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Accessibility
Symptom changes in multiple sclerosis following psychological interventions: a systematic review

Francesco Pagnini1,2,3*, Colin M Bosma3, Deborah Phillips3 and Ellen Langer3

Abstract
Background: Multiple Sclerosis is a disease of the central nervous system involving a variety of debilitating physical, sensory, cognitive and emotional symptoms. This literature review evaluated the impact of psychological interventions on the physiological symptoms associated with the illness.

Methods: A systematic literature search was conducted using Medline, PsycINFO, Scopus, and the Cochrane Library databases, as well as reference lists. Relevant studies were selected and assessed according to a preset protocol.

Results: The search produced 220 articles, with 22 meeting inclusion criteria for the review. A total of 5,705 subjects with Multiple Sclerosis were analyzed. Results from the included studies indicate a general improvement in both psychological and physiological outcomes following psychological treatment. The most highly influenced physical symptoms include fatigue, sleep disturbances, pain, and physical vitality.

Conclusions: Findings from the review suggest a positive relationship between psychological interventions and physiological Multiple Sclerosis symptoms. Implications for future research are discussed.

Keywords: Multiple sclerosis, Psychological interventions, Physical health outcomes, Mind/body connection

Background
This paper provides a brief literature review concerning the relationship between physiological difficulties associated with Multiple Sclerosis (MS) and psychological interventions intended to remediate or otherwise improve functionality and quality of life. Our specific focus is the unearthing of evidence that psychological or behavioral treatments have an impact on both the psychological well-being and the physiological consequences of the disease. We are also interested in exploring the relationship between MS symptoms and psychological issues within the broader framework of the mind-body connection. The paper summarizes the structure of this framework along with the trends in the literature; presents the etiology and primary physiological consequences of MS; a summary of its psychological consequences investigated thus far; and an application of the mind/body hypothesis in the MS field. We identify some key gaps in related research and propose potential areas for further work to address these gaps.

Consciousness and the brain: the mind-body connection
The classic mind-body problem searches for an understanding of the distinctions – or lack thereof – between physical and mental entities: Is the physical brain a distinct entity from its mental processes? How do we know, how is it defined, and what implications are there for how we understand and treat our health?

Conceptions of a dualistic framework follow the early work of Descartes who proposed that the mind is a non-physical substance distinct from the brain, that our mind (and all it encompasses) is different from our physical brain in its fundamental composition as matter. In contrast to that is the argument for materialism proposing that because the world consists only of matter, there is no true distinction between the mental and the physical, i.e., that all mental states, properties, and processes are connected and interact with physical states, properties, and processes. Much of Western culture continues to preserve a belief in the dichotomy between mind and body.

We see dualism in medical science, which maintains the notion that disorders stem from either the physical or the mental, treating the mind and the body separately [1]. Although there was an appeal that from the field of...
Physiology and key psychological consequences of multiple sclerosis

Multiple Sclerosis is a chronic degenerative disease of the central nervous system that involves functionality of the brain and spinal cord, with physical, sensory, cognitive and emotional responses ranging from mild to severe. The relatively high variability in symptomatology is determined primarily by the location of the lesions in the brain and spinal cord. Lesions in the frontal and parietal lobes result in cognitive and emotional problems; plaque in the cerebrum, brain stem and spinal cord result in functional limitations of extremities [12]. In this sense, MS is a highly individual disease, prompting interventions targeting broad categories of disease progression and psychosocial impacts. The National Multiple Sclerosis Society (NMSS) estimates prevalence of MS in the United States at 400,000, and global prevalence at over 2 million people [13].

A diagnosis of MS often has profound social and psychological consequences. Because MS usually strikes individuals in their most productive years, its impact can be overwhelming [14]. The unpredictable and variable nature of MS also makes it particularly difficult to accept. The newly diagnosed individual is faced first with the shock of a disease, which is chronic and unpredictable in its course, often with progressive impacts on critical spheres of functioning. The future undoubtedly promises reduced physical function and disability, along with disruptions in education, employment, sexual and family functioning, friendships and activities of daily living. The grim prognosis and the added unpredictability of day-to-day health in relapse-remitting MS and side effects of medication greatly impacts upon quality of life [15].

Multiple Sclerosis can also have a considerable influence on the individual’s sense of self [16,17]. Physical changes and functional limitations may lead to a sense of loss of identity or role strain especially when the individual can no longer perform previously valued activities [15]. It is frequently necessary to redefine one’s self-image in order to incorporate the limitations imposed by MS. Each time the individual experiences a new loss of function this sense of loss may be renewed. One of the major sources of psychological distress related to the physical impairments is sexual dysfunction. The most frequent complaints are erectile and ejaculatory dysfunctions in men, vaginal lubrication in women, and a loss of libido and difficulty in achieving orgasm in both genders [18]. This problem covers significant aspects of life and can arise at any time during the course of MS, with a prevalence that varies between 50% and 90% [19].

Depressive features are often reported by people who have MS. Lifetime prevalence of major depressive disorder (MDD) is approximately 50% [20]. This is three times the rate reported in the general population [21]; the high prevalence may have multiple etiologies, including psychosocial factors such as the difficulty to deal with one’s emotions, and lack of social support [22]. Depression is one of the main determinants of quality of life and may further compromise cognitive function, and may lead to suicidal intent. It often impairs relationships and reduces compliance with disease-modifying treatments [23]. In addition, people with MS and MDD have been found to suffer from high levels of anxiety [24].
The relationship between psychological issues and MS symptoms has been underestimated in the past, but there is growing evidence of increased interest within the scientific community. For example, a number of prospective studies suggest that psychological stress increases relapse risk in MS [27]. We believe that more focused investigations into the physiological outcomes of a psychological intervention may lead to a better understanding of therapeutic options for people with MS.

It is also possible that the relationship between the underlying biological mechanism of MS and depressive symptoms works in two directions. If that is the case, successful treatment of depression utilizing behavioral approaches could also affect the underlying MS physiology, encouraging consideration of psychological interventions that could reduce the symptomatology of the illness and moving from a palliative care framework for behavioral treatments to a potentially therapeutic one. There is little direct evidence for this hypothesis currently, primarily because behavioral interventions rarely include biological markers or even consider symptoms assessment among the outcomes. Thus far, psychological outcomes are most often the only ones expected and assessed at the end of a behavioral treatment [28], without considering the possibility that an intervention could impact physiological measures.

**Methods**

This review focuses on psychological interventions for the treatment of Multiple Sclerosis. A systematic search strategy was conducted with Medline, PsycINFO, Scopus and the Cochrane Library using the search terms “multiple sclerosis” in combination with “psychological intervention”, “psychological treatment”, “psychotherapy” or “psychological therapy”. Further articles were included from the reference lists of review articles. There were no time limitations for the bibliographic search, but emphasis was placed on recent publications, post 2004. The list of articles provided by database and article reference search were screened for articles that investigate the effects of psychological interventions on physical health and symptoms of people with MS. Two reviewers independently assessed articles. Susceptibility to bias was evaluated following the QUOROM Statements [29]. Only articles published in English from peer-reviewed journals were considered. Four criteria were used to select studies: 1) the study reported either primary or secondary outcomes on physical health, either self-reported or instrumentally assessed; 2) the study investigated the effects of a psychological intervention; 3) the outcomes resulted from a comparison between groups, with a randomized controlled trial; 4) study results referred to a minimum of 10 participants. Data from the included article were extracted and reported into an Excel spreadsheet. The review includes randomized clinical trials, that intrinsically present a risk of bias. It is therefore expected that results will provide a reliable recommendation (Evidence Level 1) [30].

**Results**

Database and article references search provided a list of 220 papers. Twenty-two articles met the criteria for the inclusion in the review. Included studies and their properties are reported in Table 1. Overall, a total of 5,705 subjects with MS were included in the analysis, with a large study that included 3,623 subjects [38]. Setting aside that study, sample sizes ranged from 14 to 240 subjects. Most of these studies included people with MS with a limited physical disability (e.g., EDSS < 5.5) and with the average disease duration of 8 years and a mean age over 40 years. Articles that were included describe different psychological interventions for people with MS including cognitive-behavioral interventions, relaxation training, meditation, and stress management and coping skill promotion. There was variability about the duration of the intervention ranging from a week to two years, with an average length of two months. Control groups were composed primarily of subjects on a waiting-list or by no additional treatment group (usual care only). Four studies referred to a comparison between interventions, with controls receiving what was characterized as a less efficacious treatment or a gold-standard comparison.

Psychological variables were primary outcomes in all the included papers. The impact of the interventions on these outcomes was generally positive. Overall, psychological treatments produced an improvement in quality of life and psychological well-being, reducing depressive symptoms, anxiety and perceived stress. Most of the psychological treatments obtained positive effects. These effects were emphasized when the comparison was between the treatment and a usual care or a waiting-list control group.

The majority of the psychological effects on the physical symptoms were assessed using self-report measures, referring the perception of physical variables or symptoms (e.g., fatigue, pain), or the perception of general physical health. Following the psychological intervention, perceptions of general health improved, with higher scores on the physical subscales on quality of life questionnaires. One symptom positively affected by psychological treatments is fatigue, in which subjects from experimental groups often reported a significant decrease in fatigue along with a subsequent reduction in physical limitations related to tiredness. Similarly, improvements in sleep disturbances, physical vitality, and vigor were reported. Psychological interventions also appeared to reduce the perception of pain.

Changes in physical issues do not result only from self-reported questionnaires but few studies investigated these
| Study           | Patients (n) | Severity of symptoms | Mean disease duration | Mean age | Type of intervention                                                                 | Duration of the intervention | Type of control | Results on psychological variables                                                                 | Results on symptoms                                                                 |
|-----------------|--------------|----------------------|-----------------------|---------|--------------------------------------------------------------------------------------|-----------------------------|----------------|------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Barlow et al.   | 216          | N/R                  | 12 years              |         | Chronic Disease Self-Management Course, a lay-led self-management intervention that provides participants with a range of skills and strategies | 6 weeks                    | Waiting-list | CDSMC had an impact on self-management self-efficacy and trends towards improvement on depression and MS self-efficacy were noted. All improvements were maintained at 12-months | CDSMC had an impact on MSIS physical status                                    |
| Stuifbergen et al. | 113        | 15.65 on the Incapacity Status Scale | 10.76 years           | 45,79   | lifestyle-change classes and telephone follow-up                                     | 8 weeks                    | Waiting-list | Improvement of self-efficacy, health-promoting behaviors and mental health (SF36) | Reduction of Bodily Pain as measured with the SF36, no difference on the severity of impairment as measured with the Incapacity Status Scale |
| Ghafari et al.  | 66           | EDSS <5.5            | 2 years               | 31,5    | Progressive Muscle Relaxation Technique which combines proven cognitive-behavioral strategies for coping with stress with body exercises | 63 sessions during two months | No intervention | One and two months after intervention the experimental group reported better QoL | The physical component of QoL (PCS-8) improved as well                         |
| Tesar et al.    | 29           | EDSS <5.5 (mean 3.2) | 5.1 years             | 38.2    | Psychological program which combines proved cognitive-behavioral strategies for coping with stress with body exercises | 7 weeks                    | Waiting-list | The therapy group showed long-term improvements in depressive stress coping style | The therapy group showed short-term improvement in "vitality and body dynamics". |
| Forman & Lincon | 40           | 23 on the Guys Neurological Disability Scale | 9.8 years             | 47.5    | The intervention group programme was designed for people with multiple sclerosis and focused on adjustment to illness. | 6 weeks                    | Waiting-list | Patients allocated to the group intervention reported fewer depressive symptoms than those in the control group but there were no significant differences in anxiety symptoms, self-efficacy or quality of life | No changes on the MS Impact Scale - Physical                                     |
| O'Hara et al.   | 183          | 17 (median) on the Barthel Index | 11.8 years            | 51.5    | The intervention comprised discussion of self-care based on client priorities, using an information booklet about self-care. | The discussions lasted between 1 and 2 hours and were conducted on two occasions, over a one month period | No intervention | At follow-up the intervention group had better SF-36 health scores, in mental health and vitality. Participants in the intervention group had maintained levels of independence at follow-up while the control group showed a significant decrease in independence | Participants in the intervention group reported that assistance with daily activities was less essential than individuals in the control group at follow-up. However, there were no improvements in independence in daily living, mobility or a reduction in the number of occasions individuals were assisted with activities |
| Baron et al.    | 127          | 224 on the Guys Neurological Disability | N/R                   | 48.1    | telephone administered cognitive behavioral therapy | 16 weeks                   | telephone administered supportive emotion- | Improvements in depression and anxiety | Improvement in insomnia                                                        |
| Study Authors | Number | EDSS/Disability Status | FIM Motor Score Improvement | Time | Intervention Details | Outcome Measures | Additional Notes |
|---------------|--------|------------------------|----------------------------|------|----------------------|-----------------|-----------------|
| Tompkins et al. [38] | 3623 | N/R | 48.9 (RM); 43.5 (Control) | In person 1-2 days or teleconference 4-6 weeks | PREP for participant and partner in workshop sessions or teleconference series; 8 hrs programming (1 or 2 days or 4-6 wks for teleconference) | RM improvement with increased QoL at 3 months | Number of MS symptoms at baseline not significantly different at baseline between groups but comorbidities did (with control at fewer), controlled at analysis stage. Improved communications; willingness to try; better prepared for issues; acquisition of tools to address MS issues with partner |
| Khan et al. [39] | 101 | EDSS between 2 and 8; KFS 0-2 | 10.69 (TR); 9.73 (Control) | 12 months | Individualised rehabilitation programme | waiting-list | MSIS and GHQ-28 assessed participation and QoL; no differences between control and treatment on MSIS physical or psychological or GHQ subscales |
| Sutherland et al. [40] | 22 | EDSS < = 5.0, no prior CB techniques for 6 months prior to study | Diagnosis : 9.36 yrs (TR); 6.45 yrs (Control) | 10 weeks | AT program supervised training | No intervention | HRQOL positively affected; participants in relaxation less limited by physical findings but not for the AT. AT group positively impacted regarding role limitations due to emotional problems. |
| Maguire [41] | 33 | N/R | 45.13 | 6 days | Relaxation training and ongoing work with biologically oriented imagery. | Standard care | Imagery group subjects demonstrated significant reductions in state anxiety and significant alteration in their illness imagery |
| Mathiowetz et al. [42] | 169 | Multiple Sclerosis Functional Composite score: −97 | 15 years | 6 weeks | Energy Conservation course | Waiting-list | Increase self-efficacy and some aspects of quality of life |
| Grossman et al. [43] | 150 | EDSS =3 | 47.29 | 8 weeks | A modified version of the Mindfulness-Based Stress Reduction (MBSR) | Usual Care | Improvement on Quality of Life and other measures of well-being, for at least 8 months |
| Tavee et al. [44] | 17 | 3.25 (Experimental group); 2.79 (controls) | 10.4 (Experimental group); 19.4 (Controls) | 2 months | Meditation | Standard care | General improvement on mental health |
| Van Kessel et al. [45] | 72 | EDSS =3,45 | 45 | 8 weeks | CBT based on a cognitive behavior model of fatigue | relaxation training | A significant time effect was obtained for depression, anxiety and perceived stress, with both CBT and RT appear to be clinically effective treatments for fatigue in MS patients, |

Table 1 Included studies (Continued)
| Study | Participants | EDSS | Time since diagnosis | Intervention | Follow-up | Results |
|-------|-------------|------|---------------------|--------------|-----------|---------|
| Mohr et al. [46] | 121 | 3.1 | 7.05 | Individual stress management program | 20–24 weeks | Waiting-list | Participants in the experimental group reported lower level of distress even though the effects for CBT are greater than those for RT. |
| Mohr et al. [47] | 60 | N/R | 8.5 years | Individual cognitive behavioral therapy, group psychotherapy | 16 weeks | Sertraline | Reductions on depression for each group |
| Schwartz [48] | 132 | 4.7 | 7.9 | Coping skills group | 8 weeks | Peer telephone support | Coping skills intervention yielded gains in psychosocial role performance, coping behavior, and numerous aspects of well-being. In contrast, the peer support intervention increased external health locus of control but did not influence psychosocial role performance or well-being. |
| Wassem & Dudley [49] | 27 | 3.36 | 3.49 | Nursing intervention in promoting adjustment and symptom management | 4 weeks | Not specified | Treatment participants had significant improvements in symptom management at the 4-year follow-up. |
| Lincon et al. [50] | 240 | The assessment group received a detailed cognitive assessment; the treatment group received the same cognitive assessment and a treatment programme designed to help reduce the impact of their cognitive problems | Not specified | No intervention | No effect of the interventions on mood, quality of life, subjective cognitive impairment or independence. |
| Mohr et al. [51] | 14 | 3.6 | 11.3 | Individual cognitive behavioral therapy, group psychotherapy | 16 weeks | Sertraline | Reductions on depression for each group |
| Kopke et al. [52] | 150 | United Kingdom Neurological Disability Scale =7.9 | 5.2 | Patient education program to enhance decision autonomy | 4 hours | Standard care | The patient education program led to more autonomous decision making in patients with relapsing MS. The number of relapses reported by subjects in the experimental group was considerably lower than the one from controls. |
changes with objective measurements. Results indicate that a stress-management intervention reduces the number of brain lesions associated with the relapsing-remitting process of MS, with a consequent reduction of crisis [46]. A short patient education program successfully reduced the number of relapses, compared to controls [52]. Furthermore, successful treatment of depression (either with psychological or pharmacological interventions) resulted associated with a reduction in non-specific and antigen-specific interferon production [51].

In general, with the caveat of the limited number of studies involved, when the psychological intervention lead to a better psychological outcome, such as the reduction of depressive symptoms or the improvement in psychological well-being, the assessed physical outcomes were positively influenced. A correlation can be observed between the extent of changes from a psychological perspective and the size of change in MS symptoms. More intense and efficacious psychological interventions lead to higher changes on a physical level than less intense behavioral treatments.

Articles included in the review seldom formally assessed the level of disability making it impossible to deeply investigate this aspect of findings. Future studies would benefit from a greater focus on assessment of disability in terms of functioning and inclusion of more non-self-report measures pre and post-intervention.

Discussion

Results from the studies considered in this review suggest that psychological interventions may well have a positive effect on MS symptoms. In particular, fatigue, physical vitality, sleep disturbances and pain are the physical variables investigated that appeared to benefit from such interventions, together with perception of general health. Physical changes following a psychological intervention are reported on both self-report measurements and, in a more limited number of studies, on biological measures. If results are limited to questionnaire outcomes, it could be argued that psychological interventions may not provide objective changes, but could change the perception of the physical symptomology. It appears highly likely that both subjective and objective outcomes are moving toward one specific direction: that the mind does influence the body, even effecting MS symptoms. These findings should not surprise us, as we consider increasing evidence of the mind’s influence on the body. The idea that psychological treatments, however, may influence the physical expression (i.e., symptoms) of the disease itself is relatively new and few studies dare to explore this idea. In fact, relatively few papers considered some physical symptoms as a possible outcome for psychological interventions. Most of these studies only included a limited self-report assessment of health. It is possible that researchers in the MS field have thus far not tried to influence the possibility that interventions at the psychological level can result in positive effects on the body. Those who assessed physical changes with objective measures [46,51,52] found interesting results that surely deserve to be deepened and further explored. Since a cure for the various form of MS is not yet available, it makes sense to explore every possible therapeutic option, including the possibility that psychological treatment need not be palliative or burden-relief in nature [25,28]. Not surprisingly, fatigue, physical vitality and sleep disorder are often part of diagnostic criteria in the framework of depressive disorders. This is consistent with our hypothesis as an example of the effects that the mental domain can express over the body.

A few limitations of the present study should be noted. The majority of the studies included in the review utilized self-report measures for acquiring physical outcome data. As self-report measures are inherently based on subjective perception, the quality of their construct validity may have confounded the results of the review. Another limitation was that none of the studies reviewed included outcome data of any form of disability, possibly narrowing the scope of our assessment of physical outcomes. Finally, few studies in total were eligible for review; the studies included may therefore not adequately represent the general MS population.

Conclusions

This brief review investigates the hypothesis that psychological interventions for individuals with multiple sclerosis have a positive impact not only at the psychological level, but also on the physical domains, in particular on symptoms of disease. Despite a paucity of studies that included assessment of physical variables as outcomes for psychological interventions, available data strongly suggest that the hypothesized connection does exist. In particular, fatigue, pain, physical vitality and quality of sleep, assessed by subjects’ evaluations, improve significantly after most of the interventions. Furthermore, a few cutting edge studies that assessed physical outcomes with objective measurements suggest that there are actual physical benefits, for example in terms of interferon level and brain lesions.

Our results indicate that there is a strong unexplored potential for psychological interventions to improve the quality of life of people with MS from both a psychological perspective and in terms of a reduction in symptoms. Given the potential improvement of well-being, we strongly urge research efforts be applied in this direction.

Competing interests

The authors declare that they have no competing interests.
Authors’ contributions
FP designed the research, participated to literature search and data interpretation; CMB and DP participated to literature search and data interpretation; EL participated in the study design and helped to draft the manuscript. All authors have read and have approved the final manuscript.

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