]. The criterion test was the California Verbal Learning Test (CVLT). The CVLT consists of five learning trials of a 16-word target shopping list, which can be grouped into four semantic categories of four items. In the original version, the experimenter does not indicate that the items can be grouped. Moreover, the sequence in which the words are read by the experimenter is fixed, and each subsequent item belongs to a category being different from the category to which the preceding words belong. After each learning trial, free recall was measured.

In this study, we changed the format of the CVLT twice. In the explicit condition, the experimenter told the subjects in which semantic categories the items of the shopping list could be grouped, thus explicitly indicating in which way items could be grouped during the learning trials. For the rest, the procedure was identical to the original CVLT. In the permuted condition, the sequence of the items in each trial was different from the previous ones, thus preventing the subject from adhering to an externally imposed, fixed sequence. In accordance with the mixed condition and in contrast with the explicit condition, the experimenter did not indicate that the items were derived from four categories.

The following relevant CVLT indices were included in this study: the number of words recalled per trial and across trials 1–5, and the semantic and serial clustering ratio per trial and across trials 1–5. The semantic ratio was the ratio of words from the same category recalled together over semantic clustering expected by chance given the number of words and categories recalled. The serial ratio was the ratio of words recalled in the same order as they were presented over serial clustering expected by chance given the number of words recalled. For

further information about tests, scoring and calculating, we refer to the previous study [3].

Statistical analysis

Initially, we incorporated two kinds of variables in our analysis of covariance: one in which the parameters were computed along the lines of the manual [6, 11], and one in which the parameters were log-transformed. Of the covariates sex, age, IQ, attention, depression and medication, only sex and IQ were related to the CVLT indices. The analysis of covariance was done both for the test scores, according to the manual and the log-transformed test scores with the primary class variables group and condition, and the covariates sex and IQ. Results with P -values less than 0.05 (two-tailed) are considered significant.

Results

Reference variables

In Table 1 demographic data, disease characteristics and scores of the reference tests are presented.

Criterion tests

Since the present study deals with memory performance under varying cueing conditions, the data of our previous study [3], which were obtained in the mixed condition, will be involved in the statistical analysis. The analyses of the manual scores and the log-transformed scores produced approximately the same results. Therefore, we will only present data obtained in the conventional way indicated in the manual because they allow a comparison with other studies. In view of our previous study, we focused on learning across trials. Moreover, since the data per trial (i.e. the number of words recalled, and the semantic and serial ratios) did not reveal any significant interaction between group and cueing condition, we present only the data across trials.

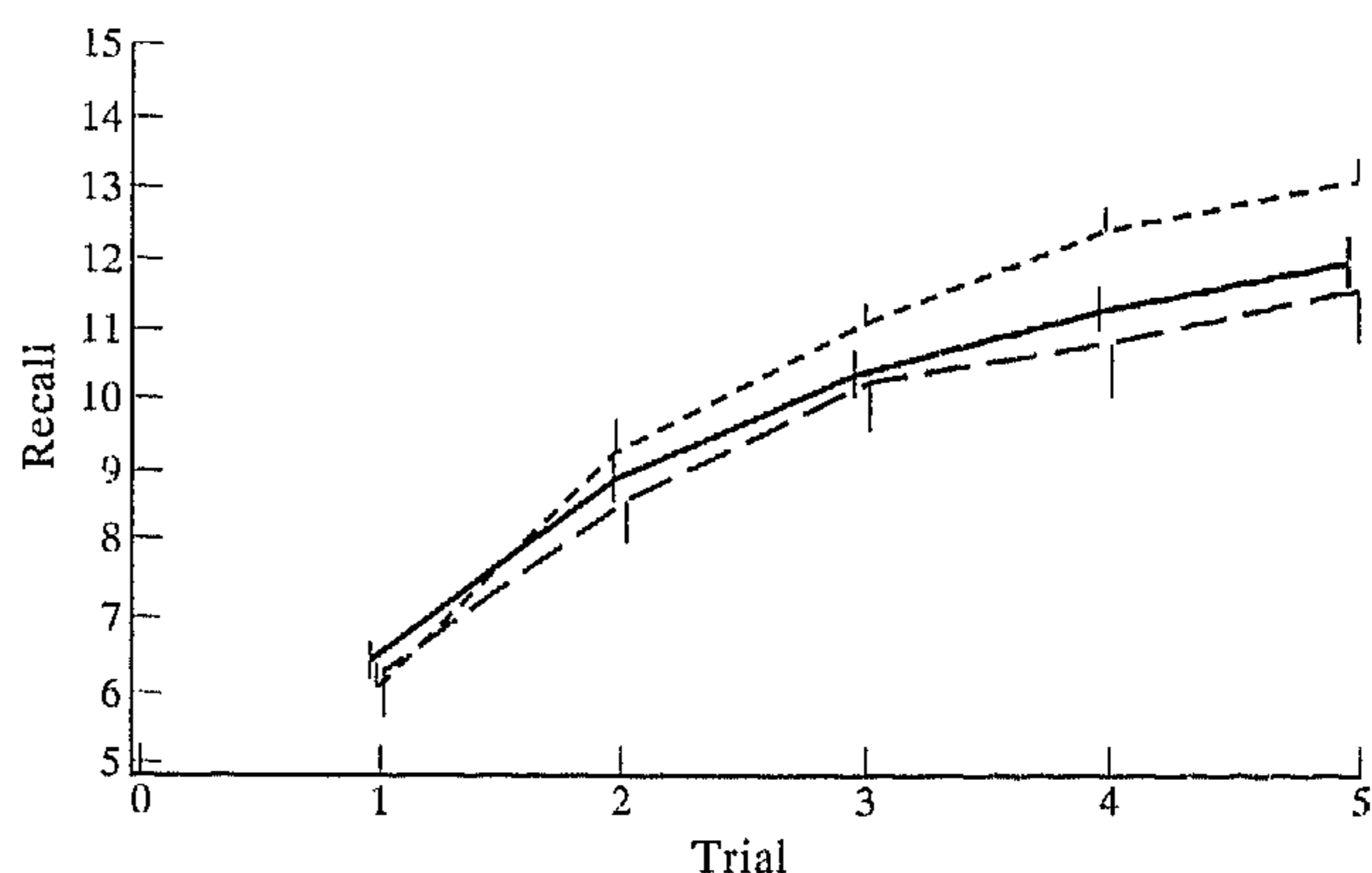


Fig. 1. Recall scores of PD patients. Mean recall (\pm S.E.M.) of the CVLT words. Mixed condition: continuous line; explicit condition: interrupted line with S.E.M. upward; permuted condition: interrupted line with S.E.M. downward. The number of words recalled is shown on the y-axis.

Number of words recalled across trials 1-5

There were no significant differences across trials between PD patients and CS in any condition. In PD patients vs CS in the mixed condition, $\beta = -0.10$ (n.s.), in the explicit condition, $\beta = 0.01$ (n.s.), and in the permuted condition, $\beta = -0.04$ (n.s.). Testing the homogeneity of the β s indicated that there was no significant interaction between group and cueing condition (Figs 1 and 2).

Semantic clustering ratio across trials 1-5

There were no significant differences across trials between PD patients and CS in any condition. In PD patients vs CS in the mixed condition, $\beta = -0.18$ [n.s.: $P = 0.07$], in the explicit condition, $\beta = 0.03$ (n.s.), and in the permuted condition, $\beta = 0.08$ (n.s.). In the log-transformed parameters of our previous study, the difference between PD patients and CS in the mixed condition was significant [$\beta = -0.21$ ($P < 0.05$)]. Testing the homogeneity of the β s revealed a significant interaction between group and cueing condition [$P < 0.05$]. Apparently, learning in PD patients was more affected by the cueing condition than that in CS (Figs 3 and 4).

Table 1. Demographic data, disease characteristics and scores of the reference tests

	Condition					
	Mixed		Explicit		Permuted	
	PD ($n = 59$) Mean S.D.	CS ($n = 30$) Mean S.D.	PD ($n = 54$) Mean S.D.	CS ($n = 11$) Mean S.D.	PD ($n = 17$) Mean S.D.	CS ($n = 27$) Mean S.D.
Age (years)	55.4 (11.5)	53.9 (11.5)	54.9 (10.3)	54.4 (6.3)	56.1 (10.1)	57.5 (13.0)
Duration of PD (years)	5.2 (0.4)		5.0 (0.6)		5.7 (0.6)	
UPDRS	15.9 (0.8)		14.2 (0.8)		17.0 (1.1)	
Total IQ	119.0 (15.5)	125.0 (11.1)	122.4 (14.6)	120.1 (15.5)	112.6 (16.9)	124.0 (12.8)
Stroop, C-B	38.3 (13.8)	39.4 (12.4)	38.2 (15.0)	36.2 (15.7)	37.1 (22.2)	37.3 (18.5)
Zung	41.5 (9.0)	34.3 (7.4)	39.2 (8.9)	33.5 (9.4)	43.7 (8.6)	37.6 (8.6)

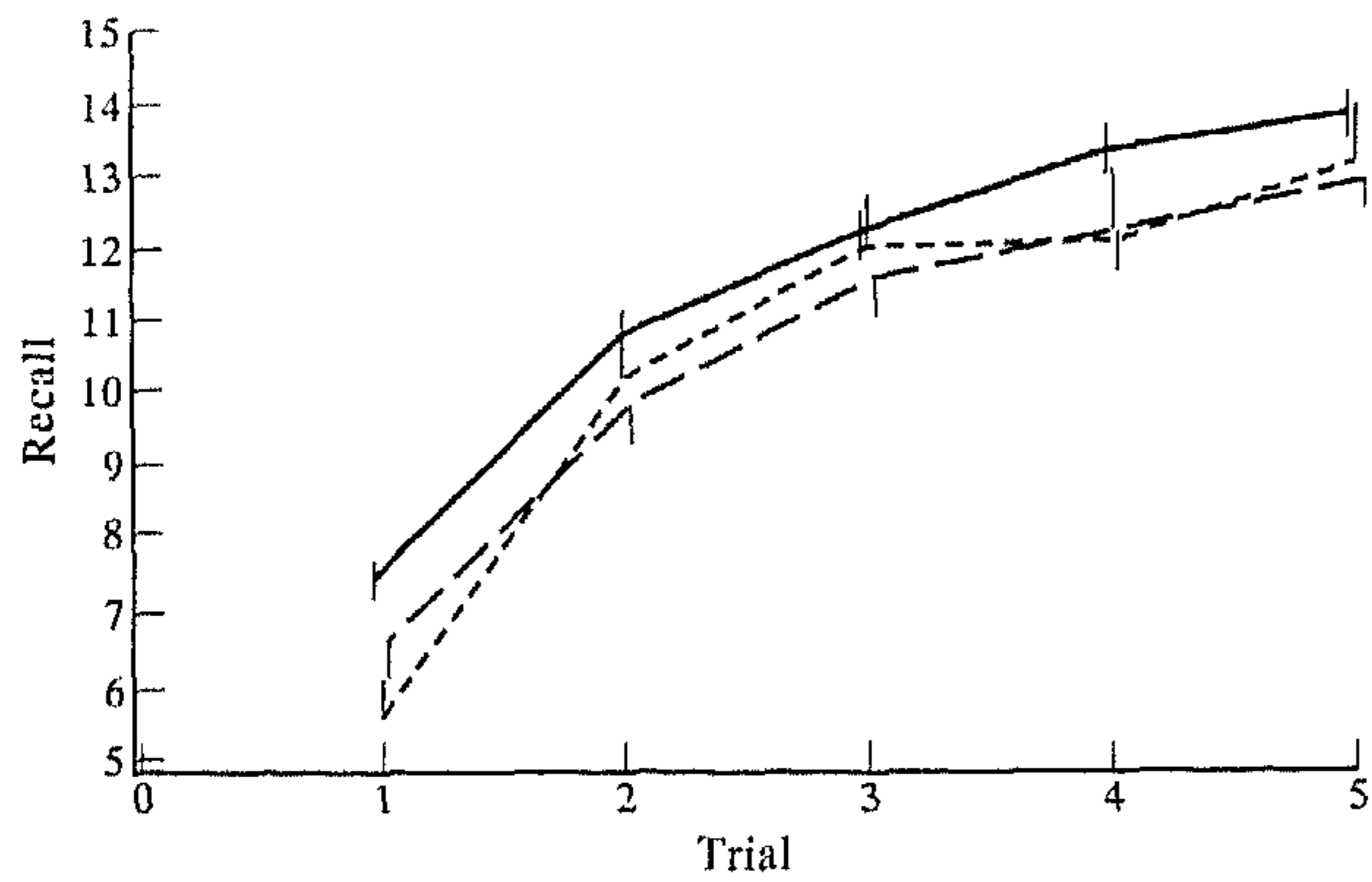


Fig. 2. Recall scores of CS. Mean recall (\pm S.E.M.) of the CVLT words. Mixed condition: continuous line; explicit condition: interrupted line with S.E.M. upward; permuted condition: interrupted line with S.E.M. downward. The number of words recalled is shown on the y-axis.

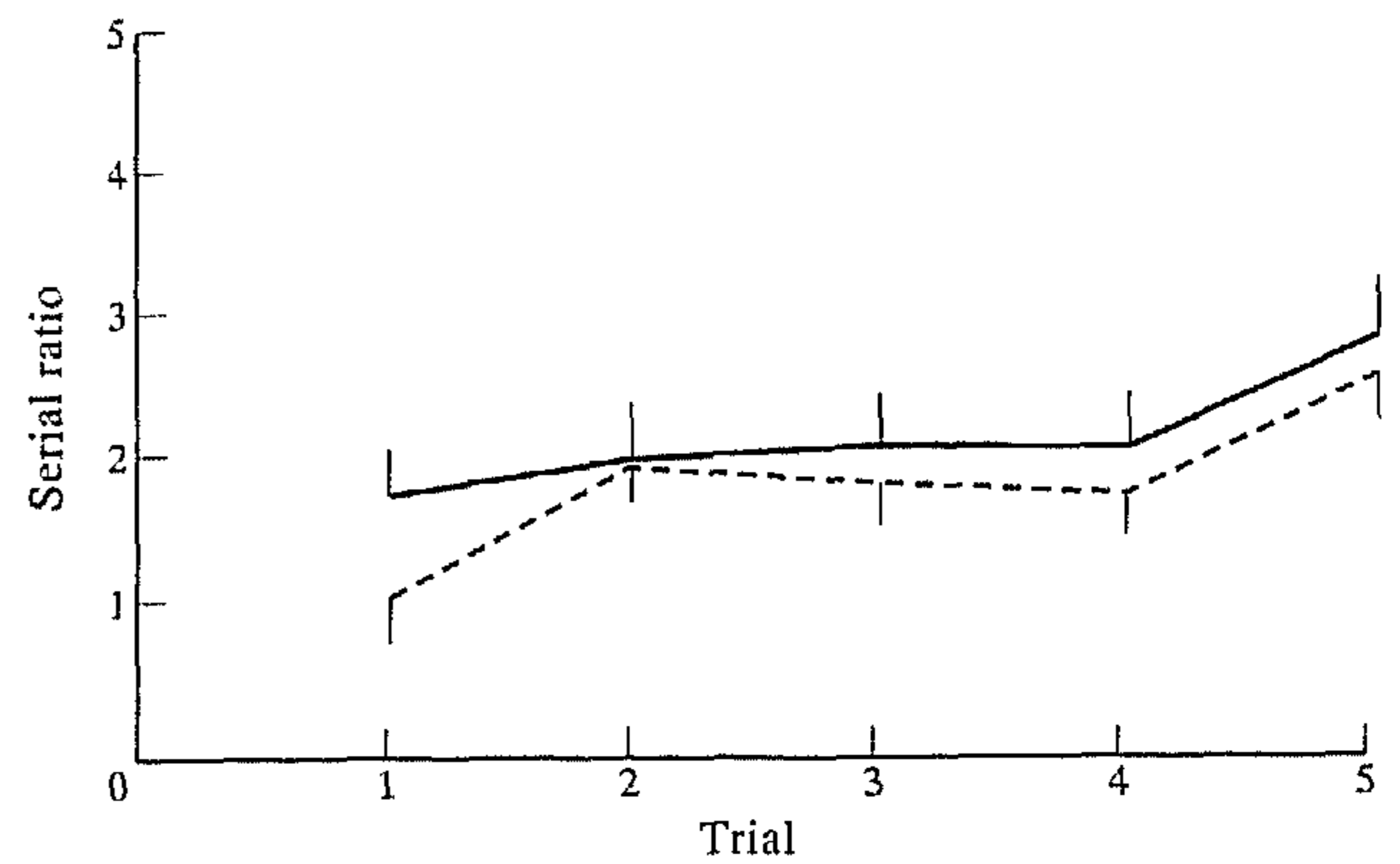


Fig. 5. Serial ratios of PD patients. Mean serial ratios (\pm S.E.M.): mixed condition: continuous line; explicit condition: interrupted line with S.E.M. upward. The serial ratios are shown on the y-axis.

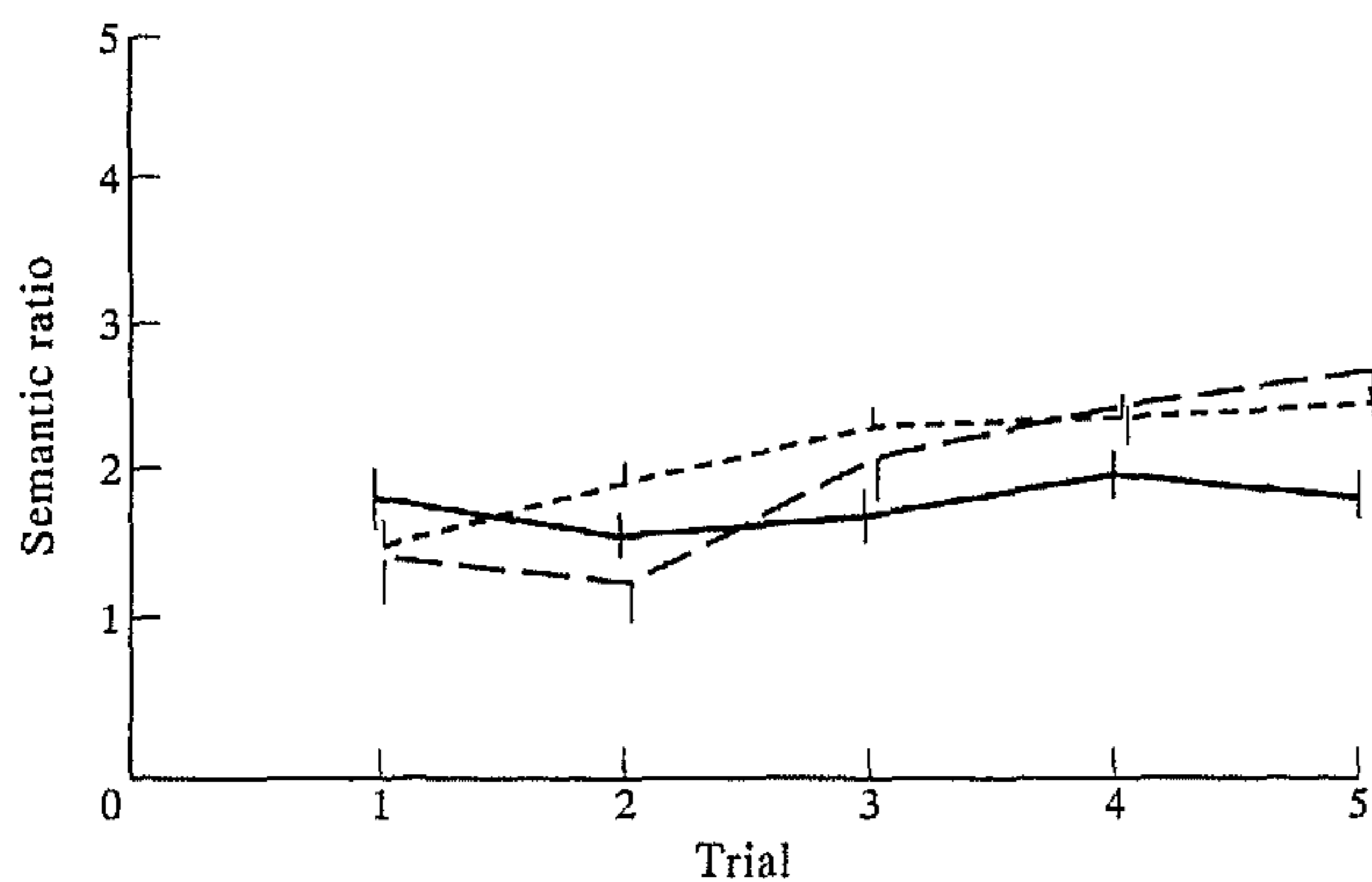


Fig. 3. Semantic ratios of PD patients. Mean semantic ratios (\pm S.E.M.): mixed condition: continuous line; explicit condition: interrupted line with S.E.M. upward; permuted condition: interrupted line with S.E.M. downward. The semantic ratios are shown on the y-axis.

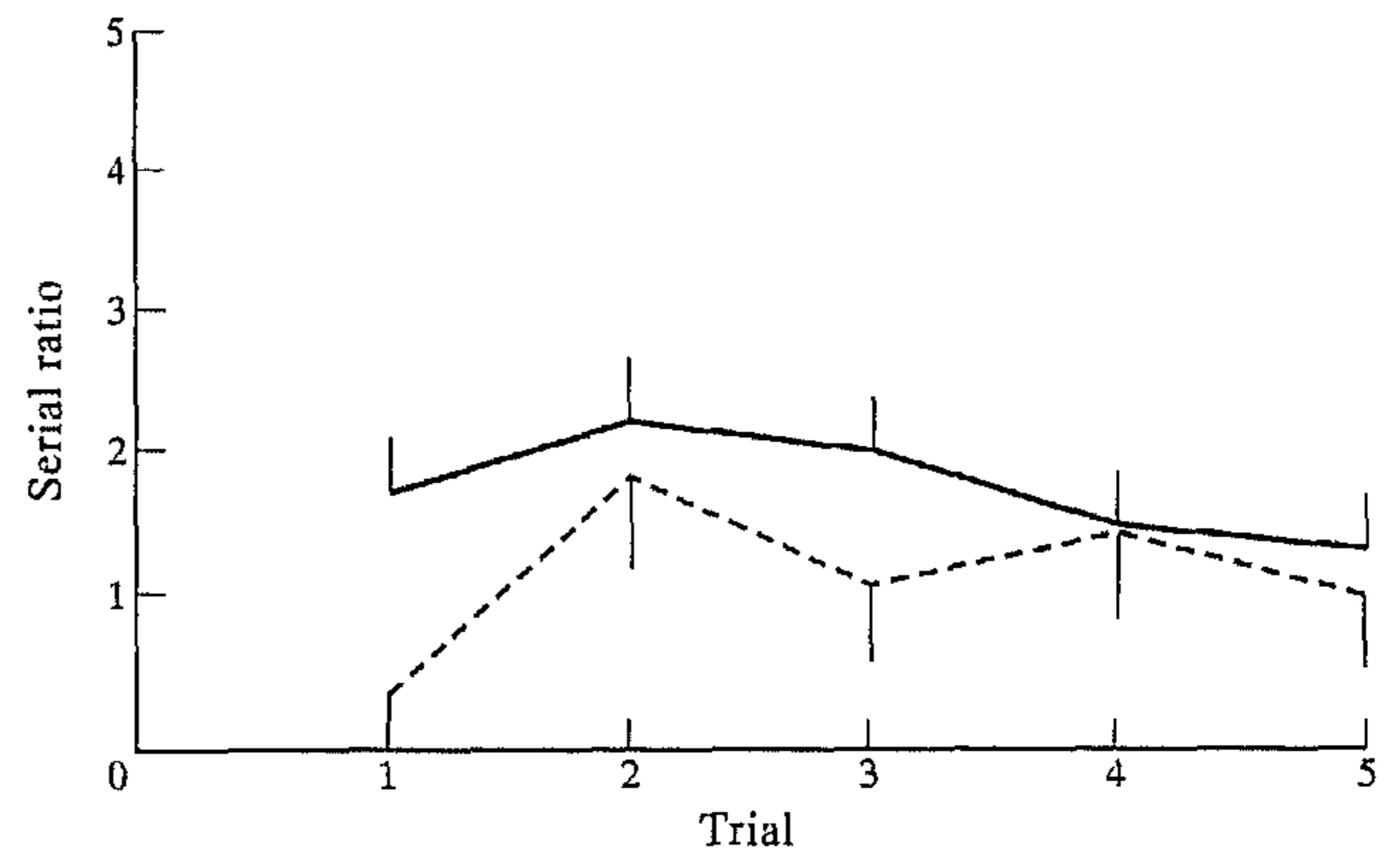


Fig. 6. Serial ratios of CS. Mean serial ratios (\pm S.E.M.): mixed condition: continuous line; explicit condition: interrupted line with S.E.M. upward. The serial ratios are shown on the y-axis.

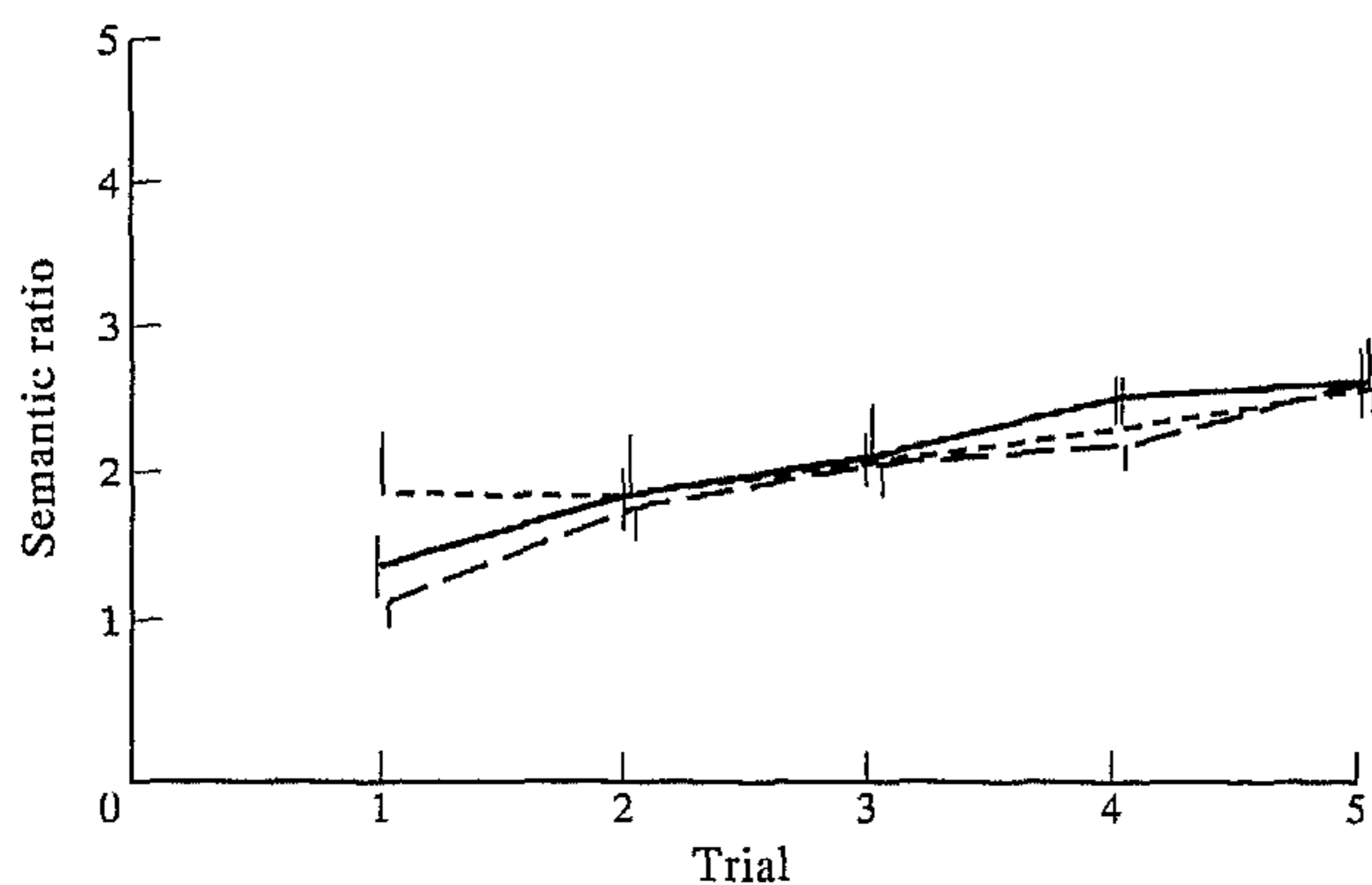


Fig. 4. Semantic ratios of CS. Mean semantic ratios (\pm S.E.M.): mixed condition: continuous line; explicit condition: interrupted line with S.E.M. upward; permuted condition: interrupted line with S.E.M. downward. The semantic ratios are shown on the y-axis.

Serial clustering ratio across trials 1-5

In the permuted condition, the sequence of items was changed in each trial of the permuted condition, and therefore the serial ratios in this condition do not make any sense: each of them refers to a new sequence, which makes any comparison within- or between groups meaningless. For this reason, we excluded them from the statistical analysis. There were no significant differences across trials between PD patients and CS in any condition. In PD patients vs CS in the mixed condition, $\beta = 0.21$ [n.s.: $P = 0.06$]; in the explicit condition, $\beta = 0.07$ (n.s.). Testing the homogeneity of the β s indicated that there was no significant interaction between group and cueing condition (Figs 5 and 6)

Discussion

The present study is a continuation of a previous study in memory performance, which showed that PD patients increasingly relied on explicit cues which prompt the external strategy of serial clustering, in comparison to CS, who profited increasingly from implicit cues which

prompt the internal and more effective strategy of semantic clustering. In this study, we investigated whether the recall of PD patients can be affected by adding or removing explicit cues. We changed the condition in which the words were presented in two ways: first, we added explicit cues by telling the subjects in which semantical clusters the words could be grouped (the explicit condition), and next, we removed explicit cues by presenting the words in a sequence, which was changed after each trial (the permuted condition). Both manipulations of the original test format deal with the encoding. Retrieval was not manipulated. We incorporated the data of the previous study in our present analysis.

After correction for IQ and sex, only the semantic ratios across the trials showed a significant interaction between group and cueing condition. The performance of PD patients was affected by the various cueing conditions in a significantly different way from that of CS. In the mixed condition, CS clustered the items increasingly more in a semantic way than PD patients, but that difference is no longer significant in the explicit or permuted condition. In contrast to CS, PD patients only profited increasingly from the presence of cues when the implicit cues were made explicit (explicit condition), or when the explicit cues were removed, and only implicit cues were left (permuted condition).

As far as the explicit condition is concerned, our results indicate that PD patients and CS responded in the same way to explicit cues, which prompted semantic clustering, which, in this condition was an external strategy. Semantic clustering in verbal memory tasks as such is no problem for PD patients as long as explicit cues to do so are present, a striking difference with memory performance of patients with Alzheimer's disease [4]. With respect to the permuted condition, the semantic ratios of PD patients and CS showed a similar pattern across the five trials. PD patients resorted to semantic clustering, when explicit cues indicating external strategies were absent, and only implicit cues were left. The impossibility to rely on serial clustering in the permuted condition did not affect the performance of PD patients in comparison with that of CS, which is not surprising in view of our previous study, in which it was shown that serial clustering is negatively correlated with the number of words recalled ($r = -0.59$). Since PD patients and CS did not differ significantly with respect to the mean performance of recall in the permuted condition, they showed an ability to generate spontaneously an effective strategy, i.e. semantic clustering. At first glance this finding is in contrast with those of the majority of studies on cognitive functioning in PD, in which it was shown that PD patients are impaired in self-generated problem-solving [22, 24]. As indicated elsewhere [6], heading for the only strategy, that is left—for example by obstruction of other strategies, such as serial clustering—can no longer be regarded as self-generated problem-solving: in the absence of concurrent explicit cues, the remaining implicit cues become virtually explicit ones, because the

subject has to resort to an internal strategy or no strategy at all.

Our manipulations of the test format involved only the presentation of the items to be recalled, not the retrieval. The differences in retrieval which we found were dependent on the way in which the items were presented. In fact, retrieval of items to be recalled was similar in PD patients and CS in the explicit and permuted conditions, which suggests that the memory impairments of our PD patients were confined to the encoding, and that retrieval, as such, was not at risk in our group of PD patients. This is an interesting finding in view of the 'frontal' hypothesis, which presumes that cognitive impairment in PD corresponds with that in frontal patients, because a decrease of dopaminergic activity of frontostriatal connections brings about frontal dysfunction [9, 16, 18, 21, 22], cf. [17, 25]. In a recent study, Gershberg and Shimamura [12] measured the use of organizational strategies in memory performance of frontal patients in a series of sophisticated experiments. Among others, they found that frontal patients profit from semantic cues either at study (i.e. encoding) or at test (i.e. retrieval). Only when semantic cues were provided at both study and test, did the semantic clustering reach normal levels. Gershberg and Shimamura suggest that both encoding and retrieval are impaired by frontal lobe damage. In the explicit condition of our experiment, however, the presentation of semantic cues at study brought the retrieval performance of PD patients to the level of that of CS, which might indicate a difference in memory impairments between PD patients and frontal patients. However, the present study does not provide conclusive evidence in this respect. Further research should focus on the effects of cueing of retrieval in a mixed condition memory task in order to establish whether memory impairments in PD are confined to encoding or whether they affect retrieval as well.

On the basis of animal experiments [1, 20], Kritikos *et al.* [14] recently suggested that explicit cues enhance the performance of PD patients by replacing defective, internally generated cues of the basal ganglia. Disregarding any differences in terminology, this suggestion is in line with the findings of our study. Since our PD patients started to cluster semantically in the mixed condition to the same extent as CS, it is clear that implicit cues can prompt PD patients to generate spontaneously an internal strategy. However, PD patients were not able to maintain the strategy adopted at the beginning in the simultaneous presence of explicit cues. In contrast, when the same strategy was prompted externally (explicit condition), or when concurrent explicit cues were removed (permuted condition), PD patients adhered to the strategy which they adopted at the beginning, but which they were not able to maintain in the mixed condition. Apparently, explicit cues, which prompt external strategies, overrule increasingly the internal processing of the implicit cues in PD patients, which indicates that this internal processing might be too weak or too defective to withstand the impact of explicit cues. Internal processing

of implicit information consequently prompts a self-generated problem-solving strategy. In many studies, it has been found that PD patients are impaired in the self-generation of problem-solving strategies. The findings of the present study are clearly in accordance with this concept. They suggest that memory impairments in PD originate—at least partly—in a diminished ability to generate internally problem-solving strategies.

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