

**The relationship between neuropsychiatric symptoms and cognition in multiple sclerosis: A systematic review**

**Applied Neuropsychology: Adult**

Johanna Helminen

*Faculty of Social Sciences, Tampere University, Tampere, Finland*

Mervi Jehkonen

*Faculty of Social Sciences, Tampere University, Tampere, Finland*

*Tays Research Services, Tampere University Hospital, Tampere, Finland*

Johanna Helminen, [helminenjk@gmail.com](mailto:helminenjk@gmail.com)

# **The relationship between neuropsychiatric symptoms and cognition in multiple sclerosis: A systematic review**

The results of previous research on the relationship between neuropsychiatric symptoms and cognition in MS have been mixed. The aim of this systematic review was to examine the evidence on the relationship between neuropsychiatric symptoms and different cognitive domains in adult ( $\geq 18$  years) MS patients. A literature search was conducted in the Ovid Medline, PsycInfo, Scopus and Web of Science databases. A total of 4216 non-duplicate records were identified, and after screening, 37 studies met the inclusion criteria and were included in the systematic review. Higher levels of depressive symptoms were related to deficits in processing speed, verbal memory, executive functions, visuospatial functions, and attention in MS patients. Symptoms of anxiety were not consistently related to any of the cognitive functions, but the relationship to deficits in visual memory received a little support. Higher levels of apathy were most clearly associated with impairment in executive functions, but the association with deficits in visuospatial functions, visual memory, working memory, and processing speed was also supported. The results indicate that more neuropsychiatric symptoms, especially depressive symptoms and apathy, are associated with cognitive dysfunction in MS patients. These results can be utilized in the clinical examination and treatment planning of MS patients.

Keywords: Cognition; neuropsychiatric symptoms; multiple sclerosis

## **Introduction**

Multiple sclerosis (MS) is a neurodegenerative autoimmune disorder with diverse symptoms (Dendrou et al., 2015). Common comorbidities often co-occurring in MS patients include psychiatric disorders (Marrie et al., 2015) and cognitive impairment (Chiaravalloti & DeLuca, 2008).

Cognitive dysfunction in MS is heterogeneous (Portaccio & Amato, 2022), but is commonly characterized by deficits in information processing speed, attention, executive functions, learning, and long-term memory (Chiaravalloti & DeLuca, 2008). The estimated prevalence of cognitive dysfunction in MS patients ranges from 34% to

65% (Benedict et al., 2020). Cognitive impairment is relatively persistent and usually progresses as the disease advances (Ouellette et al., 2018; Strober et al., 2014). In addition to neuropsychiatric symptoms, other factors may influence the profile of cognitive deficits in MS, such as disease subtype, older age, and increased physical disability (Ruano et al., 2017; Johnen et al., 2017). Furthermore, disease-modifying therapies might help preserve cognitive functions in MS patients (Preziosa et al., 2022).

Neuropsychiatric symptoms are more common in MS than in the general population (Marrie et al., 2015; Rosti-Otajärvi & Hämäläinen, 2013), and become more prevalent during the course of the disease (Marrie et al., 2015). The prevalence rates of most common neuropsychiatric symptoms in MS are presented in Table 1.

[Insert Table 1 here]

Neuropsychiatric symptoms may occur already before receiving the MS diagnosis. Especially symptoms of depression and anxiety might precede the diagnosis by up to 10 years (Disanto et al., 2018). Different neuropsychiatric symptoms can also occur simultaneously, and for example, symptoms of anxiety and depression correlate positively in MS patients (Butler et al., 2016). Psychiatric comorbidity is associated with an increase in disability progression (McKay et al., 2018), and also with pathological changes in the brain during the course of MS (Masuccio et al., 2021).

Differentiating psychiatric symptoms from MS-related somatic symptoms is challenging. For example, symptoms of depression and anxiety overlap with symptoms related to neurological changes in MS such as fatigue, changes in appetite, sleep disturbances and concentration problems (Feinstein et al., 2014). Furthermore, many self-reported measures of depression and anxiety include items measuring somatic symptoms (Hind et al., 2016; Litster et al., 2016), why the use of these instruments in MS patients may lead to overestimation of psychiatric symptoms. However, scales that

differentiate between somatic and non-somatic symptoms of depression have been developed (Benedict et al., 2003; Nyenhuis & Luchetta, 1998), and also neuroimaging study results support the different underpinnings of these symptoms (Colasanti et al., 2016; Kiy et al., 2011).

There is some evidence on the association between neuropsychiatric symptoms and cognition in MS. Research indicates an association between depressive symptoms and subjective cognitive impairment (Julian & Arnett, 2009; Maor et al., 2001), but the association between objective cognitive functioning and depression in MS patients is still not clear. There are few previous reviews regarding the issue. Arnett and colleagues (2008) found that studies with sufficient sample sizes tended to find a significant association of moderate to large effect size between depression and cognitive impairment in MS patients. Also, Feinstein (2006) suggested that studies failing to find an association between depression and cognitive dysfunction in MS suffer from methodological problems such as small sample size, cognitive tests with poor sensitivity, and depression rating scales that include vegetative symptoms overlapping with MS symptoms. Furthermore, meta-analysis by Altieri and colleagues (2023) found higher levels of depressive symptoms to be significantly associated with impairment in global cognition, attention, executive functions, memory processes, and processing speed.

A few studies have addressed the association between anxiety or other neuropsychiatric symptoms and cognition in MS. Butler and colleagues (2016) included only a few studies examining the association between anxiety and objective cognitive functioning in their systematic review, and the results were mixed. However, in population-based samples, anxiety, bipolar disorder, and depression have been found to be related to impaired cognition (Gualtieri & Morgan, 2008), and anxiety disorders

especially to deficits in episodic memory and executive functions (Airaksinen et al., 2005).

The possible association between neuropsychiatric symptoms and cognitive impairment in MS has also received support from other studies. For example, neuropsychiatric symptoms and cognitive decline are associated with partly overlapping structural changes in the brain (Silveira et al., 2019). Furthermore, treatment of neuropsychiatric symptoms may have an effect on objective cognitive functioning in MS. Yet, there have been only few studies regarding this issue in depressed MS patients and the results have been mixed. One study suggested that treatment of depression would be related to improvement of objective cognitive functioning in MS patients (Julian et al., 2007), whereas another study found a significant association only with subjective cognitive functioning (Kinsinger et al., 2010).

In light of the previous research, it is also important to note that sample selection process can influence the results regarding the relationship between neuropsychiatric symptoms and cognition. For example, Duquin and colleagues (2008) found the significant relationship between depression and cognitive impairment to be present only for volunteering MS patients receiving a compensation for their participation, but not for patients referred for evaluation of a disease related problem. They suggested that volunteering MS patients may have milder MS-related symptoms and comorbid problems, why the relationship between depression and cognition could be easier detected with statistical methods.

Neuropsychiatric symptoms and cognitive impairment have been found to be risk factors for quality of life in MS (Gil-González et al., 2020). For example, the health-related quality of life of MS patients is negatively influenced by depression (Biernacki et al., 2019), anxiety (Berrigan et al., 2016) and bipolar disorder (Jun-

O'Connell et al., 2017). This association seems to be present not only in the beginning of the disease but also years later after the disease onset (Berrigan et al., 2016; Nourbakhsh et al., 2016). Results considering the association between cognitive impairment and health-related quality of life are inconsistent, but research indicates that cognitive impairment affects especially the vocational status of MS patients (Benedict et al., 2005; Biernacki et al., 2019; Nourbakhsh et al., 2016; Ruet et al., 2013). Depression might mediate the influence of cognitive dysfunction on quality of life, especially when referring to self-reported cognition (Crouch et al., 2022). Moreover, anxiety and mood disorders as well as memory functions can influence the treatment adherence of MS patients (Bruce et al., 2010).

To date there are no previous systematic reviews that would have synthesized the evidence regarding the relationship between several neuropsychiatric symptoms and specific cognitive domains in MS. In MS patients the relationship between depressive symptoms and cognitive dysfunction has received support but the research on other neuropsychiatric symptoms is scarce and the results are mixed. However, in non-MS samples the relationship between neuropsychiatric symptoms and cognitive impairment has received support (Airaksinen et al., 2005; Gualtieri & Morgan, 2008). Since both neuropsychiatric symptoms and decline of cognitive functioning affect the quality of life and functional capacity in MS patients, it is warranted to obtain more information regarding the possible association between these comorbidities. The knowledge regarding the relationship is important when planning the treatment of MS patients and when considering the impact of MS on individual's everyday life. The aim of this systematic review was to examine the evidence on the association between different neuropsychiatric symptoms and specific cognitive domains in MS.

## Methods

This systematic review was conducted following the guidelines for Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P 2015 statement) (Moher et al., 2015). Full-text articles published in English between 1st of January 2000 and 2nd of February 2022 were searched in the Ovid Medline, PsycInfo, Scopus and Web of Science. The search terms used were *multiple sclerosis* combined with *cognition* or *neuropsychological* and *depression* or *anxiety* or *mood disorder* or *bipolar* or *euphoria* or *psychosis* or *psychotic* or *pseudobulbar affect* or *aggression* or *apathy* or *adjustment disorder* or *lack of insight* or *anosognosia*. The terms for neuropsychiatric symptoms were chosen based on previous literature on the prevalence of neuropsychiatric symptoms in MS (Feinstein, 2007; Marrie et al., 2015; Rosti-Otajärvi & Hämäläinen, 2013). The detailed search strategy is provided in the *Supplemental material*.

Studies were selected according to the following inclusion criteria: 1) they were observational studies published in English in peer-reviewed journals; 2) the study population included only adult ( $\geq 18$  years) patients diagnosed with clinically definite MS; 3) the study's objectives included assessment of the relationship between clinically diagnosed or self-reported neuropsychiatric symptoms and objective cognitive functioning; 4) the study results were based on primary data; and 5) the studies had reported the relationship of neuropsychiatric symptoms to individual cognitive tests. Studies investigating the relationship to only global cognitive z-score or to general screening measures of cognitive functioning (such as the Mini Mental State Examination), were excluded. Studies using samples that included patients with clinically or radiologically isolated syndromes or possible MS were excluded. Case

reports, dissertations, editorials, randomized controlled clinical trials, and reviews as well as theoretical and validation studies were excluded.

In the results section, the neuropsychological test results of the included studies were classified into cognitive domains utilizing the classification by Lezak and colleagues (2012) or according to the domains or latent variables defined by the study authors. The cognitive domains used in the classification were attention, executive functions, language, processing speed, verbal memory, visual memory, visuospatial functions and working memory.

The quality of included cross-sectional studies ( $n = 31$ ) was assessed with the AXIS Scale (Downes et al., 2016), whereas the quality of included longitudinal studies ( $n = 6$ ) was appraised with the Newcastle-Ottawa Scale for cohort studies (Wells et al., n.d.). The quality assessment tables are provided in the *Supplemental material* (Table 1 and Table 2).

## **Results**

The database search resulted in 7003 articles. After duplicates were removed, there were 4216 articles left for screening based on abstract and title. Of those, 3892 articles were excluded because they did not meet the inclusion criteria, resulting in 324 full-text articles for the assessment of eligibility. In the full-text screening, 287 articles were additionally excluded, and 37 articles were eventually included in this systematic review. The reference lists of the included articles were screened but no additional records were found. The number of excluded articles presented according to the reasons for exclusion is presented in Figure 1.

[Insert Figure 1 here]

The following data were extracted from the included articles: authors, year of publication, study design, sample size, MS type, age at examination, gender, measures of neuropsychiatric and cognitive symptoms, and results on the relationship between objective cognitive functioning and neuropsychiatric symptoms. The characteristics and the main findings of the included articles are presented in Table 2. The Table 2 includes only the objective cognitive tests which association with neuropsychiatric symptoms was examined. The results were considered statistically significant and reported in the main findings when the p value was .05 or less.

[Insert Table 2 here]

### ***Study characteristics***

Selected articles included a total of 5098 MS patients and the sample sizes of the included studies ranged from 22 to 699 MS patients. Mean age at the examination in the MS patient samples varied from 21.25 to 55.8 years and was not reported in three studies (Beiske et al., 2008; Johansson et al., 2016; Mohammadyfar et al., 2018). Mean disease duration ranged from 4.1 to 19 years and was not specified in six studies (Christodoulou et al., 2009; Chruzander et al., 2013; Johansson et al., 2016; Mohammadyfar et al., 2018; Nocentini et al., 2006; Ozkul et al., 2020). Twenty-nine studies reported the mean disability quantified with Expanded Disability Status Scale (EDSS) and the mean EDSS score ranged from 1.2 to 5.1, indicating mild to moderate disability. One study included only adult patients with pediatric onset MS (Krysko & O'Connor, 2016). In all included studies, except for one study (Pérez-Miralles et al., 2021), the majority of MS participants were female. In studies reporting the sex ratio (n = 33) the proportion of female participants was 70.7% and it varied from 43.6% to 90.9%.

To confirm the diagnosis of definite MS, 21 of the included studies used the McDonald criteria and the Poser criteria was applied in 10 studies. Eizaguirre and colleagues (2018) used both criteria and seven of the included studies did not specify the diagnostic criteria (Borkowska et al. 2021; Golan et al. 2018; Hanssen et al., 2014; Johansson et al., 2016; Krysko & O'Connor 2016; Leavitt et al., 2020; Mohammadyfar et al., 2018). In studies reporting the distribution by MS type (n = 35), most of the participants (82%) had RRMS.

Of the included studies, 31 were cross-sectional and six longitudinal. In the longitudinal studies (Christodoulou et al., 2009; Chruzander et al., 2013; Hildebrandt & Eling, 2014; Johansson et al., 2016; Pérez-Miralles et al., 2021; Raimo et al., 2020) the follow-up period ranged from one year to 10.5 years. Two of the longitudinal studies (Chruzander et al., 2013; Raimo et al., 2020) were follow-up studies of two cross-sectional studies (Gottberg et al., 2007; Raimo et al., 2016).

The most common neuropsychiatric symptom investigated in association with cognitive functioning in MS patients was depression, studied in 36 articles. Additionally, there were nine studies on anxiety and four studies on apathy. Apart from the study by Chiaravalloti and DeLuca (2003), all studies on anxiety and apathy also assessed depression. All the studies used self-reported measures of neuropsychiatric symptoms and only two studies confirmed the clinical diagnosis of neuropsychiatric symptoms by a clinical interview (Raimo et al., 2016, 2020).

The most studied cognitive function was *processing speed* which was assessed in 31 studies mainly using Symbol Digit Modalities Test (SDMT) or Paced Auditory Serial Addition Test (PASAT). Also, *verbal memory* (n = 24) and *executive functions* (n = 23) were studied in most of the included studies. A total of 65 different cognitive tests were employed in the included studies when different versions of each test were

counted once. Additionally, a cognitive test battery (CCTB) was used entirely in one study (Golan et al., 2018).

The main results of the included articles on the significant relationship between a specific cognitive domain and depression, anxiety and apathy are summarized and provided in *Supplemental material* (Table 3, 4 and 5). For each article it was reported if an association between a certain neuropsychiatric symptom and a cognitive function was found or not. Following, the results on the association between neuropsychiatric symptoms and cognition are discussed starting with depression, the most studied psychiatric symptom across the included studies.

### ***The relationship between depression and cognition***

Significant associations between depressive symptoms and cognition were found in 23 studies (63.9%) whereas 13 studies did not find any significant relationship. The included studies identified significant depressive symptoms using a variety of different self-reported measures. The diagnosis of depression was confirmed through a clinical interview only in the studies by Raimo and colleagues (2016, 2020). The most used depression scale was Beck Depression Inventory (BDI), which was applied in 24 studies of which three administered the fast screen of BDI (BDI-FS). The rest of the studies used Center for Epidemiological Studies Depression Scale (CES-D), Hamilton Depression Rating Scale (HAM-D) or Hospital Anxiety and Depression Scale (HADS) to assess the occurrence of depressive symptoms. In addition, Chicago Multiscale Depression Inventory (CMDI), 21-item Depression Anxiety Stress Scale (DASS-21), Geriatric Depression Scale (GDS) and Hopkins Symptom Checklist (HSCL-25) were all used once in a single study. Sundgren and colleagues (2013) distinguished nonsomatic and somatic symptoms of depression measured with BDI and reported nonsomatic symptoms to predict different cognitive functions stronger than somatic symptoms or

BDI depression scores in total.

Most studied association was between depressive symptoms and *processing speed*, which was studied by 30 studies of which 18 (60%) reported a significant association. Twenty-five of the studies were cross-sectional and 15 (60%) of them found a significant relationship between more depressive symptoms and lower processing speed. Patel and colleagues (2016) discovered that depressive symptoms predicted slower processing speed even more in the presence of auditory distractors. Furthermore, Diamond and colleagues (2008) reported that although depressed MS patients did not differ significantly from non-depressed MS group in processing speed, the depressed group had significantly more impaired processing speed than the subgroup of non-depressed MS patients with low scores on a depression scale. Additionally, in the study by Mattioli and colleagues (2011) cognitive tests were performed only by MS patients with significant depressive symptoms and no relation between depression and processing speed was found. Three out of five (60%) longitudinal studies reported a significant association between depressive symptoms and processing speed. The longitudinal studies with one-year follow-up supported the reciprocal association between more depressive symptoms and lower processing speed (Christodoulou et al., 2009; Hildebrandt & Eling, 2014; Pérez-Miralles et al., 2021), but this association was not present in 2- or 10-year follow-up studies (Chruzander et al., 2013; Johansson et al., 2016).

Twenty-two studies assessed the relationship between symptoms of depression and *verbal memory* and 12 (54.5%) of the studies reported a significant association between more depressive symptoms and poorer verbal memory performance. Twenty of the studies were cross-sectional and nine (45%) of the cross-sectional results indicated higher levels of depression to be associated with poorer verbal memory, and Shawaryn

and colleagues (2002) found MS patient's perception of illness intrusiveness to mediate this relationship. All three longitudinal studies investigating this relationship reported a significant association. Depressive symptoms were found to be associated with a decline in verbal memory over a period of one year (Christodoulou et al., 2009), and lower verbal memory was found to predict depressive symptoms at one-year follow-up (Hildebrandt & Eling, 2014; Pérez-Miralles et al., 2021).

Twenty-one studies investigated the relationship between depressive symptoms and *executive functions* of which nine (42.9%) reported a significant relationship. Most studies found depressive symptoms to be associated with poorer executive functions, but Grech and colleagues (2015) reported that when time penalty was removed, a better performance on an executive test assessing planning predicted more depressive symptoms. Denney and colleagues (2005) did not find significant differences in executive functions between depressed and non-depressed MS patients but discovered that depressed MS patients, in contrast to non-depressed, scored significantly lower than healthy controls in an executive task. Furthermore, one longitudinal study found impaired executive functions to predict more depressive symptoms after one year (Pérez-Miralles et al., 2021), while another longitudinal study did not find support for this relationship in the opposite direction, that is, depressive symptoms did not predict one year change in tasks of executive functions (Christodoulou et al., 2009). Studies finding significant relationship between depressive symptoms and executive functions had considerably bigger sample sizes (mean 210) compared to studies with non-significant results (mean 88.8).

Relationship between depressive symptoms and *attention* was examined in seven studies of which five (71.4%) reported depressive symptoms to be associated with impaired performance in attention tasks. One of these studies was longitudinal and

found worse performance on an attentional task to be associated with increase in depressive symptoms over one year (Hildebrandt & Eling, 2014). Sundgren and colleagues (2013) found support for this association only with nonsomatic symptoms of depression. Furthermore, of the studies finding significant association, two studies also controlled for the influence of psychotropic medications (Golan et al., 2018; Sundgren et al., 2013), and one study controlled for the influence of hand motor function (Heesen et al., 2010).

There were seven studies appraising the association between symptoms of depression and *visuospatial functions*, and five (71.4%) of these studies found more depressive symptoms to be associated with poorer visuospatial functions (Golan et al., 2018; Nocentini et al., 2006; Raimo et al., 2016, 2020; Sundgren et al., 2013). Two of the studies assessed depression independently from comorbid apathy (Raimo et al., 2016, 2020). In the baseline study, depression was not independently associated with visuospatial functions but patients who had comorbid depression and apathy had significantly lower performance on tasks tapping visuospatial functions when compared to patients with only apathy (Raimo et al., 2016). At the two-year follow-up of the same sample, the depressed MS patients performed worse than MS patients without depression or apathy on clock drawing task but had better performance on drawing a complex figure (Raimo et al., 2020).

There was little evidence for the association between depressive symptoms and *language* or *visual* and *working memory*. Six (37.5%) out of 16 studies assessing the relationship between depressive symptoms and visual memory found higher levels of depression to be associated with poorer visual memory. The association between language and depressive symptoms was assessed in six studies of which only two studies (33.3%), which had substantially bigger sample sizes than the other four studies,

reported more depressive symptoms to be related to worse language performance (Golan et al., 2018; Nocentini et al., 2006). Lastly, out of five studies investigating the association between depression and working memory, only one found depressed MS patients to have poorer visuospatial working memory than patients without depression or apathy (Raimo et al., 2020).

### ***The relationship between anxiety and cognition***

Out of nine studies examining the association between anxiety and cognition in MS, five studies (55.6%) found at least one significant association between more anxiety symptoms and worse performance in one cognitive domain. Anxiety was assessed with six different scales across the included studies. State-Trait Anxiety Inventory (STAI) was the most used self-reported measure and was applied in three studies. Hospital Anxiety and Depression Scale (HADS) was administered in two studies and Hamilton Anxiety Rating Scale (HAM-A), DASS-21, Hopkins Symptom Checklist (HSCL-25) and NEO Five Factor Inventory, Neuroticism scale (NEO-N) were all used once in a single study.

The most studied cognitive function in relation to anxiety was *processing speed*, but support for this relationship was weak. Out of eight studies, only Goretti and colleagues (2014) found a significant relationship between more symptoms of state anxiety and lower processing speed. Furthermore, Patel and colleagues (2016) did not find symptoms of anxiety to affect the processing speed of MS patients even when auditory distracters were present.

Results regarding the association of anxiety symptoms with *verbal* and *visual memory* were conflicting. The only longitudinal study on anxiety found more symptoms of state anxiety to be correlated with decline in verbal and visuospatial long-term memory as well as visuospatial learning over one year (Christodoulou et al., 2009). One

cross-sectional study also reported a significant association between symptoms of anxiety and verbal long-term memory, but in the opposite direction, that is higher levels of anxiety was associated with better verbal long-term memory (Borghi et al., 2013). The relationship between anxiety and verbal memory was not supported by other cross-sectional studies (Goretti et al., 2014; Karadayi et al., 2014; Leavitt et al., 2020). In addition to the longitudinal relationship between anxiety and visual memory (Christodoulou et al., 2009), the symptoms of anxiety were found to be associated with lower nonverbal memory performance in one cross-sectional study (Leavitt et al., 2020). However, another cross-sectional study did not find any significant relationship between anxiety and visual memory (Goretti et al., 2014).

Only Grech and colleagues (2015) found a significant relationship between symptoms of state anxiety and *executive functions*, whereas rest of the studies assessing this relationship did not find any significant results (Christodoulou et al., 2009; Goretti et al., 2014; Karadayi et al., 2014). None of the studies reported anxiety to be significantly associated with *attention, language, visuospatial functions* or *working memory*.

### ***The relationship between apathy and cognition***

All four studies appraising the relationship between apathy and cognition found significant associations. One study (Chiaravalloti & DeLuca, 2003) had a considerably smaller sample size (N = 26) than the other three studies which sample sizes ranged from 100 to 184 MS patients (Niino et al., 2014; Raimo et al., 2016, 2020). Four different assessment methods for apathy were used in the included studies. All the studies used self-reported questionnaires to identify apathetic MS patients (Chiaravalloti & DeLuca, 2003; Niino et al., 2014; Raimo et al., 2016, 2020), but only Raimo and colleagues (2016, 2020) confirmed the diagnosis of apathy with a clinical interview

based on proposed diagnostic criteria for apathy (Robert et al., 2009). The self-reported questionnaires used were self-report version of Apathy Evaluation Scale (AES-S), Apathy Scale (AS), and apathy scale of the Frontal Systems Behavior Scale (FrSBe).

Most consistent result, reported across all four studies (Chiaravalloti & DeLuca, 2003; Niino et al., 2014; Raimo et al., 2016, 2020), was the significant relationship between higher levels of apathy and poorer *executive functions*. Only two studies (Raimo et al., 2016, 2020) examined MS patients with “pure apathy”, i.e., apathy without depression, and found this group to perform poorer than non-apathetic patients (with or without depression) on test of executive functions tapping on inhibitory control. Raimo and colleagues (2020) found also in their follow-up study that MS patients with stable apathy over two years had lower performance than MS patients whose apathy remitted over two years on a task demanding inhibitory control. Furthermore, they found apathy in comorbidity with depression to be associated with even poorer executive functions than in non-apathetic MS patients with or without depression.

Studies finding a significant association between higher levels of apathy and lower *processing speed* used PASAT and SDMT as assessment methods (Chiaravalloti & DeLuca, 2003; Niino et al., 2014), whereas studies not finding a significant relationship between apathy and processing speed used Trail Making Test A (Raimo et al., 2016, 2020). Only studies by Raimo and colleagues (2016, 2020) examined apathy’s association with *visuospatial functions* and reported a relationship between higher levels of apathy and poorer visuospatial performance. Higher levels of apathy were also related to worse *visual memory* in two studies (Niino et al., 2014; Raimo et al., 2020) as well as to worse *working memory* in another two studies (Chiaravalloti & DeLuca, 2003; Raimo et al., 2020). However, in their baseline study, Raimo and colleagues (2016) did not find a significant relationship between apathy and neither visual nor

working memory. Relationship between apathy and *verbal memory* was studied in each four studies, but a significant relationship between higher levels of apathy and poorer verbal memory was only found in the study by Niino and colleagues (2014). Only one study investigated the association between apathy and *language* and reported no significant results (Chiaravalloti & DeLuca, 2003). None of the studies investigated the relationship between apathy and *attention*.

## **Discussion**

This is the first systematic review to summarize the evidence regarding the association between several neuropsychiatric symptoms and different cognitive domains among people with MS. The systematic literature search identified 37 studies on depression, anxiety and apathy, and the results suggested that symptoms of depression and apathy are associated with cognitive dysfunction in MS patients. Evidence on the association between anxiety and cognitive function was weak.

## ***Main results***

Relationship between higher levels of depressive symptoms and increased cognitive impairment in MS received support from the included studies and was the most frequently studied association: A total of 36 studies investigated the relationship and 23 studies found a significant result. These findings are also in line with previous reviews. Arnett and colleagues (2008) reported in their review that 10 out of 22 studies found depressive symptoms to be significantly associated with cognitive impairment in MS patients. However, they did not separately summarize the association of depression with different cognitive domains, and sample sizes of the included studies were smaller than in the studies of the current review.

Studies included in the current review provided most support for the relationship between higher levels of depressive symptoms and deficits in *processing speed* and *verbal memory*. Furthermore, studies with adequate sample sizes found consistent support for the association between more depressive symptoms and worse performance in *executive functions*. These three cognitive functions were also most investigated in the studies included in this review. The association of higher depression levels with deficits in *attention* and *visuospatial functions* received also support but was examined only in a few studies. These results are mostly in line with a recent meta-analysis which suggested higher levels of depressive symptoms in MS to have a significant relationship to impairment in working memory, attention, processing speed, verbal and spatial memory, verbal fluency, inhibitory control, and set-shifting (Altieri et al., 2023). In the current review, evidence regarding the association between symptoms of depression and *visual memory* was weak, but in contrast the results supported the relationship between depressive symptoms and visuospatial functions which was not studied in the meta-analysis by Altieri and colleagues (2023).

Relationship between more depressive symptoms and deficits in *processing speed* or *verbal memory* was supported by most of the studies examining this association and received also support from longitudinal studies. All studies finding significant relationship between depression and processing speed had taken into account the motor functions. By contrast, five of the 12 studies not finding a significant relationship primarily used written responses without controlling for motor abilities which may have influenced the results.

A few studies attempted to separate nonsomatic symptoms from somatic symptoms of depression which overlap with other MS-related symptoms. One study found nonsomatic symptoms of depression to predict different cognitive domains

stronger than somatic or total symptoms of depression (Sundgren et al., 2013) which is in line with a study by Barwick and Arnett (2011) which reported global cognitive decline to be significantly associated with nonsomatic but not with somatic symptoms of depression. However, because both psychiatric symptoms as well as MS related disability may underlie somatic symptoms, it is problematic to simply separate nonsomatic symptoms of depression from somatic symptoms.

Some of the studies excluded MS patients with major depression or had a sample with mostly patients with mild levels of depressive symptoms which might have influenced the results. The relationship between depressive symptoms and cognitive impairment might become prevalent first when greater difference in depression scores is present (Diamond et al., 2008; Golan et al., 2018). This conclusion received also support from one study reporting no significant associations between depressive symptoms and cognition when only MS patients with significant depressive symptoms were included (Mattioli et al., 2011). However, there was also contradictory evidence, and some studies found the relationship between depressive symptoms and cognition to be prevalent also in mild symptoms of depression (Borghi et al., 2013; Sundgren et al., 2013).

Results on the relationship between symptoms of anxiety and cognition are in line with a previous review reporting mixed results (Butler et al., 2016). Most of the studies included in the current review found symptoms of anxiety to have a significant association with one or two cognitive domains. However, the results were inconsistent. Results suggested that there might be a relationship between higher anxiety levels and deficits in *visual memory*, but further studies are needed to replicate the results. Studies differentiating state and trait anxiety found no significant association between trait anxiety and cognition but reported higher levels of state anxiety to be associated with

lower performance on tasks assessing *verbal* and *visual memory*, *processing speed*, as well as *executive functions*. Yet, when relevant demographic and clinical variables were taken into account, the significant relationship to executive functions disappeared (Grech et al., 2015).

Most consistent results were found regarding the association between apathy and cognition, but this relationship was studied only in four studies. Higher levels of apathy were most clearly associated with *executive dysfunction*. MS patients with apathy seemed to have difficulties with tasks demanding considerable effort and cognitive flexibility as well as inhibitory control. Studies showed some support for the relationship between higher levels of apathy and impaired *visual memory*, *visuospatial functions* and *working memory*. Additionally, higher levels of apathy were associated with impaired performance in *processing speed* tasks not depending on hand motor functioning, but not with a task demanding motor functions. The difference in these measures of processing speed may explain the discrepancy between the study results.

Variety of different self-reported measures were used to assess neuropsychiatric symptoms. Particularly, symptoms of anxiety were assessed with five different scales across nine different studies. Assessment methods of depression were less variable, but still 10 different depression scales were used. Content overlap of different anxiety and depression scales is low, and they seem to measure different aspects of anxiety and depression (Fried et al., 2017; Wall & Lee, 2022). Consequently, the heterogeneity of psychiatric scales used in the included studies can partly explain the inconsistency in the results.

Included studies used heterogenous sample selection processes which may have influenced the results regarding the relationship between neuropsychiatric symptoms and cognition in MS (Duquin et al., 2008). Additionally, studies varied in terms of age,

disability level, and the disease duration of the included participants, which might influence the severity of cognitive impairment and psychiatric symptoms in MS (Butler et al., 2016; Ruano et al., 2017).

Based on the results of the current review, the causal direction of the relationship between neuropsychiatric symptoms and cognition in MS cannot be determined. Both neuropsychiatric symptoms and cognitive impairment seem to be associated with quality of life in MS patients (Gil-González et al., 2020), and it might be possible that cognitive impairment predisposes MS patients to different neuropsychiatric symptoms via its influence on quality of life. Also, simply the awareness of impaired cognitive capacities might increase the susceptibility to psychiatric reactions.

The relationship between neuropsychiatric symptoms and cognition is not only specific for MS. For example, the relationship between higher levels of apathy and cognitive impairment has also received support in Parkinson's disease (Martin et al., 2020). Furthermore, in the general population, research indicates a relationship between depression and cognitive functioning, and both currently depressed and remitted depression patients show cognitive deficits in executive functions, attention and memory (Rock et al., 2014).

### ***Limitations and strengths***

This systematic review has several limitations which should be acknowledged. First, the included studies used variety of different assessment methods for neuropsychiatric symptoms and cognitive functions which limits the comparability of the study results to each other. In the future it would be beneficial to have consensus among researchers on assessment methods and associated cut-off values to be used in MS studies.

Furthermore, psychiatric symptoms were mainly assessed with self-reported

questionnaires, so the patients in the included studies, except in the studies by Raimo and colleagues (2016, 2020), suffered from psychiatric symptoms, not from clinically defined psychiatric disorders. Additionally, it should be noted that several cognitive functions can affect the performance on a single neuropsychological test so the classification of cognitive functions is rather artificial.

Second, stringent inclusion criteria were used resulting in an exclusion of many studies on the subject. Several studies were excluded because the samples included patients who had CIS or possible MS. Furthermore, the only study on pseudobulbar affect was excluded because it was a retrospective chart review (Hanna et al., 2016). Third, most of the included studies were cross-sectional and used correlational analysis, therefore no causal inferences about the direction of the association can be drawn. Fourth, a broad timeframe was used for the literature search, during which there were multiple revisions to the diagnostic criteria for MS, which might have caused heterogeneity between the samples of the included studies (Thompson et al., 2018). Lastly, all the included studies did not control for the relevant demographic and disease related variables, such as age, disability level, and psychotropic medications, or exclude participants in relapse. Additionally, the influence of the aforementioned variables, total lesion load or the use of disease modifying treatments on the relationship between cognition and psychiatric symptoms was not analyzed. Furthermore, many studies did not control for the presence of other psychiatric symptoms which would have been justified since psychiatric symptoms can occur comorbidly in MS (Butler et al., 2016).

A strength of this review is that it focused solely on the relationship between different neuropsychiatric symptoms and objectively measured cognition in MS patients whose diagnoses were clinically confirmed. In contrast to previous reviews (Altieri et al., 2023; Arnett et al., 2008; Butler et al., 2016), only studies with samples composed

of patients with clinically definite MS were included, as not all patients with CIS receive later definite MS diagnosis (Miller et al., 2012). Furthermore, the inclusion of studies using only objective measures of cognition increases the validity of the results because self-reported cognition seems to be more correlated with anxiety and depressive symptoms than objective cognitive functioning in MS patients (Akbar et al., 2011; O'Brien et al., 2007). A further strength of the current review is the inclusion of six different longitudinal studies that offer insight into the relationship between neuropsychiatric symptoms and cognition over time in MS. A previous review on anxiety and cognition in MS (Butler et al., 2016) includes one longitudinal study, but the reviews on the relationship between depression and cognition do not include longitudinal data (Altieri et al., 2023; Arnett et al., 2008).

### ***Conclusions***

The findings of this systematic review suggest that among MS patients higher levels of depressive symptoms are associated with impairment in *processing speed, verbal memory, executive functions, attention, and visuospatial functions*, whereas higher levels of apathy seem to be associated with deficits in *executive functions, processing speed, visuospatial functions* as well as *visual and working memory*. Little support for the relationship between symptoms of anxiety and cognition was found, but more research is needed, especially regarding association between anxiety and *visual memory*. Further research, especially longitudinal studies, is needed to gain more detailed information on the nature of the relationship between neuropsychiatric symptoms and cognition in MS. Additionally, research on the association between cognition and other common neuropsychiatric symptoms in MS, such as pseudobulbar affect and euphoria, is still scarce. Both neuropsychiatric symptoms and cognitive impairment influence treatment adherence as well as quality of life among MS patients

which highlights the importance of taken these symptoms and their relationship into account in future studies as well as in treatment planning and rehabilitation of MS patients.

### **Acknowledgments**

No acknowledgments.

### **Disclosure statement**

No potential conflict of interest was reported by the author(s).

### **Funding**

This study was financially partly supported by the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (9AA016).

### **Supplemental material**

## References

- Airaksinen, E., Larsson, M., & Forsell, Y. (2005). Neuropsychological functions in anxiety disorders in population-based samples: Evidence of episodic memory dysfunction. *Journal of Psychiatric Research, 39*(2), 207–214.  
<https://doi.org/10.1016/j.jpsychires.2004.06.001>
- Akbar, N., Honarmand, K., & Feinstein, A. (2011). Self-assessment of cognition in multiple sclerosis: The role of personality and anxiety. *Cognitive and Behavioral Neurology, 24*(3), 115–121. <https://doi.org/10.1097/WNN.0b013e31822a20ae>
- Altieri, M., Cerciello, F., Gallo, A., & Santangelo, G. (2023). The relationship between depression and cognitive performance in multiple sclerosis: A meta-analysis. *The Clinical Neuropsychologist, 1*–21.  
<https://doi.org/10.1080/13854046.2023.2192963>
- Arnett, P. A., Barwick, F. H., & Beeney, J. E. (2008). Depression in multiple sclerosis: Review and theoretical proposal. *Journal of the International Neuropsychological Society, 14*(5), 691–724.  
<https://doi.org/10.1017/S1355617708081174>
- Barwick, F. H., & Arnett, P. A. (2011). Relationship between global cognitive decline and depressive symptoms in multiple sclerosis. *Clinical Neuropsychologist, 25*(2), 193–209. <https://doi.org/10.1080/13854046.2010.538435>
- Beiske, A. G., Svensson, E., Sandanger, I., Czujko, B., Pedersen, E. D., Aarseth, J. H., & Myhr, K. M. (2008). Depression and anxiety amongst multiple sclerosis patients. *European Journal of Neurology, 15*(3), 239–245.  
<https://doi.org/10.1111/j.1468-1331.2007.02041.x>
- Benedict, R. H. B., Amato, M. P., DeLuca, J., & Geurts, J. J. G. (2020). Cognitive impairment in multiple sclerosis: Clinical management, MRI, and therapeutic avenues. *Lancet Neurology, 19*(10), 860–871. [https://doi.org/10.1016/S1474-4422\(20\)30277-5](https://doi.org/10.1016/S1474-4422(20)30277-5)
- Benedict, R. H., Fishman, I., McClellan, M. M., Bakshi, R., & Weinstock-Guttman, B. (2003). Validity of the Beck Depression Inventory-Fast Screen in multiple sclerosis. *Multiple Sclerosis, 9*(4), 393–396.  
<https://doi.org/10.1191/1352458503ms902oa>
- Benedict, R. H. B., Wahlig, E., Bakshi, R., Fishman, I., Munschauer, F., Zivadinov, R., & Weinstock-Guttman, B. (2005). Predicting quality of life in multiple sclerosis:

- Accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *Journal of the Neurological Sciences*, 231(1), 29–34. <https://doi.org/10.1016/j.jns.2004.12.009>
- Berrigan, L. I., Fisk, J. D., Patten, S. B., Tremlett, H., Wolfson, C., Warren, S., Fiest, K. M., McKay, K. A., & Marrie, R. A. (2016). Health-related quality of life in multiple sclerosis: Direct and indirect effects of comorbidity. *Neurology*, 86(15), 1417–1424. <https://doi.org/10.1212/WNL.0000000000002564>
- Biernacki, T., Sandi, D., Kincses, Z. T., Füvesi, J., Rózsa, C., Mátyás, K., Vécsei, L., & Bencsik, K. (2019). Contributing factors to health-related quality of life in multiple sclerosis. *Brain and Behavior*, 9(12), Article e01466. <https://doi.org/10.1002/brb3.1466>
- Birnboim, S., & Miller, A. (2004). Cognitive strategies application of multiple sclerosis patients. *Multiple Sclerosis*, 10(1), 67–73. <https://doi.org/10.1191/1352458504ms980oa>
- Boeschoten, R. E., Braamse, A. M. J., Beekman, A. T. F., Cuijpers, P., van Oppen, P., Dekker, J., & Uitdehaag, B. M. J. (2016). Prevalence of depression and anxiety in Multiple Sclerosis: A systematic review and meta-analysis. *Journal of the Neurological Sciences*, 372, 331–341. <https://doi.org/10.1016/j.jns.2016.11.067>
- Borghi, M., Cavallo, M., Carletto, S., Ostacoli, L., Zuffranieri, M., Picci, R. L., Scavelli, F., Johnston, H., Furlan, P. M., Bertolotto, A., & Malucchi, S. (2013). Presence and significant determinants of cognitive impairment in a large sample of patients with multiple sclerosis. *PloS One*, 8(7), Article e69820. <https://doi.org/10.1371/journal.pone.0069820>
- Borkowska, A. R., Daniluk, B., & Adamczyk, K. (2021). Significance of the diagnosis of executive functions in patients with relapsing-remitting multiple sclerosis. *International Journal of Environmental Research and Public Health*, 18(19), Article 10527. <https://doi.org/10.3390/ijerph181910527>
- Botchorishvili, N., Shiukashvili, N., Mikeladze, N., Dzagnidze, A., Mikava, N., Tighashvili, M., & Janelidze, M. (2021). Screening of cognitive impairment in patients with multiple sclerosis: A cross-sectional study in Georgia. *Neurology Research International*, 2021, 1–7. <https://doi.org/10.1155/2021/5591078>
- Bruce, J. M., Hancock, L. M., Arnett, P., & Lynch, S. (2010). Treatment adherence in multiple sclerosis: Association with emotional status, personality, and cognition.

- Journal of Behavioral Medicine*, 33(3), 219–227.  
<https://doi.org/10.1007/s10865-010-9247-y>
- Butler, E., Matcham, F., & Chalder, T. (2016). A systematic review of anxiety amongst people with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, 10, 145–168. <https://doi.org/10.1016/j.msard.2016.10.003>
- Chiaravalloti, N. D., & DeLuca, J. (2003). Assessing the behavioral consequences of multiple sclerosis: An application of the frontal systems behavior scale (FrSBe). *Cognitive and Behavioral Neurology*, 16(1), 54–67.  
<https://doi.org/10.1097/00146965-200303000-00007>
- Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *Lancet Neurology*, 7(12), 1139–1151. [https://doi.org/10.1016/S1474-4422\(08\)70259-X](https://doi.org/10.1016/S1474-4422(08)70259-X)
- Christodoulou, C., Melville, P., Scherl, W. F., Macallister, W. S., Abensur, R. L., Troxell, R. M., & Krupp, L. B. (2009). Negative affect predicts subsequent cognitive change in multiple sclerosis. *Journal of the International Neuropsychological Society*, 15(1), 53–61.  
<https://doi.org/10.1017/S135561770809005X>
- Chruzander, C., Johansson, S., Gottberg, K., Einarsson, U., Fredrikson, S., Holmqvist, L. W., & Ytterberg, C. (2013). A 10-year follow-up of a population-based study of people with multiple sclerosis in Stockholm, Sweden: Changes in disability and the value of different factors in predicting disability and mortality. *Journal of the Neurological Sciences*, 332(1), 121–127.  
<https://doi.org/10.1016/j.jns.2013.07.003>
- Colasanti, A., Guo, Q., Giannetti, P., Wall, M. B., Newbould, R. D., Bishop, C., Onega, M., Nicholas, R., Ciccarelli, O., Muraro, P. A., Malik, O., Owen, D. R., Young, A. H., Gunn, R. N., Piccini, P., Matthews, P. M., & Rabiner, E. A. (2016). Hippocampal neuroinflammation, functional connectivity, and depressive symptoms in multiple sclerosis. *Biological Psychiatry*, 80(1), 62–72.  
<https://doi.org/10.1016/j.biopsych.2015.11.022>
- Cotter, J., Vithanage, N., Colville, S., Lyle, D., Cranley, D., Cormack, F., Barnett, J. H., Murray, K., & Pal, S. (2018). Investigating domain-specific cognitive impairment among patients with multiple sclerosis using touchscreen cognitive testing in routine clinical care. *Frontiers in Neurology*, 9(5), 331–331.  
<https://doi.org/10.3389/fneur.2018.00331>

- Crouch, T. A., Reas, H. E., Quach, C. M., & Erickson, T. M. (2022). Does depression in multiple sclerosis mediate effects of cognitive functioning on quality of life? *Quality of Life Research, 31*(2), 497–506. <https://doi.org/10.1007/s11136-021-02927-w>
- Dendrou, C. A., Fugger, L., & Friese, M. A. (2015). Immunopathology of multiple sclerosis. *Nature Reviews Immunology, 15*(9), 545–558. <https://doi.org/10.1038/nri3871>
- Denney, D. R., Sworowski, L. A., & Lynch, S. G. (2005). Cognitive impairment in three subtypes of multiple sclerosis. *Archives of Clinical Neuropsychology, 20*(8), 967–981. <https://doi.org/10.1016/j.acn.2005.04.012>
- Diamond, B. J., Johnson, S. K., Kaufman, M., & Graves, L. (2008). Relationships between information processing, depression, fatigue and cognition in multiple sclerosis. *Archives of Clinical Neuropsychology, 23*(2), 189–199. <https://doi.org/10.1016/j.acn.2007.10.002>
- Disanto, G., Zecca, C., MacLachlan, S., Sacco, R., Handunnetthi, L., Meier, U. C., Simpson, A., McDonald, L., Rossi, A., Benkert, P., Kuhle, J., Ramagopalan, S. V., & Gobbi, C. (2018). Prodromal symptoms of multiple sclerosis in primary care. *Annals of Neurology, 83*(6), 1162–1173. <https://doi.org/10.1002/ana.25247>
- Downes, M. J., Brennan, M. L., Williams, H. C., & Dean, R. S. (2016). Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ Open, 6*(12), Article e011458. <https://doi.org/10.1136/bmjopen-2016-011458>
- Duquin, J. A., Parmenter, B. A., & Benedict, R. H. B. (2008). Influence of recruitment and participation bias in neuropsychological research among MS patients. *Journal of the International Neuropsychological Society, 14*(3), 494–498. <https://doi.org/10.1017/S1355617708080624>
- Eizaguirre, M. B., Vanotti, S., Merino, Á., Yastremiz, C., Silva, B., Alonso, R., & Garcea, O. (2018). The role of information processing speed in clinical and social support variables of patients with multiple sclerosis. *Journal of Clinical Neurology, 14*(4), 472–477. <https://doi.org/10.3988/jcn.2018.14.4.472>
- Feinstein, A. (2006). Mood disorders in multiple sclerosis and the effects on cognition. *Journal of the Neurological Sciences, 245*(1), 63–66. <https://doi.org/10.1016/j.jns.2005.08.020>

- Feinstein, A. (2007). *The clinical neuropsychiatry of multiple sclerosis* (2nd ed.). Cambridge University Press.
- Feinstein, A., Magalhaes, S., Richard, J.-F., Audet, B., & Moore, C. (2014). The link between multiple sclerosis and depression. *Nature Reviews Neurology*, *10*(9), 507–517. <https://doi.org/10.1038/nrneurol.2014.139>
- Fried, E. I. (2017). The 52 symptoms of major depression: Lack of content overlap among seven common depression scales. *Journal of Affective Disorders*, *208*, 191–197. <https://doi.org/10.1016/j.jad.2016.10.019>
- Gil-González, I., Martín-Rodríguez, A., Conrad, R., & Pérez-San-Gregorio, M. Á. (2020). Quality of life in adults with multiple sclerosis: A systematic review. *BMJ Open*, *10*(11), Article e041249. <https://doi.org/10.1136/bmjopen-2020-041249>
- Golan, D., Doniger, G. M., Wissemann, K., Zarif, M., Bumstead, B., Buhse, M., Fafard, L., Lavi, I., Wilken, J., & Gudesblatt, M. (2018). The impact of subjective cognitive fatigue and depression on cognitive function in patients with multiple sclerosis. *Multiple Sclerosis*, *24*(2), 196–204. <https://doi.org/10.1177/1352458517695470>
- Goretti, B., Viterbo, R. G., Portaccio, E., Nicolai, C., Hakiki, B., Piscolla, E., Iaffaldano, P., Trojano, M., & Amato, M. P. (2014). Anxiety state affects information processing speed in patients with multiple sclerosis. *Neurological Sciences*, *35*(4), 559–563. <https://doi.org/10.1007/s10072-013-1544-0>
- Gottberg, K., Einarsson, U., Fredrikson, S., Von Koch, L., & Holmqvist, L. W. (2007). A population-based study of depressive symptoms in multiple sclerosis in Stockholm County: Association with functioning and sense of coherence. *Journal of Neurology, Neurosurgery and Psychiatry*, *78*(1), 60–65. <https://doi.org/10.1136/jnnp.2006.090654>
- Grech, L. B., Kiropoulos, L. A., Kirby, K. M., Butler, E., Paine, M., & Hester, R. (2015). The effect of executive function on stress, depression, anxiety, and quality of life in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *37*(5), 549–562. <https://doi.org/10.1080/13803395.2015.1037723>
- Gualtieri, C. T., & Morgan, D. W. (2008). The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: An unaccounted source

- of variance in clinical trials. *The Journal of Clinical Psychiatry*, 69(7), 1122–1130. <https://doi.org/10.4088/JCP.v69n0712>
- Hanna, J., Feinstein, A., & Morrow, S. A. (2016). The association of pathological laughing and crying and cognitive impairment in multiple sclerosis. *Journal of the Neurological Sciences*, 361, 200–203. <https://doi.org/10.1016/j.jns.2016.01.002>
- Hanssen, K. T., Beiske, A. G., Landrø, N. I., & Hessen, E. (2014). Predictors of executive complaints and executive deficits in multiple sclerosis. *Acta Neurologica Scandinavica*, 129(4), 234–242. <https://doi.org/10.1111/ane.12177>
- Heesen, C., Schulz, K. H., Fiehler, J., Von der Mark, U., Otte, C., Jung, R., Poettgen, J., Krieger, T., & Gold, S. M. (2010). Correlates of cognitive dysfunction in multiple sclerosis. *Brain, Behavior, and Immunity*, 24(7), 1148–1155. <https://doi.org/10.1016/j.bbi.2010.05.006>
- Hildebrandt, H., & Eling, P. (2014). A longitudinal study on fatigue, depression, and their relation to neurocognition in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, 36(4), 410–417. <https://doi.org/10.1080/13803395.2014.903900>
- Hind, D., Kaklamanou, D., Beever, D., Webster, R., Lee, E., Barkham, M., & Cooper, C. (2016). The assessment of depression in people with multiple sclerosis: A systematic review of psychometric validation studies. *BMC Psychiatry*, 16(1), 278–278. <https://doi.org/10.1186/s12888-016-0931-5>
- Johansson, S., Gottberg, K., Kierkegaard, M., & Ytterberg, C. (2016). Variations in and predictors of the occurrence of depressive symptoms and mood symptoms in multiple sclerosis: A longitudinal two-year study. *BMC Neurology*, 16(1), Article 32. <https://doi.org/10.1186/s12883-016-0551-1>
- Johnen, A., Landmeyer, N. C., Bürkner, P. C., Wiendl, H., Meuth, S. G., & Holling, H. (2017). Distinct cognitive impairments in different disease courses of multiple sclerosis—A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, 83, 568–578. <https://doi.org/10.1016/j.neubiorev.2017.09.005>
- Julian, L. J., & Arnett, P. A. (2009). Relationships among anxiety, depression, and executive functioning in multiple sclerosis. *Clinical Neuropsychologist*, 23(5), 794–804. <https://doi.org/10.1080/13854040802665808>

- Julian, L., Merluzzi, N. M., & Mohr, D. C. (2007). The relationship among depression, subjective cognitive impairment, and neuropsychological performance in multiple sclerosis. *Multiple Sclerosis, 13*(1), 81–86.  
<https://doi.org/10.1177/1352458506070255>
- Jun-O'Connell, A. H., Butala, A., Morales, I. B., Henninger, N., Deligiannidis, K. M., Byatt, N., & Ionete, C. (2017). The prevalence of bipolar disorders and association with quality of life in a cohort of patients with multiple sclerosis. *The Journal of Neuropsychiatry and Clinical Neurosciences, 29*(1), 45–51.  
<https://doi.org/10.1176/appi.neuropsych.15120403>
- Karadayi, H., Arisoy, O., Altunrende, B., Boztas, M. H., & Sercan, M. (2014). The relationship of cognitive impairment with neurological and psychiatric variables in multiple sclerosis patients. *International Journal of Psychiatry in Clinical Practice, 18*(1), 45–51. <https://doi.org/10.3109/13651501.2013.845221>
- Kinsinger, S. W., Lattie, E., & Mohr, D. C. (2010). Relationship between depression, fatigue, subjective cognitive impairment, and objective neuropsychological functioning in patients with multiple sclerosis. *Neuropsychology, 24*(5), 573–580. <https://doi.org/10.1037/a0019222>
- Kiy, G., Lehmann, P., Hahn, H. K., Eling, P., Kastrup, A., & Hildebrandt, H. (2011). Decreased hippocampal volume, indirectly measured, is associated with depressive symptoms and consolidation deficits in multiple sclerosis. *Multiple Sclerosis, 17*(9), 1088–1097. <https://doi.org/10.1177/1352458511403530>
- Krysko, K. M., & O'Connor, P. (2016). Quality of life, cognition and mood in adults with pediatric multiple sclerosis. *Canadian Journal of Neurological Sciences, 43*(3), 368–374. <https://doi.org/10.1017/cjn.2015.354>
- Leavitt, V. M., Brandstadter, R., Fabian, M., Katz Sand, I., Klineova, S., Krieger, S., Lewis, C., Lublin, F., Miller, A., Pelle, G., Buyukturkoglu, K., De Jager, P. L., Li, P., Riley, C. S., Tsapanou, A., & Sumowski, J. F. (2020). Dissociable cognitive patterns related to depression and anxiety in multiple sclerosis. *Multiple Sclerosis Journal, 26*(10), 1247–1255.  
<https://doi.org/10.1177/1352458519860319>
- Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed.). Oxford University Press.
- Litster, B., Fiest, K. M., Patten, S. B., Fisk, J. D., Walker, J. R., Graff, L. A., Bolton, J. M., Sareen, J., Marriott, J. J., Berrigan, L. I., Bernstein, C. N., Zarychanski, R.,

- Singer, A., Hitchon, C. A., Peschken, C. A., Marrie, R. A., Katz, A., & Lix, L. (2016). Screening tools for anxiety in people with multiple sclerosis: A systematic review. *International Journal of MS Care, 18*(6), 273–281. <https://doi.org/10.7224/1537-2073.2016-004>
- Maor, Y., Olmer, L., & Mozes, B. (2001). The relation between objective and subjective impairment in cognitive function among multiple sclerosis patients - the role of depression. *Multiple Sclerosis, 7*(2), 131–135. <https://doi.org/10.1191/135245801678227658>
- Marrie, R. A., Reingold, S., Cohen, J., Stuve, O., Trojano, M., Sorensen, P. S., Cutter, G., & Reider, N. (2015). The incidence and prevalence of psychiatric disorders in multiple sclerosis: A systematic review. *Multiple Sclerosis Journal, 21*(3), 305–317. <https://doi.org/10.1177/1352458514564487>
- Martin, G. P., McDonald, K. R., Allsop, D., Diggle, P. J., & Leroi, I. (2020). Apathy as a behavioural marker of cognitive impairment in Parkinson's disease: A longitudinal analysis. *Journal of Neurology, 267*, 214–227. <https://doi.org/10.1007/s00415-019-09538-z>
- Masuccio, F. G., Gamberini, G., Calabrese, M., & Solaro, C. (2021). Imaging and depression in multiple sclerosis: A historical perspective. *Neurological Sciences, 42*(3), 835–845. <https://doi.org/10.1007/s10072-020-04951-z>
- Mattioli, F., Bellomi, F., Stampatori, C., Parrinello, G., & Capra, R. (2011). Depression, disability and cognitive impairment in multiple sclerosis: A cross sectional Italian study. *Neurological Sciences, 32*(5), 825–832. <https://doi.org/10.1007/s10072-011-0624-2>
- McKay, K. A., Tremlett, H., Fisk, J. D., Zhang, T., Patten, S. B., Kastrukoff, L., Campbell, T., & Marrie, R. A. (2018). Psychiatric comorbidity is associated with disability progression in multiple sclerosis. *Neurology, 90*(15), e1316–e1323. <https://doi.org/10.1212/WNL.0000000000005302>
- Miller, D. H., Chard, D. T., & Ciccarelli, O. (2012). Clinically isolated syndromes. *Lancet Neurology, 11*(2), 157–169. [https://doi.org/10.1016/S1474-4422\(11\)70274-5](https://doi.org/10.1016/S1474-4422(11)70274-5)
- Mohammadyfar, M. A., Azizpour, M., Najafi, M., & Nooripour, R. (2018). Comparison of audio-visual short-term and active memory in multiple sclerosis patients and non-patients regarding their depression, stress and anxiety level. *Nordic Psychology, 70*(2), 115–128. <https://doi.org/10.1080/19012276.2017.1362989>

- Moher, D., Shamseer, L., Clarke, M. et al. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*, 4(1), <https://doi.org/10.1186/2046-4053-4-1>
- Nabizadeh, F., Nikfarjam, M., Azami, M., Sharifkazemi, H., & Sodeifian, F. (2022). Pseudobulbar affect in neurodegenerative diseases: A systematic review and meta-analysis. *Journal of Clinical Neuroscience*, 100, 100–107. <https://doi.org/10.1016/j.jocn.2022.04.009>
- Niino, M., Mifune, N., Kohriyama, T., Mori, M., Ohashi, T., Kawachi, I., Shimizu, Y., Fukaura, H., Nakashima, I., Kusunoki, S., Miyamoto, K., Yoshida, K., Kanda, T., Nomura, K., Yamamura, T., Yoshii, F., Kira, J.-I., Nakane, S., Yokoyama, K., ... Kikuchi, S. (2014). Apathy/depression, but not subjective fatigue, is related with cognitive dysfunction in patients with multiple sclerosis. *BMC Neurology*, 14(1). <https://doi.org/10.1186/1471-2377-14-3>
- Nocentini, U., Pasqualetti, P., Bonavita, S., Buccafusca, M., De Caro, M., Farina, D., Girlanda, P., Le Pira, F., Lugaresi, A., Quattrone, A., Reggio, A., Salemi, G., Savettieri, G., Tedeschi, G., Trojano, M., Valentino, P., & Caltagirone, C. (2006). Cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. *Multiple Sclerosis*, 12(1), 77–87. <https://doi.org/10.1191/135248506ms1227oa>
- Nourbakhsh, B., Julian, L., & Waubant, E. (2016). Fatigue and depression predict quality of life in patients with early multiple sclerosis: A longitudinal study. *European Journal of Neurology*, 23(9), 1482–1486. <https://doi.org/10.1111/ene.13102>
- Nunnari, D., De Cola, M. C., D'Aleo, G., Rifichi, C., Russo, M., Sessa, E., Bramanti, P., & Marino, S. (2015). Impact of depression, fatigue, and global measure of cortical volume on cognitive impairment in multiple sclerosis. *BioMed Research International*, 2015, Article 519785. <https://doi.org/10.1155/2015/519785>
- Nyenhuis, D. L., & Luchetta, T. (1998). The Development, standardization, and initial validation of the Chicago Multiscale Depression Inventory. *Journal of Personality Assessment*, 70(2), 386–401. [https://doi.org/10.1207/s15327752jpa7002\\_14](https://doi.org/10.1207/s15327752jpa7002_14)
- O'Brien, A., Gaudino-Goering, E., Shawaryn, M., Komaroff, E., Moore, N. B., & DeLuca, J. (2007). Relationship of the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) to functional, emotional, and neuropsychological

- outcomes. *Archives of Clinical Neuropsychology*, 22(8), 933–948.  
<https://doi.org/10.1016/j.acn.2007.07.002>
- Ouellette, R., Bergendal, Å., Shams, S., Martola, J., Mainero, C., Kristoffersen Wiberg, M., Fredrikson, S., & Granberg, T. (2018). Lesion accumulation is predictive of long-term cognitive decline in multiple sclerosis. *Multiple Sclerosis and Related Disorders*, 21, 110–116. <https://doi.org/10.1016/j.msard.2018.03.002>
- Ozakbas, S., Turkoglu, R., Tamam, Y., Terzi, M., Taskapilioglu, O., Yucesan, C., Baser, H., Gencer, M., Akil, E., Sen, S., Turan, O., Sorgun, M., Yigit, P., & Turkes, N. (2018). Prevalence of and risk factors for cognitive impairment in patients with relapsing-remitting multiple sclerosis: Multi-center, controlled trial. *Multiple Sclerosis and Related Disorders*, 22, 70–76.  
<https://doi.org/10.1016/j.msard.2018.03.009>
- Ozkul, C., Guclu-Gunduz, A., Eldemir, K., Apaydin, Y., Yazici, G., & Irkeç, C. (2020). Clinical features and physical performance in multiple sclerosis patients with and without cognitive impairment: A cross-sectional study. *International Journal of Rehabilitation Research*, 43(4) 316–323.  
<https://doi.org/10.1097/MRR.0000000000000428>
- Patel, V. P., Zambrana, A., Walker, L. A. S., Herrmann, N., Swartz, R. H., & Feinstein, A. (2016). Distractibility in multiple sclerosis: The role of depression. *Multiple Sclerosis Journal - Experimental, Translational and Clinical*, 2, 1-5.  
<https://doi.org/10.1177/2055217316653150>
- Peres, D. S., Rodrigues, P., Viero, F. T., Frare, J. M., Kudsi, S. Q., Meira, G. M., & Trevisan, G. (2022). Prevalence of depression and anxiety in the different clinical forms of multiple sclerosis and associations with disability: A systematic review and meta-analysis. *Brain, Behavior, & Immunity - Health*, 24, Article 100484. <https://doi.org/10.1016/j.bbih.2022.100484>
- Pérez-Mirallès, F., Prefasi, D., García-Merino, A., Ara, J. R., Izquierdo, G., Meca-Lallana, V., Gascón-Giménez, F., Martínez-Ginés, M. L., Ramió-Torrentà, L., Costa-Frossard, L., Fernández, Ó., Moreno-García, S., Medrano, N., Maurino, J., & Casanova, B. (2021). Short-term data on disease activity, cognition, mood, stigma and employment outcomes in a cohort of patients with primary progressive multiple sclerosis (UPPMS study). *Multiple Sclerosis and Related Disorders*, 50, Article 102860. <https://doi.org/10.1016/j.msard.2021.102860>

- Portaccio, E., & Amato, M. P. (2022). Cognitive impairment in multiple sclerosis: An update on assessment and management. *NeuroSci*, 3(4), 667–676.  
<https://doi.org/10.3390/neurosci3040048>
- Preziosa, P., Conti, L., Rocca, M. A., & Filippi, M. (2022). Effects on cognition of DMTs in multiple sclerosis: Moving beyond the prevention of inflammatory activity. *Journal of Neurology*, 269(2), 1052–1064.  
<https://doi.org/10.1007/s00415-021-10832-y>
- Raimo, S., Spitaleri, D., Trojano, L., & Santangelo, G. (2020). Apathy as a herald of cognitive changes in multiple sclerosis: A 2-year follow-up study. *Multiple Sclerosis Journal*, 26(3), 363–371. <https://doi.org/10.1177/1352458519828296>
- Raimo, S., Trojano, L., Spitaleri, D., Petretta, V., Grossi, D., & Santangelo, G. (2016). The relationships between apathy and executive dysfunction in multiple sclerosis. *Neuropsychology*, 30(6), 767–774.  
<https://doi.org/10.1037/neu0000279>
- Robert, P., Onyike, C. U., Leentjens, A. F. G., Dujardin, K., Aalten, P., Starkstein, S., Verhey, F. R. J., Yessavage, J., Clement, J. P., Drapier, D., Bayle, F., Benoit, M., Boyer, P., Lorca, P. M., Thibaut, F., Gauthier, S., Grossberg, G., Vellas, B., & Byrne, J. (2009). Proposed diagnostic criteria for apathy in Alzheimer’s disease and other neuropsychiatric disorders. *European Psychiatry*, 24(2), 98–104. <https://doi.org/10.1016/j.eurpsy.2008.09.001>
- Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: A systematic review and meta-analysis. *Psychological Medicine*, 44(10), 2029–2040.  
<https://doi.org/10.1017/S0033291713002535>
- Rosti-Otajärvi, E., & Hämäläinen, P. (2013). Behavioural symptoms and impairments in multiple sclerosis: A systematic review and meta-analysis. *Multiple Sclerosis*, 19(1), 31–45. <https://doi.org/10.1177/1352458512439437>
- Ruano, L., Portaccio, E., Goretti, B., Nicolai, C., Severo, M., Patti, F., Cilia, S., Gallo, P., Grossi, P., Ghezzi, A., Roscio, M., Mattioli, F., Stampatori, C., Trojano, M., Viterbo, R. G., & Amato, M. P. (2017). Age and disability drive cognitive impairment in multiple sclerosis across disease subtypes. *Multiple Sclerosis*, 23(9), 1258–1267. <https://doi.org/10.1177/1352458516674367>
- Ruet, A., Deloire, M., Hamel, D., Ouallet, J.-C., Petry, K., & Brochet, B. (2013). Cognitive impairment, health-related quality of life and vocational status at early

- stages of multiple sclerosis: A 7-year longitudinal study. *Journal of Neurology*, 260(3), 776–784. <https://doi.org/10.1007/s00415-012-6705-1>
- Shawaryn, M. A., Schiaffino, K. M., LaRocca, N. G., & Johnston, M. V. (2002). Determinants of health-related quality of life in multiple sclerosis: The role of illness intrusiveness. *Multiple Sclerosis*, 8(4), 310–318. <https://doi.org/10.1191/1352458502ms808oa>
- Silveira, C., Guedes, R., Maia, D., Curral, R., & Coelho, R. (2019). Neuropsychiatric symptoms of multiple sclerosis: State of the art. *Psychiatry Investigation*, 16(12), 877–888. <https://doi.org/10.30773/pi.2019.0106>
- Strober, L. B., Rao, S. M., Lee, J.-C., Fischer, E., & Rudick, R. (2014). Cognitive impairment in multiple sclerosis: An 18-year follow-up study. *Multiple Sclerosis and Related Disorders*, 3(4), 473–481. <https://doi.org/10.1016/j.msard.2014.03.004>
- Sundgren, M., Maurex, L., Wahlin, A., Piehl, F., & Brismar, T. (2013). Cognitive impairment has a strong relation to nonsomatic symptoms of depression in relapsing-remitting multiple sclerosis. *Archives of Clinical Neuropsychology*, 28(2), 144–155. <https://doi.org/10.1093/arclin/acs113>
- Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M. S., Fujihara, K., Galetta, S. L., Hartung, H. P., Kappos, L., Lublin, F. D., Marrie, R. A., Miller, A. E., Miller, D. H., Montalban, X., ... Cohen, J. A. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology*, 17(2), 162–173. [https://doi.org/10.1016/S1474-4422\(17\)30470-2](https://doi.org/10.1016/S1474-4422(17)30470-2)
- Wall, A. D., & Lee, E. B. (2022). What do anxiety scales really measure? An item content analysis of self-report measures of anxiety. *Journal of Psychopathology and Behavioral Assessment*, 44(4), 1148–1157. <https://doi.org/10.1007/s10862-022-09973-9>
- Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (n.d.). *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. The Ottawa Hospital Research Institute. Retrieved January 3, 2023, from [https://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)
- Yigit, P., Acikgoz, A., Mehdiyev, Z., Dayi, A., & Ozakbas, S. (2021). The relationship between cognition, depression, fatigue, and disability in patients with multiple

sclerosis. *Irish Journal of Medical Science*, 190(3), 1129–1136.  
<https://doi.org/10.1007/s11845-020-02377-2>

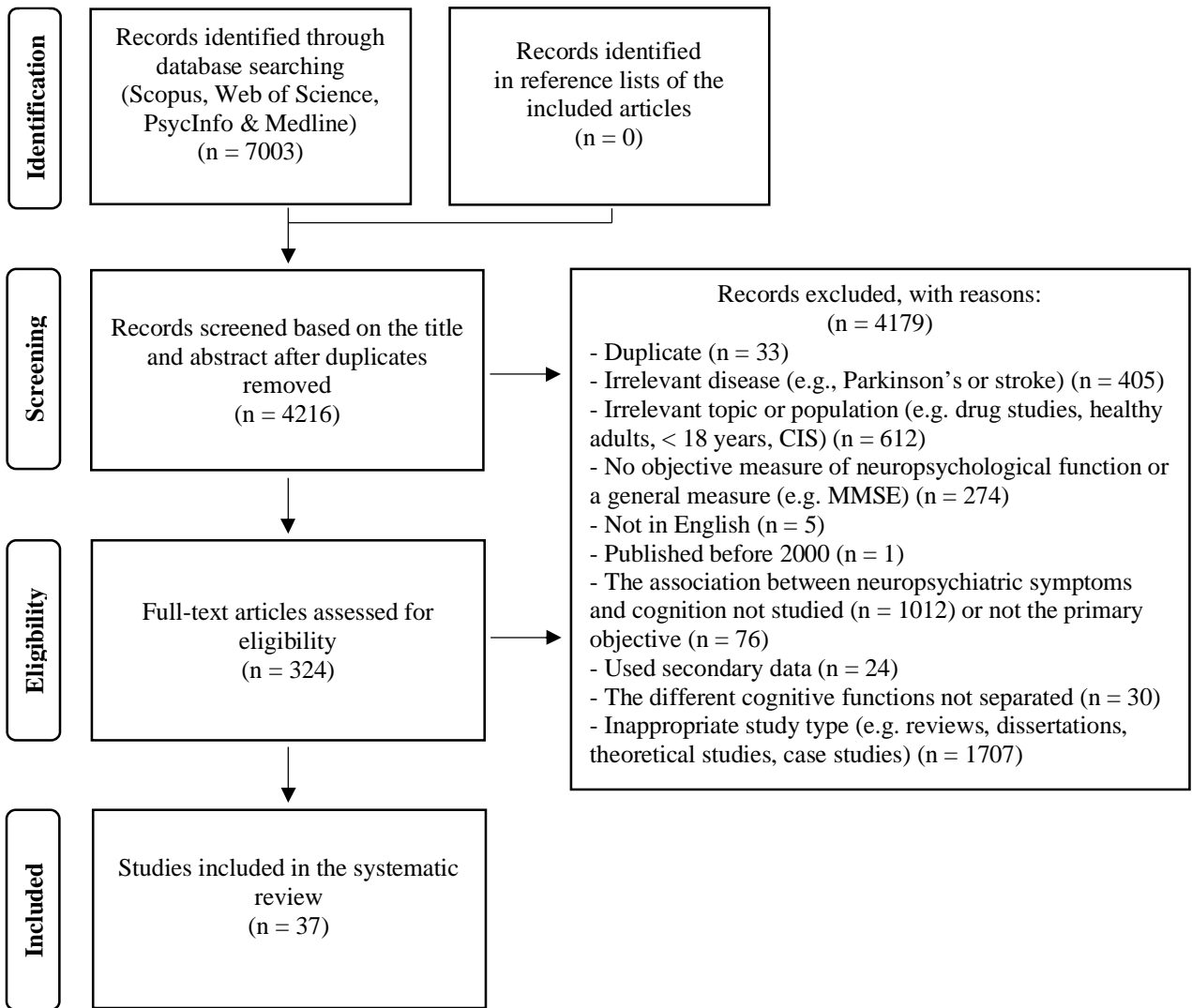


Figure 1. PRISMA flow diagram of systematic review. CIS = Clinically isolated syndrome, MMSE = Mini Mental State Examination.

## **Supplemental material**

The detailed literature search strategy for each database (p. 1), the quality assessment of the included studies (pp. 2–4), and summary of the main results of the included studies (pp. 5–6) are provided in this supplemental material.

### ***Supplementary material 1:***

#### *Search strategy in Ovid Medline & PsycInfo*

1. (multiple sclerosis and (cogniti\* or neuropsychol\*) and (depressi\* or anxi\* or mood disorder\* or bipolar or euphori\* or psychosis or psychotic or pseudobulbar affect or aggressi\* or apath\* or adjustment disorder or lack of insight or anosognosia)).mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tc, id, tm, mf]
  2. limit 1 to yr="2000 -Current"
  3. limit 2 to English language
  4. remove duplicates from 3
- Results n = 2009

#### *Search strategy in Scopus*

TITLE-ABS-KEY ( ( "multiple sclerosis" ) AND ( cogniti\* OR neuropsychol\* ) AND (depressi\* OR anxi\* OR "mood disorder\*" OR bipolar OR euphori\* OR psychosis OR psychotic OR "pseudobulbar affect" OR aggressi\* OR apath\* OR "adjustment disorder" OR "lack of insight" OR anosognosia) AND PUBYEAR > 1999 AND ( LIMIT-TO ( LANGUAGE , "English" ) ) )

Results n = 2833

#### *Search strategy in Web of Science*

TS=(( "multiple sclerosis" ) AND (cogniti\* OR neuropsychol\*) AND (depressi\* OR anxi\* OR "mood disorder\*" OR bipolar OR euphori\* OR psychosis OR psychotic OR "pseudobulbar affect" OR aggressi\* OR apath\* OR "adjustment disorder" OR "lack of insight" OR anosognosia))

Refined by: Languages: English

Timespan: 2000-01-01 to 2022-01-25

Results n = 2161

Supplement Table 1. Quality of cross-sectional studies evaluated with AXIS Scale (Downes et al., 2016).

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20	Total
Beiske et al. (2008)	1	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1	1	0	1	1	16
Birnboim & Miller (2004)	1	1	0	1	1	1	0	1	1	1	1	1	?	0	1	1	1	0	?	1	14
Borghi et al. (2013)	1	1	0	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	17
Borkowska et al. (2021)	1	1	0	1	1	0	0	1	1	1	1	1	?	0	1	1	1	0	1	1	14
Botchorishvili et al. (2021)	1	1	0	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	17
Chiaravalloti & DeLuca (2003)	1	1	0	1	1	0	0	1	1	1	1	1	?	0	1	1	1	1	?	1	14
Cotter et al. (2018)	1	1	0	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	0	16
Denney et al. (2005)	1	1	0	1	1	1	0	1	1	0	0	1	1	0	1	n.a.	1	0	?	1	12
Diamond et al. (2008)	1	1	0	1	1	1	0	1	1	1	1	1	?	0	0	1	1	0	?	?	12
Eizaguirre et al. (2018)	1	1	0	1	1	1	0	1	1	1	1	1	?	0	1	1	1	0	1	1	15
Golan et al. (2018)	1	1	0	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	17
Goretti et al. (2014)	1	1	0	1	1	1	0	1	1	1	1	1	?	0	1	1	0	0	?	1	13
Gottberg et al. (2007)	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	19
Grech et al. (2015)	1	1	0	1	1	0	0	1	1	1	1	1	?	0	1	1	1	1	1	1	15
Hanssen et al. (2014)	1	1	0	1	0	0	0	1	1	1	1	1	1	0	1	1	1	1	1	1	15
Heesen et al. (2010)	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	15
Karadayi et al. (2014)	1	1	1	1	1	?	0	1	1	1	1	1	1	n.a.	1	1	1	1	1	1	17
Krysko & O'Connor (2016)	1	1	0	1	0	1	0	1	1	1	1	1	?	0	1	1	1	1	1	1	15
Leavitt et al. (2020)	1	1	0	1	?	?	0	1	1	1	1	1	?	0	1	1	1	1	1	1	14
Mattioli et al. (2011)	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	?	1	15
Mohammadyfar et al. (2018)	1	1	0	1	1	1	0	1	1	0	1	0	?	0	1	n.a.	0	1	1	1	12
Niino et al. (2014)	1	1	0	1	1	?	0	1	1	1	1	1	?	0	1	1	1	0	1	1	14
Nocentini et al. (2006)	1	1	0	1	1	0	0	1	1	1	1	1	?	0	1	1	1	1	?	1	14
Nunnari et al. (2015)	1	1	0	1	1	1	0	1	1	1	1	1	?	0	1	1	1	1	1	1	16
Ozakbas et al. (2018)	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	0	1	1	17
Ozkul et al. (2020)	1	1	0	1	1	1	0	1	1	1	1	1	?	0	1	1	1	1	1	1	16

(Continued.)

Supplement Table 1. (Continued.)

Article	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20	Total
Patel et al. (2016)	1	1	0	1	?	?	0	1	1	1	1	1	?	0	1	1	1	1	1	1	14
Raimo et al. (2016)	1	1	0	1	1	1	0	1	1	1	1	1	1	n.a.	1	1	1	1	1	1	17
Shawaryn et al. (2002)	1	1	0	1	1	1	0	1	1	1	1	1	?	0	1	1	1	0	1	1	15
Sundgren et al. (2013)	1	1	0	1	1	1	0	1	1	1	1	1	?	0	1	1	1	0	1	1	15
Yigit et al. (2021)	1	1	0	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	17

Methods and results evaluated for psychiatric symptoms and cognition assessment. 1 = the study fulfills the criterion; 0 = the study does not fulfill the criterion; ? = the report does not enable evaluation of the criterion; n.a. = not applicable. Note that more points in the total column correspond to a higher quality of the study.

Q1. Were the aims/objectives of the study clear? Q2. Was the study design appropriate for the stated aim(s)? Q3. Was the sample size justified? Q4. Was the target/reference population clearly defined? (Is it clear who the research was about?) Q5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation? Q6. Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation? Q7. Were measures undertaken to address and categorize non-responders? Q8. Were the risk factor and outcome variables measured appropriate to the aims of the study? Q9. Were the risk factor and outcome variables measured correctly using instruments/ measurements that had been trialled, piloted or published previously? Q10. Is it clear what was used to determined statistical significance and/or precision estimates? (e.g., p values, CIs) Q11. Were the methods (including statistical methods) sufficiently described to enable them to be repeated? Q12. Were the basic data adequately described? Q13. Does the response rate raise concerns about non-response bias? Q14. If appropriate, was information about non-responders described? Q15. Were the results internally consistent? Q16. Were the results for the analyses described in the methods, presented? Q17. Were the authors' discussions and conclusions justified by the results? Q18. Were the limitations of the study discussed? Q19. Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results? Q20. Was ethical approval or consent of participants attained?

Supplement Table 2. Quality of cohort studies evaluated with Newcastle-Ottawa Scale (NOS) (Wells et al., n.d.).

Study	Selection				Comparability	Outcome			Total
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	
Christodoulou et al. (2009)	-	-	+	+	+	+	+	+	6
Chruzander et al. (2013)	+	?	+	+	+	-	+	-	5
Hildebrandt & Eling (2014)	+	?	+	+	-	-	+	+	5
Johansson et al. (2016)	+	?	+	+	+	-	+	+	6
Pérez-Miralles et al. (2021)	+	?	+	+	-	-	+	+	5
Raimo et al. (2020)	+	?	+	+	++	+	+	+	8

'exposure' = Multiple sclerosis; + = the study fulfills the criterion; - the study does not fulfill the criterion; ? = the report does not enable evaluation of the criterion. Note that more points in the total column correspond to a higher quality of the study.

Q1. Representativeness of the exposed cohort Q2. Selection of the non-exposed cohort Q3. Ascertainment of exposure Q4. Demonstration that outcome of interest was not present at start of study Q5. Comparability of cohorts on the basis of the design or analysis Q6. Assessment of outcome Q7. Was follow-up long enough for outcomes to occur Q8. Adequacy of follow up of cohort.

Supplement Table 3. The results on the relationship between depression and cognition.

Article	Attention	Executive functions	Language	Processing speed	Verbal memory	Visual memory	Visuospatial functions	Working memory
Beiske et al. (2008)				-				
Birnboim & Miller (2004)		-						
Borghi et al. (2013)				+	+			
Borkowska et al. (2021)		+						
Botchorishvili et al. (2021)				+	-	-		
Christodoulou et al. (2009)		-		+	+	+	-	
Chruzander et al. (2013)				-				
Cotter et al. (2018)	-	-		+		-		-
Denney et al. (2005)		-						
Diamond et al. (2008)		-		+	-			
Eizaguirre et al. (2018)				+				
Golan et al. (2018)	+	+	+	+	+	+	+	
Goretti et al. (2014)		+		-	-	-		
Gottberg et al. (2007)				-	+			
Grech et al. (2015)	-	+		-				-
Hanssen et al. (2014)		-						
Heesen et al. (2010)	+	-	-	+	+			
Hildebrandt & Eling (2014)	+		-	+	+		-	
Johansson et al. (2016)				-				
Karadayi et al. (2014)		-		-	-			
Krysko & O'Connor (2016)				-				
Leavitt et al. (2020)	+		-	+	-	-		
Mattioli et al. (2011)		-		-	-			
Mohammadyfar et al. (2018)								-
Niino et al. (2014)		+		+	+	+		
Nocentini et al. (2006)		+	+	+	+	+	+	
Nunnari et al. (2015)		-		+	+	+		
Ozakbas et al. (2018)				+	+	-		
Ozkul et al. (2020)		-		-	-	-		
Patel et al. (2016)				+				
Pérez-Miralles et al. (2021)		+		+	+	-		
Raimo et al. (2016)		-		-	-	-	+	-
Raimo et al. (2020)		+			-	-	+	+
Shawaryn et al. (2002)				+	+			
Sundgren et al. (2013)	+	+	-	+		+	+	
Yigit et al. (2021)				-	-	-		

+ = association; - = no association.

Supplement Table 4. The results on the relationship between anxiety and cognition.

Article	Attention	Executive functions	Language	Processing speed	Verbal memory	Visual memory	Visuospatial functions	Working memory
Beiske et al. (2008)				-				
Borghi et al. (2013)				-	+			
Christodoulou et al. (2009)		-		-	+		-	
Goretti et al. (2014)		-		+	-			
Grech et al. (2015)	-	+		-				-
Karadayi et al. (2014)		-		-	-			
Leavitt et al. (2020)	-		-	-		+		
Mohammadyfar et al. (2018)								-
Patel et al. (2016)				-				

+ = association; - = no association.

Supplement Table 5. The results on the relationship between apathy and cognition.

Article	Attention	Executive functions	Language	Processing speed	Verbal memory	Visual memory	Visuo-spatial functions	Working memory
Chiaravalloti & DeLuca (2003)		+	-	+	-			+
Niino et al. (2014)		+		+	+	+		
Raimo et al. (2016)		+		-	-	-	+	-
Raimo et al. (2020)		+		-	-	+	+	+

+ = association; - = no association.

Table 1. Most common neuropsychiatric symptoms in multiple sclerosis presented in descending order of prevalence.

Neuropsychiatric symptom	Prevalence in MS
Depression	23.7% – 30.5% (Boeschoten et al., 2016; Marrie et al., 2015; Peres et al., 2022)
Anxiety	21.9% – 35.19% (Boeschoten et al., 2016; Marrie et al., 2015; Peres et al., 2022)
Pseudobulbar affect	23.3% (Nabizadeh et al., 2022)
Aggression	23% (Rosti-Otajärvi & Hämäläinen, 2013)
Apathy	22% (Rosti-Otajärvi & Hämäläinen, 2013)
Euphoria	12% (Rosti-Otajärvi & Hämäläinen, 2013)
Lack of insight	11% (Rosti-Otajärvi & Hämäläinen, 2013)
Bipolar disorder	5.8% (Marrie et al., 2015)
Psychosis	4.3% (Marrie et al., 2015)

Table 2. Characteristics of the reviewed studies and the results on the relationship between neuropsychiatric symptoms and objective cognitive functioning in multiple sclerosis patients.

Study	Study design	MS population: N (% female), type of MS, age (mean $\pm$ SD)	Measure(s) of psychiatric symptoms	Measure(s) of cognitive functions	Significant results ( $p \leq .05$ ) on the relationship between neuropsychiatric symptoms and objective cognitive functioning
Beiske et al. (2008)	Cross-sectional	N = 140 (67.1%) 74% RRMS, 26% PPMS age: N/A	HSCL-25	PASAT	No significant association between PASAT and HSCL-25 anxiety or depression scores.
Birnboim & Miller (2004)	Cross-sectional	N = 76 (65.8%) 53 % RRMS, 47% SPMS age: 42.6 $\pm$ 8.	BDI	SAT	BDI depression scores were not significantly correlated with SAT.
Borghi et al. (2013)	Cross-sectional	N = 303 (70%) 88% RRMS, 7% SPMS, 3% PPMS, 2% RPMS age: 43.1 $\pm$ 10.8	HADS	BRB-N (PASAT, SDMT, SRT)	Higher HADS depression scores significantly predicted lower performance on SRT-LTS, SRT-CLTR, SRT-D and SDMT. Higher HADS anxiety scores significantly predicted better performance on SRT-D.
Borkowska et al. (2021)	Cross-sectional	N = 22 (90.9%) 100% RRMS age: 37.7 $\pm$ 7.1	BDI-II	COWAT, HCT, Semantic fluency, PMT, SCWT	BDI-II depression scores were positively correlated with the number of errors in the HCT.
Botchorishvili et al. (2021)	Cross-sectional	N = 68 (70.6%) 76% RRMS, 18% SPMS, 6% PPMS age: 39.2 $\pm$ 9.9	BDI	BICAMS (SDMT, CVLT-II, BVMT-R)	BDI depression scores were negatively correlated with SDMT.
Chiaravalloti & DeLuca (2003)	Cross-sectional	N = 26 (N/A) type of MS N/A age: 46.0 $\pm$ 8.0	FrSBe (self-ratings of apathy)	BNT, WAIS-R (DS), WMS-R (LM I & II), PASAT, COWAT, Semantic Fluency, SCWT, TMT, WCST	FrSBe self-ratings of apathy were negatively correlated with Semantic Fluency, DS backward and PASAT and positively correlated with WCST perseverative errors.

(Continued.)

Table 2. (Continued.)

Study	Study design	MS population: N (% female), type of MS, age (mean $\pm$ SD)	Measure(s) of psychiatric symptoms	Measure(s) of cognitive functions	Significant results ( $p \leq .05$ ) on the relationship between neuropsychiatric symptoms and objective cognitive functioning
Christodoulou et al. (2009)	Longitudinal study	N = 38 (57.9%) 74% RRMS, 26% SPMS, age at baseline: 45.5 $\pm$ 8.4	CES-D, CMDI, STAI State, PANAS	BRB-N (SRT, SPART), COWAT, MACFIMS (JOLO, D-KEFS Card Sorting Test), PASAT, SDMT	Baseline CMDI Mood scores were negatively correlated with 1 year change in SRT-CLTR, SRT-D and SPART. Baseline CMDI Evaluative scores were negatively correlated with 1 year change in SRT-D. Baseline CMDI Vegetative scores were negatively correlated with 1 year change in SRT-D and SDMT. Baseline CES-D scores were negatively correlated with 1 year change in SPART-D. Baseline STAI state anxiety scores were negatively correlated with 1 year change in SRT-CLTR, SPART and SPART Delay. Baseline PANAS Negative scores were negatively correlated 1 year change in SPART.
Chruzander et al. (2013)	Longitudinal study	N = 118 (72%) Baseline: 47% RRMS, 53% CPMS age: 49 $\pm$ 11 Follow-up: 20% RRMS, 80% CPMS	BDI-II	SDMT	Baseline BDI-II depression scores did not predict SDMT at the 10-year follow-up and baseline SDMT scores did not predict BDI-II depression scores at the 10-year follow-up.
Cotter et al. (2018)	Cross-sectional	N = 90 (75.6%) 72% RRMS, 17% SPMS, 11% PPMS age: 44.5 $\pm$ 10.9	GDS	CANTAB (Match to Sample, Paired Associates Learning, Spatial Working Memory)	Depressed MS patients showed more impaired processing speed than non-depressed MS patients. <sup>a</sup>
Denney et al. (2005)	Cross-sectional	N = 60 (66.7%) 33% RRMS, 33% PPMS, 33% SPMS age: 48.4 $\pm$ N/A	CES-D	TOL, SCWT	No significant differences between depressed MS patients and non-depressed MS patients on any of the cognitive measures. However, depressed MS patients, but not non-depressed MS patients, had significantly lower TOL point score than healthy controls.

(Continued.)

Table 2. (Continued.)

Study	Study design	MS population: N (% female), type of MS, age (mean $\pm$ SD)	Measure(s) of psychiatric symptoms	Measure(s) of cognitive functions	Significant results ( $p \leq .05$ ) on the relationship between neuropsychiatric symptoms and objective cognitive functioning
Diamond et al. (2008)	Cross-sectional	N = 48 (72.9%) 58% RRMS, 25% SSPM, 15% PPMS, 2% PRMS age: 48.3 $\pm$ N/A	CES-D	CVLT, COWAT, VTSAT	No significant differences between depressed MS patients and non-depressed MS patients on any of the cognitive measures. However, non-depressed subgroup of individuals with very low CES-D scores performed better than individuals with higher CES-D scores on VTSAT.
Eizaguirre et al. (2018)	Cross-sectional	N = 47 (66%) 100% RRMS age: 39.0 $\pm$ 13.2	BDI-II	PASAT, SDMT	BDI-II depression scores were negatively correlated with SDMT. Lower SDMT scores significantly predicted higher BDI-II scores.
Golan et al. (2018)	Cross-sectional	N = 699 (75.3%) 86% RRMS, 13% SPMS, 1% PPMS age: 46.1 $\pm$ 10.5	BDI	CCTB	BDI depression scores were negatively correlated with memory, executive functions, visual-spatial processing, verbal function, information processing speed, and attention index scores. Higher BDI scores significantly predicted lower performance on memory, executive functions, visual-spatial processing, information processing speed, and attention index scores.
Goretti et al. (2014)	Cross-sectional	N = 190 (73.7%) 100% RRMS age: 37.5 $\pm$ 9.9	BDI, STAI	BRB-N (PASAT, SDMT, SPART, SRT WLG), SCWT	In the univariate analysis STAI state anxiety score was significantly associated with failure on the SDMT and BDI depression scores were significantly associated with impairment on the SCWT. In the multivariate analysis STAI state anxiety score was associated with poorer performance on the SDMT.
Gottberg et al. (2007)	Cross-sectional	N = 166 <sup>c</sup> (71.1%) 48% SPMS, 42% RRMS, 10% PPMS age: 51 $\pm$ 12	BDI	Free recall portion of the Free Recall and Recognition of 12 Random Words Test, SDMT	Depressed MS patients performed poorer than non-depressed MS patients on Free Recall and Recognition of 12 Random Words Test.

(Continued.)

Table 2. (Continued.)

Study	Study design	MS population: N (% female), type of MS, age (mean $\pm$ SD)	Measure(s) of psychiatric symptoms	Measure(s) of cognitive functions	Significant results ( $p \leq .05$ ) on the relationship between neuropsychiatric symptoms and objective cognitive functioning
Grech et al. (2015)	Cross-sectional	N = 107 (77.6%) 78% RRMS, 22% SPMS age: 48.8 $\pm$ 11.1	BDI-II, BDI-FS, STAI	BADS (Action Program, Zoo Map, MSET), Hayling Sentence Completion, IGT, Reading Span task, SDMT, TEA (ECD, Visual Elevator), TMT, WLG	BDI-FS depression scores were significantly correlated with Zoo Map and Zoo Map without time penalty. Better performance on Zoo Map without the time penalty predicted higher BDI-FS scores. IGT Deck D was significantly correlated with STAI state anxiety, but it did not significantly predict state anxiety. BDI-II depression scores or STAI trait anxiety scores correlated with none of the objective cognitive tests.
Hanssen et al. (2014)	Cross-sectional	N = 120 (72.5%) 49% RRMS, 28% SPMS, 23% PPM age: 53.2 $\pm$ 8.1	BDI-II	COWAT, D-KEFS (SCWT), SDMT	No significant association between BDI-II scores of moderate or more severe depression and Executive Deficit Index. <sup>a</sup>
Heesen et al. (2010)	Cross-sectional	N = 50 (58%) 54% RRMS, 46% SPMS age: 43.7 $\pm$ 10	CES-D	PASAT, RAVLT, RWT, SDMT <sup>b</sup> , TAP (alertness, divided attention, shift), WST	CES-D depression scores were negatively correlated with SDMT <sup>b</sup> , RAVLT total, RAVLT-DR, TAP alertness and TAP shift.
Hildebrandt & Eling (2014)	Longitudinal study	N = 40 (65%) 100% RRMS age: 38.2 $\pm$ N/A	BDI	WAIS-R (BDT, IN, PCT, SI), CVLT, TAP (Alertness, OAT), PASAT	Increase of depression over one year was related to errors on the OAT at baseline. MS patients with depressed mood at Visit 2 had significantly lower scores than MS patients without depressive mood at Visit 2 on PASAT, CVLT total learning, CVLT short-term cued recall, CVLT long-term free recall and CVLT long-term cued recall as well as more errors and longer response time on the OAT at Visit 1.
Johansson et al. (2016)	Longitudinal study	N = 199* (67.8%) 61% RRMS, 39% PPMS/SPMS age: N/A	BDI	SDMT	SDMT scores at baseline did not predict the occurrence of depressive symptoms (BDI Total) or mood symptoms (BDI Mood) during two years (at baseline, 12 and 24 months).

(Continued.)

Table 2. (Continued.)

Study	Study design	MS population: N (% female), type of MS, age (mean $\pm$ SD)	Measure(s) of psychiatric symptoms	Measure(s) of cognitive functions	Significant results ( $p \leq .05$ ) on the relationship between neuropsychiatric symptoms and objective cognitive functioning
Karadayi et al. (2014)	Cross-sectional	N = 31 (67.7%) 90% RRMS, 7% SPMS, 3% PPMS age: $38.3 \pm 9.9$	HAM-D, HAM-A,	CT, SCWT, SDLT, RAVLT	There were no significant correlations between cognitive variables and HAM-A anxiety or HAM-D depression scores. Cognitive variables were neither predicted by depression or anxiety scores.
Krysko & O'Connor (2016)	Cross-sectional	N = 34 (55.9%) 100% RRMS age: $21.3 \pm 2.6$	BDI-II	SDMT	BDI depression scores were not significantly correlated with SDMT.
Leavitt et al. (2020)	Cross-sectional	MEM CONNECT cohort: N = 70 (75.7%) 100% RRMS age: $40.7 \pm 11.1$	BDI-II, NEO-N	BRB-N (BVMT-R), COWAT, Semantic Fluency, SCWT, SDMT, SRT, WAIS-IV (DS)	NEO-N anxiety scores were negatively correlated with nonverbal memory. <sup>a</sup> BDI-II depression scores were negatively correlated with attention and processing speed. <sup>a</sup>
Mattioli et al. (2011)	Cross-sectional	N = 255 <sup>d</sup> (66.7%) 88% RRMS, 12% CPMS age: $40 \pm 11.3$	BDI-FS	BRN-N (PASAT, SDMT, SRT), COWAT, Semantic Fluency	BDI-FS depression scores were not correlated with individual cognitive test scores. BDI-FS scores of MS patients with significant depressive symptoms were not significantly different between impaired versus unimpaired MS patients in executive function domain, attention domain or memory domain. <sup>a</sup>
Mohammadyfar et al. (2018)	Cross-sectional	N = 54 (N/A) 100% RRMS age: N/A for MS only	DASS-21	WAIS (DS)	No significant differences were reported between MS patients with and without depression or with and without anxiety on auditory short-term memory, visual short-term memory, auditory active memory, or visual active memory.
Niino et al. (2014)	Cross-sectional	N = 184 (73.4%) 91% RRMS, 8% SPMS, 1% PPMS age: $39.3 \pm 10.1$	AS, BDI-II	BRB-N (PASAT, SDMT, SPART, SRT, WLG)	AS apathy scores were negatively correlated with SRT-LTS, SRT-CLTR, SRT-D, SPART, SPART-D, SDMT, PASAT-3, PASAT-2 and WLG. BDI depression scores were negatively correlated with SRT-LTS, SPART, SPART-D, SDMT, PASAT-3, PASAT-2 and WLG.
Nocentini et al. (2006)	Cross-sectional	N = 461 (N/A) 100% RRMS age: $35.9 \pm 8.4$	BDI	CD, CDL, COWAT, IVM, MCST, PC, RCPM, RAVLT, SDMT	BDI depression scores were negatively correlated with RAVLT-IR, RAVLT-DR, IVM, CD, CDL, RCPM, PC, COWAT and SDMT. BDI scores were positively correlated with MCST-PR. BDI scores were not significantly correlated with MCST-NPE.

(Continued.)

Table 2. (Continued.)

Study	Study design	MS population: N (% female), type of MS, age (mean $\pm$ SD)	Measure(s) of psychiatric symptoms	Measure(s) of cognitive functions	Significant results ( $p \leq .05$ ) on the relationship between neuropsychiatric symptoms and objective cognitive functioning
Nunnari et al. (2015)	Cross-sectional	N= 60 (66.7%) 87% RRMS, 13% PPMS age: 39.4 $\pm$ 10.6	BDI-II	BRB-N (PASAT, SDMT, SPART, SRT, WLG)	BDI-II depression scores were negatively correlated with PASAT-3, PASAT-2, SDMT and SPART. Depressed MS-patients performed significantly worse than non-depressed MS patients on PASAT-3, PASAT-2, SDMT, SPART, SPART-D and SRT-CLTR. In a multiple regression analysis BDI-II scores significantly predicted lower performance on PASAT-3, PASAT-2, SDMT, SPART, SPART-D and SRT-CLTR.
Ozakbas et al. (2018)	Cross-sectional	N = 487 (68.6%) 100% RRMS age: 35.3 $\pm$ 9.39	BDI	BRB-N (PASAT, SDMT, SPART, SRT)	BDI depression scores were negatively correlated with PASAT, SDMT and SRT-Instant memory.
Ozkul et al. (2020)	Cross-sectional	N = 112 (77.7%) 86% RRMS, 14% PPMS age 34 $\pm$ N/A	BDI-II	BRB-N (PASAT, SDMT, SPART, SRT, WLG)	BDI-II depression scores were not significantly correlated with any of the cognitive tests.
Patel et al. (2016)	Cross-sectional	N = 101 (69.3%) 70% RRMS, 22% SPMS, 8% PPMS age: 44.6 $\pm$ N/A	HADS	SDMT with and without distracters	Depressed MS patients were significantly slower than non-depressed MS patients on the distracter SDMT and non-distracter SDMT. Significantly more depressed than non-depressed MS patients were impaired on the distracter SDMT, but this difference was not significant on the non-distracter c-SDMT. Additionally, HADS depression score was a more significant predictor of slower performance on the distracter SDMT ( $p = .034$ ) than on the non-distracter SDMT ( $p = .053$ ). There were no significant associations between anxiety and cognition.
Pérez-Miralles et al. (2021)	Longitudinal study	N = 55 (43.6%) 100% PPMS age at baseline: 55.8 $\pm$ 9.5	BDI-FS	BRB-N (PASAT, SDMT, SPART, SRT, WLG)	Lower baseline SDMT scores were associated with higher risk of depressive symptoms at month 12 and predicted depressive symptoms at month 12. Lower SRT-LTS, SRT-CLTR, SRT-D and WLG scores at baseline predicted moderate-to-severe depression at month 12.
Raimo et al. (2016)	Cross-sectional	N = 125 (79.2%) 86% RRMS, 8% SPMS, 6% PPMS age: 42.4 $\pm$ 10.6	AES-S, HAM-D, Diagnostic interviews	CAT, Corsi's test, CDT, IML, COWAT, Semantic Fluency, RAVLT, RCPM, ROCF, SCWT, TMT, Verbal Span	"Pure" apathetic (apathetic without depression) MS patients had poorer performance than non-apathetic (with or without depression) MS patients on SCWT and IML. Patients with both apathy and depression had lower scores than patients with depression only on CDT, IML and SCWT. Patients with both apathy and depression had lower scores than patients without apathy or depression on CDT, IML, RCPM, and SCWT as well as lower scores than patients with "pure" apathy on CDT and RCPM.

(Continued.)

Table 2. (Continued.)

Study	Study design	MS population: N (% female), type of MS, age (mean ± SD)	Measure(s) of psychiatric symptoms	Measure(s) of cognitive functions	Significant results ( $p \leq .05$ ) on the relationship between neuropsychiatric symptoms and objective cognitive functioning
Raimo et al. (2020)	Longitudinal study (follow-up to Raimo et al. 2016)	N = 100 (N/A) type of MS N/A age: $42.9 \pm 10.3$	AES-S, HAM-D, Diagnostic interviews	CAT, Corsi's test, CDT, IML, COWAT, Semantic Fluency, RAVLT, RCPM, ROCF, SCWT, TMT, Verbal Span	MS patients with stable apathy during 2 years had significantly lower scores than MS patients whose apathy remitted during 2 years on SCWT both at baseline as well as at follow-up. At 2-year follow-up: Patients with "pure" apathy had poorer performance than patients without apathy or depression on Corsi's test, ROCF delayed recall and SCWT, but they performed better than patients with both apathy and depression and patients with depression only on IML. Patients with depression only had lower scores than patients without apathy or depression on CDT, Corsi's test, IML, RCPM, and semantic fluency, but they performed better than patients without apathy or depression on ROCF copy. Patients with both apathy and depression had lower scores than patients without apathy or depression on CDT, Corsi's test, IML, RCPM, ROCF copy, SCWT, and semantic fluency.
Shawaryn et al. (2002)	Cross-sectional	N = 90 (64.4%) 51% RRMS, 17% SPMS, 14% PPMS, 12% PRMS 6% Unclassified age: $42.1 \pm 9.2$	BDI	CVLT, PASAT	BDI depression scores were negatively correlated with CVLT and PASAT. Poor performance on the PASAT predicted higher BDI scores. Perception of illness intrusiveness mediated the relationship between CVLT and BDI depression scores.
Sundgren et al. (2013)	Cross-sectional	N = 72 (70.8%) 100% RRMS age: $37.9 \pm 10.0$	BDI	D-KEFS (COWAT, SCWT, TMT), WAIS-III (BDT, DSCT, DS, SST), BVRT-5, SRB:1	BDI-NS depression scores were negatively correlated with processing speed, executive functions, visual perception/organization, and attention. BDI-S depression scores were negatively correlated with processing speed, executive functions, visual perception/organization, and visual memory. In multiple regression analysis BDI-NS was a stronger predictor than BDI-S and BDI Total of impairment in all cognitive domains (apart from verbal ability which was not significantly predicted by any of the depression measures). BDI-NS predicted most strongly executive functions and visual perception/organization. <sup>a</sup>
Yigit et al. (2021)	Cross-sectional	N = 200 (70%) 95% RRMS, 3% SPMS, 2% PPMS age: $36.5 \pm 9.7$	BDI	BICAMS (SDMT, CVLT-II, BVMT-R)	BDI depression scores were not significantly correlated with or neither predicted performance on any of the BICAMS subtests. There were no significant differences between depressed MS patients and non-depressed MS patients on any of the BICAMS subtests.

(Continued.)

Table 2. (Continued.)

Abbreviations in alphabetical order: AES-S = Self-reported version of Apathy Evaluation Scale; AS = Apathy Scale; BADS = Behavioral Assessment of the Dysexecutive Syndrome; BDI = Beck Depression Inventory; BDI-II = BDI-2nd Edition; BDI-FS = BDI-Fast Screen; BDI-NS = BDI nonsomatic component (items 1–13); BDI-S = BDI somatic component (items 14–21); BDT = Block Design Test; BICAMS = Brief International Cognitive Assessment for MS; BNT = Boston Naming Test; BRB-N = Rao's Brief Repeatable Battery of Neuropsychological Tests; BVMT-R = Brief Visuospatial Memory Test-Revised; BVRT-5 = Benton Visual Retention Test-5th Edition; CANTAB = Cambridge Neuropsychological Test Automated Battery; CAT = Constructional Apraxia Task; CCTB = Comprehensive Computerized Cognitive Testing Battery (NeuroTrax Corporation, Modiin, Israel); CD = freehand Copy of Drawings; CDL = Copying Drawings with Landmarks; CDT = Clock Drawing Test; CES-D = Center for Epidemiological Studies Depression Scale; CMDI = Chicago Multiscale Depression Inventory; COWAT = Controlled Oral Word Association Test; CPMS = Chronic Progressive Multiple Sclerosis; CT = Verbal and Nonverbal Cancellation Test; CVLT = California Verbal Learning Test; CVLT-II = CVLT-2nd Edition; D-KEFS = Delis-Kaplan Executive Function System; DASS = 21-item Depression Anxiety Stress Scale; DSCT = Digit Symbol Coding Test; DS = Digit Span; ECD = Elevator Counting with Distraction; F = Female; FAB = Frontal Assessment Battery; FrSBe = Frontal Systems Behavior Scale; GDS = Geriatric Depression Scale; HADS = Hospital Anxiety and Depression Scale; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; HCT = Halstead Category Test; HSCL-25 = Hopkins Symptom Checklist; IGT = Iowa Gambling Task; IML = Inverse Motor Learning Test; IN = Information; IVM = Immediate Visual Memory Test; JOLO = Judgment of Line Orientation; LM = Logical Memory; M = Male; MACFIMS = Minimal Assessment of Cognitive Function in MS; MCST = Modified Card Sorting Test; MCST-NPE = MCST-Non-Perseverative Errors; MCST-PR = MCST- Perseverative Responses; MS = Multiple sclerosis; MSET = Modified Six Elements Task; N/A = Not available; NEO-N = NEO Five Factor Inventory, Neuroticism scale; OAT = Object Alternation Test; PANAS = Positive and Negative Affect Scale; PASAT = Paced Auditory Serial Addition Task; PASAT2 = 2 s version of PASAT; PASAT3 = 3 s version of PASAT; PC = Phrase Construction; PC = Picture Completion Test; PMT = Porteus Maze Test; PPMS = Primary Progressive MS; PRMS = Progressive Relapsing MS; RAVLT = Rey Auditory Verbal Learning Test; RAVLT-DR = RAVLT Delayed Recall; RAVLT-IR = RAVLT Immediate Recall; RCPM = Raven's Progressive colored Matrices; ROCF = Rey-Osterreith Complex Figure; RPMS = Relapsing Progressive MS; RRMS = Relapsing Remitting MS; RWT = Regensburger Wortflüssigkeitstest; SAT = Strategy Application Test; SCWT = Stroop Color-Word Interference Test; SDLT = Serial Digit Learning Test; SDMT = Symbol Digit Modality Test; SI = Similarities; SPART = 10/36 Spatial Recall Test total recall over three trials; SPART-D = SPART Delayed recall; SPMS = Secondary Progressive MS; SRB:1 = Vocabulary Test; SRT = Selective Reminding Test; SRT-CLRT = SRT-Consistent Long Term Retrieval; SRT-D = SRT-Delayed recall; SRT-LTS = SRT-Long Term Storage; SST = Symbol Search Test; STAI = State-Trait Anxiety Inventory; TAP = Testbattery for Attentional Performance; TEA = Test of Everyday Attention; TMT = Trail Making Test; TOL = Tower of London; VTSAT = Visual Threshold Serial Addition Test; WAIS = Wechsler Adult Intelligence Scale; WAIS-IV = WAIS-4th Edition; WAIS-R = WAIS-Revised; WCST = Wisconsin Card Sorting Test; WLG = Word List Generation; WMS-R = Wechsler Memory Scale-Revised; WST = Wortschatztest.

<sup>a</sup>See the classifications for cognitive domains in each article. <sup>b</sup>Secondary data. <sup>c</sup>149 MS patients completed the BDI. <sup>d</sup>Cognitive tests were performed only by 46 MS patients with significant depressive levels (BDI-FS  $\geq$  4).