

Cued motor imagery in patients with multiple sclerosis

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Abstract: Motor imagery (MI) is a promising practice tool in neurorehabilitation. In patients with MS, however, impairments in MI accuracy and temporal organisation were found during clinical assessment, which may limit the benefits of MI practice. Therefore, we investigated whether the MI quality of MS patients could be optimised by means of external cueing. 14 patients with MS and 14 healthy controls physically executed and visually imagined a goal-directed upper limb task in the presence and absence of added visual and auditory cues. MI quality was assessed by means of eye-movement registration. As main results, it was found that MS patients had significant higher eye-movement times than controls during both execution and imagery, and overestimated the to-be-imagined movement amplitude when no external information was provided during imagery. External cues, however, decreased patients' MI duration and increased the spatial accuracy of their imagined movements. In sum, our results indicate that MS patients imagine movements in a better way when they are provided with external cues during MI. These findings are important for developing rehabilitation strategies based on MI in patients with MS.

Response to Reviewers: A detailed point by point response letter was added.

Leuven, Belgium, 27-12-2011

Dear Prof. Dr. Lisberger,

This letter concerns the manuscript “Cued motor imagery in patients with multiple sclerosis”, Ref. No. NSC-11-1549, which has now been revised. We thank the reviewers for their valuable comments. The reviewers’ suggestions were implemented in the manuscript, which is regarded as improved as compared to the original submission.

The specific changes that have been made are highlighted in the manuscript in blue and are listed following the order of the comments in the response letter. Thank you for your re-consideration and we look forward to hearing from you.

Yours sincerely,

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Response to the reviewers' comments and list of changes

Manuscript ID: NSC-11-1549

Title: "Cued motor imagery in patients with multiple sclerosis"

Authors: Elke Heremans, Alice Nieuwboer, Joke Spildooren, Sara De Bondt, Anne-Marie D'hooge, Werner Helsen, Peter Feys

Reviewer #1:

This study assesses whether motor imagery performance in MS patients could be improved by providing auditory or visual cues. Various parameters describing eye movements are used to quantify imagery performance in patients with MS and healthy controls. The paper is clearly written and informative. I think the manuscript can provide relevant incremental knowledge for an effective implementation of motor imagery as a neurorehabilitation tool. However, I have a couple of concerns that I think should be addressed before the paper is suitable for publication.

Major issues:

1) The figures suggest that there is little if any difference between the MS patients and the healthy controls. Only Figure 2 reports a group difference. In fact, the authors found a group X modality X cueing interaction, but that effect is remarkably absent from the figures. Without that effect clearly discussed, it is unclear what the paper has to say about between-groups differences in cueing sensitivity during motor imagery.

There was indeed a three way interaction effect between groups, modalities and cueing in the eye-movement time. However, despite this three way interaction, further analyses showed that, with regards to eye-movement time, the MS patients and controls reacted similarly to the external cues. We adapted Figure 1 as to show the data of this variable for both the MS patients and the controls during imagery and execution. During both physical execution (panel A of Figure 1) and motor imagery (panel B of Figure 1) the eye-movement times were significantly lower during the visual cueing condition than during the other conditions. With regards to eye-movement amplitude, there was a two-way interaction between cueing condition and group. This effect was shown in Figure 2. Since in the number of eye movements there were no group differences, no figure on the group data was provided on this third variable.

As requested by the reviewer, we adapted the discussion of the paper to discuss these similarities and differences between groups more clearly (2nd paragraph of the discussion, page 13).

2) It remains unclear which aspects of the imagery process might be captured by the various parameters describing ocular movements in this study. This information would be useful when these measures are introduced, i.e. at the end of the introduction.

This information was added to the end of the introduction (last paragraph of the introduction, page 4).

Minor issues:

3) page 9: 9HPT - please define

This is now written in full (“Nine Hole Peg Test”) on page 9. As well, we added a description of this test to the Methods section on page 5.

Reviewer #2:

This is a well performed study on motor imagery in patients with multiple sclerosis (MS). Quality of imagery was assessed by high-frequency registrations of eye movements. The authors found that MS patients had an improved performance when external cues were provided.

Major comment

1) An important question, however, was not addressed in this report. This is the question why the authors did not report if there was a relation of the eye and hand movements in the execution condition. As the authors did not report that they performed registration of the hand movements, they were probably not able to resolve this issue. But it would be relevant to learn in which way eye movements guided the hand movements.

This is indeed a very interesting issue. However, in this study, we specifically aimed to focus on the relationship between eye and hands during motor imagery. We indeed did not analyse the data of the hand movements. Instead, we focused on the eye-movement data since these data could be recorded during executed as well as imagined conditions, while the kinematics of the hand movements could only shed light on the execution condition.

The reason for setting up the study like this is that we believe that the relationship between eye and hand during motor imagery is a very new research domain, whereas its relationship during physical execution has already been investigated in healthy persons (e.g., Helsen et al., 2000) as well as in patients with MS in previous studies (e.g. Feys et al., 2005).

We agree with the reviewer that this work is of high relevance with regard to the present study. Therefore, we added this information to the discussion (first paragraph of the discussion, page 12-13). In this part, we provided the reader with more background information on eye-hand coordination during physical execution in healthy persons (where we refer to work by Helsen et al., 2000) and patients with MS (with reference to the work of Feys et al., 2005).

Minor comments

2) In the introduction the authors refer to other studies showing the effect of imagery on motor performance. The authors may wish to refer also to earlier work by Müller, Bütetfisch et al 2007 and Page, Levine et al. 2007).

We thank the reviewer for drawing our attention to these interesting studies. We added them to the introduction (page 3).

3) Table 1 will benefit from an additional line showing the groups statistics of the data of the 14 patients.

The group statistics were added at the bottom lines of Table1.

4) Figure 3 is said to show the number of movements. The authors should provide the time episode in which the movements were performed.

This figure represents the number of eye movements per trial, with every trial lasting 20 seconds. Since the participants were requested to (or in case of auditory cueing, paced to) make the movements at a rhythm of 0.5Hz, we believe this figure also indirectly contains information on the timing. We added the necessary information to interpret this figure (duration of the trials + movement rhythm) to the figure legend to clarify this. Furthermore, to provide the reader with detailed information on the eye-movement time in both groups during all conditions we added an altered version Figure 1.

*Highlights

- MS patients are significantly slower during motor imagery than controls.
- MS patients show a significant spatial overshoot during imagery of arm movements.
- External cueing improves motor imagery timing and accuracy in patients with MS.

Cued motor imagery in patients with multiple sclerosis

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Abstract

1 Motor imagery (MI) is a promising practice tool in neurorehabilitation. In patients with
2 MS, however, impairments in MI accuracy and temporal organisation were found
3 during clinical assessment, which may limit the benefits of MI practice. Therefore, we
4 investigated whether the MI quality of MS patients could be optimised by means of
5 external cueing. 14 patients with MS and 14 healthy controls physically executed and
6 visually imagined a goal-directed upper limb task in the presence and absence of added
7 visual and auditory cues. MI quality was assessed by means of eye-movement
8 registration. As main results, it was found that MS patients had significant higher eye-
9 movement times than controls during both execution and imagery, and overestimated
10 the to-be-imagined movement amplitude when no external information was provided
11 during imagery. External cues, however, decreased patients' MI duration and increased
12 the spatial accuracy of their imagined movements. In sum, our results indicate that MS
13 patients imagine movements in a better way when they are provided with external cues
14 during MI. These findings are important for developing rehabilitation strategies based
15 on MI in patients with MS.
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41 **Key words:** multiple sclerosis, mental practice, motor imagery, rehabilitation, cueing
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3 Motor imagery (MI) can be defined as a dynamic state during which an individual
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5 mentally simulates a given action. It is widely used in sports training and has recently
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7 gained attention as a promising practice tool in the rehabilitation of patients with
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9 neurological pathologies (Zimmermann-Schlatter et al., 2008). Several subtypes have
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11 been described, among which visual motor imagery from a first person perspective is
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13 probably applied most frequently. This type of imagery requires visualizing yourself
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15 performing an action without any overt body movement. Although during MI the action
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17 is not performed physically, it has been shown that mere mental simulation still retains
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19 many properties of the corresponding real action (Gerardin et al., 2000; Heremans et al.,
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21 2008; Jeannerod, 1997; Papaxanthis et al., 2002). Therefore, in the past decade, it was
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23 proposed as an alternative method for neurological patients to practice motor actions.
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25 Mainly for stroke patients, MI practice has been shown to be a potentially useful
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27 addition to other types of training (Braun et al., 2006; Müller et al., 2007; Page et al.,
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29 2007; Zimmermann-Schlatter et al., 2008). Also in patients with Parkinson's disease,
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31 some first evidence was found (Tamir et al., 2007; Heremans et al., 2011). For patients
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33 with other neurological pathologies, such as patients with multiple sclerosis (MS),
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35 however, the potential of MI remains unexplored. Therefore, in a previous study
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37 (Heremans et al., submitted), we first investigated to which extent these patients are still
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39 able to correctly perform MI. We found that some MS patients were well able to use
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41 this technique, whereas others showed impairments in MI accuracy and temporal
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43 organisation. The decrease in MI accuracy significantly correlated with impairments in
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45 the cognitive domain, while incongruencies in MI timing were associated with MS-

1 related motor dysfunction. As patients with decreased MI ability will most likely benefit
2 less from an MI-based exercise program, the question emerges whether external factors,
3 such as external visual or auditory cues, can be manipulated as to optimize MS patients'
4 quality of MI. In line with Nieuwboer et al. (2007), we defined cueing as external
5 temporal or spatial stimuli to facilitate initiation and continuation of movement (in our
6 case, imagery of movement). Cueing has previously been used successfully to facilitate
7 MI in healthy persons (Heremans et al., 2009), stroke patients (Hovington et al., 2010)
8 and patients with Parkinson's disease (Heremans et al., 2012). It was found that the
9 provision of external cues significantly increased the accuracy and timing of imagined
10 motor actions. In the present study, we aimed to examine whether this also counts for
11 patients with MS. To investigate the specific influence of the disease, the MS patients
12 were compared with healthy controls. As well, the most and least affected body sides
13 were compared within the patient group. All participants performed motor imagery of a
14 goal-directed upper limb task in the presence or absence of added visual and auditory
15 cues. Since motor imagery is a covert process, it is difficult to evaluate it in an objective
16 manner. In previous studies, however, it was found that during imagery of goal-directed
17 actions eye movements can serve as an overt correlate of the imagined movements
18 (Heremans et al., 2008; 2009). It was found that, if motor imagery is performed
19 correctly, both the number and the amplitude of participants' eye movements adapt to
20 the task that has to be imagined. As well, these previous studies showed that the
21 amplitude and the movement time of participants' eye movements reflect, respectively,
22 the spatial and temporal characteristics of imagined goal-directed movements.
23 Therefore, in line with these previous studies, we evaluated the quality of participants'
24 imagery process by means of eye-movement registration.

2. EXPERIMENTAL PROCEDURES

2.1. Participants

14 hospitalised patients with MS (11 males; 51.9±12.3 years) were recruited by a neurologist of the National MS Center Melsbroek and were compared with 14 healthy controls (7 males; 62.2±6.4 years). Patients' disease severity was assessed by means of the Extended Disability Status Scale (EDSS). Their cognitive functioning was evaluated by means of the Mini-Mental State Examination (MMSE) and the Neuropsychological Screening Battery for Multiple Sclerosis (NSBMS). Upper limb motor functioning was assessed by means of the Nine Hole Peg Test (9HPT). During this test, the participants have to pick up nine small pegs from a shallow container, put them one by one and as fast as possible in nine empty holes in the other part of the test device and, finally, put them back in the container. The total time to complete the task with either hand is recorded. All participants were right-handed as measured by the Edinburgh Handedness Inventory Questionnaire. Participants were excluded in case of an MMSE score <24, neurological or psychiatric comorbidity, inadequate vision or hearing, severe orthopaedic problems of the upper limb or MS relapse or related corticosteroid therapy within eight weeks preceding study entry. Patients' characteristics are provided in Table 1.

The motor imagery ability of all participants was assessed by means of the short version of the Kinesthetic and Visual Motor Imagery Questionnaire (KVIQ-10) (Malouin et al., 2007), a hand rotation task (Sharma et al., 2006) and a mental chronometry paradigm applied to the Box and Block Test (BBT) (Heremans et al.,

2011). During the BBT, participants were asked to physically transport or imagine transporting 20 wooden blocks of 2.5 cm² from one side of a box to another. The duration of physical execution and imagery of the task was compared, with a close temporal relationship between both indicating correct MI (Guillot and Collet, 2005). The results of the MI ability tests are provided in Table 1. As well, a detailed analysis of the MI ability of a larger group of MS patients, including the patients who participated in the present study, was discussed in Heremans et al. (submitted). The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, and was approved by the Ethics Committees of the National MS Center Melsbroek and the Katholieke Universiteit Leuven. All participants gave written informed consent before taking part in the study.

2.2. Apparatus

Eye movements. In line with previous work (Heremans et al., 2008), the electro-oculographic signal of the participants' right eye was measured by means of a Porti 7 device (Twente Medical Systems International, Enschede, The Netherlands) at a sample frequency of 1024 Hz. After skin preparation, Ag-AgCl surface electrodes with a diameter of 5 mm (Twente Medical Systems International, Enschede, The Netherlands) were attached to the skin at the outer and inner canthus of the right eye and in the inferior and superior areas of the right orbit. A reference electrode was adhered to the contralateral pelvic bone. A chinrest was used to restrict head movements.

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Muscle activity. Electromyographic signals of the flexor and extensor carpi radialis muscles were monitored by means of the same Porti 7 device with a sampling frequency of 1024 Hz to control for the absence of muscular activity during the imagery trials. 24 mm diameter Ag-AgCl disposable disc surface electrodes (Kendall/Arbo, Tyco Healthcare, Neustadt/Donau, Germany) were placed 2 cm apart over the middle portion of the muscle bellies, aligned with the longitudinal axis of the muscles. Similar as for EOG recording, the electrode at the left pelvic bone was used as a reference electrode. If muscular activity was increased during MI, the trial was discarded.

Wrist kinematics. The angular position of the wrist was measured by means of a high precision shaft encoder (Agilent, Palo Alto, CA; accuracy 0.09°, sample frequency 200 Hz) which was attached to the axis of a wrist orthosis. This orthosis restricted participants' wrist movements to flexion and extension movements in a horizontal plane.

2.3. Task

Participants were seated approximately 50 cm in front of a computer screen with their tested arm positioned in a wrist orthosis, fixed to the table in front of them. At both sides of the computer screen, black squares with a diameter of 1 cm² were projected. The angular position of the wrist was represented on the screen by means of a 2 cm diameter round cursor. Participants were instructed to either physically execute (EXEC) or visually imagine (MI) cyclical flexion and extension movements of the wrist to move the cursor between the targets. During the control condition (REST) participants were instructed to relax, irrespective of the stimuli that were provided. The participants kept their eyes open during all conditions. Each condition lasted 30 s, of which the first 10 s were guided by auditory (a metronome pacing the movement at 0.5 Hz) and visual (presentation of the targets at the

1 screen) stimuli. These initial externally guided movements were not included in the data
2 analysis. The remaining 20 seconds of each trial were performed in the presence of auditory
3 or visual cues only, or in the absence of cues. During the trials with auditory cues (AUD),
4 the metronome pacing at a rhythm of 0.5 Hz was continued. During the trials with visual
5 cues (VIS), visual information was provided by showing the targets. In the trials without
6 cues (NO CUES), the task had to be completely internally generated. All modalities
7 (EXEC, MI, REST) were performed three times for each cueing type. They were performed
8 in blocks of three execution, three imagery and three rest trials, with 2 min of rest in
9 between blocks. The blocks were presented in random order. To allow a comparison of the
10 patients' most and least affected side, they performed all trials at both body sides. The trials
11 with VIS and NO CUES were always performed for an inter-target distance of 20 cm,
12 corresponding to a wrist movement angle of 20°. For the AUD trials only, the targets were
13 projected at two different inter-target distances to allow us to monitor whether participants'
14 eye-movement amplitudes during MI adapted to the task requirements. This was previously
15 shown to be a control parameter for accurate MI (Heremans et al., 2008). During these
16 trials, targets were projected at inter-target distances of either 12 cm (SMALL) or 20 cm
17 (LARGE), corresponding to wrist movement angles of 12 or 20°, respectively. The use of
18 two different inter-target distances was limited to the AUD trials only to limit the duration
19 of the experiment, and as such limit the strain on the patients.

2.4. Dependent variables

24 Only horizontal eye movements were taken into consideration, as the hand movements
25 were restricted to the horizontal plane. To reduce the noise, the signal of the horizontal eye

1 movements was preprocessed with a low-pass filter using a cut-off frequency of 20 Hz.
2 The drift was removed by piecewise second order polynomial fitting. Similar to previous
3 work by Heremans et al. (2008), a standard deviation for point of gaze smaller than 1° for
4 minimum 100 ms was taken as a criterion to define fixations. The data points just before
5 and after the fixations were taken as the start and end points of the eye movements. The
6 eye-movement time was defined as the time between the end point of the previous fixation
7 and start point of the next. Furthermore, we calculated the eye-movement amplitude,
8 corresponding with the distance travelled by the eyes between those two points, as well as
9 the number of eye movements per trial.
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21 **2.5. Statistical analyses**

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26 Variables showed normal distributions (Shapiro-Wilk test) and equivalent variance
27 (Levene's test). The eye-movement data were analysed using repeated measures ANOVA's
28 with alpha set at .05. First, a repeated measures ANOVA was performed with cueing
29 condition (VIS, AUD, NO CUES) and modality (EXEC, MI, REST) as within-subject
30 factors and with group (MS, controls) as between-subject factors. This analysis was
31 performed for the data of the most affected side only in the patient group, and the side-
32 matched data for controls. Second, we analysed the differences between the most and least
33 affected side in the patient group by means of a 2 side (most, least affected side) by 3
34 cueing condition (VIS, AUD, NO CUES) by 3 modality (EXEC, MI, REST) ANOVA. For
35 this analysis, the most and least affected side were defined based on the outcome of the
36 [Nine Hole Peg Test](#). Finally, we analysed the differences between the two amplitudes that
37 were used, and this selectively for the auditory cueing condition. This was done by means
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of a repeated measures ANOVA with amplitude (SMALL, LARGE) and modality (EXEC, MI, REST) as within-subject factors and group (MS, controls) as between-group factor. In case of significant interaction effects, we proceeded with analysis of the simple effects contributing to the interaction effect (Keppel, 1991). Post hoc Tukey honestly significant difference tests were done with $\alpha = .05$.

3. RESULTS

3.1. Eye-movement time

The repeated measures ANOVA between groups, modalities and cueing conditions revealed a three-way interaction effect ($F(4,104)=7.6$; $p<0.01$). Simple effect analyses showed that, both during imagery and execution, the MS patients had significant higher eye-movement durations than the controls across all cueing conditions (MS: $M=600\pm 282$; CON: $M=284\pm 151$) (Fig. 1). During execution and imagery, all participants had a significant lower movement time when the visual cues were presented (EXEC: $M=382\pm 212$; MI: $M=366\pm 265$) than during the condition with auditory cues (EXEC: $M=543\pm 179$; MI: $M=477\pm 211$) or without cues (EXEC: $M=473\pm 161$; MI: $M=520\pm 271$) (Fig. 1). No differences in eye-movement time were found between patients' most and least affected side.

3.2. Eye-movement amplitude

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A significant interaction effect was found between cueing condition and group ($F(2,52)=3.4$; $p=0.04$). The amplitude during the conditions in which no cues were provided differed significantly from the amplitude during the conditions in which visual and auditory cues were given. Whereas during the visual and auditory cueing condition the eye-movement amplitude nicely reflected the distance to-be-covered (MS: VIS: $M=204\pm96$; AUD: $M=198\pm83$; Controls: VIS: $M=190\pm39$; AUD: $M=198\pm91$), during the no cues condition the MS patients significantly overestimated the inter-target distance ($M=227\pm115$) and the controls significantly underestimated it ($M=172\pm36$) (Fig. 2). This indicates that the provision of cues assisted the participants in performing the tasks with high spatial accuracy. No differences in eye-movement amplitude were found between the patients' most and least affected side.

For the AUD trials only, the eye-movement amplitudes were analysed to examine whether they adapted to the task requirements during imagery in a similar way as during execution. For both conditions and both groups, a main effect for amplitude was found ($F(1,26)=25.0$; $p<0.01$). The eye-movement amplitude was always significantly larger for the large inter-target distance than for the small, and was always close to the distance that needed to be covered (LARGE: $M=198\pm28$; SMALL: $M=138\pm73$).

3.3. Number of eye movements

A main effect was found for modality ($F(2,52)=51.7$, $p<0.01$), indicating that the number of eye movements was significantly smaller during rest ($M=5.1\pm3.6$) than during imagery ($M=8.7\pm2.2$) and execution ($M=9.2\pm1.3$) (Fig. 3). No differences were found between execution and imagery. This highlights the difference between the task-related eye

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movements during MI and execution in contrast to the random behaviour during rest. The number of eye movements did not differ between groups (MS: $M=7.6\pm 2.6$; CON: $M=7.6\pm 2.1$) and cueing conditions (VIS: $M=8.0\pm 2.7$; AUD: $M=7.4\pm 2.3$; NO CUES: $M=7.8\pm 2.1$). Also, no differences were found between patients' most and least affected side (most: $M=7.7\pm 2.7$, least: $M=7.6\pm 2.3$) and between the large and small inter-target distances (LARGE: $M=7.7\pm 2.4$; SMALL: $M=7.4\pm 2.3$).

16 4. DISCUSSION

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Previous studies advocated that motor imagery may be a useful tool in the rehabilitation of patients with neurological pathologies. However, pathologies of the nervous system may affect patients' ability to perform motor imagery. In patients with MS, for example, it was shown that patients' cognitive and motor impairments hindered their ability to imagine movements with good accuracy and temporal organisation (Heremans et al., submitted). Therefore, in the present study, we investigated a method to facilitate MI in patients with MS by means of external visual and auditory cueing. Patients' imagined performance was investigated using eye-movement registration. This method is based on the close coupling between eye and hand movements which has been shown extensively in the past during physical execution, and also more recently during motor imagery. Previous work by Helsen et al. (2000) showed a very tight coupling, both spatially and temporally, between hand and eye movements during goal-directed aiming, suggesting a common underlying command structure. Feys et al. (2005) showed that this coupling was very much preserved in patients with MS. More recently, it was found that the coupling between eye and hand movements was still present when hand movements were merely imagined (Heremans et al., 2008;

2011; 2012), and that, as a consequence, eye-movements could be used to investigate MI accuracy and timing (Heremans et al., 2008; 2011; 2012).

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2 In general, we found that both in patients with MS and healthy controls eye movements
3 reflected the imagined tasks. This was indicated by an adaptation of the number and
4 amplitude of the eye movements to the task requirements, which was found in both groups.
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6 As such, these results confirmed findings of previous studies in healthy persons and patients
7 with Parkinson's disease (Heremans et al., 2008; 2012). The eye-movement data also
8 captured some interesting differences between the MS patients and controls. Both the
9 spatial and temporal eye-movement parameters differed between groups and reflected as
10 such the temporal and spatial problems that MS patients experienced during MI. In line
11 with what was found during clinical assessment (Heremans et al., submitted), the eye-
12 movement data showed that MS patients were significantly slower during MI than controls.
13 As well, the patients showed a significant spatial overshoot of the to-be-imagined
14 movements. Healthy controls, on the other hand, tended to underestimate the to-be-
15 imagined distance. This may illustrate that, in the absence of cues, healthy controls opt to
16 use a more energy-efficient eye-movement strategy, whereas the overshoot seen in the
17 patient group might reflect ataxic behaviour. But although the provision of cues seemed to
18 affect the spatial parameters of the patients' and controls' eye movements in a different
19 way, in both groups it significantly increased their spatial accuracy during MI. The
20 provision of visual cues also improved the imagery timing. This effect was present in both
21 groups, but was more pronounced in the MS patients showing a profound slowness during
22 MI than in the healthy controls. As such, for both groups, external cueing showed to be a
23 useful tool to improve MI performance and might potentially be useful to aid skill learning
24 by means of imagery training.
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The application of cueing has been widely studied over the past decades, mainly in healthy persons (Lee et al., 1995; Swinnen et al., 1997) and patients with Parkinson's disease (Nieuwboer et al., 2007; Nieuwboer, 2008; Rochester et al., 2010). Recent studies, however, indicated that external cueing may also be useful for patients with MS. Baram et al. (2006; 2007), for example, showed that visual and auditory cues improved MS patients' walking speed and stride length. As well, Baram et al. found short-term residual improvements in gait after the cues were removed, suggesting therapeutic potential of cueing.

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Only recently (Heremans et al., 2009; Heremans et al., 2012; Hovington et al., 2010), the potential of external cueing was also investigated with regard to imagery of movements. Heremans et al. (2009; 2012) reported that external visual and auditory cues improved the accuracy and timing of upper limb movements in healthy persons and patients with Parkinson's disease. In accordance, Hovington et al. (2010) showed that cueing increased corticomotor excitability during MI of finger movements, and this in healthy controls as well as in patients recovering from a stroke. In the study by Hovington et al., the way cues were provided differed from our own study. During the visually cued imagery condition, the participants watched a video of the corresponding hand performing the movement that needed to be imagined. During auditory cued MI participants had to concentrate on verbal instructions describing the action. In the present study, we only provided the visual targets representing the movement endpoints, and auditory cues were delivered using a metronome guiding the movement rhythm. This was done in accordance to previous studies, arguing that external information is most supportive when it informs the performer of crucial movement features, instead of providing detailed information on all subcomponents of the movement (Swinnen et al., 1993; Hammerton, 1989). These crucial movement features may

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serve as anchor points, which are used as organizing centers within and for the entire cycle production. Beek et al. (1989) showed that during physical execution, the movement cycle as a whole can be timed and stabilized by timing the movement to a particular point in the cycle. The same principle may explain the benefits of the external cues on imagined performance that were observed in the present study. The relative effectiveness of different cueing strategies to guide MI in various populations and for various tasks, however, needs further investigation.

Future research is also needed to delineate which patients will benefit from cued MI practice. Baram et al. (2007) showed that cueing led to higher gains in gait performance in patients with baseline performance below the median than patients above the median. This might indicate that cueing could be particularly useful for patients with decreased performance, having a higher need of compensatory strategies. With respect to MI, Heremans et al. (submitted) previously showed that mainly the MS patients with cognitive problems have impairments in MI accuracy. It can be speculated that cueing strategies might be particularly helpful for these patients to guide their MI, since cueing might free up cognitive resources which can be used to perform MI. On the other hand, it should also be taken into account that these patients may have limited cognitive capacity to integrate additional information during MI, and that cueing as such could lead to cognitive overload. In patients with PD, Rochester et al. (2009) already showed that the use of external cueing is feasible to improve physical execution of gait in patients with cognitive impairment. Rochester et al. hypothesized that cues did not excessively increased cognitive demand, but instead may act as an effective cognitive strategy to facilitate task prioritization or attentional control. Further research comparing patients with and without cognitive

impairments is needed to determine whether this is also the case during imagined performance.

In summary, the present study shows that external cues can improve the quality of MI in patients with MS to a similar degree as controls. Both in patients and healthy controls external cues positively affected the spatial accuracy of the imagined movements. As well, in MS patients visual cueing led to a decrease in imagery duration. This may be important with regard to the use of MI as a practice tool in the rehabilitation of patients with MS.

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Legends of figures and tables

1
2 **Figure 1.** Eye-movement time (mean \pm SEM) of the MS patients and controls during
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4 physical execution (panel A) and motor imagery (panel B) under the different cueing
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6 conditions.
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11 **Figure 2.** Eye-movement amplitude (mean \pm SEM) per group for the different cueing
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13 conditions. Statistical significance ($p < 0.05$) is indicated by *.
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19 **Figure 3.** Number of eye movements (mean \pm SEM) per modality per trial of 20
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21 seconds, performed at a movement rhythm of 0.5Hz. Statistical significance ($p < 0.05$) is
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23 indicated by *.
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26 27 28 **Table 1.**

29 Patients' characteristics
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Figure 1

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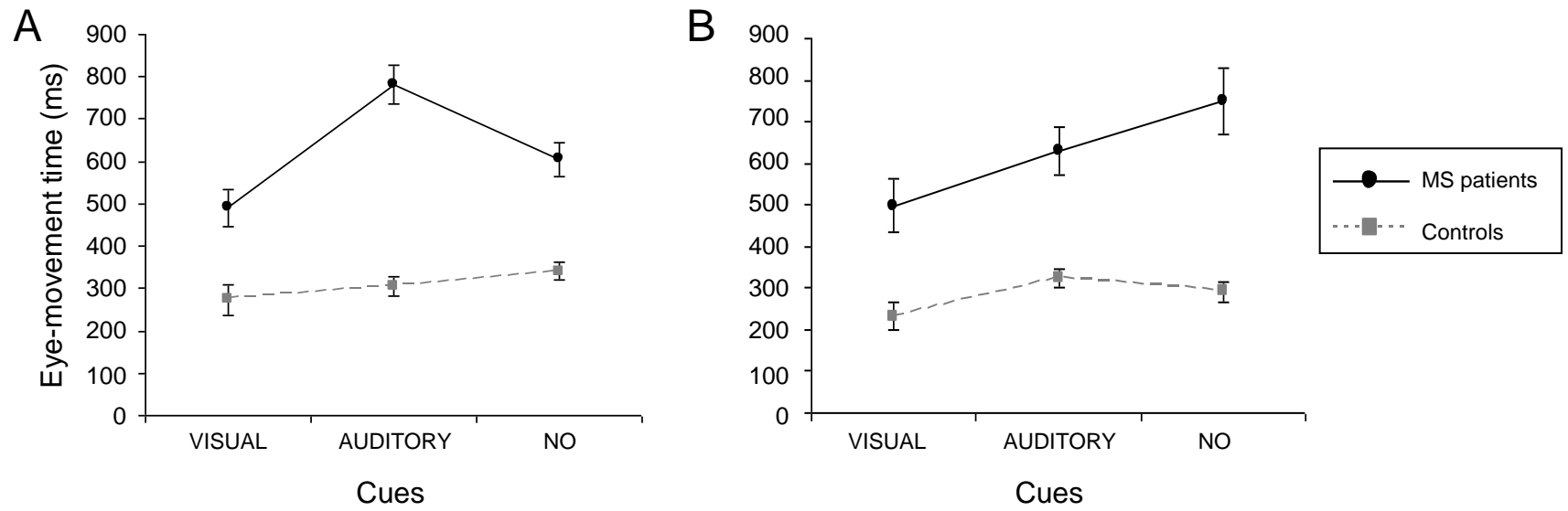


Figure 2
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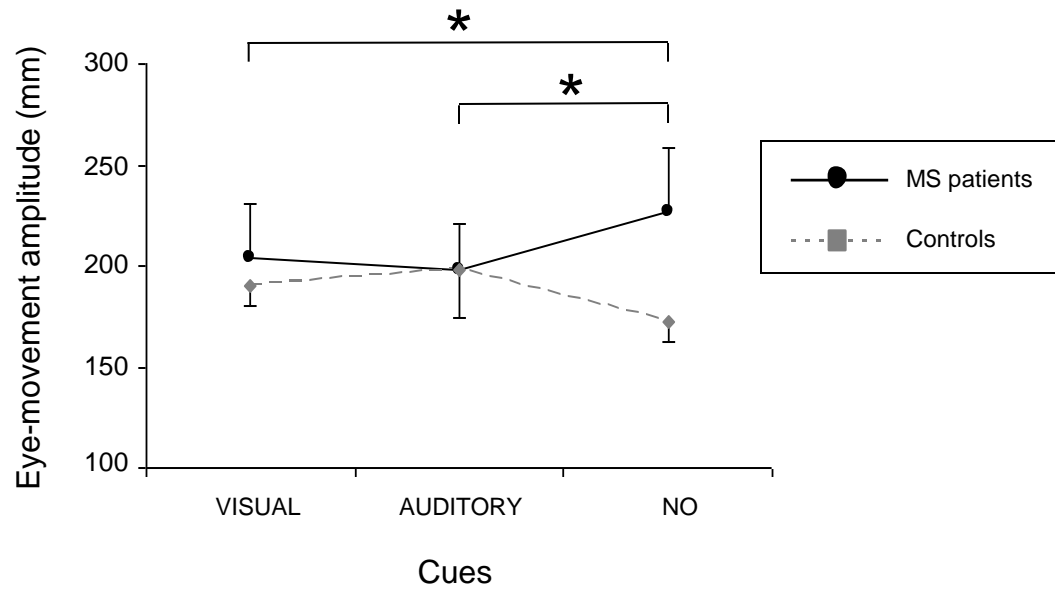


Figure 3
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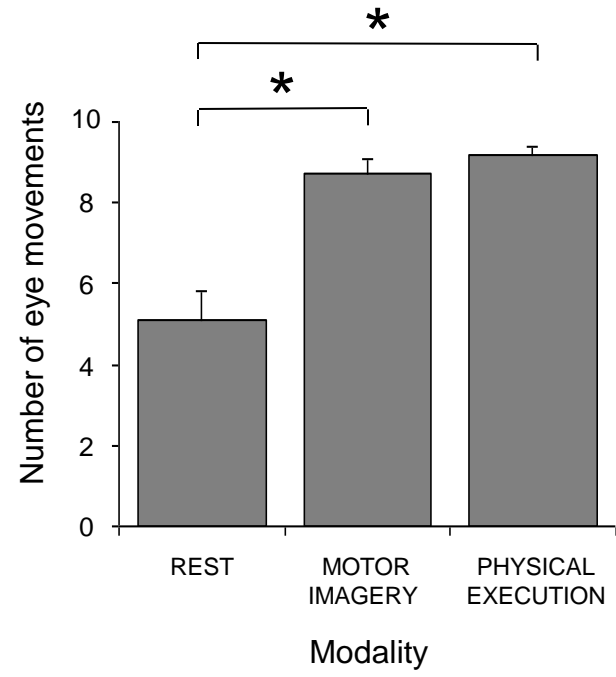


Table 1. Patients' characteristics

Patient number	Age (years)	Gender	Disease duration (years)	Type of MS	EDSS score (/10)	MMSE (/30)	NSBMS (/4)	9HPT right side (s)	9HPT left side (s)	KVIQ-10 (18-90) ^a	Hand rotation (/100) ^b	BBT EXEC right side (s)	BBT MI right side (s)	BBT EXEC left side (s)	BBT MI left side (s)
1	77	M	41	SP	7	25	1	26.5	23.9	27	77.1	20.7	30.0	23.0	26.0
2	56	M	11	PP	6.5	29	4	49.6	105.0	36	78.1	26.6	19.5	34.5	19.8
3	62	V	15	RP	3	29	4	21.9	27.2	66	86.5	21.3	22.3	25.3	28.0
4	62	M	25	SP	6.5	27	4	34.5	42.7	29	54.2	30.0	22.2	30.7	22.4
5	53	M	7	SP	7.5	28	2	27.0	29.7	69	84.4	33.3	31.3	28.1	40.0
6	50	V	17	RR	7	30	3	41.6	138.0	26	91.7	33.8	18.9	42.5	21.6
7	45	V	16	PP	8	30	3	35.2	85.0	18	69.8	30.3	28.0	49.0	45.3
8	46	M	13	SP	6.5	30	3	91.0	137.0	27	88.5	37.1	21.5	45.7	20.1
9	29	V	8	RR	7	30	4	55.7	28.8	19	89.6	25.2	28.1	31.4	33.0
10	60	V	21	SP	6	29	4	24.9	26.8	36	84.4	21.0	19.3	22.4	24.1
11	40	V	18	RP	7.5	30	4	47.3	27.2	38	72.3	41.8	39.4	40.3	34.9
12	55	V	23	SP	5.5	27	2	32.8	31.3	43	85.4	27.5	26.6	26.7	22.7
13	56	V	17	SP	6	30	4	24.2	34.0	67	93.7	17.0	20.7	25.0	24.7
14	35	M	12	SP	6.5	30	4	23.9	28.6	29	95.8	20.7	24.3	20.7	24.3
MEAN	51.9		17.4		6.5	28.9	3.3	38.3	54.7	37.9	82.3	27.6	25.2	31.8	27.6
SD	12.3		8.6		1.2	1.6	1.0	18.6	42.5	17.4	11.2	7.2	5.8	9.2	7.8

Abbreviations: SP, Secuncary Progressive; PP, Primary Progressive; RP, Relapsing Progressive; RR, Relapse Remitting; EDSS, Expanded Disability Status Scale; MMSE, Mini Mental State Examination; NSBMS, Neuropsychological Screening Battery for Multiple Sclerosis; 9HPT, Nine Hole Peg Test; KVIQ-10, Kinesthetic and Visual Imagery Questionnaire; BBT EXEC, physical execution Box and Block Test; BBT MI, motor imagery Box and Block Test

^aLower score reflects higher imagery vividness

^bHigher score reflects higher imagery vividness