Journal of Neurology (2021) 268:45–60
https://doi.org/10.1007/s00415-019-09426-6

REVIEW

Psychiatric disorders in multiple sclerosis

Maddalena Sparaco[1] · Luigi Lavorgna[1] · Simona Bonavita[1,2,3]

Received: 5 March 2019 / Revised: 6 June 2019 / Accepted: 7 June 2019 / Published online: 13 June 2019

Abstract

Background Multiple sclerosis (MS) is characterized by a large spectrum of symptoms, involving all functional systems. Psychiatric symptoms are common in people with MS (pwMS) having an important impact on quality of life and on some features of MS (fatigue, sleep, disability, adherence to disease-modifying drugs). The main psychiatric disturbances in MS are depressive, bipolar, anxiety, schizophrenic and obsessive–compulsive syndromes.

Methods Literature search for original articles and review in the databases, including PubMed and Scopus from 1959 to 2019.

Results and conclusion Studies answering the aim of this review were selected and reported. Epidemiological and clinical aspects of psychiatric syndromes (PS) in MS as well as self-report diagnostic scales and radiological correlates of PS in MS are described. Moreover, some radiological studies about primary psychiatric disorders (PD) are reported to underline how gray matter atrophy, white matter abnormalities and corpus callosum involvement in these diseases, as features in common with MS, may explain the more frequent occurrence of PD in MS than in the general population.

Keywords Multiple sclerosis · Psychiatric disorders · Magnetic resonance imaging · Quality of life · Self-report scale

Introduction

Multiple sclerosis (MS) is a multifactorial demyelinating disease of the central nervous system [1], characterized by a large spectrum of symptoms and signs, involving several functional systems (pyramidal, cerebellar, sensory, brainstem, bowel and bladder, visual, mental, ambulation) [2].

Psychiatric symptoms are common in people with MS (pwMS) and were already described by Charcot [3] and investigated also in encephalomyelitis disseminate [4]. Over time, attention has been focused on epidemiological, clinical and radiological aspects of psychiatric syndromes (PS) in MS.

✉ Simona Bonavita
simona.bonavita@unicampania.it

Luigi Lavorgna
luigi.lavorgna@unicampania.it

[1] Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Piazza Miraglia, 2, 80138 Naples, Italy

[2] MRI Research Center SUN-FISM, University of Campania "Luigi Vanvitelli", Naples, Italy

[3] Institute for Diagnosis and Care "Hermitage Capodimonte", Naples, Italy

Among PS, mood disturbances (MD) are the most common; they are more frequent in pwMS compared to the general population; indeed, pwMS have an higher annual prevalence ratio of depressive (1.77; 95% confidence interval [CI] 1.64, 1.91), and anxiety (1.46; 95% CI 1.35, 1.58) symptoms, compared to people matched for socioeconomic status, age, sex, and region of residence [5]. Several factors, including disability [6], adjustment to illness [7], and social support [8] may influence the relationship between MD and MS.

Moreover, several studies investigated the correlation between MD and MS treatment, as adverse events [9, 10]. Indeed, some disease-modifying treatments (DMTs), especially interferon beta, had been blamed to unmask depressive symptomatology [11]. However, other studies demonstrated that previous treatment of depressed mood could be a predictor of subsequent development of depressive syndrome during treatment with DMTs [12, 13].

Because development of depression and anxiety under DMTs may reduce therapeutic adherence [14, 15], diagnosis and treatment of MD in pwMS are necessary to improve patient's compliance [16].

Furthermore, in pwMS, MD as depression and anxiety are reported to be associated with a worsening of quality of life (QoL) [17, 18] and an increase of fatigue [19].

PwMS have also a significant tendency to substance abuse ranging from 3.96% to 18.2% for alcohol abuse and dependence and from 2.5 to 7.4% for drugs abuse [20, 21].

Only few studies reported the prevalence of PS in pediatric MS population; Goretti et al. [22] assessed psychosocial disorders in 56 Italian children and adolescents with MS (mean age: 17.2 ± 2.5). 30% of enrolled children and adolescents with MS received a formal diagnosis of affective disorder: depressive (15%), anxiety (5%), panic (5%) and bipolar (5%) syndrome. The authors also investigated about the influence of MS on daily-life: MS affected school activities in 28% of cases, daily living activities in 41% and social relationships in 28%. In this study, one-third of the enrolled children and adolescents showed behavioral changes, particularly aggressiveness and tendency to isolation, with impairment of social relationship, poor school performances, often requiring a support teacher.

This review aims to examine epidemiological, clinical and radiological aspects of PS as part of MS (not as true comorbidity) and their impact on QoL of pwMS; furthermore, the main evaluation scales validated for PS in MS are reported.

Materials and methods

A literature search for articles from 1959 to 2019 was conducted in the databases, including PubMed and Scopus using the following Medical Subject Headings (MeSH) terms and key words (also in combination): "multiple sclerosis", "Encephalomyelitis disseminate" "psychiatric disorders", "depression", "anxiety", "bipolar disorders", "schizophrenia", "obsessive–compulsive disorders", "suicide" "Beck Depression Inventory-II", "Chicago Multiscale Depression Inventory", "Hospital Anxiety and Depression Scale", "Center for Epidemiologic Studies-Depression scale", "Patient Health Questionnaire nine-item", "Patient Reported Outcome Measurement Information System", "Hamilton Anxiety Rating Scale", "Beck Anxiety Inventory", "State-Trait Anxiety Inventory", "7-item Generalized Anxiety Disorder Scale", "Mood Disorder Questionnaire", "magnetic resonance imaging", "quality of life". Relevant articles were identified and located individually in PubMed/MEDLINE to examine citing and cited-by articles. Studies answering the aim of this review were selected and reported.

Depressive syndrome

The most common MD in MS is the depressive syndrome with a prevalence ranging from 30.5% (95%, CI 26.3–35.1%) [23] to 31.7% (95% CI 29.8–33.5%) in pwMS compared to 20.5% (95% CI 19.8–21.2%) in the general population (PR 1.60; 95% CI 1.41–1.82) [24]. The prevalence peak is 45–59 years both in pwMS and in general population [24].

Validated scales for MS-related depression assessment

Some validated scale, including Beck Depression Inventory-II (BDI-II) [25], Chicago Multiscale Depression Inventory (CMDI) [26], Hospital Anxiety and Depression Scale (HADS) [27], Center for Epidemiologic Studies-Depression scale (CES-D) [28], Patient Health Questionnaire nine-item (PHQ-9) [29], Patient Reported Outcome Measurement Information System (PROMIS) [30, 31], Hamilton Depression Rating Scale (HDRS) [32] are used to evaluate depression in MS.

BDI-II is a 21-item self-report scale of depressive symptoms, including somatic and cognitive-affective symptoms [25]. Each item is rated on 4-point, ranging from 0 to 3. The total score is obtained by summing the ratings for the 21 items: 0–13 indicates no depression, 14–19 mild depression, 20–28: moderate depression, 29–63: severe depression. This scale has been validated either in pwMS since several years [33] or in people with recent diagnosis of MS (BDI cut-off score of 13 had sensitivity = 0.71, specificity = 0.79) [34].

CMDI is a 42-item self-reporting questionnaire with three subscales: mood, evaluative, and vegetative symptoms [26]. Nyenhuis et al. suggested that only mood subscale may be recommended for assessing depression in pwMS, because it may be considered the best one to estimate prevalence rates rather than total CMDI score (no-mood subscales in total CMDI score could overestimate both the prevalence and severity of MS related depression) [35]. Comparing the three most used self-report scales of depressive symptoms (BDI–II; BDI-Fast Screen; CMDI) in pwMS and also interviewing patients with the Structured Clinical Interview for DSM-IV disorders, Strober et al. [36] suggested for CMDI mood a cut off of 23 (100% of sensitivity and 81% of specificity), and for CMDI evaluative a cut off of 22 (73% of sensitivity and 90% of specificity).

HADS is a 14-item self-report scale to evaluate anxiety and depression symptoms [27]. It has two subscales: HADS–A for anxiety and HADS–D for depression [37]. HADS-D is the 7 item subscale of HADS, and each item is rated on 4 point Likert scale. For HADS-D, higher scores indicate worse self-reported depression. Honarmand et al. [38], validated HADS in pwMS and identified a cut-off score of 8 for the HADS-D subscales with a 90% sensitivity and 87.3% specificity (all pwMS were also interviewed with the Structured Clinical Interview for DSM-IV disorders).

CES-D [28] is a 20-item scale of depressive symptoms that has also been validated in pwMS [39]. Each item is rated on 4-point, ranging from 0 (rarely or none of the time) to 3 (most of or all the time). It is based on the

evaluation of four factors (positive affect, negative affect, somatic complaints and retarded activity, interpersonal relationships). CES-D 10 is a short version of the 20-item CES-D, with good predictive accuracy. Andersen et al. [40] identified a cut-off score of 16 for CES-D 20, and of 10 for the short version.

PHQ-9 [29] is a 9-item self-report scale that investigates depressive symptoms in the last 2 weeks. The answer for each item ranges from 0 (not at all) to 3 (nearly every day), and the total score can range from 0 to 27. Overall accuracy is 85%, sensitivity 75% and specificity 90%. Kroenke et al. [41] identified PHQ-9 score ≥ 10 to diagnose major depression (with 88% of sensitivity and 88% of specificity). In the same study, the authors suggested PHQ-9 scores of 5, 10, 15, and 20 to identify, respectively, mild, moderate, moderately severe, and severe depression. PHQ-2 is a short form of PHQ-9, including only the first two items. It could be used to screen for depression briefly. In the validation study, Koencke et al. [42] proposed a cut-off of 3 (sensitivity of 83% and specificity of 92%) to identify major depression.

PROMIS [30, 31] is a scale to investigate depressive and anxiety symptoms "in the past seven days". PROMIS-D is a 28 items questionnaire for depression, each item has 5 answer options ranging from 1 to 5 (1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Often; 5 = Always). 17 items investigate symptoms related to cognitive aspects, 9 explore the affective aspects, 1 the behavioral ones, and 1 item reflects passive suicidal ideation. The PROMIS-D-8 is the short form with eight items of the cognitive and affective categories; the total score ranges from 8 to 40. The raw scores on each item should be summed to obtain a total raw score. On T-score conversion table, the total raw score is associated with the total T-score used to evaluate severity of depression. Higher scores indicate worse depression.

The HDRS scale [32] contains 17 variables (depressed mood, guilt, suicide, initial, middle and delayed insomnia, work and interests, retardation, agitation, anxiety psychic, anxiety somatic, somatic general symptoms, somatic gastrointestinal symptoms, genital symptoms, hypochondriasis, loss of insight, loss of weight). Some are defined in terms of a series of categories of increasing intensity, while others are defined by a number of equal-valued terms. The form on which ratings are recorded also includes four additional variables: diurnal variation, derealization, paranoid symptoms, obsessional symptoms; however, although the HDRS lists 21 items, the scoring is based on the first 17. Eight items are scored on a 5-point scale, ranging from 0 = not present to 4 = severe. Nine are scored from 0–2. A score of ≤ 7 is considered to be normal (sensitivity 86.4%; specificity 92.2%).

Raimo et al. [43] assessed psychometric properties of the HDRS in a sample of non-demented italian pwMS to validate a screening instrument for grading the severity of depressive symptomatology in these patients.

The agreement between the detection of clinically relevant depressive symptoms according to cut-off score 14.5 of HDRS and diagnosis based on clinical criteria was high (overall agreement 95.7%); therefore, 14.5 is the HDRS total score with the best balance between specificity and sensitivity, and with high positive predictive value, i.e. it is the value best suited to identify pwMS with clinically relevant depressive symptoms.

Amtamann et al. [44] evaluated psychometric properties of the CES-D-10, PHQ-9, and PROMIS-D-8 in pwMS The results of this study do not support the superiority of one instrument over the others in terms of psychometric properties. Scores on all scales showed similar characteristics and their correlations were high.

Clinical features of MS-related depression

Jones et al. [45] demonstrated that depressive syndrome in MS is related to clinical phenotype (people with secondary and primary progressive MS are more depressed than relapsing remitting pwMS) and age (pwMS with age between 45 and 64 years have higher levels of depression). Depressive syndrome has an important impact on cognitive performances, fatigue, QoL, physical disability and sleep quality, therefore, treating depression in pwMS is recommended to improve these aspects [46–54].

Bakshi et al. [52] found that depression severity was significantly correlated with fatigue severity even after adjusting for disability status (at Expanded disability status scale, EDSS).

Amato et al. [53] identified depressive syndrome, fatigue and disability as significant and independent predictors of QoL in pwMS.

In a recent study, Marrie et al. [54] confirmed that depressive syndrome was associated with worse QoL, even after adjusting for age, sex, education, disability status, and physical comorbidity.

Attention has been focused on the relationship between depressive syndrome and cognitive function in MS. Cognitive impairment is frequent in MS occurring in 40–65% of pwMS [55]. It could be present early in the disease and it might be independent of physical disability [55]. Processing speed, working memory, new learning, and visual and verbal memory are the most compromised cognitive domains in pwMS [56]. Depressive syndrome could be responsible for influencing cognitive performance in pwMS, especially in worsening attention, working memory, executive functions and information processing speed [57–60]. PwMS with depression (pwMS-D) have worse cognitive measures not only compared to non-depressed healthy controls (HCs) but also to non-depressed pwMS [54–56]. In pwMS-D, compared to non-depressed pwMS and HCs, Arnett et al. [57] found significantly worse performance on a task of working

memory (reading span) ($p < 0.001$), but not on a short-term memory task (word span). Further evidence in support of this relationship comes from Diamond et al. [60] that underlined the influence of depression on processing speed, especially for more effortful tasks.

Suicide is a relevant consequence of a depressive syndrome in pwMS; epidemiological data on suicide change among different geographical area, and this variation may depend on cultural bias [61]. The standardized mortality ratio (SMR) is the most correct method to analyze suicide in MS. In pwMS, SMR for suicide is twice that of the general population [62].

Risk factors for the development of suicidal ideation include current depressive symptoms, gender (women attempt suicide more often than men, but men complete suicide more often than women [63]), young age at onset of MS, previous history of depression, social isolation, recent functional deterioration and abuse of illicit substance [64, 65].

Turner et al. [66] investigated suicidal ideation with PHQ and reported that, among 445 pwMS, 29.4% (95% CI 25.4–33.9%) reported suicide ideation and 7.9% (95% CI 5.7–10.8%) persistent suicidal ideation during the previous 2 weeks.

Strupp et al. [67] reported suicide ideation in 22.1% of 573 pwMS: of these 48.4% had a secondary progressive MS, 24.7% relapsing–remitting MS and 21.9% primary progressive MS.

Magnetic resonance imaging of MS-related depression

Many studies investigated MRI findings in pwMS with depression (pwMS-D) [68–78] (Table 1).

Table 1 Magnetic resonance imaging findings on MS-related depressive syndrome

	MRI changes in pwMS-D (compared to pwMS without depression)	Correlation between MRI findings and clinical aspects in pwMS-D*
Pujol et al. [69]		T2-LL of the arcuate fasciculus region of the left "verbal" hemisphere and BDI score
Feinstein et al. [70]	↑ T2- and T1- LL in the left inferior medial prefrontal regions ↑ atrophy of the left anterior temporal regions	
Bakshi et al. [71]		Superior frontal and superior parietal TI-LL and the presence and severity of D; lateral and third ventricular enlargement, and frontal atrophy and the severity of D
Zorzon et al. [72]		right frontal LL and right temporal brain volume and presence and severity of D
Di Legge et al. [73]		T2-LL in the right temporal region and BDI score
Feinstein et al. [74]	↓ NAWM volume in the left superior frontal region, ↑ T1-LL in the right medial inferior frontal region, ↑mean diffusivity in the NAGM of the left anterior temporal lobe region, ↓ FA in the NAWM of the left anterior temporal lobe	
Bonavita et al. [75]	↑ FC in the anterior cingulate cortex ↓ FC in posterior cingulate cortex	
Rocca et al. [76]	↓ FC between the hippocampi and: right middle temporal gyrus, left precuneus right superior orbitofrontal gyrus	
Pravatà et al. [77]	↓ cortical thickness in fronto-temporal regions	↓ thickness in frontal cortex and presence of D, ↓ thickness of right entorhinal cortex and the severity of D
van Geest et al. [78]	↓ WM volume of the uncinate fasciculus, ↓ FA of the uncinate fasciculus, ↓ FC between the amygdala and frontal regions	

*Except for Di Legge et al. [73], that considered clinically isolated syndrome (CIS) suggestive of MS

MRI magnetic resonance imaging, *D* depression, *pwMS-D* people with multiple sclerosis with depression, *LL* lesion load, *NAWM* normal appearing white matter, *NAGM* normal appearing gray matter, *FA* fractional anisotropy, *FC* functional connectivity, *WM* white matter, *CIS* clinically isolated syndrome, *DMN* default mode network, *BDI* seck depression inventory

Pujol et al. [69] reported a significant correlation between BDI scores and T2-lesion load (LL) of the arcuate fasciculus region of the left "verbal" hemisphere.

Feinstein et al. [70] detected higher T2- and T1-LL in the left inferior medial prefrontal regions and greater atrophy of the left anterior temporal regions, in pwMS-D compared to pwMS without depression. Using a logistic regression analysis, they identified two independent predictors of depression in pwMS: left medial inferior prefrontal cortex T2-LL and left anterior temporal cerebrospinal fluid volume.

Bakshi et al. [71] speculated that superior frontal and superior parietal LL and atrophy, with consequent cortical-subcortical disconnection, might play a role in determining depressive syndrome in MS.

Zorzon et al. [72] reported that the presence and severity of a depressive syndrome in pwMS were related with right frontal LL and right temporal brain volume; moreover, the severity of the depressive syndrome was correlated with total temporal brain volume and right hemisphere brain volume.

Di Legge et al. [73] showed, in patients with clinically isolated syndrome (CIS) suggestive of MS, a positive correlation between severity of depressive scores (at BDI) and T2-LL in the right temporal region.

Using diffusion tensor imaging (DTI), Feinstein et al. [74] identified, in pwMS-D, a smaller normal appearing white matter (NAWM) volume in the left superior frontal region, a greater T1-LL in the right medial inferior frontal region, a higher mean diffusivity in the normal appearing gray matter (NAGM) of the left anterior temporal lobe region, a reduced fractional anisotropy (FA) in the NAWM of the left anterior temporal lobe.

Resting-state (RS) functional-MRI (fMRI) has detected functional connectivity (FC) changes of the default mode network (DMN) in pwMS-D, both in the anterior cingulate cortex (increased FC) and posterior cingulate cortex (reduced FC). These results suggested specific features of depression in MS. Moreover, reduced FC in the posterior cingulate cortex in pwMS-D, as a similar finding in pwMS with cognitive impairment but not depressed, suggested a possible functional link between depression and cognitive impairment in MS [75].

Rocca et al. [76] using RS-fMRI identified a reduced FC between the hippocampi and cortical-subcortical regions of DMN (right middle temporal gyrus, left precuneus and right superior orbitofrontal gyrus), that strongly correlated with the severity of depression. The authors concluded that the disruption of RS-FC between hippocampal and specific region of DMN might be related to depressive syndrome occurrence.

Pravatà et al. [77] focused attention on cortical gray matter (GM) and detected in pwMS-D a reduced cortical thickness in fronto-temporal regions. The decrease of thickness in frontal cortex was the best predictor of depressive syndrome, while the reduced thickness of right entorhinal cortex was correlated with the severity of depression.

In a recent study, van Geest et al. [78] found reduced white matter (WM) volume and reduced FA of the uncinate fasciculus, decreased FC between the amygdala and frontal regions in pwMS-D compared to pwMS without depression. Because pwMS-D had a shorter disease duration than pwMS without depression, they also demonstrated that disease duration, FA of the uncinate fasciculus, and FC of the amygdala could explain 48% of variance in the severity of depression.

In conclusion, MRI studies support a structural and functional link between MS pathology and occurrence of depressive symptoms in pwMS.

Anxiety syndrome

In MS, the prevalence of an anxiety syndrome is 35.6% (95% CI 33.7–37.7%) compared to 29.6% (95% CI 28.8–30.5%) in the general population (PR 1.24; 95% CI 1.12–1.38). 45–59 years is the prevalence peak both in pwMS and in the general population [24]. Recently, Boeschoten et al. [23] reported in pwMS an anxiety prevalence of 22.1% (95% CI 15.2–31.0%).

Validated scales of MS-related anxiety

Validated scales to evaluate anxiety in MS include Hamilton Anxiety Rating Scale (HAM-A) [79], HADS [27], Beck Anxiety Inventory (BAI) [80], and State-Trait Anxiety Inventory (STAI) [81], 7-item Generalized Anxiety Disorder Scale (GAD-7) [82], PROMIS-A [30, 31].

HAM-A is a14 items scale that measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety) [79]. Each item has a score between 0 (not present) and 4 (severe), with a total score range of 0–56. A cut off < 17 indicates mild severity, 18–24 mild to moderate and ≥ 25 severe anxiety. However, it should be kept in mind that HAM-A is not sensitive to distinguish between anxiolytic and antidepressant effects and between somatic anxiety and somatic side effects [83].

HADS-A [27] is a part of HADS that evaluates anxiety symptoms. It is a 7-item subscale, and each item is rated on 4 point Likert scale. Higher total scores indicate worse self-reported anxiety. Honarmand et al. [38], validated HADS in pwMS and identified a cut-off score of 8 for the HADS-A subscales with 88.5% sensitivity and 80.7% specificity.

BAI is a 21-item self-report scale of anxiety symptoms [80]. Each item is rated on 4-point. Total score is obtained by summing the ratings for the 21 items, high score indicates severe anxiety. A score of 0–21 indicates low anxiety, 22–35

indicates moderate anxiety, ≥ 36 potentially concerning levels of anxiety.

STAI consists of two scales with 20 items each. The first scale investigates the state anxiety, while the second one explores the trait anxiety [81]. This scale has been validated in pwMS and can be a useful tool to measure the severity of anxiety. To identify high levels of state and trait anxiety in pwMS, Santangelo et al. [84] proposed three screening cut-off values (1, 1.5 and 2 standard deviations above the mean for both scales), that can be differently used depending on the aim. In this study, STAI showed good internal consistency, with Cronbach's alpha values > 0.9 (similar to previous validation studies, 0.86 for high school students).

GAD-7 is 7-items self-report scale to screen for generalized anxiety disorder. Each item is scored from 0 to 3, so the total score ranges from 0 to 21 [82]. To identify generalized anxiety disorder, Spitzer et al. [82] proposed a score of 10 as a reasonable cut-off (89% sensitivity and 82% specificity). In the same study, 5, 10, and 15 were considered as scores to indicate mild, moderate, and severe levels of anxiety. Terrill et al. [85] demonstrated good reliability and internal validity (Cronbach alpha 0.75) of the GAD-7 in MS.

PROMIS-A [30, 31] is a self-report scale to investigate anxiety symptoms "in the past seven days". Each item has 5 answer options ranging from 1 (never) to 5 (always). The raw scores on each item should be summed to obtain a total raw score. On T-score conversion table, the total raw score is associated with the total T-score used to evaluate severity of anxiety. In pwMS, Senders et al. [86] evaluated the feasibility and validity of PROMIS in detecting an anxiety syndrome and compared this scale to BDI, STAI, Modified Fatigue Impact Scale (MFIS) and Medical Outcomes Study Pain Effects Scale (PES), referring to the anxiety subscales. Good validity of PROMIS was shown for anxiety ($p = 0.09$) but also for depression ($p = 0.08$). Marrie et al. [87], investigated the validity and reliability of some anxiety scales in pwMS (HADS, PROMIS, GAD-7, OASIS). They identified that HADS-A was the test with highest sensitivity (82% with a cut-off of 8). In the above reported anxiety scales, specificity ranged from 83 to 86% (except for 68% of the HADS-A).

Clinical aspects of MS-related anxiety

Anxiety syndrome in MS is related to female gender (among people with relasping remitting MS, women are more anxious than men), younger age (pwMS with age between 15 and 24 years have higher levels of anxiety while pwMS older than 65 years have lower levels of anxiety) [45], time since MS onset (in particular, there is a significant correlation between non-somatic symptoms of anxiety and recent diagnosis of MS and between somatic symptoms and longer time since MS onset) [88].

MS diagnosis could be a risk factor to develop anxiety, indeed the prevalence of self-reported anxiety symptoms at time of MS onset is 2.7%, while it becomes 6.2% by the time of MS diagnosis [89].

There is a possible correlation between anxiety syndrome and cognitive impairment in MS, and several studies investigated this aspect [89–92]. Anxiety is associated to worse performance on objective cognitive evaluation, in particular, executive functioning, visual memory, and information processing speed could be hampered by anxiety [90–93].

Although several study investigated anxiety symptoms in pwMS, few studies on MS underlined a distinction between state and trait anxiety [84–93]. As already mentioned, STAI is the scale that distinguishes these types of anxiety in MS [84]. Goretti et al. [93] underlined a correlation between state anxiety (measured with STAI) and failure at the Symbol Digit Modalities Test ($p = 0.042$), and at the Paced Auditory Serial Auditory Test-3 ($p = 0.068$); therefore, in pwMS state anxiety may worsen performance on attention and information processing speed tasks.

Magnetic resonance imaging of MS-related anxiety

In pwMS, MRI features of anxiety have not been studied so extensively as those of depression (Table 2).

In a study on 95 pwMS, 97 people with chronic rheumatoid disease and 110 HCs, Zorzon et al. [72] did not find any correlation neither between anxiety and LL nor between anxiety and brain volume.

In a study on 37 people with CIS suggestive of MS, Di Legge et al. [73] showed no correlation neither between baseline scores for anxiety and T1- and T2-LL nor between anxiety and volume and number of Gadolinium enhancing lesions detected at monthly brain MRI during the first six months of follow-up.

The anatomic substrate of anxiety in the general population was investigated with non-conventional MRI to correlate anxiety with the involvement of several brain regions.

In people with generalized anxiety disorder (GAD), Zhang et al. detected by DTI an increased FA in the amygdala [94] and in the postcentral gyrus [95], while other authors identified a reduced FA bilaterally in the uncinate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, anterior thalamic radiation and corona radiate, in the body of corpus callosum [96, 97].

In people with GAD, a RS-fMRI study identified an intra-amygdala connectivity abnormality (basolateral and centromedial subregions connectivity patterns were significantly less distinct compared to HCs) and altered frontoparietal executive control network (significantly increased connectivity between dorsolateral prefrontal cortex and amygdala, compared to HCs) [98].

Table 2 Magnetic resonance imaging of MS-related anxiety syndrome and in generalized anxiety

	MRI changes in pwMS-As	Correlation between MRI findings and clinical aspects in pwMS-As*
Zorzon et al. [72]		No correlation between A and LL No correlation between A and brain volume
Di Legge et al. [73]		No correlation between baseline scores for A and T1- and T2-LL No correlation between A and volume and number of Gd + lesions detected at monthly brain MRI during the first six months of follow-up
	MRI changes in pwGAD	Correlation between MRI findings and clinical aspects in pwGAD
Zhang et al. [95] Zhang et al. [94]	↑FA in amygdala postcentral gyrus,	
Liao et al. [96] Wang et al. [97]	↓ FA bilaterally in uncinate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, anterior thalamic radiation corona radiate, in the body of corpus callosum	
Etkin et al. [98]	Intra-amygdala connectivity abnormality: ↓ FC in basolateral and centromedial subregions Frontoparietal executive control network abnormality: ↑ connectivity between dorsolateral prefrontal cortex and amygdala	
Qiao et al. [99]	↑ FC in left amygdala, right insula, right putamen, right posterior cingulate cortex, right thalamus, ↓ FC in left middle frontal gyrus, right superior frontal gyrus, left middle temporal gyrus, ↓ FC Between the middle frontal gyrus and amygdala and putamen, between the putamen and right superior frontal gyrus (via the thalamus)	FC in the left amygdala and the anxiety severity (measured with HAM-A)
s	MRI changes in pwPD	Correlation between MRI finding and clinical aspects in pwPD
Sobanski, et al. [100] Asami et al. [101] Lai et al. [102]	↓ GM volume in: medial prefrontal, inferior frontal orbitofrontal cortex	
Han et al. [103]	↑ FA in left anterior cingulate regions right posterior cingulate regions	Clinical severity of PD (at PD Severity Scale) and WM connectivity in the left anterior and right posterior cingulate regions
Lai et al. [104]	↓ FA in right inferior fronto-occipital fasciculus, left superior longitudinal fasciculus, left body of the corpus callosum	
Kim et al. [105]	↓ FA in frontal WM corpus callosum	FA in the frontal WM and corpus callosum and clinical severity at BAI

*Except for Di Legge et al. [73], that considered clinically isolated syndrome (CIS) suggestive of MS

Magnetic resonance imaging (MRI); anxiety (A); anxiety syndrome (As); people with generalized anxiety disorder (pwGAD); people with panic disorder (pwPD); lesion load (LL); gray matter (GM); fractional anisotropy (FA); functional connectivity (FC); white matter (WM); Hamilton Anxiety Rating Scale (HAM-A); Beck Anxiety Inventory (BAI)

Qiao et al. [99] pointed out in people with GAD, increased FC in the left amygdala, right insula, right putamen, right posterior cingulate cortex, right thalamus, and decreased FC in the left middle frontal gyrus, right superior frontal gyrus, and left middle temporal gyrus, a weaker connectivity between the middle frontal gyrus and amygdala and putamen, between the putamen and right superior frontal gyrus (via the thalamus). Moreover, in people with GAD, there is a significant positive correlation between the anxiety severity (measured with HAM-A) and the FC in the left amygdala ($r = 0.80$, $p < 0.001$).

In people with panic disorder, some authors reported the reduction of GM volume in the medial prefrontal, inferior frontal and orbitofrontal cortex [100–102].

In people with panic disorder, compared to HCs, Han et al. [103] identified by DTI, significantly increased FA in the left anterior and right posterior cingulate regions, and a positive correlation between clinical severity (measured with Panic Disorder Severity Scale) and WM connectivity of these regions; Lai et al. [104] reported a decreased FA in the WM tracts of the right inferior fronto-occipital fasciculus, left superior longitudinal fasciculus, and left body of the corpus callosum. Furthermore, tract-based spatial statistics analysis showed decreased FA (positively correlated with clinical severity at BAI) in the frontal WM and corpus callosum [105].

The link between anxiety occurrence in pwMS and WM pathology, either focal or diffuse, should be further investigated.

Bipolar syndrome

In pwMS, the prevalence of bipolar syndrome (BS) ranges from 0% to 16.2% [20]; Marrie et al. estimated an age-standardized prevalence of 5.83% (95% CI 5.01–6.65%) for BD in pwMS and of 3.45% (95% CI 3.17–3.73%) in the general population (PR 1.70; 95% CI 1.55–1.87) [24].

The Mood Disorder Questionnaire (MDQ) is widely used to screen patients most likely to have bipolar disorders and, although not validated in MS, based on clinical experience, it may also be used to evaluate BS in pwMS. It is a self-report questionnaire to screen a lifetime history of bipolar spectrum disorder symptoms, derived from the DSM-IV criteria. The first question (with 13 items) asks the presence of symptoms or behaviors of bipolar disorders in a period of time, the second question asks if some of the symptoms occurred together during the same period of time, the third evaluates the impact of bipolar behaviors on daily life. Screen for Bipolar Spectrum Disorder is considered positive when patients answer "Yes" to ≥ 7 items of the first question; "Yes" to the second question; and "Moderate" or "Serious" to the third question. This screening score was chosen for its good sensitivity (0.73, 95% CI 0.65–0.81) and good specificity (0.90, 95% CI 0.84–0.96) [106, 107].

As bipolar mood symptoms in pwMS may be subtle, the Hypomania Checklist (HCL-32) [108] might be the more reliable instrument (although not yet validated in MS); indeed, recent meta-analyses [109, 110] found that HCL-32 is one of the most accurate assessments available for detecting hypomania, The scale includes a checklist of 32 possible symptoms of hypomania, each rated yes or no. The rating "yes" would mean the symptom is present or this trait is "typical of me," and "no" would mean that the symptom is not present or "not typical" for the person. In the validation study, the cut-off value of 14 distinguished between unipolar and bipolar conditions with a sensitivity of 80.1% and a specificity of 51.4%.

Correlation between BS and MS is not clear, but there is a possible link between MS diagnosis and risk of BS onset. The topic about bipolar disorder association with some autoimmune diseases is discussed, and not clear [111].

There are some hypotheses concerning the comorbidity of MS and bipolar disorders; one hypothesis is that the disease itself may cause psychiatric manifestations, while another hypothesis suggests that both diseases have a common underlying pathophysiological process [112]. Increased oxidative stress plays an important role in the pathogenesis of both MS [113]) and bipolar disorders [114], furthermore, demyelinating lesions of pwMS occur in areas of the brain that regulate the affective functioning, emotions, and pleasure involved in bipolar disorders [115].

Marrie et al. reported a prevalence of 0.5% of BS at time of MS onset and a 1% at the time of MS diagnosis [87].

PwMS with family history of bipolar disorders have major probability of BS development, and some authors suggested a possible genetic susceptibility for both diseases [116–118]. Some drugs used for acute relapse and some symptomatic treatments in MS (corticosteroid, baclofen and psychoactive substances) may trigger the onset of bipolar symptoms [109–121]. Therefore, it becomes mandatory to identify pwMS at potential risk of developing BS, to correctly associate the symptomatic treatment to DMT.

Magnetic resonance imaging of bipolar disorders in the general population

Many studies investigated the anatomic substrate of bipolar disorders in the general population with Positron Emission Tomography [122], post-mortem identification of inflammatory biomarkers [123] and MRI [124–129], but only a few compared MRI abnormalities between bipolar disorders and MS [130] (Table 3).

At conventional brain MRI, people with bipolar disorders (pwBD) show no-specific abnormalities such as ventricular enlargement, sulcal prominence and T2 signal hyperintensities.

Table 3 Comparison of magnetic resonance imaging findings in people with bipolar disorders

	MRI changes in pwBD (compared to HCs)
Bruno et al. [128]	↑ MD in the right posterior frontal and bilateral prefrontal regions, ↑ FA in the inferior, middle-temporal and middle–occipital regions
Bruno et al. [128]	↓ MT ratio in the anterior cingulate and subgyral WM without significant volumetric differences at VBM
Lagopoulos et al. [129]	↓ FA in the genu, body and splenium of corpus callosum ↓ FA in the superior and anterior corona radiata
	MRI changes in pwBD (manic phase) and in pwMS (compared to HCs)
Piaggio et al. [130]	In pwBD → ↓FA, ↑MD and RD in corpus callosum, decreasing trend of DTI alterations from the genu to the body and to the splenium In pwMS → ↓FA, ↑MD and RD in corpus callosum, increasing trend of DTI alterations from the genu to the body and to the splenium

MRI magnetic resonance imaging, *pwBD* people with bipolar disorders, *HCs* healthy controls, *pwMS* people with multiple sclerosis, *FA* fractional anisotropy, *MD* mean diffusivity, *RD* radial diffusivity, *WM* white matter, *MT* magnetization transfer, *VBM* voxel-based morphometry

Several MRI studies investigated about hyperintensities location in pwBD identifying these signal abnormalities especially in deep WM and subcortical GM, in particular in the frontal region; other ones investigated only periventricular WM [124–126].

In pwBD, using DTI, some authors identified specific WM abnormalities, especially in the fronto-temporal regions (increased mean diffusivity in the right posterior frontal and bilateral prefrontal regions), and increased FA in the inferior, middle—temporal and middle—occipital regions [127].

In pwBD (compared to HCs) Bruno et al. [128] reported by magnetization transfer imaging (MTI) a reduced MT ratio in the anterior cingulate and subgyral WM without significant volumetric differences at voxel-based morphometry (VBM). In the corpus callosum of pwBD, other authors found a decreased FA in the genu, body and splenium and in the superior and anterior corona radiata, compared to HCs [129].

Using DTI, Piaggio et al. [130] reported WM changes in the corpus callosum both in pwBD and in pwMS without BS, with an opposite pattern in spatial distribution: a greater involvement of the anterior region in pwBD and of the posterior region in pwMS without BS.

In pwMS with BS, WM abnormalities, functional changes and microstructural damage should be investigated with MRI advanced techniques to evaluate the morpho-structural correlations between BS and MS. Ventricular enlargement, WM abnormalities, corpus callosum involvement demonstrated in pwBD without MS suggest that brain atrophy, WM plaques, and corpus callosum pathology occurring in pwMS may be considered as a pathological substrate triggering BS onset.

Schizophrenic syndrome

The prevalence of a schizophrenic syndrome (SCZ) in MS ranges from 0 to 7.4% [20]; it has been reported in 0.06% of pwMS at MS onset and in 0.08% at MS diagnosis [89].

Etiological and pathogenic mechanisms remain unclear for both MS and schizophrenia in the general population, and the correlation between these two diseases need to be clarified. However, some authors identified many similarities between these diseases: the age of onset (in young adults), clinical course (with periods of remission and exacerbation), immunological variations (proinflammatory immune state) [131, 132].

Magnetic resonance imaging in schizophrenia (Table 4)

Although no MRI specific studies in pwMS with SCZ are reported, the occurrence of psychotic symptoms in MS, has been reported in patients with the involvement of periventricular WM, around the temporal horn [133].

A meta-analysis underlined the association between schizophrenia and abnormalities of GM (reduced volume of bilateral insula/inferior frontal cortex, superior temporal gyrus, anterior cingulate gyrus/medial frontal cortex, thalamus and left amygdala), and WM (decreased FA in interhemispheric fibers, anterior thalamic radiation, inferior longitudinal fasciculi, inferior frontal occipital fasciculi, cingulum and fornix). The authors, considering epidemiological and clinic feature of schizophrenia, underlined that chronic illness was associated with both severe GM and WM abnormalities, male gender and negative symptoms only with more severe GM loss [134].

Bagary et al. [135] performed an MTI study in patients with first-episode of schizophrenia and detected (when compared to HCs) a reduced MT ratio bilaterally in the medial prefrontal cortex (right greater than left), insula (left greater than right), and WM incorporating the fasciculus uncinatus (left greater than right).

In addition, Watson et al. [136] studied patients with first-episode of schizophrenia, with VBM methods, and

Table 4 Magnetic resonance imaging findings in people with schizophrenia

	MRI changes in pwS (compared to HCs)	Correlation between MRI finding and clinical aspects in pwS
Bagary et al. [135]	↓ MT ratio bilaterally in: medial prefrontal cortex (right > left), insula (left > right), ↓ MT ratio WM in the fasciculus uncinatus (left > right)	
Watson et al. [136]	↓ cortical GM in: hippocampus, thalamus, striatum, cerebellum	
Joo et al. [137]	↑ RD in left thalamo-occipital tracts, right uncinate fascicle, right middle longitudinal fascicle, right superior longitudinal fascicle	
Hua et al. [138]	↓ FC between thalamus and prefrontal cortex and the cerebellum, ↑ connectivity between thalamus and motor/sensory cortex	FC alterations between thalamus and some brain areas (prefrontal cortex, cerebellum, motor/sensory cortex) significantly correlated with the disease duration

MRI magnetic resonance imaging, *pwS* people with schizophrenia, *HCs* healthy controls, *GM* gray matter, *FC* functional connectivity, *WM* white matter, *MT* magnetization transfer, *RD* radial diffusivity

identified cortical GM reduction in hippocampus, thalamus and striatum and cerebellum.

A recent study of tractography investigated WM abnormalities in the brain of 122 patients with schizophrenia, compared to 129 HCs, using public neuroimaging data from SchizConnect. The authors identified significant radial diffusivity (RD) and trace increases in left thalamo-occipital tracts and the right uncinate fascicle, and a significant RD increase in the right middle longitudinal fascicle and the right superior longitudinal fascicle in patient with schizophrenia [137].

Using the blood-oxygenation-level-dependent (BOLD) fMRI at 7 Tesla, Hua et al. identified FC alterations between thalamus and some brain areas (impaired connectivity to the prefrontal cortex and the cerebellum, and enhanced connectivity to the motor/sensory cortex), significantly correlated with the disease duration [138].

Although schizophrenia is not characterized by focal abnormalities of WM such as in MS, some studies underlined the possible role of WM in schizophrenia: e.g. a dysregulation of myelin-associated gene expression, reduction in oligodendrocyte numbers, and ultrastructural abnormalities of myelin sheaths [139].

Future studies considering these findings may be important to explain a possible link between schizophrenia and MS.

Obsessive–compulsive syndrome

The prevalence of obsessive–compulsive syndrome (OCS) in MS is 8.6%, compared to 2.5% in the general population [140].

The pathogenesis of the obsessive–compulsive disorder is unknown, though some authors speculated that, in addition to genetic factors, autoimmune mechanisms may play an important role in the development of this disease [141], thus making possible a pathogenetic link between the two.

Magnetic resonance imaging in obsessive–compulsive disorder (Table 5)

In primary obsessive–compulsive disorder patients, MRI studies revealed structural and functional abnormalities in the fronto-striato-thalamic circuitry [142].

Using DTI, a significantly increased FA in the genu and body of corpus callosum and WM of right superior frontal gyrus and corpus callosum was detected in obsessive–compulsive disorder patients, compared to HCs [143].

Moreover, significant decreased FA in orbitofrontal and dorsolateral prefrontal projections of the corpus callosum

Table 5 Magnetic resonance imaging findings in people with of obsessive–compulsive disorder

MRI changes in pwOCD (compared to HCs)	
Christopher et al. [146]	↑ GM in thalami, left orbitofrontal cortex right dorsolateral prefrontal cortex
Li et al. [143]	↑ FA in the genu and body of corpus callosum and WM of right superior frontal gyrus and corpus callosum
Oh et al. [144]	↓ FA in orbitofrontal and dorsolateral prefrontal projections of the corpus callosum
Diwadkar et al. [147]	↑ dACC modulation of cortical, striatal, and thalamic regions, during working memory tasks
Boedhoe et al. [148]	In adult pwOCD: ↓ transverse temporal cortical surface area ↓ inferior parietal cortical thickness In pediatric pwOCD: ↓ inferior and superior parietal cortices
MRI changes in pwMS with OCS (compared to pwMS without any psychiatric disturbance)	
Tinelli et al. [149]	↓ GM volume in right inferior temporal gyrus, middle temporal gyrus inferior frontal gyrus; No difference in FA between these two groups

MRI magnetic resonance imaging, *pwOCD* people with obsessive–compulsive disorder, *OCS* obsessive–compulsive syndrome, *HCs* healthy controls, *GM* gray matter, *WM* white matter, *dACC* dorsal anterior cingulate cortex, *FA* fractional anisotropy

has been reported in obsessive–compulsive disorder patients, compared to HCs [144].

A meta-analysis underlined that obsessive–compulsive disorder patients have increased WM volume and FA in the parallel right thalamic radiation and cortico-spinal tract through the internal capsule; increased WM volume but decreased FA in anterior body of corpus callosum and cingulum bundle, middle longitudinal fasciculus, inferior fronto-occipital fasciculus, forceps major of the corpus callosum, arcuate fasciculus and superior longitudinal fasciculus; decreased WM volume but increased FA in the crossing of right superior longitudinal fasciculus, cortico-spinal tract, frontal aslant tract and anterior body of the corpus callosum; and decreased WM volume and FA in right superior longitudinal fasciculus [145].

Christopher et al., with a VBM method, showed a significant increase of more GM in the thalami, left orbitofrontal and right dorsolateral prefrontal cortex in obsessive–compulsive disorder patients without major depression, compared to HCs. The involvement of the latter two areas was related to worse symptoms severity [146].

Dysfunctional brain network interactions during working memory task have been recently demonstrated in young patients (mean age is 17.3) with obsessive–compulsive disorder, compared to age-matched HCs; increased dorsal anterior cingulate cortex (dACC) modulation of cortical, striatal, and thalamic regions was evident during working memory and maintained regardless of working memory demand suggesting that these interactions may be related to a combination of network inefficiencies and dACC hyper-activity [147].

In a meta- and mega-analyses comprising the largest study of cortical morphometry in about 1900 obsessive–compulsive disorder patients compared to HCs, Boedhoe et al. showed that the parietal cortex is consistently implicated in both adults and children with obsessive–compulsive disorder. Particularly, widespread cortical thickness abnormalities (mainly temporal and inferior parietal cortices) were found in medicated adult obsessive–compulsive disorder patients, and more pronounced reduction surface area (mainly in frontal regions) were found in medicated pediatric obsessive–compulsive disorder patients, thus showing distinct morphological features in different stages of development and illness, that may be moderated by medication [148].

Using a VBM analysis, Tinelli et al. [149] demonstrated a reduced GM volume in the right inferior temporal gyrus, in the middle temporal gyrus and in the inferior frontal gyrus in pwMS with OCS, compared to pwMS without any psychiatric disturbance; contrariwise, at tract-based spatial statistics, they did not identify any difference in FA between these two groups.

The widespread involvement of WM in primary obsessive–compulsive disorder let suppose that WM pathology in pwMS may be the pathological substrate of such psychiatric disturbance.

Temperament and association with mood disorders

Recently, Özkan et al. [150] investigated the affective temperaments of pwMS by the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego-Autoquestionnaire (TEMPS-A) tests; they also explored pwMS for hypomanic and bipolar disorders, respectively, with the HCL-32 [108], the MDQ and evaluated possible association with clinical and demographic characteristics. Higher MDQ and TEMPS-A hyperthymic scores were found in relapsing remitting versus secondary progressive pwMS. They suggested that, because previous studies reported a higher hyperthymic temperament in pwBD [151], considering the episodic course of illness in bipolar disorders, rather than chronic progressive symptoms, and that temperament is a subclinical liability in mood disorders, bipolarity might be specifically related to relapsing remitting MS rather than progressive MS.

Conclusion

This review reports epidemiological, clinical evaluation tools and neuroradiological features of PS in pwMS (as part of the disease) and in people with primary psychiatric disorders. Considering the relevant influence of psychiatric symptoms in worsening cognitive performance, QoL, physical disability, fatigue, sleep quality and adherence to DMTs, early diagnosis and treatment of PS in pwMS are beneficial to improve the QoL of pwMS and their caregivers, the adherence to therapy and, as a consequence, the outcome of both MS and PS.

Depressive and anxiety syndrome are the most common PS in MS playing an important role in pwMS life, therefore, they have been more extensively investigated. However, other PS, even more impacting on QoL, such as OCS, SCZ and BS may affect pwMS.

Some radiological studies about primary psychiatric disorders are reported to underline how GM atrophy, WM abnormalities and corpus callosum involvement in these diseases, as features in common with MS, might possibly explain the more frequent occurrence of PS in MS.

In pwMS MRI aspects of OCS, SCZ and BS have not been studied so extensively as those of the depressive syndrome; future investigations should point to detect the possible causative role of MS in triggering PS.

Funding No sources of funding, from any agency in the public, commercial, or not-for-profit sectors, were received.

Compliance with ethical standards

Conflicts of interest Authors declare no conflict of interest in relation to the current work.

References

1. Compston A, Coles A (2008) Multiple sclerosis. Lancet 372(9648):1502–1517
2. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33(11):1444–1452
3. Charcot J-M (1877) Lectures on the diseases of the nervous system, delivered at La Salpetriere. New Sydenham Society, London, pp 194–195
4. Boerner RJ, Kapfhammer HP (1999) Psychopathological changes and cognitive impairment in encephalomyelitis disseminata. Eur Arch Psychiatry Clin Neurosci 249(2):96–102
5. Marrie RA, Walld R, Bolton JM et al (2017) Estimating annual prevalence of depression and anxiety disorder in multiple sclerosis using administrative data. BMC Res Notes 10:619
6. Tsivgoulis G, Triantafyllou N, Papageorgiou C et al (2007) Associations of the Expanded Disability Status Scale with anxiety and depression in multiple sclerosis outpatients. Acta Neurol Scand. 115(1):67–72
7. José Sá M (2008) Psychological aspects of multiple sclerosis. Clin Neurol Neurosurg. 110(9):868–877
8. Beckner V, Howard I, Vella L et al (2010) Telephone-administered psychotherapy for depression in MS patients: moderating role of social support. J Behav Med. 33(1):47–59
9. Schippling S, O'Connor P, Knappertz V et al (2016) Incidence and course of depression in multiple sclerosis in the multinational BEYOND trial. J Neurol 263(7):1418–1426
10. Gasim M, Bernstein CN, Graff LA et al (2018) Adverse psychiatric effects of disease-modifying therapies in multiple Sclerosis: a systematic review. Mult Scler Relat Disord 26:124–156
11. Jacobs LD, Beck RW, Simon JH et al (2000) Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med 343(13):898–904
12. Patten SB, Metz LM (2001) Interferon beta-1 a and depression in relapsing-remitting multiple sclerosis: an analysis of depression data from the PRISMS clinical trial. Mult Scler 7(4):243–248
13. Feinstein A, O'Connor P, Feinstein K (2002) Multiple sclerosis, interferon beta-1b and depression. A prospective investigation. J Neurol 249(7):815–820
14. Turner AP, Williams RM, Sloan AP et al (2009) Injection anxiety remains a long-term barrier to medication adherence in multiple sclerosis. Re-habil Psychol 54(1):116–121
15. Di Matteo MR, Lepper HS, Croghan TW (2000) Depression is a risk factor for non compliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 160(14):2101–2107
16. Mohr DC, Goodkin DE, Likosky W et al (1997) Treatment of depression improves adherence to interferon Beta-1b therapy for multiple sclerosis. Arch Neurol 54:531–533
17. Lobentanz IS, Asenbaum S, Vass K et al (2004) Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. Acta Neurol Scand 110(1):6–13
18. Fruehwald S, Loeffler-Stastka H, Eher R et al (2001) Depression and quality of life in multiple sclerosis. Acta Neurol Sci 104(5):257–261

19. Brown RF, Valpiani EM, Tennant CC et al (2009) Longitudinal assessment of anxiety, depression, and fatigue in people with multiple sclerosis. Psychol Psychother 82(Part1):41–56
20. Marrie RA, Reingold S, Cohen J et al (2015) The incidence and prevalence of psychiatric disorders in multiple sclerosis: a systematic review. Mult Scler 21(3):305–317
21. Bombardier CH, Blake KD, Ehde DM et al (2004) Alcohol and drug abuse among persons with multiple sclerosis. Mult Scler 10:35–40
22. Goretti B, Portaccio E, Ghezzi A et al (2010) Psychosocial issue in children and adolescents with multiple sclerosis. Neurol Sci 31:467–470
23. Boeschoten RE, Braamse AMJ, Beekman ATF (2017) Prevalence of depression and anxiety in multiple sclerosis: a systematic review and meta-analysis. J Neurol Sci 372:331–341
24. Marrie RA, Fisk JD, Yu BN et al (2013) Mental comorbidity and multiple sclerosis: validating administrative data to support population-based surveillance. BMC Neurol 13:16
25. Beck AT, Steer RA, Brown GA (1996) Beck depression inventory-II (BDI-II) manual. Pearson, Oxford
26. Nyenhuis DL, Rao S, Zajecka JM et al (1995) Mood disturbance versus other symptoms of depression in multiple sclerosis. J Int Neuropsychol Soc 1:291–296
27. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361–370
28. Radloff LS (1977) The CES-D Scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1:385–401
29. Spitzer RL, Kroenke K, Williams JB (1999) Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary care evaluation of mental disorders. Patient Health Questionnaire. JAMA 282(18):1737–1744
30. Cella D, Yount S, Rothrock N et al (2007) The patient-reported outcomes measurement information system (PROMIS): progress of an NIH roadmap cooperative group during its first two years. Med Care 45(5 Suppl 1):S3–S11
31. DeWalt DA, Rothrock N, Yount S et al (2007) Evaluation of item candidates: the PROMIS qualitative item review. Med Care 45(5 Suppl 1):S12–S21
32. Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62
33. Quaranta D, Marra C, Zinno M et al (2012) Presentation and validation of the multiple sclerosis depression rating scale: a test specifically devised to investigate affective disorders in multiple sclerosis patients. Clin Neuropsychol 26(4):571–587
34. Sullivan MJ, Weinshenker B, Mikail S et al (1995) Screening for major depression in the early stages of multiple sclerosis. Can J Neurol Sci 22:228–231
35. Nyenhuis DL, Luchetta T, Yamamoto C et al (1998) The development, standardization, and initial validation of the Chicago multiscale depression inventory. J Pers Assess 70(2):386–401
36. Strober LB, Arnett PA (2015) Depression in multiple sclerosis: the utility of common self-report instruments and development of a disease-specific measure. J Clin Exp Neuropsychol 37(7):722–732
37. Nicholl CR, Lincoln NB, Francis VM et al (2001) Assessment of emotional problems in people with multiple sclerosis. Clin Rehabil 15(6):657–668
38. Honarmand K, Feinstein A (2009) Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. Mult Scler 15(12):1518–1524
39. Verdier-Taillefer MH, Gourlet V, Fuhrer R et al (2001) Psychometric properties of the Center for Epidemiologic Studies-Depression scale in multiple sclerosis. Neuroepidemiology 20(4):262–267
40. Andresen EM, Malmgren JA, Carter WB et al (1994) Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med 10(2):77–84
41. Kroenke K, Spitzer RL, Williams JBW (2001) The PHQ-9 validity of a brief depression severity measure. J Gen Intern Med 16(9):606–613
42. Kroenke K, Spitzer RL, Williams JBW (2003) The patient health questionnaire-2: validity of a two-item depression screener. Med Care 41(11):1284–1292
43. Raimo S, Troiano L, Spitaleri D et al (2015) Psychometric properties of the Hamilton Depression Rating Scale in multiple sclerosis. Qual Life Res 24(8):1973–1980
44. Amtmann D, Kim J, Chung H (2014) Comparing CESD-10, PHQ-9, and PROMIS depression instruments in individuals with multiple sclerosis. Rehabil Psychol 59(2):220–229. https://doi.org/10.1037/a0035919
45. Jones KH, Ford DV, Jones PA et al (2012) A large-scale study of anxiety and depression in people with multiple sclerosis: a survey via the web portal of the UK MS Register. PLoS ONE 7(7):e41910. https://doi.org/10.1371/journal.pone.0041910
46. Julian L, Merluzzi NM, Mohr DC (2007) The relationship among depression, subjective cognitive impairment, and neuropsychological performance in multiple sclerosis. Mult Scler 13(1):81–86
47. Wilken JA, Sullivan C (2007) Recognizing and treating common psychiatric disorders in multiple sclerosis. Neurologist 13(6):343–354
48. Mohr DC, Hart SL, Goldberg A (2003) Effects of treatment for depression on fatigue in multiple sclerosis. Psychosom Med 65(4):542–547
49. Hart S, Fonareva I, Merluzzi N et al (2005) Treatment for depression and its relationship to improvement in quality of life and psychological well-being in multiple sclerosis patients. Qual Life Res 14(3):695–703
50. Vitkova M, Gdovinova Z, Rosenberger J et al (2014) Factors associated with poor sleep quality in patients with multiple sclerosis differ by disease duration. Disabil. Health J 7(4):466–471
51. Jones KH, Jones PA, Middleton RM et al (2014) Physical disability, anxiety and depression in people with MS: an internet-based survey via the UK. MS Register. PLoS ONE 9(8):e104604
52. Bakshi R, Shaikh ZA, Miletich RS et al (2000) Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. Mult Scler 6(3):181–185
53. Amato MP, Ponziani G, Rossi F et al (2001) Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. Mult Scler 7(5):340–344
54. Marrie RA, Patten SB, Berrigan LI et al (2018) Diagnoses of depression and anxiety versus current symptoms and quality of life in multiple sclerosis. Int J MS Care 20(2):76–84
55. Julian LJ (2011) Cognitive functioning in multiple sclerosis. Neurol Clin 29:507–525
56. Chiaravalloti ND, DeLuca J (2008) Cognitive impairment in multiple sclerosis. Lancet Neurol 7:1139–1151
57. Arnett PA, Higginson CI, Voss WD et al (1999) Depression in multiple sclerosis: relationship to working memory capacity. Neuropsychology 13:546–556
58. Arnett PA, Higginson CI, Voss WD et al (1999) Depressed mood in multiple sclerosis: relationship to capacity-demanding memory and attentional functioning. Neuropsychology 13:434–446
59. Arnett PA, Higginson CI, Randolph JJ (2001) Depression in multiple sclerosis: relationship to planning ability. J Int Neuropsychol Soc 7:665–674
60. Diamond BJ, Johnson SK, Kaufman M et al (2008) Relationships between information processing, depression, fatigue

and cognition in multiple sclerosis. Arch Clin Neuropsychol 23(2):189–199
61. Scalfari A, Knappertz V, Cutter G et al (2013) Mortality in patients with multiple sclerosis. Neurology 81(2):184–192
62. Manouchehrinia A, Tanasescu R, Tench CRJ et al (2016) Mortality in multiple sclerosis: meta-analysis of standardised mortality ratios. Neurol Neurosurg Psychiatry 87(3):324–331
63. Brenner P, Burkill S, Jokinen J et al (2016) Multiple sclerosis and risk of attempted and completed suicide—a cohort study. Eur J Neurol 23(8):1329–1336
64. Jefferies K (2006) The neuropsychiatry of multiple sclerosis. Adv Psychiatr Treat 12:214–220
65. Feinstein A (2002) An examination of suicidal intent in patients with multiple sclerosis. Neurology 59:674–678
66. Turner AP, Williams RM, Bowen JD et al (2006) Suicidal ideation in multiple sclerosis. Arch Phys Med Rehabil 87(8):1073–1078
67. Strupp J, Ehmann C, Galushko M et al (2016) Risk factors for suicidal ideation in patients feeling severely affected by multiple sclerosis. J Palliat Med 19(5):523–528
68. Bonavita S, Tedeschi G, Gallo A (2013) Morphostructural MRI abnormalities related to neuropsychiatric disorders associated to multiple sclerosis. Mult Scler Int 2013:102454
69. Pujol J, Bello J, Deus J et al (1997) Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. Neurology 49(4):1105–1110
70. Feinstein A, Roy P, Lobaugh N et al (2004) Structural brain abnormalities in multiple sclerosis patients with major depression. Neurology 62(4):586–590
71. Bakshi R, Czarnecki D, Shaikh ZA et al (2000) Brain MRI lesions and atrophy are related to depression in multiple sclerosis. NeuroReport 11(6):1153–1158
72. Zorzon M, de Masi R, Nasuelli D et al (2001) Depressiosn and anxiety in multiple sclerosis. A clinical and MRI study in 95 subjects. J Neurol 248(5):416–421
73. Di Legge S, Piattella MC, Pozzilli C et al (2003) Longitudinal evaluation of depression and anxiety in patients with clinically isolated syndrome at high risk of developing early multiple sclerosis. Mult Scler 9:302–306
74. Feinstein A, O'Connor P, Akbar N et al (2010) Diffusion tensor imaging abnormalities in depressed multiple sclerosis patients. Mult Scler 16(2):189–196
75. Bonavita S, Sacco R, Esposito S et al (2017) Default mode network changes in multiple sclerosis: a link between depression and cognitive impairment? Eur J Neurol 24(1):27–36
76. Rocca MA, Pravatà E, Valsasin P et al (2015) Hippocampal-DMN disconnectivity in MS is related to WM lesions and depression. Hum Brain Mapp 36(12):5051–5063
77. Pravatà E, Rocca MA, Valsasina P et al (2017) Gray matter trophism, cognitive impairment, and depression in patients with multiple sclerosis. Mult Scler 23(14):1864–1874
78. van Geest Q, Boeschoten RE, Keijzer MJ et al (2018) Frontolimbic disconnection in patients with multiple sclerosis and depression. Mult Scler J 1:1352458518767051
79. Hamilton M (1959) The assessment of anxiety states by rating. Br J Med Psychol 32:50–55
80. Beck AT, Steer RA (1990) Beck anxiety inventory (BAI) manual. Pearson, Oxford
81. Spielberger CD, Gorsuch RL, Lushene RE (1970) Manual for the state-trait anxiety inventory. Consulting Psychologists Press, Palo Alto
82. Spitzer RL, Kroenke K, Williams JB, Lowe B (2006) A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 166:1092–1097
83. Maier W, Buller R, Philipp M et al (1988) The Hamilton anxiety scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. J Affect Disord 14(1):61–68
84. Santangelo G, Sacco R, Siciliano M et al (2016) Anxiety in multiple sclerosis: psychometric properties of the state-trait anxiety inventory. Acta Neurol Scand. 134(6):458–466
85. Terrill AL, Hartoonian N, Beier M et al (2015) The 7-item generalized anxiety disorder scale as a tool for measuring generalized anxiety in multiple sclerosis. Int J MS Care 17:49–56
86. Senders A, Hanes D, Bourdette D et al (2014) Reducing survey burden: Feasibility and validity of PROMIS measures in multiple sclerosis. Mult Scler 20(8):1102–1111
87. Marrie RA, Zhang L, Lix LM et al (2018) The validity and reliability of screening measures for depression and anxiety disorders in multiple sclerosis. Mult Scler Relat Disord 20:9–15. https://doi.org/10.1016/j.msard.2017.12.007
88. Hartoonian N, Terrill AL, Beier ML et al (2015) Predictors of anxiety in multiple sclerosis. Rehabil Psychol 60(1):91–98
89. Marrie RA, Horwitz RI, Cutter G et al (2011) Association between comorbidity and clinical characteristics of MS. Acta Neurol Scand 124:135–141
90. Stenager E, Knudsen L, Jensen K (1994) Multiple sclerosis: correlation of anxiety, physical impairment and cognitive dysfunction. Italian J Neurol Sci 15:97–101
91. Morrow SA, Rosehart H, Pantazopoulos K (2016) Anxiety and depressive symptoms are associated with worse performance on objective cognitive tests in MS. J Neuropsychiatry Clin Neurosci 28:118–123
92. Julian LJ, Arnett PA (2009) Relationships among anxiety, depression, and executive functioning in multiple sclerosis. Clin Neuropsychol 23(794–804):16
93. Goretti B, Viterbo RG, Portaccio E et al (2014) Anxiety state affects information processing speed in patients with multiple sclerosis. Neurol Sci 35:559–563
94. Zhang Y, Li L, Yu R, Liu J, Tang J, Tan L et al (2013) White matter integrity alterations in first episode, treatment-naive generalized anxiety disorder. J Affect Disord 148:196–201. https://doi.org/10.1016/j.jad.2012.11.060
95. Zhang L, Zhang Y, Li L, Li Z, Li W, Ma N et al (2011) Different white matter abnormalities between the first-episode, treatment-naive patients with posttraumatic stress disorder and generalized anxiety disorder without comorbid conditions. J Affect Disord 133:294–299. https://doi.org/10.1016/j.jad.2011.03.040
96. Liao M, Yang F, Zhang Y, He Z, Su L, Li L (2014) White matter abnormalities in adolescents with generalized anxiety disorder: a diffusion tensor imaging study. BMC Psychiatry 14:41. https://doi.org/10.1186/1471-244X-14-41
97. Wang W, Qian S, Liu K, Li B, Li M, Xin K et al (2016) Reduced white matter integrity and its correlation with clinical symptom in first-episode, treatment-naive generalized anxiety disorder. Behav Brain Res 314:159–164. https://doi.org/10.1016/j.bbr.2016.08.017
98. Etkin A, Prater KE, Schatzberg AF et al (2009) Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. Arch Gen Psychiatry 66:1361–1372. https://doi.org/10.1001/archgenpsychiatry.2009.104
99. Qiao J, Li A, Cao C et al (2017) Aberrant functional network connectivity as a biomarker of generalized anxiety disorder. Front Hum Neurosci 11:626. https://doi.org/10.3389/fnhum.2017.00626
100. Sobanski T, Wagner G, Peikert G et al (2010) Temporal and right frontal lobe alterations in panic disorder: a quantitative volumetric and voxel-based morphometric MRI study. Psychol Med 40:1879–1886

101. Asami T, Yamasue H, Hayano F et al (2009) Sexually dimorphic gray matter volume reduction in patients with panic disorder. Psychiatry Res 173:128–134
102. Lai CH, Wu YT (2012) Fronto-temporo-insula gray matter alterations of first episode, drug-naive and very late-onset panic disorder patients. J Affect Disord 140:285–291
103. Han DH, Renshaw PF, Dager SR, Chung A, Hwang J et al (2008) Altered cingulate white matter connectivity in panic disorder patients. J Psychiatr Res 42:399–407
104. Lai CH, Wu YT (2013) Fronto-occipital fasciculus, corpus callosum and superior longitudinal fasciculus tract alterations of first-episode, medication-naive and late-onset panic disorder patients. J Affect Disord 146:378–382
105. Kim B, Kim JH, Kim MK et al (2014s) Frontal white matter alterations in short-term medicated panic disorder patients without comorbid conditions: a diffusion tensor imaging study. PLoS ONE 9(4):e95279
106. Hirschfeld RM, Williams JB, Spitzer RL et al (2000) Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. Am J Psychiatry 157(11):1873–1875
107. Hirschfeld RM, Holzer C, Calabrese JR et al (2003) Validity of the mood disorder questionnaire: a general population study. Am J Psychiatry 160(1):178–180
108. Angst J, Adolfsson R, Benazzi F et al (2005) The HCL-32: a self-assessment tool for hypomanic symptoms in outpatients. J Affect Disord 88:217–233
109. Carvalho AF, Takwoingi Y, Sales PM et al (2015) Screening for bipolar spectrumdisorders: a comprehensive meta-analysis of accuracy studies. J Affect Disord 172:337–346
110. Takwoingi Y, Riley RD, Deeks JJ (2015) Meta-analysis of diagnostic accuracy studies in mental health. Evid Based Ment Health 18(4):103–109
111. Eaton WW, Pedersen MG, Nielsen PR et al (2010) Autoimmune diseases, bipolar disorder, and nonaffective psychosis. Bipolar Disord 12:638–646
112. Joffe RT, Lippert GP, Gray TA et al (1987) Personal and family history of affective illness in patients with multiple sclerosis. J Affect Disord 12:63–65
113. Carta MG, Moro MF, Lorefice L et al (2014) The risk of bipolar disorders in multiple sclerosis. J Affect Disord 155:255–260
114. Andreazza AC, Cassini C, Rosa AR et al (2007) Serum S100B and antioxidant enzymes in bipolar patients. J Psychiatr Res 41:523–529
115. Zarate CA Jr, Singh J, Manji HK (2006) Cellular plasticity cascades: targets for thedevelopment of novel therapeutics for bipolar disorder. Biol Psychiatry 59:1006–1020
116. Bozikas VP, Anagnostouli MC, Petrikis P et al (2003) Familial bipolar disorder and multiple sclerosis: a three-generation HLA family study. Progress Neuropsychopharmacol Biol Psychiatry 27(5):835–839
117. Kosmidis MH, Bozikas VP, Giannouli V et al (2012) Familial comorbidity of bipolar disorder and multiple sclerosis: genetic susceptibility, coexistence or causal relationship? Behav Neurol 25(4):341–349
118. Schiffer RB, Weitkamp LR, Wineman NM et al (1988) Multiple sclerosis and affective disorder. Family history, sex, and HLA-DR antigens. Arch Neurol 45(12):1345–1348
119. Bhangle SD, Kramer N, Rosenstein ED (2013) Corticosteroid-induced neuropsychiatric disorders: review and contrast with neuropsychiatric lupus. Rheumatol Int 33:1923–1932
120. Lorefice L, Fenu G, Fois M et al (2018) Pulse steroid therapy in multiple sclerosis and mood changes: an exploratory prospective study. Mult Scler Relat Disord 20:104–108
121. Geoffroy PA, Auffret M, Deheul S et al (2014) Baclofen-induced manic symptoms: case report and systematic review. Psychosomatics 55(4):326–332
122. Haarman BC, Riemersma-Van der Lek RF, de Groot JC et al (2014) Neuroinflammation in bipolar disorder-A [(11)C]-(R)-PK11195 positron emission tomography study. Brain Behav Immun 40:219–225
123. Rao JS, Harry GJ, Rapoport SI et al (2010) Increased excitotoxicity and neuroinflammatory markers in postmortem frontal cortex from bipolar disorder patients. Mol Psychiatry 15(4):384–392
124. Altshuler LL, Curran JG, Houser P et al (1995) T2 hyperintensities in bipolar disorder: magnetic resonance imaging comparison and literature meta-analysis. Am J Psychiatry 152:1139–1144
125. Lloyd AJ, Moore PB, Cousins DA et al (2009) White matter lesions in euthymic patients with bipolar disorder. Acta Psychiatr Scand 120(6):481–491
126. Beyer JL, Young R, Kuchibhatla M, Krishnan KR et al (2009) Hyperintense MRI lesions in bipolar disorder: a meta-analysis and review. Int Rev Psychiatry 21(4):394–409
127. Bruno S, Cercignani M, Ron MA (2008) White matter abnormalities in bipolar disorder: a voxel-based diffusion tensor imaging study. Bipolar Disord 10(4):460–468
128. Bruno SD, Barker GJ, Cercignani M et al (2004) A study of bipolar disorder using magnetization transfer imaging and voxel-based morphometry. Brain 127(11):2433–2440
129. Lagopoulos J, Hermens DF, Hatton SN et al (2013) Microstructural white matter changes in the corpus callosum of young people with bipolar disorder: a diffusion tensor imaging study. PLoS ONE 8(3):e59108
130. Piaggio N, Schiavi S, Martino M et al (2018) Exploring mania-associated white matter injury by comparison with multiple sclerosis: a diffusion tensor imaging study. Psychiatry Res Neuroimaging 281:78–84
131. Arneth BM (2017) Multiple sclerosis and schizophrenia. Int J Mol Sci 18(8):1760
132. Müller N, Schwarz MJ (2010) Immune system and schizophrenia. Curr Immunol Rev 6(3):213–220
133. Feinstein A, du Boulay G, Ron MA (1992) Psychotic illness in multiple sclerosis: a clinical and magnetic resonance imaging study. Br J Psychiatry 161:680–685
134. Bora E, Fornito A, Radua J, et al. (2011) Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and ******meta-regression analysis. Schizophr Res.
135. Bagary MS, Symms MR, Barker GJ et al (2003) Gray and white matter brain abnormalities in first-episode schizophrenia inferred from magnetization transfer imaging. Arch Gen Psychiatry 60(8):779–788
136. Watson DR, Anderson JM, Bai F et al (2012) A voxel based morphometry study investigating brain structural changes in first episode psychosis. Behav Brain Res 227:91–99
137. Joo SW, Yoon W, Shon SH et al (2018) Altered white matter connectivity in patients with schizophrenia: an investigation using public neuroimaging data from SchizConnect. PLoS ONE 13(10):e0205369
138. Hua J, Blair NIS, Paez A et al (2019) Altered functional connectivity between sub-regions in the thalasmus and cortex in schizophrenia patients measured by resting state BOLD fMRI at 7T. Schizophr Res 206:370–377
139. Haroutunian V, Davis KL (2007) Introduction to the Special Section: Myelin and oligodendrocyte abnormalities in schizophrenia. Int J Neuropsychopharmacol 10:499–502
140. Korostil M, Feinstein A (2007) Anxiety disorders and their clinical correlates in multiple sclerosis patients. Mult Scler 13(1):67–72

141. Hoekstra P, Minderaa R (2005) Tic disorders and obsessive-compulsive disorder: Is autoimmunity involved? Int Rev Psychiatry 17(6):497–502
142. Menzies L, Chamberlain SR, Laird AR et al (2008) Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev 32(3):525–549
143. Li F, Huang X, Yang Y et al (2011) Microstructural brain abnormalities in patients with obsessive-compulsive disorder: diffusion-tensor MR imaging study at 3.0 T. Radiology 260(1):216–223
144. Oh JS, Jang JH, Jung WH et al (2012) Reduced fronto-callosal fiber integrity in unmedicated patients with OCD: a diffusion tractography study. Hum Brain Mapp 33(10):2441–2452
145. Radua J, Grau M, van den Heuvel OA et al (2014) Multimodal voxel-based meta-analysis of white matter abnormalities in obsessive-compulsive disorder. Neuropsychopharmacology 39(7):1547–1557
146. Christopher JC, Lencz T, Robinson DG et al (2008) Gray matter structural alterations in obsessive–compulsive disorder: relationship to neuropsychological functions. Psychiatry Res 164(2):123–131
147. Diwadkar VA, Burgess A, Hong E et al (2015) Dysfunctional activation and brain network profiles in youth with obsessive-compulsive disorder: a focus on the dorsal anterior cingulate during working memory. Front Hum Neurosci 9:149
148. Boedhoe PSW, Schmaal L, Abe Y et al (2018) Cortical abnormalities associated with pediatric and adult obsessive-compulsive disorder: findings from the ENIGMA obsessive–compulsive disorder working group. Am J Psychiatry 175(5):453–462
149. Tinelli E, Francia A, Quartuccio EM et al (2013) Structural brain MR imaging changes associated with obsessive-compulsive disorder in patients with multiple sclerosis. Am J Neuroradiol 34(2):305–309
150. Özkan A, Altinbaş K, Koç ER et al (2016) Affective temperament profiles in patients with multiple sclerosis: association with mood disorders. Noro Psikiyatr Ars 53(4):311–316
151. Rihmer Z, Akiskal KK, Rihmer A et al (2010) Current research on affective temperaments. Curr Opin Psychiatry 23:12–18