VRIJE UNIVERSITEIT BRUSSEL

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THE INFLUENCE OF INTERNUCLEAR OPHTHALMOPLEGIA ON THE RESULTS OF THE SYMBOL DIGIT MODALITIES TEST IN PATIENTS WITH MULTIPLE SCLEROSIS

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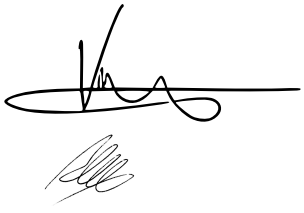

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
AUC	Area under the curve
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BRB-N	Brief Repeatable Battery of Neuropsychological Tests
CIS	Clinically isolated syndrome
CLT	Consistent long term
CNS	Central nervous system
CSF	Cerebrospinal fluid
CST	Concept Shifting Test
EDSS	Expanded Disability Status Scale
EMQ	Eye Movement Questionnaire
F	Female
FS	Functional system
HADS	Hospital Anxiety and Depression Scale
INO	Internuclear ophthalmoplegia
LTS	Long term storage
M	Male
MCT	Memory Comparison Test
MLF	Medial longitudinal fasciculus
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NHPT	Nine-Hole Peg Test
OCT	Optical coherence tomography
ODS	Oculus dexter and sinister (left and right eye)
ON	Optic neuritis
PASAT	Paced Auditory Serial Addition Test
PDI	Proton density imaging
PPMS	Primary progressive multiple sclerosis
Pv/Am	Peak velocity divided by amplitude
RNFL	Retinal nerve fibre layer
RRMS	Relapsing remitting multiple sclerosis
SCWT	Stroop Colour Word Test
SDMT	Symbol Digit Modalities Test
SF-CIS	Subjective Fatigue subscale of the Checklist Individual Strength
SPART	10/36 Spatial Recall Test
SPMS	Secondary progressive multiple sclerosis
SRT	Selective Reminding Test
T25-FW	Timed 25-Foot Walk
UMC	University Medical Centre
VDI	Versional dysconjugacy index
VFQ25	Visual Function Questionnaire 25
VIF	Variance inflation factor
WLGT	Word List Generation Test

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ABSTRACT

Background and objective: Internuclear ophthalmoplegia (INO) and cognitive decline are both frequent manifestations in multiple sclerosis (MS). The Symbol Digit Modalities Test (SDMT) is the most used cognitive test in MS patients and relies on visual scanning. The purpose of this study was to investigate the influence of abnormal eye movements in INO on the SDMT score in MS patients.

Methods: In this retrospective, observational, cross-sectional study, data from 199 MS patients from the Amsterdam MS cohort were analysed. The presence of INO was detected using infrared oculography. All patients completed four questionnaires and underwent a neurological and neuropsychological examination, a magnetic resonance imaging scan, and an optical coherence tomography scan. Using multiple linear regression analysis, with correction for confounders, the influence of INO on the SDMT score and other neuropsychological tests was studied.

Results: Of the 199 MS patients, 62 patients were diagnosed with INO. The SDMT score was significantly lower in the INO group compared to the non-INO group. After correction for sex, visual acuity, disease duration, EDSS score, RNFL thickness, and CGM volume, the versional dysconjugacy index of the peak velocity divided by amplitude of the leftward eye movements was significantly associated with the SDMT score.

Conclusion: The results of this study suggest that the presence of a right INO, meaning that the eye movement disorder is manifested when looking to the left, negatively affects the SDMT score. In clinical practice, this translates into caution in interpreting the SDMT score if a right INO is present.

Keywords: multiple sclerosis, internuclear ophthalmoplegia, Symbol Digit Modalities Test, cognitive impairment

1. INTRODUCTION

1.1. MULTIPLE SCLEROSIS

1.1.1. Epidemiology

Multiple sclerosis (MS) is the most common chronic, immune-mediated, demyelinating disease of the central nervous system (CNS). In the last decade, the prevalence of MS has increased in every world region (1-3). It is estimated that 2.8 million people worldwide suffer from MS (2, 4). There is an association between latitude and MS prevalence, with the prevalence increasing from south to north (1, 3, 5). Women are two to three times as likely to be living with MS than men (2, 4). MS is typically diagnosed in people between the ages of 20 and 40 years (4, 6, 7), with an average of 32 years old (2). This makes MS a common cause of neurological disability in young adults (2, 3).

1.1.2. Aetiology

Both genetic and environmental factors are involved in the development of MS (1, 3, 7). The presence of genetic factors is demonstrated by the fact that first-degree relatives of patients with multiple sclerosis have a higher risk of the disease than the general population (6). Twin studies also show that co-occurrence of MS is more common in monozygotic twins than in dizygotic twins (8). Genome-wide association studies linked more than 200 genetic variants to MS. None of them are obligatory or sufficient to cause this disease (3, 6). The main genetic risk associated with MS is variation in the HLA-DRB1 locus (1, 3), where heterozygotes for HLA-DRB1*15 have a three-times higher risk of MS. Implicated environmental factors include Epstein-Barr virus infection, smoking, hypovitaminosis D, and obesity (1, 3-5). The timing of exposure to these risk factors plays an important role, with childhood and adolescence as the most decisive periods. Migration studies show that immigration before adolescence acquires the risk of the new country, while immigration after adolescence retains the risk of the original country (1, 7).

1.1.3. Disease courses

Three major clinical courses of MS have been described. Relapsing remitting multiple sclerosis (RRMS) is seen in 85% of patients, which is characterized by

exacerbations and remissions. An exacerbation or relapse has a minimum duration of 24 hours (7, 9). A relapse mostly develops over hours to days, then reaches a plateau for several weeks, and then recovers completely or incompletely (1, 9). After a mean of 15 years, around 75% of the patients with RRMS progress to a form of the disease in which there are no more exacerbations, but a progressive decline. This form is called secondary progressive multiple sclerosis (SPMS). Primary progressive multiple sclerosis (PPMS) is seen in 15% of patients, in which the disease is progressive from the onset (1, 7, 9). Patients with PPMS are approximately ten years older at disease onset than RRMS patients (3, 9).

Clinically isolated syndrome (CIS) refers to a first clinical attack, suggestive of MS. This resembles a typical MS exacerbation. CIS could indicate MS if additional activity occurs. For some patients with a first clinical attack, a diagnosis of RRMS can be made if an MRI scan shows dissemination in time and space (see section '1.1.6. Diagnosis') (9, 10).

1.1.4. Pathogenesis

Multiple sclerosis is characterised by neuroinflammation, demyelination and neurodegeneration (1, 3). In the CNS, outgrowths of oligodendrocytes form the myelin sheath of axons. This myelin layer ensures that the conduction of signals through the nerves runs efficiently. In MS, demyelination occurs in various places in the brain and spinal cord, which leads to impaired conduction of signals (3).

Before and during the development of a demyelination focus, there is a locally disturbed blood-brain barrier, through which mainly autoreactive lymphocytes against myelin-proteins enter the CNS. These cause an inflammatory process, resulting in damage to the oligodendrocytes and demyelination (3, 4). Remyelination often occurs after a few weeks, which repairs damaged myelin to some extent (3, 7). The disease course RRMS is dominated by inflammation and focal demyelinated plaques. In the progressive disease courses, the demyelinated plaques are less important, while diffuse white and grey matter atrophy plays a bigger role (1, 4, 7).

1.1.5. Clinical presentation

MS is a heterogeneous disease in which the type and severity of neurological deficits and symptoms depend on the location of the lesions. Several symptoms and syndromes are common in patients with MS, but none of them are unique to

MS (9, 11). Sensory complaints are a part of the presenting syndrome in a third of the cases (11). Optic neuritis is characterised by visual blurring or loss, painful eye movements, affected colour vision, and relative afferent pupillary defect. Optic neuritis the presenting symptom in 20% of MS patients. Common brainstem manifestations include internuclear ophthalmoplegia, facial weakness, trigeminal neuralgia, vertigo, and dysphagia. Motor symptoms (e.g., focal weakness in the limbs, hyperreflexia, Babinski sign, spasticity) affect nearly 90% of the patients at some point. Fatigue and autonomic dysfunctions (including bowel, bladder, and sexual dysfunctions) are one of the most debilitating symptoms that affects the majority of the MS patients (11, 12). Cerebellar symptoms, such as ataxia, unsteady gait, and dysarthria, mainly occur in the progressive course of MS. Depression, headaches and cognitive impairment are common symptoms as well in MS (11). Patients with RRMS often present with sensory complaints in the limbs and visual loss (in the context of optic neuritis), while patients with PPMS most often present with a spinal cord syndrome (9).

1.1.6. Diagnosis

The 2017 McDonald criteria are currently used to diagnose MS. These criteria combine clinical, imaging, and laboratory examinations. Dissemination in time and space of the lesions or neurological symptoms is essential for the diagnosis (10, 11, 13).

Dissemination in space is fulfilled in each of the following conditions:

- The patient has at least two clinical attacks of MS, that implicate different sites in the CNS.
- The patient has one clinical attack with hyperintense T2 lesions (MRI scan) in at least two of the four MS-typical regions of the CNS: periventricular, (juxta)cortical, infratentorial, and spinal cord.

Dissemination in time is fulfilled in each of the following conditions:

- The patient has at least two clinical attacks, characteristic of MS, separated by at least one month.
- The patient’s MRI shows simultaneous gadolinium-enhancing (i.e., new lesion) and non-enhancing (i.e., old lesion) lesions in the CNS.
- The patient’s MRI shows new hyperintense T2-lesions on a follow up-MRI, with already lesions on the previous MRI.
- Cerebrospinal fluid (CSF)-specific oligoclonal bands are present (13, 14).

There are little differences between the current 2017 McDonald criteria and the previous 2010 McDonald criteria.

- According to the current criteria, the presence of CSF oligoclonal bands is sufficient to meet the criterion 'dissemination in time'.
- Cortical and juxtracortical lesions visible on MRI now also contribute to the determination of dissemination in space.
- Both symptomatic and asymptomatic MRI lesions now contribute to the determination of dissemination in space or time.

The current criteria give the ability to diagnose MS more rapidly. This means that patients diagnosed with MS according to the 2010 criteria also meet the 2017 criteria. The criteria became more sensitive, not more specific (10, 13).

For the primary progressive disease course, MS can be diagnosed if there is one year of disability progression and if two of the following criteria are fulfilled:

- The patient has at least one T2 hyperintense lesion characteristic of MS in at least one of the following brain regions: periventricular, (juxta)cortical or infratentorial.
- The patient has at least two T2 hyperintense lesions in the spinal cord.
- CSF oligoclonal bands are present (13).

1.2. INTERNUCLEAR OPHTHALMOPLEGIA IN MULTIPLE SCLEROSIS

1.2.1. Epidemiology

Internuclear ophthalmoplegia (INO), also referred to as internuclear ophthalmoparesis, is one of the most common eye movement disorders in MS. This conjugate gaze abnormality is present in 25% to 35% of all MS patients (15-17). Although MS is more prevalent in women, MS patients with INO are more often male (15). In the general population, brainstem stroke is the most common cause of INO (18).

1.2.2. Clinical features

INO is characterized by a slowed adduction movement of the ipsilateral eye. Additionally, this adduction movement may also be limited, and an abduction nystagmus of the contralateral eye may occur, as illustrated in Figure 1. During convergence, the ipsilateral adduction is often preserved. This dissociation of

ipsilaterally delayed and possibly limited adduction during saccades, and the maintenance of ipsilateral adduction during convergence may be lacking (18, 19).

The Uhthoff phenomenon describes the worsening of clinical signs and symptoms in MS due to rise in body temperature. The disturbed eye movements in MS patients with INO are also more pronounced in situations such as high environment temperature, fever, and during exercise. This was determined by infrared oculography (see section '2.3.4. Infrared oculography') (18, 20).

INO can occur as a temporary symptom of an MS relapse or as a chronic condition, resulting from incomplete recovery from a previous relapse or from a progressive disease course. In most patients, symptoms and signs improve after several months, although a proportion of patients have permanent residual damage (19). The study of Bolaños et. al. showed that 61.9% of INOs caused by demyelination recovered completely after a period of nine months (21).

Due to the impaired horizontal conjugate eye movements in INO, patients may complain of diplopia, oscillopsia, reading fatigue, visual confusion, and loss of stereopsis (15, 18). On the other hand, patients with chronic INO are typically asymptomatic or have nonspecific visual complaints (19). In general, MS patients with INO have half as much vision related quality of life compared to MS patients without INO (16).

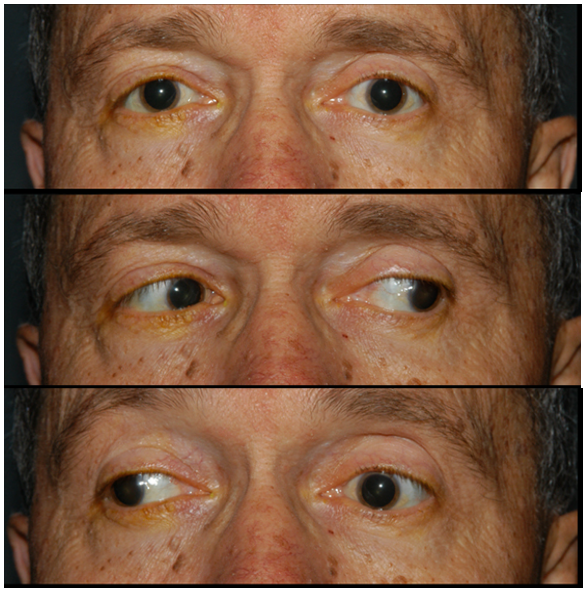


Figure 1: Disturbed eye movements in internuclear ophthalmoplegia (22).
Eye movements in a patient with a left INO. The top picture depicts the patient in a primary gaze position. The middle picture shows a saccade to the left, with normal eye movements. The bottom picture shows a saccade to the right, with the left eye showing an adduction restriction, due to damage of the left medial longitudinal fasciculus.

1.2.3. Aetiology and oculomotor circuitry

In MS, INO is caused by the demyelination and axonal damage of the medial longitudinal fasciculus (MLF). This pair of white matter fibre tracts is located at midbrain and pontine level, ventral to the fourth ventricle and cerebral aqueduct. The side of the INO is named by the side of the adduction deficit, which is ipsilateral to the MLF lesion. This means that in people with a left INO, the eye movement disorder becomes visible when looking to the right. Both MLFs are located close to each other near the midline, making bilateral damage due to MS frequent (18).

The MLF is mainly involved in coordinating synchronous horizontal eye movements (18, 19). During horizontal eye movements, the paramedian pontine reticular formation (i.e., the horizontal gaze centre) sends signals to the abducens nucleus, which contains two sets of neurons. The first set of neurons forms the abducens nerve, which innervates the ipsilateral lateral rectus muscle. This muscle is responsible for abduction of the ipsilateral eye. The second set of interneurons crosses the midline to form the MLF. The MLF sends signals to the medial rectus subnucleus of the oculomotor nucleus. From here, the oculomotor nerve departs and innervates the medial rectus muscle. This muscle generates an adduction movement of the contralateral eye (18, 23). The described oculomotor circuitry is illustrated in Figure 2.

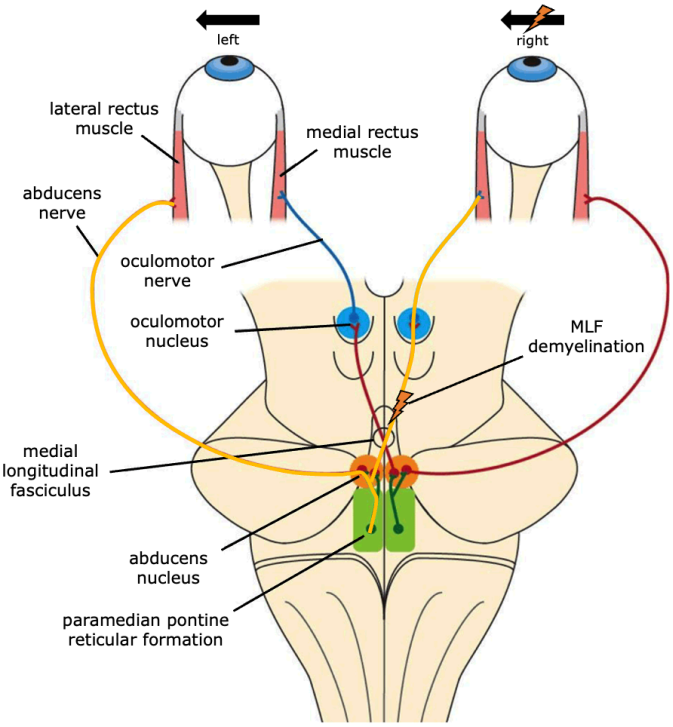


Figure 2: Oculomotor circuitry for horizontal eye movements (adapted from 24).
The yellow-coloured path shows the circuit required to look left. In case of demyelination of the right MLF, signal conduction from the abducens nucleus to the oculomotor nucleus is delayed. This results in a delayed and possibly limited adduction movement of the right eye when looking to the left.

1.2.4. Evaluation and diagnosis

Clinical detection of INO by bedside neurological examination is performed by assessing the patient's saccades. This can be performed by asking the patient to alternately fixate two peripheral targets (e.g., the examiner's fingers) (19). The accuracy of the clinical examination to determine INO is moderate. Both false-positive and false-negative findings are common (16, 25). Frohman et. al. showed that in clinical examination the subtle forms of INO were overlooked in 71%, as well as the moderate forms in a quarter. Severe INO was not detected in 6% (25).

An objective and accurate diagnosis of INO can be made using infrared oculography (16, 25). During infrared oculography, eye movements are accurately traced by an eye tracker that determines the eye position based on the pupil and corneal light reflex (16).

The best MRI sequence to show MLF lesions is proton density imaging (PDI). In a study of 58 MS patients with INO, all patients had visible MLF lesions on PDI, while on T2 weighted images and fluid-attenuated inversion recovery, lesions at the MLF were visible in 88% and 48% of patients, respectively (26).

1.3. COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS

1.3.1. Prevalence

The prevalence of cognitive impairment in MS is estimated between 43% and 70% (27). The most affected cognitive domains are information processing speed and visual memory, but also the domains of attention, executive function, working memory, visuospatial processing and verbal memory can be affected (27-29). The cognitive deficits occur in every disease course, nevertheless, in the secondary progressive disease course, the cognitive complaints are more prevalent and more severe (27, 29).

1.3.2. Daily life impact

Cognitive complaints have an impact on the daily lives of patients that should not be underestimated. Cognitively impaired patients are less likely to be employed, participate in fewer social activities, report more sexual dysfunction, experience more difficulties in performing routine household tasks, and are more vulnerable to psychiatric disorders than cognitively intact patients (27, 30). Cognitive impairment is one of the most important predictors of quality of life (31-33).

1.3.3. Cognitive reserve

The onset of cognitive impairment does not necessarily correlate with disease duration, nor does it follow the same pattern of severity as physical disability (27, 33). This can be partly explained by cognitive reserve. The cognitive reserve is the ability of the brain to compensate for changes caused by normal aging or for damage caused by an underlying disease. Greater cognitive reserve, i.e., higher education level or higher premorbid intelligence, protects against the progression of cognitive dysfunction in MS (29, 34).

1.3.4. Cognitive testing

Various cognitive test batteries have been developed to assess functioning in different cognitive domains. The Rao's Brief Repeatable Battery of Neuropsychological Tests (BRB-N) is widely used in MS. The BRB-N consists of five tests that assess the cognitive domains most frequently affected in MS (35). Despite the development of many cognitive test batteries, these are rarely used routinely because they require trained personnel, are time-consuming and therefore expensive (36, 37). For this reason, the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) was developed. This is a short test battery that can easily be performed in a clinical setting. The BICAMS battery consists of three cognitive tests for the assessment of information processing speed, verbal memory, and visual memory. This takes about 15 minutes (38). If there is a lack of time for one of the cognitive test batteries, the Symbol Digit Modalities Test (SDMT) is the recommended test to assess the cognitive function of MS patients (38, 39).

1.3.4.1. The Symbol Digit Modalities Test

The SDMT has become the most popular test for cognitive evaluation of MS patients due to its brevity, high reliability, and psychometric validity (29, 37). This test has a high sensitivity to cognitive impairment and cognitive change in MS (38, 40). It is an excellent sentinel test for overall cognitive impairment in MS (36, 40) and predates cognitive impairment in other cognitive domains at the group level (41). The SDMT has been designed to assess information processing speed, but the performance of a patient also depends on other functions, such as working memory, linked learning and visual scanning (29). As the SDMT is a test that is fast, reliable, and easy to do, it has replaced the Paced Auditory Serial Addition Test (PASAT) (39). While both tests were designed to capture information

processing speed, the PASAT is extremely sensitive to practice effects (42) and generally considered more stressful by people with MS (42, 43). The SDMT is part of almost all the cognitive test batteries used in MS (37) and is also widely used in the research field. In many clinical trials, the SDMT is the only cognitive outcome measure (39).

1.3.5. Magnetic resonance imaging as marker for cognition

Several associations have been described between magnetic resonance imaging (MRI) findings and cognitive test results in patients with MS. A negative association between the lesion volume on T2-weighted imaging and the SDMT and PASAT performance has been found (44). A significant decrease in thalamic volume and whole brain volume has been observed in cognitive impaired MS patients compared with cognitive preserved MS patients (45). Several studies showed an association between cognitive decline and both cortical and subcortical grey matter atrophy (29, 46-48).

1.3.6. Optical coherence tomography as marker for cognition

Optical coherence tomography (OCT) is a non-invasive imaging test that uses light waves to produce cross-sectional images of the retina. The device sends an infrared light beam via the pupil into the eye on the retina. Various structures of the retina then reflect this light back, which is captured by the device. The signal reflected from a retinal structure contains time-of-flight information, providing spatial information of this structure (49). An OCT scan can distinguish the ten individual layers of the retina, and it also provides quantitative measures of the thickness of these layers (50).

A meta-analysis showed a significant association between the retinal nerve fibre layer (RNFL) thickness and information processing speed. A thicker RNFL is associated with a better SDMT performance and higher PASAT scores (50). Multiple studies demonstrated a significant correlation between RNFL thickness and the MRI-characteristics T2 lesion volume (51), whole brain atrophy, (51, 52) and thalamus volume (52). The outcome of the meta-analyse performed by Petzold and colleagues highlights the accuracy and robustness of RNFL thickness as a marker for neurodegeneration in MS (53).

1.4. HYPOTHESIS AND OBJECTIVE

The SDMT relies on visual scanning (29, 54) and the extent to which impaired visual scanning reduces the patient's SDMT results is unknown. This is important considering that INO is present in about a quarter to a third of all MS patients (15, 16) and that the SDMT is the most important test to assess the cognitive function of patients with MS (29, 37). Previous research demonstrated that INO is associated with worse cognition (15). The study of Chen and colleagues already suggested that oculomotor functions influence the SDMT performance (55). The aim of this study was to determine whether and to what extent the disrupted eye movements in INO influence the SDMT performance.

We hypothesized that the disrupted eye movements in INO negatively affect the SDMT scores, given the oculomotor demands of this test. Furthermore, we suspected that INO also influences other visual cognitive tests to a greater or lesser extent, depending on the degree of eye movements required by these tests. Finally, we hypothesized that the relationship between SDMT and PASAT scores would be stronger in the non-INO group than in the INO group, because in patients with INO the disrupted scanning affects the SDMT and not the PASAT.

2. METHODOLOGY

2.1. PATIENT POPULATION

In this retrospective, single-centre, observational, cross-sectional study, data from 199 MS patients from the Amsterdam MS cohort were analysed. The data collection took place between July 2015 and February 2018. All patients were diagnosed with multiple sclerosis according to the most recent McDonald criteria at the time. All participants were between 18 and 80 years old.

The patients were invited at the Amsterdam University Medical Centre (UMC), location VUmc for a one-day program in which all data, except the questionnaires, were collected. The visit consisted of an interview, a clinical assessment, a neuropsychological examination, an MRI scan, an OCT scan, and an infrared oculography measurement. In total, the visit lasted approximately six hours. An example of the schedule of an examination day is shown in Table 1. Section '2.3. Data acquisition' describes in detail how the information was collected. Within one week after the visit to the Amsterdam UMC, all patients filled out questionnaires on fatigue, anxiety, depression, and vision-related quality of life.

Table 1: Example of the schedule of an examination day.

Hour	Examination
11h – 11h15	Informed consent form
11h15 – 11h45	OCT scan
11h45 – 12h30	Lunch
12h30 – 13h15	Interview and neurological examination
13h15 – 14h30	Neuropsychological examination
14h30 – 14h45	Multiple sclerosis functional composite
14h45 – 16h	Infrared oculography
16h – 17h	MRI

2.2. ETHICS

All participants provided written informed consent. The study was approved by the Medical Ethical Committee on Human research of the Amsterdam UMC (study number 2015.227), in accordance with the tenets of the Declaration of Helsinki.

2.3. DATA ACQUISITION

2.3.1. Anamnesis and clinical assessment

2.3.1.1. Demographic and MS-related information

During the interview, demographic and MS-related information were collected (see Table 5 in section '3.1. Patient characteristics'). The level of education was ranked according to the Verhage scale. This scale ranges from one, where patients did not complete primary education, to seven, where patients obtained a university degree. Table 2 shows this education ranking (56). Disease duration was counted from the year of the first manifestation of neurological symptoms suggestive of MS.

Table 2: Description of education levels, based on the Verhage categories. Adapted from (56).

Level	Verhage categories
1	Less than 6 years of primary education
2	Finished primary education
3	Primary education and less than 2 years of low-level secondary education
4	Finished low-level secondary education
5	Finished average-level secondary education
6	Finished high-level secondary education
7	University degree

2.3.1.2. Visual acuity

The patients' vision was assessed using the Snellen chart. Patients performed the test with refractive correction using their glasses or contact lenses.

2.3.1.3. Neurological examination

A neurological examination was performed to determine the patient's score on the Expanded Disability Status Scale (EDSS). The EDSS is a scale to measure clinical disability in MS patients, ranging from zero to ten. A score of zero is given on a normal neurological examination, while ten means death due to MS. The functional systems (FS) assessed to determine the EDSS score include visual functions, brainstem functions, pyramidal functions, cerebellar functions, sensory functions, bowel and bladder functions, cerebral functions, and ambulation (9). Table 3 shows which findings during the clinical neurological examination correspond to which EDSS score.

Table 3: The Expanded Disability Status Scale (9).

Score	Findings during the neurological examination
0.0	Normal neurological examination.
1.0	Minimal signs in one FS, no disability.
1.5	Minimal signs in more than one FS, no disability.
2.0	Minimal disability in one FS.
2.5	Minimal disability in two FS.
3.0	Fully ambulatory, with moderate disability in one FS, or mild disability in three or four FS.
3.5	Fully ambulatory, with moderate disability in one FS and one or two FS grade 2; or two FS grade 3; or five FS grade 2.
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 meters.
4.5	Fully ambulatory without aid; relatively severe disability, usually consisting of one FS grade 4 or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities.
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities.
6.0	Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 meters with or without resting.
6.5	Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 meters without resting.
7.0	Unable to walk beyond about five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair 12 hours a day.
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair.
8.0	Essentially restricted to bed or chair or perambulated in wheelchair but may be out of bed itself much of the day. Retains many self-care functions. Generally, has effective use of arms.
8.5	Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions.
9.0	Helpless bed patient; can communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow.
10	Death due to MS.

2.3.1.4. Nine-Hole Peg Test and Timed 25-Foot Walk Test

The Nine-Hole Peg Test (NHPT) and the Timed 25-Foot Walk Test (T25-FW) were performed. The NHPT measures finger dexterity and upper extremity function. In this test, patients were asked to insert nine pegs one by one into the holes of the board as quickly as possible, and then remove them one by one. This is illustrated in Figure 3A. The task was first performed twice with the dominant hand, then twice with the non-dominant hand. The four attempts were timed, and the score was the average number of seconds it took to complete the task (57, 58).

The T25-FW assesses mobility and leg function. Patients were asked to walk 25 feet (approximately 7.6 meters) as quickly as possible but safely in an

unobstructed hallway, illustrated in Figure 3B. The outcome measure was the number of seconds the patient needed for this task. The score of the T25FW was the average of two attempts (58, 59).

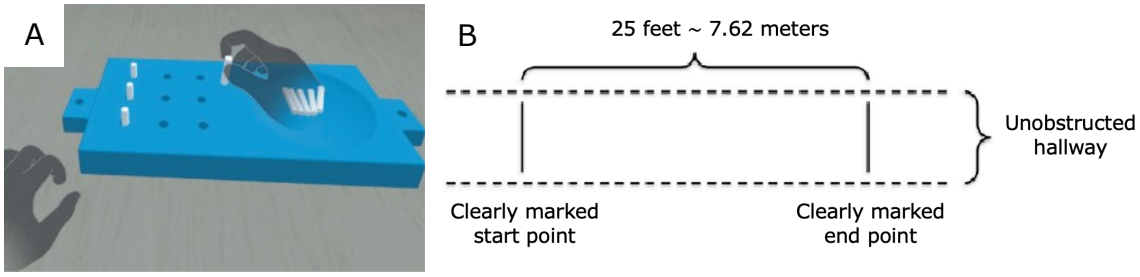


Figure 3: The Nine Hole Peg Test and The Timed 25-Foot Walk Test.

A. The Nine Hole Peg Test, where the nine pegs must be inserted into the nine holes one by one as quickly as possible. The time was started as soon as the hand touched the first peg and was stopped as soon as the last peg was placed in the board (60).
B. The Timed 25-Foot Walk Test, where patients walked 25 feet as fast as possible but safely in an unobstructed hallway (61).

2.3.2. Optical Coherence Tomography

OCT imaging was performed on a spectral domain OCT (Spectralis by Heidelberg engineering, Germany) in both eyes. This measurement was performed in a room with dim lighting. Pharmacological pupillary dilators were not used. A peripapillary ring scan was taken, manually centred around the optic nerve head. The thickness of each retinal layer was calculated using automated segmentation software provided by the manufacturer. More details of this procedure can be found in Corie, et. al. 2018 (62).

2.3.3. Neuropsychological examination

Table 4 shows an overview of the cognitive tests administered, combined with the main cognitive domain that each test evaluates. The Brief Repeatable Battery of Neuropsychological Tests (BRB-N) was administered, which contains five cognitive tests. The SDMT and the PASAT are both used to measure information processing speed and sustained attention. The Selective Reminding Test (SRT) assesses verbal memory, while the 10/36 Spatial Recall Test (SPART) evaluates visuospatial memory. The Word List Generation Test (WLGT) evaluates verbal fluency (35). Additionally, the Stroop Colour Word Test (SCWT) which evaluates attention and inhibition, the Memory Comparison Test (MCT) which assesses working memory, and the Concept Shifting Test (CST) which appraises executive functioning were administered (63).

Table 4: Components of the neuropsychological examination.

Cognitive test	Main cognitive domain
Symbol Digit Modalities Test	Information processing speed
Paced Auditory Serial Addition Test	Information processing speed
Selective Reminding Test	Verbal memory
10/36 Spatial Recall Test	Visuospatial memory
Word List Generation Test	Verbal fluency
Stroop Colour Word Test	Attention
Memory Comparison Test	Working memory
Concept Shifting Test	Executive functioning

2.3.3.1. Symbol Digit Modalities Test

In the SDMT, the patients were presented a page with at the top a key that pairs digits 1 to 9 with nine symbols. Below, there were eight rows containing only symbols. This page of the SDMT is presented in Figure 4A. The patients were instructed to verbally report the corresponding number for the symbols. They first practiced on the first ten symbols of the first row. After the practice trial, they had to give much as possible correct responses in 90 seconds. The score of this test is the number of correct answers given within 90 seconds. A higher score reflects a better performance. In total, the test required about five minutes to complete (64, 65).

2.3.3.2. Paced Auditory Serial Addition Test

During the PASAT (3-second version), the patients heard every 3 seconds a number below 10 and had to add each time the consecutive digit to the preceding digit. A total of 61 numbers were presented. This auditive test is visualised in Figure 4B. The patients listened to an audio recording because subtle differences in administration procedures can significantly affect the outcome (66). The dependent measure was the number of correct answers across the test, between 0 and 60. The higher the score, the better the performance. The real test preceded by a practice trial, that existed of ten digits (66, 67).

2.3.3.3. Selective Reminding Test

In the SRT, the researcher read out 12 unrelated words, after which the patient was instructed to name as many of these words as possible in random order. In the five consecutive trials, the examinator only repeated the words that the patient forgot to name in the preceding trial. The patient was instructed each time to name the set of 12 words. After minimal 15 minutes, the patient was asked to name these 12 words again, during which delayed recall is tested. The list of words used

in this study is shown in Figure 4C. To determine the score of the SRT, the long-term storage (LTS) score and the consistent long term (CLT) score were calculated for each trial. The LTS score is the number of words mentioned in two consecutive trials. The CLT score is the number of words said until the last trail. The final score is the average of four components: the LTS score of the first trial, the cumulative LTS score, the cumulative CLT score and the delayed recall score. A higher score reflects a better performance (68).

2.3.3.4. 10/36 Spatial Recall Test

In the SPART, patients were shown a 6x6 board with ten black dots indicated for ten seconds. After these ten seconds, the patients received a blank 6x6 board and were instructed to recreate the pattern with checkers. This task was repeated twice, with the same pattern. After about 20 minutes, the patients were asked to place the pattern on the board again. The score is the average number of correct answers for the three trials and the delayed recall trial. The higher the score, the better the performance. The SPART is visualised in Figure 4D (68).

2.3.3.5. Word List Generation Test

In the WLGT, patients tried to name as many words within the category 'fruit and vegetables' as possible within 90 seconds. The score is the number of words the patients mentioned. Inflections of the same word or its perseverations were counted as one answer. No penalty points were charged for incorrect words. A higher test score reflects better performance (68).

2.3.3.6. Stroop Colour Word Test

The SCWT assesses the patient's attention as well as his ability to suppress a reflex response (this is called inhibition). The test consisted of three parts. In the first part, the patients received a card on which the words red, blue, yellow, and green were printed a hundred times, spread over ten lines. The patients had to read these words as quickly as possible, from the left to the right, line by line. In the second part, patients received a card with boxes in the colours red, blue, yellow, and green. This time the patients were instructed to name the colour of the boxes. Finally, the patients received a third card on which the words red, blue, yellow, and green were printed, but the ink was a different colour than the word. The patients were instructed not to read the words, but to name the colour of the ink. The first two rows of the three cards are presented in figure 4E (69). The score is

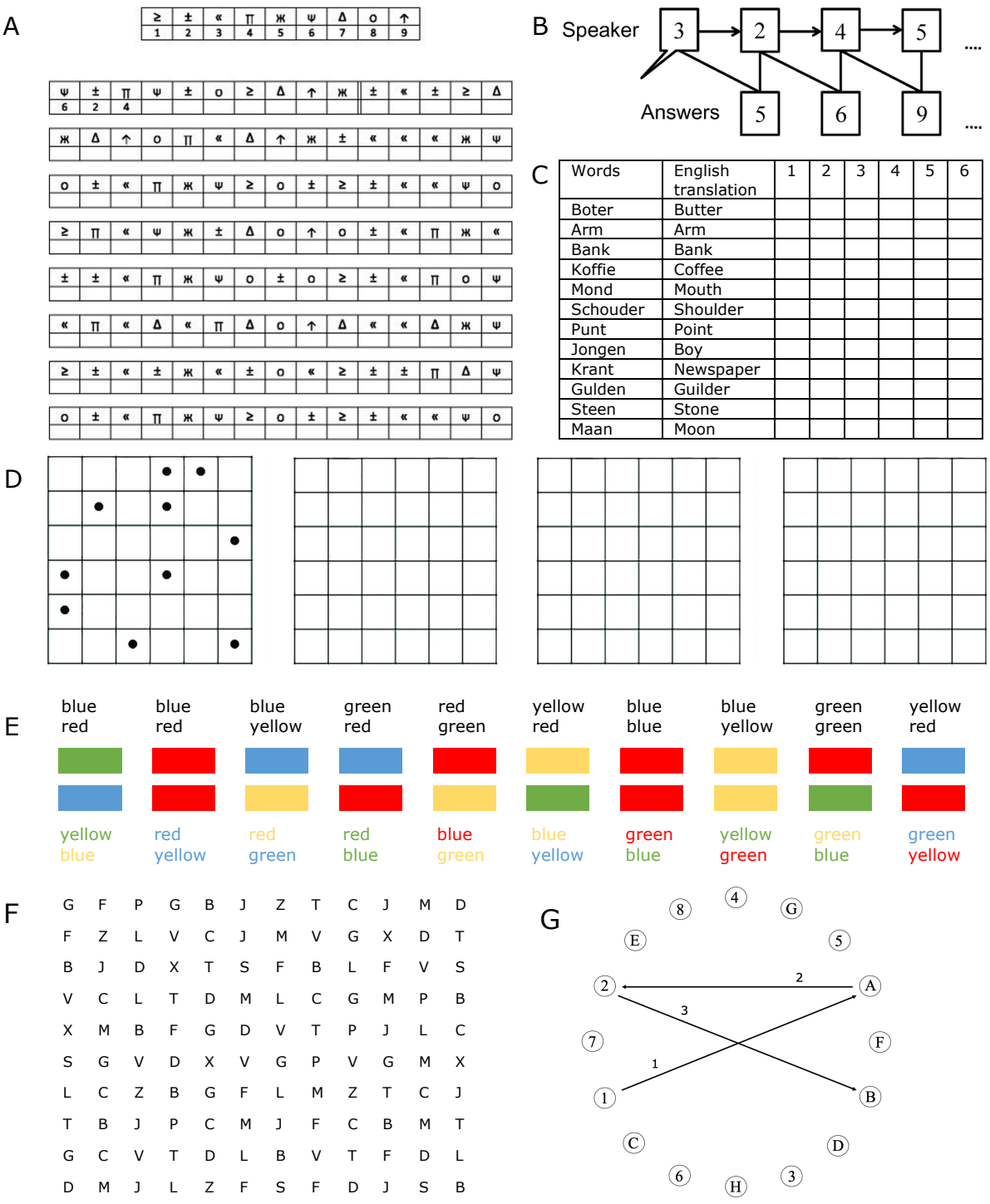
the average time it takes to read these cards. This implies that a higher score reflects a poorer performance.

2.3.3.7. Memory Comparison Test

During the MCT, patients were shown a page containing one or more letters for five seconds, with the instruction to remember this/these letter(s). Immediately afterwards they received a page containing 120 letters, divided into ten rows. They were instructed to cross out the memorized letter(s) row by row, as quickly and as accurately as possible. The real task was preceded by a practice test in which the patient was shown a percent sign instead of a letter. After the practice test, there were four series of increasing numbers of letters to memorize (maximum four). The page on which patients had to cross out four memorized letters is shown in Figure 4F. The score is the average time of these 5 trials (including the practise trial). The higher the score, the worse the performance.

2.3.3.8. Concept Shifting Test

The CST consisted of four trials. In the first trial, the patients were shown a page containing 16 circles with numbers in it, ranging from 1 to 16. The patients were instructed to cross out all the numbers as quickly as possible, in ascending order. The second trail was analogous to the first, but with letters instead of numbers, from A to P. In the third trial, patients received an analogous page with both letters and numbers in the circles, which is shown in Figure 4G. Patients were instructed to start at the first digit and move from there to the first letter, then to the second digit, and so on. Each of these three trials was preceded by a simplified version of the test (i.e., fewer numbers and/or letters). Finally, a baseline measurement was performed, during which patients were given three pages with 16 empty circles printed on each. They were instructed to cross out the circles as quickly as possible, starting at the top circle and moving clockwise (70). The average time of the three baseline measurements was subtracted from the three tests. The final score is the average of the three tests, corrected for the baseline measurement. A higher score reflects a poorer performance.



Words	English translation	1	2	3	4	5	6
Boter	Butter						
Arm	Arm						
Bank	Bank						
Koffie	Coffee						
Mond	Mouth						
Schouder	Shoulder						
Punt	Point						
Jongen	Boy						
Krant	Newspaper						
Gulden	Guilder						
Steen	Stone						
Maan	Moon						

Figure 4: Neuropsychological examination.

A. The SDMT with a key code at the top of the page, and eight rows below that contain only symbols. Patients had to verbally indicate the corresponding number to the symbols (71).

B. Flow of the PASAT in which patients had to add the last two digits each time (72).

C. The words used during the SRT.

D. The 6x6 board with a pattern of 10 black dots of the SPART (73).

E. The first two rows of the three cards of the SCWT are presented. The first card contains the words of four colours. The second card contains boxes in these four colours. The third card contains the words of colours, printed in a different colour than the word (74).

F. Page of the MCT. Patients were instructed to cross out the memorised letters S, Z, X, and P.

G. Page of the CST. Patients had to combine the numbers and letters in ascending order (70).

2.3.4. Infrared oculography

2.3.4.1. Set-up of the infrared oculography measurement

Infrared oculography was administered to accurately track the eye movements of patients. Eye movements were assessed through an EyeLink 1000 Plus eye tracker (SR Research, Ottawa, Canada). This device uses the pupil and corneal light reflection to determine the position of the eye. Data were sampled at 1000 Hz. Patients were seated at a distance of 92 cm of the monitor screen (HP EliteDisplay, E241i, 24 inch) and 55 cm of the camera. The patients' head was stabilised with a chin and a forehead rest. This measurement was performed in a noiseless room with dim lighting. The set-up of this measurement is shown in Figure 5A. The target used for the test consists of a black circle with a white circle in it, with a black cross in the centre of the white circle. This was shown on a white background. The target is illustrated in Figure 5B. This procedure is extensively described in Nij Bijvank et. al., 2019 (16).

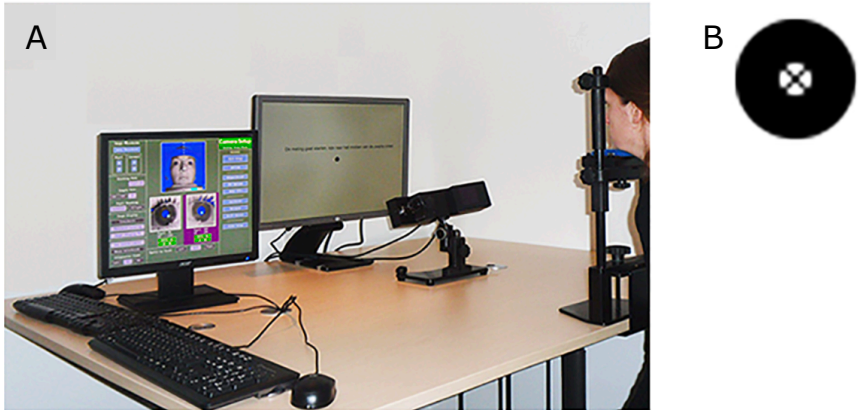


Figure 5: The set-up of the infrared oculography measurement (75)

A. Patients were seated 92 cm of the monitor screen and 55 cm of the camera, while their head was placed in a chin and forehead rest.
B. The target used during the prosaccade task.

2.3.4.2. Prosaccade task

To detect INO, the prosaccade task of the validated standardized infrared oculography protocol 'DEMoNS' was used, which is described in detail in Nij Bijvank et. al., 2018 (75). The test was preceded by a nine-point calibration and validation procedure. The validated prosaccade protocol contained five series of 12 horizontal prosaccades from the centre of the monitor screen to a location eight degrees or 15 degrees left or right from the centre. After a fixation period between 1.0 and 3.5 seconds, the target appeared for 1.5 seconds at an eccentric location. The patients were instructed to focus on the target and to follow it as closely as

possible. Data were analysed automatically and offline, using an in-house written program in MATLAB (75). To pass quality control, at least 50% of prosaccades at 15 degrees from the centre needed to be captured (15).

2.3.4.3. Area under the curve and peak velocity divided by amplitude

Because the device accurately detected the position of the left and right eyes at each time point, it was possible to construct for each eye an accurate curve with time on the x-axis and horizontal eye positions on the y-axis. This allowed calculation of the area under this curve (AUC) of the saccadic trajectory per eye, after the patient performed a horizontal saccade during the prosaccade task. Figure 6 demonstrates these curves of a patient with INO and a patient without INO. Besides the AUC, another important parameter is the peak velocity of the saccade divided by its amplitude (Pv/Am). This parameter can be calculated for both eyes with the data obtained by infrared oculography.

Both the AUC and the Pv/Am parameters are important to quantify INO. By dividing the value of these parameters of the abducting eye by the value of the parameters of the adducting eye, we obtain a quantification of the severity of INO. This is called the versional dysconjugacy index (VDI). The VDI therefore describes the ratio of the abducting and adducting eye movements. For example, if an eye movement is made to the left, the VDI AUC can be calculated by dividing the AUC of the saccadic trajectory of the left eye by the AUC of the saccadic trajectory of the right eye. Because both eyes work together perfectly in normal circumstances, this ratio is close to 1. In INO there is an adduction delay, which makes this ratio higher. The higher the VDI-values (VDI AUC and VDI Pv/Am), the more severe the INO (16). Figure 6 shows the saccadic trajectory curves of both eyes during a leftward saccade in an INO patient and in a non-INO patient. The corresponding VDI AUC and VDI Pv/Am values are presented.

2.3.4.4. Defining INO

To define INO, we used the cut-offs mentioned in Nij Bijvank et. al., 2019 (16). Patients were classified in the INO group if during prosaccades at 15 degrees left or right from the centre, the VDI AUC was more than 1.174 and/or the VDI Pv/Am was more than 1.180. This corresponds to a specificity of 0.98 and a sensitivity of 0.97 (comparison: MS versus HC) (16). For each VDI parameter, the average was taken per patient, distinguishing between saccades to the left and to the right.

This made it possible to create four groups: patients without INO, patients with a left INO, patients with a right INO, and patients with bilateral INO.

'VDI AUC left' and 'VDI Pv/Am left' are parameters of eye movements to the left. If one or both parameters are abnormal, this indicates a right INO. 'VDI AUC right' and 'VDI Pv/Am right' are rightward eye movement parameters. If one or both parameters are abnormal, this indicates a left INO.

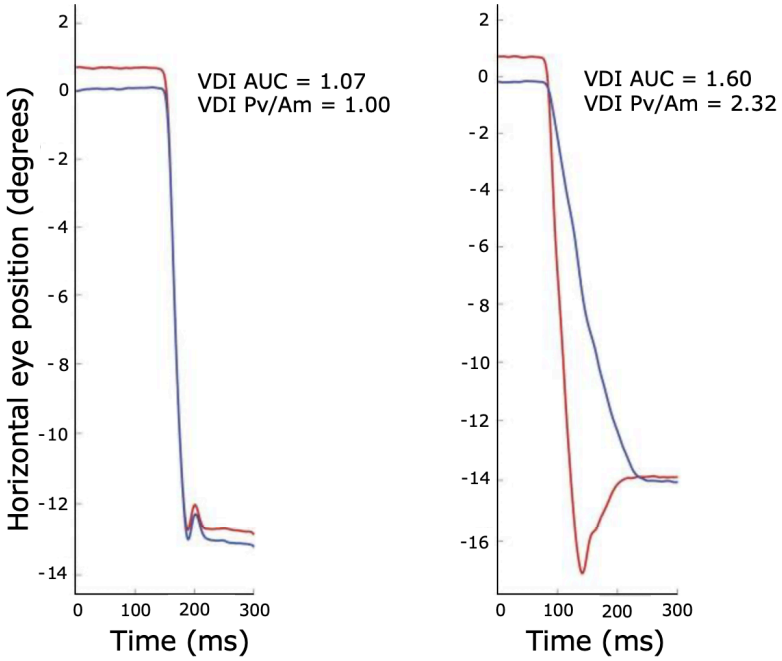


Figure 6: The curves show the saccadic trajectory of both eyes of two different MS patients during a leftward saccade. The x-axis represents time, and the y-axis represents the horizontal eye position. The red line represents the left eye; the blue line represents the right eye (16).

The left curve shows a leftward saccade of a patient without INO. Both eyes work synchronously, there is no adduction delay. The VDI AUC left is 1.07 and the VDI Pv/Am left is 1.00.

The right curve shows a leftward saccade of a patient with INO. The right eye lags behind the left eye, representing an adduction delay. The VDI AUC left is 1.60 and VDI Pv/Am left is 2.32; both values are above the cut-off defining a right INO (16).

2.3.5. Magnetic Resonance Imaging

The MRI measurements were made with a three-Tesla scanner (signa HDxt, eight-channel coil), as described in Schoonheim et. al. 2022 (76). The total T2-lesion load was determined using fluid-attenuated inversion recovery through automated segmentation. Lesion filling was performed using Lesion Automated Processing. Whole brain volume and cortical grey matter volume were calculated on the lesion-filled 3DT1 with SIENAX. The thalamus volume was subtracted using FIRST. Whole

brain volume, cortical grey matter volume and thalamus volume were normalized for head size. More details are described in Schoonheim et. al. 2022 (76).

2.3.6. Questionnaires

After the research day at the VUmc, the patients received online questionnaires. They were asked to complete these questionnaires within one week of their visit.

2.3.6.1. Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) was developed to screen for anxiety and depression in patients in hospital settings. Pais-ribeiro et. al. demonstrated the suitability of HADS for the identification of mood changes in patients with MS. The HADS consists of two subscales, each containing seven statements. The patient gave a score for each statement from zero to three, with the maximum score of each subscale being 21. The higher the score, the more serious the depressive or anxious symptoms (77).

2.3.6.2. Subjective Fatigue subscale of the Checklist Individual Strength

The Subjective Fatigue subscale of the Checklist Individual Strength (SF-CIS) measures subjective fatigue related to MS. This questionnaire consists of eight statements that determine how the patient felt over the last two weeks. The patient had to indicate to what extent the statement applies to him, on a scale from one to seven. The SF-CIS score provides an image of fatigue that considers fluctuations over time. A higher score indicates more subjective fatigue (78).

2.3.6.3. National Eye Institute Visual Function Questionnaire

The National Eye Institute Visual Function Questionnaire (NEI VFQ-25) is one of the most frequently used vision-related quality of life questionnaires. The effect of eye disorders on daily functioning and quality of life is measured using 25 questions. The items can be classified into 12 subscales: general health, general vision, ocular pain, difficulty with near-vision activities, difficulty with distance-vision activities, limitation of social functioning due to vision, role limitations due to vision, dependency on others due to vision, driving difficulties, difficulty with colour vision, and difficulty with peripheral vision. The composite VFQ-25 score is the average score of all items except for the general health item. A higher score means a better vision-related quality of life (79).

2.3.6.4. Eye Movement Questionnaire

The Eye Movement Questionnaire (EMQ) is a questionnaire developed at the Amsterdam UMC (location VUmc) to identify complaints due to eye movement disorders in MS patients. The questionnaire consists of seven questions that assess diplopia, oscillopsia, blurred vision, and difficulty focusing on objects. Patients responded to each question with a score from 1 (no complaints) to 5 (very serious complaints). The score on the test varies from 7 to 35, with a higher score indicating more serious complaints due to eye movement problems. (16)

2.4. STATISTICAL ANALYSES

All statistical analyses were performed using the statistical software program R version 4.2.1. The graphs were created with this program. Statistical significance was determined at a p-level of 0.05.

2.4.1. Patient characteristics

Assessment of the normal or non-normal distribution of the data was done both graphically and using the Shapiro-Wilk test. With a large sample size, the statistical methods are very sensitive to non-normality, which means there is a chance that normal data will be incorrectly treated as non-normal. Therefore, the data were also studied graphically using histograms, which was decisive (80).

Differences in variables between MS patients with INO and MS patients without INO were analysed using the independent samples t-test for parametric continuous variables, the Mann-Whitney U test for non-parametric continuous variables and the chi-square test for categorical variables (81).

2.4.2. Univariate correlations between the SDMT and all other variables

The univariate correlations between the SDMT score and the demographic variables, the disease-related variables, the outcome measures of technical examinations and the questionnaires were determined. If both variables showed a normal distribution, the Pearson's correlation coefficient (r) was used. If one or both variables were not normally distributed, the Spearman's rho (ρ) was used. To calculate the correlation between a continuous variable and a dichotomous variable, the point biserial correlation coefficient was used (82). A correlation was considered as strong if the correlation coefficient was higher than 0.7 or lower than -0.7. A correlation was considered as weak if the correlation coefficient was lower

than 0.3 or higher than -0.3. A moderate correlation had a correlation coefficient between 0.3 and 0.7 or between -0.7 and -0.3 (83).

2.4.3. Linear regression analysis with SDMT results as dependent variable and INO as independent variable

2.4.3.1. Model with y = SDMT and x = INO binary

To examine whether INO has an influence on the SDMT results, an explanatory model with INO as binary independent variable (present or absent) and SDMT score as continuous dependent variable was constructed. First, a simple linear regression model was constructed to investigate the influence of INO on the SDMT performance without correction for confounders. Then, all detected confounders were combined in a multiple linear regression model to study the influence of INO on the SDMT scores, with adjustment for these covariates.

2.4.3.1.1. Detection of confounders

First, a selection of possible confounders was made based on:

1. The univariate correlations between the SDMT and the other available variables (see Table 7).
2. The differences in demographic and disease-related variables, technical examinations, and questionnaires between the INO and non-INO groups (see Table 5)
3. The relationships seen in the literature between variables and the SDMT score, and between variables and the presence of INO.

Thereafter, each possible confounder was added and removed one by one to the simple linear regression model to detect the real confounders. If the slope coefficient of the variable INO changed at least by 10%, the added variable was considered a confounder.

Then, all detected confounders were combined in a multiple regression model. Multicollinearity was detected by using the variance inflation factor (VIF). If the VIF was more than 4, which indicates considerable collinearity between two confounders, we included the strongest confounder in the model (84). Thereafter, a correlogram of all detected confounders was created, showing all correlations between the confounders. This was to examine the strength and significance of these correlations and to check multicollinearity in a different way.

An alternative way to build a model, which served as a check for what is described above, is the step function in the program 'R'. In this way, the model with the most suitable confounders is selected via algorithms.

The other assumptions of a multiple linear regression model were checked. The presence of a linear relationship between the dependent variable and the independent variables was checked using scatter plots. The normality of the residuals was assessed visually by a histogram of the standardized residuals. The spread of the error terms across the predictor variable was visually checked to assess homoscedasticity (85, 86).

2.4.3.2. Model with y = SDMT and x = INO categorical

An explanatory model was constructed, adding the SDMT score as a continuous dependent variable and INO as a categorical variable, instead of the binary INO variable in the previous models. A distinction was made between the presence of a left INO, a right INO or a bilateral INO, using the absence of INO as the reference group. This allowed us to investigate whether a certain INO subgroup has more influence on the SDMT score.

2.4.3.3. Model with y = SDMT and x = a continuous VDI-parameter

To investigate whether the influence of INO on the SDMT scores is stronger as the INO becomes more severe, four models with the SDMT score as continuous dependent variable were created. Each of the four models contained a different continuous VDI-parameter as primary predictor. Two of these models allowed examining the influence of a left INO on SDMT performance, with VDI AUC right and VDI Pv/Am right as primary predictors. The models with VDI AUC left and VDI Pv/Am left allowed us to study the influence of a right INO on the SDMT scores.

2.4.4. Linear regression analysis with other cognitive tests as dependent variable and INO as independent variable

Seven other explanatory models were created with each time a different cognitive test result as continuous dependent variable and the presence or absence of INO as binary independent variable. The same confounders as in the explanatory models for the SDMT were used. This allowed us to assess the influence of INO on other cognitive (visual or auditive) test results and to compare this with the influence of INO on the SDMT performance.

Furthermore, four explanatory models were constructed for each cognitive test, each with a different VDI-parameter as continuous independent variable. This allowed us to investigate whether a more severe INO had more influence on these cognitive tests, distinguishing between a left INO and a right INO.

2.4.5. Form of the available data from the cognitive test results

The raw SDMT scores and raw PASAT scores were used in the analyses. For the other cognitive tests, z-scores were used, based on a healthy control group. Adjustments were made for age, sex, and education if these parameters had a significant effect on the test score. For cognitive tests where a higher score reflects poorer performance, the z-scores were multiplied by -1. This means that for each cognitive test, a higher z-score reflects a better performance.

2.4.6. Correlation between SDMT and PASAT scores

In the second part of this study, we investigated the influence of INO on the SDMT performance by comparing the SDMT scores and PASAT scores. Both tests assess information processing speed and sustained attention. While the SDMT is a visual test that involves many scanning movements, the PASAT is purely auditory.

2.4.6.1. Comparing ρ by Fisher z transformation and observed z test statistic

The correlation coefficient between the SDMT and PASAT scores was calculated in the INO group and non-INO group. To statistically compare these Spearman correlation coefficients of both groups, the Fisher-z transformation was used. The z-scores were compared and analysed for statistical significance by determining the observed z test statistic.

2.4.6.2. Multiple linear regression with effect modification

A model with effect modification was created to study the influence of INO on the relationship between SDMT and PASAT results. The PASAT score was the continuous dependent variable, while the SDMT score and the presence of INO were the independent variables. The interaction term indicates whether the presence of INO influences the relation between the SDMT and PASAT scores.

Each possible confounder was added and removed one by one to the simple linear regression model to detect the real confounders. If the interaction term changed at least by 10%, the variable was considered a confounder. A model with these confounders as covariates was constructed.

3. RESULTS

3.1. PATIENT CHARACTERISTICS

3.1.1. Characteristics of the studied cohort

From the Amsterdam MS cohort, 199 patients with clinical definite MS were included in this study. From each patient, the SDMT score, the PASAT score and the VDI-parameters to determine INO were available. The patient characteristics and test results of the whole MS group as well as the two subgroups (INO versus non-INO) are presented in Table 5.

The patients in this study had an average age of 54.1 years. They had a mean disease duration of 20.9 years and a median EDSS score of 3.5. Disease duration was counted from the year in which the first symptoms suggestive of MS occurred. Women represented two-thirds of the cohort. Most patients had a relapsing remitting disease course (63%), followed by a secondary progressive course (26%) and a primary progressive course (12%). Almost half of the patients have suffered from optic neuritis. The mean visual acuity with refractive correction was 1.0. The level of education was ranked according to the Verhage scale, with a median score of 5, which corresponds to a finished average-level secondary education. The median score on the NHPT was 20.4 seconds, the median score on the T25-FW Test was 4.8 seconds. The raw test scores of the SDMT and PASAT are presented. The mean SDMT score was 50.2 and the median PASAT score was 53. Of the other cognitive tests, z-scores are presented, with correction for age, sex, and education if these parameters had a significant effect on the test score. A higher z-score reflects a better performance.

3.1.2. INO versus non-INO group

Based on the mean VDI AUC and mean VDI Pv/Am values at 15-degree saccades to the left and to the right, the 199 MS patients were divided into a group with INO and a group without INO. Sixty-two patients exceeded the cut-off value of 1.174 for VDI AUC and/or 1.180 for VDI Pv/Am. Consequently, they were placed in the INO group. The other 137 patients ended up in the non-INO group. Figure 7 shows the distribution of mean VDI AUC and mean VDI Pv/Am values for saccades 15 degrees to the left or right in the study population.

Of the male patients, 44% had an INO, while in the female patients only 24% had an INO. MS patients with INO had a longer disease duration (mean of 23.0 years versus 19.9 years) and a higher EDSS score (median of 4 versus 3.5). The INO group contained more patients with a progressive disease course than the non-INO group (50% versus 30%). MS patients with INO had worse scores on both the NHPT (median of 22.2 versus 19.2) and the T25-FW Test (median of 5.6 versus 4.7). The INO patients scored significantly worse on the SDMT, the CST, the SRT, the MCT, and the SCWT. The median score on the EMQ (median of 4 versus 2) and on the HADS depression scale (median of 3 versus 2) was significantly higher in the INO group.

Age, education level, visual acuity, and history of optic neuritis were similar in both subgroups, as well as the results on the PASAT, the WLGT, and the SPART. No differences were detected on the RNFL thickness and the MRI parameters between the INO group and non-INO group. The results of the VFQ-25, the FS-CIS and the HADS anxiety scale did not differ significantly between both groups.

3.1.3. INO subgroups

Of the 62 INO patients, 21 (34%) of them had an INO when looking to the left (which is a right INO), 19 (31%) patients had an INO when looking to the right (which is a left INO), and 22 (35%) patients had a bilateral INO. The variables that were considered confounders in the explanatory models (see below) were also determined in the INO subgroups. This selection of patient characteristics and test results of the INO subgroups is shown in Table 6. The unilateral INO groups and the bilateral INO group were similar in terms of age, disease duration, sex, visual acuity, disease course, EDSS score, and CGM volume. The average RNFL thickness of the left and right eyes was significantly lower in the bilateral INO group than in the unilateral INO groups.

Table 5: Patient characteristics and test results within each group.

	All patients, N = 199	**MS patients without INO**, N = 137	**MS patients with INO**, N = 62	**p-value** (INO vs non-INO)
Demographics				
Age (years)[2]	54.1 (± 10.7)	53.4 (± 11.1)	55.9 (± 9.8)	**0.048**[B] 0.109[A]
Sex (M/F)[1]	68/131 (34%/66%)	38/99 (28%/72%)	30/32 (48%/52%)	**0.007**[C]
Education level[3*]	5 (3; 1-7)	4 (2; 1-7)	5 (3; 1-7)	0.983[B]
Disease related characteristics				
Disease duration[2**]	20.9 (± 8.4)	19.9 (± 8.1)	23.0 (± 8.7)	**0.022**[B] **0.020**[A]
EDSS score[3]	3.5 (3; 0.0 - 8.5)	3.5 (2; 0.0 - 8.5)	4 (3; 1.5 - 8.5)	**0.006**[B]
Optic neuritis[1]	95 (48%) (15 unknown)	64 (47%) (11 unknown)	31 (50%) (4 unknown)	0.762[C]
Vision ODS[2]	1.0 (± 0.3)	1.1 (± 0.3)	1.0 (± 0.3)	0.370[B] 0.336[A]
Disease course				**0.018**[C]
RRMS[1]	126 (63%)	95 (69%)	31 (50%)	
PPMS[1]	21 (11%)	14 (10%)	7 (11%)	
SPMS[1]	52 (26%)	28 (20%)	24 (39%)	
Progressive[1]	73 (37%)	42 (30%)	31 (50%)	**0.032**[C]
NHPT[3]	20.4 (5.1; 14.2-56.3)	19.2 (4.2; 14.2 -56.3)	22.2 (4.3; 15.0 -39.2)	**4.954 x 10^{-6}** [B]
T25-FW Test[3]	4.8 (2.1; 2.8 -18.7)	4.7 (1.8; 2.8-15.8)	5.6 (1.9; 3.2 -18.7)	**0.003**[B]
Cognitive tests				
SDMT[2]	50.2 (± 10.7)	51.3 (± 10.4)	47.8 (±11.1)	**0.041**[A]
PASAT[3]	53 (11; 7-60)	53 (11; 7-60)	54 (10; 11-60)	0.484[B]
CST[3]	-0.70 (1.63; -6.78 - 1.36)	-0.64 (1.40; -4.97 - 1.02)	-0.93 (1.61; -6.78 - 1.36)	**0.029**[B]
SRT[2]	-0.90 (±1.20)	-0.75 (± 1.18)	-1.23 (± 1.20)	**0.025**[B]
WLGT[2]	-0.61 (±0.96)	-0.59 (± 0.98)	-0.66 (± 0.91)	0.685[A]
SPART[2]	-1.05 (±1.30)	-1.10 (± 1.33)	-0.94 (± 1.21)	0.591[B] 0.450[A]
MCT[3]	-0.95 (1.85; -6.42 - 1.33)	-0.70 (1.84; -6.42 - 1.21)	-1.48 (1.61; -6.30 - 1.33)	**0.002**[B]
SCWT[3]	-0.63 (1.46; -5.86 - 1.20)	-0.49 (1.41; -5.86 - 1.20)	-0.96 (1.31; -3.94 - 1.18)	**0.040**[B]
Infrared oculography				
VDI AUC left[3]	1.073 (0.112; 0.713 - 1.718)	1.062 (0.075; 0.713 - 1.171)	1.185 (0.218; 0.961 - 1.718)	**2.904 x 10^{-15}** [B]
VDI AUC right[3]	1.079 (0.099; 0.636 -1.935)	1.052 (0.084; 0.636 - 1.160)	1.189 (0.303; 0.750 -1.935)	**5.307 x 10^{-13}** [B]
VDI Pv/Am left[3]	1.069 (0.112; 0.886 - 3.003)	1.047 (0.088; 0.886 - 1.176)	1.2002 (0.258; 0.906 - 3.003)	**2.341 x 10^{-11}** [B]
VDI Pv/Am right[3]	1.065 (0.113; 0.832 - 2.684)	1.036 (0.092; 0.832 -1.168)	1.175 (0.227; 0.842 - 2.684)	**4.647 x 10^{-14}** [B]
OCT				
Mean RNFL thickness[2]	83.69 (± 13.38)	85.19 (±13.18)	79.88 (± 13.32)	0.066[B] 0.053[A]
MRI parameters				
Total T2-lesion load (mm^3)[3]	14229 (15793; 1770 - 67500)	13563 (15785; 1770 - 67500)	18531 (15005; 2841 - 58249)	0.054[B]
Whole brain volume (mm^3)[2]	1437957 (± 80298)	1442637 (± 83817)	1427258 (± 71263)	0.236[A]
Cortical grey matter volume (mm^3)[2]	748410 (± 57801)	753561 (± 61384)	736606 (± 47088)	0.077[A]
Thalamus volume (mm^3)[2]	17601 (± 2242)	17699 (± 2341)	17377 (± 2002)	0.186[B] 0.380[A]
Questionnaires				
Total score VFQ-25[3]	2.5 (0.3; 1.2 - 4.0)	2.4 (0.3; 1.2 - 4.0)	2.5 (0.3; 1.7 – 3,9)	0.120[B]
Total score EMQ[3]	3 (6; 0 - 21)	2 (5; 0 - 18)	4 (5; 0 - 21)	**5.500 x 10^{-4}** [B]
FS-CIS[2]	33.9 (± 13.0)	32.8 (± 12.8)	36.3 (± 13.0)	0.063[B] 0.097[A]
HADS: depression scale[3]	3 (4; 0 - 14)	2 (4; 0 - 14)	3 (4; 1 – 12)	**0.033**[B]
HADS: anxiety scale[3]	4 (4; 0 - 13)	4 (4; 0 - 13)	4 (3; 1 - 13)	0.913[B]

[1]Absolute number (percentage); [2]Mean (± standard deviation); [3]Median (interquartile range; total range). [A]t-test; [B]Mann-Whitney U test; [C]Chi-square test.

*Level of education according to the Verhage scale. **Counted from date of onset.

Bold type denotes significant outcomes ($p < 0.05$).

Abbreviations: M, male; F, female; EDSS, Expanded Disability Status Scale; ODS, oculus dexter and sinister (left and right eye); RRMS, relapsing remitting multiple sclerosis; PPMS, primary progressive

multiple sclerosis, SPMS, secondary progressive multiple sclerosis; NHPT, Nine-Hole Peg Test; T25-FW, Timed 25-Foot Walk; SDMT, Symbol Digit Modalities Test; PASAT, Paced Auditory Serial Addition Test; CST, Concept Shifting Test; MCT, Memory Comparison Test; SCWT, Stroop Colour Word Test; SPART, 10/36 Spatial Recall Test; SRT, Selective Reminding Test; WLGT, Word List Generation Test; VDI, versional dysconjugacy index; AUC, area under the curve; Pv/Am, peak velocity divided by amplitude; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer; MRI, magnetic resonance imaging; VFQ-25, Visual Function Questionnaire 25; EMQ, Eye Movement Questionnaire; SF-CIS, Subjective Fatigue subscale of the Checklist Individual Strength; HADS, Hospital Anxiety and Depression Scale.

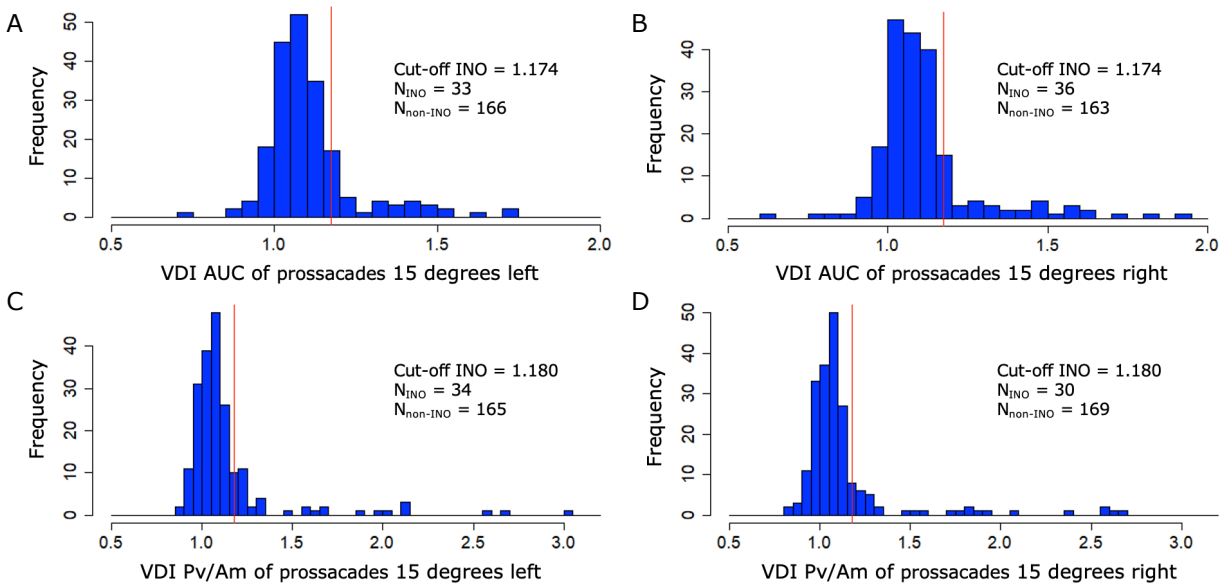


Figure 7: Distribution of the mean VDI-parameters at 15-degree saccades in the study population.

A. Histogram of the VDI AUC at 15 degrees to the left. The red vertical line represents the cut-off value of 1.174. Based on this parameter, 33 patients belong to the INO group.
B. Histogram of the VDI AUC at 15 degrees to the right. The red vertical line represents the cut-off value of 1.174. Based on this parameter, 36 patients belong to the INO group.
C. Histogram of the VDI Pv/Am at 15 degrees to the left. The red vertical line represents the cut-off value of 1.180. Based on this parameter, 34 patients belong to the INO group.
D. Histogram of the VDI Pv/Am at 15 degrees to the right. The red vertical line represents the cut-off value of 1.180. Based on this parameter, 30 patients belong to the INO group.

Table 6: Selection of patient characteristics and test results of the INO subgroups.

	Right INO N = 21	**Left INO** N = 19	**Bilateral INO** N = 22	**P-value***
Age[2]	55.5 (± 9.6)	58.0 (± 8.9)	54.4 (± 10.7)	0.418[A]
Sex (M/F)[1]	9/12 (43%/57%)	8/11 (42%/58%)	13/9 (59%/41%)	0.235[C]
Vision ODS[2]	1.0 (± 0.4)	1.0 (± 0.3)	1.0 (± 0.2)	0.914[A]
Disease duration[2**]	24.4 (± 11.3)	23.5 (± 7.2)	21.2 (± 6.9)	0.194[A]
Progressive course[1]	9 (43%)	8 (42%)	14 (64%)	0.185[C]
EDSS[3]	4 (3; 1.5-7.0)	4 (2; 1.5-8.0)	4 (2.5; 2.0-8.5)	0.191[B]
Mean RNFL thickness[2]	81.4 (± 21.4)	84.6 (6.3)	73.9 (± 7.2)	**0.020[A]**
CGM volume[2]	747946 (±53761)	718407 (±35422)	736400 (±45075)	0.980[A]

[1]Absolute number (percentage); [2]Mean (± standard deviation); [3]Median (interquartile range; total range). [A]t-test; [B]Mann-Whitney U test; [C]Chi-square test. **Counted from date of onset.
Bold type denotes significant outcomes ($p < 0.05$).

3.2. LINEAR REGRESSION ANALYSIS WITH SDMT RESULTS AS DEPENDENT VARIABLE AND INO AS INDEPENDENT VARIABLE

3.2.1. Univariate correlations between the SDMT and all other variables

The univariate correlations between the SDMT and the demographic variables, the disease-related variables, the outcome measures of technical examinations and the questionnaires were determined. The results are shown in Table 7.

Weak negative correlations were seen between the SDMT score and the disease duration, the age, the two continuous VDI Pv/Am parameters to determine INO, and the scores on the questionnaires assessing vision problems and eye movement problems. Moderate negative correlations were seen between the SDMT score and a progressive disease course, the EDSS score, the NHPT score, the T25-FW score and the total lesion load on T2 weighted MRI scan.

Weak positive correlations were found between the SDMT score and the level of education as well as the average thickness of the RNFL of the left and right eyes. Finally, moderate positive correlations were found between the SDMT score and visual acuity, whole brain volume, CGM volume and thalamus volume.

No associations were found between the SDMT score and sex, history of optic neuritis and the questionnaires assessing the level of fatigue, anxiety, and depression. Two of the four VDI parameters to determine INO (VDI AUC left and VDI AUC right) were also not associated with the SDMT performance.

Table 7: Correlations between the SDMT score and demographic variables, disease-related variables, technical examinations, and questionnaires.

	Correlation coefficient	P-value		Correlation coefficient	P-value
Demographics			**Infrared oculography**		
Age [A]	-0.359	**1.880×10^{-7}**	VDI AUC left [B]	-0.121	0.090
Sex (female) [C]	-0.085	0.234	VDI AUC right [B]	-0.046	0.515
Education [B]	0.160	**0.029**	VDI Pv/Am left [B]	-0.215	**0.002**
Disease-related characteristics			VDI Pv/Am right [B]	-0.164	**0.021**
Disease duration [A]	-0.272	**1.101×10^{-4}**	**MRI-parameters**		
Optic neuritis (yes) [C]	-0.080	0.260	Total T2-lesion load [B]	-0.366	**1.776×10^{-6}**
Disease course [B] (progressive course)	-0.393	**9.845×10^{-9}**	Whole brain volume [A]	0.474	**2.238×10^{-10}**
EDSS [B]	-0.447	**4.416×10^{-11}**	CGM volume [A]	0.489	**7.224×10^{-11}**
Mean NHPT [B]	-0.525	**9.007×10^{-13}**	Thalamus volume [A]	0.470	**4.583×10^{-10}**
T25-FW Test [B]	-0.392	**2.629×10^{-7}**	**Questionnaires**		
Vision ODS [A]	0.345	**1.963×10^{-6}**	Score VFQ-25 [B]	-0.197	**0.006**
OCT			Score EMQ [B]	-0.203	**0.004**
Mean RNFL thickness[A]	0.258	**0.004**	SF-CIS [A]	-0.101	0.165
			HADS: depression scale [B]	-0.051	0.594
			HADS: anxiety scale [B]	0.042	0.662

[A] Pearson correlation coefficient (r); [B] Spearman's rho correlation coefficient (ρ); [C] Point biserial correlation coefficient.

Abbreviations: EDSS, Expanded Disability Status Scale; NHPT, Nine-Hole Peg Test; T25-FW, Timed 25-Foot Walk; RNFL, retinal nerve fibre layer; VDI, versional dysconjugacy index; AUC, area under the curve; Pv/Am, peak velocity divided by amplitude; CGM, cortical grey matter; VFQ-25, Visual Function Questionnaire 25; EMQ, Eye Movement Questionnaire; SF-CIS, Subjective Fatigue subscale of the Checklist Individual Strength; EMQ, Eye Movement Questionnaire; HADS, Hospital Anxiety and Depression Scale.

3.2.2. Model with y = SDMT and x = INO binary

The simple linear regression analysis with the SDMT score as continuous dependent variable and the presence or absence of INO as binary independent variable shows that the presence of INO has a statistically significant negative influence on the SDMT performance (ß = -3.446, p = 0.035). This simple linear regression model, shown in Table 8, has an R^2 of 0.017.

Thereafter, a multiple linear regression model is constructed with the confounders sex, visual acuity, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates in the model, which is shown in Table 9. This model has an R^2 of 0.389. After correction for confounders, the presence of INO has no significant influence on the SDMT performance (ß = 1.621, p = 0.391). This model shows a significant influence of visual acuity, disease duration, EDSS score, and CGM volume on the SDMT results.

Table 8: Simple linear regression model with the SDMT score as continuous dependent variable and INO as binary independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	51.285	0.905	56.643	**$< 2 \times 10^{-16}$**
INO	-3.446	1.622	-2.124	**0.035**

Table 9: Multiple linear regression model with the SDMT score as continuous dependent variable and the presence of INO as binary independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-25.420	15.540	-1.635	0.106
INO	1.621	1.880	-0.862	0.391
Sex	-0.554	1.743	-0.318	0.751
Vision	7.184	3.183	2.257	**0.026**
Disease duration	0.367	0.128	2.856	**0.005**
EDSS	-1.114	0.540	-2.064	**0.042**
RNFL thickness	8.692×10^{-2}	6.754×10^{-2}	1.287	0.201
CGM volume	7.923×10^{-5}	1.669×10^{-5}	4.746	**7.860×10^{-6}**

3.2.3. Model with y = SDMT and x = INO categorical

The simple linear regression model with SDMT score as continuous dependent variable and INO as independent categorical variable in presented in Table 10. In this model a distinction was made between the presence of a left INO (when looking to the right), a right INO (when looking to the left) or a bilateral INO. The non-INO group was used as reference group. The results of the analysis show that none of the INO subgroups have a significant influence on the SDMT results.

Thereafter, a model adjusting for confounders was constructed, which is shown in Table 11. This model shows that after correction, no INO subgroup has a significant influence on the SDMT performance. In this model, visual acuity, disease duration, and CGM volume have a significant influence on the SDMT performance. The uncorrected model has an R^2 of 0.009, while the corrected model has an R^2 of 0.397.

Table 10: Simple linear regression model with the SDMT score as continuous dependent variable and INO as independent categorical variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	51.2847	0.9093	56.398	**$< 2 \times 10^{-16}$**
Left INO	-2.4952	2.6056	-0.958	0.339
Right INO	-4.3323	2.4943	-1.737	0.084
Bilateral INO	-3.4210	2.4446	-1.399	0.163

Table 11: Multiple linear regression model with the SDMT score as continuous dependent variable and INO as independent categorical variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-28.500	15.590	-1.828	0.071
Left INO	2.588	3.058	0.846	0.400
Right INO	-3.958	2.863	-1.382	0.170
Bilateral INO	-3.057	2.881	-1.061	0.292
Sex	-0.450	1.737	-0.259	0.796
Vision	7.575	3.173	2.387	**0.019**
Disease duration	0.346	0.131	2.650	**0.010**
EDSS	-0.919	0.551	-1.668	0.099
RNFL thickness	6.978×10^{-2}	6.825×10^{-2}	1.022	0.309
CGM volume	8.424×10^{-5}	1.683×10^{-5}	5.005	**2.880×10^{-6}**

3.2.4. Model with Y = SDMT and X = a continuous VDI-parameter

Four explanatory models were constructed, each time with the SDMT score as continuous dependent variable and one of the four VDI parameters as continuous independent variable.

3.2.4.1. Model with VDI AUC left as primary predictor variable

The simple linear regression model with SDMT performance as continuous dependent variable and VDI AUC left as continuous independent variable shows that a right INO has no significant influence on the SDMT results. This model has an R^2 = 0.0004 and is presented in Table 12. After adjustment for the aforementioned confounders, right INO has no influence on the SDMT score. However, an influence of vision, disease duration, and CGM volume was detected. This corrected model has R^2 = 0.406 and is shown in Table 13.

Table 12: Simple linear regression model with the SDMT score as continuous outcome variable and the VDI AUC left as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	55.974	6.079	9.207	**$< 2 \times 10^{-16}$**
VDI AUC left	-5.209	5.453	-0.955	0.341

Table 13: Multiple linear regression model with the SDMT score as continuous outcome variable and the VDI AUC left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-12.040	17.310	-0.695	0.489
VDI AUC left	-11.850	6.540	-1.812	0.073
Sex	-0.497	1.714	-0.290	0.773
Vision	7.524	3.131	2.403	**0.018**
Disease duration	0.323	0.127	2.534	**0.013**
EDSS	-1.042	0.533	-1.954	0.054
RNFL thickness	6.637×10^{-2}	6.769×10^{-2}	0.981	0.330
CGM volume	8.081×10^{-5}	1.643×10^{-5}	4.918	**3.970×10^{-6}**

3.2.4.2. Model with VDI Pv/Am left as primary predictor variable

The simple linear regression model with SDMT performance as continuous dependent variable and VDI Pv/Am left as continuous independent variable shows that a right INO has a significant negative influence on the SDMT results, with ß = -5.683 and p = 0.030. This model, which is shown in Table 14, has an R^2 = 0.019.

After adjustment for the same confounders, a right INO still has a significant negative influence on SDMT performance, with ß = -9.078 and p = 0.006. This model also shows a significant influence of visual acuity, disease duration, and CGM volume on the SDMT scores. The corrected model, which is shown in Table 15, has an R^2 = 0.434.

Table 14: Simple linear regression model with the SDMT score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	56.672	3.049	18.589	**< 2 x 10^{-16}**
VDI Pv/Am left	-5.683	2.599	-2.187	**0.030**

Table 15: Multiple linear regression model with the SDMT score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-17.84	15.20	-1.174	0.244
VDI Pv/Am left	-9.078	3.214	-2.824	**0.006**
Sex	-0.346	1.672	-0.207	0.837
Vision	6.804	3.028	2.247	**0.027**
Disease duration	0.351	0.123	2.853	**0.005**
EDSS	-1.010	0.520	-1.941	0.055
RNFL thickness	7.368 x 10^{-2}	6.440 x 10^{-2}	1.144	0.256
CGM volume	8.381 x 10^{-5}	1.608 x 10^{-5}	5.214	**1.190 x 10^{-6}**

3.2.4.3. Model with VDI AUC right as primary predictor variable

The uncorrected model with the SDMT score as continuous outcome variable and the VDI AUC right as continuous independent variable shows that a left INO has no significant influence on the SDMT results. This model with an R^2 of 0.002 is shown in Table 16. After correction for the same confounders, left INO still has no influence on the SDMT performance. This multiple linear regression model, which has an R^2 of 0.387, is presented in Table 17. A significant influence of visual acuity, disease duration, EDSS score, and CGM volume on the SDMT is seen.

Table 16: Simple linear regression model with the SDMT score as continuous outcome variable and the VDI AUC right as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	53.959	5.166	10.445	**< 2 x 10^{-16}**
VDI AUC right	-3.366	4.590	-0.733	0.464

Table 17: Multiple linear regression model with the SDMT score as continuous outcome variable and the VDI AUC right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-21.090	17.690	-1.192	0.236
VDI AUC right	-36.540	5.349	-0.683	0.496
Sex	-0.558	1.750	-0.319	0.751
Vision	7.019	3.172	2.213	**0.029**
Disease duration	0.354	0.128	2.763	**0.007**
EDSS	-1.110	0.541	-2.053	**0.043**
RNFL thickness	9.263×10^{-2}	6.688×10^{-2}	1.385	0.170
CGM volume	7.822×10^{-5}	1.693×10^{-5}	4.621	**1.280×10^{-5}**

3.2.4.4. Model with VDI Pv/Am right as primary predictor variable

The uncorrected model with the SDMT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable shows that a left INO has no significant influence on the SDMT results. This model with an R^2 of 0.001 is shown in Table 18. After correction for the same confounders, left INO still has no influence on the SDMT performance. This multiple linear regression model, which has an R^2 of 0.385, is presented in Table 19. Again, a significant influence of visual acuity, disease duration, EDSS score, and CGM volume on the SDMT is seen.

Table 18: Simple linear regression model with the SDMT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	52.806	3.027	17.447	**$< 2 \times 10^{-16}$**
VDI Pv/Am right	-2.297	2.593	-0.886	0.377

Table 19: Multiple linear regression model with the SDMT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-25.380	16.070	-1.580	0.118
VDI Pv/Am right	-1.091	2.957	-0.369	0.713
Sex	-0.409	1.744	-0.235	0.815
Vision	7.068	3.255	2.171	**0.033**
Disease duration	0.351	0.129	2.725	**0.008**
EDSS	-1.095	0.542	-2.019	**0.047**
RNFL thickness	9.142×10^{-2}	6.879×10^{-2}	1.329	0.187
CGM volume	8.011×10^{-5}	1.672×10^{-5}	4.792	**6.560×10^{-6}**

3.3. LINEAR REGRESSION ANALYSIS WITH OTHER COGNITIVE TESTS AS DEPENDENT VARIABLE AND INO AS INDEPENDENT VARIABLE

3.3.1. MODELS WITH Y = COGNITIVE TEST AND X = INO BINARY

Explanatory models were constructed for seven other cognitive tests, each time with the cognitive test result as a continuous dependent variable and the presence of INO as a binary independent variable. Both uncorrected and corrected models were made, with the latter each time corrected for sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume.

3.3.1.1. Paced Auditory Serial Addition Test

The simple linear regression analysis with the PASAT score as continuous dependent variable and INO as binary independent variable shows that the presence of INO has no statistically significant influence on the PASAT performance. This model, shown in Table 20, has an R^2 of -0.002.

The multiple linear regression model with correction for the aforementioned confounders, which is shown in Table 21, has an R^2 of 0.199. The presence of INO still has no significant influence on the PASAT performance. This model shows a significant influence of sex, RNFL thickness, and CGM volume on the PASAT results.

Table 20: Simple linear regression model with the PASAT score as continuous outcome variable and the presence of INO as binary independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	49.861	0.837	59.573	**$< 2 \times 10^{-16}$**
INO	1.139	1.500	0.759	0.449

Table 21: Multiple linear regression model with the PASAT score as continuous outcome variable and the presence of INO as binary independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-7.030	17.190	-0.409	0.684
INO	0.472	2.079	0.227	0.821
Sex	-5.152	1.928	-2.672	**0.009**
Vision	-4.399	3.520	-1.250	0.215
Disease duration	0.178	0.142	1.255	0.213
EDSS	-0.710	0.597	-1.188	0.238
RNFL thickness	0.157	7.470×10^{-2}	2.097	**0.039**
CGM volume	6.759×10^{-5}	1.846×10^{-5}	3.661	**4.260×10^{-4}**

3.3.1.2. Concept Shifting Test

The simple linear regression analysis with the CST score as continuous dependent variable and the presence or absence of INO as binary independent variable shows that the presence of INO has a statistically significant negative influence on the CST performance (β = -0.5549; p = 0.015). This model, which is shown in Table 22, has an R^2 of 0.032.

Thereafter, a multiple linear regression model with correction for the same confounders is constructed, which is shown in Table 23. This model has an R^2 of 0.190. After correction for confounders, the presence of INO has no significant influence on the CST performance. A significant influence of disease duration, EDSS score, and RNFL thickness on the CST results is seen.

Table 22: Simple linear regression model with the CST score as continuous outcome variable and the presence of INO as binary independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-0.7764	0.1249	-6.218	**4.64×10^{-9}**
INO	-0.5549	0.2260	-2.455	**0.015**

Table 23: Multiple linear regression model with the CST score as continuous outcome variable and the presence of INO as binary independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-4.681	1.880	-2.489	**0.015**
INO	-0.424	0.228	-1.858	0.067
Sex	0.217	0.211	1.030	0.306
Vision	0.527	0.409	1.290	0.201
Disease duration	3.265×10^{-2}	1.558×10^{-2}	2.096	**0.039**
EDSS	-0.133	6.559×10^{-2}	-2.023	**0.046**
RNFL thickness	1.677×10^{-2}	8.231×10^{-3}	2.038	**0.045**
CGM volume	2.332×10^{-6}	2.041×10^{-6}	1.142	0.257

3.3.1.3. Selective Reminding Test

The simple linear regression analysis with the SRT score as continuous dependent variable and the presence or absence of INO as binary independent variable shows that the presence of INO has a statistically significant negative influence on the SRT performance (β = -0.4711; p = 0.023). This model, which is shown in Table 24, has an R^2 of 0.027.

Thereafter, a multiple linear regression model with correction for the same confounders is constructed, which is shown in Table 25. This model has an R^2 of 0.082. After correction for confounders, the presence of INO has no significant influence on the SRT performance. This model shows a significant influence of CGM volume on the SRT results.

Table 24: Simple linear regression model with the SRT score as continuous outcome variable and the presence of INO as binary independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-0.7548	0.1136	-6.643	**4.92×10^{-10}**
INO	-0.4711	0.2055	-2.292	**0.023**

Table 25: Multiple linear regression model with the SRT score as continuous outcome variable and the presence of INO as binary independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-6.967	2.247	-3.101	**0.003**
INO	-0.255	0.271	-0.940	0.350
Sex	0.396	0.253	1.565	0.121
Vision	-9.841×10^{-2}	0.477	-0.206	0.837
Disease duration	1.061×10^{-2}	1.863×10^{-2}	0.570	0.570
EDSS	3.031×10^{-2}	7.706×10^{-2}	0.393	0.695
RNFL thickness	5.732×10^{-3}	9.842×10^{-3}	0.582	0.562
CGM volume	6.948×10^{-6}	2.428×10^{-6}	2.862	**0.005**

3.3.1.4. Word List Generation Test

The simple linear regression analysis with the WLGT score as continuous dependent variable and the presence or absence of INO as binary independent variable shows that the presence of INO has no statistically significant influence on the WLGT performance. This model, which is shown in Table 26, has an R^2 of -0.005.

Thereafter, a multiple linear regression model with correction for the same confounders is constructed, which is shown in Table 27. This model has an R^2 of 0.112. After correction for confounders, the presence of INO still has no significant influence on the WLGT performance.

Table 26: Simple linear regression model with the WLGT score as continuous outcome variable and the presence of INO as binary independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-0.592	0.091	-6.468	**1.21×10^{-9}**
INO	-0.066	0.166	-0.395	0.694

Table 27: Multiple linear regression model with the WLGT score as continuous outcome variable and the presence of INO as binary independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-2.251	1.796	-1.253	0.214
INO	-0.260	0.217	-1.201	0.233
Sex	-2.545×10^{-2}	0.202	-0.126	0.900
Vision	0.558	0.382	1.464	0.147
Disease duration	8.879×10^{-3}	1.490×10^{-2}	0.596	0.553
EDSS	-0.117	6.162×10^{-2}	-1.904	0.060
RNFL thickness	-1.005×10^{-2}	7.870×10^{-3}	-1.277	0.205
CGM volume	2.922×10^{-6}	1.941×10^{-6}	1.505	0.136

3.3.1.5. 10/36 Spatial Recall Test

The simple linear regression analysis with the SPART score as continuous dependent variable and the presence or absence of INO as binary independent variable shows that the presence of INO has no statistically significant influence on the SPART performance. This model, which is shown in Table 28, has an R^2 of -0.003.

Thereafter, a multiple linear regression model with correction for the same confounders is constructed, which is shown in Table 29. This model has an R^2 of 0.156. After correction for confounders, the presence of INO still has no significant influence on the SPART performance. This model shows a significant influence of CGM volume on the SPART results.

Table 28: Simple linear regression model with the SPART score as continuous outcome variable and the presence of INO as binary independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-1.101	0.123	-8.930	**1.03×10^{-15}**
INO	0.163	0.223	0.731	0.466

Table 29: Multiple linear regression model with the SPART score as continuous outcome variable and the presence of INO as binary independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-6.392	2.276	-2.809	**0.006**
INO	0.393	0.275	1.428	0.157
Sex	-0.224	0.256	-0.878	0.382
Vision	0.155	0.482	0.322	0.748
Disease duration	1.108×10^{-2}	1.882×10^{-2}	0.589	0.558
EDSS	-0.126	7.831×10^{-2}	-1.610	0.111
RNFL thickness	9.720×10^{-3}	9.949×10^{-3}	0.977	0.331
CGM volume	6.369×10^{-6}	2.461×10^{-6}	2.587	**0.011**

3.3.1.6. Memory Comparison Test

The simple linear regression analysis with the MCT score as continuous dependent variable and the presence or absence of INO as binary independent variable shows that the presence of INO has a statistically significant negative influence on the MCT performance (β = -0.705 and p = 0.006). This model, which is shown in Table 30, has an R^2 of 0.041.

Thereafter, a multiple linear regression model with correction for the same confounders is constructed, which is shown in Table 31. This model has an R^2 of 0.241. After correction for confounders, the presence of INO has no significant influence on the MCT performance. This model shows a significant influence of the EDSS score and CGM volume on the MCT results.

Table 30: Simple linear regression model with the MCT score as continuous outcome variable and the presence of INO as binary independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-1.018	0.142	-7.176	**2.9×10^{-11}**
INO	-0.705	0.255	-2.765	**0.006**

Table 31: Multiple linear regression model with the MCT score as continuous outcome variable and the presence of INO as binary independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-7.223	2.539	-2.845	**0.006**
INO	-0.165	0.303	-0.543	0.588
Sex	0.538	0.282	1.907	0.060
Vision	0.337	0.544	0.619	0.538
Disease duration	3.671×10^{-2}	2.080×10^{-2}	1.765	0.081
EDSS	-0.265	8.735×10^{-2}	-3.034	**0.003**
RNFL thickness	1.444×10^{-2}	1.095×10^{-2}	1.320	0.191
CGM volume	6.030×10^{-6}	2.752×10^{-6}	2.191	**0.031**

3.3.1.7. Stroop Colour Word Test

The simple linear regression analysis with the SCWT score as continuous dependent variable and the presence or absence of INO as binary independent variable shows that the presence of INO has no statistically significant influence on the SCWT performance. This model, which is shown in Table 32, has an R^2 of 0.001.

Thereafter, a multiple linear regression model with correction for the same confounders is constructed, which is shown in Table 33. This model has an R^2 of 0.176. After correction for confounders, the presence of INO still has no significant influence on the SCWT performance. This model shows a significant influence of the CGM volume on the SCWT results.

Table 32: Simple linear regression model with the SCWT score as continuous outcome variable and the presence of INO as binary independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-0.814	0.134	-6.086	**8.92×10^{-9}**
INO	-0.257	0.238	-1.080	0.282

Table 33: Multiple linear regression model with the SCWT score as continuous outcome variable and the presence of INO as binary independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-11.640	2.845	-4.089	**9.87×10^{-5}**
INO	-0.198	0.340	-0.583	0.562
Sex	-0.192	0.316	-0.606	0.546
Vision	-0.492	0.610	-0.806	0.422
Disease duration	2.819×10^{-2}	2.331×10^{-2}	1.209	0.230
EDSS	-5.068×10^{-2}	9.790×10^{-2}	-0.518	0.606
RNFL thickness	1.746×10^{-2}	1.227×10^{-2}	1.423	0.158
CGM volume	1.277×10^{-5}	3.085×10^{-6}	4.140	**8.21×10^{-5}**

3.3.1.8. In summary: models of cognitive tests with INO as binary variable

Below, an overview of the results of the models with the cognitive test result as dependent continuous variable and the presence of INO as binary independent variable is given.

Table 34 shows the results of the uncorrected models. This shows that the presence of INO has a statistically significant negative influence on the SDMT, CST, SRT, and MCT scores.

Table 35 shows the results of the models corrected for sex, visual acuity, disease duration, EDSS score, RNFL thickness, and CGM volume. After adjustment for these confounders, the presence or absence of INO no longer influences any test.

Table 34: Overview of the slope coefficients and the corresponding p-values of the uncorrected models with INO as binary independent variable and the test score as continuous outcome variable.

Cognitive test	β INO (95% CI)	P-value
Symbol Digit Modalities Test*	-3.446 (-6.645 - -0.247)	**0.035**
Paced Auditory Serial Addition Test*	1.139 (-1.818 - 4.096)	0.449
Concept Shifting Test**	-0.555 (-1.001 - -0.108)	**0.015**
Selective Reminding Test**	-0.471 (-0.877 - -0.065)	**0.023**
Word List Generation Test**	-0.066 (-0.393 - 0.262)	0.694
10/36 Spatial Recall Test**	0.163 (-0.277 - 0.603)	0.466
Memory Comparison Test**	-0.705 (-1.208 - -0.201)	**0.006**
Stroop Colour Word Test**	-0.257 (-0.727 - 0.213)	0.282

*Calculations performed with raw test data. **Calculations performed with z-scores.

Table 35: Overview of the slope coefficients and the corresponding p-values of models with INO as binary independent variable and the test score as continuous outcome variable, corrected for sex, visual acuity, disease duration, EDSS score, RNFL thickness, and CGM volume.

Cognitive test	β INO (95% CI)	P-value
Symbol Digit Modalities Test*	-1.621 (-5.356 - 2.115)	0.391
Paced Auditory Serial Addition Test*	0.472 (-3.659 - 4.603)	0.822
Concept Shifting Test**	-0.424 (-0.877 - 0.030)	0.067
Selective Reminding Test**	-0.255 (-0.793 - 0.284)	0.350
Word List Generation Test**	-0.260 (-0.691 - 0.171)	0.233
10/36 Spatial Recall Test**	0.393 (-0.154 - 0.941)	0.157
Memory Comparison Test**	-0.164 (-0.767 - 0.438)	0.588
Stroop Colour Word Test**	-0.198 (-0.873 - 0.477)	0.562

*Calculations performed with raw test data. **Calculations performed with z-scores.

3.3.2. MODELS WITH Y = COGNITIVE TEST AND X = CONTINUOUS VDI-PARAMETER

3.3.2.1. Paced Auditory Serial Addition Test

3.3.2.1.1. VDI AUC left

The simple linear regression model with PASAT performance as continuous dependent variable and VDI AUC left as continuous independent variable shows that right INO has no significant influence on the PASAT results. This model, which is shown in Table 36, has an R^2 = -0.004. After adjustment for the same confounders, a right INO still has no significant influence on the PASAT performance. This model shows a significant influence of sex and CGM volume on the PASAT scores. The corrected model, which is shown in Table 37, has an R^2 = 0.198.

Table 36: Simple linear regression model with the PASAT score as continuous outcome variable and the VDI AUC left as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	47.899	5.575	8.592	**2.61×10^{-15}**
VDI AUC left	2.095	5.001	0.419	0.676

Table 37: Multiple linear regression model with the PASAT score as continuous outcome variable and the VDI AUC left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-5.245	19.420	-0.270	0.788
VDI AUC left	-1.063	7.336	-0.145	0.885
Sex	-5.194	1.922	-2.702	**0.008**
Vision	-4.213	3.512	-1.200	0.233
Disease duration	0.178	0.143	1.248	0.215
EDSS	-0.717	0.598	-1.182	0.240
RNFL thickness	0.151	0.076	1.984	0.050
CGM volume	6.736×10^{-5}	1.843×10^{-5}	3.655	**4.340×10^{-4}**

3.3.2.1.2. VDI Pv/Am left

The simple linear regression model with PASAT performance as continuous dependent variable and VDI Pv/Am left as continuous independent variable shows that right INO has no significant influence on the PASAT results. This model, which is shown in Table 38, has an R^2 = -0.0004. After adjustment for the same

confounders, a right INO still has no significant influence on the PASAT performance. This model shows a significant influence of sex, RNFL thickness, and CGM volume on the PASAT scores. The corrected model, shown in Table 39, has an R^2 = 0.199.

Table 38: Simple linear regression model with the PASAT score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	47.381	2.817	16.822	**< 2 x 10^{16}**
VDI Pv/Am left	2.493	2.401	1.039	0.300

Table 39: Multiple linear regression model with the PASAT score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-7.422	17.470	-0.425	0.672
VDI Pv/Am left	0.836	3.695	0.226	0.822
Sex	-5.196	1.922	-2.704	**0.008**
Vision	-4.283	3.481	-1.230	0.222
Disease duration	0.182	0.141	1.286	0.202
EDSS	-7.213	0.598	-1.206	0.231
RNFL thickness	0.156	0.074	2.103	**0.038**
CGM volume	6.697 x 10^{-5}	1.848 x 10^{-5}	3.624	**4.830 x 10^{-4}**

3.3.2.1.3. VDI AUC right

The simple linear regression model with PASAT performance as continuous dependent variable and VDI AUC right as continuous independent variable shows that left INO has no significant influence on the PASAT results. This model, which is shown in Table 40, has an R^2 = -0.005. After adjustment for the same confounders, a left INO still has no significant influence on the PASAT performance. This model shows a significant influence of sex and CGM volume on the PASAT scores. The corrected model, which is shown in Table 41, has an R^2 = 0.207.

Table 40: Simple linear regression model with the PASAT score as continuous outcome variable and the VDI AUC right as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	51.357	4.734	10.847	**< 2 x 10^{16}**
VDI AUC right	-1.025	4.207	-0.244	0.808

Table 41: Multiple linear regression model with the PASAT score as continuous outcome variable and the VDI AUC right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	2.527	19.440	0.130	0.897
VDI AUC right	-5.674	5.878	-0.965	0.227
Sex	-5.386	1.923	-2.801	**0.006**
Vision	-3.904	3.486	-1.120	0.266
Disease duration	0.178	0.140	1.264	0.210
EDSS	-0.722	0.594	-1.215	0.228
RNFL thickness	0.145	0.073	1.979	0.051
CGM volume	6.426×10^{-5}	1.860×10^{-5}	3.455	**8.460×10^{-4}**

3.3.2.1.4. VDI Pv/am right

The simple linear regression model with PASAT performance as continuous dependent variable and VDI Pv/Am right as continuous independent variable shows that left INO has no significant influence on the PASAT results. This model, which is shown in Table 42, has an R^2 = -0.004. After adjustment for the same confounders, a left INO still has no significant influence on the PASAT performance. This model shows a significant influence of sex and CGM volume on the PASAT scores. The corrected model, which is shown in Table 43, has an R^2 = 0.208.

Table 42: Simple linear regression model with the PASAT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	48.828	2.774	17.601	**$< 2 \times 10^{16}$**
VDI Pv/Am right	1.229	2.377	0.517	0.606

Table 43: Multiple linear regression model with the PASAT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-1.730	17.610	-0.098	0.922
VDI Pv/Am right	-3.369	3.241	-1.040	0.301
Sex	-5.122	1.911	-2.680	**0.009**
Vision	-3.382	3.567	-0.948	0.346
Disease duration	0.166	0.141	1.178	0.242
EDSS	-0.684	0.594	-1.151	0.253
RNFL thickness	0.134	0.075	1.774	0.080
CGM volume	6.707×10^{-5}	1.832×10^{-5}	3.661	**4.260×10^{-4}**

3.3.2.2. Concept Shifting Test

3.3.2.2.1. VDI AUC left

The simple linear regression model with CST performance as continuous dependent variable and VDI AUC left as continuous independent variable shows that a right INO has a significant influence on the CST results, with ß = -1.605 and p = 0.026. This model, which is shown in Table 44, has an R^2 = 0.026. After adjustment for the same confounders, a right INO still has a significant influence on the CST performance, with ß = -2.002 and p = 0.014. The corrected model, which is shown in Table 45, has an R^2 = 0.216.

Table 44: Simple linear regression model with the CST score as continuous outcome variable and the VDI AUC left as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	0.843	0.800	1.053	0.294
VDI AUC left	-1.605	0.712	-2.255	**0.026**

Table 45: Multiple linear regression model with the CST score as continuous outcome variable and the VDI AUC left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-2.534	2.093	-1.211	0.229
VDI AUC left	-2.002	0.797	-2.513	**0.014**
Sex	0.251	0.207	1.212	0.229
Vision	0.547	0.402	1.359	0.178
Disease duration	0.024	0.015	1.535	0.128
EDSS	-0.117	0.065	-1.800	0.075
RNFL thickness	0.014	8.265×10^{-3}	1.695	0.094
CGM volume	2.682×10^{-6}	2.009×10^{-6}	1.335	0.186

3.3.2.2.2. VDI Pv/Am left

The simple linear regression model with CST performance as continuous dependent variable and VDI Pv/Am left as continuous independent variable shows that a right INO has a significant influence on the CST results, with ß = -1.061 and p = 0.005. This model, shown in Table 46, has an R^2 = 0.043. After adjustment for the same confounders, right INO still has a significant influence on the CST performance, with ß = -0.960 and p = 0.017. This model shows a significant influence of RNFL thickness on the CST scores. The corrected model, shown in Table 47, has an R^2 = 0.212.

Table 46: Simple linear regression model with the CST score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	0.261	0.440	0.594	0.554
VDI Pv/Am left	-1.061	0.376	-2.820	**0.005**

Table 47: Multiple linear regression model with the CST score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-4.116	1.883	-2.185	**0.032**
VDI Pv/Am left	-0.960	0.395	-2.433	**0.017**
Sex	0.266	0.207	1.285	0.202
Vision	0.444	0.402	1.106	0.272
Disease duration	0.029	0.015	1.923	0.058
EDSS	-0.120	0.065	-1.859	0.066
RNFL thickness	0.017	8.060×10^{-3}	2.104	**0.038**
CGM volume	2.943×10^{-6}	2.021×10^{-6}	1.456	0.149

3.3.2.2.3. VDI AUC right

The simple linear regression model with CST performance as continuous dependent variable and VDI AUC right as continuous independent variable shows that left INO has no significant influence on the CST results. This model, which is shown in Table 48, has an R^2 = -0.0006. After adjustment for the same confounders, a left INO still has no significant influence on the CST performance. This model shows a significant influence of EDSS score and RNFL thickness on the CST scores. The corrected model, which is shown in Table 49, has an R^2 = 0.171.

Table 48: Simple linear regression model with the CST score as continuous outcome variable and the VDI AUC right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-0.294	0.691	-0.426	0.671
VDI AUC right	-0.583	0.611	-0.954	0.342

Table 49: Multiple linear regression model with the CST score as continuous outcome variable and the VDI AUC right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-3.832	2.152	-1.781	0.079
VDI AUC right	-0.766	0.653	-1.173	0.244
Sex	0.227	0.214	1.060	0.292
Vision	0.489	0.413	1.186	0.239
Disease duration	0.029	0.016	1.871	0.065
EDSS	-0.132	0.066	-1.990	**0.050**
RNFL thickness	0.018	8.248×10^{-3}	2.235	**0.028**
CGM volume	2.133×10^{-6}	2.086×10^{-6}	1.023	0.309

3.3.2.2.4. VDI Pv/Am right

The simple linear regression model with CST performance as continuous dependent variable and VDI Pv/Am right as continuous independent variable shows that a left INO has no significant influence on the CST results. This model, which is shown in Table 50, has an $R^2 = 0.010$. After adjustment for the same confounders, a left INO has a significant influence on the CST performance, with ß = -0.974 and p = 0.022. The corrected model, which is shown in Table 51, has an $R^2 = 0.208$.

Table 50: Simple linear regression model with the CST score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-0.225	0.460	-0.490	0.625
VDI Pv/Am right	-0.642	0.399	-1.608	0.110

Table 51: Multiple linear regression model with the CST score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-3.745	1.932	-1.939	0.056
VDI Pv/Am right	-0.974	0.419	-2.325	**0.022**
Sex	0.231	0.208	1.111	0.270
Vision	0.587	0.406	1.446	0.152
Disease duration	0.026	0.015	1.685	0.096
EDSS	-0.119	0.065	-1.825	0.072
RNFL thickness	0.014	8.332×10^{-3}	1.700	0.093
CGM volume	2.684×10^{-6}	2.019×10^{-6}	1.329	0.188

3.3.2.3. Selective Reminding Test

3.3.2.3.1. VDI AUC left

The simple linear regression model with SRT performance as continuous dependent variable and VDI AUC left as continuous independent variable shows that a right INO has no significant influence on the SRT results. This model, which is shown in Table 52, has an R^2 = 0.004. After adjustment for the same confounders, a right INO still has no significant influence on the SRT performance. The corrected model, which is shown in Table 53, has an R^2 = 0.086. This model shows a significant influence of CGM volume on the SRT scores.

Table 52: Simple linear regression model with the SRT score as continuous outcome variable and the VDI AUC left as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	0.060	0.765	0.079	0.937
VDI AUC left	-0.086	0.682	-1.264	0.208

Table 53: Multiple linear regression model with the SRT score as continuous outcome variable and the VDI AUC left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-5.903	2.518	-2.344	**0.021**
VDI AUC left	-1.035	0.943	-1.099	0.275
Sex	0.419	0.251	1.669	0.099
Vision	-0.068	0.479	-0.142	0.887
Disease duration	6.184×10^{-3}	0.019	0.331	0.741
EDSS	0.037	0.077	0.477	0.635
RNFL thickness	4.459×10^{-3}	0.010	0.445	0.657
CGM volume	7.126×10^{-6}	2.421×10^{-6}	2.943	**0.004**

3.3.2.3.2. VDI Pv/Am left

The simple linear regression model with SRT performance as continuous dependent variable and VDI Pv/Am left as continuous independent variable shows that a right INO has a significant influence on the SRT results, with ß = -0.816 and p = 0.039. This model, which is shown in Table 54, has an R^2 = 0.021. After adjustment for the same confounders, a right INO has no significant influence on the SRT performance. This model shows a significant influence of CGM volume on the SRT scores. The corrected model, which is shown in Table 55, has an R^2 = 0.101.

Table 54: Simple linear regression model with the SRT score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	0.021	0.452	0.046	0.963
VDI Pv/Am left	-0.816	0.392	-2.083	**0.039**

Table 55: Multiple linear regression model with the SRT score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-6.469	2.256	-2.868	**0.005**
VDI Pv/Am left	-0.765	0.471	-1.624	0.108
Sex	0.430	0.249	1.727	0.088
Vision	-0.142	0.470	-0.302	0.763
Disease duration	8.867×10^{-3}	0.018	0.483	0.630
EDSS	0.040	0.076	0.521	0.604
RNFL thickness	5.247×10^{-3}	9.689×10^{-3}	0.542	0.590
CGM volume	7.418×10^{-6}	2.411×10^{-6}	3.077	**0.003**

3.3.2.3.3. VDI AUC right

The simple linear regression model with SRT performance as continuous dependent variable and VDI AUC right as continuous independent variable shows that a left INO has a significant influence on the SRT results, with ß = -1.551 and p = 0.007. This model, which is shown in Table 56, has an R^2 = 0.039. After adjustment for the same confounders, a left INO has no significant influence on the SRT performance. This model shows a significant influence of CGM volume on the SRT scores. The corrected model, which is shown in Table 57, has an R^2 = 0.078.

Table 56: Simple linear regression model with the SRT score as continuous outcome variable and the VDI AUC right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	0.834	0.644	1.294	0.197
VDI AUC right	-1.551	0.571	-2.718	**0.007**

Table 57: Multiple linear regression model with the SRT score as continuous outcome variable and the VDI AUC right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-6.334	2.541	-2.493	**0.015**
VDI AUC right	-0.544	0.767	-0.709	0.480
Sex	0.400	0.254	1.573	0.119
Vision	-0.116	0.477	-0.242	0.809
Disease duration	8.680×10^{-3}	0.019	0.467	0.642
EDSS	0.031	0.077	0.400	0.691
RNFL thickness	6.572×10^{-3}	9.777×10^{-3}	0.672	0.503
CGM volume	6.797×10^{-6}	2.458×10^{-6}	2.766	**0.007**

3.3.2.3.4. VDI Pv/Am right

The simple linear regression model with SRT performance as continuous dependent variable and VDI Pv/Am right as continuous independent variable shows that left INO has a significant influence on the SRT results, with ß = -0.749 and p = 0.046. This model, which is shown in Table 58, has an R^2 = 0.019. After adjustment for the same confounders, left INO has no significant influence on the SRT performance. This model shows a significant influence of CGM volume on the SRT scores. The corrected model, which is shown in Table 59, has an R^2 = 0.085.

Table 58: Simple linear regression model with the SRT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-0.062	0.426	-0.145	0.885
VDI Pv/Am right	-0.749	0.372	-2.015	**0.046**

Table 59: Multiple linear regression model with the SRT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-6.496	2.327	-2.791	**0.006**
VDI Pv/Am right	-0.526	0.503	-1.045	0.299
Sex	0.408	0.252	1.621	0.109
Vision	-0.074	0.459	-0.154	0.878
Disease duration	6.885×10^{-3}	0.019	0.370	0.712
EDSS	0.039	0.077	0.501	0.617
RNFL thickness	4.397×10^{-3}	0.010	0.436	0.664
CGM volume	7.171×10^{-6}	2.424×10^{-6}	2.958	**0.004**

3.3.2.4. Word List Generation Test

3.3.2.4.1. VDI AUC left

The simple linear regression model with WLGT performance as continuous dependent variable and VDI AUC left as continuous independent variable shows that right INO has no significant influence on the WLGT results. This model, which is shown in Table 60, has an R^2 = 0.005. After adjustment for the same confounders, right INO still has no significant influence on the WLGT performance. The corrected model, which is shown in Table 61, has an R^2 = 0.097.

Table 60: Simple linear regression model with the WLGT score as continuous outcome variable and the VDI AUC left as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-1.367	0.582	-2.349	**0.020**
VDI AUC left	0.679	0.518	1.309	0.192

Table 61: Multiple linear regression model with the WLGT score as continuous outcome variable and the VDI AUC left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-2.336	2.034	-1.149	0.254
VDI AUC left	-0.112	0.761	-0.147	0.884
Sex	2.253×10^{-4}	0.203	0.001	0.999
Vision	0.525	0.387	1.357	0.178
Disease duration	6.837×10^{-3}	0.015	0.453	0.651
EDSS	-0.116	0.062	-1.861	0.066
RNFL thickness	-8.789×10^{-3}	8.093×10^{-3}	-1.086	0.281
CGM volume	3.040×10^{-6}	1.956×10^{-6}	1.555	0.124

3.3.2.4.2. VDI Pv/Am left

The simple linear regression model with WLGT performance as continuous dependent variable and VDI Pv/Am left as continuous independent variable shows that right INO has no significant influence on the WLGT results. This model, which is shown in Table 62, has an R^2 = -0.005. After adjustment for the same confounders, right INO still has no significant influence on the WLGT performance. The corrected model, which is shown in Table 63, has an R^2 = 0.099.

Table 62: Simple linear regression model with the WLGT score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-0.756	0.328	-2.304	**0.023**
VDI Pv/Am left	0.127	0.281	0.453	0.652

Table 63: Multiple linear regression model with the WLGT score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-2.326	1.835	-1.267	0.209
VDI Pv/Am left	-0.159	0.383	-0.414	0.680
Sex	2.302×10^{-3}	0.203	0.011	0.991
Vision	0.517	0.383	1.349	0.181
Disease duration	7.123×10^{-3}	0.015	0.477	0.635
EDSS	-0.115	0.062	-1.843	0.069
RNFL thickness	-8.904×10^{-3}	7.884×10^{-3}	-1.129	0.262
CGM volume	3.108×10^{-6}	1.962×10^{-6}	1.584	0.117

3.3.2.4.3. VDI AUC right

The simple linear regression model with WLGT performance as continuous dependent variable and VDI AUC right as continuous independent variable shows that a left INO has no significant influence on the WLGT results. This model, which is shown in Table 64, has an R^2 = -0.003. After adjustment for the same confounders, left INO still has no significant influence on the WLGT performance. The corrected model, which is shown in Table 65, has an R^2 = 0.101.

Table 64: Simple linear regression model with the WLGT score as continuous outcome variable and the VDI AUC right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-0.258	0.502	-0.514	0.608
VDI AUC right	-0.317	0.445	-0.712	0.477

Table 65: Multiple linear regression model with the WLGT score as continuous outcome variable and the VDI AUC right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-1.861	2.040	-0.912	0.364
VDI AUC right	-0.392	0.616	-0.637	0.526
Sex	-0.015	0.204	-0.074	0.941
Vision	0.534	0.383	1.393	0.167
Disease duration	6.971×10^{-3}	0.015	0.467	0.642
EDSS	-0.117	0.062	-1.882	0.063
RNFL thickness	-8.984×10^{-3}	7.847×10^{-3}	-1.145	0.256
CGM volume	2.846×10^{-6}	1.973×10^{-6}	1.443	0.153

3.3.2.4.4. VDI Pv/Am right

The simple linear regression model with WLGT performance as continuous dependent variable and VDI Pv/Am right as continuous independent variable shows that a left INO has no significant influence on the WLGT results. This model, which is shown in Table 66, has an R^2 = -0.002. After adjustment for the same confounders, left INO still has no significant influence on the WLGT performance. The corrected model, which is shown in Table 67, has an R^2 = 0.120.

Table 66: Simple linear regression model with the WLGT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-0.356	0.336	-1.058	0.292
VDI Pv/Am right	-0.228	0.293	-0.781	0.436

Table 67: Multiple linear regression model with the WLGT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-1.687	1.855	-0.910	0.366
VDI Pv/Am right	-0.599	0.401	-1.495	0.139
Sex	-0.015	0.201	-0.075	0.941
Vision	0.591	0.382	1.550	0.125
Disease duration	4.831×10^{-3}	0.015	0.326	0.746
EDSS	-0.108	0.062	-1.749	0.084
RNFL thickness	-0.012	8.029×10^{-3}	-1.464	0.147
CGM volume	3.163×10^{-6}	1.932×10^{-6}	1.637	0.105

3.3.2.5. 10/36 Spatial Recall Test

3.3.2.5.1. VDI AUC left

The simple linear regression model with SPART performance as continuous dependent variable and VDI AUC left as continuous independent variable shows that right INO has no significant influence on the SPART results. This model, which is shown in Table 68, has an R^2 = -0.003. After adjustment for the same confounders, a right INO still has no significant influence on the SPART performance. This model shows a significant influence of CGM volume on the SPART scores. The corrected model, which is shown in Table 69, has an R^2 = 0.139.

Table 68: Simple linear regression model with the SPART score as continuous outcome variable and the VDI AUC left as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-1.639	0.792	-2.070	**0.040**
VDI AUC left	0.528	0.705	0.749	0.455

Table 69: Multiple linear regression model with the SPART score as continuous outcome variable and the VDI AUC left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-6.735	2.589	-2.602	**0.011**
VDI AUC left	0.536	0.968	0.553	0.581
Sex	-0.260	0.257	-1.012	0.315
Vision	0.186	0.488	0.381	0.704
Disease duration	0.015	0.019	0.803	0.424
EDSS	-0.130	0.079	-1.639	0.105
RNFL thickness	8.702×10^{-3}	0.010	0.851	0.397
CGM volume	6.182×10^{-6}	2.484×10^{-6}	2.488	**0.015**

3.3.2.5.2. VDI Pv/Am left

The simple linear regression model with SPART performance as continuous dependent variable and VDI Pv/Am left as continuous independent variable shows that right INO has no significant influence on the SPART results. This model, which is shown in Table 70, has an R^2 = -0.006. After adjustment for the same confounders, a right INO still has no significant influence on the SPART performance. This model shows a significant influence of CGM volume on the SPART scores. The corrected model, which is shown in Table 71, has an R^2 = 0.141.

Table 70: Simple linear regression model with the SPART score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-0.945	0.445	-2.125	**0.035**
VDI Pv/Am left	-0.093	0.381	-0.244	0.808

Table 71: Multiple linear regression model with the SPART score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-5.729	2.331	-2.458	**0.016**
VDI Pv/Am left	-0.350	0.488	-0.718	0.475
Sex	-0.259	0.256	-1.010	0.315
Vision	0.217	0.484	0.448	0.655
Disease duration	0.014	0.019	0.728	0.469
EDSS	-0.123	0.079	-1.556	0.123
RNFL thickness	6.413×10^{-3}	9.966×10^{-3}	0.644	0.522
CGM volume	6.370×10^{-6}	2.490×10^{-6}	2.558	**0.012**

3.3.2.5.3. VDI AUC right

The simple linear regression model with SPART performance as continuous dependent variable and VDI AUC right as continuous independent variable shows that a left INO has no significant influence on the SPART results. This model, which is shown in Table 72, has an R^2 = -0.004. After adjustment for the same confounders, left INO still has no significant influence on the SPART performance. This model shows a significant influence of CGM volume on the SPART scores. The corrected model, which is shown in Table 73, has an R^2 = 0.138.

Table 72: Simple linear regression model with the SPART score as continuous outcome variable and the VDI AUC right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-1.429	0.680	-2.102	**0.037**
VDI AUC right	0.338	0.602	0.562	0.575

Table 73: Multiple linear regression model with the SPART score as continuous outcome variable and the VDI AUC right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-6.582	2.600	-2.532	**0.013**
VDI AUC right	0.330	0.787	0.420	0.676
Sex	-0.249	0.259	-0.961	0.339
Vision	0.207	0.486	0.426	0.671
Disease duration	0.014	0.019	0.739	0.462
EDSS	-0.127	0.079	-1.604	0.112
RNFL thickness	7.709×10^{-3}	9.958×10^{-3}	0.774	0.441
CGM volume	6.369×10^{-6}	2.514×10^{-6}	2.533	**0.013**

3.3.2.5.4. VDI Pv/Am right

The simple linear regression model with SPART performance as continuous dependent variable and VDI Pv/Am right as continuous independent variable shows that left INO has no significant influence on the SPART results. This model, which is shown in Table 74, has an $R^2 = 0.003$. After adjustment for the same confounders, left INO still has no significant influence on the SPART performance. This model shows a significant influence of CGM volume on the SPART scores. The corrected model, which is shown in Table 75, has an $R^2 = 0.138$.

Table 74: Simple linear regression model with the SPART score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-1.582	0.454	-3.483	6.420×10^{-4}
VDI Pv/Am right	0.474	0.395	1.200	0.232

Table 75: Multiple linear regression model with the SPART score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-6.361	2.388	-2.664	**0.009**
VDI Pv/Am right	0.225	0.518	0.434	0.665
Sex	-0.256	0.257	-0.995	0.323
Vision	0.193	0.489	0.395	0.694
Disease duration	0.015	0.019	0.774	0.441
EDSS	-0.130	0.080	-1.640	0.105
RNFL thickness	$8.51\& \times 10^{-3}$	0.010	0.827	0.411
CGM volume	6.163×10^{-6}	2.488×10^{-6}	2.478	**0.015**

3.3.2.6. Memory Comparison Test

3.3.2.6.1. VDI AUC left

The simple linear regression model with MCT performance as continuous dependent variable and VDI AUC left as continuous independent variable shows that a right INO has a significant influence on the MCT results, with ß = -1.679 and p = 0.041. This model, which is shown in Table 76, has an R^2 = 0.021. After adjustment for the same confounders, right INO has no significant influence on MCT performance. This model shows a significant influence of EDSS score and CGM volume on the MCT scores. The corrected model, which is shown in Table 77, has an R^2 = 0.251.

Table 76: Simple linear regression model with the MCT score as continuous outcome variable and the VDI AUC left as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	0.636	0.917	0.694	0.489
VDI AUC left	-1.679	0.815	-2.059	**0.041**

Table 77: Multiple linear regression model with the MCT score as continuous outcome variable and the VDI AUC left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-5.722	2.855	-2.005	**0.048**
VDI AUC left	-1.292	1.069	-1.208	0.230
Sex	0.547	0.279	1.965	0.053
Vision	0.362	0.540	0.671	0.504
Disease duration	0.032	0.021	1.513	0.134
EDSS	-0.255	0.087	-2.929	**0.004**
RNFL thickness	0.012	0.011	1.085	0.281
CGM volume	6.190×10^{-6}	2.731×10^{-6}	2.267	**0.026**

3.3.2.6.2. VDI Pv/Am left

The simple linear regression model with MCT performance as dependent continuous variable and VDI Pv/Am left as independent continuous variable shows that a right INO has a significant influence on the MCT results, with ß = -1.187 and p = 0.006. This model, which is shown in Table 78, has an R^2 = 0.041. After adjustment for the same confounders, a right INO still has a significant influence on the MCT performance, with ß = -1.104 and p = 0.036. This model also shows

a significant influence of sex, EDSS score, and CGM volume on the MCT scores. The corrected model, which is shown in Table 79, has an $R^2 = 0.277$.

Table 78: Simple linear regression model with the MCT score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	0.116	0.504	0.229	0.819
VDI Pv/Am left	-1.187	0.430	-2.760	**0.006**

Table 79: Multiple linear regression model with the MCT score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-6.312	2.512	-2.513	**0.014**
VDI Pv/Am left	-1.104	0.518	-3.132	**0.036**
Sex	0.564	0.274	2.061	**0.042**
Vision	0.288	0.530	0.544	0.588
Disease duration	0.035	0.020	1.741	0.085
EDSS	-0.251	0.085	-2.937	**0.004**
RNFL thickness	0.013	0.011	1.190	0.237
CGM volume	6.624×10^{-6}	2.693×10^{-6}	2.459	**0.016**

3.3.2.6.3. VDI AUC right

The simple linear regression model with MCT performance as continuous dependent variable and VDI AUC right as continuous independent variable shows that a left INO has no significant influence on the MCT results. This model, which is shown in Table 80, has an $R^2 = 0.012$. After adjustment for the same confounders, left INO still has no significant influence on the MCT performance. This model shows a significant influence of EDSS score and CGM volume on the MCT scores. The corrected model, which is shown in Table 81, has an $R^2 = 0.242$.

Table 80: Simple linear regression model with the MCT score as continuous outcome variable and the VDI AUC right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	0.063	0.783	0.081	0.936
VDI AUC right	-1.163	0.693	-1.679	0.095

Table 81: Multiple linear regression model with the MCT score as continuous outcome variable and the VDI AUC right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-6.472	2.856	-2.266	**0.026**
VDI AUC right	-0.575	0.856	-0.672	0.503
Sex	0.531	0.282	1.883	0.063
Vision	0.352	0.543	0.611	0.543
Disease duration	0.035	0.021	1.708	0.091
EDSS	-0.264	0.087	-3.029	**0.003**
RNFL thickness	0.015	0.011	1.357	0.178
CGM volume	5.839×10^{-6}	2.774×10^{-6}	2.105	**0.038**

3.3.2.6.4. VDI Pv/Am right

The simple linear regression model with MCT performance as dependent continuous variable and VDI Pv/Am right as independent continuous variable shows that a left INO has no significant influence on the MCT results. This model, which is shown in Table 82, has an $R^2 = 0.017$. After adjustment for the same confounders, left INO still has no significant influence on the MCT performance. This model shows a significant influence of EDSS score and CGM volume on the MCT scores. The corrected model, which is shown in Table 83, has an $R^2 = 0.254$.

Table 82: Simple linear regression model with the MCT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-0.265	0.523	-0.506	0.613
VDI Pv/Am right	-0.866	0.454	-1.907	0.058

Table 83: Multiple linear regression model with the MCT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-6.395	2.607	-2.453	**0.016**
VDI Pv/Am right	-0.743	0.557	-1.335	0.186
Sex	0.534	0.278	1.920	0.058
Vision	0.407	0.542	0.751	0.455
Disease duration	0.033	0.021	1.588	0.116
EDSS	-0.254	0.087	-2.923	**0.004**
RNFL thickness	0.011	0.011	1.029	0.307
CGM volume	6.260×10^{-6}	2.728×10^{-6}	2.295	**0.024**

3.3.2.7. Stroop Colour Word Test

3.3.2.7.1. VDI AUC left

The simple linear regression model with SCWT performance as continuous dependent variable and VDI AUC left as continuous independent variable shows that a right INO has no significant influence on the SCWT results. This model, which is shown in Table 84, has an R^2 = -0.005. After adjustment for the same confounders, right INO still has no significant influence on the SCWT performance. This model shows a significant influence of CGM volume on the SCWT scores. The corrected model, which is shown in Table 85, has an R^2 = 0.193.

Table 84: Simple linear regression model with the SCWT score as continuous outcome variable and the VDI AUC left as continuous independent variable.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-0.430	0.855	-0.503	0.616
VDI AUC left	-0.417	0.759	-0.549	0.584

Table 85: Multiple linear regression model with the SCWT score as continuous outcome variable and the VDI AUC left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	-9.576	3.187	-3.004	**0.004**
VDI AUC left	-1.753	1.194	-1.468	0.146
Sex	-0.181	0.311	-0.583	0.561
Vision	-0.454	0.603	-0.752	0.454
Disease duration	0.021	0.023	0.917	0.362
EDSS	-0.037	0.097	-0.384	0.702
RNFL thickness	0.014	0.012	1.133	0.260
CGM volume	1.298×10^{-5}	3.049×10^{-6}	4.256	**5.39×10^{-5}**

3.3.2.7.2. VDI Pv/Am left

The simple linear regression model with SCWT performance as continuous dependent variable and VDI Pv/Am left as continuous independent variable shows that a right INO has no significant influence on the SCWT results. This model, which is shown in Table 86, has an R^2 = 0.001. After adjustment for the same confounders, right INO still has no significant influence on the SCWT performance. This model shows a significant influence of CGM volume on the SCWT scores. The corrected model, which is shown in Table 87, has an R^2 = 0.202.

Table 86: Simple linear regression model with the SCWT score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-0.390	0.473	-0.824	0.411
VDI Pv/Am left	-0.443	0.404	-1.098	0.274

Table 87: Multiple linear regression model with the SCWT score as continuous outcome variable and the VDI Pv/Am left as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-10.820	2.839	-3.810	**2.64×10^{-4}**
VDI Pv/Am left	-1.040	0.585	-1.777	0.079
Sex	-0.163	0.309	-0.527	0.600
Vision	-0.543	0.598	-0.908	0.367
Disease duration	0.026	0.023	1.160	0.249
EDSS	-0.037	0.097	-0.387	0.699
RNFL thickness	0.016	0.012	1.336	0.185
CGM volume	1.335×10^{-5}	3.043×10^{-6}	4.387	**3.320×10^{-5}**

3.3.2.7.3. VDI AUC right

The simple linear regression model with SCWT performance as continuous dependent variable and VDI AUC right as continuous independent variable shows that a left INO has no significant influence on the SCWT results. This model, which is shown in Table 88, has an R^2 = -0.004. After adjustment for the same confounders, a left INO still has no significant influence on the SCWT performance. This model shows a significant influence of CGM volume on the SCWT scores. The corrected model, which is shown in Table 89, has an R^2 = 0.173.

Table 88: Simple linear regression model with the SCWT score as continuous outcome variable and the VDI AUC right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-0.4911	0.7261	-0.676	0.500
VDI AUC right	-0.362	0.642	-0.563	0.574

Table 89: Multiple linear regression model with the SCWT score as continuous outcome variable and the VDI AUC right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-11.520	3.210	-3.589	**5.580×10^{-4}**
VDI AUC right	-0.189	0.962	-0.197	0.845
Sex	-0.179	0.317	-0.565	0.573
Vision	-0.512	0.610	-0.840	0.403
Disease duration	0.027	0.023	1.154	0.252
EDSS	-0.050	0.098	-0.513	0.610
RNFL thickness	0.018	0.012	1.513	0.134
CGM volume	1.277×10^{-5}	3.118×10^{-6}	4.097	**0.620×10^{-5}**

3.3.2.7.4. VDI Pv/Am right

The simple linear regression model with SCWT performance as continuous dependent variable and VDI Pv/Am right as continuous independent variable shows that left INO has no significant influence on the SCWT results. This model, which is shown in Table 90 has an R^2 = -0.003. After adjustment for the same confounders, left INO still has no significant influence on the SCWT performance. This model shows a significant influence of CGM volume on the SCWT scores. The corrected model, which is shown in Table 91, has an R^2 = 0.188.

Table 90: Simple linear regression model with the SCWT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-0.542	0.486	-1.113	0.267
VDI Pv/Am right	-0.315	0.422	-0.747	0.456

Table 91: Multiple linear regression model with the SCWT score as continuous outcome variable and the VDI Pv/Am right as continuous independent variable, with confounders sex, vision, disease duration, EDSS score, RNFL thickness, and CGM volume as covariates.

	Slope coefficient	Standard error	T-value	P-value
(Intercept)	-10.760	2.925	-3.680	**4.110×10^{-4}**
VDI Pv/Am right	-0.800	0.625	-1.280	0.204
Sex	-0.193	0.312	-0.618	0.538
Vision	-0.419	0.608	-0.688	0.493
Disease duration	0.024	0.023	1.029	0.306
EDSS	-0.039	0.098	-0.400	0.690
RNFL thickness	0.014	0.012	1.151	0.253
CGM volume	1.303×10^{-5}	3.060×10^{-6}	4.257	**5.370×10^{-5}**

3.3.2.8. In summary: models of cognitive tests with INO as continuous variable

Below, an overview of the models with each time one of the eight cognitive tests as continuous dependent variable and one of the four VDI-parameters as continuous independent variable is given.

Table 92 shows the slope coefficients and the associated p-values of the uncorrected models. This shows that the presence of a right INO has a statistically significant influence on the following cognitive tests:

- The SDMT, in the model with VDI Pv/Am left (β = -5.683 and p = 0.030).
- The CST, in the model with VDI AUC left (β = -1.605 and p = 0.026) as well as in the model with VDI Pv/Am left (β = -1.061 and p = 0.005).
- The SRT, in the model with VDI Pv/Am left (β = -0.816 and p = 0.039)
- The MCT, in the model with VDI AUC left (β = -1.679 and p = 0.041) and in the model with VDI Pv/Am left (β = -1.187 and p = 0.006).

The presence of a left INO only influences the SRT score, in the model with VDI Pv/Am right (β = -0.749 and p = 0.046), as well as in the model with VDI AUC right (β = -1.551 and p = 0.007).

Table 93 shows the results of the models corrected for sex, visual acuity, disease duration, EDSS score, RNFL thickness, and CGM volume. After adjusting for these confounders, the following test results are still negatively affected by INO:

- The SDMT performance is negatively affected by a right INO, in the model with VDI Pv/Am left (β = -9.078 and p = 0.006).
- The CST performance is negatively affected by both a left and right INO, in the model with VDI AUC left (β = -2.002 and p = 0.014), the model with VDI Pv/Am left (β = -0.960 and p = 0.017), and the model with VDI Pv/Am right (β = -0.974 and p = 0.022).
- The MCT performance is negatively affected by a right INO, in the model with VDI Pv/Am left (β = -1.104 and p = 0.036).

Table 92: Overview of the slope coefficients and the corresponding p-values of the uncorrected models with the continuous INO variables per cognitive test.

Cognitive test	VDI-parameter	β INO (95% CI)	P-value
SDMT*	VDI AUC left	-5.209	0.341
	VDI Pv/Am left	-5.683	**0.030**
	VDI AUC right	-3.366	0.464
	VDI Pv/Am right	-3.297	0.377
PASAT*	VDI AUC left	2.095	0.676
	VDI Pv/Am left	2.493	0.300
	VDI AUC right	-1.025	0.808
	VDI Pv/Am right	1.229	0.606
CST**	VDI AUC left	-1.605	**0.026**
	VDI Pv/Am left	-1.061	**0.005**
	VDI AUC right	-0.583	0.342
	VDI Pv/Am right	-0.642	0.110
SRT**	VDI AUC left	-0.862	0.208
	VDI Pv/Am left	-0.816	**0.039**
	VDI AUC right	-1.551	**0.007**
	VDI Pv/Am right	-0.749	**0.046**
WLGT**	VDI AUC left	0.679	0.192
	VDI Pv/Am left	0.127	0.652
	VDI AUC right	-0.317	0.477
	VDI Pv/Am right	-0.228	0.436
SPART**	VDI AUC left	0.528	0.455
	VDI Pv/Am left	-0.093	0.808
	VDI AUC right	0.338	0.575
	VDI Pv/Am right	0.474	0.232
MCT**	VDI AUC left	-1.679	**0.041**
	VDI Pv/Am left	-1.187	**0.006**
	VDI AUC right	-1.163	0.095
	VDI Pv/Am right	-0.866	0.058
SCWT**	VDI AUC left	-0.417	0.584
	VDI Pv/Am left	-0.443	0.274
	VDI AUC right	-0.362	0.574
	VDI Pv/Am right	-0.315	0.456

*Calculations performed with raw test data. **Calculations performed with z-scores.

Table 93: Overview of the slope coefficients and the corresponding p-values of the models with the continuous INO variables per cognitive test, corrected for sex, visual acuity, disease duration, EDSS score, RNFL thickness, and CGM volume.

Cognitive test	VDI-parameter	β INO (95% CI)	P-value
SDMT*	VDI AUC left	-11.850	0.073
	VDI Pv/Am left	-9.078	**0.006**
	VDI AUC right	-3.654	0.496
	VDI Pv/Am right	-1.091	0.713
PASAT*	VDI AUC left	-1.063	0.885
	VDI Pv/Am left	0.836	0.822
	VDI AUC right	-5.674	0.337
	VDI Pv/Am right	-3.369	0.301
CST**	VDI AUC left	-2.002	**0.014**
	VDI Pv/Am left	-0.960	**0.017**
	VDI AUC right	-0.766	0.244
	VDI Pv/Am right	-0.974	**0.022**
SRT**	VDI AUC left	-1.035	0.275
	VDI Pv/Am left	-0.765	0.108
	VDI AUC right	-0.544	0.480
	VDI Pv/Am right	-0.526	0.299
WLGT**	VDI AUC left	-0.112	0.884
	VDI Pv/Am left	-0.159	0.680
	VDI AUC right	-0.392	0.526
	VDI Pv/Am right	-0.600	0.139
SPART**	VDI AUC left	0.536	0.581
	VDI Pv/Am left	-0.350	0.475
	VDI AUC right	0.330	0.676
	VDI Pv/Am right	0.225	0.665
MCT**	VDI AUC left	-1.292	0.230
	VDI Pv/Am left	-1.104	**0.036**
	VDI AUC right	-0.575	0.503
	VDI Pv/Am right	-0.743	0.186
SCWT**	VDI AUC left	-1.753	0.146
	VDI Pv/Am left	-1.040	0.079
	VDI AUC right	-0.189	0.845
	VDI Pv/Am right	-0.800	0.204

*Calculations performed with raw test data. **Calculations performed with z-scores.

3.4. Correlation between SDMT and PASAT scores

In the non-INO group, the PASAT and SDMT results have a statistically significant positive linear relationship, with ρ = 0.506 and p = 2.806 x10^{-10}. In the INO group, also a statistically significant positive linear relationship is found between these two cognitive tests, with ρ = 0.311 and p = 0.014. These correlations between the SDMT and PASAT scores in both groups are illustrated in Figure 7.

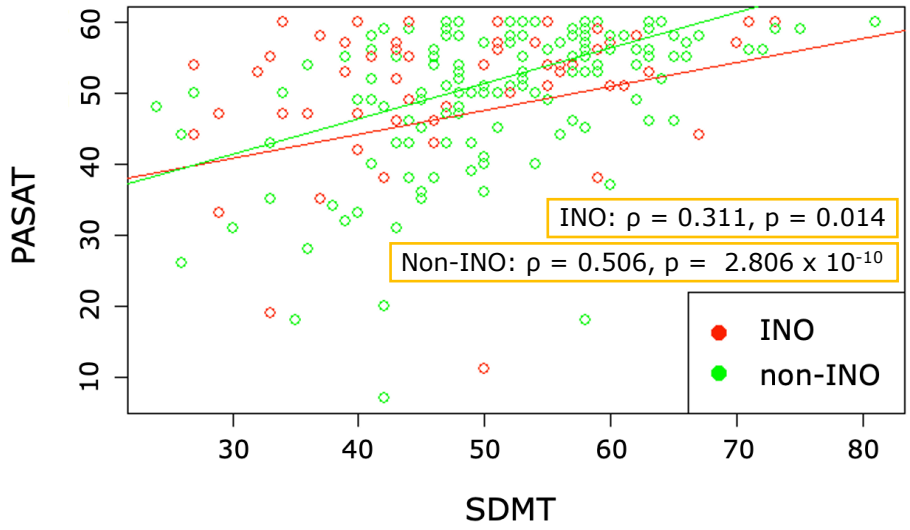


Figure 7: Scatterplots of the correlation between SDMT and PASAT scores in the INO group and the non-INO group. The Spearman correlation coefficient and p-value are shown per group. The yellow boxes indicate statistically significant results.

3.4.1. Comparing ρ by Fisher z transformation and observed z test statistic

To compare the Spearman correlation coefficients between the INO and non-INO group, the Fisher's z transformation was done, whereafter the z scores were compared and analysed for statistical significance by determining the observed z test statistic. After the Fisher's z transformation, a z-score of 0.557 is obtained in the non-INO group, and a z-score of 0.322 is obtained in the INO group. The observed z test statistic is 1.504, with an associated p-value of 0.066. We retain the null hypothesis that the two correlations are not significantly different.

3.4.2. Multiple linear regression analysis with effect modification

In this linear regression model with the PASAT score as continuous dependent variable and the SDMT score and the presence of INO as independent variables, the interaction term (SDMT x INO) was added. This interaction term aims to study the influence of INO on the relationship between the PASAT and SDMT scores. The

SDMT score is a continuous independent variable, while the INO is a binary independent variable.

3.4.2.1. Uncorrected model

Table 94 shows the uncorrected model. The SDMT score has a significant positive influence on the PASAT results, with ß = 0.463 and p = 1.83 x 10^{-9}. The presence of INO also has a significant positive influence on the PASAT score, with ß = 13.349 and p = 0.036. Because the beta of the interaction term is not significant (ß = -0.222 and p = 0.079), there is no significant influence of the presence of INO on the relation between the SDMT and PASAT scores.

The regression line in the non-INO group is: PASAT = 26.101 + 0.463 x SDMT.
The regression line in the INO group is: PASAT = 39.450 + 0.241 x SDMT.
The interaction term is the difference in slope between these two lines.

Table 94: Multiple linear regression analysis with effect modification. The PASAT score is the continuous dependent variable, the SDMT score is the continuous independent variable, and INO is the binary independent variable. The interaction term 'SDMT x INO' shows the relationship between the SDMT and PASAT scores.

	Slope coefficient	**Standard error**	**T-value**	**P-value**
(Intercept)	26.101	3.841	6.796	**1.28 x 10^{-10}**
SDMT	0.463	0.073	6.310	**1.83 x 10^{-9}**
INO	13.349	6.317	2.113	**0.036**
SDMT x INO	-0.222	0.126	-1.764	0.079

3.4.2.2. Model corrected for vision, age, and sex

Table 95 shows the model corrected for vision, age, and sex. The SDMT score has a significant positive influence on the PASAT results, with ß = 0.508 and p = 6.61 x 10^{-10}. The presence of INO has a positive significant influence on the PASAT score, with ß = 13.479 and p = 0.036. Because the beta of the interaction term is not significant (ß = -0.239 and p = 0.061), there is no significant influence of the presence of INO on the relation between the SDMT and PASAT scores.

The regression line in the non-INO group is: PASAT = 34.071 + 0.508 x SDMT - 2.529 x vision - 0.092 x age - 3.937 if female.
The regression line in the INO group is: PASAT = 47.547 + 0.269 x SDMT - 2.529 x vision - 0.092 x age - 3.937 if female.
The interaction term is the difference in slope between these two lines.

Table 95: Multiple linear regression analysis with effect modification, corrected for vision, age, and sex. The PASAT score is the continuous dependent variable, the SDMT score and the presence of INO are the variables. The interaction term shows the relationship between the SDMT and PASAT scores.

	Slope coefficient	**Standard error**	**T-value**	**p-value**
(Intercept)	34.071	6.813	5.001	**1.38×10^{-6}**
SDMT	0.508	0.078	6.540	**6.61×10^{-10}**
INO	13.476	6.388	2.109	**0.036**
SDMT x INO	-0.239	0.127	-1.887	0.061
Vision	-2.529	2.282	-1.108	0.269
Age	-0.092	1.392	-1.309	0.192
Sex (female)	-3.937	0.127	-2.828	**0.005**

4. DISCUSSION

4.1. PRESENCE OF INO AND RELATED CHARACTERISTICS

In the studied cohort, 62 of the 199 (31%) MS patients had an INO. This is in line with the prevalence of INO in the previous studies using infrared oculography with identical thresholds for diagnosing INO in MS patients (15, 16).

We found an association between the presence of INO and male sex. Although only 34% of the cohort is male, 44% of them have an INO, while the prevalence of INO among women is only 24%. Although this finding has previously been described in the literature, the reason for this is not known yet (15, 16). An explanation is that men with MS are more susceptible to a progressive disease course, a more rapid disability progression, and neurodegeneration (87).

A progressive disease course is significantly more common in the INO group. The INO-group also has a longer disease duration, more disability, poorer arm function, and poorer gait function. The association between INO and EDSS score (15, 16) and between INO and arm function (15) is already described in previous studies.

4.2. COGNITIVE TEST SCORES IN THE INO AND NON-INO GROUPS

In the studied cohort, the MS patients with INO scored statistically significantly worse on the SDMT than the non-INO group, while the PASAT scores did not differ significantly between the two groups. These results are within expectations, given that the SDMT is a visual test, requiring many eye movements, while the PASAT is purely auditory.

Similarly, the CST, SCWT and the MCT are cognitive tests with a high oculomotor demand. In these tests, the INO group scores significantly worse than the non-INO group. The SPART requires little eye movements and the WLGT is purely auditory. In these tests, there is no significant difference in the results between the INO and the non-INO group. These findings support the hypothesis that the disturbed eye movements in INO influence the score of eye movement-requiring cognitive tests.

The above findings do not take into account the influence of confounders. For this reason, we used regression models to investigate whether the INO group is generally more affected by the disease or whether INO has a negative influence on the SDMT score. These results and their interpretation are discussed in the following paragraphs.

4.3. REGRESSION MODELS WITH SDMT AS INDEPENDENT VARIABLE

4.3.1. Influence of eye movements on the SDMT in the literature

In the literature, it has been shown that SDMT scores represent deficits in sensory, cognitive, and motor processing (54, 55, 88, 89). Due to the important visual scanning, speech, and word finding component, the SDMT is a sensitive, but aspecific test for information processing speed (54). Studies have already shown the need to take into account the patient's oculomotor and oral motor functions when interpreting the SDMT score (54, 55, 88).

4.3.2. Linear regression analysis with INO as binary variable

Multiple linear regression models were constructed to investigate the effect of INO on the SDMT results. The simple linear regression model with INO as binary independent variable and the SDMT as continuous dependent variable shows that the presence of INO significantly reduces the SDMT score. According to this model, patients with INO score 3.4 points less on the SDMT. After correction for confounders (sex, visual acuity, disease duration, EDSS score, RNFL thickness, and CGM volume), this significant effect disappeared. An explanation for this could be that the influence of INO on the SDMT is more expected in patients with a right INO, where the eye movement disorder occurs when looking to the left. The largest eye movements during the SDMT are made when each time a new line has to be started. This requires a large eye movement to the left. INO as a binary variable may be too coarse. For this reason, the models with the categorical variables were constructed.

4.3.3. Linear regression analysis with INO as categorical variable

In both the uncorrected and corrected models with INO as independent categorical variable and the SDMT as dependent continuous variable, it appears that no INO subgroup (left, right, and bilateral) has a significant influence on the SDMT results. One potential limitation we should mention is that we may lack the statistical power to detect such an effect when we look at the INO subgroups. These groups contain 19, 21 and 22 people. Due to these small numbers, INO may have an influence on the SDMT score that cannot be demonstrated statistically.

4.3.4. Linear regression analysis with INO as continuous variable

To avoid the power problem encountered with the models with INO as categorical variable, but still distinguish between left and right INO, models were created with the continuous VDI-parameters as independent variables. These models made it possible to investigate whether a more severe INO resulted in a greater reduction of the SDMT score.

The uncorrected model as well as the corrected model with VDI Pv/Am left as continuous independent variable show a significant influence of INO on the SDMT performance. The VDI Pv/Am left has in the corrected model (corrected for sex, visual acuity, disease duration, EDSS score, RNFL thickness, and CGM volume) a slope coefficient of -9.078 and a p-value of 0.006. A normal VDI value is 1, which means that everyone would drop 9 points here. People with a VDI of 1.5 would drop 14 points on the SDMT, which means that these people lose 5 points on the SDMT because of their disturbed eye movements.

The model with VDI AUC left as continuous independent variable shows no significant influence of INO on the SDMT results (β = -11.850, p = 0.073). Although the other VDI-parameter that defines a right INO has a significant impact on the SDMT, this one does not. The p-value is close to a significant result; there may also be a power problem here. The models with VDI AUC right and VDI Pv/Am right both show no significant influence on the SDMT. This can be explained by the smaller amplitude of eye movements required to the right during the SDMT, as described above.

4.3.5. Clinical relevance of these findings

To decide the clinical relevance of these findings, we determined how many INO patients scored clinically significantly worse on the SDMT due to their impaired eye movements. A right INO is diagnosed when patients have a VDI Pv/Am left that exceeds 1.180 (16). The literature describes that a decrease in the SDMT score of 4 points is clinically relevant (90). If we convert from which VDI value patients achieve a clinically relevant worse score on the SDMT due to their eye movement disorder, the VDI Pv/Am left is 1.62. In the studied cohort, 52% of patients with a right INO had a VDI Pv/Am left higher than this value. This means that more than half of the patients with a right INO score clinically significantly worse on the SDMT due to their eye movement disorder.

4.4. REGRESSION MODELS WITH OTHER COGNITIVE TESTS AS INDEPENDENT VARIABLE

Several regression models were constructed with other cognitive test results as continuous dependent variable and INO as independent variable. The aim was to investigate whether INO also influences other cognitive test results.

4.4.1. Linear regression analysis with INO as binary variable

The simple linear regression analysis with the cognitive test score as continuous dependent variable and the presence of INO as binary independent variable shows that INO has a statistically significant influence on the CST, SRT, and MCT. According to these models, people with INO score 0.55 z-points less on the CST, 0.47 z-points less on the SRT, and 0.71 z-points less on the MCT. After adjustment for confounders (sex, visual acuity, disease duration, EDSS score, RNFL thickness, and CGM volume), these significant effects disappeared. A potential explanation for this is that the influence of INO on these cognitive tests is more expected if the INO is present in a certain direction. We also saw this with the SDMT, where a right INO had a significant influence on the SDMT score, but a left INO did not. For this reason, the models with the continuous VDI-parameters were constructed.

4.4.2. Linear regression analysis with INO as continuous variable

Four models were constructed for each cognitive test, each with one of the four continuous VDI-parameters as the continuous independent variable and the cognitive test score as the continuous dependent variable.

These uncorrected models show the influence of a right INO on both the CST and the MCT, and the influence of both left and right INO on the SRT. After adjustment for confounders, INO still influences the CST and the MCT. It is noteworthy that these two tests require many rapid eye movements.

In the corrected models, the MCT is only affected by a right INO, while the CST is affected by both a left and a right INO. This can be explained by looking at the eye movements required during these cognitive tests. The MCT requires large eye movements to the left when starting new lines, similar to the SDMT. The CST, on the other hand, requires rapid eye movements in all directions.

4.5. LIMITATIONS OF THE PASAT

In the second part of this study, we investigated the influence of INO on the SDMT performance by comparing the SDMT and PASAT scores. This was complicated by the limitations of the PASAT.

The first limitation of the PASAT is the strong learning effect (42, 91-93). Patients with RRMS have a greater learning effect than those with progressive disease courses (92). It has previously been shown that high learners are younger, have a lower EDSS score and have larger brain volume (93). Given the long disease duration of the cohort (20.9 ± 8.4 years), the active participation of these patients in scientific research, and the PASAT used to be a commonly used cognitive test, the learning effect of the PASAT is undoubtedly present here. This makes the PASAT less informative.

In addition, many PASAT results were close to 60 (the maximum score) in our study population. Due to this ceiling effect, some of the information is missing. A part of the cohort has even a better cognitive function that cannot be quantified with this test (42).

These limitations of the PASAT made comparisons between the PASAT and SDMT scores difficult. The SDMT has a weaker learning effect than the PASAT and does not have this ceiling effect (40).

4.5.1. Interpretation of the results of analyses with the PASAT

In this study, the correlation coefficient between the SDMT and PASAT scores was calculated in the INO group and non-INO group. When comparing these correlation coefficients, we found a result that is borderline insignificant ($p = 0.066$). Figure 7 strongly suggests that this may be due to the ceiling effect of the PASAT.

The multiple linear regression analyses with effect modification also showed borderline insignificant results. The p-value of the interaction term is 0.079 in the uncorrected model and 0.061 in the corrected model. This could also be explained by the ceiling effect and learning effect of the PASAT. The presence of INO always has a significant influence in these models, which supports our hypothesis.

4.6. OTHER FINDINGS FROM THE REGRESSION ANALYSES

The multiple linear regression models with the SDMT as a continuous dependent variable repeatedly showed a significant positive influence of vision on the SDMT score (see Table 9, Table 11, Table 13, Table 15, Table 17, and Table 19). People

with poor visual acuity may, therefore, score worse on the SDMT. This test includes small symbols that are very similar and may not be properly distinguished due to reduced visual acuity. The models with the other cognitive tests show no significant influence of vision on the cognitive test score. This is an interesting finding that should be studied in more detail in further research. It has previously been described in the literature that visual cognitive tests are negatively affected by reduced vision (94, 95).

A remarkable finding is that women score worse on the PASAT than men. According to the regression model, women score approximately5 points less (see Table 21, Table 37, Table 39, Table 41, and Table 43). Some studies also document that men score better on the PASAT (96, 97). Other studies show no influence of sex on the PASAT score (98).

4.7. LIMITATIONS OF THIS STUDY

4.7.1. Lack of exclusion criteria

No strict exclusion criteria were defined in this study. Once the patient was diagnosed with MS, was over 18 years old and could come to the study site, he or she could participate in the study.

It was not documented whether the INO was acute in the context of a relapse, or if the INO was chronically present, due to an unrecovered relapse or due to a progressive course of the disease. This is important because people with acute INO experience more visual complaints than people with chronic INO (19).

Furthermore, no information was available whether the patient had optic neuritis at the time of the examinations. Considering that optic neuritis is characterized by visual blurring or loss and painful eye movements (11, 12), this is likely to have a significant influence on SDMT performance.

Finally, the presence of dysarthria was not considered in this study. Dysarthria affects tests that require a spoken response, especially if this is timed (99). Studies have already shown the need to take into account the patient's oral motor function when interpreting the SDMT score (54, 55, 88). The prevalence of dysarthria in MS patients is approximately 45% (100-102).

4.7.2. Insufficient attention to other eye movement disorders

This study did not consider other eye movement disorders than INO, although other eye movement disorders also occur frequently in MS patients. Below are a number of eye conditions that should be taken into account.

Patients with a one-and-a-half syndrome have both an INO and an ipsilateral horizontal gaze palsy (19, 23). In a left one-and-a-half syndrome, there is adduction limitation of the left eye and nystagmus of the right eye when looking to the right, due to damage to the left MFL. When looking to the left, both eyes show impaired horizontal eye movements due to damage of the left paramedian pontine reticular formation or the nucleus of nerve VI (103). MS is the cause in 30% of one-and-a-half syndrome cases (19, 104).

Wall-eyed bilateral internuclear ophthalmoplegia is a condition in which patients have bilateral INO as well as exotropia and loss of convergence. This is more common in the progressive disease courses (19).

Nerve VI palsies are uncommon in MS but must be considered if patients younger than 50 years have this isolated palsy. In this situation, MS is the cause in 10-24% of the cases (104).

Skew deviation is a vertical misalignment of the eyes caused by damage to the prenuclear vestibular input. In MS, it is often in combination with INO (23). Skew deviation is more frequently seen in RRMS than in the progressive courses (19).

Various types of nystagmus are common in MS. The most disabling type is acquired pendular nystagmus (23, 104). Upbeat nystagmus is more common during a relapse, while the other types are more common in the progressive disease courses (19).

4.7.3. Design of the study

Given the retrospective setting of this study, it was only possible to work with the available data. A limitation due to this, is the way in which the cognitive test results are presented. The combination of both raw scores and z-scores complicates the interpretation of these results.

4.7.4. Size of the study

The small number of patients in the INO group, and particularly in each INO subgroup, makes it difficult to demonstrate statistical significance, as these smaller groups have little power.

4.8. FUTURE RESEARCH

It is noteworthy that the number of studies on the influence of eye movements on cognitive test results is very limited. The findings of this study suggest that further research into the influence of eye movements on test results is promising, also outside the MS population.

To confirm the findings of this study and to investigate more closely the influence of INO on the SDMT, it is necessary to investigate larger study populations with larger numbers in the INO subgroups. Attention should be paid to other components that may influence the SDMT, such as phatic disorders and visual disorders (as described above).

Future longitudinal analyses could show how the SDMT and VDI-parameters change relative to each other. For example, we would expect that patients who have recovered from a severe INO would have a better score on the SDMT (compared to their previous score where they had INO).

In recent years, a lot of research has been done into the digitalization of the SDMT. These studies show a high correlation between the digital SDMT scores and the conventional SDMT scores. The smartphone SDMT has the potential to replace the conventional SDMT (105-108). It would be very interesting to investigate whether MS patients with INO would also score lower on this smartphone version SDMT than MS patients without INO. However, we expect not, as the amplitude of the eye movements on the smartphone version is much smaller.

5. CONCLUSION

The results showed an association between the presence of INO and the SDMT score. Using regression analyses, we investigated whether the INO group is generally more affected by the disease or whether INO has a negative influence on the SDMT score. There appears to be a disease progression component, causing both increased INO and cognitive decline. After adjustment for disease duration, EDSS score, RNFL thickness, CGM volume, sex, and visual acuity, we see that a right INO still has a significant negative influence on the SDMT score. When we look at other cognitive tests that require a lot of eye movements, we also see a significant influence of INO on these test results. According to the results of this study, half of the patients with a right INO scored clinically significantly worse on the SDMT due to this eye movement disorder. Further research is needed to confirm these findings. We suggest that the SDMT results of people with an eye movement disorder, particularly INO, should be interpreted with caution.

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