The Influence of Optic Neuritis and RNFL thickness in the Relationship Between Visual and Cognitive Impairments in Multiple Sclerosis

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Abstract

Objective: This study aimed to investigate the relationship between visual and cognitive functioning in people with multiple sclerosis (MS), building upon existing literature that has identified an interplay between these two domains. Specifically, the study aimed to assess the impact of Optic Neuritis (ON), a common visual impairment in MS, and Retinal Nerve Fiber Layer (RNFL) thickness, located behind the optic nerve, as moderators in this relationship.

Methods: 107 people with MS were referred to Royal Dutch Visio participated in the study. Correlations, partial correlations, and ANOVA analyses were conducted to explore visual-cognitive functioning. Additionally, a systematic review of 42 papers was carried out to identify existing patterns in this relationship in existing literature.

Results: Data revealed significant correlations between visual impairments and cognitive functioning (eg. r = -.342, r = -.391), as did the systematic review (eg. r = -.41, r = -.07), supporting the hypothesis that these functions are interconnected. After accounting for RNFL thickness, significant correlations remained (r = -341, r = .389). However, when controlling for a history of ON, this relationship was not significant ($\varepsilon 2$ > .027).

Conclusions: The systematic review highlighted several significant relationships between visual and cognitive functions, particularly concerning visual acuity and memory. In the data, RNFL thickness emerged as an important factor to consider when investigating the visual-cognitive relationship in MS. This finding emphasizes the need for further research on the impact of RNFL thickness on visual and cognitive functioning, as well as its influence on quality of life.

The influence of Optic Neuritis in the relationship between visual and cognitive impairments in Multiple Sclerosis

In order to provide effective assistance and rehabilitation to people following neurological accidents or diagnoses, it is imperative for a neuropsychologist to possess comprehensive training in administering therapeutic interventions. The role of such a specialist encompasses aiding these patients in attaining the highest level of functional ability and normalcy following a specific diagnosis, such as multiple sclerosis (MS). MS is a neurodegenerative disorder of the central nervous system (CNS), in which the immune system attacks the myelin sheath of axons in the brain, spinal cord as well as the optic nerves. (Compston & Coles, 2008). The myelin sheath is a thin layer of lipids and proteins covering the axon, which helps information transfer between axons to occur more efficiently, thus damage to the myelin sheath impairs efficient information transfer, leading to slow or impaired information transfer (Vorvick, 2021). Neuropsychological manifestations of MS frequently present themselves as deficits in visual and cognitive function (Jakimovski et al., 2021), especially because the myelin sheaths of the optic nerves are particularly prone to inflammation (Armstrong,1999), causing damage to the visual system (Heesen et al., 2008).

Visual Impairments

Vision symptoms of MS include temporary vision loss (McNamara, 2015), but also impairments of visual functioning (Costello, 2016). Up to 80% of people with MS experience some form of visual impairment, such as lowered visual acuity and contrast sensitivity (Balcer & Frohman, 2015), binocular vision, visual field problems (Nakajima et al., 2010), reduced color vision (Villoslada et al., 2012), blurred vision, and double vision (Balcer, 2015). People suffering from MS describe their visual impairments as interfering with vision-related quality of life

(Mowry et al., 2009; Garcia-Martin et al., 2013; Salter et al., 2013) as it disrupts daily activities and the ability to independently participate in society (WHO, 2001). For example, impaired driving ability is a major concern for people with MS (Mowry et al., 2009). The severity, permanence and recovery of visual impairments commonly encountered in MS can vary, but their reported interference in the person's quality of daily functioning and quality of life are consistent (Feaster & Bruce, 2011), making them an important factor to take into consideration when treating people with MS.

Optic Neuritis (ON)

Optic Neuritis (ON) is the most common cause of visual problems in people with MS (Kale, 2016). ON occurs when the optic nerve becomes inflamed or damaged due to swelling (Bennet, 2019), and can cause impairments in visual processing, decreased visual acuity, contrast sensitivity or visual field defects (Nakajima et al., 2010), and sometimes temporary vision loss. ON is seen in nearly 20% of people with MS (Bhatti et al., 2005).

The severity and duration of ON can impact the retinal nerve fiber layer (RNFL) thickness, which is a key measure of optic nerve damage. Additionally, people without ON can also have a thinner RNFL thickness due to inflammations and central nervous system diseases (Güngör & Ahmet, 2017). In a study by Jakimovski and colleagues (2021), it was found that RNFL thickness was significantly correlated with visual acuity ($r = 0.19$, $p = 0.008$), Symbol Digit Modalities Test (SDMT) scores ($r = -0.39$, $p < 0.001$), and Brief Visuospatial Memory Test-Revised (BVMT-R) scores ($r = -0.36$, $p < 0.001$). These findings suggest that RNFL thickness can have a significant impact on visual and visuo-perceptual functions, this being caused by a history of ON or otherwise. Moreover, Jakimovski et al. (2021) found a significant correlation between RNFL thickness and visual functions, even in MS patients without a history of ON. This highlights the importance of monitoring RNFL thickness as a potential marker of optic nerve damage in individuals with MS. Additionally, the impact of ON on the optic nerve and RNFL thickness is also of importance to measure as it may be the initial cause of a thinning of the retina.

In summary, ON is a common visual complication in MS that can result in significant visual impairments, including changes in RNFL thickness. Measuring RNFL thickness can help identify individuals at risk for visual impairments, and may aid in the management of MS-related visual complications.

Cognitive Impairments

In addition to visual impairments, people with MS commonly experience cognitive impairments that can affect their daily functioning and quality of life (Chiaravalotti & DeLuca, 2008). These impairments may result from damage to the myelin sheath in brain areas that are crucial for cognitive processing (Amato et al., 2020). Deficits in cognitive and visual perceptual functions can lead to difficulties with higher-order cognitive tasks that involve visual demands, such as reading, driving, and social interaction (Chiaravalotti & DeLuca, 2008).

Executive dysfunction is one of the most commonly reported cognitive impairments in people with MS, and can manifest as difficulties with planning, decision-making, and problem-solving (Chiaravalotti & DeLuca, 2008). Processing speed is also often affected, with people with MS experiencing slowed information processing, attentional deficits, and difficulty multitasking (Chiaravalotti & DeLuca, 2008).

Verbal memory deficits are also common, with individuals with MS experiencing difficulty recalling verbal information such as names, lists, and instructions (Chiaravalotti &

DeLuca, 2008). Moreover, anxiety and depression frequently arise in people with MS, which can further impact cognitive functioning and overall quality of life (Chiaravalotti & DeLuca, 2008).

It is important to note that visual and cognitive impairments in MS often co-occur and may interact with each other (Vleugels, 2001). The complex relationship between visual and cognitive impairments in MS is an area of active research and has important implications for understanding and treating the disease, as it can help to understand the interplay of these functions and help to guide future comprehensive assessments and treatment plans.

The Relationship Between Vision and Cognition in MS

Current literature suggests that not only do visual and cognitive impairments occur in isolation, they also seem to co-occur and display a relationship with one another (van der Feen et al., 2023). Vleugels (2001) suggests that while cognitive impairments are present on their own in people with MS, slowed visual information processing may be an underlying cause of visuoperceptual neuropsychological task impairment. Similarly, Feaster (2011) notes that many cognitive tests used to assess people with MS require intact vision. Cognitive performance has been correlated with visual performance in cognitive domains such as information processing speed and memory (Wieder, 2013), as well as visuospatial processing (Jakimovski et al., 2021), executive functions (Wieder et al., 2013), and language (Ridder et al., 2017).

Current literature further suggests that visual and cognitive functions in MS are related to one another. Specifically, visual acuity and cognitive measures such as information processing and memory, as well as low contrast sensitivity with cognition have been found in a study by Wieder (2013). Additionally, RNFL thickness has been associated with cognitive impairment (Toledo et al., 2008.). Finally, studies have found that poor vision is correlated with poorer performance in *all* cognitive and motor domains (Feaster, 2011).

In other words, it is crucial to consider vision when conducting neuropsychological assessments as it can alter the results of cognitive tests. Thus, understanding the relationship between vision and cognition is essential to avoid misinterpreting a person's test results as solely indicative of cognitive impairment when in fact the results may be influenced by visual factors. This lack of consensus relating to the relationship between the two functional impairments calls for further research into the relationship between vision and cognition in MS, in order to properly understand the cause and further direction of treatment.

The Present Research

To this end, this paper aims to bring some clarity to the relationship between visual and cognitive functions in MS, as well as the possible influence of ON and RNFL thickness. Although the current literature shows that there seems to be a relationship between visual and cognitive function in MS, and that there seems indeed to be a difference in these functions when the history of ON is present, no clear consensus has been reached thus far. The present paper will conduct both a systematic review and data analysis in order to further shed clarity into this relationship.

Systematic Review

The systematic review aims to answer the question ‘What is the relation between visual functioning, cognition, and perception?’. It is expected that a clear relationship between visual and cognitive functions in MS will be found. Specifically, it is hypothesised that cognitive functions more closely connected to vision (such as visuospatial processing, or visual spatial attention) will be those correlated the strongest to visual function.

Data Analysis

Through statistical data analysis, further questions will be answered. Firstly, the same question as the review will be answered with the data: What is the relationship between visual functioning, cognition, and perception? The hypothesis for this question is similar to that of the review, however in the data we expect high correlations between visual functions and cognitive functions that require some vision, such as visual construction or, visual spatial memory or visual spatial attention.

Secondly, do the visual, visual perception and cognition tests results differ in people with MS with and without ON history? Here, I hypothesise that data will show that people with a history of ON will have higher visual, thus cognitive, impairment. Thirdly, I ask whether people with a history of ON will act as a moderator variable on the relationship between visual and cognitive test scores, wherein I expect that a history of ON will indeed act as a moderator between visual and cognitive variables in that it will make the correlations stronger.

Lastly, I ask whether a lowered RNFL thickness also acts as a moderator variable on the relationship between visual and cognitive test scores. The hypothesis for this question is also that a lowered RNFL thickness does have an influence in the relationship between visual and cognitive functioning, in that it will make the correlations stronger.

Method

Systematic Review

A systematic review on literature from databases PubMed and Web of Science was carried out to find the patterns in current research regarding the relationship between visual and cognitive functions, both in people with and without MS. Search terms can be found in table 1. Search terms were separated into neuropsychological terms, visual terms, and relationship terms. Each group was placed into a different search box. All terms were searched for in a ‘In title of paper' filter. Inclusion criteria included only human subjects, papers published after 1999, and peer-reviewed papers.

Exclusion criteria included papers that referred to psychological disorders (i.e. depression, anxiety) as cognitive variables, papers referring to brain anatomy rather than cognitive functioning, papers assessing neurological conditions (i.e. mild cognitive impairment, Alzheimer's), and papers assessing visual disorders such as glaucoma or other eye diseases. Relevant data from the included papers were synthesised and summarised in a table. Relevant information included relationships between visual and cognitive functions in people with and without MS, the impact of visual/cognitive impairments on MS symptoms, the influence of RNFL thickness on visual or cognitive symptoms, and whether any discernible patterns are found within these relationships.

In order to try and avoid bias within the papers as much as possible, the author and a second evaluator assessed the eligibility of the papers, first based on titles and abstracts, followed by full texts. The two evaluators then reached full consensus on which papers to include in the review and which to exclude. Final papers were then assessed by a third independent evaluator who agreed with the final paper decision.

Table 1

Search terms for systematic review, used in databases PubMed and Web of Science

Terminology	Search Terms

Cognitive/Neuropsychological Terms	(“Cognitive Funct*” OR “Cognitive Impairment” OR “Cognition” OR “Cognitive Dysfunction” OR “Cognitively impair*” OR “Cognitive test*”, “Executive Function*”, OR “planning” OR “working memory” OR “information process*” OR “attention*” OR “memory” OR “processing speed” OR “verbal fluency” OR “Neuropsychological Assessment” OR “Neuropsychological Evaluation” OR “Cognitive Assessment” OR “Neuropsychological test*” OR “visual spatial” OR “visual-spatial” OR “visuospatial”)
Visual Terms	AND (“Visual Function*” OR “Visual Impairment” OR “Visual Dysfunction” OR “visual test*” OR “visual assessment” OR “Visual Acuity” OR “Visual Field” OR “Color Vision” OR “Stereopsis” OR “Eye Movements” OR “Nystagmus” OR “Optokinetic Nystagmus” OR “Vestibulo-Ocular Reflex” OR “Smooth Pursuit” OR “Saccades” OR “Optical Coherence Tomography” OR “OCT” OR “contrast sensitivity” OR “HCVA” OR “LCVA” OR “High visual acuity” OR “Low visual acuity”)
Relationship Terms	AND (“Relationship” OR “Correlation” OR “Link” OR “Associated” OR “Related” OR “Correlated” OR “Linked” OR “Connect*” OR “Relation” OR “Association”)

Participants

In an earlier study (van der Feen et al., 2023) people with MS who were referred to Royal Dutch Visio for rehabilitation and advice were included in the study. These people all reported visual complaints. People with MS without visual complaints were also included in the study as a control group. In the present research, both the treatment and the control group were merged into one large group, for a total sample of N=106. The mean age of the participants was

52.2 years of age, with standard deviation (SD) of 12.2 years. Participants had a wide age range, from 21 to 79 years of age. 28 men and 78 women made up the sample. All participants completed a visual and neuropsychological assessment, for which the results were used in the data analysis.

For the purpose of data analysis, participants were further subdivided into history vs no history of ON. The age of participants with a history of ON was 49.7, with standard deviation of 12.1. The age of participants without a history of ON was 53.0, with standard deviation of 12.

Materials

Every participant received a full neuropsychological assessment as standard care during a neurologist visit. As every visual and cognitive function test used is beyond the scope of this paper, the author chose to include only visual acuity, contrast sensitivity, visual field and nystagmus for visual measures; and visual construction skills, memory, executive functions, attention and object perception for cognitive measures, as these are most often reported in the systematic review results, thus to align the systematic review and data analysis results.

Visual Functions

Visual Acuity. Visual acuity testing was carried out with a Snellen chart of letters (Tsui & Patel, 2020). The participants stood 4 metres away from the Snellen chart at 500 lux, and read smaller and smaller letters until they were no longer able to discern the letter shown to them. The Snellen chart is scored as a fraction, with the nominator being the distance of the participant's eyes to the chart, while the denominator indicates the distance someone with perfect vision would be at in order to read the same letters.

Contrast Sensitivity. Contrast sensitivity was measured using the Vistech and GECKO tests, both at 3 metres distance and brightness of 500 lux. The Vistech test (Ginsburg, 1984) consists of participants looking at a series of cards with letter and line patterns. As the cards continue, the contrast of these patterns decreases. The person participating in the test must identify the direction of the lines/letters in the cards. The GECKO (Kooijman et al., 1994) test is a similar, but computerised, test to that of the Vistech. The test also includes a number of patterns that get lower and lower in contrast, and also asks the person taking the test to identify the orientation of these patterns. However, the GECKO test is adaptive in that it adjusts the difficulty level according to the patient's last answer. In this study, contrast sensitivity was assessed on a categorical scale, in that 0 meant normal, and 1 meant impaired.

Visual Field. Visual field was tested using the Humphrey Field Analyzer (HFA) test (Heijl, 1985), with 24-2 SITA Fast. This is a device with a 'perimeter' part, shaped like a bowl, in which the participant looks into. The HFA then shows lights of different brightness and intensity in the participant's visual field. The person taking the test has to click a button whenever they see a light, and the machine creates a map of the person's visual field, which is used as the 'score' of the test. In this case, the test was done with a 24-degree radius of the centre point of the visual field, and the lights were shown with 2-degree increments. The scores for visual field were numbered 0 = normal and 1 = impaired for the present study.

Nystagmus. Nystagmus was measured in a session with a trained orthoptist, who assessed whether nystagmus was present or absent in patients.

Cognitive Materials

Visual construction. Visual construction was measured using the Taylor Complex Figure Test (Taylor, 1969). It assesses the participant's ability to reproduce a complex figure while looking at the original. The Taylor test is scored based on accuracy, with points awarded for correct placement of parts of the figure.

Memory. Different levels of memory were assessed with subscales of the Digit Span test, the 15 Words test, and the Corsi test.

Short term. Short term memory was assessed using the Digit Span test. This test is a subscale of the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 2008). In this test, the participant is given a series of numbers that they have to repeat back to the tester. There are two versions of this test, both the Digit Span forward, in which the participant must repeat the numbers back in the same order as it was given to them, or the Digit Span backward, in which they must repeat the numbers in reverse order. For short-term memory, the Digit Span forward subscale was used. The Digit Span is scored based on the correct number of digits repeated in the correct order.

Working memory. Working memory was also assessed using the Digit Span test. In this case, the digit span backward subtest was used. The scoring for the Digit Span backward is the same as for the forward subtest, in which the number of correct digits in the correct order is the participant's final score.

Verbal memory. Verbal memory was assessed using the 15 Words test (Saan & Delman, 1986). In this test, the participant is assessed on their ability to learn and repeat a list of 15 unrelated words. The participant is asked to repeat these words over five trials, both immediately after being read the list, as well as with time intervals. The total score of the test was used for this study.

Visual Spatial Memory. Visual spatial memory was assessed by use of the Corsi block-tapping test (Corsi, 1972). In this test, the participant is required to remember and repeat a pattern of block-tapping in a nine-block board. If a participant repeated a series of the same number incorrectly, the test was stopped. Scoring is done based on the longest series of block taps.

Executive Functions. Executive functions were also assessed by use of the Digit Span test. Specifically, the backward and sorting subscales were used for executive function measures. The Digit Span is scored based on the correct number of digits repeated in the correct order.

Visual Attention. Visual attention was assessed by use of the Bells test (Gauthier et al., 1989). In this test, the participant must cross a series of bells on a digital tablet. The bells are surrounded by a series of distractors, such as keys, birds, and other objects. The participant must ignore these distractions and focus on finding and circling the bells in the paper. Scoring is based on the number of correctly crossed out bells

Object Perception. Object perception was assessed by use of the Silhouettes test Warrington & James, 2013). In this test, the participant is given incomplete, black-and-white silhouettes of objects, and is asked to identify the object. Scoring is based on the number of correctly identified objects.

Procedure

All participants provided informed consent prior to participating in the study. Participants in completed a two-hour visual assessment test as well as a two-hour neuropsychological assessment. Neuropsychological assessment tests were carried out in all participants to assess for visual and cognitive (dys)function. Demographic characteristics were asked for, and medical history of each participant including MS type and history of Optic Neuritis were extracted from medical files at the patients' hospitals.

Data Analysis

Analyses of bivariate relationships of the visual and cognitive tests were carried out. Based on the research questions assessing the relationship between visual and cognitive functions, a correlation analysis was carried out. To assess the relationship between optic neuritis history and visual/cognitive test results, a Kruskal-Wallis ANOVA was carried out, in which participants were separated into history vs no history of ON, and effect sizes were assessed by use of ε2. To assess the moderating effect of both ON history and RNFL thickness on the visuo-cognitive relationship, partial correlation analyses for both ON history and RNFL thickness were carried out.

Results: Literature Review

9499 papers were found between the PubMed and Web of Science search engines. Once duplicates were removed and exclusion criteria applied, a total of 2600 papers were left. Once the two initial raters reviewed the titles and abstracts for inclusion and exclusion criteria, the list yielded a list of 157 papers. When the third rater cross-checked the list of final papers, a total of 70 papers were left. A further 28 papers were removed upon further analysis of the complete text due to not investigating the visual and cognitive functions required for the analysis, rather investigating factors such as glaucoma, depression, or other non-relevant variables. The final number of papers was 42. A summary of the main findings can be found below.

Table 3

Relationships between Visual and Cognitive Functions in Current Literature

Cognitive	Visual acuity	Contrast sensitivity	Saccades	Color vision/contrast	Visual field	OCT	Subjective Visual Impairment
Attention	β = -.29* (Parada et al., 2021) r = .27 (Skeel et al., 2006) r = .33** (Skeel et al., 2003) r = -.23** (Zheng et al., 2018) r = -.36* (Kaido,et al., 2020) OR = .85 (Hong,et al., 2016) r = .37*** (Bruce et al., 2007) r = .18* (Effendi-Tenang et al., 2020) r = 31*** (Jakimovski et al., 2021) r = .33* (Feaster & Bruce, 2011) OR=2.59; CI= [1.89-3.56] (Ong et al., 2012) β = −.27; CI= [−.37, −.17]*** (Lim et al., 2020) r = .46* (Anstey et al., 2002) r = .17* (Wieder et al., 2013) β = 2.17** (Nguyen et al., 2018)	r = .16* (Effendi-Tenang et al., 2020) r = .17 (Skeel et al., 2006) r = -.40** (Ridder et al., 2017) r = -.40* (Anstey et al., 2006) r = .29*** (Wieder et al., 2013)	r = .46* (Stuart et al., 2017) β = .996* (Stuart et al., 2019) r = .39* (Rodríguez-Labrada et al., 2011) r = -.50* (Fielding et al., 2009) r = .29* (Noiret et al., 2017) r = -.13 (Nieman et al., 2000) r = -.13 (Crawford et al., 2005)	r = -.24 (Matar et al., 2019) r = -.62* (Anstey et al., 2002)	β = .20, CI = [.02,.38] (Diniz-Filho et al., 2017)	β = 2.17** (Nguyen et al., 2018)	

Executive Functions	r = -.06 (Varadaraj et al., 2021) r = .21* (Effendi-Tenang et al., 2020) *β* =−.34, SE= .11 (Dearborn et al., 2018) r = .33** (Feaster & Bruce, 2011) β = 13.21** (Parada et al., 2021) *β* = .26, CI = [-.15, .66] (Grant et al., 2022) β = -.7** (Ehrlich et al., 2021a) r = -.28* (Valentijn et al., 2005) r = .17 (Skeel et al., 2003) r = .46* (Anstey et al., 2002)	r = .16* (Effendi-Tenang et al., 2020) r =.05* (Varadaraj et al., 2021)	r = .054 (Noiret et al., 2017) r = .09 (Hutton et al., 2004) r = -.13 (Nieman et al., 2000) β = -.059 (Stuart et al., 2019) r = .02 (Crawford et al., 2005) r = -.48* (Rodríguez-Labrada et al., 2011)	r = -.62* (Anstey et al., 2002)	r = -.04* (Varadaraj et al., 2021) β = .20, CI = [.02,.38] (Diniz-Filho et al., 2017)
Fluency	β = -.5* (Ehrlich et al., 2021a)		r = -.53** (Rodríguez-Labrada et al., 2011)	r = -.31 (Matar et al., 2019)	
Intelligence	r = .20* (Clay et al., 2009)	r = .17* (Clay et al., 2009)	r = .06 (Hutton et al., 2004)		
Language	r = .12 (Skeel et al., 2006) β = -.29* (Parada et al., 2021) r = -.23** (Zheng et al., 2018) r = -.36* (Kaido,et al., 2020) OR = .85 (Hong,et al., 2016) β = −.27; CI= [−.37, −.17]***	r = -.02 (Skeel et al., 2006) r = .54*** (Ridder et al., 2017)	β = 0.20, CI = [.02,.38] (Diniz-Filho et al., 2017) r = .05 (Noiret et al., 2017)	r = -.36 (Matar et al., 2019)	

	(Lim et al., 2020)						
Memory	r = -.10*** (Varadaraj et al., 2021) r = .16 (Skeel et al., 2006) *β* = −.296, SE= .113 (Dearborn et al., 2018) r = .09* (Clay et al., 2009) F = 2.94* (Anstey et al., 2001) r = .46** (Lövdén & Wahlin, 2005) *β* = -.11, CI = [.22,.00]*** (Grant et al., 2022) r = .33* (La Fleur, 2014) r = .37*** (Bruce et al., 2007) r = -.31*** (Jakimovski et al., 2021) r = .17* (Wieder et al., 2013) OR=2.59;CI= [1.89-3.56]* (Ong et al., 2012) F (1,213) = 5.21, MSE = 8.9 (Lindenberger et al., 2001) β = -3.2* (Ehrlich et al., 2021) [1] β = −.27; CI= [−.37, −.17]*** (Lim et al., 2020) r = .38* (Valentijn et al., 2005) β = 2.17** (Nguyen et al., 2018)	r = .19 (Skeel et al., 2006) r = .11* (Clay et al., 2009) r = -.26* (Anstey et al., 2006) r = .54*** (Ridder et al., 2017) r = .29*** (Wieder et al., 2013)	r = -.41** (Fielding et al., 2009) r = .13 (Hutton et al., 2004) β = .01 (Stuart et al., 2019) β = .20, CI = [.02,.38] (Diniz-Filho et al., 2017) r = -.56*** (Nieman et al., 2000)	r = -.24 (Matar et al., 2019)		β = 2.17** (Nguyen et al., 2018)	β=−.25* (He et al., 2022)

Processing Speed	r = -.10*** (Varadaraj et al., 2021) r = .24* (Clay et al., 2009) F = 33.1*** (Anstey et al., 2001) r = .56** (Lövdén & Wahlin, 2005) r = .37* (Feaster & Bruce, 2011) r = .38* (Valentijn et al., 2005) r = .37*** (Bruce et al., 2007) r = .31*** (Jakimovski et al., 2021) r = .17* (Wieder et al., 2013) β = 2.17** (Nguyen et al., 2018)	r = -.07*** (Varadaraj et al., 2021) r = .27* (Clay et al., 2009) r = -.26* (Anstey et al., 2006) r = .29*** (Wieder et al., 2013)	r = -.41** (Fielding et al., 2009)		r = -.04* (Varadaraj et al., 2021)	β = 2.17* (Jakimovski et al., 2021) β = 2.17** (Nguyen et al., 2018)
Recall	β = -.29* (Parada et al., 2021) r = -.23** (Zheng et al., 2018) r = -.36* (Kaido,et al., 2020) OR = .85 (Hong,et al., 2016) OR=2.59; CI= [1.89-3.56]* (Ong et al., 2012) r = -.39*** (Drobny et al., 2009) β = .15* (Nguyen et al., 2018) r = .38** (Feaster & Bruce, 2011) r = .31*** (Jakimovski et al.., 2021)	r = .54*** (Ridder et al., 2017) r = .34*** (Wieder et al., 2013)	r = -.21 (Noiret et al., 2017)	r = -.36 (Matar et al., 2019)	β = 0.20, CI = .02,.38 (Diniz-Filho et al., 2017)	β = .15* (Nguyen et al., 2018)

Recognition	IOP = 49.3 6 8.5** (Hirji et al., 2020) r = .46* (Anstey et al., 2002)		F = 4.56** (Glen et al., 2013)	r = -.62* (Anstey et al., 2002)	F = 4.56** (Glen et al., 2013)	IOP = 49.3 6 8.5** (Hirji et al., 2020)
Visuospatial Skills	r = -.38*** (Jakimovski et al., 2021) *β* = −.161, SE= .090 (Dearborn et al., 2018) r = -.04 (Skeel et al., 2006) r = -.226** (Zheng et al., 2018) r = -0.36* (Kaido,et al., 2020) OR = .85 (Hong,et al., 2016) β = -.29* (Parada et al., 2021)	r = .39** (Skeel et al., 2006)	r = -.16 (Hutton et al., 2004) r = .05 (Noiret et al., 2017) r = -.05 (Crawford et al., 2005)	r = -.36 (Matar et al., 2019)	β = 0.20, CI = .02,.38 (Diniz-Filho et al., 2017)	*β* = .17* (Jakimovski et al., 2021)
Global Cognition	r = -.12*** (Varadaraj et al., 2021) r = .242* (Effendi-Tenang et al., 2020) β = .1* (Ehrlich et al., 2021) [1] HR = 1.86, CI= [1.09–3.18] (Ehrlich et al., 2021b)[2] *β* =−.254, SE= .082 (Dearborn et al., 2018)	r = -.09*** (Varadaraj et al., 2021) r = .186* (Effendi-Tenang et al., 2020)	β = -.053** (Stuart et al., 2019)		r = -.06* (Varadaraj et al., 2021)	

*Note. * For p<0.05, ** for p<.001, *** for p<.0001. r =correlation; β = slope; OR = odds-ratio, OR<2.59 considered significant at the p<.05 level; CI = Confidence Interval;* F = F-statistic; *IOP = intraocular pressure, HR = hazard ratio of developing global cognitive impairment*

Visual Functions

Visual Acuity

A total of 27 papers found relationships between visual acuity and a range of cognitive variables, 22 of them finding relationships between the two, while five did not (see Table 3). Cognitive functioning with visual acuity included 15 papers finding relationships with attention, most of which included moderate coefficient sizes, ranging from $r = .17$ to $r = .47$. Most papers found relationships of the positive direction, thus indicating that as visual acuity functioning increases, attention functioning increases too.

Ten papers found relationships with executive functions, with eight of them finding significant relationships in the positive direction (ranging from $r = .21$ to $r = .46$), and two finding negative relationships, with coefficients of $r = -.06$ and $r = -.7$. Interestingly, the significant papers found positive associations between visual acuity and executive functions, while the nonsignificant papers yielded negative correlations, showing the potential pattern of visual acuity and executive functions being consistently positively correlated.

One paper found a significant negative relationship between visual acuity and verbal fluency, with a coefficient of $\beta = -\ .5$, a small but statistically significant value. Similarly, only one paper investigated the relationship between visual acuity and intelligence, yielding a positive correlation coefficient of $r = .20$.

In the domain of language, six papers investigated the relationship between visual acuity and language abilities. Interestingly, the majority of these papers reported results in the negative direction, with coefficients such as $\beta = -.29$, $r = -.36$, and $\beta = -.27$. This negative relationship between visual acuity and language abilities can be explained by the potential impact of visual difficulties on reading and comprehension, which in turn may affect language performance.

Seventeen papers examined the association between visual acuity and memory. Most of these papers found significant positive relationships, with correlation coefficients such as $r = .16$, $r = .33$, or $F = 2.94$. However, it is worth noting that six papers yielded negative relationships, such as $r = -.10$ or $\beta = -.11$. The varying direction of these relationships may be attributed to different factors, including the specific type of test used to assess memory, or the heterogeneity of the MS population.

Among the studies exploring visual acuity and processing speed, eleven papers were identified. Remarkably, all but one of these papers reported positive relationships, with correlation coefficients such as $r = .24$, $F = 33.1$, or $r = .56$. This consistent positive association suggests that higher visual acuity is associated with faster processing speed, indicating that visual clarity may facilitate the rapidity of information processing in individuals with MS.

The relationship between visual acuity and recall was examined in seven papers, and the results were almost evenly split between positive and negative directions. Examples of these findings include coefficients of $\beta = -.29$, $r = -.23$, and $\beta = .15$, $r = .38$. The mixed direction of these relationships can be explained due to the fact that some papers measured acuity in a high level of acuity, while other papers measured acuity impairment, thus changing the direction of the final coefficient, however upon closer examination the general pattern showed that worse acuity lead to worse recall, giving a similar conclusion to that of acuity and processing speed, in that visual clarity may facilitate recall.

Two papers specifically investigated the association between visual acuity and recognition. These studies reported a positive correlation coefficient of $r = .46$ and an intraocular pressure value of 49.3, indicating a potential link between higher visual acuity and improved recognition abilities.

Examining the relationship between visual acuity and visuospatial skills, seven papers consistently found negative associations, with examples including coefficients of $r = -.38$ or $\beta = -.16$. This negative relationship can be attributed to the impact of visual acuity impairments on spatial perception and the ability to accurately interpret and manipulate visual spatial information.

Five papers examined the relationship between visual acuity and global cognition. Interestingly, two papers reported negative relationships ($r = -.12$, $\beta = -.254$), while three papers found positive relationships ($r = .242$, $\beta = .1$, $CI = [1.09–3.18]$). This variation in the direction of the relationship may be influenced by factors such as cognitive measures employed, in that some studies measured general cognition with global cognitive z-scores, while others used general intelligence tests or an array of test batteries.

Most of the papers found significant relationships between acuity and cognitive functions, with the exception of Skeel et al. (2006), and Hong et al. (2016), which did not find a significant relationship between acuity and attention. Additionally, Varadaraj et al. (2021), Dearborn et al. (2018), Grant et al. (2022), and Skeel et al. (2003) did not find a significant relationship between acuity and executive functioning. Other non-significant relationships found included between acuity and language, memory, recall, visuospatial skills, and global cognition (see table 3).

Contrast Sensitivity

Contrast sensitivity was examined in seven studies investigating its relationship with cognitive functions. It was found to be associated with several cognitive domains. Specifically, it showed relationships with attention in five studies, with coefficients such as $r = .16$ and $r = -.40$ resulting from these. The change in direction is explained due to some studies measuring healthy contrast sensitivity, while the negative results stem from studies measuring contrast sensitivity impairment. Executive functions and contrast sensitivity were investigated in two studies and results showed positive relationships with coefficients $r = .16$ and $r = .05$. Intelligence was investigated in one study, finding a correlation of $r = .17$ with contrast sensitivity, indicating that as contrast sensitivity functioning increased, so did intelligence.

Language and contrast sensitivity were measured in two studies, memory in five studies, processing speed in four studies, one of which yielded a positive correlation ($r = .54$), and one negative one ($r = -.02$). This change in direction could be due to the heterogeneity of the samples or the methodology of the studies, however it is of note that the study by Skeel et al. ($r = -.02$) did not yield a statistically significant correlation, while that of Ridder et al. ($r = .54$) did.

Contrast sensitivity and recall were assessed in two studies, both yielding significant positive correlations ($r = .54$, $r = .34$), similarly to the findings between contrast sensitivity and visuospatial skills in one study ($r = .39$). Finally, contrast sensitivity and global cognition were measured in two studies, one of which yielded a significant negative correlation ($r = -.09$) and one nonsignificant positive correlation ($r = .186$). However, these two studies measured healthy contrast sensitivity, in the case of the nonsignificant positive correlation, and contrast sneisitivy impairment, in the case of the significant negative correlation. This thus shows a pattern of worse contrast sensitivity being correlated with worse global cognition.

There were no investigations on the relationship between contrast sensitivity and fluency or recognition. While one study reported non-significant relationships between contrast sensitivity and attention, language, and memory, the remaining studies found significant associations.

Saccades

Ten studies examined the association between saccades and cognitive measures. Among these, seven studies focused on attention, with two of them reporting non-significant findings ($r = -.13$ for both studies). The remaining five studies found significant relationships, with coefficients ranging from $r = .29$ to $r = -.50$. These findings suggest that saccades may play a role in attentional processes. Six studies investigated the relationship between saccades and executive functions, but only one study found a significant association ($r = -.48$), indicating that saccades are connected to lower executive functioning. Interestingly, this same study also identified a significant relationship between saccades and fluency ($r = -.53$), indicating the same pattern. One study explored saccades in relation to intelligence, but no significant association was found ($r = .06$). Two studies investigated the link between saccades and language, but neither found a significant relationship ($\beta = 0.20$, $r = .05$) indicating that saccades may not be strongly related to language processing.

Regarding memory, five studies explored the relationship with saccades, with three studies reporting non-significant results ($r = .13$, $\beta = 0.1$, $\beta = 0.20$). Two studies, however, found significant associations with memory, with coefficients of $r = -.41$ and $r = -.56$, suggesting a potential link between saccades and worse memory processes. One study found a significant association between saccades and processing speed ($r = -.41$), indicating that saccades may be related to worse cognitive processing speed. Another study investigated saccades in relation to recall but did not find a significant relationship ($r = -.21$), suggesting that saccades may not strongly influence recall performance. Only one study examined saccades and recognition, which revealed a significant association ($F = 4.56$), suggesting that saccades may play a role in visual recognition processes. Three studies explored saccades and visuospatial skills but did not find any significant relationships ($r = -.16$, $r = .05$, $r = -.05$), indicating that saccades may not be strongly associated with visuospatial abilities. Finally, one study identified a significant association between saccades and global cognition (β = -.053), suggesting that saccades may have implications for worse cognitive functioning.

Color Vision

Only two papers investigated the relationship between color vision and cognitive functions (see table 3), and one found significant relationships with cognitive functions such as attention, executive functions, and facial recognition (r = -.62 for all cognitive functions), indicating that impairments in this visual function can lead to worse performance in these cognitive functions. The second paper however, found non-significant relationships between color vision/contrast and cognitive functions such as attention (r = -.24), fluency (r = -.31), language (r = -.36), memory (r = -.24), recall (r = -.36), and visuospatial skills (r = -.36).

Visual Field

In regards to visual field research, only three papers investigated a relationship with cognitive functioning (see table 3), but of the research done, two found significant relationships with cognitive functions such as executive functions (r = -.04), processing speed (r = -.04), recognition (F = 4.56) and global cognition (r = -.06), all indicating that as visual field impairment increases, these cognitive functions decrease. One paper however, by Diniz-Filho et al. (2017), did not find a relationship between visual field and the cognitive functions they assessed in their paper, those being attention, executive functions, recall, and visuospatial skills, with coefficients for these functions being β = .20.

OCT measures

In relation to OCT measures, significant positive relationships were found in all of the three papers investigating such a relationship (see table 3), with cognitive measures such as attention (β = 2.17), memory (β = 2.17), recall (β = .15), processing speed (β = 2.17), recognition (*IOP* = 49.3) and visuospatial skills (β = .17), indicating a relationship between thicker RNFL thickness and a higher level of impairment in these cognitive functions.

Other Visual Functions

He et al. (2022) measured the level of subjective visual impairment on cognitive tests measuring memory and mental status (clinical symptoms), and found a regression coefficient of β = −.25. This study showed that as self-reported visual impairment got worse over time, so did memory and mental status.

Cognitive measures

Most cognitive function findings mirror those of the visual functions; however, patterns were found for specific cognitive functions that were heavily investigated in research. Findings related to cognitive functions are explained below.

Memory

Memory was the most extensively studied cognitive function in relation to visual functions, with 25 papers examining their association. Among these, 16 papers investigated the relationship between memory and visual acuity, with three of them reporting non-significant findings (*r* = .16, β = -.296, *F* = 5.21), while the rest of the papers reported significant findings in both positive (*r* = .09, *r* = .33) and negative (*r* = -.10, *r* = -.31) directions, as explained in the visual acuity section. Four papers explored the association between memory and contrast sensitivity, although one of them did not find a significant relationship (*r* = .19). Five papers investigated memory in relation to saccades, but three out of the five did not yield significant results (*r* = .13, β = .01, β = .20). A single study examined memory and color vision/contrast, but no significant association was found (*r* = -.24). On the other hand, two individual papers investigated memory with OCT and subjective visual impairment, respectively, and both reported a significant relationship (*β* = 2.17 and *β* = -.25). None of the included studies explored memory in relation to visual field functioning.

Executive Functions

Executive function research also showed present relationship with all visual measures, with 17 papers finding significant relationships with visual measures such as visual acuity, for which coefficients varied between negative (*r* = -.28, *β* = -.7) and positive (*r* = .21, *r* = .33) directions depending on the study measuring impaired or healthy functioning respectively. Contrast sensitivity results with executive functioning showed an overall significant positive direction (*r* = .16, *r* = .05), showing a pattern of healthy executive functions being related to healthy contrast sensitivity functioning. Studies with saccades showed a range of nonsignificant positive correlations (*r* = .054, *r* = .09) and a single significant negative correlation (*r* = -.48), showing that the presence of saccades could be linked to a lower performance in executive functioning, Color vision/contrast was related to executive functioning in that impairment in this visual function was negatively correlated (*r* = -.62) to executive function performance. Finally visual field showed mixed findings, with one paper finding a significant negative relationship amongst the two (*r* = -.04) and another finding a nonsignificant positive relationship (*β* = .20).

Attention

A total of 18 papers investigated the relationship between attention and a range of visual functions. Of these, 11 found a relationship with visual acuity, with more than half finding that as visual acuity increases, so does attention functioning (*r* = .33, *r* = .27, etc.). The same pattern was found in contrast sensitivity (*r* = .16, *r* = .29, etc.), and saccades (*r* = .46, *r* = .39, etc.). In terms of visual field, attention yielded a nonsignificant relationship in the positive direction (*β* =

.20) indicating a potential lack of relationship between the two functions. Finally, one OCT study showed a slope of $\beta = 2.17$ with attention, indicating a relationship between retinal thickness and attention functioning.

MS sample

Six of the papers in the review included a sample made up of people with MS. A table of the results can be found in Table 4.

Table 4

Relationship Between Visual and Cognitive functions for samples of people with MS

Cognitive	Visual Acuity	Contrast sensitivity	Saccades	OCT
Attention	r = .37*** (Bruce et al., 2007) r = .31*** (Jakimovski et al., 2021) r = .17* (Wieder et al., 2013) β = 2.17** (Nguyen et al., 2018) r = .33** (Feaster & Bruce, 2011)	r = .29*** (Wieder et al., 2013)	r = -.50* (Fielding et al., 2009)	β = 2.17** (Nguyen et al., 2018)
Executive Functions	r = .33** (Feaster & Bruce, 2011)			
Memory	r = .37*** (Bruce et al., 2007) r = .31*** (Jakimovski et al., 2021) r = .17*	r = .54*** (Ridder et al., 2017) r = .29*** (Wieder et al., 2013)	r = -.41** (Fielding et al., 2009)	β = 2.17** (Nguyen et al., 2018)

	(Wieder et al., 2013) β = 2.17** (Nguyen et al., 2018)			
Processing Speed	r = .37*** (Bruce et al., 2007) r = .31*** (Jakimovski et al., 2021) r = .17* (Wieder et al., 2013) β = 2.97** (Nguyen et al., 2018)	r = .29*** (Wieder et al., 2013)	r = -.41** (Fielding et al., 2009)	β = .17* (Jakimovski et al., 2021) β = 2.17** (Nguyen et al., 2018)
Recall	r = .31*** (Jakimovski et al., 2021) β = .22* (Nguyen et al., 2018)	r = .34*** (Wieder et al., 2013)		β = .15* (Nguyen et al., 2018)
Visuospatial Skills	r = -.38*** (Jakimovski et al., 2021) β = .22* (Nguyen et al., 2018			β = .17* (Jakimovski et al., 2021)

Note. ** for significant results= * for p<0.05 significance, ** for p<.001, *** for p<.0001.*

Wieder et al. (2013) tested the relationship of visual acuity and contrast sensitivity with cognitive performance in patients with relapsing-remitting MS through a cross-sectional study. They measured cognitive performance by use of the Paced Auditory Serial Addition Test (PASAT), which assesses attention, concentration, working memory, and processing speed (Diehr et al., 1998). RNFL thickness was also measured by use of OCT scans. Researchers found that RNFL thickness and PASAT test scores were related to contrast sensitivity levels with a coefficient of $r = .17$, even when controlling for RNFL thickness. This positive association shows that as RNFL thickness worsened, the performance on these cognitive tests worsened alongside it.

This finding of RNFL thickness correlating with cognitive impairment was also found in a study by Jakimovski et al. (2021). Researchers investigated the relationship between visual and cognitive impairments in people with MS, and found that visual acuity and RNFL thickness were indeed correlated with cognitive scores in the SDMT (Symbol Digit Modalities Test) which measures processing speed and working memory, as well as with recall performance ($r = .31$ for both, $p < .001$ and $p = .008$ respectively), and were predictors of cognitive status in MS patients. They found that once controlling for RNFL thickness, the variance in cognitive performance could be explained by RNFL thickness (R^2 change = .263-.361, standardised $\beta = .17$, $p = .039$).

Nguyen et al. (2018) tested the relationship between visual acuity measures and neuropsychological assessment and found a significant association between visual acuity and processing speed ($\beta = 2.17$, $p = .005$), as well as visual acuity with recall ($\beta = .15$, $p = .04$) tests in the total sample. In the relapsing remitting MS sample, these correlations were significantly stronger, with visual acuity having a strong association with processing speed ($\beta = 2.97$, $p = .001$), visuospatial testing ($\beta = .32$, $p < .001$), and recall ($\beta = .22$, $p = .012$).

Fielding et al. (2009) investigated the visual and cognitive relationship in 25 MS participants, and found that MS patients had worse memory-related performance than healthy controls when testing saccade-related performance, for which MS patients were generally less accurate than healthy controls ($r = -.41$). The same pattern between MS participants and healthy controls was found for functions of attention ($r = -.50$) and processing speed ($r = -.41$).

Feaster & Bruce (2011) investigated the link between visual acuity and cognitive performance in people with relapsing-remitting as well as other MS types. Researchers found that different types of visual acuity (high-contrast, near, and low-contrast) had significant associations with motor, as well as various cognitive (PASAT, RAVLT) tests, with all associations being significant at the $p < .05$ level ($r = .33$).

Finally, Bruce et al. (2007) investigated the relationship between neuropsychological and visual tests in MS patients. Researchers found a significant relationship between visual acuity disturbances and tests of visual attention as well as processing speed ($r = .37$, $p < .001$ for both).

Results: Study Data Analysis

Participants and demographics

The final sample consisted of 106 participants. Demographic and medical information is shown in table 5. Not all participants had data available on whether they had had a past history of ON, thus only participants who had this information were available to researchers ($n = 93$).

Table 5

Demographics for total sample N=106 and separated by history of ON (n = 93)

Category	Total (N = 106)	ON history (n = 29)	No ON history (n = 64)
Age (M (SD))	52.2(12.2)	49.7 (12.1)	53.9 (12.0)
Gender			

Male	28	5	18
Female	78	24	46
Type of MS			
CDMS	1	0	0
PPMS	13	2	10
RRMS	51	16	29
SPMS	36	11	23
TMS	1	0	0
Unknown type MS	2	0	1

Note. 13 participants missing due to absent ON history information. CDMS= clinically definite MS, PPMS = Primary Progressive MS, RRMS = Relapsing Remitting MS, SPMS = Secondary Progressive MS, TMS = Tumefactive MS.

Assumption Checks

Tests of normality and homogeneity were violated for all variables, thus leading to analyses of group differences in ANOVA analyses being done with a non-parametric Kruskal-Wallis analysis of ANOVA on ranks.

Relationship Between Visual and Cognitive Functions

To assess the research questions relating to the relationship between visual and cognitive variables, correlation analyses were carried out. Data analyses yielded significant negative correlations between Visual Acuity and cognitive function tests such as the 15 Words test (r = -

.342, *p* <.001), the Corsi test (*r* = -.273, *p* = .008), the Silhouettes test (*r* = -.319, *p* = .002), and the digit span test (*r* = -.218, *p* = .029). Additionally, a single significant positive correlation was found between Contrast Sensitivity and the Silhouettes test (*r* = .220, *p* = .047). Visual Field yielded significant negative correlations with the 15 Words test (*r* = -.350, *p* = .002), and Nystagmus with the Corsi test (*r* = -.234, *p* = .022) and the Silhouettes test (*r* = -.391, *p* = <.001). The Taylor Complex Figure test and the Bells test yielded no significant correlations with any of the visual functions. Visual Acuity seems to be the most influential visual variable, with significant correlations with four of the cognitive tests, while the 15 Words test, Corsi test and Silhouettes tests all yielded two significant correlations each with visual variables.

Table 6

Non-partialled correlation Matrix of visual and cognitive variables for full sample N = 106

		Visual Acuity	Contrast Sensitivity	Visual Field	Nystagmus
Taylor	Pearson's r	-.171	.199	-.099	-.139
	p-value	.106	.079	.408	.186
15WT	Pearson's r	-.342***	.134	-.350**	-.178
	p-value	< .001	.221	.002	.077
Corsi	Pearson's r	-.273**	.087	-.012	-.234*
	p-value	.008	.442	.917	.022
Silhouettes	Pearson's r	-.319**	.220*	-.197	-.391***
	p-value	.002	.047	.095	< .001
Bells	Pearson's r	-.142	.117	-.010	-.051
	p-value	.171	.297	.930	.621
Digit span	Pearson's r	-.218*	-.028	-.109	-.037
	p-value	.029	.801	.348	.711

Note. *=p<.05, **=p<.01, ***=p<.001

To investigate whether a history of ON leads to a difference in visual-cognitive functions in people with MS, as well as to assess the strength and direction of this potential influence, a partial correlation analysis was carried out while controlling for a history of ON. Table 7 shows partial correlations results. When controlling for ON, significant correlations were still found between Visual Acuity and the 15 Words test (r = -.302, p = .005), Corsi test (r = -.257, p = .021), and Silhouettes Test (r = -.270, p = .015), albeit with larger p-values. Of interest is that the previously found significant correlation between Visual Acuity and the Digit Span test disappears, replaced by a statistically insignificant correlation (r = .178, p = .099). Interestingly, when accounting for a history of ON, the significant correlation between Contrast Sensitivity and the Silhouettes is no longer significant (r = .206, p = .085). This is also the case for the significant correlation between the Visual Field and 15 Words test (r = -.022, p = .863). Instead, the Visual Field function yields new significant correlations with cognitive tests once a history of ON is accounted for. These new correlations include the Visual Field with the Taylor test (r = -.329, p = .007), the Corsi test (r = -.274, p = .030), and the Digit Span test (r = -.329, p = .007). Similarly, once accounting for a history of ON, the correlation between Nystagmus and the Silhouettes test is also no longer significant (r = -.078, p = .483), rather a new significant correlation arises between Nystagmus and the 15 Words test (r = -.248, p = .025). This partial correlation analysis shows that accounting for a history of ON in the sample does create changes in the relationships between visual and cognitive functions in people with MS.

Table 7

Partial correlation matrix, controlling for ON variable

		Acuity	Contrast Sensitivity	Visual Field	Nystagmus
Taylor	Pearson's r	-.179	.151	-.329**	-.139
	p-value	.116	.214	.007	.200

		Acuity	Contrast Sensitivity	Visual Field	Nystagmus
15WT	Pearson's r	-.302**	.169	-.022	-.248*
	p-value	.005	.150	.863	.025
Corsi	Pearson's r	-.257*	.104	-.274*	-.425***
	p-value	.021	.393	.030	< .001
Silhouettes	Pearson's r	-.270*	.206	-.001	-.078
	p-value	.015	.085	.994	.483
Bells	Pearson's r	-.126	.077	-.108	-.050
	p-value	.260	.525	.385	.641
Digit span	Pearson's r	-.178	-.030	-.329**	-.139
	p-value	.099	.796	.007	.200

Note. *=p<.05, **=p<.01, ***=p<.001

ANOVA analyses were carried out to test the magnitude of the effect of a history of ON on the severity of visual and cognitive function impairments. Due to the violation of the normality assumption, nonparametric versions of ANOVA were carried out. Kruskal-Wallis outputs can be seen below.

Table 8

ANOVA analysis of cognitive test of people with ON and no ON history, n = 93

	$\chi2$	Mean	SD	df	p	$\varepsilon2$
Taylor	2.164	33.4	3.76	1	.141	.027
Digit span	.273	24.6	5.67	1	.602	.003
15WT	.570	43.9	12.1	1	.450	.007
Bells	.011	31.6	4.48	1	.918	.000
Corsi	.020	41.3	17.1	1	.889	.000
Silhouettes	1.547	6.80	1.84	1	.214	.019

Table 9

ANOVA analysis for visual scores of people with ON and no ON history, n = 93

	χ2	Mean	SD	df	p	ε2
Visual Acuity	.032	-.002	.141	1	.857	.000
Contrast Sensitivity	.164	2.00	.210	1	.685	.002
Visual Field	.602	.500	.802	1	.438	.009
Nystagmus	.370	.133	.342	1	.543	.004

As seen in the tables, differences between groups were statistically insignificant, both in the visual and cognitive variable grouping, with *p*-values ranging from $p = .438$ (Visual Field) to $p = .857$ (Visual Acuity) in the visual variables, and from $p = .141$ (Taylor test) to $p = .918$ (Bells test) in the cognitive variables. This is also shown in the effect sizes, all of which are considered to be weak, with effect sizes of $\varepsilon 2 = .14$ or above considered moderate (Field & Field, 2020). In this output, no effect sizes were larger than $\varepsilon 2 = .027$ (Taylor test), which is still considered to be small (Field & Field, 2020). This output shows there is no significant difference in visual and cognitive impairments in participants with and without a history of ON. This output additionally answers the third research question, which regarded the influence of ON history in the relationship between visual and cognitive variables.

Influence of RNFL thickness on visual and cognitive variables

Finally, in regards to the question of a difference in RNFL thickness and its effect on the relationship between visual and cognitive functions, another partial correlation analysis was carried out, accounting for RNFL thickness.

Table 10

Partial correlation matrix controlling for RNFL thickness variable, N = 106

		Acuity	Contrast Sensitivity	Visual Field	Nystagmus
Taylor	Pearson's r	-.068	-.047	.360**	-.037
	p-value	.600	.719	.005	.775
15WT	Pearson's r	-.341**	.172	-.089	-.212
	p-value	.006	.175	.490	.093
Corsi	Pearson's r	-.068	-.044	.360**	-.037
	p-value	.600	.738	.005	.774
Silhouettes	Pearson's r	-.179	.389**	.360**	-.038
	p-value	.169	.002	.005	.773
Bells	Pearson's r	-.064	-.046	.361**	-.037
	p-value	.620	.721	.005	.775
Digit span	Pearson's r	-.214	.092	-.047	.034
	p-value	.086	.467	.717	.785

Note. *=p<.05, **=p<.01, ***=p<.001

Data analyses yielded significant negative correlations between Visual Acuity and the 15 Words test (r = -.341, p = .006), Contrast Sensitivity and the Silhouettes test (r = .389, p = .002), and Visual Field with the Taylor Complex Figure (r = .360, p = .005), Corsi test (r = .360, p = .005), Silhouettes test (r = .360, p = .005), and Bells test (r = .361, p = .005). No significant correlations were found between Nystagmus and any of the Cognitive tests. Correlations were generally in the positive direction, with the exception of the correlation between Visual Acuity and the 15 Words test. These results show a large influence of RNFL thickness on Visual Field functioning, followed by Contrast Sensitivity and Visual Acuity.

Discussion

Systematic Review: the relationship between vision and cognition

The present study and review aimed to investigate the relationship between visual and cognitive functioning in people with MS. In the context of this study, the systematic review allowed for a comprehensive examination of the association between visual and cognitive functioning in MS. By systematically reviewing and analyzing multiple studies, the review identified consistent patterns and associations, strengthening the validity of the findings. Furthermore, the systematic review methodology facilitated the identification of potential sources of biases or inconsistencies in the literature, which can inform future research and guide the development of targeted interventions.

The systematic review findings suggest a clear association between these domains, with visual acuity and contrast sensitivity emerging as important in the relationship with cognitive status in MS patients; and RNFL thickness being linked to cognitive test performance, while a history of ON was not found to be a significant moderator in this relationship.

Several studies have shown that cognitive performance in MS patients is related to visual acuity and contrast sensitivity levels (Wieder et al., 2013; Nguyen et al., 2018; Feaster & Bruce, 2011). Specifically, the review showed that lower visual acuity and contrast sensitivity were found to be associated with poorer performance on tests of attention, processing speed, working memory, and recall. These findings are consistent with previous research indicating that visual processing deficits in MS are associated with reduced cognitive function (Balcer et al., 2018). This pattern of findings suggests that cognitive functioning relies on somewhat intact visual functioning and vice versa, highlighting the importance of assessing and addressing visual impairments in the management of cognitive function in MS.

Moreover, the systematic review suggests that RNFL thickness may be an important predictor of cognitive status in MS patients (Wieder et al., 2013; Jakimovski et al., 2021).

Researchers found that lower RNFL thickness was associated with cognitive impairment, even when controlling for visual acuity and contrast sensitivity levels. These findings suggest that RNFL thickness may serve as a potential biomarker for cognitive dysfunction in MS patients.

Overall, the current review highlights the importance of assessing visual functioning as well as cognitive functioning in MS patients, as there seems to be a clear interplay between both types of functioning, wherein only measuring one and leaving the other aside may not show the full picture. Future studies should continue to investigate the relationship between visual functioning, cognition, and perception in MS patients, in order to identify potential biomarkers and develop targeted interventions to improve cognitive and visual outcomes in this population. For one, the review did not go into detail on the specific mechanisms underlying the interplay between visual and cognitive functioning impairments. Understanding these mechanisms would contribute to a more comprehensive understanding of the relationship between visual and cognitive functions in the MS population.

Furthermore, future studies could explore additional factors that may influence the relationship between visual and cognitive impairments in MS. For example, the impact of psychological factors such as depression, anxiety, or fatigue on visual and cognitive outcomes in MS patients warrants further investigation. These psychological comorbidities may interact with visual and cognitive impairments, potentially exacerbating symptoms and influencing treatment outcomes. By considering these factors in future research, a more nuanced understanding of the complex relationship between visual functioning, cognition, and psychological well-being in MS patients can be achieved.

Data analysis: the relationship between vision and cognition

Additionally to the review, data analysis findings also provided important insights into the relationship between visual and cognitive functions. Data results indicated that visual function performance was related to cognitive functioning performance. These results support our hypothesis that visual and cognitive functions are related, and is in line with the systematic review in finding the same relationship. Data results showed that visual acuity function is related to cognitive functions such as memory and object perception, as well as contrast sensitivity with object perception. Visual Field functioning seems to be related to verbal memory, and Nystagmus with object perception. These findings are supported by existing literature (Wieder et al., 2013; Nguyen et al., 2018; Feaster & Bruce, 2011; Balcer et al., 2018), and have implications for both the clinical assessment as well as treatment management of people with MS.

For one, clinicians testing people with MS for cognitive impairments should be aware of the clear interplay between visual and cognitive functioning impairment, particularly in tasks requiring attention, processing speed, working memory, and recall as these cognitive functions seem to be the most correlated with visual impairment. Secondly, interventions aimed at improving cognitive functioning in MS should not ignore the impact of visual functioning impairments on cognition in MS, but should take this into consideration when creating adaptive treatment practices. Finally, the specific relationships identified between visual functions and cognitive domains provide insights into the underlying mechanisms of cognitive impairment in MS. For example, the association between visual acuity and memory suggests that visual information plays a crucial role in encoding and retrieving episodic memories. Understanding these mechanisms could inform the development of targeted interventions that capitalize on the interplay between visual and cognitive processes.

When separating the sample into groups of history vs no history of ON to test whether this led to a different level of visual cognitive impairment, results showed that the magnitude of the impact of ON on the severity of visual and cognitive impairments was not statistically significant. This does not support our hypothesis that a history of ON would lead to significantly more impairments in visuo-cognitive functioning in people with MS, and does not line up with previous literature finding support this same hypothesis (Jakimovski et al., 2021; Nakajima et al., 2010). This contradiction may be due to several reasoens. First and foremost, there is a possibility that the difference in sample size and methodology of the present study and the current literature are the cause for differing results, as the literature investigated both a sample of children (Jakimovski et al., 2021) and the impact of scotoma due to ON as their main source of visual impairment (Nakajima et al., 2010). This difference in methodology may have caused a heterogeneity in data results.

Secondly, we must consider the variability of ON itself. For one, ON varies in its severity, duration, and recurrence on the person, which may lead to long-term impacts on their visual and cognitive functioning. This severity of ON was not indicated in the literature assessed, thus there could be variability in the impact of ON severity affecting visual, and thus cognitive, functioning. This must be taken into consideration for future studies, as simply separating people into having or not having a history of ON, and not considering the severity of their ON, may be too broad a category potentially creating a confounder in the data.

Thirdly, we must consider the time since the last episode of ON the person suffered from. It is possible that a person who suffered from ON in the last 6 months can have very different functioning skills to a person who last suffered from ON 6 years prior. This limitation was also present in the literature, in that studies measured both the age at onset of the first ON episode, as well as the number of ON relapses, but did not assess the length of each of these episodes, thus creating a potential confound in the data that must be taken into consideration in future studies.

When controlling for a history of ON, results showed most relationships between visual and cognitive functions remained, with the exception of a new relationship between nystagmus and verbal memory. This new relationship may be due to the abnormal eye movements associated with nystagmus potentially disrupting the stable gaze necessary for optical information processing, which could lead to impairments in encoding visual information, and thus in retrieving this information later on. This relationship only being present once a history of ON was accounted for suggests that the presence of ON may mask or overshadow the impact of nystagmus on verbal memory, as a history of ON can result in visual deficits, as has been shown in the literature (Nakajima et al., 2010), and these deficits could directly influence verbal memory functioning. In addition to this finding, all correlations between contrast sensitivity and cognitive functioning disappeared upon controlling for a history of ON, which suggests that ON may be a mediator in the relationship between contrast sensitivity and cognitive functioning in people with MS. This may be due to the side effects of ON, such as reduced visual acuity and contrast sensitivity (Nakajima et al., 2010) directly impacting cognitive performance, thus obscuring the effects of contrast sensitivity on cognition.

Interestingly, visual field functioning exhibited substantial changes in its relationship with cognitive functioning before and after accounting for a history of ON. Initially, visual field was found to be correlated only with verbal memory. However, once the influence of ON was taken into account, visual field functioning was found to be correlated not only with verbal memory but also with visual construction, visual spatial memory, and executive functioning. This significant alteration emphasizes the impact of ON on an individual's ability to perform visual-related cognitive tasks. The observed changes suggest that the presence of ON may have an influence on a person's capacity to carry out visual-related cognitive functions, extending beyond verbal memory. These findings raise important implications for MS patients with a history of ON, highlighting the potential long-term consequences of ON on visual function. Prior research has indicated that individuals with a history of ON may experience more severe visual field defects, as well as more pronounced visual and cognitive impairments, compared to those without ON (Nakajima et al., 2010).

In relation to the hypothesis that RNFL thickness is associated with higher levels of impairment in visual-cognitive relationships, the examination of partial correlations accounting for RNFL thickness revealed a greater number of significant correlations. Specifically, these correlations were observed between visual acuity and verbal memory, contrast sensitivity and object perception, and visual field with visual construction, visual spatial memory, object perception, and visual attention. These findings suggest that RNFL thickness plays a significant role in shaping the relationship between visual and cognitive functions in individuals with MS. More specifically, we can speculate based on the results of the data and the systematic review that RNFL thickness may be linked to impairments in visual field, which in turn could contribute to difficulties in cognitive functions that rely on visual processing. This highlights the importance of considering the structural integrity of the RNFL in understanding and addressing the visual-cognitive impairments observed in MS. These results support our hypothesis that RNFL thickness is a moderating factor in the relationship between vision and cognition in MS, and is consistent with existing literature that has identified RNFL thickness as an important biomarker for visual and cognitive impairments in individuals with MS (Jakimovski et al., 2021; Nakajima et al., 2010; Feaster & Bruce, 2011). The presence of significant associations between

RNFL thickness and multiple aspects of visual and cognitive functioning further supports the notion that assessing RNFL thickness can provide valuable insights into the extent and nature of visual-cognitive deficits in MS. By clarifying the relationship between RNFL thickness and visual-cognitive impairments, these findings offer potential avenues for targeted interventions and treatments. Developing strategies to preserve or enhance RNFL thickness may help mitigate the impact of visual impairments on cognitive functioning in individuals with MS. Furthermore, monitoring changes in RNFL thickness over time could serve as a valuable marker for tracking disease progression and evaluating the effectiveness of interventions aimed at preserving visual and cognitive abilities. Additionally, not only the presence but the severity and timeline of ON episodes must be taken into consideration both when testing a person for visual and cognitive functioning, as well as when planning out their treatment.

The review results align with the data analysis in measures of visual acuity, contrast sensitivity and RNFL variables. While the review yielded more significant results than the data analysis did, this could be explained by a level of publication bias in the field, whereas nonsignificant findings are less commonly found than significant ones. A level of scepticism must be maintained when considering how many nonsignificant findings that have been filed in a drawer may be present in comparison to ones that have been published in databases for public access. Another possible explanation for the difference in significant results between the review and data analysis is the variation in methodologies and sample characteristics across the included studies. The review encompassed a broader range of studies with diverse designs, populations, and measurement approaches. On the other hand, the data analysis focused on a specific sample and employed standardized measures, potentially reducing variability and increasing statistical power. The variation in methodologies and sample characteristics could contribute to discrepancies in the findings and emphasize the importance of considering the context and limitations of each approach.

Strengths and Limitations

The tests used in the present study may have led to better-than-expected performance from the participants, due to the nature of the tests being quite specific. Choosing tests that could have encapsuled more broad cognitive functions, such as the DAT or the TMT tests could have led to potentially broader results that were more in line with the present study. On the other hand, tests such as the 15 words test or the digit span are considered strong tests for the cognitive functions they measure, and were thus chosen for this thesis as a potential strength in measuring cognitive functions. On the other hand, the use of a systematic review in conjunction with the primary data analysis strengthens the validity and reliability of the research findings. The systematic review allowed for the identification of potential biases in the existing literature and facilitated the synthesis of diverse sources of evidence. The use of a systematic review as part of the scientific analysis not only helps to support or disprove our hypotheses, but it helps to reduce potential study publication or outcome reporting biases through the use of an accurate and reliable analysis (deVries et al., 2018).

Conclusions and Further Directions

This study aimed to investigate the relationship between visual and cognitive impairments in individuals with MS, with a specific focus on the impact of a history of ON and RNFL thickness. The findings revealed significant correlations between visual and cognitive measures, particularly when considering the RNFL thickness in the MS sample. These findings have important clinical implications and suggest directions for further research.

The patterns found in the present paper suggest a need for more detailed investigation into the presence of ON as well as the strength of the RNFL when testing the visual and cognitive functioning of people with MS. By considering the visual impairment as a potential confounder in cognitive test results, more accurate assessments of cognitive function can be achieved, leading to better clinical management and treatment planning. The present study supported this by demonstrating significant relationships between visual-cognitive tests and non-visual cognitive measures. This reinforces the interplay between vision and cognition in neuropsychological testing and visual assessments. The interplay between visual and cognitive functions in people with MS complicates the isolation of specific skills or functions. Therefore, it is essential to recognize and address the joint origin of visual and cognitive decline, rather than to try to isolate one or the other. Future research could explore how the interplay of these functions can be used to create more comprehensive assessment tools and interventions.

Regarding treatment options, it is important to not only consider the importance of visual and cognitive function in people with MS, but to also take into consideration their quality of life. Treatment strategies should not only focus on improving overall MS symptoms but also prioritize interventions that enhance visual and cognitive outcomes. For example, rehabilitative approaches that target visual processing deficits, such as visual training programs or assistive technologies, may help individuals with MS improve their visual and cognitive abilities. Additionally, multidisciplinary interventions that address psychological well-being, including strategies to prevent or manage comorbid conditions like depression and loneliness, should be integrated into the treatment plan.

In conclusion, this study provides valuable insights into the relationship between visual and cognitive impairments in individuals with MS. The findings support the need for tailored cognitive assessments, highlight the interplay between vision and cognition, and emphasize the importance of comprehensive treatment approaches. Further research should focus on developing targeted interventions, investigating the underlying mechanisms of the visual-cognitive relationship, and exploring the long-term impact of visual impairments on cognitive outcomes in individuals with MS. By addressing these areas, we can advance our understanding and improve the management of visual and cognitive impairments in this population.

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