Working memory in the presence of distraction in people with Multiple Sclerosis: underlying neural mechanisms of a novel paradigm

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Recent neuroimaging research identified different pathways of how distraction is processed in WM, showing involvement of the lateral prefrontal cortex and striatum (15,21,22). It has been described that if a combined demand of WM and distraction is...

Ethical review	Approved WMO
Status	Pending
Health condition type	Central nervous system infections and inflammations
Study type	Observational non invasive

Summary

ID

NL-OMON53232

Source
ToetsingOnline

Brief title
Working Memory and Distraction in People with MS

Condition

- Central nervous system infections and inflammations

Synonym
'MS', 'Multiple Sclerosis'

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Distraction, fMRI, Multiple Sclerosis, Working memory

Outcome measures

Primary outcome

The main endpoint measure of the study is the regional task-based Blood Oxygen Level Dependent (BOLD) response measured by fMRI during a visual and verbal WM task paradigm with delayed distraction and distraction at encoding compared to the control condition without distraction (14).

Secondary outcome

The secondary endpoints measure target the behavioural and neural differences between PwMS and healthy controls in the visual and verbal WM task paradigm with delayed distraction and distraction at encoding.

• Differences in regional task-based BOLD response changes measured by fMRI during a visual and verbal WM task paradigm with delayed distraction and distraction at encoding between PwMS and healthy controls

• Differences in task performance of visual and verbal WM with delayed distraction and distraction at encoding between PwMS and healthy controls

• Differences in resting state brain activity between PwMS and healthy controls

Other study parameters include:

• Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS(27)) in order to assess cognitive functioning in PwMS

• Forward and backward digit span (WAIS-IV (28)) to assess phonological WM

performance in all participants

• Corsi Block Tapping Test (29,30) to assess visuospatial WM performance in all participants

• Sensory Processing Sensitivity Questionnaire (38) to assess sensory processing sensitivity in all participants

Study description

Background summary

Working memory (WM), a brain system that temporarily stores, maintains and manipulates information (1), plays a crucial role in the age-related decline of cognitive functions (2) and can be impaired as the result of various clinical conditions, including Multiple Sclerosis (MS) (3). In MS, a neurodegenerative and inflammatory disease of the central nervous system, cognitive impairment including WM is among the most prevalent symptoms reported by patients within the first year of the disease (4,5). Due to its central role in higher order cognitive functions such as planning, reasoning or learning, WM impairments can lead to serious problems in daily life. Hence, major effort is devoted in developing WM interventions to improve cognitive functioning in the general population and rehabilitate patients with impaired WM (6-8).
As patient-specific rehabilitation typically focuses on the rehabilitation of motor and occupational skills, cognitive problems receive less attention during multidisciplinary inpatient rehabilitation (9). This observation indicates a limited availability and dissemination problem of cognitive rehabilitation in the clinical context, especially when considering the extensive research on cognitive training that has been performed in healthy people. Indeed, WM interventions have shown small to medium effects for improving related tasks, but increases in WM capacity or transfer to other cognitive functions have been reported inconsistently in healthy older adults and people with MS (PwMS) (10-12). This inconsistency may be explained through task-related processes of WM training that may influence the performance on outcome tasks (13). Thus, we studied WM capacity improvements after an in-house developed, digital model-based WM training with distractors by comparing it to the same training without distractors, a dual-n-back and a control training in a randomized clinical trial on 120 healthy older adults. The results showed improved WM capacity after WM and distractor training only, suggesting that distraction filtering might be sensitive to WM capacity improvements when trained with WM in older adults (14) and thus to be a promising approach in increasing WM capacity not only in older adults but also in patients with WM

impairment such as pwMS.
Recent findings suggest the importance of WM to be resilient to distraction of irrelevant information when understanding WM functioning in the real world (15). Distractors in WM tasks can either be presented together with to-be-remembered items (encoding distraction) or while they are held in mind (delay distraction) (16), leading to a distorted task-response which limits WM capacity or degrades memory completely (15) and results in forgetting (2). It has been described that older adults and people with impaired WM performance have difficulties to suppress distractors during WM tasks (16-18). In PwMS, impaired recall has been described compared to healthy controls if distractors are presented during encoding and retention of a WM task (19). However, it has been hypothesized that auditory distractors in spatial WM tasks may serve as cues for shifting attention to target items as it led to improved performance in PwMS compared to healthy controls (20). Thus, distractor resilience has not only been discussed as a critical source of individual differences in WM capacity (16,17) but as a proxy for memory-related deficits (2,19).
Recent functional Magnetic Resonance Imaging (fMRI) findings support the presence of different pathways coping with distraction during WM tasks in healthy people. Whereas an active top-down inhibition through the lateral prefrontal gyrus has been shown to inhibit sensory processing of distractors, the striatum has been suggested to act as a gate, that blocks distractors from being encoded into WM (15). Increased cortical activity has been observed when distractors were present during encoding and delay, but not when participants were asked to suppress distractors during encoding. These findings have been linked to performance, where people with higher ability to suppress delayed distractors show greater suppression of distractors during encoding (21). When comparing younger and older adults on a WM and distraction task in their corresponding brain activity, differences were only detected behaviorally with older adults showing difficulties in task performance, but not in brain activation. Results suggest that both young and old adults reach a neural capacity limit, suggesting a shared use of neural resources with increasing distractor and WM load (22).
In summary, the investigation of WM in the presence of distraction has gained in interest in the past years. Behavioral work suggests resilience to distraction in WM as a crucial proxy for individual WM capacity differences among cognitively healthy (16,17) as well as impaired people (2,18,20) and that WM in presence of distraction is sensitive to improve WM capacity after training (14). Although neural mechanisms involved in the suppression of distractors have been described, the link between behavioral and neural correlates for a comprehensive understanding of real-world WM functioning is still unclear (15). In addition, the underlying neural differences of WM and distraction between cognitively healthy and PwMS have not been investigated (19,20).

Study objective

Recent neuroimaging research identified different pathways of how distraction

is processed in WM, showing involvement of the lateral prefrontal cortex and striatum (15,21,22). It has been described that if a combined demand of WM and distraction is present, the brain might reach a neural capacity limit, indicating no additional available resources to respond to the increase in cognitive demand(22). However, behavioural work suggests resilience to distraction in WM as a crucial proxy for individual WM capacity differences among cognitively healthy (16,17) and impaired people (18,20). Thus, the proposed study aims at studying regional brain activity in PwMS and healthy controls on two WM tasks including distractors as well as the differences in behavioural task performance and brain activation between both groups.

Primary Objective:
I. To examine regional brain activity measured by fMRI during a visual and verbal WM task with delayed distraction and distraction at encoding compared to a control condition without distraction in PwMS and healthy controls.

Secondary Objectives:
I. To examine differences in regional brain activity between PwMS and healthy controls on a visual and verbal WM task with delayed distraction and distraction at encoding
II. To examine differences in behavioural task performance on two WM tasks including distraction between PwMS and healthy controls
III. To examine differences in resting state brain activity measured by fMRI between PwMS and healthy controls

Study design

This study follows a cross-sectional design with one single assessment including a cognitive assessment and MRI session that will be performed at the Leiden Institute of Brain and Cognition (LIBC) at the Leiden University Medical Center (LUMC) in Leiden. In total 68 participants will be included in the study. The sample will consist of 34 PwMS recruited from the Dutch MS Society and social media (e.g. Facebook groups) and 34 age and sex matched healthy adults recruited from public notice boards, in order to study if brain activation during the WM and distraction paradigm is related to the clinical condition or not. Each participant, patient and control, will undergo a single appointment of the duration of approximately 120 minutes, including a cognitive assessment (approximately 30 minutes), an structural and functional brain MRI (approximately 45 minutes) and an online questionnaire which can be filled out after the study session at home (approximately 15 minutes).

Study burden and risks

The risk of the proposed cognitive assessments as well as the task performed during the MRI scan is negligible, as the task difficulties are adjusted to the patient population. Brain imaging using MRI is a non-invasive and safe

procedure, where thorough screening for compatibility is done. To exclude any risks, all participants will be screened for contraindications including metal parts, pregnancy and claustrophobia before undergoing the MRI scan. The confined space inside the MRI device for the duration of 45 minutes of the scan as well as the time investment of the participant for travel to the study location and participation involves some burden for the participants. Therefore, all participants are asked to undergo the cognitive and MRI assessment once with a maximal duration of 90 minutes for the whole study participation to ensure a minimal burden for patients.

In daily life we are constantly confronted with co-occurring inputs from visual or verbal sources that demand the ability to select relevant information. Impaired ability to filter distracting information may limit the WM capacity and thus hamper the independent conquering of daily life tasks. Studying if WM and distraction may differentiate between cognitively healthy and impaired people and identifying neural mechanisms at play will be beneficial in the sense that it will lead to novel insights on how WM is impaired. Furthermore, the current study will follow the current notion that including distractors in neuropsychological tasks may detect real-world deficits and thus offer a strategy to prevent cognitive impairment (53). To that end, the proposed study displays the first step in understanding if WM in presence of distraction can act as a target to improve WM functioning in PwMS. In summary, the insights of the proposed research would pave the way for understanding WM and developing accessible rehabilitation strategies that can ameliorate WM impairments and thus benefit patients in increasing their quality of life.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

For PwMS:
• Confirmed relapse onset MS diagnosis according to the McDonald 2017 criteria
• Expanded Disability Status Scale (EDSS) score < 7
• relapse free period >= 3 months
• unchanged therapy for >= 2 months at time of inclusion.
• Age 18-65 years
• Language: Dutch
• Pregnancy
• Inability to use the right hand

For healthy controls:
• Age 18-65 years
• Language: Dutch
• Pregnancy
• Inability to use the right hand

Exclusion criteria

see inclusion criteria D4a.

Study design

Design

Study type: Observational non invasive

Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-06-2023
Enrollment:	68
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	12-07-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	29-01-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL83936.058.23