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COGNITIVE FUNCTIONING IN POST-POLIO PATIENTS WITH AND WITHOUT GENERAL FATIGUE

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***Objective and design:* This study examined 2 main hypotheses. First, whether patients with post-polio suffering from general fatigue ($n = 10$) demonstrate cognitive deficits compared with patients with post-polio without general fatigue ($n = 10$). Secondly, by systematically varied test order administration we examined whether such differences varied as a function of increasing cognitive load during cognitive testing.**
***Subjects:* Twenty patients diagnosed with post-polio syndrome, 10 with general fatigue and 10 without fatigue.**
***Results:* Neither of the 2 hypotheses were confirmed. The group with general fatigue reported elevated levels of depression. However, no systematic association between level of depression and cognitive performance could be detected.**
***Conclusion:* The results of this study provide no evidence that general fatigue or cognitive load affects cognitive functioning in post-polio.**

Key words: post-polio, fatigue, cognition.

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INTRODUCTION

Many people who survive polio suffer, after a relatively stable period of 20–40 years, symptoms such as increased muscle weakness and physical fatigue. Other symptoms, such as muscle pain, joint pain, feelings of cold, cold intolerance, insomnia or respiratory problems, are also common (1, 2). In Sweden the prevalence of post-polio syndrome (PPS) has been estimated to be 189 per 100,000 of the general population (3).

General fatigue in PPS is commonly described in terms of central fatigue evolving from the central nervous system and a peripheral fatigue evolving from the peripheral nervous system (4). The majority of patients with PPS complain of increased fatigue (5–9), either specifically related to muscles or in a generalized form. A study comparing patients with PPS, multiple sclerosis (MS) and chronic fatigue syndrome (CFS) with healthy controls, showed that 78–89% of the patients with PPS and MS and all of the patients with CFS experience fatigue. All groups experienced significantly more fatigue than the control group (10). Importantly, in studies by Bruno et al., a phenomenon called brain fatigue, with symptoms such as deficient attention, concentration, information processing, lexical search or non-verbal retrieval, has been documented in patients with PPS (11, 12).

The increasing cognitive effort required during the time period in which cognitive tests are administered is well documented, an effect usually controlled for by counterbalancing procedures (13). Thus, the extent to which the concept of brain fatigue is valid may depend on the amount of cognitive effort demanded during cognitive assessment, where increasing cognitive load will cause increasing brain fatigue which in turn causes deficient cognitive performance. To the best of our knowledge this has not been studied previously, nor has the extent to which such effects vary due to the presence of general fatigue as a permanent symptom.

An important potential confounder in this context is the presence or absence of depression. First, patients with PPS are more likely to suffer from depression compared with physically healthy controls (14, 15). Secondly, depression is well known to exert an impact on cognitive performance (16, 17). Thirdly, in the study by Berlly et al. (5) it was found that, among depressed patients with PPS, 100% reported lack of energy (non-depressed 85%), 70% had heavy sensations of muscles (non-depressed 52%), and 65% reported inability to concentrate (non-depressed 29%). Importantly, the studies mentioned above indicate that presence of depression in PPS is indicative both of pronounced fatigue symtomatology and cognitive problems. Pain is another factor that it is important to consider. First, pain is a common symptom in PPS (1, 2) and, secondly, pain may affect cognitive abilities such as attention and memory (18, 19).

The main aims of the present study were, first, to examine the extent to which general fatigue is associated with cognitive deficits among post-polio patients, and whether the deficits are general or selective. Secondly, we sought to determine whether cognitive performance among persons suffering from PPS varies also as a function of increasing load, and, if so, whether such effects are pronounced among patients with PPS and general fatigue.

METHODS

Subjects

Twenty persons participated in the study. They were selected among the available patients diagnosed with PPS at the post-polio outpatient clinic,

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Huddinge University Hospital according to the diagnostic criteria given by Halstead et al. (20) and Halstead and Rossi (21). All patients had completed a questionnaire including questions on fatigue before the first appointment in the outpatient clinic. The questionnaire has been developed and used in studies from the Sahlgrenska University Hospital in Gothenburg (22). Responses were classified as either presence or absence of general fatigue and, for each participant in the present study, verified by inspection of their clinical history. Inclusion criteria were presence of PPS and either presence or absence of general fatigue. Persons diagnosed with a degenerative brain disease were excluded. All available patients without general fatigue were selected ($n = 10$). We performed random sampling within the group of patients with general fatigue ($n = 10$). Within each selected group there were 5 women and 5 men. Of the patients with general fatigue, 3 refused to participate and were replaced with other randomly selected patients identified by the same inclusion and exclusion criteria. All procedures were approved by the ethics committee at Karolinska Institutet, and in accordance with the Helsinki Declaration of 1975.

Self-reports

During assessment participants were first asked to complete a background inventory involving demographic and polio-related questions. A visual analogue scale (VAS) measuring present subjective experience of pain was also included in the inventory. Participants were then asked to complete the Beck's Depression Inventory scale (BDI) (23). Finally, the participants were asked to indicate their subjective experience of fatigue on a VAS scale. Then cognitive testing was started. In the middle of the testing, i.e. after 5 tests, the participants were again asked to indicate their subjective experience of fatigue. This procedure was repeated immediately after completion of the cognitive testing.

Cognitive testing

Design and procedure. The cognitive battery comprised 10 tasks, where we sampled 2 tasks from each of the domains of verbal fluency, mental speed, episodic memory, visuospatial ability and semantic memory. By using 2 tasks from each domain, we sought to increase reliability in order to compensate the relatively small group sizes. The 5 domains represent basic cognitive resources where the first 4 domains are known to be sensitive to health problems, whereas semantic memory is generally insensitive to the same influences (24). Although the concept of brain fatigue is not yet well examined in terms of effects on cognitive abilities (11, 12), the abilities reported to be sensitive to brain fatigue are covered in the present battery. Load was operationalized as test order making the assumption that the later during the assessment a task was administered, the higher the load. Hence, each task was randomly allotted a unique number between 1 and 10. The first test order was 1 2 3 4 5 6 7 8 9 10, the second administration order was 2 3 4 5 6 7 8 9 10 1 and so on. The 10 test orders were randomly distributed within each fatigue by sex group. All participants were individually tested by the same psychologist and the duration of the testing was 2 hours on average.

Verbal fluency. Verbal fluency was assessed by means of letter fluency (FAS) and category fluency tests. In FAS, subjects were asked to generate as many words as possible beginning with the letters F, A and S, respectively. Time limit was 60 seconds for each letter (20). In category fluency (animals/professions/grocery store) subjects were asked to list as many animals, professions and grocery store items, respectively, as possible. The time limit was 60 seconds for each category (26). Possible scores were, for both types of fluency tests, 0–.

Mental speed. Mental speed was assessed by means of trail making Test and Digit Cancellation. A shortened version of the Trail Making Test (TMT) A & B (27) was used. In part A, the circles were numbered 1–13. In part B, the circles were numbered 1–6 and letters A–F. The TMT was administered according to standard procedures. Accuracy and the number of seconds needed to finish each part were registered. Performance time was unlimited. In the analyses, time scores were used where a high score indicated poor performance and a low score better performance. Possible ranges were 0–.

In the Digit Cancellation task, a sheet of randomized numbers from 1 to 9 was presented. The participant had to cross with a pen as many as possible of the digit 4 in a period of 60 seconds. Numbers of correctly marked 4s were scored (28). The possible range was 0–42.

Episodic memory. In the first test of episodic memory 12 randomly chosen words were presented, each shown to the participant on a printed card and read out loud by the test leader. Directly after the presentation, participants were asked to recall as many of the 12 words as possible. After recall, the 12 words were presented again, but this time intermixed with 12 distracter words. Here the participants were supposed to recognize the 12 target words among the distracters (29). Possible range in the recall condition was 0–12. In the recognition condition, performance was computed by means of subtracting incorrect from correct yes-responses. Hence, the possible range was -12–$+12$.The second test of episodic memory comprised 12 words belonging to 4 semantic categories (professions, furniture, instruments and clothes) in random order which where shown to the participant on a printed card and read out loud by the test leader. Directly after the presentation, participants were asked to recall as many words as possible. After the free recall, participants were presented with the 4 categories and asked to recall again as many words as possible in each category (30). The possible range for both free and cued recall was 0–12.

Visuospatial ability. The Block Design test from the WAIS-R was administered using standard procedures (31). Performance was scored according to WAIS-R criteria, and the possible performance range was 0–51. The Mental Rotation test comprised 20 items, each consisting of 1 criterion figure, 2 correct alternatives and 2 distracters. The correct answer was always identical to the criterion figure, but dimensionally rotated in space. Two marks were given if both answers were correct, 1 mark for 1 correct answer and 0 for 1 correct and 1 faulty answer as well as for 2 wrong answers. The time limit was 10 minutes and the subjects were informed after 5 minutes that half of the time remained (32). The possible performance range was 0–40.

Semantic memory. A modernized version of SRB:1 was administered using standard procedures (33). SRB:1 is a Swedish word synonym test, the administration time is 7 minutes, and the possible range of scores is 0–30. The test was scored according to SRB:1 criteria. The Information test from the WAIS-R, finally, was administered using standard procedures and scoring (31), where the possible range is 0–29.

Statistical methods

Analysis of variance (ANOVA) was used for analyses of the background data. For the main analyses analysis of covariance (ANCOVA) was applied, examining the effects of group and test order after statistical control for BDI scores. In each of the analyses, BDI scores were entered first, followed by the respective Test Order variable, indicating for each task the relative position during assessment, the Group variable (fatigue, non-fatigue) and the Test Order by Group interaction term. Additional analyses were done by means of two-tailed Pearson correlations.

RESULTS

Initial ANOVAs revealed that, except for BDI ($F = 5.80$, $p < 0.05$), there where no significant differences between the fatigued and not fatigued groups with respect to the descriptive data displayed in Table I. The subjective fatigue data were analysed by means of a 2 (Group) by 3 (Time) repeated measurement ANOVA. The results revealed significant main effects of Group, $F(1, 18) = 7.79$, $p < 0.05$, and Time, $F(2, 36) = 9.39$, $p < 0.01$. The Group by Time interaction was not significant ($p > 0.20$). The main effect of Group was due to that the fatigue group reported higher levels of subjective fatigue (mean = 52.9) than the non-fatigue group (mean = 27.7). The main effect of Time was due to that both groups reported increasing levels of subjective fatigue during the cognitive assessments (see Table I).

Regarding the cognitive performance measures, there were no significant effects of BDI, Test Order, Group, or Test order by Group interaction in any analyses (all $p > 0.05$). The βs for the

Table I. *Demographic, polio, pain, depression and subjective fatigue across groups. Figures are means with SD in parenthesis unless otherwise stated*

	Fatigue $n = 10$	Not fatigue $n = 10$
Age (years)	60.6 (9.7)	59.4 (8.9)
Females (%)	50	50
Education (years)	11.3 (2.1)	11.4 (3.7)
Other diagnoses (not acute) (*n*)	0.7 (0.8)	0.7 (0.8)
Polio duration (years)	55.9 (8.3)	52.1 (3.7)
Age at incidence of polio (years)	4.6 (2.9)	7.3 (9.3)
Subjective pain at testing (VAS)	16.0 (21.5)	29.1 (25.2)
BDI total	10.5 (5.5)*	4.8 (5.0)
Subjective fatigue before testing	48.2 (22.6)	14.8 (11.8)
Subjective fatigue in the middle of testing	50.6 (26.8)	25.5 (16.4)
Subjective fatigue after the testing	59.9 (29.5)	42.8 (28.4)

*Significant group difference. $p < 0.05$. BDI = Beck's Depression Inventory scale.

effects of test order were generally indicating that administration of a task late during the test session resulted in slightly poorer performance. Table II displays summary statistics for all cognitive variables across groups. Note that although the battery comprised 10 tests, 13 outcomes are shown. This is because TMT A and B were analysed separately, and the 2 tests of episodic memory comprised a recognition (random words) and a cued recall (organizable words) test in addition to the free recall conditions.

In a series of additional correlation analyses, we examined further that the 2 groups differed significantly with respect to levels of subjective fatigue at the time of cognitive testing. The purpose of the analyses was to examine further the impact of present fatigue on cognitive performance. In order to minimize the risk of chance correlations we began by reducing the number of variables. Hence, we created a subjective fatigue composite score by summing the 3 indicators of subjective fatigue. Next, we z-transformed all cognitive performance scores and created 5 domain specific composite scores (i.e. verbal fluency, mental speed, episodic memory, visuospatial ability and semantic memory) by summing the obtained z-scores within each domain. Next, we correlated within each group subjective fatigue with each of the cognitive composite scores. Results revealed that subjective fatigue was not associated with any of the performance measures within the fatigue group (all $p > 0.15$). In the non-fatigue group however, subjective fatigue correlated significantly and negatively with visuospatial ability ($r = -0.73$, $p = 0.01$), indicating that the higher the level of subjective fatigue, the lower performance on the visuospatial tasks.

Table II. *Summary of cognitive performance statistics across groups. Figures are means with SD in parenthesis*

Cognitive variables	Fatigue ($n = 10$)	Not fatigue ($n = 10$)
Letter fluency; FAS	42.4 (12.6)	40.7 (7.6)
Category fluency; D/Y/M	61.8 (22.1)	59.9 (17.8)
TMT A	14.9 (5.2)	12.2 (2.9)
TMT B	29.9 (24.8)	28.6 (10.2)
Digit cancellation, correct answers	18.8 (4.3)	17.8 (4.5)
Free recall random words	7.3 (1.2)	7.7 (1.6)
Recognition random words; hits−false alarms	8.5 (2.4)	9.7 (1.4)
Free recall organizable words	7.8 (1.9)	7.9 (2.4)
Cued recall organizable words	8.5 (1.7)	8.6 (2.2)
Block design	28.0 (9.5)	30.7 (8.4)
Mental rotations	12.1 (8.0)	15.5 (9.2)
SRB 1	24.2 (3.2)	25.6 (1.9)
Information	20.6 (3.2)	21.9 (2.5)

TMT = Trail Making Test; SRB 1 = Word synonym test. A lower score in TMT A and B is better. In all other tests a high score indicates better performance. FAS: please see explanation in M&M.

DISCUSSION

The main results of this study revealed that no statistically significant effects of group (fatigue, non-fatigue), ordering of tests (load), or group by ordering interactions could be detected. Additional correlation analyses revealed, however, that subjective fatigue at the time of testing was related to visuospatial ability, but only among the group clinically diagnosed as post-polio without general fatigue.

The existence of brain fatigue in patients with PPS is controversial and few studies have examined this in a systematic fashion. Previous studies using the term brain fatigue in a post-polio context (6, 11, 34) define brain fatigue as problems with attention and cognition, but the results are somewhat inconsistent. In the study by Bruno et al. (11) a severe fatigue post-polio group performed at a lower level in visuospatial tests than did a non- and a mild fatigue post-polio group. By contrast, the study by Bruno and Zimmerman (34) reported no differences in neuropsychological test performance between fatigue and non-fatigue groups of post-polio patients. The cognitive domain, if any, discriminating between groups in the studies mentioned above is mental speed, but not in a consistent manner. The present study suggest that there are no differences in cognitive abilities as a function of general fatigue among patients with PPS, not even when the intention is to trigger brain fatigue.

Turning to subjective fatigue, the general fatigue and the non-fatigue groups in our study reported different levels of subjective fatigue during the time of cognitive testing such that the group with general fatigue reported significantly higher levels. Although this result may confirm their diagnosis of general fatigue, it is notable that a significant increase in fatigue was found in both groups during the time of cognitive testing. In the additional correlation analyses on the association between subjective estimation of fatigue and cognitive performance, we found a selective association between subjective fatigue and performance on the visuospatial tasks in the group without a clinical diagnosis of general fatigue. Although we reduced the number of variables by creating composite scores, this finding may still be due to multiple testing. The result calls for replication before any definite conclusions may be drawn. One may, however, hypothesize that the outcome reflects an unknown relative distribution of peripheral and central fatigue in the 2 groups not covered by the present data (4), causing more pronounced effects among the group without general fatigue on the 2 perhaps most difficult tests of the battery. The inclusion of a healthy control group would perhaps have clarified this matter.

The second single significant group difference was detected in the BDI scores. Similarly, Schanke et al. (15) found a severe fatigue group to score higher on depression compared with a mild fatigue group. However, the impact of BDI scores on cognitive performance was minimal in this study, and could therefore not account for the absence of significant effects of group or load.

Because of the limited number of patients with PPS but not general fatigue available for study, the samples were rather small. Thus, the statistical power of the study is low due to the small number of subjects studied. Therefore, mean differences between groups have to be rather large to be statistically significant. However, the lack of significant effects may not be due only to small groups and resulting lack of power. The fact that the small group effects were in opposite directions, where the fatigue group outperformed the non-fatigue group in some of the tasks and the reverse pattern was the case for other tasks (see Table II), complicates the picture and suggest instead that no clear difference as a function of general fatigue is to be expected even with an increased sample size. The premier contribution of this study was to suggest an experimental design for systematic examination of brain fatigue. However, the main findings of the study clearly indicated that no cognitive performance differences could be detected and that systematic varying of test order did not significantly trigger brain fatigue. Thus, the proposed battery lacks clinical relevance in this context, or rather that brain fatigue as expressed in cognitive test performance is an invalid concept.

Finally, by using easy administration with a VAS scale we sought to avoid that assessment of subjective fatigue in the test situation would interfere with the experimental manipulation of cognitive load. For future studies it might prove valuable to use more sophisticated subjective fatigue instruments that differentiate between, for instance, peripheral and central fatigue, and also to take into account that these types of instruments may vary considerably, for example in terms of sensitivity to severity or change (35).

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