A Randomised Computer-assisted Rehabilitation Trial of Attention in Pediatric Multiple Sclerosis: A Post-hoc Analysis.

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Research Article

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Abstract

**Background:** Cognitive decline is one of the most remarkable features of Multiple Sclerosis (MS) and particularly in pediatric onset MS (POMS). The Symbol Digit Modalities Test (SDMT), a simple, brief measure of information processing speed (IPS) has been proposed and it is increasingly used to explore cognitive functions in MS clinical trials. Recently a 4-point worsening on the SDMT score has been demonstrated to significantly correlate with a clinically meaningful cognitive decline.

**Methods:** The primary objective of this post-hoc analysis of a randomised computer-assisted rehabilitation trial for attention impairment in POMS was to test the clinical meaningfulness of the changes of SDMT scores by applying a 4-point SDMT cut-off. POMS exposed to specific computer training (ST) and nonspecific training (nST) were compared. All analyses were post hoc and not pre-specified. To evaluate the clinical meaningfulness of longitudinal changes over time of the SDMT in the ST and nST groups we applied a categorization of the delta SDMT scores (delta SDMT: SDMT score at T1 – SDMT score at T0) as follow: between -3 and 3 = not clinically significant; \( \leq -4 \) = clinically significant worsening; \( \geq 4 \) = clinically significant improvement. The proportion of patients reporting a clinically significant SDMT improvement were compared between the 2 groups by using the chi-square test.

**Results:** Twenty-five % of POMS reported no clinically significant changes, 12.5% a clinically significant worsening and 62.5% patients a clinically significant improvement in the SDMT score at the end of the training program. The proportion of patients reporting a clinically significant improvement of the SDMT was significantly (p=0.008) higher (100%) in patients exposed to the ST in comparison to that (25%) in nST group.

**Conclusions:** In our RCT the use of the 4-point SDMT cut-off allows us to demonstrate the clinical meaningfulness of the results obtained by a home-based computerized program for retraining attention dysfunction in POMS patients with attention impairment. Further studies are needed to confirm the clinical validity of this cut-off and its applicability in the routine clinical practice setting

Introduction

There’s a growing need to find new and more robust disability outcome measures to be used in multiple sclerosis (MS) randomised clinical trials (RCTs) and in clinical practice. The most common outcomes currently used, annualized relapse rate and sustained Expanded disability Status Scale (EDSS) progression, miss an important dimension of MS-related disability, namely, decline in cognitive function. Indeed, cognitive dysfunction is one of the most remarkable features of MS (1) and particularly in pediatric onset MS (POMS).

The percentage of patients with POMS with at least a mild cognitive deficit ranges from 30 to 50%. (2–6) Therefore, the Multiple Sclerosis Functional Composite (MSFC), including a cognitive test, the Paced Auditory Serial Addition Test (PASAT), has been suggested (7) as an alternative and more complete
outcome measure in MS RCTs, but it has some limitations due to the difficulty interpreting the clinical meaning of z-score change and because it seems to be not fully accepted by MS patients (8, 9).

Currently the Simbol Digit Modalities Test (SDMT), a simple, brief measure of information processing speed (IPS) has been proposed (10) and it is increasingly used to explore cognitive functions in MS clinical trials, since it requires little time and no special equipment, does not demonstrate significant ceiling effects, has a good test–retest reliability and very low practice effects as there are alternate forms available (11).

Recently a detailed analysis of the psychometric qualities, sensitivity to change and clinical meaningfulness of SMDT in comparison to the Paced Auditory Serial Addition Test (PASAT) has been performed by the Multiple Sclerosis Outcome Assessments Consortium (MSOAC) (10). The results of this analysis proved the SDMT to be superior to the PASAT suggesting SDMT should be considered the measure of choice for MS trials in assessing IPS. In particular, they found that a 4-point worsening on the SDMT score significantly correlated with clinically meaningful cognitive decline as evidenced by a 5-point worsening on the Physical Component Summary (PCS) of the Health Status Questionnaire (SF-36). Moreover, previous studies confirmed that this degree of change in the SDMT is clinically meaningful, when correlated to relapses and employment status. (12, 13)

In a recent double-blind RCT (14) we assessed the efficacy of a home-based computerized program for retraining attention dysfunction in a cohort of POMS patients with attention impairment. We found that after a 3-month cognitive training, the specific computer training (ST) exposure was associated to a significantly more pronounced reduction of the Cognitive Impaired Index (CII) in comparison to the non-specific training (nST) exposure. In particular, POMS treated with a ST had a significant higher improvement in their performances on SDMT in comparison to those receiving a n-ST suggesting that a cognitive rehabilitation program that targets attention is a suitable tool for improving global cognitive functioning in POMS patients.

Here, we present a post-hoc analysis aimed to assess the robustness of treatment effects, applying the 4-point SDMT cut-off, as proposed by MSOAC (10), on the results of our cognitive rehabilitation trial.

**Methods**

**Study population, Procedures and intervention**

A detailed description of the study population, procedures and intervention has been previously reported elsewhere (14).

Briefly, 16 POMS patients failing in at least 2/4 attention tests on a neuropsychological battery were randomized to ST or nST (15), performed at home, in one-hour sessions, twice/week for three months. A neuropsychological test battery was administered, using alternative versions of the tests, at baseline (T0), and within one week following the end of the three months training program (T1).
The neuropsychological test battery comprised tests which cover different cognitive domains.

The SDMT was administered to assess IPS.

The primary objective of this post-hoc analysis was to test the effects of our cognitive rehabilitation trial by comparing the delta SDMT scores, applying a 4-point SDMT cut-off, in ST and nST groups.

**Statistical analysis**

All analyses were post hoc and not pre-specified. To quantify the clinical impact of longitudinal changes over time of the SDMT in the cohorts of patients exposed to ST and to nST we have applied the following categorization of the delta SDMT scores (delta SDMT:=SDMT score at T1 – SDMT score at T0) by using a 4-point SDMT cut-off:

- delta SDMT between −3 and 3 = not clinically significant SDMT change;
- delta SDMT ≤ −4 = clinically significant SDMT worsening;
- delta SDMT ≥ 4 = clinically significant SDMT improvement.

Thereafter, we compared the proportion of patients reporting a clinically significant SDMT improvement at the end of the 3 months training program by using the chi-square test.

Statistical analysis was performed by using SPSS software (SPSS, version 22.0; SPSS, Chicago, Ill).

**Results**

The comparisons of baseline demographic and clinical characteristics and of the baseline NP of POMS subgroups who underwent ST and n-ST are reported in Table 1.
Table 1
Baseline demographic and clinical characteristics of POMS subgroups underwent specific and non specific training

| Variable                                      | Specific Training (n = 8) | Non Specific Training (n = 8) | p - value (t, U, or Fisher’s exact test) |
|-----------------------------------------------|--------------------------|------------------------------|----------------------------------------|
| Sex (F/M)                                     | 5/3                      | 4/4                          | 1.0                                    |
| Age, years                                    | 15.8 (2.0)               | 15.7 (1.5)                   | 1.0                                    |
| Disease Duration, years                       | 3.5 (3.5)                | 3.3 (2.6)                    | 0.96                                   |
| Handedness, n. right-handed (%)               | 7 (87.5)                 | 8 (100)                      | 0.97                                   |
| Disease modifying therapy, n                  |                          |                              |                                        |
| Nothing                                       | 2                         | 2                            | 0.67                                   |
| Interferon beta                               | 6                         | 4                            |                                        |
| Glatiramer Acetate                            | 0                         | 1                            |                                        |
| Natalizumab                                   | 0                         | 1                            |                                        |
| Annualized Relapse Rate                       | 0.4 (0.5)                | 0.3 (0.5)                    | 0.72                                   |
| EDSS, median (min - max)                      | 2.0 (1.0–3.5)            | 3.0 (1.0–3.5)                | 0.28                                   |
| **Baseline neuropsychological performances**  |                          |                              |                                        |
| SRT- LTS                                      | 29.9 (12.6)              | 24.6 (6.5)                   | 0.2                                    |
| SRT - CLTR                                    | 22.1 (11.0)              | 20.4 (7.5)                   | 0.6                                    |
| SPART                                         | 19.3 (4.4)               | 22.8 (2.0)                   | 0.1                                    |
| SDMT                                          | 24.5 (4.6)               | 20.5 (3.6)                   | 0.1                                    |
| Trail Making Test A                           | 39.4 (11.5)              | 34.6 (9.8)                   | 0.5                                    |
| Trail Making Test B                           | 108.4 (61.4)             | 107.9 (79.4)                 | 1.0                                    |
| SRT-D                                         | 6.3 (2.8)                | 5.8 (1.5)                    | 0.2                                    |
| SPART-D                                       | 6.8 (1.0)                | 7.0 (1.4)                    | 1.0                                    |

Abbreviations: POMS = pediatric onset multiple sclerosis; EDSS = Expanded Disability Status Scale; ST = specific training; nST = non specific training; SRT-LTS = Selective Reminding Test Long Term Storage; SRT-CTLR = Selective Reminding Test – Consistent Long-Term Retrieval; SRT-D = Selective Reminding Test – Delayed; SPART = Spatial Recall Test; SPART-D = Spatial Recall Test – Delayed; SDMT = Symbol Digit Modalities Test.
At baseline, no differences were found between the 2 treatment arms regarding sex, age, and in terms of NP performances.

After the 3-month cognitive training, patients exposed to the ST showed a significant improvement in SDMT performances ($p < 0.0001$) in comparison to those treated with nST.

More in details, a significant effect for time (Baseline (T0) vs Post – Treatment (T1) comparison) was found for the mean (SD) SDMT values (ST group: 24.5 (4.6) vs 46.3 (6.7); nST group: 20.5 (3.6) vs 20.8 (4.1), $p < 0.0001$).

By applying the 4 points cut-off of the delta SDMT scores, 4 (25%) patients reported no clinically significant changes, 2 (12.5%) patients a clinically significant worsening and 10 (62.5%) patients a clinically significant improvement in the SDMT score at the end of the training program.

The proportion of patients reporting a clinically significant improvement of the SDMT was significantly ($p = 0.008$) higher in patients exposed to the ST ($8/8; 100\%$) in comparison to that in patients exposed to nST ($2/8; 25\%$) (Table 2).

Table 2

| Classes of SDMT changes in POMS subgroups underwent specific and non specific training | Specific Training (n = 8) | Non Specific Training (n = 8) | p - value |
|---|---|---|---|
| Not clinically significant changes | 0 | 4 | 0.008 |
| Clinically significant worsening | 0 | 2 | |
| Clinically significant improvement | 8 | 2 | |
Among the other patients exposed to the nST 4/8 (50%) reported stable SDMT scores (delta SDMT between −3 and +3, meaning a not clinically significant change), 2/8 (25%) had a significant deterioration.

Moreover, the overall improvement of the delta-CII was significantly higher in patients reporting a clinically significant improvement of the SDMT at the end of training in comparison to those who presented with a not clinically significant change and those with a clinically significant worsening of the SDMT (p = 0.038). (Fig. 1)

**Discussion**

Rehabilitation treatment with a computerized cognitive training specifically designed to exercise the attention domain resulted in a significant improvement of overall cognitive performances and in particular of the SDMT scores. With this post-hoc analysis we have also demonstrated that a specific attention training is associate with clinically meaningful changes of SDMT scores in the short term.

It is noteworthy that all patients exposed to the ST exhibited a clinically meaningful improvement of the SDMT scores in comparison to only 2/8 patients exposed to the nST at the end of the 3-month cognitive training.

To the best of our knowledge, this is the first report of the application of the 4-point SDMT cut-off, proposed by MSOAC (10), to the results of a RCT in order to test if the degree of changes in the SDMT scores obtained after a specific cognitive training were clinically meaningful.

The research about functional measurers capable to explore from different perspectives, including the non-motor disability, the overall impact of MS on disability has a long-lasting history.

In 1996 the MSFC was proposed as a multiple domains measure to detect and summarize walking impairment (via the time 25-foot walk test), upper extremity dexterity (via the 9-hole peg test) and cognition (via the PAST) abilities in patients with MS. (16)

Thereafter, most of the RCTs performed to evaluate the efficacy of disease modifying therapies included the MSFC as an outcome measure, but due to the difficulty interpreting the clinical meaning of z-score change and because it seems that MS patients not fully accept the tests (especially the PASAT), MSFC has not been extensively used in clinical practice. (8, 9)

The use of SDMT as an outcome measure in RCTs and observational studies has progressively gained more attention in the recent years. The SDMT performances have been found to be associated with different magnetic resonance imaging measures of MS disease progression (17–20).

Moreover, SDMT scores are predictive of different patient-related outcomes, such as employment and driving abilities (21–24), but also of future cognitive decline (25).
Given all these premises and based on its predictive validity, the very high level of sensitivity and specificity and the facility of administration, this cognitive test is often used in clinical practice to perform a basic cognitive screening helping to identify patients at high risk for cognitive impairment who need a more structured neuropsychological evaluation.

Recently, the psychometric properties of SDMT and PASAT have been compared and the former proved to be superior to the PASAT in assessing the IPS in patients with MS. (10)

Furthermore, a 4-point change in the SDMT has been proved to be a cut-off able to discriminate clinically meaningful changes from test scores changes due to practice effect or simply to the chance. (10, 26)

In our RCT the use of the 4-point SDMT cut-off allows us to demonstrate the clinical meaningfulness of the results obtained by a home-based computerized program for retraining attention dysfunction in POMS patients with attention impairment. Further studies are needed to confirm the clinical validity of this cut-off and its applicability in the routine clinical practice setting.

**Declarations**

**Availability of data and materials**

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

**Authors’ contributions**

MS defined the study concept and design, recruited patients and collected, analysed and interpreted the data.

RGV performed the neuropsychological evaluations and collected, analysed and interpreted the data.

LM performed the study supervision and a critical revision of the manuscript for intellectual content.

PI defined the study concept and design and collected, analysed and interpreted the data.

All authors read and approved the final manuscript.

**Ethics approval and consent to participate.**

The study was conducted with approval of the institutional review board

(Comitato Etico Indipendente Azienda Ospedaliero-Università Consorziale Policlinico - Approval Number: 0070059/CE). Parents of the participants signed an informed consent.
Competing interests

Marta Simone reports no disclosures.
Rosa Gemma Viterbo has received speaker honoraria from Biogen Idec and Teva.
Lucia Margari reports no disclosures.
Pietro Iaffaldano has served on scientific advisory boards for Biogen Idec and Bayer-Shering, and has received funding for travel and/or speaker honoraria from Genzyme, Biogen Idec, Merck-Serono, Teva and Novartis.

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