A multifaceted approach to understand cognitive impairment in MS: exploring the nonlinearity of cognition

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7.1

Summary and General Discussion

In this thesis, our aim was to comprehensively investigate cognitive impairment in people with MS, transitioning from biomarker-based detection to understanding cognition and developing a tool to assess its daily impact. Cognitive impairment is highly prevalent in MS, affecting 34-65% of adults.[1] Impairments in cognition can occur at all disease stages, even in the absence of neurological symptoms, and can profoundly affect daily life.[1, 2] Traditionally, imaging measures such as (cortical) grey matter atrophy only moderately correlate with cognitive impairment,[1] highlighting the need for a multifaceted approach. In this thesis, we employed such a multifaceted approach by integrating a variety of perspectives, stemming from imaging and fluid biomarkers, neuropsychology, and self-reported outcomes, to capture the complexity of cognitive impairment in MS more comprehensively.

After introducing the topic in **chapter 1**, we explored the potential of fluid and imaging biomarkers for detecting cognitive impairment in **chapter 2.1**. In **chapter 3.1 and 3.2**, we aimed to better understand the structural and functional brain mechanisms underlying cognitive impairment, whereas in **chapters 4.1 and 4.2**, our emphasis shifted to investigating patterns of cognitive impairment itself. In **chapter 5.1**, we used symptom network analysis to integrate objective cognitive performance, cognitive complaints, and psychological factors. In **chapter 6.1 and 6.2**, we developed and evaluated a new tool to measure the daily impact of cognitive impairment. In this chapter (**chapter 7**), our findings will be summarized and discussed, offering recommendations for researchers, people with MS, and professionals in the field, as well as exploring future directions for scientific research. The discussion is organized thematically rather than following the chronological order of the chapters, starting with signaling and ending with understanding (see Figure 1).

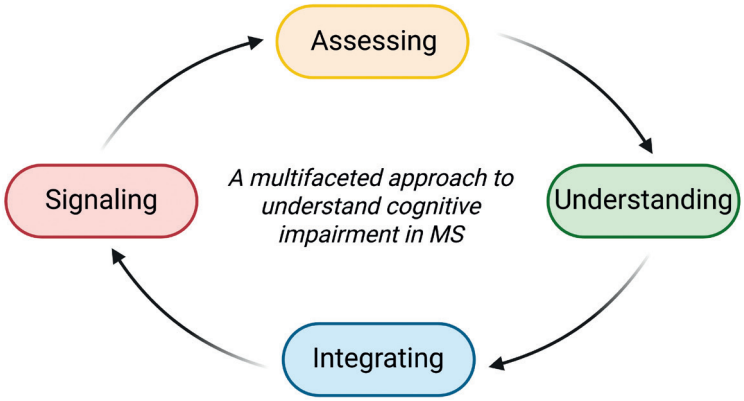

Figure 1. Thematic organization of the discussion, progressing from signaling to integrating information on cognitive impairment in MS.

PART 1: SIGNALING COGNITIVE IMPAIRMENT

Key questions for signaling cognitive impairment in MS

- What is the potential of fluid biomarkers (i.e., NfL and GFAP in both serum and CSF) for detecting cognitive impairment in MS?
- What is the added diagnostic potential of these fluid biomarkers in comparison with conventional imaging markers?

Diagnostic markers for cognitive functioning

This thesis began by aiming to enrich the set of biomarkers available for detecting cognitive impairment in MS, a crucial step for effective screening, monitoring, and treatment of cognitive impairment. Currently, referrals for neuropsychological assessments usually rely on observed cognitive deficits reported by people with MS themselves, their proxies (e.g., partners, family members, and close ones), and/or health care professionals (e.g., neurologists and rehabilitation physicians). However, recognizing cognitive symptoms that require further investigation can be challenging for people with MS, their proxies, and health care professionals, as these impairments may manifest in various subtle ways that may go unnoticed and can occur without accompanying neurological signs or symptoms.[1] Early detection is crucial for enabling symptom management and timely interventions, which may help prevent negative consequences.[3] As novel disease-modifying therapies for MS continue to be developed, aimed at reducing relapses and slowing disease progression that might also impact the management of cognition, establishing a process for the early identification of cognitive impairment is needed to optimize treatment outcomes for people with MS. Most research in this area has focused on developing and improving questionnaires, clinical tools, and brain imaging techniques. However, fluid biomarkers, which can be readily assessed in routine clinical practice with minimal burden on patients, represent a promising but underexplored tool for early cognition screening. While these biomarkers are currently used primarily to monitor overall disease activity, disease progression, and the efficacy of disease-modifying therapies, their potential role in detecting cognitive impairment remains to be fully explored.[3]

In **chapter 2.1**, we therefore explored the diagnostic value of fluid and imaging biomarkers in cognitive impairment. Our objective was to determine whether previously validated fluid biomarkers, either alone or in combination with conventional imaging measures, could help identify cognitively impaired individuals among those with preserved cognition. Such stratification would be helpful to indicate which patient might need (a referral for) a neuropsychological assessment. In this chapter, we specifically evaluated the diagnostic potential of neurofilament

light (NfL) and glial fibrillary acidic protein (GFAP) in both serum and cerebrospinal fluid (CSF), alongside conventional magnetic resonance imaging (MRI) measures, to identify cognitive impairment in MS. NfL serves as an indicator of neuro-axonal damage, reflecting the intermediate cytoskeletal protein of axons (providing support to the axons),[4] while GFAP is thought to reflect the intermediate cytoskeletal protein of astrocytes.[5] Our results align with previous studies,[6, 7] demonstrating elevated levels of both NfL and GFAP only in the serum of cognitively impaired people with MS compared to cognitively preserved individuals. Higher levels of NfL in both CSF and serum were linked exclusively to reduced information processing speed (IPS), the most commonly impaired cognitive domain thought to underlie overall impairment.[1] This finding supports the hypothesis that NfL may serve as a biomarker for general cognitive decline rather than being sensitive to specific impairments.[3, 7] Using serum levels of NfL and GFAP, we effectively differentiated cognitively impaired from cognitively preserved people with MS, achieving diagnostic performance comparable to that of grey matter atrophy as an indicator. Interestingly, serum NfL proved more effective than GFAP, as no significant correlations were found between serum GFAP levels and cognitive functioning across different domains.

Role of fluid biomarkers: Elevated levels of NfL and GFAP are associated with cognitive impairment in MS, particularly in patients with reduced IPS. NfL is currently the most promising fluid biomarker for tracking reduced IPS in MS, demonstrating diagnostic performance comparable to traditional imaging methods. However, its clinical utility remains limited due to challenges such as sensitivity to inflammation and disease activity.

Despite growing interest, research on fluid biomarkers, particularly NfL, and cognition in MS remains limited and inconclusive.[8-10] Many studies are hindered by small sample sizes, inconsistent definitions of cognitive impairment, and limited neuropsychological test batteries.[3] Furthermore, while NfL is widely regarded as a neurodegenerative marker, its levels are significantly influenced by inflammation and lesion activity, posing challenges for its clinical applicability.[11] For instance, serum NfL levels have been shown to explain additional variance in cognitive impairment at diagnosis,[10, 12] but they are also associated with indicators of disease activity, such as Expanded Disability Status Scale scores and the presence of relapses in recently diagnosed people with MS.[13] Its role in more progressive forms of MS still requires further validation.[14, 15] NfL's sensitivity to inflammatory processes present practical challenges, while its association with disease activity highlights its broader utility in monitoring MS progression. This underscores the need for multimodal approaches to fully realize its potential.[14, 16]

In line with the aim of identifying clear clinical markers for cognitive impairment, we chose to operationalize cognitive status as a binary outcome (impaired versus preserved cognition) based on standardized cut-offs on neuropsychological assessments. While this approach reflects clinical decision-making and facilitates the development of diagnostic tools, it does imply a simplification of a complex and continuous construct. We recognize that dichotomizing cognitive performance may lead to a loss of nuance and statistical power, and that future work could benefit from incorporating dimensional approaches that better capture the spectrum of cognitive functioning in MS.

Multi-modal marker

Combining serum NfL with grey matter volume as a "multi-modal marker" enhanced diagnostic accuracy for cognitive impairment, achieving high sensitivity (85%) but lower specificity (58%). This finding suggests that combining these two biological measures together provides a more effective tool for identifying cognitive impairment than using either measure alone. The sensitivity of NfL, particularly when combined with cortical thickness, has been highlighted in previous work.[10, 14, 17] For instance, while serum NfL levels alone did not distinguish newly diagnosed relapsing-remitting MS patients from healthy controls, their combination with global and regional cortical thickness significantly added explained variance in identifying cognitive impairment.[10] These results underscore the value of multi-modal markers.

When working towards multi-modal markers, the question arose whether CSF and serum levels of NfL may be equally useful for detecting cognitive impairment. Although studies report high correlations between CSF and serum levels,[18, 19] the correlation is not perfect, suggesting the two may not be entirely interchangeable. Notably, cognitive functioning tends to correlate more strongly with CSF biomarkers than with serum biomarkers.[14] Our recent study (in preparation) further investigated these relationships, reporting moderate-to-high correlations between serum and CSF levels of NfL (r = 0.548 and r = 0.666 in two separate cohorts) and a moderate correlation for GFAP (r = 0.462). While these findings demonstrate a significant relationship, the moderate-to-high correlations indicate room for improvement. This discrepancy may help explain the occasional lack of association between serum NfL levels and cognition, particularly in early MS, where CSF may be more sensitive to ongoing axonal damage directly related to cognitive impairment.[20] Nonetheless, serum remains the preferred fluid biomarker due to its less invasive collection method compared to CSF, which requires a lumbar puncture.

While the multi-modal marker demonstrated strong sensitivity in detecting cognitive impairment, there was a trade-off in its ability to rule out individuals without impairment (low specificity). This finding suggests that the marker tended to misclassify a substantial number of cognitively preserved individuals as impaired.

High sensitivity is more important for screening purposes, as the primary goal is to identify all patients with actual impairment for subsequent referral to more comprehensive evaluations. However, improving the specificity of such tools is important to reduce unnecessary referrals, minimizing costs, and patient burden. To address these challenges, future research should focus on incorporating additional markers to enhance diagnostic accuracy and establishing clinically meaningful cut-offs for multi-modal markers to implement advanced measures into clinical practice.

Multi-modal markers show promise: A multi-modal marker combining serum NfL and grey matter volume shows promise for detecting cognitive impairment in MS with high sensitivity but lower specificity.

Information processing speed

While the primary focus of the chapters in this thesis was not exclusively on IPS, its influential role in shaping broader cognitive performance, monitoring disease progression, and predicting cognitive decline emerged consistently, warranting specific mention. In recent years, the use of the Symbol Digit Modalities Test (SDMT)[21] to measure IPS has gained increasing recognition.[22] Reduced IPS is acknowledged as an early impairment in MS progression,[23] often preceding deficits in other cognitive domains.[24] Research suggests that an impairment in IPS is a highly sensitive indicator for detecting and monitoring broader cognitive decline in MS, as this domain is thought to underlie or support various cognitive functions.[22, 25]

In **chapter 2.1**, we observed significant associations between NfL for IPS only, but not with other cognitive domains. Additionally, IPS had the highest number of moderate correlations with conventional imaging measures (four out of five): grey matter volume, lesion load, thalamic volume, and hippocampal volume, with the exception of white matter volume. These findings highlight the predominant relationship of IPS and brain pathology.[26] The diagnostic potential of serum NfL levels for assessing cognitive impairment in MS aligns with findings from existing literature, which have consistently shown that elevated NfL levels (in serum and CSF) were associated with reduced IPS,[3, 14, 27] and with future processing speed performance.[7] However, it is important to note that IPS was the most frequently evaluated cognitive domain in these studies, and at times the only domain studied, potentially leading to a biased emphasis on this domain in relation to fluid biomarkers.[3] Other cognitive domains, such as verbal learning and memory, visuospatial memory and verbal fluency, have also shown associations with NfL levels.[3, 12, 20] For example, one study found that people with MS with NfL levels above the 90th percentile had a nearly 16-fold greater risk of impairments in verbal learning over nine years compared to

people with lower levels of NfL, despite an overall weak correlation between serum NfL and cognition.[28]

Additional findings from **chapter 4.1** highlight that people with MS who had isolated IPS impairments were three times more likely to experience cognitive deterioration over time compared to those with isolated impairment in other cognitive domains (69% for IPS versus 18-31% for other domains). These results align with existing literature, reinforcing that an initial impairment in IPS can serve as a reliable predictor of subsequent cognitive decline.[24, 29] Similarly, our insights from **chapter 4.2** identified IPS as the most important cognitive domain for classifying cognitive status (i.e., cognitively impaired versus preserved). Compared to other domains such as attention, inhibition, verbal fluency, verbal memory, and visuospatial memory, IPS emerged as the most important factor and was also the most prevalent impairment across all identified cognitive profiles. In **chapter 5.1**, we found that performance in IPS provided valuable insights into the co-occurrence of psychological and cognitive symptoms (discussed further in Part 3 of this discussion). Collectively, these findings underscore the potential of IPS as a key focus for developing advanced digital assessment tools. This development could build upon existing platforms, such as the Multiple Screener,[30] which is currently undergoing validation to establish its reliability and effectiveness for clinical use.[31]

IPS as key indicator: IPS emerges as a crucial marker of cognitive impairment in MS, serving as an early and sensitive indicator of broader cognitive decline and a predictor of future cognitive deterioration. Its associations with brain pathology and biomarkers, particularly NfL, highlight its diagnostic and prognostic value, while its prevalence across cognitive profiles underscores its importance in classifying cognitive status.

PART 2: ASSESSING COGNITIVE IMPAIRMENT

Key questions for assessing cognitive impairment in MS

- Can we develop and validate a tool to assess the impact of cognitive functioning in daily life making use of IADL?
- By differentiating between cognitive and physical difficulties in this tool, can we better understand the cognitive impact of MS in everyday functioning?

Impact of MS on daily life

In this part of the thesis, we examined the impact of cognitive impairment on daily life in people with MS. MS significantly affects quality of life, often due to challenges in daily functioning that may necessitate caregiver assistance.[32] The extent of this impact is shaped by a combination of disease-related factors, such as cognitive and physical impairment, alongside demographic and social factors, including education, age, employment and the availability of social support.[33-37] Following diagnosis, people with MS often report reduced participation in various activities compared to healthy controls.[38] These challenges are evident in critical domains like work, social engagement, driving, medical decision-making and adherence, as well as financial management.[39, 40] Gaining a deeper understanding of these impacts is essential to designing targeted interventions that promote independence and enhance the overall quality of life for people with MS.

Current neuropsychological assessments, while considered the gold standard for identifying the full spectrum of cognitive impairment,[41] are inherently time-consuming, require trained personnel, and can be burdensome for people with MS.[39, 42] Moreover, the controlled test setting, designed to minimize distractions, limits the ecological validity of the results as it does not fully reflect real-world conditions and how these deficits are experienced in daily life.[43] Consequently, translating test findings and improvements in test scores to meaningful improvements in daily functioning can be challenging. While cognitive rehabilitation studies have shown promise in addressing specific impairments, it remains unclear whether these interventions lead to meaningful improvements in daily life. Additionally, the lack of consensus on what constitutes a clinically meaningful change in the context of daily functioning further complicates this translation.[44] This challenge is further amplified by the absence of established diagnostic criteria for cognitive impairment in MS.[45] The DSM-5 provides general clinical guidelines for cognitive disorders, but these do not fully capture MS-related cognitive and functional impairments, complicating diagnosis and treatment evaluation.

Existing self-reported tools, such as the Multiple Sclerosis Neuropsychological Questionnaire[46] or the Multiple Sclerosis Impact Scale,[47] provide limited insights into daily activity performance, especially for instrumental activities of daily living (IADL). IADLs involve complex tasks that require multiple cognitive processes.[48] In other fields, such as aging and dementia, questionnaires like the Amsterdam IADL questionnaire (A-IADL-Q) have demonstrated value by showing associations with (early) cognitive changes,[49] cross-cultural applicability,[50] and the ability to detect clinically meaningful changes over time.[51] However, this questionnaire has not been validated for MS and may not fully capture the unique characteristics and challenges faced by people with MS. In MS, distinguishing whether difficulties in daily activities stem from cognitive impairments (e.g., memory or attention) or physical impairments (e.g., movement) is particularly relevant but remains understudied, which further limits the applicability of such tools.[52]

Development and validation of the MS-IADL-Q

To address this need, we developed the "Multiple Sclerosis Instrumental Activities of Daily Living Questionnaire" (MS-IADL-Q) in **chapter 6.1**, specifically designed to address the common challenges faced by people with MS in daily life. The MS-IADL-Q was inspired by the A-IADL-Q[48] and its adaptations in neuro-oncology and HIV. An initial version of the MS-IADL-Q was evaluated for relevance and clarity based on feedback from people with MS, their proxies, and (inter)national healthcare providers. Based on their feedback, some items were removed or merged for clarity, while new items were added to better reflect the challenges experienced in daily life. These adjustments addressed items such as managing work-related tasks, participating in social and leisure activities, planning and executing daily activities, and navigating environmental and social interactions. The final result was a comprehensive 50-item questionnaire tailored to the specific needs and experiences of people with MS.

In **chapter 6.2**, we evaluated the psychometric properties of the 50-item MS-IADL-Q to assess the cognitive and physical impact of MS on daily life. We assessed various psychometric properties, including structural validity, construct validity, internal consistency, test-retest reliability, and inter-rater reliability, applying both classical test theory and item response theory methodologies. A detailed overview of the key psychometric properties of patient-reported outcome measures (PROMs), according to the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN)[53] guidelines can be found in Box 1.

Box. 1. Key psychometric properties of patient-reported outcome measures (PROMs).

Psychometric property	Definition
Content validity	Refers to the extent to which the items of a PROM comprehensively cover the domain of interest, involving participants to rate the relevance and comprehensibility of items.
Structural validity	Relates to the degree to which the scores of a PROM adequately reflect the dimensionality of the construct being measured. This is often evaluated using factor analysis techniques.
Internal consistency	Reflects the extent to which items on a single scale or subscale are interrelated, usually assessed with Cronbach's alpha or Omega coefficients.
Cross-cultural validity or measurement invariance	Examines whether a PROM is equally valid across different cultural or demographic groups, ensuring that items are interpreted similarly by all participants.
Measurement error	Involves the amount of error in the scores of a PROM not attributed to true differences among participants, often quantified by the Standard Error of Measurement or Smallest Detectable Change.
Reliability	Concerns the extent to which a PROM yields consistent results under consistent conditions, evaluated through methods like Intraclass Correlation Coefficients or Kappa statistics.
Criterion validity	The degree to which the scores of a PROM are an adequate reflection of a "gold standard".
Construct validity	Assesses how well a PROM measures the theoretical construct it intends to measure, commonly tested through hypotheses about expected correlations with other measures or known group differences.
Responsiveness	Indicates the ability of a PROM to detect clinically meaningful changes over time, often validated by testing pre-defined hypotheses about changes in PROM scores relative to other measures or interventions.
Translation and adaptation	When translating a PROM into another language or adapting it for another culture, a rigorous process must be followed to ensure that the new version retains the original's measurement properties.

We found support for the structural and construct validity of a 32-item MS-IADL-Q, covering domains such as household duties, administration, appliances, leisure, transport, care & multitasking, and work. Figure 2 outlines the psychometric properties that have been assessed (in color) and those that remain to be evaluated (in white).The questionnaire's unidimensional structure effectively measured overall difficulty in daily activities while distinguishing between cognitive and physical difficulties, offering separate subscales for each. For people with MS, the most challenging IADLs included work-related activities, multitasking, grocery shopping, cooking, leisure, and driving. The strongest associations with the MS-IADL-Q were found for cognitive complaints and fatigue, suggesting that individuals who report greater cognitive difficulties or higher levels of fatigue tend to experience more

difficulty with daily activities as measured by the MS-IADL-Q. The MS-IADL-Q showed strong internal consistency and satisfactory test-retest and inter-rater reliability. We observed distinct influences of cognitive and physical functioning on various daily activities, also at an individual level, emphasizing the need for patient-tailored interventions. These findings emphasize the MS-IADL-Q's utility in assessing the multifaceted impact of MS.

Future research should explore its sensitivity to change over time, cross-cultural validity, construct validity against objective performance measures, clinical meaningfulness (by generating norms and clinical cutoffs), and diagnostic accuracy, particularly in comparison to established measures like the SDMT.[54, 55] Comparisons with neuropsychological assessments and physical measures, such as the Expanded Disability Status Scale, will further clarify its usefulness. Additionally, criterion validity could be evaluated by developing computerized adaptive versions of the test or short forms of the questionnaire, allowing for comparisons with the 32-item MS-IADL-Q. These efforts will strengthen the MS-IADL-Q's value in both clinical and research settings and enhance understanding of the impact of MS on daily life functioning.

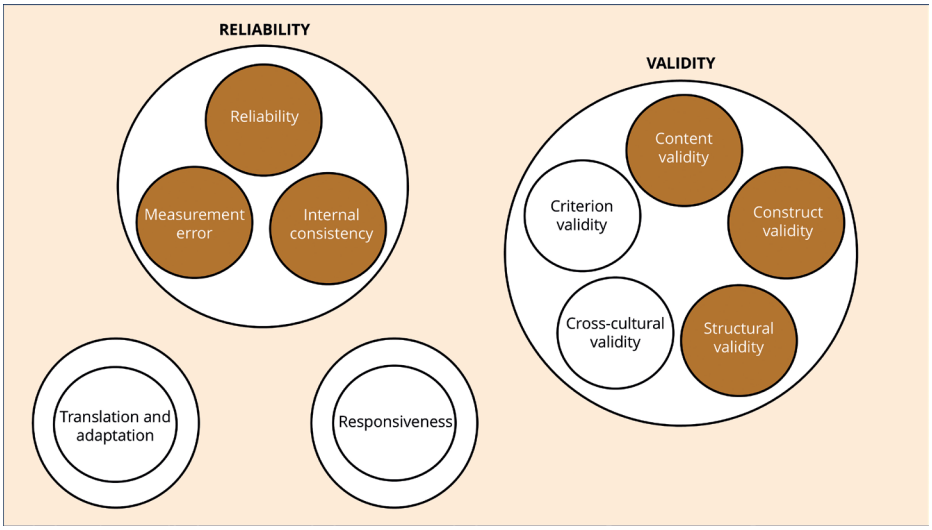

Figure 2. Overview of the psychometric properties relevant in the context of patient-reported outcome measures. The assessed properties of the MS-IADL-Q in chapter 6 are depicted in brown.

Validation of the MS-IADL-Q: The MS-IADL-Q is a valid and reliable tool for measuring the cognitive and physical impact of MS on daily life, offering a more comprehensive understanding of everyday functioning.

Individual adaptability: Experiences with daily activities vary greatly among people with MS. The MS-IADL-Q accommodates this variability by customizing to individual abilities, making it a flexible tool and a potential standardized outcome measure. This adaptability has significant clinical implications, bridging the gap between cognitive rehabilitation in clinical settings and research interventions.

Adaptive testing

To further enhance the relevance and efficiency of the MS-IADL-Q for people with MS, we explored the use of a post-hoc adaptive scoring approach, i.e., computerized adaptive testing (CAT), as discussed in **chapter 6.2**. CAT customizes the questionnaire in real-time based on individual responses. It dynamically selects the most relevant questions for each person, focusing on their specific areas of cognitive and physical difficulties, thereby reducing the number of questions and minimizes testing time.[56] Our analysis in **chapter 6.2** showed that the post-hoc simulated CAT scores were highly correlated with the true levels of IADL functioning when all 32 items were administered (r = 0.991), while the average number of activities administered was significantly reduced to 19.18. However, the performance of CAT scores in a prospective study has yet to be determined.

In a broader context, digitized cognitive assessment batteries present a promising alternative to traditional paper-and-pencil methods for assessing cognitive functioning, either as standalone tools or in combination with traditional neuropsychological assessment.[57] Testing software can reduce administration and scoring errors, tailor tasks to individual abilities (through CAT for instance), and efficiently provide detailed information on performance.[58] Digital versions of existing cognitive tests are also gaining popularity, allowing for remote administration. For instance, the Multiple Screener, a newly developed digital tool based on the Brief International Cognitive Assessment for MS (BICAMS), offers a self-guided, 15-minute assessment of key cognitive domains, including IPS, verbal and visuospatial learning, and memory, while also incorporating measures of depression, anxiety, fatigue, and self-reported cognitive complaints.[30] The Multiple Screener is currently undergoing validation to compare its effectiveness against traditional paper-and-pencil assessments and the MS-IADL-Q.[31] While remote testing could make screening

and monitoring of cognitive impairments more accessible, it also introduces new challenges, such as variability in testing environments and the potential need for assistance or support, which may still impose burdens on personnel.[57] These challenges are important to consider when evaluating the feasibility and scalability of remote cognitive assessments, particularly in clinical and research settings where standardized testing conditions are crucial for reliable results.

Use of computerized adaptive testing: Adaptive scoring techniques, such as computerized adaptive testing, reduce the number of questions needed while maintaining accuracy, making the assessment more personalized and less burdensome for people with MS.

Expanding the role of the MS-IADL-Q

The MS-IADL-Q holds promise for advancing cognitive rehabilitation, where treatment effects are often mild-to-moderate and highly variable across individuals.[59] Traditional measures to assess intervention effects in this context typically focus on specific cognitive tasks but may overlook the broader impact on daily life functioning.[44] The MS-IADL-Q addresses this gap by offering a comprehensive view of how cognitive changes affect daily activities, aligning with a shift toward evaluating real-world outcomes in rehabilitation.[60] One critical challenge in understanding and addressing cognitive impairment in MS is the absence of established MS-specific diagnostic criteria for major cognitive disorder.[45] While the DSM-5 provides general guidelines, these criteria do not necessarily capture the nuances of cognitive impairment in MS.[45] Because there are no universally accepted diagnostic standards for cognitive impairment in MS, the issue is not merely that current research fails to align with them, but rather that we lack a standard framework altogether.[61] This contributes to inconsistencies in recognition and diagnosis. Moreover, while under-recognition of cognitive impairment in MS is often discussed, reliance on neuropsychological assessment alone, without considering real-world functioning, may actually lead to over-recognition in some cases.[62] Since a neuropsychological assessment is already widely used in clinical practice, incorporating daily life assessments such as the MS-IADL-Q would not necessarily result in additional diagnoses, but rather refine diagnostic accuracy by integrating both cognitive performance and functional outcomes. By focusing on the real-world impacts of cognitive decline, tools like the MS-IADL-Q can help bridge the gap created by the lack of MS-specific criteria and complement traditional cognitive tests, offering a more holistic understanding of impairment. Integrating IADL performance into diagnostic frameworks could better reflect the multifaceted nature of cognitive and functional decline in MS, similar to the Cognitive-Functional Composite designed for early dementia.[63] Furthermore, assessing both cognitive

and physical impacts on IADL performance has the potential to inform personalized treatment strategies. The MS-IADL-Q enables clinicians to define relevant activities at an individual level and track improvements in daily functioning alongside cognitive performance. Incorporating daily functioning measures into diagnostic and treatment paradigms could not only enhance individual care but also advance the field toward more nuanced and comprehensive approaches to rehabilitation and research in MS.

PART 3: UNDERSTANDING COGNITIVE IMPAIRMENT

Key questions for <u>understanding</u> cognitive impairment in MS

- What patterns of isolated cognitive impairments can be identified and how do they inform our understanding of the progression of cognitive impairment in MS?
- How do distinct cognitive profiles in MS, identified through latent profile analysis, capture individual variability in cognitive impairment, and what insights do they offer into the progression and heterogeneity of cognitive decline?

Different 'flavors' of cognitive impairment

In this part of the thesis, we aimed to investigate cognitive impairment in MS through two complementary approaches: examining isolated cognitive deficits and identifying broader cognitive profiles. **Chapter 4.1** and **chapter 4.2** present these frameworks, offering more specific insights into the diverse presentation of cognitive impairment. By moving beyond the binary classification of cognitive status (impaired versus preserved), we aimed to explore the variability and complexity of cognitive impairment in MS.

Isolated cognitive impairments

In **chapter 4.1**, isolated cognitive impairment was defined as a *z*-score below -1.5 in one cognitive domain, without deficits in other domains using the same threshold. Multi-domain impairment involved deficits in two or more cognitive domains, while cognitively preserved individuals showed intact functioning across all domains. The study aimed to examine the prevalence, progression over five years, and MRI correlates of these isolated impairments (the latter is discussed in Part 4).

At baseline, 31% of the people with MS displayed isolated cognitive impairment, 43% had multi-domain impairment, leaving only 26.4% of patients fully cognitively preserved. Among isolated impairments, executive functioning was most frequently affected (34%), suggesting it can occur as a stand-alone impairment, warranting targeted interventions. This was unexpected, as IPS is typically identified as the earliest and most frequently impaired domain in MS.[1, 23, 24] Executive functioning impairments are often seen in later stages of cognitive decline.[24] Notably, studying isolated impairments provided insights into the frequency and progression of specific deficits rather than their timing, offering a complementary perspective to traditional approaches. Indeed, in the multi-domain impairment group, IPS was the most frequently affected domain, with 73% of individuals impacted.

The longitudinal analysis revealed distinct patterns in the progression of isolated impairments. Isolated IPS impairments had significant prognostic value, with

affected individuals being three times more likely to experience cognitive deterioration over time compared to those with other forms of isolated impairments (69% vs. 18–31%). This aligns with earlier findings that baseline IPS impairment is a reliable predictor of future cognitive decline.[24, 29] Conversely, isolated memory impairments were the most stable (56% remained impaired over five years) with no additional domains being affected. Memory impairments are common in MS,[1] and are typically associated with difficulties in learning new information rather than their recollection.[64, 65] The relative stability of this memory impairment suggests a potential for targeted interventions, which currently favor strategy-based compensatory approaches and exercise interventions.[44]

Isolated attention impairments were the most dynamic, with the highest likelihood of transitioning to preserved cognitive status in five years. This variability may reflect the impact of factors like stress, fatigue, and mood disturbances on attention,[66-68] or the sensitivity of attention measures to detect change. Alternatively, the observed transitions to preserved status may reflect actual improvements in attention. Although reported on a different time-scale, short-term improvements in attention have been observed following a seven-week attention training program.[69] In this study, functional connectivity patterns that resemble that of healthy controls were associated with higher training responsivity. The relative dynamic nature of isolated attention impairments might thus highlight both its plasticity and sensitivity.

Frequency and evolution: In people with MS, cognitive impairments manifest either as isolated deficits in specific cognitive domains or as impairments across multiple domains. Isolated impairments, particularly in executive functioning, were the most common, affecting 31% of individuals. IPS was the most affected domain in multi-domain impairments. Longitudinal analysis showed that isolated impairments in attention had the highest chance of returning to a cognitively preserved state, while IPS impairments indicated a greater risk of cognitive decline. Isolated memory impairments remained relatively stable over time, suggesting that targeted interventions aimed at improving memory could be highly beneficial.

Profiles of cognitive impairments

In **chapter 4.2**, we shifted our focus to identifying cognitive profiles, which represent distinct cognitive performance patterns of groups of individuals with similar patterns of strengths and weaknesses across various cognitive domains. Cognitive profiles offer a more advanced understanding of cognitive dysfunction in MS by moving beyond the examination of isolated domains or cognitive status to capture the complexity of how impairments co-occur and interact within individuals.[70] Using

latent profile analysis across six cognitive domains (attention, inhibition, IPS, verbal fluency, verbal memory, and visuospatial memory), we analyzed a combined sample of 1213 people with MS collected from ten individual research studies. We aimed to determine whether cognitive profiles could be identified and whether these profiles reflected distinct trajectories. For descriptive purposes, profiles were evaluated against demographic and clinical variables, as well as PROMs (i.e., questionnaires on mood, anxiety, and fatigue) and were benchmarked against cognitive status.

We identified six distinct cognitive profiles, organized along a continuum of cognitive decline and characterized by differences in demographic and clinical variables as well as PROMs. Visuospatial memory emerged as the primary differentiator between profiles. For example, individuals in Profile 5 (consisting of 371 people with MS, 72% female, 78.2% with relapsing-remitting MS, mean age of ~46 years, and 35.3% cognitively impaired) exhibited poorer overall cognitive performance but retained preserved memory function. This finding was unexpected, given IPS's central role as the most frequently impaired across all profiles, with prevalence ranging from 22.4% in the most preserved profile to 76.6% in the most impaired profile. These results highlight the importance of assessing both IPS and memory, particularly visuospatial memory, for a comprehensive evaluation of cognitive impairment, as exemplified by the BICAMS.[71]

Cognitive profiles: Six distinct cognitive profiles were identified, ranging from preserved cognitive function to significant impairment, with visuospatial memory emerging as a key differentiator.

Cognitive profiles versus traditional analyses: The identified cognitive profiles provide a more nuanced understanding of MS-related cognitive impairment compared to traditional domain-specific analyses. These profiles highlight distinct patterns of cognitive strengths and weaknesses across domains, revealing how various impairments co-occur and interact within individuals.

Future perspectives of cognitive profiles

To enhance clinical relevance, an important next step is to validate the cognitive profiles in external datasets to assess their generalizability.[72] Current profile estimation is data-driven and depends on the variables included in the model, leading to variations in the number of profiles identified across studies.[73] The assessment of generalizability could include examining their consistency across

subgroups and time points.[74] Cognitive profiles may also be integrated with MRI measures to improve classification accuracy and contribute to understanding the neurobiological underpinnings of cognitive impairment.[70, 73] A shift toward risk stratification is expected to help identify and manage factors associated with cognitive decline.[75] Future applications may integrate latent profile analysis with structural equation model trees, which combine decision trees and latent profile analysis to improve classification accuracy.[76] This approach could predict cognitive profile membership in new patients and assess metrics such as sensitivity and specificity. Such predictive tools will enable clinicians to align individuals with MS to specific profiles and tailor interventions accordingly, advancing personalized care.

Given the progressive nature of MS, understanding how cognitive profiles evolve over time is crucial. Advanced analytical techniques such as latent transition analysis and growth mixture modeling can track changes in profiles and identify cognitive trajectories. Latent transition analysis examines how individuals shift between different latent profiles or classes over time, making it particularly useful for studying cognitive trajectories in MS.[77] For instance, someone in a memory-impaired profile may transition to a multi-domain impaired profile as cognitive decline progresses. Growth mixture modeling, on the other hand, identifies subgroups with distinct patterns of cognitive decline.[78] For example, one subgroup might exhibit steady deterioration in memory and processing speed, while another shows a slower decline limited to executive function. Identifying such trajectories may inform targeted interventions for high-risk groups and highlight protective factors in slower-progressing subgroups.

Finally, cognitive profiles have potential for tailoring rehabilitation strategies.[70] For instance, a recent study demonstrated that individuals with single-domain impairments benefitted more from restorative cognitive rehabilitation than those with multi-domain impairments.[79] Improvements were more pronounced in individuals with lower baseline functioning, who had greater room for improvement. Conversely, cognitively preserved individuals may derive less benefit of a rehabilitation program due to a ceiling effect.[44] However, early identification of individuals with more preserved cognitive profiles remains important, as targeted preventive interventions may help delay or prevent further cognitive decline, even if immediate improvements are less evident. This aligns with findings that early interventions can optimize long-term outcomes by maintaining existing cognitive functions and preventing progression.[69] The dual approach of focusing on those with lower baseline functioning for restorative interventions and those with preserved profiles for preventive care ensures tailored strategies for all cognitive profiles.

Broader cognitive batteries needed: The investigation of cognitive profiles demonstrated that impairments in domains such as memory play a critical role in differentiating levels of cognitive performance. While the SDMT effectively detects processing speed deficits, it does not capture the full spectrum of cognitive impairment, particularly in memory, which emerged as a key factor in these profiles. To fully understand the nuances of cognitive impairment in MS, it is essential to use broader cognitive batteries that assess both memory and IPS concurrently. This approach emphasizes the importance of integrating multiple domains to capture the interplay of cognitive deficits.

PART 4: INTEGRATING INFORMATION ON COGNITIVE IMPAIRMENT

Key questions for integrating information on cognitive impairment in MS

- What do variations in fluid biomarkers (e.g., NfL and GFAP in both serum and CSF) reveal about the underlying pathological mechanisms of cognitive impairment in MS, specifically the interplay between axonal damage, glial activation and disease progression?
- How does structure-function coupling relate to cognitive impairment, and what can fluctuations in coupling tells us about cognitive functioning in MS?
- How do objective cognitive performance, self-reported cognitive difficulties, and psychological factors interact within a symptom network in MS, and what insights does symptom network analysis offer into the multidimensional nature of cognitive impairment and its contributing factors?

Adopting a multifaceted perspective

This section of the thesis focused on investigating the underlying pathological mechanisms of cognitive impairment in MS through a multifaceted approach. This section begins by discussing insights from fluid biomarkers (**chapter 2.1**), then explores changes in brain networks associated with cognition (**chapter 3.2**), identifies a role for grey matter atrophy for cognitive decline (**chapter 4.1**), and concludes by considering the value of studying cognition from a multidimensional, network-based perspective (**chapter 5.1**). Our overarching goal was to deepen our understanding of the mechanisms driving cognitive impairment in MS by integrating insights across these domains. By combining findings from biomarkers, brain and symptom networks, and structural changes in grey matter, we aimed to provide a more cohesive picture of how these factors converge to influence cognitive impairment in MS. This integrative approach allows for a more comprehensive framework to uncover novel aspects of the disease and refine strategies for early detection and intervention.

Biomarkers and cognitive impairment: insights from NfL and GFAP

In **chapter 2.1**, we examined diagnostic markers, specifically serum and CSF levels of NfL and GFAP, to better understand the mechanisms underlying cognitive impairment in MS. These biomarkers reflect normal or pathogenic processes, with CSF being particularly valuable due to its close proximity to the central nervous system.[80] Our findings revealed that reduced IPS was correlated with elevated NfL levels in both CSF (r = -0.364) and serum (r = -0.286), with the strongest correlation observed in CSF. However, fluid biomarkers showed fewer associations with cognitive domains (10% of possible correlations, small-to-moderate effect sizes) compared to imaging markers, which exhibited 36% of possible correlations with moderate

effect sizes. The strongest correlations were found between individual cognitive domains and grey matter volume, rather than white matter volume. This indicates that cognitive impairment may result from gradual, widespread brain changes that are more accurately captured by imaging markers than by fluid biomarkers.[4, 81]

Despite its recognition as a marker of neurodegeneration,[82] GFAP showed limited associations with cognition in our study. Although GFAP is generally less influenced by inflammation than NfL and is considered a reliable marker of disease progression,[82] previous studies have found no association between serum GFAP levels and concurrent or future cognitive decline. In contrast, serum NfL levels were consistently linked to cognitive outcomes.[83] This suggests that neuronal damage, as reflected by NfL,[84] may play a more direct role in cognitive impairment than astrocytic reactivity, indicated by GFAP.[82] GFAP might hold greater relevance in progressive MS subtypes, where astrocytic activation and neurodegeneration are more pronounced.[85, 86] Changes in NfL are thought to reflect focal white matter pathology and inflammation-driven axonal injury in MS.[16, 19, 87-89] Our findings align with the hypothesis that axonal damage contributes to deficits in IPS. As a structural protein, CSF-NfL is thought to signal cortico-subcortical disconnection, a process critical for efficient IPS.[8] Early neuro-axonal loss has been linked to reduced IPS,[14] and the SDMT, widely used to assess IPS, appears to be particularly sensitive to cognitive variations,[90] explaining its consistent relevance in these studies. Alternatively, neuro-axonal damage may disrupt interconnected neuronal networks essential for efficient information processing, leading to elevated serum NfL levels and cognitive impairment.[14, 16]

Fluid biomarkers as indicators: Elevated NfL levels in both CSF and serum were consistently linked to reduced IPS, reinforcing its role as an indicator of neuro-axonal damage. In contrast, GFAP demonstrated limited associations with cognitive outcomes, suggesting its relevance may be more pronounced in progressive MS subtypes characterized by increased astrocytic activation.

Network disruptions and the role of structure-function coupling

MS is increasingly recognized as a network disease, with lesions and diffuse damage disrupting structural and functional brain connections.[91] These disruptions may impair information transfer between brain regions, leading to a cascade of network changes that contribute to MS symptoms, including cognitive impairment.[92] Rather than reflecting isolated pathology, cognitive impairments in MS appear to result from widespread disconnection,[93] which reduces the brain's ability to compensate for structural damage through functional adaptations.[94] Notably, functional connectivity alterations have been observed even without accompanying structural

damage,[95] suggesting that functional networks can adapt to or exacerbate the effects of MS-related damage.[96]

Expanding on this complex interplay, **chapter 3** of this thesis investigated how structural and functional interactions contribute to cognitive decline in MS. In **chapter 3.1**, we emphasized integrating structural and functional analyses to identify individuals at risk of network changes that may compromise cognitive functioning. Specifically, we proposed that this integrated approach would involve investigating "structure-function coupling". This quantifies the overlap between structural white matter pathways (or tracts) and functional connectivity, defined as the statistical interdependence or synchronization of activity between brain regions.[95] In other words, structure-function coupling measures the degree to which the functional connectivity is dependent on the underlying tracts. Hypothetically, high structure-function coupling would suggest strong overlap between structural integrity and brain function, while low coupling would indicate more independent, flexible functional activity. In healthy controls, coupling is typically low, allowing functional networks to remain flexible and adaptable despite static structural networks.[97] However, in MS, structural damage limits the availability of intact pathways, restricting how functional networks can reorganize. As a result, the brain's functional repertoire, i.e., its ability to dynamically adapt and reconfigure connections, becomes more constrained. [98] This constraint is reflected in increased structure-function coupling, as functional activity becomes more reliant on the remaining structural tracts. In other words, rather than directly causing a reduction in functional repertoire, higher coupling is a consequence of reduced flexibility due to structural damage. This loss of adaptive capacity may contribute to cognitive decline as the brain's ability to compensate for damage diminishes.

In **chapter 3.2**, we tested this hypothesis by analyzing both static coupling (i.e., the overlap between directly connected structural tracts and functional connectivity) and dynamic coupling (i.e., the variability of coupling), which is suggested to reflect the potential for rearrangement or instability of functional pathways within the structural network. Variability of coupling refers to the dynamic fluctuations in the relationship between structural connectivity and functional connectivity over time. This variability was measured using a sliding-window approach that captures the temporal stability or instability of these interactions during a resting-state functional MRI scan.[99] Our analysis covered whole-brain and network-specific investigations, focusing on key resting-state networks, including the default-mode, frontoparietal, dorsal attention, ventral attention, somatomotor, visual, and deep grey matter networks.[100] Among cognitively impaired individuals with MS, static coupling was significantly higher in tracts connecting the dorsal attention and somatomotor networks to the rest of the brain, compared to cognitively preserved individuals and healthy controls. Coupling followed a stepwise progression: healthy controls

had the lowest levels, cognitively preserved individuals had intermediate levels, and cognitively impaired individuals had the highest levels. This pattern suggests that as structural damage increases, the brain's functional repertoire declines, particularly in tracts integrating networks across the brain. The involvement of the somatomotor network, comprising the bilateral sensorimotor cortices[100] and traditionally linked to physical disability,[101] is particularly noteworthy. Recent evidence suggests this network also supports integrative, top-down cognitive control,[102] highlighting its role in cognitive impairment.

Static structure-function coupling: Static structure-function coupling followed a stepwise progression, with the highest coupling in cognitively impaired people with MS. This increased coupling is hypothesized to result in less flexible and more constrained functional networks, particularly affecting the integration of major networks in the brain.

Dynamic coupling analyses revealed increased variability (or instability) in tracts within the visual and deep grey matter networks (the latter consisting of subcortical structures such as the thalamus, hippocampus and basal ganglia),[100] in cognitively impaired individuals. This instability might indicate that as MS progresses, the functional repertoire becomes more constrained and less adaptable, limiting the brain's ability to dynamically reorganize and compensate for structural damage. Previous studies identified structure-function decoupling in similar networks (including the somatomotor, deep grey matter, visual, and dorsal attention networks) when comparing people with MS to healthy controls; however, these studies often relied on limited cognitive measures, hindering the ability to draw broader conclusions.[103]

Dynamic structure-function coupling: Dynamic structure-function coupling variability in specific brain networks, such as the somatomotor, visual, and deep grey matter networks, was found to increase in cognitively impaired individuals. This suggests that as MS progresses, functional network instability becomes more pronounced, contributing to cognitive decline.

Other research highlights that in early MS, lower static structure-function coupling in the visual network may reflect compensatory mechanisms when cognition remained preserved,[95] while worse cognitive performance after five years was associated with increased whole-brain coupling.[98] Together, these findings suggest a shift from within-network to between-network coupling as the disease advances. As

MS progresses, structure-function coupling might become increasingly unstable, leading to greater variability and reduced functional flexibility. Further evidence supporting this hypothesis found that long-range structural connections, essential for integrating information across the brain,[104] were more vulnerable to MS-related damage than short-range connections.[105] This disruption appeared to impair global information processing, contributing to reduced IPS.[105] Furthermore, a study using magnetoencephalography found that cognitively impaired people with MS showed increased structure-function coupling for these long-range connections, in contrast to short-range connections.[106] These results, combined with our network-specific findings, emphasize the importance of regional analyses in capturing localized changes that whole-brain approaches may miss.

Regional application: Our findings suggest that a more localized or modular approach to measuring structure-function coupling might be necessary to capture the intricacies of cognitive impairment in MS.

Our findings demonstrate the intricate interplay between structural damage and functional network disruptions in MS. As structural pathways deteriorate, functional networks increasingly rely on the remaining (impaired) connections, leading to reduced adaptability and a constrained functional repertoire. However, the directionality of this relationship remains uncertain: while structural damage likely constrains functional flexibility, functional network dysfunction may also exacerbate structural damage, potentially through mechanisms such as excitotoxicity.[107] This bidirectional interplay warrants further investigation to clarify how these processes evolve over time. Stable interactions within these functional networks, as indicated by coupling variability, appeared important for preserving cognitive function. Although direct correlations of structure-function coupling have been criticized as overly simplistic,[106] emerging techniques, such as graph frequency analysis, offer promising tools for quantifying higher-order interactions.[108] Finally, longitudinal studies incorporating advanced imaging techniques and comprehensive cognitive assessments will be crucial for drawing more definitive conclusions about the causal relationships between structural and functional changes in MS.

The role of grey matter atrophy in predicting cognitive decline

In **chapter 4.1**, we aimed to examine the longitudinal associations between isolated cognitive impairments and neuroimaging measures, including cortical grey matter volume, white matter volume, lesion load, thalamus volume, hippocampus volume, cortical lesions, and fractional anisotropy. Reduced IPS was associated with reduced cortical grey matter volume and fractional anisotropy, while isolated memory impairments were linked to decreased cortical grey matter and reduced

hippocampus volume. However, no neurobiological correlates were identified for isolated impairments in executive functioning or attention, suggesting that distinct cognitive functions may have unique neuroanatomical correlates, underscoring the complexity of these relationships in MS.

While analyzing isolated cognitive impairments offered insights into their prevalence and progression, its utility in linking these impairments to conventional or global MRI measures appeared limited. Efforts to predict isolated cognitive decline over five years using imaging markers did not yield significant results. The difficulty in identifying neuroimaging correlates for attention and higher-order executive functioning likely stems from their reliance on specific brain regions, including the fronto-parietal cortex (e.g., dorsolateral prefrontal cortex, anterior cingulate cortex, and posterior parietal cortex)[109] and frontal regions (e.g., the prefrontal cortex).[110] These areas were not fully captured by the imaging measures used in this study. Additionally, the relatively small sample sizes in the isolated groups limited the ability to perform detailed regional structural analyses. Future studies should integrate regional structural imaging and expand collaborations, potentially on an international scale, to increase sample sizes and facilitate more targeted analyses.

Neuroimaging markers: Neuroimaging markers such as cortical grey matter volume, white matter volume, and lesion load were linked to specific cognitive impairments. For example, reduced IPS was associated with reduced cortical grey matter and fractional anisotropy, while memory impairment was linked to hippocampal and cortical grey matter atrophy. However, no neurobiological correlates were identified for impairments in executive function or attention, suggesting that different cognitive domains may have distinct neuroanatomical correlates.

A notable finding was the consistent involvement of cortical grey matter in both IPS and memory impairment, even though cortical lesions did not appear as significant predictors. Cortical lesion accumulation has been linked to greater clinical and cognitive burden,[1, 111] making this absence surprising. However, our recent work (outside the scope of this thesis and therefore not included) revealed a more nuanced relationship.[112] Using methods similar to those in this thesis, we found that the integrity of normal-appearing cortex within the default-mode network best predicted verbal memory, visuospatial memory, and inhibition over five years. Mediation analyses showed that cortical lesions indirectly influenced cognitive decline by contributing to atrophy in normal-appearing cortical regions, underscoring the importance of cortical atrophy in cognitive impairment. Throughout this thesis, grey matter atrophy consistently emerged as the strongest correlate of cognitive function, even when considered independently of white matter

lesion load. This finding aligns with studies in early-stage MS, where individuals with similar white matter lesion burden exhibited greater cognitive decline if they showed widespread grey matter atrophy.[113] Cognitive domains reliant on cortical functions, such as memory, appear particularly susceptible to cortical atrophy,[114] making them key targets for studying isolated cognitive impairments. These results emphasize the need to better understand the interplay between cortical lesions and grey matter atrophy and to investigate their temporal relationship. Such insights could guide early intervention and improve prognosis.

A network perspective on cognition

In **chapter 2.1**, we examined people with MS visiting the "Second Opinion MS and COGnition" (SOMSCOG) outpatient clinic who reported cognitive complaints. Approximately 75% of these individuals scored above the clinical cutoff of 27 on the Multiple Sclerosis Neuropsychological Questionnaire,[46, 115] indicating the presence of self-perceived cognitive problems at the time of their visit. However, only about 56% were classified as cognitively impaired based on the neuropsychological assessments. This discrepancy raised a key question: could these cognitive complaints predict later cognitive impairment as assessed by neuropsychological evaluations? Cognitive complaints are often more closely linked to mood and fatigue than to objective cognitive test results,[116] which are factors that are frequently overlooked or controlled for in cognitive rehabilitation studies to focus on the direct effects of interventions.[59] However, the exclusion of factors such as mood and fatigue contrasts with real-world clinical practice, where addressing comorbidities is essential for effectively managing cognitive complaints in people with MS.

In **chapter 5.1**, we applied symptom network analysis to examine how objective cognitive domains (attention, inhibition, IPS, verbal fluency, verbal memory, and visuospatial memory) relate to PROMs for anxiety, fatigue, and cognitive complaints. Symptom networks quantify the co-occurrence and unique relationships between symptoms, offering insights into multidimensional symptom interrelatedness.[117] In our networks, nodes represented cognitive domains or PROMs, while edges denoted partial correlations controlling for other variables.[118] This approach allowed us to investigate how symptom interactions differ depending on cognitive status and the presence of cognitive complaints. We hypothesized the presence of a subjective-objective discrepancy in the symptom network, which would differ between individuals with and without impaired IPS, as well as between those with low versus high cognitive complaints. To test this hypothesis, we compared symptom networks based on global strength, defined as the sum of edges within the network, which reflects the overall interrelatedness of nodes.[118] A higher global strength indicates stronger overall interrelations among symptoms.

Our analysis revealed distinct modules for objective cognitive domains and PROMs, with weak connections between them, confirming the subjective-objective discrepancy reported in previous studies.[119-121] Despite this separation, unique associations between cognitive domains and PROMs emerged, indicating an interconnected symptom network rather than isolated clusters. Individuals with impaired IPS exhibited lower global network strength, suggesting reduced symptom interrelatedness compared to those with preserved IPS. However, no such difference was observed between individuals with low versus high cognitive complaints. These findings suggest a nonlinear relationship between cognitive and psychological symptoms that varies by cognitive status. This is particularly intriguing, as one might typically expect higher levels of depression, anxiety, and fatigue to align with more pronounced cognitive deficits.[1]

Subjective-objective discrepancy: In our symptom network analysis, we found that psychological and cognitive symptoms formed separate modules, with weak connections between them. However, patient-reported outcomes still showed unique associations with objective cognitive measures, reinforcing the value of a multidimensional approach in assessing cognitive function.

Nonlinearity of cognition: Individuals with impaired IPS showed lower symptom interrelatedness compared to those with preserved IPS. This suggests a nonlinear relationship between psychological and cognitive symptoms, depending on cognitive status, and highlights the complexity of managing cognitive impairment in MS.

Importantly, symptom networks do not measure the frequency or severity of symptoms but rather their patterns and co-occurrence, offering a different perspective.[117] While individuals with impaired IPS in our study scored worse on clinical variables and PROMs, the co-occurrence of their symptoms differed from those with preserved IPS. Cognitive and psychological symptoms appeared more widespread in people with reduced IPS, potentially reflecting reduced accuracy in self-assessing their cognitive functioning due to broader deficits.[122, 123] These findings highlight the need for multidimensional approaches, such as symptom network analysis, to monitor emerging symptoms and disentangle the role of comorbidities in understanding cognitive impairment.

Taken together, these findings not only highlight the value of symptom network analysis for understanding cognitive functioning in MS but also raise important considerations for interpreting earlier chapters in this thesis. While most analyses

in this thesis relied on objectively defined cognitive impairment, we acknowledge that subjective and objective cognitive measures often diverge. This discrepancy may influence how associations between biomarkers, cognitive profiles, and daily functioning should be interpreted. For example, associations with objectively defined impairment might not fully capture the cognitive difficulties experienced by patients in daily life, particularly in those with comorbid psychological symptoms. Conversely, some findings may reflect a broader mix of cognitive and psychological symptoms, rather than isolated cognitive decline. These insights underscore the importance of integrating both subjective and objective perspectives when developing clinical tools and interpreting research findings. Relying solely on self-reported measures can be problematic, as they often show weak correlations with objective assessments and may obscure the nuanced interrelationships between symptoms.[124, 125] Integrating both perspectives may enhance the ecological validity of assessments and improve the alignment between research outcomes and real-world functioning.

Future studies should investigate how the subjective-objective discrepancy evolves over time and whether complaints align more closely with objective measures as MS cognitive functioning declines. Examining how this discrepancy emerges in intervention studies could provide valuable insights into optimizing treatment outcomes. Prospective, longitudinal studies are needed to explore the potential of monitoring symptom networks to help identify patterns of cognitive and psychological symptoms.[126] These findings align with existing literature highlighting the complex interplay between subjective experiences and objective measures of cognitive decline in MS,[119-121] underscoring the importance of integrating multidimensional approaches. Understanding these dynamics could refine cognitive rehabilitation strategies and provide a foundation for more person-centered and effective interventions.

An illustration: using symptom network analysis to understand intervention effects

This section introduces a translation of how the subjective-objective cognitive discrepancy manifests in a clinical trial, highlighting the potential of multidimensional approaches for understanding intervention effects. The following study, drawn from secondary outcomes of the REMIND-MS trial, serves as an illustrative example and is not included in this thesis.[127] In the REMIND-MS trial, the effects of mindfulness-based cognitive therapy (MBCT) and compensatory cognitive rehabilitation therapy (CRT) were evaluated in people with MS (MBCT: n = 36, CRT: n = 37, enhanced treatment-as-usual: n = 37).[128] Previous results demonstrated positive effects of both interventions on objective cognitive function and cognitive complaints.[129] While both groups initially reported improvements in cognitive complaints, these benefits did

not persist beyond six months. Over the same period, MBCT improved IPS, whereas CRT was more effective in achieving personalized cognitive goals.

Given the complex symptom interrelationships discussed in **chapter 5.1**, we sought to understand how MBCT and CRT influenced objective cognitive outcomes and self-reported measures, including psychological symptoms, quality of life, well-being, and daily life functioning. MBCT, in particular, has demonstrated efficacy in reducing depression,[130] fatigue,[131] and improving mental quality of life.[132, 133] However, it remained unclear whether its cognitive effects were mediated by psychological improvements or occurred independently. Post-intervention, we found that MBCT significantly reduced fatigue, depressive symptoms, and brooding (a repetitive focus on negative thoughts), while also improving mental quality of life. Similarly, CRT reduced depressive symptoms and enhanced mental quality of life in the short term, indicating benefits beyond cognitive outcomes. Importantly, improvements in psychological symptoms and mindfulness skills mediated reductions in cognitive complaints but did not influence IPS, suggesting that IPS improvements from CRT were independent of psychological changes.

Symptom network analysis, as described in **chapter 5.1**, could provide a framework for interpreting these findings, although no symptom network was directly constructed from this study's data. If these findings were examined within a symptom network, based on the approach outlined in **chapter 5.1**, we would expect to observe reduced interrelatedness among symptoms in individuals with impaired IPS, reflecting distinct pathways of improvement. This reduced interrelatedness might explain why improvements in psychological well-being mediated reductions in cognitive complaints but did not directly enhance objective cognitive performance. It suggests that psychological and cognitive improvements operate through distinct mechanisms. For instance, while improved psychological well-being may reduce cognitive complaints by alleviating mood-related biases, objective cognitive improvements like enhanced IPS are likely supported by targeted interventions addressing specific cognitive processes, such as those facilitated by MBCT in this trial. These findings underscore the potential of symptom network analysis in disentangling the pathways through which interventions influence psychological and cognitive outcomes. Longitudinal studies are essential to validate these results and elucidate the distinct mechanisms underlying psychological and cognitive improvements.[125]

CONCLUSIONS AND FUTURE PERSPECTIVES

Concluding remarks

This thesis provides a comprehensive investigation into cognitive impairment in MS, encompassing biomarker-based detection, exploration of underlying mechanisms, and assessment of daily life impacts. Cognitive impairment affects up to 65% of people with MS and significantly influences quality of life, even in the absence of other neurological symptoms. Our findings underscore the complexity and the heterogeneity of cognitive impairment, emphasizing the need for multidimensional approaches that integrate biomarkers, imaging, psychological factors, and real-world functional measures. Our key findings are depicted in Figure 3.

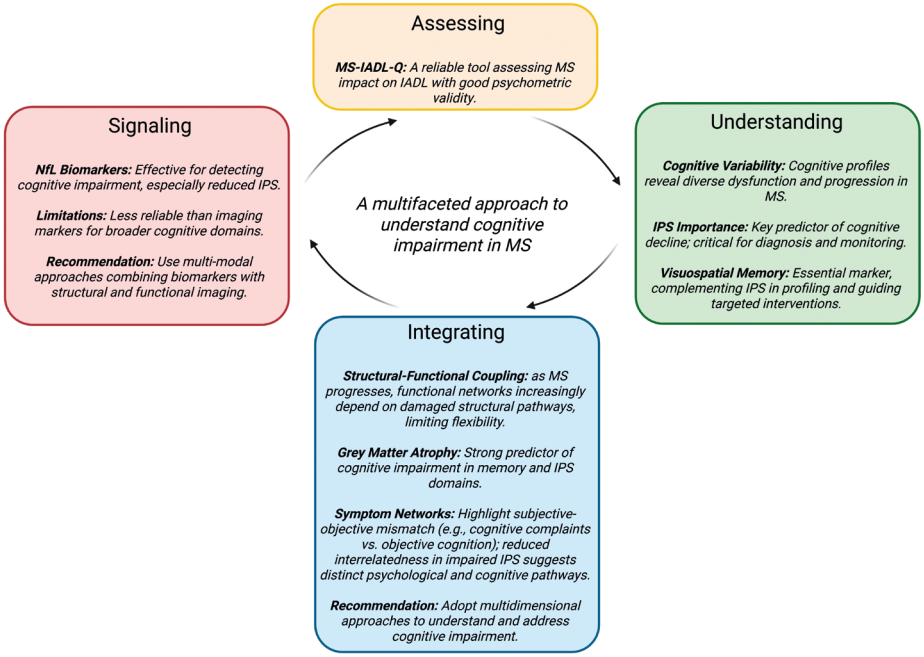

Figure 3. An overview of the key findings of current thesis, following the thematic organization, progressing from signaling to integrating information on cognitive impairment in MS.

Future perspectives

The **methodological considerations** in this thesis highlight important challenges and opportunities for advancing the understanding of cognitive impairment in MS. First, the variability in cognitive domains and profiles assessed across studies highlights the challenge of developing definitions and measures that are both standardized and flexible enough to capture the heterogeneity of cognitive impairment in MS. Standardization is critical not only for ensuring comparability across studies but also for improving the clinical diagnosis of cognitive impairment,

as the absence of unified MS-specific criteria currently complicates identification and treatment decisions. While consistency in assessment tools is essential, the diverse presentations of cognitive impairment in MS necessitate measures that account for individual differences and context-specific factors. Small sample sizes, particularly in the context of studying isolated impairments and fluid biomarker, limited statistical power and the ability to explore regional neuroanatomical correlates. Addressing these limitations will require expanded collaborations, including international data-sharing initiatives and meta-analysis of individual participant data.[134] The multimodal integration of fluid biomarkers, structural imaging, and functional network analyses has proven valuable but requires further refinement. For example, while NfL holds promise as a marker of neuro-axonal damage, its sensitivity to inflammatory processes complicates its applicability in progressive MS. Similarly, the complex interplay between grey matter atrophy, cortical lesions, and functional adaptations demands further exploration. Efforts to enhance ecological validity through tools like the MS-IADL-Q are promising, as they bridge the gap between clinical assessments and real-world functioning. However, additional research is needed to validate such tools against objective performance measures and across diverse populations to ensure broader applicability.

To overcome these limitations, we propose specific **action points**:

- **Conduct longitudinal studies:** Prospective studies are essential for tracking the evolution of cognitive impairment, subjective-objective discrepancies, and functional outcomes over time. These studies should span multiple time intervals, such as short-term follow-ups (6-12 months) to capture immediate changes and long-term observations (5-10 years or more) to identify early markers, track progression, and refine interventions.
- **Stratify individuals by cognitive risk profiles:** Future research should focus on stratifying individuals based on cognitive risk profiles, leveraging latent profile analysis, and integrating neuroimaging and biomarker data to predict cognitive trajectories.
- **Adopt emerging methodologies:** Techniques such as multilayer analysis, graph frequency analysis and growth mixture modeling, provide innovative ways to understand complex interactions between structural damage, functional adaptations, and cognitive outcomes.
- **Expand symptom network analysis:** Symptom network analysis has potential in clarifying the mechanisms through which interventions affect psychological and cognitive outcomes. Longitudinal and intervention studies using these approaches could provide actionable insights for tailoring rehabilitation strategies.
- **Leverage digital tools for cognitive assessment:** Digital tools, including the MS-IADL-Q, offer efficient and scalable solutions for cognitive assessment. These tools should be validated for sensitivity to change, cross-cultural applicability, and their ability to capture multidimensional impacts.

- **Utilize Ecological Momentary Assessment (EMA):** EMA combines frequent, real-time data collection with advanced methodologies, such as digital tools, to maximize ecological validity.[135] For instance, participants can report symptoms or complete brief cognitive tests multiple times a day, capturing experiences in everyday contexts, while also allowing individual symptom networks to be constructed.

Adopting multifaceted approaches necessitates **conceptual integration**. While the **International Classification of Functioning, Disability, and Health (ICF) framework** is widely used in rehabilitation settings, we propose expanding its application to provide a more comprehensive framework for understanding cognitive impairment in MS.[136] The ICF integrates medical, cognitive, psychological, social, and environmental factors, offering a holistic perspective on how these domains influence overall functioning.[137] Unlike symptom-focused models, it considers the impact of a health condition, like MS, on daily activities, social participation, and well-being. An illustration of the application of the ICF to MS can be found in Figure 4.

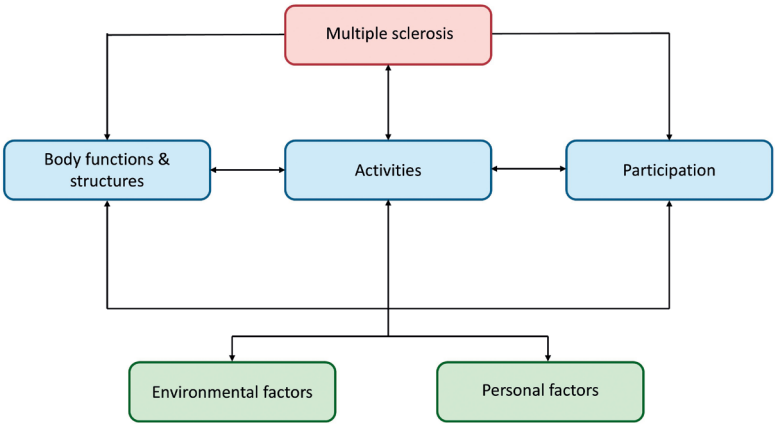

Figure 4. A depiction of the International Classification of Functioning, Disability, and Health (ICF) framework for MS, adapted from Coenen and colleagues.[138]

The ICF provides a standardized classification system to describe and evaluate functioning across different domains while mapping contextual factors, such as environmental and personal influences, that impact overall health. By linking specific outcomes (e.g., cognitive deficits or fluid biomarkers) to broader health dimensions like emotional well-being, quality of life, and societal participation, the ICF offers a structured framework for assessing and addressing the multifaceted nature of cognitive impairment in MS.

By categorizing functioning into interconnected domains (e.g., body functions and structures, activities, and participation) and integrating biomedical, psychological, and social factors, the ICF offers a comprehensive framework for linking clinical,

cognitive, and psychosocial measures to real-world impacts. For instance, it can help explain how reduced IPS leads to challenges in employment or social engagement, ultimately affecting emotional health and overall quality of life. Additionally, the ICF emphasizes the influence of contextual factors, such as family support or personal coping strategies, on broader health outcomes, identifying areas where targeted interventions can improve functioning and well-being. By integrating diverse data sources (e.g., clinical assessments, neuroimaging, and psychological evaluations), the ICF provides a cohesive model to understand how cognitive deficits relate to fluid biomarkers and self-reported outcomes. Moreover, it can help clarify why individuals with similar clinical findings may experience different functional outcomes, as variations in activities, participation, and contextual factors shape how impairments translate into daily life challenges. Mapping these interrelated factors supports personalized intervention strategies, illustrating how addressing depression or enhancing social support can improve cognitive and overall health outcomes. Finally, its standardization, approved and recommended by the WHO,[139] facilitates interdisciplinary collaboration and international research, making it a versatile tool for advancing MS care and research.[140]

Understanding how factors of functioning within the ICF framework interact **early** in the disease course is crucial for predicting long-term outcomes. Ideally, these interactions should be studied from the moment of diagnosis. An illustrative example is the "**Temprano**" study initiated at the Amsterdam UMC, which investigates early brain changes in recently diagnosed relapsing-remitting MS patients. This study embodies the multidimensional approach discussed earlier, integrating biomarkers, imaging, psychological factors, and assessment of daily life functioning. By identifying early changes, the study aims to inform strategies to delay or prevent the negative impacts of MS while advancing our understanding of cognitive impairment through the comprehensive integration of diverse data sources, as proposed in this thesis. Specifically, participants diagnosed with relapsing-remitting MS within the past 6-12 months and healthy controls, undergo three assessments over two years (see Figure 5). These assessments include MRI scans, cognitive testing, blood sampling, PROMs, and, for people with MS, neurological exams to evaluate their cognitive and physical functioning. By examining early disease mechanisms, the Temprano study aims to generate insights that not only improve long-term outcomes for people with MS but also support the development of more targeted interventions.

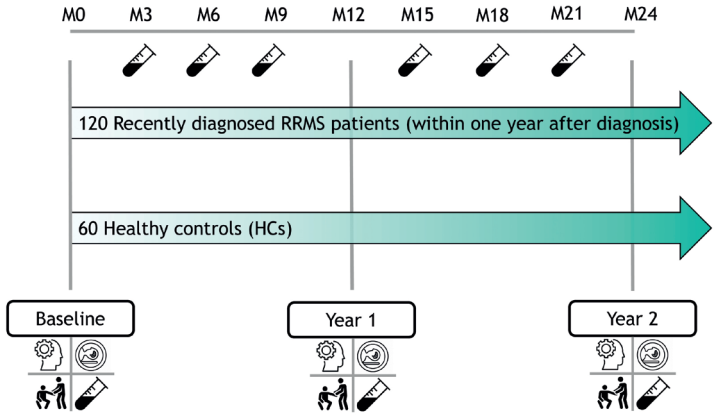

Figure 5. Overview of the study design of the "Temprano" cohort.

Finally, a promising future avenue emerging from this thesis could involve targeted interventions aimed at disrupting dysfunctional network dynamics, thereby illuminating the mechanisms underlying cognitive impairment in MS. One such approach is **transcranial magnetic stimulation** (TMS), a non-invasive technique that uses magnetic fields to stimulate specific brain regions. By targeting areas critical to cognitive processes, TMS has the potential to recalibrate neural circuits, promote neuroplasticity, and enhance cognitive function. Although research on repetitive TMS (rTMS) in MS is still in its early stages, preliminary findings show potential benefits, including reductions in spasticity and fatigue.[141] Notably, one study demonstrated improved working memory performance after high-frequency rTMS targeting the right dorsolateral prefrontal cortex, effectively restoring brain activity to normal levels.[142] These findings point towards the potential of rTMS as a tool for cognitive rehabilitation and warrant further exploration in this population.

Key recommendations for cognition in MS based in this thesis

For researchers:

1. **Standardize cognitive measures:** Adopt uniform definitions and cognitive tests across studies to improve comparability and reliability of findings related to cognitive impairment in MS.
2. **Embrace multimodal approaches:** Combine fluid biomarkers (e.g., NfL and GFAP), imaging markers, and network analyses to better understand the complex mechanisms of cognitive decline. Prioritize longitudinal studies to investigate directionality and progression over time.
3. **Focus on IPS:** Given its role as an early indicator of broader cognitive decline, IPS should be a core component of diagnostic tools, intervention studies, and digital cognitive assessments.

4. **Innovate with advanced methodologies:** Apply graph frequency analysis, latent profile analysis, and symptom network modeling to capture the dynamic interplay between structural damage, functional network disruption, and cognitive outcomes.
5. **Advance data sharing:** Collaborate internationally to increase sample sizes, improve the generalizability of cognitive profiles, and enhance the validity of predictive models.

For neuropsychologists:

1. **Enhance early screening:** Use a combination of biomarkers, imaging, and tests like the Symbol Digit Modalities Test (SDMT) to identify subtle cognitive impairments early, even in the absence of physical symptoms.
2. **Include memory tests:** When the aim extends beyond screening or monitoring cognitive impairment, incorporate cognitive tests for verbal and visuospatial memory.
3. **Incorporate daily life functioning:** Integrate tools like the MS-IADL-Q to assess the impact of cognitive impairments on daily activities.
4. **Monitor subjective-objective discrepancies:** Recognize the divergence between cognitive complaints and objective test results.
5. **Collaborate across disciplines:** Facilitate interdisciplinary approaches combining neuropsychology, neurology, rehabilitation, and psychiatry to address comorbidities like depression and fatigue that influence cognitive outcomes.

For people with MS:

1. **Understand early warning signs:** Be proactive in reporting cognitive changes, such as reduced processing speed or memory difficulties, to healthcare providers to enable early diagnosis and intervention.
2. **Utilize comprehensive assessments:** If possible, ask for evaluations that include traditional neuropsychological tests and tools like the MS-IADL-Q to better understand how cognitive changes affect daily life.
3. **Ask your health care provider for cognitive rehabilitation programs:** Participate in cognitive rehabilitation programs (e.g., MBCT or CRT) if cognitive complaints impact daily functioning and quality of life.
4. **Embrace technology:** Use digital tools and mobile apps for ongoing cognitive assessments and training to receive valuable feedback between clinical visits.
5. **Participate in research:** Consider contributing to research studies to help advance understanding and treatment of cognitive impairment in MS.

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