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Original article

Slowing of information processing speed without motor slowing in multiple sclerosis observed during two crossing-off tasks

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ABSTRACT

Introduction. – Slowing of information processing speed (IPS) is often considered one of the primary deficits seen in multiple sclerosis (MS). IPS is usually measured by tasks that involve many cognitive functions. The aim of this study was to determine whether similar IPS slowing can also be observed during two simple, timed, psychomotor crossing-off tasks.
Method. – The Crossing-Off Test (COT), a simple psychomotor task, was performed under two conditions (COT1 corresponded to writing habits, COT2 used horizontal sweeping) in 25 relapsing–remitting MS patients (EDSS 0–1) and 25 healthy controls.
Results. – The MS group compared with the control group was impaired on COT1 ($P = 0.0043$) and not on COT2 ($P = 0.4$), and the COT1 performance of MS patients with EDSS 1 was more impaired than those of patients with EDSS 0 ($P = 0.008$).
Discussion/conclusion. – These results indicate that only some of the IPS cognitive subcomponents linked with COT1 tasks are initially involved in the slowing of IPS during MS, suggesting that different mechanisms are involved in each tested version of the COT.

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1. Introduction

Cognitive impairment is a frequent occurrence even during the earliest stages of multiple sclerosis (MS) [1–3], and information processing speed (IPS) is considered one of the primary deficits in patients with MS, along with attention and executive disorders, and working-memory impairment [1–5]. IPS impairment is linked with damage to the white-matter projections involved in large-scale cortical integrative networks. In addition, damage to deep and cortical gray matter in these networks is also involved in IPS impairment [3]. IPS measurements in MS are based on repeated complex tasks that require the successful completion of a variety of cognitive functions [6] and highly controlled executive tasks [7]. For example, the Symbol Digit Modalities Test (SDMT), Trail Making Test (TMT) and Paced Auditory Serial Addition Test (PASAT), all commonly used to explore IPS in MS, are complex tasks involving many cognitive processes (and especially controlled executive functions such as working memory, dual-tasking and task switching). Memory impairment in MS is considered to be primarily associated with processing speed, with working memory exerting less influence [8].

Controlled and automatic processes are different cognitive functions [9]. However, these processes are not totally independent [10]. Automatic processing has been described as a possible factor in the slowing of MS [11]. Indeed, Logan [12] suggests a continuum between automatic, less automatic and controlled processes. Furthermore, the involvement of each of these processes in the IPS impairment of patients with MS is still poorly understood. Different dissociations between the two processing strategies in MS have been reported in the literature with the use of different methodologies [13,14]. Grafman et al. [15] reported that patients with MS performed normally during automatic measures of frequency and modality monitoring, but were impaired on effortful memory measurements. Conversely, Takeda et al. [16] suggested that patients with MS, even with minor cognitive impairments, have IPS slowing that only affects automatic processing, whereas Kujala et al. [11] reported that both automatic and controlled processing is affected in MS. The relatively complex paradigms used in these studies differed widely in terms of automatic and controlled conditions. Therefore, any comparisons between the two conditions are relatively limited by the methodology and might explain the variability of the results.

The Crossing-Off Test (COT) is a simple psychomotor task elaborated as a simplified version of a speed-writing test [17,18]. The task has been used to evaluate IPS performance in healthy subjects [19,20], in patients with Parkinson's disease without dementia [21] and in patients with Alzheimer's disease [22]. Working memory is not involved in the task.

Relapsing–remitting MS patients without minor disabilities (mean Expanded Disability Status Scale [EDSS] score: 0.70) presented with early impairment in the COT [23,24]. Our a priori hypothesis was that IPS would be more impaired in the more complex/composite tasks than in the simpler ones; as complex tasks involve larger networks, MS lesions are more likely to have a greater impact on such complex processes.

Thus, the aim of the present study was to determine whether the slowing of IPS in MS patients was similarly observed during two parallel versions of a relatively simple psychomotor task with no working-memory involvement: the COT.

2. Method

2.1. Subjects

A total of 25 right-handed patients with a relapsing–remitting MS diagnosis [25] and 25 healthy controls, matched for age and education level, were included in the present study (Table 1). Patients underwent a complete examination performed by neurologists, and were recruited on the basis of the absence of psychiatric disorders and functional deficits (EDSS $\leq$ 1; pyramidal, sensory and cerebellar functional systems in the right upper limbs were 0, and there was no impairment of either instrumental or basic activities of daily living). Two neuropsychological screening tests were taken by the MS patients: one, the Mini-Mental State Examination (MMSE) assesses global cognitive efficiency; the other, the Isaacs Set Test (IST), is a composite verbal fluency test with four semantic

Table 1 – Demographic data and Crossing-Off Test (COT) performance by multiple sclerosis patients and their matched controls.

	Multiple sclerosis	Controls	P
Number of subjects	25	25	
Gender (male/female)	8/17	8/17	1.000
Age, years (mean/SD)	32.4 (sd 6.24)	31.7 (sd 7.75)	0.3869
Level of education (high/average/low)	17/8/0	18/7/0	0.758
Disease duration	5 (sd 4.63)	n. a.	n. a.
EDSS (mean, range)	0.56 [0–1]	n. a.	n. a.
MMSE/30 (mean/SD)	28.24 (sd 1.59)	n. a.	n. a.
MIS/8 (mean/SD)	7.84 (sd 0.47)	n. a.	n. a.
IST, words (mean/SD)	41.08 (sd 8.39)	n. a.	n. a.
COT 1 (seconds)	37.6 (sd 6.07)	33.3 (sd 2.84)	0.0023
COT 2 (seconds)	31.2 (sd 2.86)	30.6 (sd 2.34)	0.46
COT1–COT2 (seconds)	6.4 (sd 4.72)	2.7 (sd 0.99)	0.0003

EDSS: Expanded Disability Status Scale; n.a.: not applicable; SD/sd: standard deviation; MMSE: Mini-Mental State Examination; MIS: Memory Impairment Screen; IST: Isaacs Set Test.

categories successively used to assess IPS, executive functions and lexical access.

The study was approved by the local ethics committee at Besançon University Hospital. All patients gave their written consent to be included in the study.

2.2. Material and procedure

The COT [17,18] includes 12 identical horizontal segments regularly distributed over eight lines. Our subjects were instructed to cross off the middle of each segment as quickly as possible. Their completion time, measured in seconds, was the primary outcome of the test.

Subjects performed the COT based on two different counterbalanced conditions (Fig. 1). In the first (COT1), the original version mimicking writing motor processes, subjects had to cross out the middle of each segment as quickly as possible from left to right, then stop at the end of the line, return to the left side of the next line and then repeat the crossing-off from left to right on that line, and so on.

In the second condition (COT2), subjects had to use horizontal sweeps to cross out the middle of each segment as quickly as possible from left to right on the first line, then from right to left on the second line, and from left to right again on the third line and so on in an alternating fashion.

2.3. Data analyses

The performance difference between COT1 and COT2 was calculated to limit the graphomotor component of the COT in the analysis. A Shapiro–Wilk test was performed to assess normality of data. For variables that did not follow a normal distribution, a Mann–Whitney test was conducted. Student's *t*-test was used to compare variables with a normal distribution, and Welch's correction *t*-test was applied in cases of unequal variance.

Analysis of variance (Anova) was performed to compare MS patients with EDSS 1 and EDSS 0 and the control group. $P < 0.05$ was considered statistically significant. Level of education and disease duration were added as covariables in the analysis to evaluate these confounding factors. Pearson's correlation coefficients for COT scores and the MMSE or IST were also analyzed.

Effect sizes were measured by Cohen's *d*, with small, medium and large effects defined as 0.2, 0.5 and 0.8, respectively, or as eta-squared (η^2), with small, medium and large effects defined as 0.01, 0.06 and 0.14, respectively.

All computations were performed with Stata software (release 8.0, StataCorp, College Station, TX, USA).

3. Results

Performance results for the two study groups under the two COT conditions are presented in Table 1. COT performance did not differ in the healthy control subjects according to level of education (COT1 W(25) = −0.366, $P = 0.7140$; COT2 W(25) = −0.031, $P = 0.9756$; and COT1–COT2 W(25) = −1.144, $P = 0.2526$).

Patients with MS were significantly slower and had a wider range of performance (standard deviation [SD]) than the controls on COT1. The size effect was considered large ($d = 0.929$). However, no significant difference was observed between the two groups on COT2, and the size effect was considered small ($d = 0.259$). The difference between the two task conditions (COT1–COT2) was significantly greater in the MS patients compared with the controls. The size effect was considered small ($d = 0.433$).

Performance results of the MS subgroups (EDSS 0 and EDSS 1) and control group for the two COT conditions are shown in Table 2. MS patients with EDSS 1 were more impaired than those with EDSS 0 and the controls on COT1 ($P = 0.008$ and $P = 0.0001$, respectively; $\eta^2 = 0.345$), whereas no differences were observed between MS patients with EDSS 0 and the controls on COT1. In addition, the EDSS 1 group showed more impairment on the IST.

No differences were observed across the three groups on COT2 ($P = 0.525$). Also, the differences between COT1–COT2 were significantly greater between MS patients with EDSS 0 and the control group ($P = 0.04$), and between MS patients with EDSS 1 and the controls ($P = 0.0009$). However, the difference between COT1–COT2 was not significantly different between

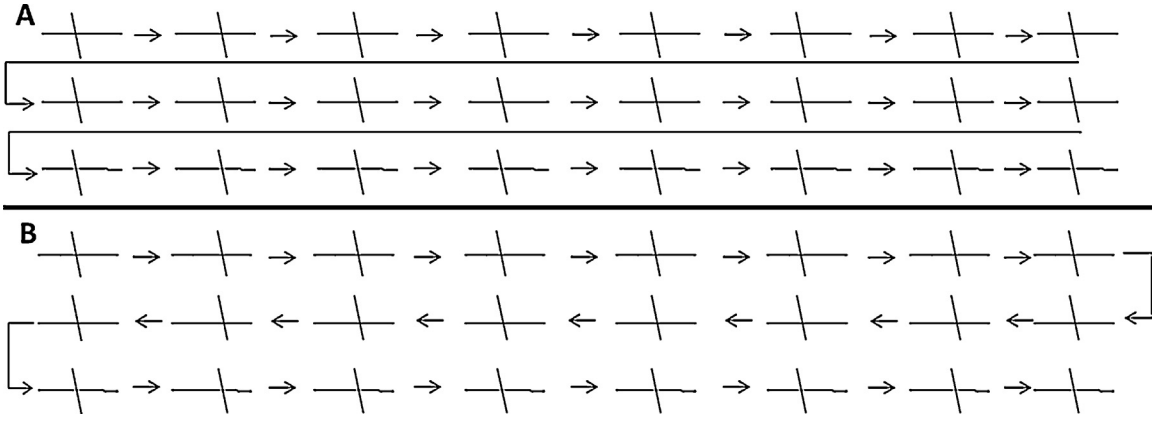

Fig. 1 – The Crossing-Off Test: (A) the original version (COT1) mimicking writing motor processes; and (B) the parallel version (COT2) using horizontal sweeps of the page from left to right on the first line, then from right to left on the second line, and then from left to right again on the third line, and so on in an alternating fashion.

Table 2 – Crossing-Off Test (COT) performance of the multiple sclerosis patient subgroups according to Expanded Disability Status Scale (EDSS) and their matched controls.

	EDSS = 0	EDSS = 1	Control	P
Number of subjects	11	14	25	
Age, years (mean/SD)	31.54 (sd 7)	33 (sd 5.75)	31.7 (sd 7.75)	0.59
Gender (male/female)	4/7	4/10	8/17	0.87
Level of education (high/average/low)	7/4/0	10/4/0	17/8/0	0.87
Disease duration, years (mean/SD)	3.36 (sd 2.6)	6.5 (sd 5.61)	n. a.	0.1056
MMSE/30 (mean/SD)	28.63 (sd 1.2)	27.92 (sd 1.81)	n. a.	0.2779
MIS/8 (mean/SD)	7.81 (sd 0.6)	7.85 (sd 0.36)	n. a.	0.7710
IST, words (mean/SD)	47.18 (sd 7.3)	36.28 (sd 5.71)	n. a.	0.0004
COT1 (seconds)	34.54 (sd 4.56)	40.43 (sd 5.96)	33.3 (sd 2.84)	0.0008[a,b]
COT2 (seconds)	28.9 (sd 1.7)	33 (sd 2.22)	30.6 (sd 2.34)	0.525
COT1–COT2 (seconds)	5.63 (sd 4.5)	7.43 (sd 4.91)	2.7 (sd 0.99)	0.005[c,d]

EDSS: Expanded Disability Status Scale; n.a.: not applicable; SD/sd: standard deviation; MMSE: Mini-Mental State Examination; MIS: Memory Impairment Screen; IST: Isaacs Set Test.
[a] EDSS 1 > EDSS 0 ($P = 0.008$; $\eta^2 = 0.345$).
[b] EDSS 1 > controls ($P = 0.0001$; $\eta^2 = 0.345$).
[c] EDSS 0 > controls ($P = 0.04$; $\eta^2 = 0.271$).
[d] EDSS 1 > controls ($P = 0.0009$; $\eta^2 = 0.271$).

patients with EDSS 0 and EDSS 1 ($P = 0.14$), although those effects were considered large ($\eta^2 = 0.271$).

Level of education and disease duration did not influence our results. A significant correlation was observed between COT1 performance and the IST ($r = -0.4646$, $P = 0.0193$).

4. Discussion

The present study showed that IPS impairment was observed on only one of the two different COT tasks in MS patients with no sensorimotor deficit in their right upper limbs. Thus, the slowing of IPS is not global. Only the original version of the COT (COT1) showed impairment compared with the healthy, non-MS subjects. This suggests that the COT1 is not just a visuomotor tapping test, as IPS impairment of the motor skill component might have had an impact on both versions of the COT. Also, the difference between COT1 and COT2 results suggests that, in addition to the motor skills involved in both COT versions, different subcomponents of IPS are involved in each COT version, and the specific subcomponents involved in COT1 were selectively impaired in the MS patients with no motor speed impairment.

In addition, only COT1 was correlated with the IST, a composite test involving IPS, executive functions (especially the flexibility involved in switching between semantic categories) and language (lexical access). COT1 involved a larger number of different processes requiring process coordination (first, to cross out each segment from left to right; second, to stop at the end of the line; third, to go back to the left side of the next line; and finally, to repeat the crossing-out of each segment from left to right) compared with COT2 (horizontal sweeps down the page, alternating from left to right, then from right to left).

The degree of automaticity is related to training, serial vs parallel processing, level of effort, robustness of stressors, degree of control, effects on long-term memory and priority encoding [9]. Both COT versions require coordination between visuospatial, perceptive and motor processing initially to perform the crossing-off task [26,27]. Both our COT tasks are thought to involve highly automatic processes (writing habits in COT1, and natural visual exploration in COT2). However, the horizontal sweep was an error frequently observed during the original COT version (COT1) in both healthy and pathological populations [19–22], suggesting that the horizontal sweep is a more intuitive, ecological and optimized form of visual exploration [28]. Visual exploration is acquired earlier in childhood than the writing habit, which is also education-dependent. However, level of education did not influence our results, as no subjects with low levels of education (with few writing and reading habits) were included in our study. Moreover, the distance required to do the crossing-off task in COT2 is shorter than in COT1. Thus, COT2 can be considered an optimized version of the COT. Yet, no differences were observed on COT2 between MS patients and controls, suggesting that the cognitive subcomponents of IPS involved in COT2 and motor function speed are initially spared in early MS. This suggests that the IPS impairment dissociation of COT1 vs COT2 might be explained by the cognitive subcomponents of IPS selectively involved in COT1.

In MS patients with no cognitive impairment, increased frontal lobe activation has been observed corresponding to executive compensatory processes, representing an adaptive response to obtain a performance comparable to that of the control subjects [29,30]. Compensatory processes are involved even in relatively simple tasks, such as the ''Go/No Go'' paradigm. Recruitment of high-level decision-making frontal lobe areas is correlated with the decrease in processing speed. Decreased cerebellar activation suggests an inability to generate automatic processes [31]. An approach that integrates the continuum concept of automatic and controlled processes of IPS [12] in MS may help us to understand the mechanisms involved in IPS impairment. The neural correlate of COT1 and COT2, especially in MS populations, might provide some clue as to what those mechanisms are. Computerized versions of the COT may perhaps also add information regarding the automaticity

involved during these tests (speed of the first line vs last line, for example).

Comparisons between MS patients with EDSS 1 and those with EDSS 0 were limited by our small sample size, and our results should be interpreted with caution. However, both the COT1 and IST performances were more impaired in MS patients with minor disabilities (EDSS 1) than those with no disabilities (EDSS 0). The differences between COT1 and COT2 (COT1–COT2) in MS patients with EDSS 1 and EDSS 0 were similar in both patient groups and significantly larger than those of the control group. This result suggests that impairments of subcomponents of IPS specifically involved in COT1 were observed in both MS subgroups. The difference between COT1 and COT2 also appeared to be more sensitive in MS patients with EDSS 0. No influence of disease duration on our results was observed. Thus, the use of COT1 and COT2 might help in the detection of early cognitive alterations arising in MS.

Our study has a few limitations. The small number of MS patients may have induced a bias. However, the size effect observed between our groups for COT1 performance was considered large despite the small population, suggesting a relatively strong effect. Therefore, the dissociation observed between COT1 and COT2 suggests that specific cognitive processes were involved in the IPS impairment of MS patients during COT1. Another limitation is that no extensive neuropsychological assessment was performed in our MS patients. Nevertheless, our MS patients had only mild disabilities (mean EDSS = 0.56; mean MMSE score = 28.24) and no impairment of either instrumental or basic activities of daily living, thereby suggesting that no patients had severe cognitive impairment.

Further studies are needed to compare the COT with other screening tests used in MS populations, such as the SDMT and PASAT, to validate the use of the COT in the early stages of MS, including clinically isolated syndromes and radiologically isolated syndromes.

Greater knowledge of the different processes involved in IPS and the timing of these disorders in MS could lead to the development of specific rehabilitation programs based on the specific subcomponents involved.

5. Conclusion

Our study suggests that only some cognitive IPS subcomponents linked with the original COT tasks (COT1) are initially involved in the slowing of IPS during MS, with no impairment of motor speed.

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Disclosure of interest

The authors declare that they have no competing interest.

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