PAPER

Effects of peripheral cooling on intention tremor in multiple sclerosis

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Objective: To investigate the effect of peripheral sustained cooling on intention tremor in patients with multiple sclerosis (MS). MS induced upper limb intention tremor affects many functional activities and is extremely difficult to treat.

Materials/Methods: Deep (18°C) and moderate (25°C) cooling interventions were applied for 15 minutes to 23 and 11 tremor arms of patients with MS, respectively. Deep and moderate cooling reduced skin temperature at the elbow by 13.5°C and 7°C, respectively. Evaluations of physiological variables, the finger tapping test, and a wrist step tracking task were performed before and up to 30 minutes after cooling.

Results: The heart rate and the central body temperature remained unchanged throughout. Both cooling interventions reduced overall tremor amplitude and frequency proportional to cooling intensity. Tremor reduction persisted during the 30 minute post cooling evaluation period. Nerve conduction velocity was decreased after deep cooling, but this does not fully explain the reduction in tremor amplitude or the effects of moderate cooling. Cooling did not substantially hamper voluntary movement control required for accurate performance of the step tracking task. However, changes in the mechanical properties of muscles may have contributed to the tremor amplitude reduction.

Conclusions: Cooling induced tremor reduction is probably caused by a combination of decreased nerve conduction velocity, changed muscle properties, and reduced muscle spindle activity. Tremor reduction is thought to relate to decreased long loop stretch reflexes, because muscle spindle discharge is temperature dependent. These findings are clinically important because applying peripheral cooling might enable patients to perform functional activities more efficiently.

Upper limb tremor affects the performance of many activities of daily living¹ and is estimated to be present in up to half of those patients with multiple sclerosis (MS).² Intention tremor, clinically defined as an increase in tremor amplitude during visually guided movements towards a target at the termination of the movement, is related to lesions in the cerebellum or connected pathways, and is often used synonymously with cerebellar tremor.^{2–3} The origin of cerebellar tremor is thought to be central, although it may be raised or modulated through stretch reflex oscillations because of a dysfunction of feedforward loops within the central nervous system.^{4–5} The susceptibility of tremor amplitude and frequency to mechanical loads indicates the involvement of stretch elicited peripheral feedback mechanisms in the manifestation of cerebellar tremor.^{6–8} In support of this view, tremor was elicited in patients with pure cerebellar syndromes during a load compensating task.⁹ Other studies decreased the sensory input to the central nervous system. A reduction of cerebellar tremor during handwriting has been found after the application of an ischaemic block to the arm.¹⁰ In patients with MS and upper limb tremor, some functional improvement¹¹ and a reduced postural but not intention tremor amplitude during pointing tasks¹² was reported after immersion of the arm in ice water for one minute. The authors of these studies suggested that the cooling induced tremor reduction was related to a decrease in the sensory input provided by muscle spindle afferences.¹²

The treatment of intention tremor in patients with MS has been disappointing because drugs and physical treatments are not very effective.¹³ Therefore, understanding the peripheral mechanisms involved in tremor generation is important because it may lead to new therapeutic approaches. In line

with previous research,^{11–12} our present study investigated the effect of peripheral cooling on intention tremor caused by MS. A wrist step tracking task was used because tremor in MS is more frequently present in the distal rather than the proximal joints,² and is usually most pronounced in the distal joints.¹⁴ The step tracking task was previously shown to be valid for assessing intention tremor.¹⁵ The cooling intervention was restricted to the forearm affecting the wrist flexors and extensor muscles, which are primarily involved in the wrist step tracking task. The wrist joint was not included to avoid substantial cooling of the wrist joint or nearby skin receptors. The cooling intervention persisted for 15 minutes so that intramuscular structures were also affected because intramuscular temperature decreases start later and are more gradual than those seen in the skin. In addition to the deep cooling intervention, a proportion of the patients also received a moderate cooling intervention to examine whether the effects on voluntary tracking and involuntary tremor were proportional to the intensity of cooling. Evaluations were performed before and up to 30 minutes after the cooling intervention.

MATERIALS AND METHODS

Patients and clinical assessment

Eighteen patients with intention tremor (eight men and 10 women; mean age, 44.5 years; range, 18–63) were selected from patients with clinically definite MS¹⁶ by neurologists of the Belgian National MS Centre in Melsbroek. Intention tremor appeared bilaterally in all but one patient. Arms showing clinically detectable spasticity, muscle paresis, or

Abbreviations: MS, multiple sclerosis

Table 1 Clinical characteristics of the patient group

Patient	Age (years)	Sex	Duration of MS (years)	Type of MS	EDSS	Finger–nose test		Pouring water		Spirography		Finger tapping test	
						Left	Right	Left	Right	Left	Right	Left	Right
1	18	F	2	RR	6	3	4	3	4	2	4	20	5
2	32	F	3	PP	6,5	2	2	3	2	2	1	15	20
3	34	F	13	RR	6,5	3	4	4	4	1	2	23	21
4	36	F	12	PP	7,5	3	2	3	4	2	2	25	10
5	37	F	9	PP	6	1	3	1	4	1	3	27	26
6	39	M	3	SP	6	1	3	1	4	2	4	42	18
7	39	F	11	PP	7	3	–	3	–	2	–	18	–
8	39	F	13	PP	6,5	3	3	4	4	3	4	13	17
9	45	F	8	SP	6	1	2	1	1	2	2	16	19
10	47	M	3	PP	6	2	2	2	1	2	1	29	46
11	49	M	3	PP	6	1	3	0	2	1	2	49	33
12	49	M	14	PP	6	3	4	2	4	2	4	23	3
13	52	M	36	PP	6,5	3	4	3	4	2	4	16	28
14	53	F	28	SP	6,5	2	3	2	3	2	3	14	26
15	53	M	24	SP	7	3	4	3	4	2	4	12	3
16	54	M	15	RR	5,5	3	1	2	1	1	1	28	41
17	62	F	13	PP	6	3	2	3	3	3	1	20	19
18	63	M	12	PP	6	3	2	4	1	3	1	14	30

EDSS, Expanded Disability Status Scale (0–10); PP, primary progressive; RR, relapsing-remitting; SP, secondary progressive.

sensory loss were not included. Further exclusion criteria were decreased visual acuity and cognitive dysfunction interfering with the execution of the step tracking task. Patients with hypersensitivity to cold or disturbances in the peripheral circulation were not included because of the risks related to the cooling intervention. Fahn's tremor rating scale¹⁷ was used for the clinical assessment of intention tremor during the finger to nose test,^{18–19} and to rate the performance on functional tasks, such as pouring water and spirometry.²⁰ Furthermore, the finger tapping test,^{20–21} during which the number of taps on a calculator key is counted over a period of 10 seconds, was performed. Table 1 summarises the clinical characteristics of the patient group. Our study was conducted according to the ethical standards laid down in the 1964 Declaration of Helsinki and was approved by the local ethics committee. Before participation, informed consent was obtained from all participants.

Cooling intervention and evaluation

Cooling of the forearm was achieved by means of a cryomanchet, which was wrapped around the forearm with exclusion of the wrist joint and hand. A cooling fluid continuously circulated through the cryomanchet from a cooling device that allowed precise regulation of the fluid's temperature (Iglotronics®, Morlsel, Belgium; fig 1). The skin

Figure 1 The cooling device and cryomanchet.

temperature of the arm was continuously monitored by means of two probes (Fluke®, Everett, Washington, USA): one was attached to the dorsal side of the forearm, 5 cm distal from the elbow joint, and the other to the dorsal side of the wrist joint. The room temperature was kept constant at 19°C. Supervision of the heart rate and the central body temperature was performed by means of a heart rate meter (Polar®, Kempele, Finland) and a digital clinical thermometer, respectively.

Two different cooling intensities were applied. The forearm was cooled down until the skin temperature near the elbow dropped to 25°C and 18°C for the moderate and deep cooling interventions, respectively. From this point on, the temperature was kept as constant as possible for the following 15 minutes (ranges, 15–18°C and 22–25°C, respectively).

Evaluations were performed before and up to 30 minutes after cooling with time intervals of 10 minutes (pre, post 0', post 10', post 20', post 30'). At each test time, the skin temperature at the elbow and wrist, the heart rate, and the body temperature were registered, and the step tracking task (confer infra) and finger tapping test were performed. In a small number of patients (three for each cooling intervention), a physician measured the sensory and motor nerve conduction velocity of the ulnar nerve during a separate test

Figure 2 Illustration of the transport and target phase in a movement trial of a patient with intention tremor.

session. These neurophysiological measurements were performed before, immediately after, and 20 minutes after cooling.

Step tracking task

The wrist step tracking task and data analysis were identical to those in previous studies,¹⁵ and are summarised here. Participants were seated in front of a computer screen with their forearm and hand placed in a wrist orthosis, which was fixed to the arm of the chair. An angle encoder, attached to the orthosis, recorded wrist flexion and extension movements at a sampling rate of 200 Hz with an accuracy of 0.05°. A wooden cover prevented direct sight of the actual wrist movement, which was displayed on the screen as an unfilled circle. A displayed target consisted of two vertical lines and was presented at either side of the screen with an intertarget distance of 200 mm, corresponding to a wrist movement of 40°. The participants performed reciprocal wrist movements between the two stationary targets respecting the rhythm of a metronome (0.25 Hz; that is, an inter-beep interval of two seconds). The patients were instructed to fit the cursor as accurately as possible on the target while initiating the subsequent movement to the alternative target in response to the beep. Two test blocks of 15 movement trials were performed at each test moment. The first five movement trials were not recorded to allow the participants to catch the rhythm. Each movement trial was divided into a "transport" and "target" phase (fig 2). The transport phase started when the velocity exceeded 50 mm/s and ended when velocity dropped below 50 mm/s. The transport phase was followed by the target phase, which lasted until the initiation of the following movement.

The duration and peak velocity of the transport phase were considered to be indicators of movement speed. Tremor severity in the target phase was estimated using the additional path length and the number of directional changes. The additional path length was computed as the total length of the trajectory covered during the target phase minus the distance between the start and endpoint position of the target phase. As shown before,^{15, 22} this reflects overall tremor amplitude. The number of directional changes was obtained by counting the number of zero crossings in the velocity profile and reflected both voluntary error corrections and involuntary oscillations. Because intention tremor is an action tremor, related to the execution of voluntary movements, the number of directional changes was regarded as an estimate of the overall frequency of the intention tremor. To exclude any influence of target phase duration differences across different evaluations, the values of the additional path length and number of directional changes were converted to values on the same denominator (target phase duration of one second). The absolute initial and endpoint error were

defined as the mean absolute difference between the wrist and the target position at the end of the transport and the target phases, respectively.

Statistical analyses

The results were analysed in terms of the number of hands.^{15, 23, 24} Twenty three arms of 18 patients were subjected to the deep cooling intervention, whereas 11 arms of nine patients also underwent the moderate cooling intervention during a separate test session. Data from six hands, equally divided between both cooling conditions, were not included in the data analysis because their very large tremor amplitudes prevented an adequate rhythmical execution of the task and impeded the accurate mathematical determination of the start and end of each movement trial. As such, the results of 20 and eight arms that received the deep and moderate cooling intervention, respectively, were analysed. A repeated measure ANOVA (pre, post 0', post 10', post 20', post 30') was conducted for 11 variables (heart rate, central body temperature, wrist and elbow skin temperature, finger tapping test, transport phase duration, peak velocity, additional path length, number of directional changes, absolute initial error, and endpoint error) for both the deep ($n = 20$) and moderate cooling intervention ($n = 8$). Bonferroni post hoc tests were used to correct for multiple comparisons. To compare the effects of the different cooling intensities on tremor, a two way ANOVA of intervention (deep, moderate cooling) and test moment (post 0', post 10', post 20', post 30') was performed for the additional path length and number of directional changes. Only arms that were subjected to both the deep and moderate cooling intervention were included in this analysis ($n = 8$). Values after cooling were expressed as a percentage of the value before the cooling. The level of significance was set at $p < 0.05$.

RESULTS

The cooling interventions were well tolerated by the patients and did not influence their heart rate or central body temperature. The effects of the deep and moderate cooling interventions will first be discussed separately, followed by a comparison of the effects of both cooling interventions on nerve conduction velocity and tremor in the matching arms.

Deep cooling intervention

Table 2 provides an overview of the results before and after the deep cooling intervention ($n = 20$). The skin temperature differed significantly between test moments (fig 3), both at the elbow ($F(4.76) = 196.6$; $p < 0.0001$) and at the wrist ($F(4.76) = 76.3$; $p < 0.0001$). The temperature was significantly reduced immediately after cooling (on average by 13.5°C at the elbow and by 2.5°C at the wrist). Warm up after removal of the cryomanchet was significant at the elbow and seemed to happen in a curvilinear way, with the fastest recuperation during the first 10 minute period. Although warm up continued over the entire testing period, normalisation of the elbow skin temperature did not take place within 30 minutes. In contrast to the elbow, the skin temperature at the wrist further decreased after 10 minutes and showed no warm up within the evaluation period.

The subjects performed significantly worse on the finger tapping test immediately after cooling, but their performance after 10 minutes was very similar to that before cooling ($F(4.76) = 5.8$; $p < 0.001$). Cooling significantly reduced the movement speed during the transport phase of the step tracking task, as revealed by an increase in the transport phase duration ($F(4.76) = 17.1$; $p < 0.0001$) and a decrease in the peak velocity ($F(4.76) = 20.0$; $p < 0.0001$). The movement speed recovered significantly during the 30 minute post cooling evaluation period, although it remained

Figure 3 Mean skin temperature (°C) at the elbow and wrist before and after deep cooling.

Table 2 Overview of the results before and after the deep cooling intervention (n = 20)

	Pre	Post 0'	Post 10'	Post 20'	Post 30'
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Temperature elbow (°C)	30.1 (1.6)	16.4 (1.7)	23.4 (2.4)	25.1 (2.6)	26.3 (2.5)
Temperature wrist (°C)	28.0 (2.4)	25.6 (2.3)	24.8 (2.5)	24.7 (2.6)	24.8 (2.8)
Finger tapping test (n)	20.2 (5.4)	17.8 (5.7)	18.6 (5.6)	19.2 (5.9)	20.0 (6.1)
Transport phase duration (ms)	463 (108)	682 (195)	620 (190)	609 (204)	568 (200)
Peak velocity (mm/s)	1008 (300)	657 (189)	704 (243)	762 (282)	811 (329)
Additional path length (mm)	97.3 (109.1)	20.6 (26.3)	25.4 (23.5)	29.1 (26.5)	34.5 (31.1)
Directional changes (n)	4.0 (1.9)	1.8 (1.5)	2.2 (1.7)	2.2 (1.5)	2.6 (1.8)
Absolute initial error (mm)	23.9 (4.7)	18.5 (4.6)	20.9 (6.8)	21.3 (6.0)	20.8 (4.3)
Absolute endpoint error (mm)	15.6 (20.8)	11.7 (9.4)	10.5 (7.4)	9.5 (6.0)	9.0 (6.5)

lower than it was before cooling. The absolute initial error was significantly smaller immediately after cooling, but this improvement in accuracy had already disappeared after 10 minutes ($F(4.76) = 5.4$; $p < 0.001$). The deep cooling intervention had an effect on both the additional path length and the number of directional changes, as illustrated in fig 4.

During the entire post cooling testing period, the additional path length was reduced to about one third of the value measured before cooling ($F(4.76) = 11.7$; $p < 0.0001$) and showed no significant recovery. In line with the findings of the additional path length, fewer directional changes were made after deep cooling ($F(4.76) = 25.6$; $p < 0.0001$), with a significant recuperation occurring 30 minutes after cooling. The deep cooling intervention did not influence the endpoint accuracy.

Moderate cooling intervention

Table 3 provides an overview of the results before and after the moderate cooling intervention (n = 8). Immediately after cooling, the skin temperature was significantly reduced, both at the elbow (on average by 7°C; $F(4.28) = 38.3$; $p < 0.0001$) and wrist (on average by 1.4°C; $F(4.28) = 13.3$; $p < 0.0001$). The skin temperature at the elbow recovered significantly during the first 10 minutes after removal of the cryomanchet. However, there was no normalisation to precooling values. In contrast, no warm up of the wrist temperature was seen within the 30 minute test period.

The moderate cooling intervention did not alter the performance in the finger tapping test. During the step tracking task, no significant changes in the transport phase duration, peak velocity, or the absolute initial and endpoint errors were seen after moderate cooling. However, both the overall tremor amplitude and frequency were significantly

reduced immediately after cooling ($F(4.28) = 3.8$; $p < 0.05$ and $F(4.28) = 6.9$; $p < 0.001$, respectively), without showing a significant recuperation during the 30' post cooling evaluation period.

Differential effect of both cooling interventions on nerve conduction velocity and tremor

The supplementary neurophysiological measurements revealed in all six patients that the ulnar motor and sensory nerve conduction velocity was normal (≥ 47 m/s) before cooling and reduced immediately after deep cooling (on average by 15.2 and 3.9 m/s, respectively) and moderate cooling (on average by 6 and 2.9 m/s, respectively). The motor nerve conduction velocity was still reduced 20 minutes after both deep and moderate cooling (on average by 8.7 and 5.1 m/s, respectively), whereas the sensory nerve conduction velocity was normalised. In general, the values for nerve conduction velocity were below normal after the deep cooling intervention, whereas they always remained within normal ranges after the moderate cooling intervention. Figure 5 presents the results of the additional path length and number of directional changes after deep and moderate cooling for the matching arms (n = 8). Tremor measures after cooling are presented as a percentage of the value before cooling. Both cooling intensities affected the overall tremor amplitude and frequency. However, across conditions, the mean reduction of the additional path length was greater after deep cooling (63.5%) than after moderate cooling (46.5%) ($F(1.14) = 7.2$; $p < 0.05$). In the same way, the mean reduction of the number of directional changes was greater after deep cooling (42.3%) than after moderate cooling (18.4%) ($F(1.14) = 4.9$; $p < 0.05$).

Figure 4 Illustration of the step tracking performance of a patient with intention tremor (A) before and (B) immediately after the deep cooling intervention.

Table 3 Overview of the results before and after the moderate cooling intervention (n = 8)

	Pre	Post 0'	Post 10'	Post 20'	Post 30'
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Temperature elbow (°C)	29.8 (1.8)	22.8 (2.2)	25.7 (1.1)	26.6 (1.2)	27.4 (1.3)
Temperature wrist (°C)	27.9 (1.8)	26.5 (1.8)	25.7 (2.0)	25.7 (1.8)	25.8 (1.8)
Finger tapping test (n)	23.6 (5.6)	21.9 (4.6)	22.5 (5.7)	24.1 (6.0)	22.9 (5.1)
Transport phase duration (ms)	540 (117)	641 (159)	621 (126)	581 (166)	579 (137)
Peak velocity (mm/s)	863 (328)	757 (266)	754 (240)	809 (339)	825 (314)
Additional path length (mm)	64.2 (67.8)	36.7 (50.6)	39.0 (45.2)	31.7 (30.2)	32.1 (27.8)
Directional changes (n)	3.9 (1.8)	2.5 (1.5)	2.7 (2.1)	2.7 (1.3)	2.7 (1.5)
Absolute initial error (mm)	25.1 (5.5)	22.0 (7.6)	21.0 (6.4)	21.4 (5.4)	21.8 (3.8)
Absolute endpoint error (mm)	12.8 (8.5)	10.3 (5.6)	9.5 (5.9)	9.6 (5.9)	9.4 (4.3)

DISCUSSION

The major finding of our present study is the clear reduction of overall tremor amplitude and frequency during the step tracking task after two different intensities of sustained cooling of the forearm in patients with MS. The effect on tremor seemed to be proportional to the intensity of the cooling. After both the deep and moderate cooling interventions, the reduction in tremor persisted over the entire post cooling evaluation period of 30 minutes. Of note, the accuracy of the voluntary tracking was not negatively affected by the cooling intervention.

Figure 5 Differential effects of deep and moderate cooling interventions on tremor measures in matched arms (n = 8): (A) additional path length and (B) number of directional changes. The results have been converted to a percentage of the value before cooling.

The immediate effects of sustained cooling on intention tremor in our present study are somewhat different from the results after dipping the arm in ice water, as previously reported in patients with MS and tremor.^{11, 12} In these earlier studies, no immediate cooling effects on intention tremor were found during pointing tasks,¹² although the immersion of the arm had led to a similar reduction of the skin temperature at the elbow as the moderate cooling intervention in our present study. However, a functional improvement on specific clinical tests was found between 15 and 45 minutes after the dipping of the arm in ice water.¹¹ The apparent contradictory findings between studies may be related to the time needed for the cooling to reach its maximal impact on the deeper structures of the arm. It is well known that the skin temperature does not linearly reflect the cooling induced changes of the intramuscular temperature. An important factor to predict the intramuscular temperature is the elapsed time since the start of the cooling intervention.²⁵ As such, immersion of the arm in ice water^{11, 12} did not show an immediate effect on tremor, whereas the sustained cooling intervention probably did because it was applied during a period long enough to affect the deeper structures of the arm.

Cerebellar tremor is thought to be modulated through increased long latency stretch reflexes.⁴ The results of studies manipulating the sensory input suggest that cerebellar tremor is partially driven by stretch elicited peripheral feedback.^{8-10, 12} Several peripheral structures may be affected by cooling and therefore account for the great reduction of intention tremor after the sustained cooling interventions.

Nerve conduction velocity is known to be directly related to the limb temperature.^{26, 27} In our study, too, the nerve conduction velocity was obviously decreased immediately after the deep cooling intervention, as revealed by the slower performance on the finger tapping test, a significantly longer transport phase duration with decreased peak velocity during step tracking, and neurophysiological measurements of the motor and sensory ulnar nerve conduction velocity. Cooling had less effect on the velocity of sensory nerve conduction compared with motor nerve conduction. However, the area in which sensory ulnar nerve conduction velocity was measured included the hand that was not directly cooled by the cryomanchet. In contrast, the value of the motor ulnar nerve conduction velocity mainly reflects the conduction velocity at the forearm. When one regards intention tremor as the result of oscillations in the peripheral feedback circuitry,⁷ it can be assumed that the cooling induced sensory and motor nerve conduction delay significantly contributed to the decrease in the overall tremor frequency. In support of this view, the overall frequency of intention tremor increased as the movement speed increased over the post cooling period of 30 minutes. However, the reduction of nerve conduction velocity cannot fully explain the pronounced reduction of the

overall tremor amplitude. In fact, the reduction of tremor amplitude persisted throughout the 30 minute evaluation period even though the indicators of nerve conduction velocity had changed significantly. In addition, a significant reduction of overall tremor amplitude and frequency was also found in a smaller sample of arms after the moderate cooling intervention, when the nerve conduction velocity was not greatly influenced.

The prolonged tremor reduction may be related to the changed mechanical properties of the wrist joint and muscles as a result of sustained cooling. Although the wrist joint was not included in the cooling pad, its skin temperature also decreased to some extent, with no warming up occurring during the entire evaluation period. The reduced skin temperature at the wrist is most probably the result of cold conduction by deeper tissues of the arm, such as muscle fibres. Therefore, it is still possible that stiffness of the wrist joint may have been increased to some extent after cooling.²⁸ Changes in mechanical properties of the muscles may have contributed to the reduction of tremor amplitude, because an increase of muscle stiffness during passive movements has been found after sustained cooling of the calf muscles.²⁹ The degree of muscle stiffness is probably related to the depth of cooling, and therefore may explain the dose related response of tremor reduction in our present study.

The cooling induced changes in nerve conduction velocity and mechanical properties may impede the performance of active movements. Participants in the study of Lakie *et al* reported a reduced force output and difficulty in producing rapidly alternating movements when the forearm was cooled for a longer period of time.³⁰ Deep cooling increases the muscle relaxation time and decreases the maximum voluntary force.^{31, 32} In our present study, however, patients with MS executed the step tracking task after either cooling intervention at least as accurately as before cooling. Therefore, we conclude that the voluntary movement control required for the accurate performance of the step tracking task was sufficiently preserved after cooling.

There is also another factor that may explain the prolonged reduction of overall tremor frequency and amplitude after cooling. The excitability of muscle spindles, which are an essential part of the reflex loop, is known to be temperature dependent.^{33–35} Although muscle spindle activity and spinal reflexes are not considered to be abnormal in patients with cerebellar dysfunction,^{36, 37} decreasing the stretch sensitivity of the muscle spindles and thus also the long latency stretch reflexes, by means of cooling, may have had an important effect on tremor.³³

We acknowledge that we provided no direct evidence in our present study that cooling reduced the activity of muscle spindles and their afferences. Another, more simple explanation could be that the reduction of tremor was merely the result of learning to perform the step tracking task more efficiently. However, the immediate pronounced effect of both cooling interventions on tremor, the significant recuperation of the overall tremor frequency 30 minutes after the deep cooling, and the dose related effect of cooling on overall tremor amplitude and frequency contradict the hypothesis that the results are solely attributed to learning processes.

Unfortunately, the treatment of intention tremor is still unsatisfactory.¹³ The finding that intention tremor in MS can be influenced by affecting peripheral structures is of clinical importance. The cooling interventions applied in our present study are thought to lead to substantial functional improvements, because the tremor measures of the step tracking task have been shown to be closely related to clinical ratings of intention tremor during the finger to nose test or pouring water.¹³ However, it must be noted that the reported cooling interventions may be less effective in patients with MS who

have considerable proximal tremor during the performance of functional activities requiring movements in the proximal joints. It is also unclear whether patients with MS who have very severe tremor would experience the same benefits of the moderate cooling intervention as was reported in our study.

Although the effects of cooling on intention tremor are probably temporary, we showed that they persist for at least 30 minutes. The effects may even be sustained for longer because essential and physiological tremor were reported to be reduced for as much as 90–120 minutes after a shorter cooling intervention than that applied in our present study.^{11, 30, 38} As such, cooling of the arm may be useful before performing activities of daily life such as applying make up, taking a meal, or writing and signing documents. As a consequence, this may lead to a decrease in patients' dependency and improvements in their self esteem. Cooling of the peripheral limb did not affect physiological parameters, such as heart rate and central temperature, suggesting that the intervention was physically not too demanding for patients and could be regarded as relatively safe. As a matter of course, a medical consultation would still be advisable to prevent patients with contraindications from using the cooling device.

CONCLUSIONS

Our present study investigated the effect of sustained cooling of the forearm on intention tremor in patients with MS. Two cooling intensities were applied, which both reduced overall tremor amplitude and frequency without compromising the accuracy of the step tracking movements. The degree of tremor reduction appeared to be related to the cooling intensity. These findings could lead to immediate clinical implementations.

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