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Sleep patterns, depression, physical activity levels, fatigue, and mental toughness in patients with multiple sclerosis (MS); results from cross-sectional, longitudinal and intervention studies

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Erklärung zur wissenschaftlichen Lauterkeit

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Brand S, Kalak N, Gerber M, Clough PJ, Lemola S, Sadeghi Bahmani D**,** Pühse U, Holsboer-Trachsler E. During early to mid adolescence, moderate to vigorous physical activity is associated with restoring sleep, psychological functioning, mental toughness and male gender. Journal of Sports Sciences, 2017;35:426-434. (Impact factor: 2.246)

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Sleep patterns, depression, physical activity levels, mental toughness and fatigue in patients with multiple sclerosis (MS) – Results from cross-sectional, longitudinal and intervention studies

Overview and background

Worldwide, multiple sclerosis (MS) is the most common chronic autoimmune demyelinating and inflammatory disease of the central nervous system, with long term effects on both physical and mental functioning (Compston & Coles, 2008; Howard, Trevick, & Younger, 2016; Reich, Lucchinetti, & Calabresi, 2018; Thompson, Baranzini, Geurts, Hemmer, & Ciccarelli, 2018).

My experience of working as a psychologist on the MS ward of a university hospital in Iran for two years left me with many questions related to this disorder; the experience brought me to appreciate the complexity of the disease, patients' situations and treatment procedures. To summarize, I realized that the disease and its treatment are highly complex not only because of the neurological impairment the disease produces, but also the interplay and mutual influence of mental and physical deficits. In addition, MS sufferers are confronted with a broad range of problems caused by disease symptoms, neurological deficits, and the degenerative and progressive nature of the disease, along with their awareness of their future status as physically disabled, and quite possibly ending up in a wheelchair. All in all, these difficulties and challenges make the MS patient's situation very demanding; they also underline why MS patients need the supported of specialists and comprehensive rehabilitation programs. This means that, in order to enable patients with MS to continue to participate in society, to maintain their quality of life, to avoid dependency on others, it is crucial that they have access to rehabilitation, and that we do not focus purely on medication aimed at ameliorating symptoms.

It is important not only to appreciate the importance of rehabilitation intervention but also to select the appropriate form of rehabilitation, matched to the needs of the individual patient, taking into account the risks and differences in outcome of any particular rehabilitation program for each patient, and their imitations. All this is necessary in developing the main aims, which are caring for patients and improving their functioning. Our research team, which includes experts in

the fields of neurology, sleep research, psychology and sport sciences in Iran and Switzerland, has undertaken series of studies to investigate and improve the treatment of MS sufferers. I have spent the last three years of my academic life looking for ways to improve patients' treatment and their everyday lives. To these ends, I undertook a series of studies conducted in Iran and Switzerland.

While on the one hand in running these studies, I had to overcome a number of challenges including difficulties recruiting patients, constructing designs for the studies in the context of ab limited literature, using questionnaires in both Farsi and German, and traveling back and forth between Kermanshah, Esfahan and Tehran in Iran, and between Basel and Valens in Switzerland. On the other hand, the 'merits' were as follows:

a) running several studies in three different treatment centers
b) recruitment and assessment of up to 500 patients with MS who were willing and able to participate in cross-sectional and longitudinal studies
c) running studies which included psychoeducation, instruction, and information about treatment for both patients and their caregivers
d) combining sleep research, sport science and psychology in the pursuit of improvements and innovations in treatment
e) introducing the concept of mental toughness into research on psychological functioning in MS patients. This concept was initially elaborated in the field of sport psychology to explain athletes' performances, while the research group led by Markus Gerber took the mental toughness concept into domains beyond those inhabited by sport professionals and sport psychology
f) following up subjective sleep patterns and physical activity patterns in a small sample of patients with MS at disease onset
g) publishing several successful and well-received papers in international and peer-reviewed journals (overall impact factor points: 11.835 (16.535))
h) presenting up to 18 oral and 26 poster presentations on the results of my work at international congresses
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j) receiving three awards (2015: poster prize at the Annual Meeting of the Swiss Society of Biological Psychiatry; 2017: Travel grant of 400 EUR and a free registration 290 EUR to acknowledge the quality of the scientific contribution to the European Committee for Research and Treatment in Multiple Sclerosis (ECTRIMS), Paris; 2018: award for excellent scientific research, Karger Publisher, Basel)

k) developing enthusiasm to continue my research

My research activities do not come to an end with the presentation of this thesis in psychology of the Faculty of Psychology of the University of Basel (Basel, Switzerland). Rather, the next steps are to conduct intervention studies looking at the effects of physical activity and to combine assessments of subjective psychological improvements and objective sleep improvement with fMRI data as proxies for brain plasticity.

The present research statement is structured as follows

Following a brief introduction explaining why treatment is crucial for patients with MS, I develop the case for the necessity of non-pharmacological treatments of MS, and the advantages of physical activity and exercise as known and proven interventions for healthy people, for patients with neurodegenerative disease and mental disorders, and for patients with MS (based on current and previous research on the importance and function of rehabilitation intervention). Then, I discuss the feasibility of physical activity for MS patients as compared to healthy individuals. Next, I describe the results of physical activity as dynamic elements in the symptoms of MS, based on the findings of our studies. The following chapter focuses on the impact of physical activity on sleep, both among the healthy and among patients with MS. My work is the first to assess the influence of physical activity on objective sleep parameters in patients with MS. Finally, I explain in more detail the psychological concept of mental toughness and why this concept emerges as a useful and 'economic' way to assess patients' capacity to cope with stress, to build up commitment, to retain confidence, and to live with a disease that has an uncertain course.

Treatment of Multiple Sclerosis

Individuals with MS can present with various combinations of physical and mental deficits such as physical weakness, spasticity, motor and sensory dysfunction, fatigue, depression, sleep complaints, pain, cognitive dysfunction, psychosocial and behavioral problems; these symptoms limit the individual's capacity to function and participate in social life (Compston & Coles, 2008; Reich et al., 2018; Thompson et al., 2018).

Medical rehabilitation and treatment are defined as "a set of measures that assist individuals who experience disability to achieve and maintain optimal physical, sensory, intellectual, psychological and social function in interaction with their environment" (http://www.who.int/disabilities/publications/care/en/). Medical rehabilitation is a complex interdisciplinary intervention, offering a series of goal-oriented and individualized steps tailored to each patient's specific needs. Improving function is about reducing dependency and increasing participation as the main goals of any rehabilitation program. Given the degenerative character of MS over time, and additional growing disability due to the aging process, rehabilitation is strongly recommended for patients with MS, both in health care settings and also in their private lives (Khan, Amatya, Gosney, Rathore, & Burkle, 2015). The most common and well-validated forms of rehabilitation for MS patients focus on cognitive rehabilitation, physical activity and exercise programs (Khan & Amatya, 2017). The first of these has a proven impact on memory and information processing speed (Sokolov, Grivaz, & Bove, 2018).

Why exercise?

Influence of exercise on healthy individuals

In several epidemiological studies significant cross-sectional correlations have been found between mental health and participation in physical activity and exercise. Among adults, regular physical activity and exercise is associated with lower prevalence rates for major depression, agoraphobia, panic disorder, social and specific phobia (Stubbs et al., 2018). In a Norwegian study, greater leisure-time physical activity was related to reduced symptoms of depression while interestingly work-related physical activity had no additional positive (or negative) impact (Ten Have, de Graaf, & Monshouwer, 2011). In a similar vein, Ekelund et al. (2016) concluded from their meta-analysis that people engaged in sedentary jobs reduced their risk of early mortality the more engaged they were in physical activity during their leisure time. Sedentary behavior is also an issue from an economic perspective; Ding et al. (2016) estimated in their analysis that in 2013

the costs of coping with non-communicable diseases as a result of sedentary behavior were up to USD 53.8 billion.

In addition, many studies have demonstrated that physical activity and exercising enhance brain plasticity, benefitting cognitive functioning and psychological wellbeing. Physical activity induces functional and structural changes in the brain, these changes producing psychological and biological benefits (Fernandes, Arida, & Gomez-Pinilla, 2017). This process is referred to as neuroplasticity; in effect, brain structure and brain functions change and adapt as a function of their utility and regular use. Physical activity and exercise promote this neuroplasticity (Neville & Bavelier, 2002) and thereby facilitate positive psychological and biological effects that influence brain and cognitive functioning (Mandolesi et al., 2018). Fernandes et al. (2017) showed that these neuroplasticity processes involve epigenetic mechanisms based on alterations in gene expression and gene protein products. Last, physical activity and exercise play an important role in slowing the aging process, both in normal and pathological cases.

Influence of exercise in neurodegenerative disorders

Neurodegenerative disease such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) increase in probability with age.

Neurodegenerative diseases result in progressive deficits of neuronal function and structure. These diseases are characterized by protein aggregation and misfolding, oxidative stress, and mitochondrial dysfunction, though the underlying neurobiological processes remain for the present unknown. However, physical activity and exercise appear to have a neuroprotective function with respect to several neurodegenerative disorders, including Alzheimer's and Parkinson's. Although there exists evidence that physical activity and exercising have positive effects on the symptoms of patients with neurodegenerative disorders, the neurophysiological mechanisms that underpin these effects remain unclear. There are two main hypotheses: 1) physical activity and exercising protect neurons against oxidative stress; 2) physical activity and exercising enhance expression of BDNF and other neuronal trophic factors that promote the maintenance, survival and functioning of neuronal progenitors and of neuronal tissues (Campos et al., 2016).

Influence of exercise in mental disorders

Several epidemiological and interventional studies have shown that physical activity and exercise, whether employed as sole or adjuvant therapies, can prevent or at least delay the onset of various mental disorders (Deslandes et al., 2009; Gerber, Holsboer-Trachsler, Puhse, & Brand, 2016; Knochel et al., 2012; Maier & Jette, 2016; Mangerud, Bjerkeset, Lydersen, & Indredavik, 2014; Nyboe & Lund, 2013; Rosenbaum, Tiedemann, Sherrington, Curtis, & Ward, 2014; Rosenbaum, Tiedemann, et al., 2015; F. Schuch et al., 2017; Stubbs et al., 2018). This observation holds true for a broad variety of psychiatric disorders including major depressive disorders (Archer, Josefsson, & Lindwall, 2014; Bailey, Hetrick, Rosenbaum, Purcell, & Parker, 2017; Booth, Roberts, & Laye, 2012; Brondino et al., 2017; Carek, Laibstain, & Carek, 2011; Gerber, Holsboer-Trachsler, et al., 2016; Knochel et al., 2012; Lindegard, Jonsdottir, Borjesson, Lindwall, & Gerber, 2015; Lindwall, Gerber, Jonsdottir, Borjesson, & Ahlborg, 2014; Pedersen & Saltin, 2015; Perez-Lopez, Martinez-Dominguez, Lajusticia, & Chedraui, 2017; Sartori et al., 2011; Scholz, Knoll, Sniehotta, & Schwarzer, 2006; Schuch et al., 2017; Schuch, Morres, Ekkekakis, Rosenbaum, & Stubbs, 2016; Stubbs, Rosenbaum, Vancampfort, Ward, & Schuch, 2016; Sun, Lanctot, Herrmann, & Gallagher, 2017; Vancampfort, Stubbs, et al., 2015; Wu, Lee, & Huang, 2017), schizophrenia (Battaglia et al., 2013; Knochel et al., 2012; Pajonk et al., 2010; Rosenbaum et al., 2014; Brendon Stubbs et al., 2018; Tarpada & Morris, 2017; Vancampfort, De Hert, Stubbs, Ward, et al., 2015; Vancampfort et al., 2017), posttraumatic stress disorders (Martin, Dick, Scioli-Salter, & Mitchell, 2015; Rosenbaum, Tiedemann, et al., 2015; Rosenbaum, Vancampfort, et al., 2015; Vancampfort et al., 2016), and substance use disorder (Booth et al., 2012; Giesen, Deimel, & Bloch, 2015; Hallgren, Vancampfort, Giesen, Lundin, & Stubbs, 2017; Vancampfort, De Hert, Stubbs, Soundy, et al., 2015).

In addition, Ten Have et al. (2011) found that rates for psychiatric symptoms were lower among those who exercised at least once a week for one hour, though without any linear dose-response relationship.

Likewise, the overall incidence of mental disorders, somatoform disorders, anxiety, and dysthymic disorders is lower among people who have higher rates of physical activity (Strohle et al., 2007). Furthermore, a four-year prospective study revealed that physical activity also reduced rates of depressive and anxiety disorders among the elderly (Pasco et al., 2011). Finally, in a three-year follow-up study patients engaging in physical activity programs proved to be more likely to recover from mental disorders (Ten Have et al., 2011). Importantly, even single bouts of exercise have the potential to improve the psychological state of patients with mental issues. Compared to the beginning of an exercising session, at the end of the session, inpatients with

mental issues reported improvements in mood, rumination, social orientation, and well-being (Brand et al., 2018). This study also found that such improvements occurred regardless of patients' psychiatric diagnosis and regardless of the type of intervention, supporting a so-called transdiagnostic approach to the treatment of psychiatric disorders (Norton et al., 2013; Norton & Paulus, 2016; Norton & Roberge, 2017; Pearl & Norton, 2017), and also supporting the conclusion that any kind of exercise is better than none.

Various mechanisms have been proposed as explanations for the beneficial effect of physical activity for individuals with psychiatric disorders. a) On a neurophysiological level, a number of changes occur during regular physical activity and exercise training. For example, physical activity and exercise have been found to normalize reduced levels of BDNF, which have neurotrophic and neuroprotective effects (Strohle et al., 2007; Zschucke, Gaudlitz, & Strohle, 2013). b) Animal studies indicate that levels of neurotransmitters such as endorphins and serotonin increase after exercise (Fumoto et al., 2010); such findings might explain why mood is generally enhanced following exercise and why stress reactivity improves (Gerber, Brand, Elliot, Holsboer-Trachsler, & Puhse, 2014; Gerber, Brand, Elliot, et al., 2013; Gerber, Brand, Herrmann, et al., 2014; Gerber, Endes, et al., 2016; Gerber, Feldmeth, et al., 2015; Gerber, Jonsdottir, Arvidson, Lindwall, & Lindegard, 2015; Gerber, Lindwall, et al., 2015; Lang et al., 2017; Lindwall et al., 2014). Potential cognitive changes associated with physical activity and exercise include learning and extinction, changes in health attitudes/behaviors, experience of mastery, a shift from external to internal locus of control, social reinforcement, and better strategies for coping with stress (Brendon Stubbs et al., 2018).

Patients with mental disorders also display a high comorbidity of physical conditions such as respiratory, cardio-vascular, metabolic, and neurologic disease (Gerber, Endes, et al., 2016; Gerber, Lindwall, Lindegard, Borjesson, & Jonsdottir, 2013). Many of these conditions are associated with an unhealthy lifestyle including poor nutrition, and smoking. Therefore, physical activity and exercise are promising options for reducing physical comorbidity (Zschucke et al., 2013). For example, in a cross-sectional study, patients with psychiatric diagnoses participating in regular physical activity and exercise reported better health-related quality of life (Zschucke et al., 2013).

Multiple sclerosis (MS) is an immune-mediated demyelinating disease that affects the central nervous system (CNS)—leading to progressive physical disability, along with more marked psychiatric symptoms (Compston & Coles, 2008; Reich et al., 2018; Thompson et al., 2018). Consequently, many of the above explanations for the relevance of exercise as an intervention and rehabilitation plan also holds for patients with MS. Views on the benefits of exercise for MS sufferers have been mixed, with some arguing that it could actually increase morbidity due to injuries. However, within the last 25 years, there was a shift in the paradigm from avoidance of any kind of unnecessary physical activity to advocacy of an active life style (Asano, Duquette, Andersen, Lapierre, & Mayo, 2013; Giesser, 2015). Not surprising, there is no scientific evidence that regular physical activity has a negative impact on the course of MS (Giesser, 2015).

The consensus now is that regular physical activity has the potential to improve the fitness levels of MS sufferers (Heine, van de Port, Rietberg, van Wegen, & Kwakkel, 2015; Platta, Ensari, Motl, & Pilutti, 2016; Schmidt & Wonneberger, 2014), and to reduce medication-induced side effects such as metabolic syndrome, weight gain, diabetes, osteoporosis and hypertension. Impressively, Pilutti et al. (2014) concluded from their meta-analysis that regular physical activity appears to reduce the risk of further relapses. However, this effect was not confirmed in a prospective study. Tallner et al. (2012) prospectively assessed 632 patients with MS and over the following two years observed no differences in relapses between those who were physically very active and those who were physically inactive. In contrast, Dalgas and Stenager (2012) and Motl and Pilutti (2016) concluded in their systematic reviews that regular physical activity potentially has a positive impact on the course of the disease. However, they also noted that comparisons of results are difficult due to the heterogeneity of methodological approaches (subjective vs. objective physical activity measurements; differences in physical activity; frequency, intensity, duration and type of intervention).

In a further step, Motl et al. (2012) showed that amount of regular physical activity before disease onset was predictive of amount of physical activity after disease onset. With respect to this finding, we showed in our first study (Sadeghi Bahmani et al., 2016), that, at disease onset, amount of moderate physical activity in MS patients (average age 31) did not differ significantly from that observed in adolescents and young adults. However, compared to these healthy samples, patients with MS at disease onset reported lower vigorous physical activity levels. In our second, longitudinal study (Sadeghi Bahmani et al., 2018) we showed that two years after

disease onset overall physical activity levels increased; more specifically, vigorous physical activity but also sedentary behavior decreased, but moderate physical activity increased.

Next, Prakash and colleagues (Prakash et al., 2007; Prakash, Snook, Motl, & Kramer, 2010) showed that among MS patients better physical fitness was associated with a higher volume of grey matter substance and a greater complexity of white matter substance. Their results suggest that among MS patients regular physical activity is associated with a higher degree of neural plasticity.

Last, Bansi and colleagues (Bansi, Bloch, Gamper, & Kesselring, 2013; Bansi, Bloch, Gamper, Riedel, & Kesselring, 2013) showed that among MS patients a three-week intervention program improved the immune system and increased the release of neurotrophins (Florindo, 2014)).

Patterns of exercising in patients with MS at disease onset and two years later

As described above, and as confirmed in our previous study (Razazian et al., 2016), exercising has a positive impact on MS patients' psychological characteristics. However, three important questions remain: 1. What is the level of physical activity of MS patients at disease onset? 2. Does this pattern of physical activity at disease onset differ from those for healthy adolescents or young adults? 3. Does the pattern of physical activity change over the two years following disease onset?

To answer these questions, we recruited 23 patients (mean age31 years) who were at disease onset (Sadeghi Bahmani et al., 2016). We assessed depression, fatigue, and sleep complaints along with their physical activity levels (in four different categories: vigorous PA, moderate PA, sedentary PA, walking) using the International Physical Activity Questionnaire (Craig et al., 2003). We found that at disease onset patients reported medium vigorous physical activity and walking levels, high moderate physical activity and moderate sedentary time. We also found that, compared to adolescents and young adults, levels of vigorous physical activity were lower, sedentary time was higher, but moderate physical activity levels were very similar.

In a follow-up-study (Sadeghi Bahmani et al., 2018) we assessed these patients two years after disease onset and observed the following changes: compared to disease onset, vigorous physical activity had declined, walking time and moderate physical activity had increased, and sedentary time had decreased.

Multiple sclerosis, exercising, and depression and fatigue

Previous research has shown that patients with MS are at increased risk of symptoms of depression (Berzins et al., 2017; Boeschoten et al., 2017; de Cerqueira, Semionato de Andrade, Godoy Barreiros, Teixeira, & Nardi, 2015; Ensari, Adamson, & Motl, 2015; Fiest et al., 2016; Hind et al., 2016; Joffe, 2005; Perez, Gonzalez, & Lazaro, 2015). Thus, as is the case for patients with major depressive disorders, physical activity interventions are also successful in reducing symptoms of depression in MS patients (Coote et al., 2017; Ensari et al., 2015; Motl, McAuley, Snook, & Gliottoni, 2009; Pedersen & Saltin, 2015; Razazian et al., 2016).

Fatigue involves lack of physical and mental energy. Fatigue is a core symptom of MS, and up to 90% of patients with MS complain that they sometimes or often suffer from fatigue (Braley, 2018; Braley & Boudreau, 2016). Forty-six to 66% of patients with MS complain about daily symptoms of fatigue (Popp et al., 2017), and about 30% report that fatigue is their most debilitating symptom of MS (Caminero & Bartolome, 2011).

Veauthier et al. (2016) argue for a thorough diagnostic procedure to distinguish fatigue from daytime sleepiness, sleep disorders, and possible side effects of medications. Safari et al. (2017) concluded from a synthesis of meta-analyses that regular physical activity, when compared to no interventions, reduces fatigue. Furthermore, combining different types of intervention (yoga, resistance training, endurance training; balancing) leads to larger effect sizes when compared to endurance training alone. In addition, cognitive-behavioral therapies and self-management interventions appear to be equally successful.

Exercise and paresthesia

Paresthesia is an umbrella term to describe sensations of tingling, tickling, pricking, and burning. While interventions of physical activity interventions have focused on fatigue, depression and quality of life, our team was the first to examine effects with respect to paresthesia (Razazian et al., 2016). In this study we investigated the impact, compared to a control condition, of yoga and aquatic exercising on paresthesia, fatigue, and depression in patients with MS. At baseline and two months later participants completed questionnaires covering a number of factors including symptoms of depression and fatigue. They also rated degree of paresthesia using a 10-point visual scale; higher scores indicated more severe symptoms of paresthesia. Results showed that, compared to the control group, patients in the

intervention groups improved with respect paresthesia, fatigue, and depression. Partial correlations additionally showed that paresthesia declined as a function of reduction in symptoms of depression.

Multiple sclerosis, exercise and sleep

Several meta-analyses and reviews indicate that patients with MS have impaired sleep (Bamer, Johnson, Amtmann, & Kraft, 2008; Braley & Boudreau, 2016; Brass, Duquette, Proulx-Therrien, & Auerbach, 2010; Caminero & Bartolome, 2011; Fleming & Pollak, 2005; Hughes, Dunn, & Chaffee, 2018; Veauthier, 2015; Veauthier et al., 2016; Veauthier & Paul, 2014). These impairments include Restless Legs Syndrome, Obstructive Sleep Apnea, and insomnia. However, we have also found that, in a sample of MS patients in their early 30s, sleep quality indices at disease onset did not differ from the sleep quality indices of adolescents and young adults (Sadeghi Bahmani et al., 2016). Moreover, the sleep quality indices of this group did not differ two years later

Next, despite the fact that there have been numerous clinical and non-clinical studies of the positive influence of physical activity and exercise interventions on sleep, there are very few controlled studies of this influence among MS patients. To the best of our knowledge, Siengsukon et al. (2016) were the first to perform such an intervention study. They randomly allocated 28 MS patients to one of the following two conditions: moderate-intensive aerobic exercise or low-intensive walking and stretching. In each case the intervention lasted 12 weeks and the activities took place three times a week for 30 minutes. Outcome variables were sleep quality (Pittsburgh Sleep Quality Index), daytime sleepiness (Epworth Sleepiness Scale), fatigue, and depression. Results showed that sleep quality improved descriptively from baseline to the study end, while a significant improvement was observed only in the low-intensive walking and stretching condition; daytime sleepiness improved only in the moderate-intensive aerobic exercise condition. Interestingly, improvements in sleep and daytime sleepiness were not associated with depression or fatigue. Given the paucity of research on physical activity interventions aimed at improving sleep among MS patients, the first aim of our intervention study was to determine whether an intervention involving physical activity intervention would improve both objective and subjective sleep (Siengsukon et al., 2016). We assessed 46 patients in a rehabilitation center and undertaking a program of regular exercise; the assessment was made three weeks before discharge and again at discharge. All participants completed a series of

questionnaires covering sociodemographic data, sleep complaints, depression, fatigue, paresthesia, and physical activity. We also measured cognitive performance and assessed sleep EEG at baseline and study end (three weeks later). We found that sleep onset latency was significantly shortened, sleep efficacy improved, and the time of awakenings after sleep onset shortened. There were no significant differences between baseline and study end on any other dimension of sleep continuity (total sleep time, sleep period time; numbers of awakenings after sleep onset). As regards sleep architecture (stages 1-4 and REM-sleep) no significant mean differences were observed. However, the results for objective sleep were in the same direction as our findings for subjective sleep (Sadeghi Bahmani et al. under review in: Therapeutic Advances in Neurological Disorders since October 2018).

Mental toughness: A new avenue in the assessment of psychological functioning in patients with Multiple Sclerosis

Mental toughness (MT) is a psychological construct describing the capacity of a person to be consistently successful in facing difficulties in life. MT consists of the following dimensions: Control (emotions and own life), Commitment (to one's achievements and aims), Challenge (changes in life taken as opportunities and not as threats), and Confidence (in other people and in one's own abilities) (Clough, Earle, & Sewell, 2002; Perry, Clough, Crust, Earle, & Nicholls, 2013). Thus, MT refers to the tendency to treat threats and stress as opportunities to thrive (Thelwell, 2005), actively to seek out and cope with challenges (Crust, 2008), and successfully to deal with setbacks and difficulties (Clough et al., 2002; Dewhurst, Anderson, Cotter, Crust, & Clough, 2012). Defined in these ways, MT encompasses a range of cognitive-emotional processes involved in coping, motivation, and self-efficacy, and in dealing with unpredictable situations, and social circumstances (Sadeghi Bahmani et al., 2016). Lin (2017) in their review described MT as an umbrella term for psychological resources which are associated with a broad range of mental health outcomes. In particular, these authors emphasized the "mental toughness advantage"; MT traits are associated with positive goal traits, more efficient coping strategies, and positive outcomes in education and mental wellbeing. Studies of non-clinical samples have showed higher MT scores to be associated with lower scores for symptoms of depression and stress (Brand et al., 2014b; Gerber, Brand, Feldmeth, et al., 2013; Gerber, Feldmeth, et al., 2015; Gerber, Kalak, et al., 2013; Kaiseler, Polman, & Nicholls, 2009).

Despite the broad range of research on mental toughness and its relationships with coping and both subjective (Brand et al., 2014b) and objective sleep (Brand et al., 2014a) three questions had not been answered: 1) What are the roots in childhood of mental toughness traits in adolescence? 2) What mental toughness traits characterize MS patients at disease onset, and when compared to adolescents and young adults? 3) Do mental toughness traits change two years after disease onset? These questions were addressed in three studies.

In the first study (Sadeghi Bahmani et al., 2016) children first assessed in kindergarten were followed up nine years later at age 14. When the children were five their parents and teachers completed the Strengths and Difficulties Questionnaire (SDQ), covering internalizing and externalizing problems, hyperactivity, negative peer relationships, and prosocial behavior. At the follow-up, participants completed a booklet of questionnaires covering socio-demographic data, mental toughness, and sleep disturbances. We found that higher prosocial behavior, more positive peer relationships, and lower internalizing and externalizing problems at age five, as rated by parents and teachers, were associated at age 14 with greater self-reported mental toughness, which is to say higher scores for confidence, control, commitment, and challenge. We concluded that mental toughness at age 14 years appears to have its origins in early childhood. However, it is also conceivable that the roots of mental toughness might be found even earlier in life.

In the second study (Sadeghi Bahmani et al., 2016) we asked about the mental toughness of MS patients at disease onset, when compared to the mental toughness of adolescents and young adults. It turned out that MS patients had similar mental toughness levels to adolescents, while young adults had higher MT scores than both these groups. Overall this pattern of results suggests that for MS patients at disease onset, mental toughness traits as proxies for capacity to cope with stress, goal-oriented behavior, stable self-esteem, self-efficacy, and self-motivation are not showing signs of pre-clinical decline.

In the third study (Sadeghi Bahmani et al., 2018) we investigated whether mental toughness changes two years after disease onset. Our results showed that this was not the case. Those patients with higher mental toughness scores at disease onset also had higher mental toughness scores two years later. It is also worthy of note that mental toughness was unrelated to changes in sleep patterns or physical activity levels, and in particular was unrelated to Expanded Disability Status Scores (Kurtzke, 1983).

I am also a co-author of the following papers:

In Sabouri et al. (2016) based on a sample of 341 adults, we found that higher mental toughness scores were associated with higher physical activity scores, but also with higher scores on Dark Triad traits. Briefly, the concept of the Dark Triad (Paulhus & Williams, 2002) refers to a personality construct consisting of psychopathy, narcissism, and Machiavellianism. The term "dark" reflects the notion that individuals with high scores on the Dark Triad have patterns of behavior that are disapproved in society. The key message of this paper is that individuals with greater mental toughness may be physically more active, but on the other hand behave in more socially undesirable ways.

In Brand et al. (2016) we tested 1361 adolescents (mean age = 13.37 years) and found that mental toughness was associated with vigorous physical activity and positive psychological functioning.

In Jahangard et al. (2017) we found greater mental toughness to be associated with higher levels physical activity and hypomania in a sample of 206 young adults. Closer examination revealed that hypomania scores were predicted by scores on the mental toughness subscales of control and challenge, and by physical activity. Overall, it appears that, at least among young adults, those with higher mental toughness scores are also those with higher scores for hypomania, treated here as a proxy for positive mood, greater creativity and stronger interest in social interaction.

To summarize, the following papers were used to complete the present thesis:
First authorships and important publication of Razazian et al., 2016

Razazian, N., Yavari, Z., Farnia, V., Azizi, A., Kordavani, L., Sadeghi Bahmani, D., Holsboer-Trachsler, E., Brand, S., 2016. Exercising Impacts on Fatigue, Depression, and Paresthesia in Female Patients with Multiple Sclerosis. Medicine and science in sports and exercise 48(5), 796-803. Impact factor: 3.983
Key messages: An eight-weeks lasting intervention of yoga and aquatic exercising improved symptoms of depression, fatigue and above all paresthesia in female patients with MS.

Sadeghi Bahmani, D., Gerber, M., Kalak, N., Lemola, S., Clough, P.J., Calabrese, P., Shaygannejad, V., Puhse, U., Holsboer-Trachsler, E., Brand, S., 2016. Mental toughness, sleep disturbances, and physical activity in patients with multiple sclerosis compared to healthy adolescents and young adults. Neuropsychiatric Disease and Treatment 12, 1571-1579. Impact factor: 1.86

Key messages: At disease onset, patients with MS show similar sleep patterns, mental toughness scores and physical activity levels as adolescents and young adults. Accordingly, onset of MS is not associated with preclinical changes in sleep, physical activity and psychologial functioning.

Sadeghi Bahmani, D., Esmaeili, L., Shaygannejad, V., Gerber, M., Kesselring, J., Lang, U.E., Holsboer-Trachsler, E., Brand, S., 2018. Stability of Mental Toughness, Sleep Disturbances, and Physical Activity in Patients With Multiple Sclerosis (MS) - A Longitudinal and Pilot Study. Frontiers in psychiatry 9, 182. Impact factor: 3.532
Key messages: Two years after disease onset, patterns of sleep and physical activity remained fairly stable. Patterns of physical activity changed in a favorable direction: Sedentary time decreased, vigorous physical activity decreased, but moderate physical activity increased between disease onset and two years later. Further, MS does not necessarily lead to a reduction of physical activity.

Sadeghi Bahmani, D., Hatzinger, M., Gerber, M., Lemola, S., Clough, P.J., Perren, S., von Klitzing, K., Von Wyl, A., Holsboer-Trachsler, E., Brand, S., 2016. The origins of mental toughness – prosocial behavior and low internalizing and externalizing problems at age 5 predict higher mental toughness scores at age 14. Frontiers in Psychology 7. Impact factor: 2.46
Key messages: Five-years old children with high prosocial behavior, low internalizing and externalizing problems, as rated by their parents and teachers, report higher scores of Mental toughness at the age of 14 years. Mental tougness appears to have its roots in childhood.

Sadeghi Bahmani, D., Kesselring, J., Papadimitriou, M., Bansi, J., Pühse, U., Gerber, M., Holsboer-Trachsler, E., Brand, S. In patients with Multiple Sclerosis (MS) both objective and subjective sleep, depression, fatigue and paresthesia improved after three weeks of regular exercise. Submitted to Therapeutic Advances in Neurological Disorders and under review since October 2018. (Impact factor: 4.70)

Key messages: An intensive three-weeks lasting physical activity and rehabilitation program improved subjective and above all objective sleep in patients with MS. Further, depression, fatigue and paresthesia improved, while Mental toughness scores remained stable.

Total impact factors: 11.835 (16.535)

Moreover, the following publications (co-authorships) were added:

Sabouri, S., Gerber, M., Sadeghi Bahmani, D., Lemola, S., Clough, P.J., Kalak, N., Shamsi, M., Holsboer-Trachsler, E., & Brand, S. (2016). Examining Dark Triad traits in relation to mental toughness and physical activity in young adults. *Neuropsychiatric Disease and Treatment 12*, 229-235.
Key messages: Young adults reporting higher scores in mental toughness also report higher scores in Dark Triad traits, along with higher physical activity.

Brand, S., Kalak, N., Gerber, M., Clough, P.J., Lemola, S., Sadeghi Bahmani, D., Puhse, U., & Holsboer-Trachsler, E. 2017. During early to mid adolescence, moderate to vigorous physical activity is associated with restoring sleep, psychological functioning, mental toughness and male gender. *Journal of Sports Sciences, 35*, 426-434.
Key messages: Among 1361 young adolescents, higher mental toughness scores were associated with higher vigorous physical activity and favorable psychological functioning.

Jahangard, L., Rahmani, A., Haghighi, M., Ahmadpanah, M., Sadeghi Bahmani, D., Soltanian, A.R., Shirzadi, S., Bajoghli, H., Gerber, M., Holsboer-Trachsler, E., & Brand, S. 2017. "Always Look on the Bright Side of Life!" - Higher Hypomania Scores Are Associated with Higher Mental Toughness, Increased Physical Activity, and Lower Symptoms of Depression and Lower Sleep Complaints. *Frontiers in Psychology, 8*, 2130.
Key messages: Among a sample of young adults, higher mental toughness scores are associated with higher physical activity and above all with higher hypomania scores.

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