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# Fatigue in multiple sclerosis
# Reciprocal relationships with physical disabilities and depression

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**Abstract**

**Objective:** To explore relations of fatigue, physical disabilities, and depression in patients with multiple sclerosis (MS) cross-sectionally and over time. **Methods:** Ninety-eight MS patients were interviewed twice at an interval of a year. Relationships of physical and mental fatigue, and reduced activity and motivation with depression and physical disabilities were established cross-sectionally by regression analyses and longitudinally by structural equation modelling. **Results:** Cross-sectionally, physical fatigue was related with physical disabilities, and mental fatigue was associated with depression. Prospectively, physical fatigue was a predictor of the physical disabilities of a year later. The reverse relationship of physical disabilities predicting the physical fatigue of one year later was, however, not significant, while depression predicted this physical fatigue and reduced activity of a year later. Depression did not predict the later mental fatigue nor was depression predicted by preceding fatigue experiences. **Conclusions:** Fatigue in MS should be studied over time as relationships of fatigue with physical and mental health change during the course of a year. Moreover, differentiating in fatigue experiences sheds light on the relationship of fatigue with physical and mental health. 

*Keywords:* Depression; Fatigue; Multiple sclerosis; Physical disabilities

## Introduction

Fatigue is the most common problem in multiple sclerosis (MS). Up to 80% of patients with MS complain of fatigue and fatigue is reported to be the first and most troubling symptom in one third to half of the patients [1–3]. The impact of fatigue on daily life is considerable as it prevents sustained physical exertion, interferes with responsibilities, limits work and social role performance, and is related to less satisfaction with quality of life [2–6]. Fatigue in MS appears to be unrelated to clinical measures of neurological impairment [2,3,7], neuropsychological performance [4], or disease duration [5]. Disease course has not been found to be related to fatigue in MS [5], with the exception of patients with chronic progressive MS who are more at risk of being fatigued [8]. The relationship of fatigue with depression is unclear in MS patients [2,4,5,7]. No association with depression has been found when fatigue is conceptualised as a unidimensional construct [2,7]. However, when multiple fatigue characteristics are distinguished, mental fatigue, but not physical fatigue, has been shown to be related to anxiety and depression [5].

Clinical reviews point to different aspects of fatigue in MS, including physical exertion preceding normal fatigue, fatigue as a symptom of depression, and overuse of muscles supplied by demyelinated nerves which is associated with fatigue in specific areas of the body [9]. Moreover, many MS patients complain of lassitude, which is a form of fatigue that presents as overwhelming sleepiness [9,10].

To the best of our knowledge, this clinical suggestion of different kinds of fatigue in MS patients has only been studied in the research of Ford et al. [5], who were able to distinguish mental from physical fatigue. In the present study, an attempt was made to study different kinds of fatigue in MS patients, and to clarify relationships of physical and mental health with different aspects of fatigue in MS. It was hypothesised that MS patients experience different kinds of fatigue and that physical fatigue would be related primarily to physical health and mental fatigue to

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mental health. We also aimed at exploring the time frame of possibly prospective relationships of physical and mental health with fatigue. At present, the literature is not conclusive whether fatigue precedes physical or mental deterioration or whether physical and mental health are rather to be considered as precursors of fatigue. Different temporal relationships may point to different interventions strategies in trying to relieve the burden of fatigue in MS patients. Theoretically, fatigue can precede poor physical health or it can be a consequence of it.

Fatigue associated with the greater energy needed to conduct signals in nerves with damaged myelin sheaths can be viewed as a consequence of having MS [10]. When fatigued patients are less inclined to exercise and perform physical activities, their physical condition and stamina deteriorate as skeletal muscles lose their oxidative capacity and more oxygen is required for the performance of comparable activities than is needed by muscles in good condition [11]. Finally, fatigue may just be a concomitant factor of ill health instead of a precursor or consequence of it.

In the present study, depression is considered as a proxy of mental health as most empirical research on fatigue in the context of mental health is restricted to depression, and depression has also been extensively studied in MS patients. Fatigue or lack of energy is considered to be a symptom of depression [12], however, fatigue is neither sensitive nor specific for the diagnosis of depression [13,14]. In the general population, depressive mood was established in 50% of the long-term fatigued but it was not clear whether depressive feelings preceded fatigue or whether they were a consequence of it [15]. The relationships of depression and fatigue may be reciprocal. Depression may precede fatigue when social withdrawal, which often accompanies depression, leads to a shift in attention from external cues towards internal cues and physical symptoms such as fatigue [16]. People with a depressive mood do, indeed, report more symptoms half a year later and they are more pessimistic that any actions they take would relieve their symptoms [17,18]. On the other hand, losses such as restrictions in work, leisure activities, or social interactions because of enduring fatigue may increase depressive feelings.

## Method

Patients were invited to participate in the study via the newsletter of the MS patients organisation in the context of a larger study on MS [19,20]. A total of 130 respondents who finished the first questionnaire were invited to answer the questionnaire again, after a year. Ninety-eight usable questionnaires were returned (75%). Nonresponse was not selective for demographic characteristics or disease duration. The sample thus consisted of 98 patients, 65% were female. Mean age was 48 years (S.D. = 10.2). Seventy-nine percent of the male patients and 68% of the female patients were married or living with a partner. The educational level was below high school level for 11%, 48% had completed high school, and 25% had completed college; education level was unknown in 11%. Average time since first complaints was 14 years (S.D. = 9.3) and time since diagnosis was 9.5 years (S.D. = 6.7) at the time of first measurement. Of a list of 20 MS-related complaints other than fatigue, patients suffered from a mean of six complaints at both times of measurement (S.D. = 3.3 and 3.4 at Time 1 and Time 2, respectively). Moreover, 86% at Time 1 and 85% at Time 2 indicated that fatigue was one of their symptoms. Complaints remained unchanged during the last month in 58% of the respondents at Time 1 and in 55% at Time 2, worsened for 14% and 17% at Times 1 and 2, respectively, improved in 9% and 7%, respectively, and varied in 18% and 21%, respectively. Combining these data indicates that the majority suffered from the relapsing–remitting form of MS. In 38% of the sample, complaints remained unchanged at the month before Time 1 measurement as well as the month before Time 2 measurement. Complaints had become worse at both measurement times in 5%, had improved at both measurements in 2%, and were variable in the remaining 55%.

### Measures

Dimensions of *fatigue* were assessed by the Multidimensional Fatigue Inventory (MFI) [21], which consists of five subscales measuring general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. Each scale consists of four items with a five-point response format (range 4–20). Physical fatigue refers to physical sensations and mental fatigue to cognitive symptoms of fatigue; sample items are respectively: 'Physically I feel able to do only a little' and 'Thinking requires effort.' Reduced activities measure the perceptions of reduction in activities as a result of fatigue with items as 'I feel very active,' indicating a low reduction in activity. Reduced motivation establishes the motivation to perform activities, a sample item is 'I am not up to much.' Cronbach's alphas at Time 1 and Time 2 were .73 and .79 (physical fatigue), .83 and .81 (mental fatigue), .69 and .56 (reduced activity), and .63 and .69 (reduced motivation). General fatigue was not used as this scale is a summary of all fatigue experiences and should be not used together with the four fatigue dimensions in the same analysis [Smets, personal communication].

*Depression* was used as a proxy for mental health in the current study. It was established by the Beck Depression Inventory (BDI), which can range from 0 to 64 [22]. Cronbach's alphas were .96 and .85 at Time 1 and Time 2, respectively. The omission of items on work ability (item 15), fatigue (item 17), and health concerns (item 20), when using the BDI in MS patients, has been disputed [23,24]. We

decided to use the full BDI as all analyses with the corrected BDI showed the same results as with the full BDI.

*Physical disabilities* were viewed as a proxy for physical health. Physical disabilities were assessed by the physical subscales of the 68-item version of the Sickness Impact Profile (SIP-68) [25]. The scores on somatic autonomy, mobility control, and mobility range were summed to measure physical disabilities. The scale ranges from 0 to 39 with higher scores indicating more disabilities. Alphas of this sample were .81 and .65 at Time 1 and Time 2, respectively.

Table 1
Mean scores on depression, physical disabilities, and fatigue at Time 1 and Time 2 ($N = 98$)

| | Time 1 | Time 2 |
|---|---|---|
| | *M* (S.D.) | *M* (S.D.) |
| Depression | 8.84 (5.7) | 9.55 (6.3) |
| Physical disabilities | 11.20 (6.6) | 11.92 (6.5) |
| Physical fatigue | $14.43_a$ (3.9) | $15.38_b$ (3.9) |
| Mental fatigue | $9.30_a$ (4.4) | $9.85_b$ (4.3) |
| Reduced activity | $12.30_a$ (4.1) | $13.08_b$ (3.7) |
| Reduced motivation | 11.50 (3.1) | 11.98 (2.9) |

Subscripts a and b = significant change from Time 1 to Time 2, $p < .05$; all means of fatigue subscales within a column differ significantly at $p < .05$.

## Analyses

Cross-sectional relations of fatigue dimensions with depression and physical disabilities were first studied by regression analyses. Physical disabilities and depression were regressed on each of the fatigue dimensions. Demographic characteristics, which correlated with fatigue, were controlled for in the first step. In the second step, the four fatigue subscales were entered. Next, the fatigue subscales were regressed on physical disabilities and depression, respectively. Demographic characteristics were controlled for in the first step, and physical disabilities and depression were entered in the second step. If the regression coefficient from variable *a* to variable *b* is positive, and the regression coefficient from *b* to *a* is (almost) zero, then it is more plausible that *a* precedes *b* instead of *b* preceding *a* [26].

A longitudinal path model was analysed in order to establish the relationships over a year while taking the cross-sectional relationships into account. The analysis was done by structural equation modelling with Maximum Likelihood method (LISREL 8.12) [27]. Because of the small sample size, we used only the observed variables instead of an analysis with latent variables. The first model was restricted to the covariances of the corresponding variables at the two times of measurement. Next, we analysed models in which cross-lagged paths from depression and physical disabilities to the fatigue scales were allowed. Thereafter, the cross-lagged paths from fatigue scales to depression and physical disabilities were allowed. Parameter estimates with a nonsignificant *t* value ($t < 2$) were omitted. Residual correlations between variables at similar positions in the model, that is, between the four fatigue scales and between depression and physical disabilities, were allowed when standardised residuals suggested this correlation to exist. The fit of the final model was evaluated by means of parameter estimates (all significant), standardised residuals (absolute value $< 2.58$), and a number of overall fit measures provided by the LISREL program. The Comparative Fit Index (CFI) and the standardized root mean square residual (SRMR) were used in addition to the chi-square test. These fit indices are sensitive to misspecification of the model, and are recommended for small sample sizes [28]. Chi-square/degrees of freedom should not be larger than 2. An adequate fit of the model is indicated by a CFI equal or above .95, and an SRMR below .08 [28].

## Results

### *Dimensions of fatigue, fatigue severity, and its stability over one year*

First, fatigue in MS seemed to consist of different aspects as the correlation of mental fatigue with physical fatigue was low. Moreover, reduced activity and reduced

Table 2
Hierarchical regression of depression and physical disabilities on fatigue dimensions at Time 1 ($N = 98$)

| | Physical fatigue (Time 1) | | Mental fatigue (Time 1) | | Reduced activity (Time 1) | | Reduced motivation (Time 1) | |
|---|---|---|---|---|---|---|---|---|
| | β | $R^2$ ch | β | $R^2$ ch | β | $R^2$ ch | β | $R^2$ ch |
| Step 1 | | .06* | | .01 | | .01 | | .02 |
| Age | .15 | | −.16 | | .09 | | .18 | |
| Step 2 | | .24** | | .19** | | .13** | | .12** |
| Physical disabilities (Time 1) | .40** | | .08 | | .12 | | −.07 | |
| Depression (Time 1) | .18 | | .39** | | .29** | | .36** | |
| Adjusted $R^2$ | | .30** | | .18** | | .11** | | .11** |

$R^2$ ch = $R^2$ change.
* $p < .05$.
** $p < .01$.

Table 3
Hierarchical regression of fatigue dimensions on depression and physical disabilities at Time 1 ($N = 98$)

| | Depression (Time 1) | | Physical disabilities (Time 1) | |
|---|---|---|---|---|
| | β | $R^2$ ch | β | $R^2$ ch |
| Step 1 | | .00 | | .07* |
| Age | − .07 | | .19* | |
| Step 2 | | .30** | | .24* |
| Physical fatigue (Time 1) | .18 | | .45** | |
| Mental fatigue (Time 1) | .35** | | .15 | |
| Reduced activity (Time 1) | .08 | | .03 | |
| Reduced motivation (Time 1) | .18 | | − .09 | |
| Adjusted $R^2$ | | .24** | | .27* |

$R^2$ ch = $R^2$ change.
* $p < .05$.
** $p < .01$.

motivation were closely related to each other, and reduced activity was also strongly associated with physical fatigue (Appendix).

Table 1 shows that MS patients suffered most from physical fatigue (e.g., physical fatigue with reduced activity: Time 1 $t(97) = -5.4$, $p < .00$), while mental fatigue bothered them less than other fatigue experiences (e.g., mental fatigue with reduced motivation: Time 1 $t(97) = -4.3$, $p < .01$). Physical fatigue and mental fatigue became significantly worse during the course of one year and patients showed less activities one year later [respective $t$ values: $t(98) = 3.0$, $p < .00$; $t(97) = -2.0$, $p < .05$; $t(97) = -2.2$, $p < .05$].

*Cross-sectional relations between fatigue, depression, and physical disabilities*

By hierarchical regression analyses, the relative contributions of physical disabilities and depression on fatigue dimension were assessed after controlling for age. Regression analyses were also used to predict depression and physical disabilities from fatigue dimensions. Results are shown in Tables 2 and 3, respectively. Physical fatigue was significantly predicted by physical disabilities, while depression was a significant predictor of all other fatigue dimensions. On the other hand, physical disabilities were predicted by physical fatigue, and depression was predicted by mental fatigue. Inspection of the regression coefficients of Tables 2 and 3 indicated that the strength of relationships was reciprocal, i.e., when measured at the same time physical disabilities enhanced physical fatigue and vice versa. The same holds for depression and mental fatigue.

*Longitudinal path model of fatigue dimensions, depression, and physical disabilities*

Table 4 shows that a model without cross-lagged paths between fatigue measures on the one hand and depression or physical disabilities on the other hand (Model 1) did not fit the data. A model in which significant cross-lagged paths between fatigue measures on the one hand and depression or physical disabilities on the other hand were allowed also did not fit the data (Model 2 to Model 5). However, the fit clearly improved when measures of fatigue were allowed to correlate at Time 2 (Model 6). These three fatigue measures had the same place in the model and the standardised residuals suggested these correlations to be allowed. Finally, the fit of the model improved further by allowing cross-lagged paths from reduced activity and motivation to mental fatigue (Model 7). This post hoc modification was justified as relations among fatigue subscales are to be expected on theoretical grounds.

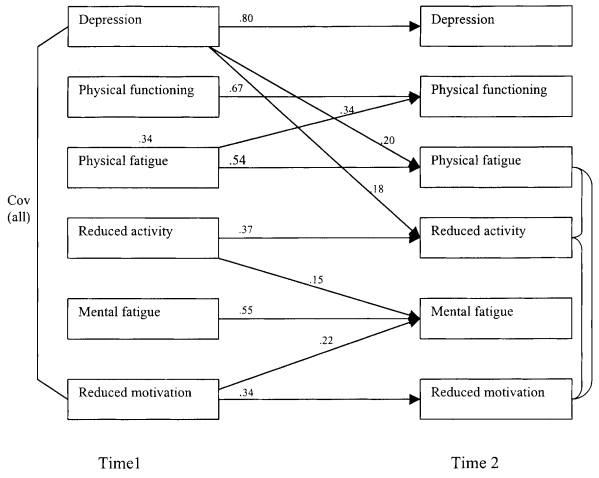
Fig. 1 depicts the final longitudinal path model. Physical fatigue significantly explained variance in physical disabilities of one year later, but there was no significant relationship between these variables the other way around. In contrast, depression was one of the predictors of physical fatigue and reduced activity one year later while it was not predicted by the fatigue of a year before. Moreover, mental fatigue after a year was not only predicted by the mental fatigue of the year before, but also by the reduced activity and motivation of the former period.

The curve at the left hand of the figure shows that most variables covariated at Time 1. The curves between physical fatigue, reduced activity, and reduced motivation at Time 2 indicate correlations between these variables (error covariance of physical fatigue with reduced activity = 4.03,

Table 4
Results of model search: goodness-of-fit tests

| Model descriptions | $\chi^2$ | *df* | *p* | SRMR | CFI |
|---|---|---|---|---|---|
| 1. Covariances of Time 1 and Time 2 variables | 146.33 | 45 | .00 | .13 | .82 |
| 2. 1+ cross-lagged paths from depression and physical disabilities to fatigue measures | 131.01 | 37 | .00 | .13 | .83 |
| 3. 2 without nonsignificant paths | 138.42 | 44 | .00 | .13 | .83 |
| 4. 3+ cross-lagged paths from fatigue measures to depression and physical disabilities | 105.64 | 36 | .00 | .086 | .88 |
| 5. 4 without nonsignificant paths | 111.37 | 42 | .00 | .10 | .88 |
| 6. 5+ error correlations between physical fatigue, reduced activity, and motivation Time 2 | 58.74 | 39 | .022 | .087 | .96 |
| 7. 6+ cross-lagged paths from reduction in activity and motivation to mental fatigue | 47.23 | 37 | .12 | .068 | .98 |

SRMR = standardised root mean square residual; CFI = Bentler's Comparative Fit Index.




Time 2: one year after time

Fig. 1. Final path model of fatigue, depression, and physical disabilities.

$t = 4.16$; error cov physical fatigue/reduced motivation = 2.28, $t = 2.76$; error cov reduced activity/reduced motivation = 4.19, $t = 4.28$).

## Discussion

MS patients in this study suffered from serious fatigue problems. Physical fatigue was more severe than mental fatigue. Compared with men and women in the general population [29], disease-free cancer patients [30], and even cancer patients who had recently undergone radiotherapy, a condition notorious for its fatiguing consequences [30], the MS patients involved in our study were more physically and mentally fatigued and showed more reduction in activities and motivation. Our results corroborate other studies on fatigue among MS patients [5,31].

The main aim of our study was to study different types of fatigue experiences of MS patients and the relations of these experiences with physical and mental health. We restricted our study to depression with respect to mental health and operationalised physical health in the number of physical disabilities. Physical fatigue was mainly related to physical disabilities, and mental fatigue was related to depression when measured at the same moment, which was in line with our hypotheses and the findings of other studies [4,5]. The picture becomes more differentiated in the long run. When studied over the course of one year, physical fatigue preceded the physical disabilities of a year later, but physical disabilities did not significantly precede fatigue. In addition, depression seemed to precede physical fatigue and reduced activities, but depression after a year was not longitudinally related to the fatigue of a year before.

Thus, in the physical domain, a poorer physical condition as a consequence of fatigue may have brought along more physical disabilities [11]. Moreover, depressed patients shift their attention towards internal cues and they hold pessimistic views concerning the effects of actions to relieve symptoms [16,18]. In our study, depressed patients may have paid more attention to fatigue symptoms with the consequence of experiencing more symptoms, and fatalistic views on coping effectiveness may have led to more inactivity. For the time being, these hypotheses remain speculative as physical condition, attention to internal versus external cues, and views of the effectiveness of efforts to reduce fatigue were not assessed in this study. Moreover, the finding that one variable precedes another variable in a longitudinal design does not automatically imply that the former variable causes the latter one. A third variable, for instance, disease activity, may causally explain the association.

Our results contradict studies which found depression and fatigue to be unrelated [2,7] and show that cross-sectional relations of physical and mental fatigue with depression change over time. Mental fatigue and reduced motivation were cross-sectionally related to depression but there was no relationship in the long run. A number of explanations may account for this result. Mental fatigue and reduced motivation may be more of a concomitant of depression than preceding or following it. Another plausible explanation is that the time frame of this study is too long, i.e., depression, mental fatigue, and reduced motivation may influence each other in shorter time lags.

Our study contains a number of weaknesses that may be informative for future research. First, the results should be replicated as it has been shown that models resulting from structural equation modelling are sometimes difficult to replicate. Second, the lag of one year was chosen rather arbitrarily in this study, as suggestions of appropriate time lags are not available. Possibly, the more stable relationships are captured with a lag of one year, while more dynamic fluctuations may take place in the shorter term. Studies with different time lags, including daily symptom diaries, and more than two measurement points, are needed to further probe the reciprocal relationships of fatigue with physical and mental health. Moreover, disease activity should be measured in future studies as MS can fluctuate considerably over time.

Despite these shortcomings, we believe that our study is important for further research on fatigue in MS patients. Conceptualising fatigue in MS as a multidimensional concept will help to better determine relationships with other variables. Fatigue among MS patients has been measured with self-report measures as the ‘Fatigue Severity Scale’ (FSS) [32], the ‘Checklist of Individual Strength’ (CIS) [7], ‘Fatigue Impact Scale’ [3], ‘Multidimensional Assessment of Fatigue’ (MAS) [33], ‘Fatigue Assessment Inventory’ (FAI) [30], and the ‘Fatigue Rating Scale’ (FRS) [34]. For the moment, a combination of fatigue measurements will be needed to chart all fatigue dimensions in MS.

Although the course of MS is unpredictable [35], the odds are that fatigue will increase over time and interventions will be needed. Up to now, interventions on fatigue in MS show

different success rates. An aerobic fitness program did not result in lower general fatigue as measured with the FSS, but the program reduced depression and enhanced the quality of life of the participants [36]. Treatment with the stimulant amantadine has been effective in the reduction of specific MS fatigue, i.e., the lassitude which presents as an overwhelming sleepiness [37–41]. However, amantadine had no effect on FSS-scores and on depression [41]. Given the use of global measurements of fatigue as a treatment outcome in these studies, more specific effects on fatigue dimensions may have remained unclear. Comparison studies on fatigue measurements in MS are needed in order to compare and establish the effectivity of interventions [42]. In addition, our results point to the importance of treating depression in MS patients. A recent meta-analysis showed that depression worsened when not treated and that antidepressant medication and psychotherapy aimed at the improvement of coping skills were effective in the reduction of depression [43].

To the best of our knowledge, this study is the first in which different fatigue dimensions in MS were measured prospectively. Despite the small sample size and weaknesses in the design, we feel that our results raise important questions concerning the complexity of fatigue experiences of MS patients and their relations with physical and mental health. Considering the detrimental impact of fatigue on the daily life of MS patients, enhanced research efforts are called for.

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## Appendix. Correlations at Time 1 and Time 2 ($N = 98$)

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Age | | | | | | | | | | | | | |
| 2. Time since diagnosis | **.46** | | | | | | | | | | | | |
| 3. Physical disabilities 1 | **.27** | **.20** | | | | | | | | | | | |
| 4. Depression (Time 1) | −.05 | −.03 | **.40** | | | | | | | | | | |
| 5. Physical fatigue (Time 1) | **.24** | .09 | **.51** | **.33** | | | | | | | | | |
| 6. Mental fatigue (Time 1) | −.16 | −.04 | .19 | **.45** | .19 | | | | | | | | |
| 7. Reduced activity (Time 1) | .12 | .07 | **.27** | **.34** | **.55** | .16 | | | | | | | |
| 8. Reduced motivation (Time 1) | .15 | −.00 | **.20** | **.33** | **.33** | .15 | **.60** | | | | | | |
| 9. Physical disabilities (Time 2) | **.25** | **.22** | **.78** | **.28** | **.54** | .13 | **.27** | .19 | | | | | |
| 10. Depression (Time 2) | −.07 | −.06 | **.28** | **.72** | **.32** | **.37** | **.23** | **.31** | .33 | | | | |
| 11. Physical fatigue (Time 2) | .08 | .06 | **.41** | **.50** | **.64** | **.22** | **.44** | **.34** | **.50** | **.47** | | | |
| 12. Mental fatigue (Time 2) | −.16 | .04 | **.21** | **.41** | .19 | **.62** | **.33** | **.33** | .11 | **.42** | **.26** | | |
| 13. Reduced activity (Time 2) | .04 | .08 | .18 | **.23** | **.30** | .15 | **.55** | **.47** | **.29** | **.45** | **.58** | **.29** | |
| 14. Reduced motivation (Time 2) | .13 | .17 | .13 | .18 | **.21** | −.01 | **.36** | **.43** | **.20** | **.32** | **.38** | **.25** | **.60** |

$r > .20$, $p < .05$; $r > .26$, $p < .01$; $r > .33$, $p < .001$.