Review Article

Association between myasthenia gravis and cognitive function: A systematic review and meta-analysis

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Abstract

The course of myasthenia gravis (MG) is complicated by increased reports of cognitive defects in both human and animal models, which suggests potential central nervous system (CNS) damage. We conducted a systematic review of the relationships between MG and cognitive function. This systematic review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Major databases were searched to examine the neuropsychological studies of adults with MG. Weighted effect sizes were pooled by cognitive domain. Eight studies representing 300 subjects were included. Eight cognitive domain categories were identified: (i) Mini-Mental State Examination (MMSE), (ii) language, (iii) processing speed, (iv) verbal learning and memory, (v) visual learning and memory, (vi) attention span, (vii) response fluency, and (viii) motor performance. Nine (cognitive domain categories, MMSE, language, processing speed, verbal learning and memory (except for delayed recall memory), and motor performance) of 16 cognitive tasks revealed significant moderate effect sizes. Verbal logical-delayed memory, finger tapping with the preferred hand, and the Symbol Digit Modalities Test showed a greater magnitude relationship to cognitive function than did other specific cognitive domains. Verbal learning and memory seems to be the most significant affected according to cognitive domain categories. For MG, the ability of attention, response fluency, visual learning, and memory seems to be reserved. The MG patients seem to perform significantly worse than the non-MG controls in a range of cognitive domains. Our findings should be interpreted with caution because of the clinical and methodological heterogeneity of included studies.

Key Words

Cognitive impairment, meta-analysis, myasthenia gravis

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Introduction

Understanding how disease processes affect functional interactions in the central nervous system (CNS) represents a core challenge of neuroscience research. Currently, myasthenia gravis (MG) is considered to be an uncommon autoimmune neuromuscular disorder. However, the course of MG is complicated by increased reports of cognitive defects in both human and animal models, which may suggest partial or potential CNS damage.[1-3] The observation of cognitive deficits among many MG patients may have several explanations:

1. There may be a hypothetical pathogenic central effect of antibodies (Abs) against the acetylcholine receptor (AChR);[4]
2. certain individuals may not possess protective factors, such as age, disease severity, and type of treatment;[5]
3. mood disturbance; and
4. a possible effect of nonspecific immunological processes.

To evaluate these possibilities, researchers have attempted to detect subtle cognitive differences between MG patients and controls;[6-8] however, the results vary widely across studies because of limited sample sizes and differences in the study populations and evaluation criteria. Thus, there is inadequate conclusive evidence to confirm cognitive deficit in MG patients. To determine whether an association exists between MG and cognitive function decline, we conducted a systematic review and meta-analysis of the literature.

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Materials and Methods

Data sources

This systematic review was undertaken following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] We searched Medline, Web of Science, Embase, PsycINFO, and the Chinese Biomedical

Research literature to retrieve relevant studies published from inception to July 2014. Various combinations of search terms were used, including; myasthenia gravis, neuropsycholog*, neurocognitive, cognitive, impairment, deficit, and functioning. To identify the articles missed by our original search strategy, we reviewed the references of the identified articles.

Inclusion/exclusion criteria

Two reviewers (Zhifeng Mao and Xueqiang Hu) screened all abstracts of the identified articles based on the following inclusion criteria:

1. The study population consisted of adults (wholly or predominantly);
2. a comparison control group (non-MG group) was included;
3. the study reported results for one or more separable cognitive domains (i. e., not only the global cognitive status), and
4. provided data with reporting of performance means and standard deviation for both patients and controls.

Exclusion criteria included:

1. Studies of mixed populations were excluded unless separate results for patients with MG were reported;
2. studies investigating individuals with preexisting dementia; and
3. reviews, editorials, letters, case series, and case reports.

Data extraction

Two reviewers independently selected studies that fulfilled the inclusion criteria and extracted the MG data and the mean cognitive function scores in the MG and non-MG groups [Table 1]. Missing data were obtained from the authors whenever possible.

Nonrandomized meta-analyses were performed, and study quality was assessed using a modified version of the Newcastle-Ottawa Scale [Table 2].[16-18] Up to eight points were assigned to each study based on the quality of the MG and non-MG group selection, comparability of groups, and the cognitive function assessment.

Table 1: Characteristics of the included studies

Author	Study design	Control-Matched	MG patients						Controls			Outcome: Domain Assessed
			GMG (%)	Age	% Male	Disease duration	Treatment (%)	No.	Age	% Male	No.	
Bartel *et al*.,[5] 1995	Cross-sectional	Age, gender, education	93.8	54	31.2	7.7 years	AChE (75) PRED (75)	16	NR	NR	16	(i), (iv), and (vii)
Chen *et al*.,[10] 2006	Cross-sectional	Age, education	52.2	37.4 (15.3)	53.6	5.56 (2.13)	AChE (91.3) PRED (68.1)	69	39.3 (14.9)	52.8%	36	(ii), (iii),(vi), and (viii)
Iwasaki *et al*.,[11] 1990	Cross-sectional	Age, education	100	41.5 (13.6)	29.6	4.5 years	AChE (75) PRED (0)	27	42.1 (13.0)	NR	27	(i) and (iii)
Marra *et al*.,[12] 2009	Cross-sectional	Age, gender, education	NR	71.8 (6.1)	58	11.1-14.6	AChE (83) PRED (75)	100	72.8 (7.2)	48.4	31	(i), (ii), (iii), (iv), (v), and (vi)
Paradis *et al*.,[13] 1994	Cross-sectional	Age, race, education	NR	44.4	40	9.6 (11.69)	NR	15	41.9	18.2	11	(ii), (iii), (iv), and (v)
Paul *et al*.,[8] 2000	Cross-sectional	Age, education	100	71 (13.35)	NR	7.74 (6.71)	AChE (75) PRED (46)	28	51.2 (15.4)	NR	18	(iv), (v), and (vi)
Sitek *et al*.,[14] 2009	Cross-sectional	Age, education	87.9	47 (12)	NR	8 (7)	AChE (58) PRED (46)	33	49 (12)	NR	30	(i), (v), (vi), (vii), and (viii)
Tucker *et al*.,[15] 1988	Cross-sectional	Age, education	NR	52.9 (20.6)	NR	NR	AChE (NR) PRED (12.5)	12	48.4 (10.2)	NR	10	(ii) and (iii)

GMG = Generalized myasthenia gravis, AChE = acetylcholinesterase inhibitor therapy, NR = not record, PRED = prednisone. The following codes were used for outcome domain assessed: (i) Mini-Mental State Examination (MMSE), (ii) language, (iii) verbal learning and memory, (iv) visual learning and memory, (v) attention span, (vi) response fluency, (vii) motor performance, and (viii) processing speed

Table 2: Study quality assessment

Author	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability on the basis of design or analysis	Assessment of outcome blind?	Nonresponse rate	Total score
Bartel *et al*.[5]	1	NR	1	1	2	0	1	6
Chen *et al*.[10]	1	NR	1	1	2	0	1	6
Iwasaki *et al*.[11]	1	0	1	1	2	0	1	6
Marra *et al*.[12]	1	1	1	1	2	0	1	7
Paradis *et al*.[13]	1	NR	0	1	2	0	1	5
Paul *et al*.[8]	1	NR	1	1	2	0	1	6
Sitek *et al*.[14]	1	NR	1	1	2	0	1	6
Tucker *et al*.[15]	1	NR	1	1	2	0	1	6

0 = definitely no (high risk of bias), 1 = Mostly no, 2 = Mostly yes, 3 = definitely yes (low risk of bias), NR = not record

Classification of neuropsychological tests and cognitive domain

Neuropsychological measures were defined by objectively assessing a recognized cognitive domain. Eight cognitive domains categories were identified:

1. Mini-Mental State Examination (MMSE),
2. Language,
3. Verbal learning and memory,
4. Visual learning and memory,
5. Attention span,
6. Response fluency,
7. Motor performance, and
8. Processing speed.

The domain of "attention" in the current study refers to immediate memory span ability, as measured by digit span forwards and digit span backwards, and does not reflect more complex attentional processes, such as sustained attention. Neuropsychological instruments that potentially measure separate functions but are traditionally clustered within a single domain (i. e., attentional switching and verbal fluency as both measures of "executive functioning") were analyzed separately because previous research has suggested that the inappropriate aggregation of performances across a range of tests purported to test a common function can obscure the neuropsychological findings. The classification of neuropsychological tests by cognitive domain can be seen in Table 3.

Statistical analyses

The pooling of effect sizes and heterogeneity tests was performed using Review Manager 5.2 software. Pooled effect sizes were calculated for each cognitive domain. Random effects modeling for the weighted mean difference was used because it provides a more conservative estimate and, thus, is less likely to overestimate the true effect size. For certain cognitive tests, in which lower scores represented superior performance, the sign of the effect size was reversed to facilitate comparisons across measures. Cohen's classification of effect sizes was used; the effect sizes of $d \leq 0.20$ are small, $d = 0.50$ are medium, and $d \geq 0.80$ are large.[19] Critical values for pooled effect sizes were set at 0.05.

Homogeneity in effect sizes was tested using the Q statistic (χ^2) for each cognitive domain. To quantify the degree of heterogeneity, the I^2 statistics was also calculated, with the values of 25, 50, and 75% generally reflective of small, moderate, and high heterogeneity, respectively.[20] A more liberal critical value of 0.10 was used for testing homogeneity because this procedure has been shown to lack power and, as such, was more susceptible to Type II errors (falsely accepting the null hypothesis).

Results

Study description

Our search was performed on December 15, 2013, and it identified 240 articles [Figure 1]. Of these articles, 200 were excluded on the basis of titles or abstracts, and 40 reports were identified for full-text review. One additional report was identified by searching relevant reference lists or by hand searches of the main journals of neurology. Finally, eight

Table 3: Effect size statistics

Cognitive domain	Studies	*n*	Effect size (Cohen d)	95% CI		Z	*P*	Homogeneity statistics			
				LL	UL			Q (df)	*P*	Tau	I^2 (%)
MMSE	3	102	−0.33	−0.62	−0.04	2.26	0.02	1.77 (2)	0.41	0.00	0
Language											
Boston naming test	4	138	−0.34	−0.63	−0.04	2.22	0.03	3.38 (3)	0.34	0.01	11
Verbal learning and memory											
Logical-immediate memory	4	123	−0.58	−0.86	−0.29	3.93	<0.0001	2.48 (3)	0.48	0.00	0
Logical-delayed memory	4	123	−0.75	−1.32	−0.19	2.61	0.009	9.25 (3)	0.03	0.22	68
Immediate recall memory	4	139	−0.49	−0.49	−0.04	2.15	0.03	6.95 (3)	0.07	0.11	57
Delayed recall memory	4	139	−0.45	−0.92	0.02	1.87	0.06	7.79 (3)	0.05	0.14	61
Visual learning and memory											
Immediate recall memory	4	101	−0.27	−0.67	0.13	1.32	0.19	4.9 (3)	0.18	0.06	39
Delayed recall memory	2	43	−0.33	−0.80	0.15	1.35	0.18	0.00 (1)	0.98	0.00	0
Attention span											
Digit forward	4	118	−0.12	−0.40	0.15	0.87	0.39	2.83 (3)	0.42	0.00	0
Digit backward	4	118	−0.14	−0.44	0.16	0.93	0.35	3.4 (3)	0.33	0.01	12
Response fluency											
Letter fluency	3	103	−0.56	−1.17	0.05	1.81	0.07	7.86 (2)	0.02	0.22	75
Semantic fluency	3	144	−0.10	−0.36	0.16	0.76	0.45	1.14 (2)	0.57	0.00	0
Motor performance											
Finger tapping with preferred hand	2	49	−0.75	−1.17	−0.34	3.54	0.0004	0.06 (1)	0.81	0.00	0
Finger tapping with nonpreferred hand	2	49	−0.67	−1.09	−0.26	3.18	0.001	0.02 (1)	0.88	0.00	0
Processing speed											
Trial Making Test A	2	102	−0.54	−0.85	−0.22	3.30	0.0010	0.02 (1)	0.90	0.00	0
Symbol Digit Modalities Test	2	97	−0.71	−1.14	−0.28	3.24	0.001	1.42 (1)	0.23	0.03	30

Significant results for each meta-analysis in bold. CI = Confidence interval, LL = lower limit, UL = upper limit, df = degrees of freedom, MMSE = Mini-Mental State Examination

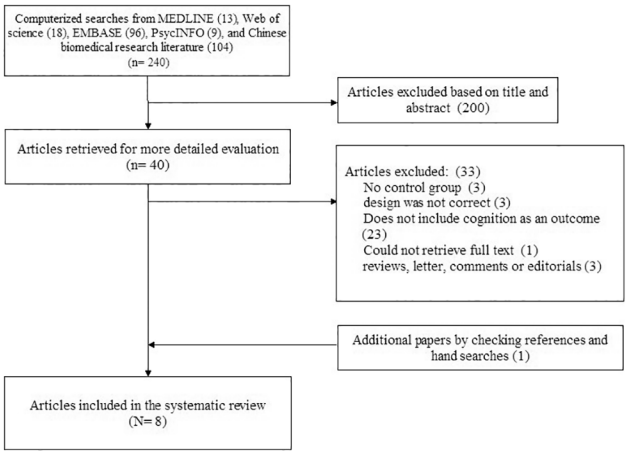


Figure 1: Flow chart of the systematic review search

studies fulfilled the inclusion criteria and were included in this review.[5,8,10-15] The number of patients ranged from 12 to 100. The total number of participants was 300 in the MG group and 179 in non-MG group [Table 1]. All studies used healthy people as controls. All studies had similar age and education for patients and controls.

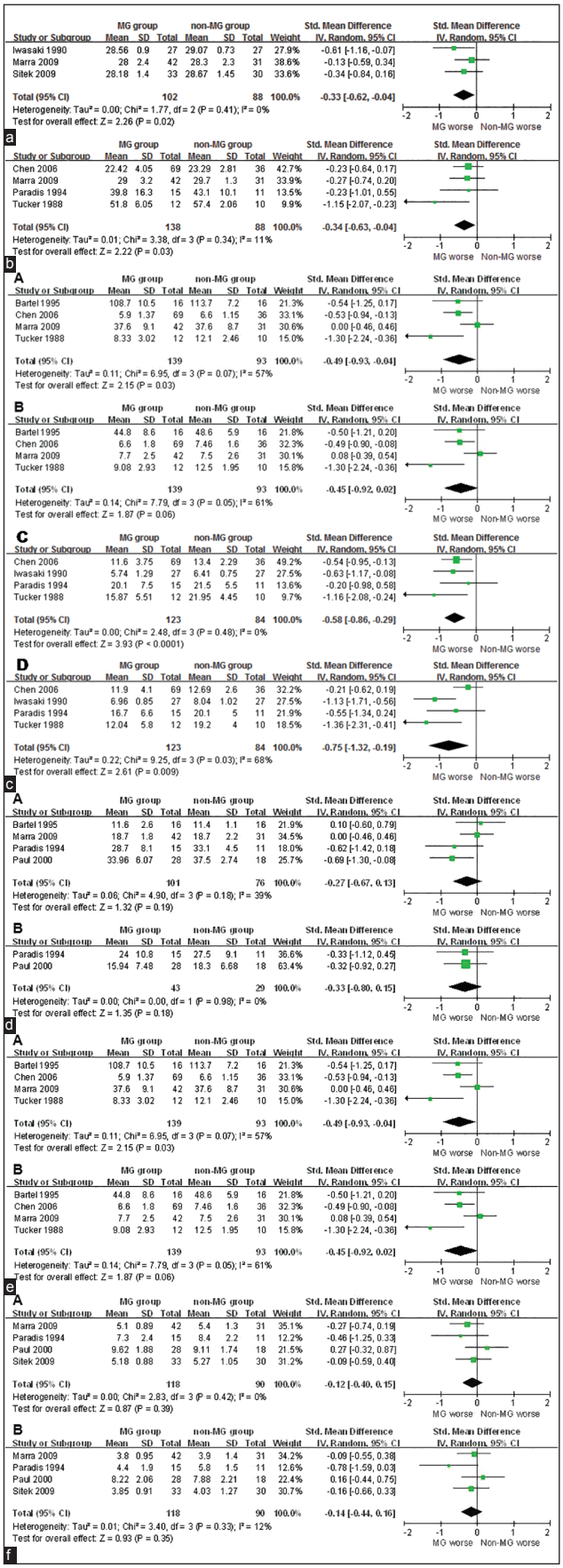
Study quality

Seven studies received quality scores of ≥6 (of 8), and the remaining study received a quality score of 5 [Table 2]. Only one study consecutively enrolled patients.[12] Most studies did not report their enrolment details; thus, it was unclear whether the participants were representative of the population from which they were recruited. None of the studies featured blinded cognitive function assessments. All studies were cross-sectional rather than longitudinal.

Quantitative analysis of cognitive function

We performed meta-analyses of all exposure-outcome associations with two or more separate populations for a total of16 separate meta-analyses. All studies addressing the same domain-specific cognitive function in people with MG were meta-analyzed. The effect size differences for the cognitive variables, together with their confidence intervals, significance tests, and homogeneity statistics, are reported in Table 3. Forest plots are displayed in the Appendix 1.

Nine (cognitive domain categories, MMSE, language, processing speed, verbal learning and memory (except for delayed recall memory), and motor performance) of 16 cognitive tasks revealed moderate effect sizes. Verbal logical-delayed memory (d = −0.75), finger tapping with the preferred hand (d = −0.75), and the Symbol Digit Modalities Test (d = −0.71) were significantly greater than all other domains; only logical-delayed memory exhibited significant in homogeneity (P = 0.03). Verbal learning and memory domain (logical-immediate memory, logical-delayed memory, and immediate recall memory) seems to be the most significant affected according to cognitive categories. In contrast, there was no evidence of significantly worse MG regarding attention, response fluency, and visual learning and memory [Table 3 and Appendix 1]. We used sensitivity analyses to assess the robustness of our conclusions. One study used an elderly



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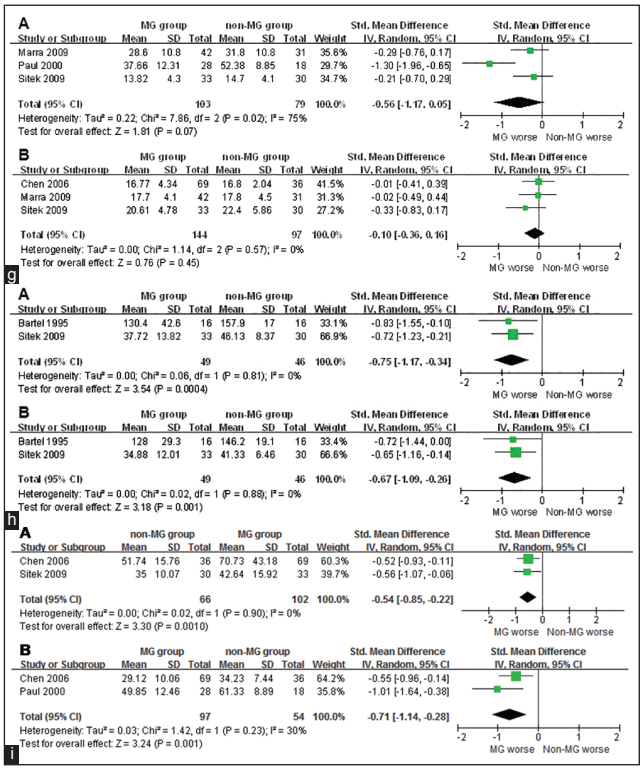

Appendix 1: (a) Forest plot of individual and pooled effect sizes for MMSE (b) Forest plot of individual and pooled effect sizes for language (Boston naming test) (c) Forest plot of individual and pooled effect sizes for verbal learning and memory: immediate recall memory (A) and delayed recall memory (B); logical-immediate memory (C) and logical-delayed memory (D) (d) Forest plot of individual and pooled effect sizes for verbal immediate recall memory (A) and verbal delayed recall memory (B) (e) Forest plot of individual and pooled effect sizes for visual immediate recall memory (A) and visual delayed recall memory (B) (f) Forest plot of individual and pooled effect sizes for attention span: digit forward (A) and digit back (B) (g) Forest plot of individual and pooled effect sizes for response fluency: letter fluency (A) and semantic fluency (B) (h) Forest plot of individual and pooled effect sizes for motor performance: finger tapping with the preferred hand (A) and finger tapping with the non-preferred hand (B) (i) Forest plot of individual and pooled effect sizes for processing speed: the Trail Making Test A (A) and Symbol Digit Modalities Test (B)

patient group (mean age, 71.8 years);[12] after removing this study from our analyses, the results remained nearly the same, except that the significant results found in language testing and delayed recall memory were reversed. Generalized MG (GMG) was the main group in most studies except one study;[10] after removing this study from our analyses, the results remained nearly the same, except that the ability of language and immediate recall memory found to be reserve in GMG. In addition, language score varies in each study (especially, in Tucker *et al*. and Paradis *et al*.). The heterogeneity of scores is explained by the different type of Boston Naming Test (BNT) using shorter and full edition among these studies, with naming nouns 0-30 (30 score at most) in studies of Chen *et al*., and Marra *et al*., and naming nouns 0-50 in studies by Tucker *et al*., and Paradis *et al*. We then summed upseparate effect size by different naming nouns groups to test the robust of result. However, both patients using BNT 0-30 and 0-50 showed no evidence significantly worse than control groups, with $P = 0.11$ and 0.15, respectively.

Discussion

The aims of this systematic review were to describe the literature and to examine the pooled data to evaluate whether adults with MG exhibited worse performance in each of the cognitive domains studies compared to controls without MG. The evidence from this review suggested that:

1. The MG patients might perform worse than the non-MG controls in a range of cognitive domains.
2. Delayed recall memory seems to also be associated with MG patients after removing the elderly group study using sensitivity analyses. Altogether, the results showed that patients also performed significantly worse in verbal learning and memory tests. However, the ability of immediate recall memory seems to be reserve in GMG patients.
3. Verbal logical-delayed memory, finger tapping with the preferred hand, and the Symbol Digit Modalities Test showed a somewhat greater relationship with cognitive function than did other specific cognitive domains; verbal learning and memory domain seems to be the most significant affected according to cognitive categories.
4. The ability of attention, response fluency, visual learning, and memory seems to be reserve in MG patients. However, these findings are tentative because of the methodological heterogeneity there is lack of rigorous empirical evidence to support this finding. Several issues need to be borne in mind, however, in the interpretation of these results.

Potential biases

This result could, in theory, be explained by publication bias, the preferential publication of studies that achieve statistical significance and non-publication of studies that do not. However, other explanations may also account for this distribution of data. In particular, this pattern often arises as a result of clinical heterogeneity of the studies. Clearly, studies will employ different inclusion and exclusion criteria, different types of therapists, different types of neuropsychological parameters (i. e., shorter and full edition in the same test, like BNT mentioned in results section), and so on; all of which can have an impact on the effect size. Although there was nearly no statistical evidence of heterogeneity in this meta-analysis (only letter fluency showed high heterogeneity with $I^2 = 75\%$), but power to detect heterogeneity was low because of the small number of available reports. It must also be borne in mind that MG patients included were generally less severely impaired. For example, only outpatients were included in one study.[14] It is reasonable that increased reports of cognitive defects in MG with more disease severity (in particular, among inpatients and those patients with unstable condition). We recognize that this is likely to be a conservative estimate because underreporting (or under recognition) of cognitive defects in more severe patients.

In addition, one study used patients self-selected inclusion method.[8] Thus, MG patients with mild cognitive defects may fail to be recruited in the study. This will also cause potential underreporting. Even with above consideration,

we still identified some evidence of cognitive deficits in MG patients, although most significantly domains were mild to moderate effect sizes. Finally, the wisdom of the inclusion of unpublished data has been contested. Unpublished studies have not undergone formal peer review; and the fact that the study was not submitted for publication, raises questions about the quality of the work. As a consequence, we still know little about the relationship between cognitive defects and MG.

On the other hand, the lack of statistically significant findings in some neuropsychological parameters, even after pooling, is possibly a result of type 2 error. For example, delayed recall memory was assessed by only two studies in this meta-analysis [Table 3]. The infrequent reporting and small number of patients, make it particularly difficult to demonstrate significant effects.

Our results differ from one published comprehensive narrative review.[21] The review reported that verbal and visual learning were the cognitive domains most commonly affected in MG. In contrast, our meta-analysis found that only the verbal learning deficit was consistent with previous reviews. The previous conclusions in the original studies were based on whether the relationship between MG and cognitive test scores was statistically significant. Because statistical significance depends on the sample size, solely focusing on this criterion could mask a small consistent effect in underpowered studies. Furthermore, we found that MMSE, logical memory, and motor performance were affected in MG patients; these results were not found in the previous review.

The current study highlighted some of the demographic limitations inherent in the neuropsychological research of MG. In keeping with expectations, the disease subtypes appeared to explain some of the heterogeneity in cognitive outcomes. That is, relative to the controls, the MG patients appeared to show more severe deficits in the cognitive domains. Future studies should consider adjusting the raw scores for severity using normative data from large samples, which would ensure that the patients are compared with more valid controls. This suggestion is particularly important given that normative samples are typically more representative of the general population than small control samples. Furthermore, when additional analyses were conducted and one study with elderly patients was included, as mentioned above, the association between language ability and MG became nonsignificant.[12] We believe that that this discrepancy indicated that age might partly influence performance on the language ability test.

Strength and limitations

The meta-analysis approach allowed us to calculate pooled results, and thus, offers greater confidence in the results. We used an a priori method to identify 16 cognitive domains and classified the neuropsychological measures by subtests according to these domains to facilitate systematic comparisons. We also examined the potential methodological challenges across the studies to inform future research efforts. The review was limited by the availability of only eight studies that met the inclusion criteria. This finding highlights the paucity of peer-reviewed studies and the methodological complexity of studying this population. The limited availability of independent samples also inhibited the generalizability of the findings. Because of the small number of studies, it was not feasible to conduct meta-regression models with multiple predictors and interactions. Hence, it is difficult to determine whether demographicor clinical characteristics, or a combination of both, were more likely to be associated with neuropsychological heterogeneity. For similar reasons, it is unclear whether different symptom patterns and severity levels, beyond the current characterization of severity as either 'euthymic' or 'symptomatic', were associated with different neuropsychological profiles. Finally, it is quite possible that unpublished studies of nonsignificant differences (the so-called "file drawer problem") are underrepresented. However, due to the small number of identified studies, a funnel plot was not constructed to assess the risk of publication bias.

Recommendations for future research and practice

The greatest differences between the controls and the MG patients were in the areas of verbal logical-delayed memory, finger tapping with the preferred hand, and the Symbol Digit Modalities Test [Table 3]. Therefore, cognitive remediation or training may be an appropriate intervention, although it has not been previously studied in this population. Compensatory cognitive training, for example, has shown positive effects on cognition and functional capacity in multiple sclerosis.[22] An understanding of the day-to-day impact of any identified deficits would help to determine their clinical significance and identify potential treatment targets. In addition, we found that all analyses yielded effect sizes in the expected direction (poor cognitive function associated with MG samples, see Appendix). However, the fact that most studies found that different cognitive function domains were associated with MG, means that the cognitive function dimensions that are affected by MG are still debatable. We noted one of the included studies that drew conclusion mainly based on the MMSE scale (and memory tests).[11] However, the MMSE score is a low resolution screening instrument that neither has specificity nor sensitivity (especially for those who have mild cognitive impairment) to draw conclusion. Furthermore, MMSE scores could be easily affected by age, education, and cultural background. We did not exclude this study from our review, but note that it highlights an important methodological issue in studies of future cognitive design.

MG may affect different cognitive domains (depending on differences in how neuropsychological and neurocognitive assessments are conducted) and define cognitive decline. Future studies should examine the relationship between MG and specific (core) cognitive domain function in greater detail. Given the relatively modest effect sizes detected in the current review, it is unlikely that neuropsychological functioning is sensitive enough to diagnose mild cognitive impairment. However, neuropsychological indicators may be more useful in helping clinicians to identify and prioritize their patients' treatment needs at an early phase and monitor treatment responses to programs designed to ameliorate cognitive deficits. Cross-sectional methodology was used nearly in all studies, which limits the conclusions that can be drawn about the impact of the course of MG. Thus, studies examining longitudinal change in cognitive function, particularly after treatment, are needed.

Conclusion

In conclusion, our study provides some evidence that cognitive functioning is reduced in MG, despite the acknowledged difficulties in analysis of outcome of chronic and rare diseases with unpredictable and fluctuating courses. However, our findings should be interpreted with caution because of the clinical and methodological heterogeneity of included studies. Despite the limitations of meta-analysis and a lack of methodological rigor in the primary studies, we believe our results provide the best picture currently available to inform clinicians, patients, and policy makers about possible cognitive deficits in MG. The review suggests a need to develop and to empirically investigate the feasibility of cognitive rehabilitation at an early stage of the disorder. A number of methodologies should be integrated to explore these hypotheses and further elucidate the underlying mechanisms of MG patients. Additionally, the possible negative impact of medication, number of mood episodes, history of psychotic symptoms, and other clinical cognition variables deserve to be further investigated.

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