Biological outcome measurements for behavioral interventions in multiple sclerosis

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Abstract: Behavioral interventions including exercise, stress management, patient education, psychotherapy and multidisciplinary neurorehabilitation in general are receiving increasing recognition in multiple sclerosis (MS) clinical practice and research. Most scientific evaluations of these approaches have focused on psychosocial outcome measures such as quality of life, fatigue or depression. However, it is becoming increasingly clear that neuropsychiatric symptoms of MS are at least partially mediated by biological processes such as inflammation, neuroendocrine dysfunction or regional brain damage. Thus, successful treatment of these symptoms with behavioral approaches could potentially also affect the underlying biology. Rigidly designed scientific studies are needed to explore the potential of such interventions to affect MS pathology and biological pathways linked to psychological and neuropsychiatric symptoms of MS. Such studies need to carefully select outcome measures on the behavioral level that are likely to be influenced by the specific intervention strategy and should include biomarkers with evidence for an association with the outcome parameter in question. In this overview, we illustrate how biological and psychological outcome parameters can be combined to evaluate behavioral interventions. We focus on two areas of interest as potential targets for behavioral interventions: depression and fatigue.

Keywords: biomarkers, depression, fatigue, multiple sclerosis, behavioral interventions, cortisol, magnetic resonance imaging (MRI), cytokines, inflammation

Behavioral interventions in multiple sclerosis

Multiple sclerosis (MS) is a demyelinating, inflammatory disease of the central nervous system (CNS) with a presumed autoimmune origin. Neuropsychiatric symptoms including anxiety, depression, fatigue, and cognitive distur- bances are very common and have a major impact on activity and participation in life. Few drugs targeting neuropsychiatric symptoms have been tested in MS and the trials conducted have yielded disappointing results for fatigue [Brown et al. 2010] or cognitive impairment [Lovera et al. 2010; Christodoulou et al. 2008]. Behavioral interventions such as psychotherapy [Thomas et al. 2006], neurorehabilitation [Khan et al. 2007], and exercise [Motl et al. 2010] have been shown to beneficially affect quality of life and symptom domains including depression, fatigue, and possibly cognitive function. In addition, emerg- ing

evidence suggests that techniques such as

meditation may be effective in decreasing depres- sion and fatigue [Grossman et al. 2010].

While an increasing body of evidence supports the efficacy of behavioral interventions as symptomatic treatments in MS, little is known about potential underlying mechanisms. As we discuss in this review, symptoms such as depression and fatigue have been shown not simply to be a psychological reaction to the burden of a debilitating disease but may be caused by certain biological aspects of MS itself. If this is the case, behavioral interventions may also have direct effects on the underlying biology.

To enhance our understanding of how behavioral interventions work in MS, it is therefore essential that clinical trials include biological measures. Inclusion of biological outcome parameters is most promising if there is already evidence that the behavioral intervention has an effect on the clinical outcome variable. When selecting a potential biomarker for behavioral intervention trials in MS, it is important to choose a parameter that meets several criteria:

a. The biomarker has to be linked to the clin- ical outcome variable of interest, either symptom-related (e.g. depression, fatigue, cognitive impairment) or a measure of disease activity (MRI activity, relapse, or dis- ability progression).

b. The biological outcome parameter has to be modifiable, and has to be modifiable in the desired direction. For example, genetic mar- kers might be useful as biomarkers of neuro- psychiatric symptoms or as indicators of treatment response but are not suitable as outcomes.

c. The biomarker has to be reliably and objec- tively measurable.

d. The duration of the study has to be suffi- ciently long with an appropriate number of assessments for the biological and clinical outcome parameters to change. For exam- ple, if the outcome parameters are highly dynamic, such as markers of inflammation, shorter interventions with more frequent assessments may be most appropriate. For markers of degenerative processes (such as disability, cognitive function, and markers of brain damage such as atrophy), longer study periods will be required.

In the current review, we propose biological out- come parameters for two highly relevant symp- tom domains in MS: depression and fatigue.

Pathogenesis of MS-related depression

Patients with MS frequently suffer from depres- sion. In this population, the point prevalence for major depressive disorder (MDD) has been esti- mated as between 13% and 30% with a lifetime risk of up to 50% [Siegert and Abernethy, 2005]. Depression in MS is associated with cognitive impairment [Heesen et al. 2010; Feinstein, 2006], negatively affects work performance [Vickrey et al. 1995] and decreases quality of life [Jonsson et al. 1996]. Importantly, depression can decrease treatment compliance [Mohr et al. 1997] and is one of the strongest predictors of suicide [Feinstein, 1997]. Despite the high clini- cal relevance, depression remains underdiag- nosed and undertreated in MS [Goldman, 2005].

Depression as a response to MS diagnosis or therapy? One obvious possibility is that the high rate of depression may simply reflect a psychological reaction to a chronic debilitating disease with

an unpredictable disease course. However, depression in MS is not related to the severity of neurological impairment [Moller et al. 1994], and can occur at any stage of the disease [Sullivan et al. 1995]. Early studies had suggested that depression may be induced by disease-modifying drugs such as interferon beta (IFNb). The occur- rence of depression after IFNb therapy was later found to be better explained by a previous history of depression [Feinstein et al. 2002]. Therefore, biological aspects of the disease itself may at least in part be responsible for the high prevalence of depression in MS.

Neurobiology of depression

Potential biological substrates of MS depression remain poorly understood (see Pucak et al. [2007] for a review). Lessons, however, may be learned from clinical and preclinical studies of idiopathic depression in psychiatry. It has become clear that the classical ‘monoamine hypothesis’ of depression is too simplistic and current pathogenetic concept of depressive disor- ders include a range of neurobiological mecha- nisms (see Krishnan and Nestler [2008] for a review). A large body of evidence has impli- cated hypothalamic pituitary adrenal (HPA) axis hyperactivity in depression [Pariante and Lightman, 2008]. Preclinical models suggest that stress and excess glucocorticoid levels may cause cellular and molecular changes in the CNS, possibly mediated by reduction of brain- derived neurotrophic factor (BDNF) [Duman and Monteggia, 2006]. These mechanisms are thought to contribute to damage in suscep- tible brain areas such as the hippocampus [Macqueen and Frodl, 2011]. The hippocampus plays a crucial role for learning, mood regulation and HPA axis control, and hippocampal atrophy is frequently observed in MDD [Koolschijn et al. 2009]. Additional biological substrates of depres- sion may include inflammatory pathways [Dantzer et al. 2008] or disturbed energy homeo- stasis involving leptin and grehlin [Krishnan and Nestler, 2010].

Neuroanatomical substrates of MS depression

Owing to the widespread CNS involvement in MS, damage to brain regions involved in mood regulation is a promising candidate for biological correlates of MS-associated depression. Some studies using magnetic resonance imaging (MRI) have reported associations of MS depression with lesion load in frontal, parietal, or temporal areas [Feinstein et al. 2004; Zorzon et al., Bakshi et al. 2000a]. However, studies have rarely implicated the same region and others have failed to show an association altogether [Zorzon et al. 2002]. More consistent correla- tions have been found with regional atrophy, in particular in the temporal lobe [Feinstein et al. 2004; Zorzon et al. 2002, 2001]. Using advanced imaging techniques, Feinstein and col- leagues have found that subtle white and gray matter abnormalities in frontal and temporal regions are linked to depression in MS [Feinstein et al. 2010]. Together, these studies suggest that brain areas, particularly in the tem- poral lobe, may play an important role in MS-related depression.

A neuroendocrine limbic pathology of MS-related depression? Hyperactivity of the HPA axis [Pariante and Lightman, 2008] and hippocampal atrophy [Koolschijn et al. 2009] are among the most consistently reported biological abnormalities in idiopathic MDD. Interestingly, HPA axis hyper- activity is detectable in up to 50% of MS patients [Heesen et al. 2007] and gene variants involved in HPA axis regulation have recently been associ- ated with MS [Briggs et al. 2010]. HPA axis hyperactivity in MS is associated with progressive disease and global neurodegeneration [Gold et al. 2005; Heesen et al. 2002; Schumann et al. 2002; Then Bergh et al. 1999]. One study recently demonstrated that subtle increases in HPA axis activity are already detectable in early disease stages [Ysrraelit et al. 2008].

Significant associations between HPA axis activ- ity and depressive symptoms have been reported in relapsing remitting (RR) MS patients during relapse [Fassbender et al. 1998] but not in mixed groups that included relapsing and progressive patients [Then Bergh et al. 1999]. In RRMS during remission, higher levels of depressive symptoms (as defined by a cut-off on the Beck Depression Inventory II [BDI-II]) are associated with normal morning cortisol but elevated eve- ning cortisol compared with age- and sex- matched healthy controls, indicating insufficient negative feedback during the circadian nadir [Gold et al. 2010]. Recently, this has been con- firmed in a sample of RRMS patients who met diagnostic criteria for current MDD: normal morning but elevated evening cortisol levels were found in MS patients with comorbid MDD compared to nondepressed MS patients [Gold et al. 2011].

Hippocampal damage and loss of volume is observable in MS patients [Dutta et al. 2011; Benedict et al. 2009; Papadopoulos et al. 2009; Sicotte et al. 2008; Geurts et al. 2007, 2006] as well as its animal model, experimental autoim- mune encephalomyelitis (EAE) [Ziehn et al. 2010; Sajad et al. 2009]. Supporting a neuroen- docrine limbic link of MS-associated depression, smaller hippocampal volumes, particularly in the cornu ammonis (CA) 2 3 and dentate gyrus (DG) subfields, are associated with elevated levels of depressive symptoms as well as increased evening cortisol [Gold et al. 2010]. This is of

par- ticular interest because the CA2 3 fields are most susceptible to damage by prolonged cortisol treatment in primates [Sapolsky et al. 1990]. In rodents, high levels of endogenous glucocorti- coids have effects localized to the CA3 region of the hippocampus [Conrad, 2008] and chronic stress has been shown to cause retraction of den- drites in the CA3 and decrease neurogenesis in the DG [McEwen, 1999]. These observations are in line with reports from experimental models and clinical studies of idiopathic MDD. However, as will be discussed later, there are also some intriguing differences in neuroendo- crine limbic correlates of idiopathic MDD and MS depression.

Are neurobiological substrates of MS depression modifiable? There is ample evidence from psychiatric studies that HPA axis abnormalities in MDD can be modified by antidepressive therapy [Mason and Pariante, 2006]. Similarly, a normalization of HPA axis reactivity has been described in MS patients treated with the antidepressant moclobe- mide [Then Bergh et al. 2001]. Intriguingly, new evidence suggests that in addition to normaliza- tion of HPA axis responses, successful therapy of depression may also be able to reverse volume loss in brain areas such as the hippocampus. Based on experimental data in rodents and pri- mates, smaller hippocampal volumes in MDD had long been thought to be mediated by neuro- nal apoptosis [Sapolsky, 2000] or by decreasing neurogenesis [Henn and Vollmayr, 2004]. However, postmortem studies failed to show sig- nificant neuronal apoptosis in the hippocampus of patients with MDD and the effect on neuro- genesis is likely too small to account for the con- siderable decreases in hippocampal volume [Czeh and Lucassen, 2007]. Thus, it has recently been proposed that hippocampal atrophy in depression is mediated by potentially reversible mechanisms (e.g. reduced extracellular fluid con- tent, cellular shrinkage, and dendritic retraction) rather than neuronal apoptosis [Czeh and Lucassen, 2007]. Interestingly, dendritic remodeling is also likely to most strongly affect the CA3 and DG since incoming fibers from the entorhinal cortex to the dentate gyrus are rami- fied several hundredfold between the dentate gyrus and CA3 pyramidal neurons, making this an area of particularly dense synaptic connections [McEwen, 2003].

In line with this hypothesis, cross-sectional evi- dence suggestive of normal volumes in the CA23DG subregions of the hippocampus and normal HPA axis functioning MS patients suc- cessfully treated with selective serotonin reuptake inhibitors (SSRIs) has been found [Gold et al. 2010].

Similar cross-sectional observations have been reported for total hippocampal volume in psychi- atric patients with MDD [Sheline et al. 2003]. Although this should be interpreted with caution, it is consistent with some longitudinal data show- ing that SSRI therapy could potentially reverse hippocampal volume loss in posttraumatic stress disorder (PTSD) [Vermetten et al. 2003]. However, two small longitudinal studies in MDD showed inconsistent findings [Colla et al. 2007; Vythilingam et al. 2004]. In line with reversibility of glucocorticoid (GC)-induced hip- pocampal damage, increases in hippocampus volume have been observed in Cushing's patients after surgical

normalization of HPA axis activity [Starkman et al. 2003, 1999].

Alternatively, certain subtypes of depression that are not associated with hippocampal volume loss may be more responsive to pharmacological ther- apy, as has been shown for idiopathic MDD [Macqueen and Frodl, 2011]. The possibility to reverse hippocampal atrophy in depressed subjects, both with idiopathic MDD as well as MS-associated depression, should thus be inves- tigated in adequately powered longitudinal studies. In this regard, behavioral as well as phar- macological strategies should be evaluated.

Is MS-associated depression neurobiologically different from idiopathic MDD? There is some indirect evidence that, although HPA axis hyperactivity and hippocampal atrophy have been reported in MS-related depression as well as idiopathic MDD, the neurobiological correlates of depressive symptoms may not be identical.

Cortisol profiles in idiopathic MDD have been demonstrated to be characterized by an elevated morning, but normal evening cortisol concentra- tion [Hinkelmann et al. 2009]. A meta-analysis of 20 studies examining salivary cortisol in MDD and healthy controls showed larger group differ- ences in the morning than in evening samples [Knorr et al. 2010]. In a detailed assessment of circadian cortisol over a 24-h period in a small sample of well-characterized depressed inpa- tients, the largest effect sizes with the highest spe- cificity and sensitivity for MDD were found in the morning between 10:00 and 12:00 [Paslakis et al. 2010]. Conversely, depression in MS patients is linked to elevated evening concentra- tions, but normal morning cortisol secretion [Gold et al. 2011, 2010].

The circadian peak levels of cortisol release are mostly dependent on low-affinity glucocorticoid receptors (GRs), while high-affinity mineralocor- ticoid receptors (MRs) are most important for the regulation of the circadian trough of cortisol secretion. The differential alterations in cortisol profiles may thus suggest that depression in MS is associated with relative MR dysfunction but normal GR function.

In contrast, we hypothesize that in psychiatric patients with MDD, MR signaling is largely intact while GR signaling is disturbed. Decreased GR expression has been shown in postmortem tissue from MDD patients in frontal and temporal brain regions, although notably not in the hippocampus [Webster et al. 2002]. In addition, functional tests of the HPA axis in vivo and immune cells in vitro have indicated GR dysfunction in MDD [Marques et al. 2009]. Some studies suggest intact or even enhanced MR expression and signaling in this population [Juruena et al. 2010, 2009, 2006; Wang et al. 2008; Young et al. 2003], although severe depres- sion leading to suicide [Lopez et al. 1998] or treatment-resistant depression [Juruena et al. 2009] may also be linked to MR dysfunction.

In idiopathic MDD, studies using hippocampal surface mapping techniques have found evidence for hippocampal volume loss mostly clustered in the subiculum as well as the

CA1 [Ballmaier et al. 2008; Posener et al. 2003]. In contrast, reduced volumes in the CA2 3 and DG subfields in depressed RRMS patients have been reported utilizing high-resolution manual tracings of ana- tomically defined hippocampal subregions [Gold et al. 2010]. Intriguingly, within the human hip- pocampus, MR are highly expressed in the den- tate gyrus and CA2-3 but at significantly lower levels in CA1 [Seckl et al. 1991].

While this suggests distinct subregional hippo- campal substrates and a selective dysfunction of MR and GR in MS-associated and idiopathic depression, this has not been tested directly.

If indeed biological substrates of MS depression (see Box 1) differ from those of idiopathic MDD, a different clinical phenotype of MS depression may be expected. This has rarely been investi- gated. However, it has been hypothesized that MS depression tends to be characterized by per- vasive mood changes, diurnal variation in mood, and suicidal ideation among others [Rickards, 2005]. Depression is one of the strongest pre-dictors of suicide in MS [Feinstein, 2002, 1997]. The suicide rate in MS may be as high as 15% [Giannini et al. 2010], which appears to be higher than in idiopathic MDD [Bostwick and Pankratz, 2000]. Pharmacotherapy is moderately effective in MS depression [Goldman, 2005] but there are no comparative studies with treatment response in idiopathic MDD. In general, depres- sion in medical populations has lower treatment response and remission rates compared with patients without comorbidity [Otte, 2008]. Specific features of clinical phenotype in MS-associated depression compared with idio-pathic MDD have not been well studied and it is unknown whether they correlate with the bio- logical substrates.

Biology of MS-related fatigue

Both physical and mental fatigue are experienced by up to two thirds of MS patients and are often perceived as the most debilitating symptoms [Stuke et al. 2009; Fisk et al. 1994]. Fatigue is commonly being described as an overwhelming feeling of exhaustion or weakness during exercise and a complete lack of energy. Importantly, fati- gue represents the leading cause for absence from work [Smith and Arnett, 2005]. Symptoms of fatigue seem to be strongly linked to a reduction in the quality of life of those affected, indepen-dent of physical disability [Chaudhuri and Behan, 2004].

The pathological mechanisms responsible for the high frequency in MS are still unknown. An early study found no evidence that conduction block in the patients' central motor pathways was linked to complaints of fatigue in MS [Sheean et al. 1997].

Sympathetic nervous system dysfunction

Autonomic dysfunction including cardiovascular abnormalities is often seen in MS. It has been hypothesized that dysregulation of the sympa- thetic nervous system (SNS) might partially account for development of fatigue in the sense of an impairment of sympathetic

vasomotor activity [Flachenecker et al. 2003]. In another study, autonomic dysregulation has been observed to be associated with symptoms of fati- gue only in a subgroup of MS patients [Merkelbach et al. 2001]. The authors therefore concluded that the autonomic cardiovascular system was of minor relevance to MS fatigue. Sympathovagal imbalance has been suggested to play a role for the development of chronic fatigue syndrome (CFS), an ill-defined condition pre- sumably linked to impaired bodily clearance of inflammatory stimuli. In MS, Egg and colleagues were not able to find an association between fati- gue and pupillary unrest, which is tightly linked to wakefulness and the ascending arousal system of the body [Egg et al. 2002]. Keselbrener and colleagues found evidence for an impairment of the sympathovagal balance response to standing in patients with MS who experienced fatigue and suggested premature reduction in vagal activity in these patients [Keselbrener et al. 2000].

Structural brain damage or dysfunction

Early studies using MRI studies have failed to find any consistent link between fatigue and quantification of MS lesion load or localization [Bakshi et al. 1999; Mainero et al. 1999; van der Werf et al. 1998]. However, more recently, lesion load in parietotemporal and frontal regions was found to be correlated with fatigue [Sepulcre et al. 2009]. A number of studies support a role for structural damage of both gray and white matter structures for fatigue [Pellicano et al. 2010; Penner and Calabrese, 2010; Sepulcre et al. 2009; Tedeschi et al. 2007; Codella et al. 2002]. One longitudinal study could demonstrate that fatigue may predict global atrophy progres- sion [Marrie et al. 2005].

Functional imaging studies in MS fatigue have supported the hypothesis of cortical reorganiza- tion in MS fatigue, characterized by increased ipsilateral and contralateral activation [Filippi et al. 2002]. Studies using functional MRI (fMRI) and positron emission tomography (PET) have shown associations of fatigue with altered cerebral activation patterns and glucose metabolism indicating hypofunction in frontos- triatal, motor areas, limbic structures, and the basal ganglia [Tellez et al. 2008; Marrie et al. 2005; Filippi et al. 2002; Bakshi et al. 1999; Roelcke et al. 1997].

Neuroendocrine abnormalities

Some studies in non-MS patients with CFS [Van Houdenhove et al. 2009; Van Den Eede et al. 2007] suspected abnormalities in neuroendo- crine systems such as the HPA axis to be linked to the development of fatigue. In addition, administration of pharmacological doses of corti- sol has been found to ameliorate symptoms tran- siently in CFS patients [Cleare et al. 1999]. Still, there is no consistent evidence for a specific dys- function of the HPA axis [Cleare, 2003] in CFS. Consequently in the case of MS-related fatigue involvement of the HPA axis has been hypothe- sized and tested. Gottschalk and colleagues reported MS patients with fatigue to exhibit enhanced HPA axis activity, shown by signifi- cantly increased adrenocorticotropic hormone (ACTH) concentrations after administration of dexamethasone [Gottschalk et al. 2005]. This could however not

be confirmed in a later study using the combined dexamethasone CRH sup- pression test [Heesen et al. 2006]. Tellez and col- leagues found no changes in circulating cortisol levels comparing fatigued and nonfatigued MS patients [Tellez et al. 2006]. This latter study, however, revealed an interesting association between fatigue and low serum levels of dehydro- epiandrosterone (DHEA), a cortisol antagonist with anti-inflammatory properties, and dehydro- epiandrosterone sulfate (DHEAS). A small study has also suggested a contribution of low levels of melatonin in MS fatigue [Sandyk and Awerbuch, 1994].

Cytokines

A large body of evidence from animal studies sug- gests that cytokines, both endogenous and exog- enous, can induce fatigue-like symptoms in animals [Miller et al. 2009]. Here, cytokines including interleukin (IL) 1a, IL-1b, IL-6, tumor necrosis factor (TNF) a and IFNg are involved in the induction of so-called 'sickness behavior'.

In line with this hypothesis, Flachenecker and colleagues have provided evidence for a link between increases in TNFa mRNA in immune cells and MS fatigue [Flachenecker et al. 2004]. This association was later confirmed at the pro- tein level by Heesen and colleagues who reported higher TNFa and IFNg production in vitro by MS patients suffering from fatigue [Heesen et al. 2006]. In this study, TNFa production was significantly correlated with daytime sleepi- ness. More recently, higher frequency of IFNg and TNFa producing CD8 T cells was shown to correlate with measures of fatigue [Gold et al. 2011].

It appears that these associations are specific to peripheral cytokines rather than linked to inflam- matory markers in general. For example, no asso- ciation was found between MS fatigue and serum C-reactive protein (CRP), soluble intercellular adhesion molecule-1 (sICAM-1), and urinary neopterin excretion [Giovannoni et al. 2001]. In addition, there exists no evidence that CNS inflammation as measured by gadolinium enhancing lesions is linked to fatigue [Marrie et al. 2005].

The importance of dissecting fatigue from depression Fatigue and depression often co-occur in MS and most studies report moderate correlations between these symptoms [van der Werf et al. 2003; Voss et al. 2002; Bakshi et al. 2000b; Ford et al. 1998; Schwartz et al. 1996]. This sug- gests that while linked in MS, fatigue and depres- sion may be mediated by at least partially independent pathological mechanisms. Of note, the association seems to differ between the differ- ent components of fatigue, with depression being more closely related to mental fatigue than phys- ical fatigue [Ford et al. 1998].

Animal studies suggesting a role of cytokines for sickness behavior [Raison et al. 2006] may have relevance for both depression and fatigue in MS and could explain the partial overlap. 'Neuropsychiatric symptoms' such as anorexia, loss of body weight, reduced

social exploration, and decreased preference for sucrose solution have been demonstrated in the animal model of MS, EAE [Pollak et al. 2000], were associated with inflammatory mediators including TNFa and IL-1b [Pollak et al. 2003a], and responded to anti-inflammatory medication [Pollak et al. 2003b]. One recent study suggests that in MS,

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HPA abnormalities are correlated with affective symptoms of depression while INFg and TNFa are more closely associated with measures of fati- gue than with depression [Gold et al. 2011]. Low levels of melatonin have been reported to be a potential biomarker for MS depression [Akpinar et al. 2008] as well as for MS fatigue [Sandyk and Awerbuch, 1994]. Unfortunately, neither of these studies explored differential association of fatigue or depression with melatonin. Future studies should aim to better differentiate between depression (see Box 1) and fatigue (see Box 2), both biologically as well as phenomenologically.

Behavioral interventions as putative disease- modifying therapies in MS As reviewed above, there is an increasing body of evidence that depression and fatigue are linked to biological substrates and that behavioral inter- ventions can be effective in ameliorating the neu- ropsychiatric symptoms. Some of these substrates such as regional brain atrophy or mar- kers of inflammation are also thought to be rele- vant in MS pathogenesis or progression [Sospedra and Martin, 2005]. Thus, behavioral interventions might not only be relevant as symp- tomatic treatments but could also represent puta- tive disease-modifying therapies. However, to date, there is very little direct evidence for this

possibility since behavioral intervention studies have rarely obtained biological markers. One small study showed that successful treatment of MS depression (either pharmacologically or with psychotherapy) can reduce IFNg production by OKT3 or MBP-stimulated immune cells [Mohr et al. 2001]. Two small trials showed a beneficial effect of antidepressive pharmacotherapy on enhancing lesions [Mostert et al. 2008] and pos- sibly gray and white matter integrity [Sijens et al. 2008]. Since behavioral and pharmacological therapies are comparably effective in MS depres- sion, the effect of psychotherapy on lesion load and atrophy should be explored in future studies. A randomized controlled trial with 150 patients using patient education showed a decreased relapse rate in the intervention group [Kopke et al. 2009]. However, no biological or paraclini- cal markers of disease activity were obtained, so this should be interpreted with caution.

A large body of evidence from preclinical and clinical studies suggests that exercise may have beneficial effects on cognition and possibly underlying neuroanatomical substrates [Hillman et al. 2008]. In line with this literature, one recent cross-sectional study indicated that higher physi- cal fitness levels in MS are associated with gray matter volume and white matter integrity in MS

Box 1. Biological substrates of depression suitable as outcome measures.

Markers of hypothalamic pituitary adrenal (HPA) axis activity, preferably circadian profiles over at least 2 days with at least three assessments: awakening, midday (11:00 15:00), and evening (20:00 22:00). A low-dose oral dexamethasone suppression test may provide a helpful functional estimate of HPA axis feedback regulation. In vivo and in vitro tests using selective agonists and antag- onists of glucocorticoid receptor (GR) and mineralocortcoid receptor (MR) may help to better understand the molecular mechanisms underlying HPA axis dysregulations in multiple sclerosis (MS) depression.

MRI markers of brain areas involved in mood regulation and neuroendocrine control, most importantly the hippocampus and frontal areas. It is advisable to use advanced imaging techniques such as diffusion tensor imaging [Feinstein et al. 2010] or high-resolution volumetric analyses [Gold et al. 2010; Sicotte et al. 2008] since the reported brain abnormalities in MS depression are subtle and are likely not detectable with conventional MRI.

Box 2. Biological substrates of fatigue suitable as outcome measures.

Inflammatory markers, peripheral rather than central. Most promising candidates are cytokines such as tumor necrosis factor (TNF) a and interferon (IFN) g, which have been linked to fatigue in several chronic disorders including multiple sclerosis (MS), cancer, and hepatitis and might thus represent a common pathway for fatigue symptomatology.

Markers of brain activation associated with MS fatigue using functional magnet resonance imaging (fMRI) may be useful, particu- larly in short term studies. However, the evidence of increased activation networks as a correlate of fatigue is not conclusive. While in early stages there might be efficient compensatory coactivation (without fatigue), this may evolve into inefficient recruitment in later stages (with fatigue) and finally loss of activation in advanced MS (with fatigue). Outcome measures including regional atrophy in gray matter structures such as the basal ganglia [Pardini et al. 2010] may be promising if the intervention is long enough (>1 year) to reasonably expect a change in these markers. More sensitive nonconventional MRI techniques such as diffusion tensor imaging of white matter structures or spectroscopy may be able to detect changes in short-term trials.

Markers of sympathetic function such as blood pressure responses or serum catecholamine levels to the isometric hand-grip (IHG) exercise [Khurana and Setty, 1996] or to active change of posture [Flachenecker et al. 2001].

[Prakash et al. 2010]. Exercise has been shown to partially prevent neuronal damage in EAE, the animal model of MS [Rossi et al. 2009].

There is also some cross-sectional [Luders et al. 2009] as well as preliminary longitudinal evi- dence [Holzel et al. 2008] that meditation may positively affect hippocampal volumes in healthy controls. Given the effect of meditation on depression and fatigue in

MS [Grossman et al. 2010] and the involvement of subregional hippo- campal atrophy in MS depression [Gold et al. 2010] these studies are in line with the possibility that meditation may affect regional atrophy in MS.

In summary, there are indications for the poten- tial of behavioral interventions to affect MS pathology, but the few available trials have been conducted in very small samples of subjects and should be interpreted with caution. Adequately powered longitudinal studies with sensitive and pathologically relevant outcome measures are largely lacking. However, we believe that there is now sufficient indirect evidence to start testing the effect of behavioral interven- tions on disease-related endpoints such as those used in drug trials. A number of prospec- tive studies have consistently indicated that psy- chological stress increases relapse risk in MS [Mohr et al. 2004], so interventions targeted at reducing stress may have the potential to affect disease activity in MS. A large randomized controlled study by Mohr and colleagues [ClinicalTrials.gov identifier: NCT00147446] using a stress management intervention has recently been completed. The primary endpoints in this study are enhancing lesions on MRI and relapse rate and results are expected shortly. Only rigidly designed trials like this will ultimately tell if behavioral interventions can affect MS pathology.

Conclusion

Despite the high clinical relevance of neuropsy- chiatric MS symptoms, their pathogenetic sub- strates are still poorly understood. This may in part explain the disappointing results of clinical trials for novel symptomatic drug therapies. Thus, it is paramount to enhance our knowledge of the underlying neurobiology of these symp- toms. This is a prerequisite for designing new therapies, both pharmacological as well as behav- ioral, and essential for better monitoring their effectiveness in clinical trials.

Some evidence suggests behavioral interventions to affect biological pathways of neuropsychiatric MS symptoms and possibly disease mechanisms as well. These interventions thus may have ther- apeutic potential, not only as a symptomatic treatment but also as putative disease-modifying therapies. However, few adequately powered and well-designed studies have tested behavioral ther- apies in MS and even fewer have included bio- markers that could help to better understand the mechanisms underlying the therapeutic benefits.

More translational and interdisciplinary research in this area is urgently needed to expand the treatment repertoire for patients, particularly those in the progressive phase of the disease, who currently have few therapeutic options but may benefit from behavioral interventions.

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Conflict of interest statement

None declared.

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