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Corticospinal inhibition and alexithymia in multiple sclerosis patients – An exploratory study

Moussa A. Chalah^{1,2}, Jean-Pascal Lefaucheur^{1,2}, Alain Créange^{1,3}, Samar S. Ayache^{1,2,*}

1. EA 4391, Excitabilité Nerveuse et Thérapeutique, Université Paris-Est-Créteil, Créteil, France
2. Service de Physiologie - Explorations Fonctionnelles, Hôpital Henri Mondor, Assistance Publique - Hôpitaux de Paris, Créteil, France.
3. Service de Neurologie, Hôpital Henri Mondor, Assistance Publique - Hôpitaux de Paris, Créteil, France.

***Corresponding author:** Samar S. Ayache, Service de Physiologie – Explorations Fonctionnelles, Hôpital Henri Mondor, Assistance Publique – Hôpitaux de Paris, 94010, Créteil, France. Email address: samarayache@gmail.com

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Abbreviations

CSP: Cortical Silent Period

EDSS: Expanded Disability Status Scale

ESS: Epworth Sleepiness Scale

FSS: Fatigue Severity Scale

FDR: False Discovery Rate

HADS: Hospital Anxiety and Depression Scale

IHI: Interhemispheric Inhibition

MEP: Motor Evoked Potentials

MFIS: Modified Fatigue Impact Scale

MS: Multiple Sclerosis

rMT: resting Motor Threshold

SDMT: Symbol Digit Modalities Test

TAS: Toronto Alexithymia Scale

TMS: Transcranial Magnetic Stimulation

Abstract:

Objectives: Alexithymia is a multicomponent personality construct that could occur in up to 53% of patients with multiple sclerosis (MS), with recent works proposing higher rates of alexithymia in progressive MS. Among the available models of alexithymia, some propose a deficient interhemispheric communication and an aberrant GABAergic transmission at its origin. However, no single study has addressed the underlying mechanism of alexithymia in MS. The aim of this work was to assess the relationship between GABAergic neurotransmission and alexithymia in progressive MS by means of transcranial magnetic stimulation (TMS).

Methods: Twelve patients with high alexithymia and fifteen patients with low alexithymia were included based on Toronto Alexithymia Scale (TAS). Sociodemographic, clinical and neuropsychological data were recorded. The following corticospinal excitability measures were obtained: resting motor threshold, cortical silent period (CSP which reflects cortical GABAergic function), and interhemispheric inhibition (i.e., GABAergic function mediated by interhemispheric fibers).

Results: No significant group differences were observed regarding sociodemographic, clinical or neuropsychological variables. Patients with high alexithymia scores exhibited shorter CSP than those with low alexithymia scores (81.87 ± 45.72 ms vs. 145.27 ± 77.26 ms, respectively, $p < 0.05$). A significant inverse correlation was also found between TAS scores and CSP duration ($r = -0.59$, $p < 0.05$).

Conclusion: This study offers insights into the neurophysiological mechanisms of alexithymia in MS. Reduced GABAergic transmission, as reflected by short CSP, seems to be associated with alexithymia in this population. Future studies would benefit from a more comprehensive evaluation of cortical and interhemispheric mechanisms in MS patients with alexithymia.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system and is the most common non-traumatic cause of disability in young adults. Its pathophysiology includes inflammation, demyelination, axonal loss and gliosis [1]. MS patients frequently suffer from cognitive and emotional symptoms. Among the latter, alexithymia could affect up to 53% of patients, with recent data suggesting high rates of alexithymia in progressive MS [1,2].

Alexithymia is a multicomponent construct characterized by difficulty in identifying and/or describing feelings, difficulty in differentiating feelings from bodily sensations, an externally oriented thinking, and a limited imagination reflected by paucity of dreams and fantasies [1]. Other manifestations, such as poor quality of sleep, anxiety and depression, have been described in the context of alexithymia [3].

Its pathophysiology is still not clear, with initial clinical and experimental data proposing an ‘interhemispheric deficit model’ of alexithymia which entails a dysfunction in the interhemispheric communication between the right ‘affective’ hemisphere and the left ‘cognitive’ hemisphere [1,4]; a dysfunction that may impair the processing of emotions. In addition, recent neurophysiological data suggest a defective GABAergic transmission in alexithymia [5,6].

A further understanding of the underlying mechanisms of alexithymia might have clinical implications and would improve patients’ quality of life. Transcranial magnetic stimulation (TMS), a neurophysiological noninvasive technique, has recently emerged as an appealing tool to unveil the pathophysiology of various neuropsychiatric diseases [7]. To date, very few TMS studies have addressed alexithymia [5,6], and none of them were done in MS. Hence, the primary objective of this work was to assess, by means of TMS, the neurophysiological mechanisms of this construct in progressive MS. The hallmark of progressive forms is

neurodegeneration compared to neuroinflammation and demyelination that predominate the pathophysiology of relapsing-remitting form [8]. A secondary objective was to perform a clinical and neuropsychological evaluation to control for potential confounding variables that could be associated with alexithymia [1,3].

Material and Methods

The study was conducted at the neurology department of Henri Mondor Hospital, Creteil, France. Adult patients aged between 18 and 75 years, with a confirmed diagnosis of primary or secondary progressive MS, according to 2017 revised McDonald's criteria, were included [9]. Patients had to be right-handed (Edinburgh Handedness Inventory [10]), free of relapses or steroids treatment in the last three months and receiving a stable treatment in the last six months. Patients were not included if they had contraindications to TMS (i.e., history of seizures, presence of ferromagnetic implants in the head area), medications known to alter the corticospinal excitability [11], severe visual or motor deficits that could alter testing, intellectual impairment as per the Mini Mental State Exam (score < 24) [12], or documented neuropsychiatric disorders.

Twelve patients with high alexithymia scores and 15 patients with low alexithymia scores were included based on the 20-item Toronto alexithymia scale (TAS, cutoff score: 55) [13,14]. The scale contains three factors: difficulty in identifying feelings (7 items), difficulty in describing feelings (5 items), and externally oriented thinking (8 items).

The local ethical committee has approved the study protocol which was performed in conformity with the declaration of Helsinki. All patients voluntarily gave their written informed consent prior to inclusion.

Clinical, sociodemographic and neuropsychological data

Sociodemographic and clinical data were collected. All patients underwent a full neurological exam, and were evaluated for (i) physical disability using the Expanded Disability Status Scale (EDSS) [15], (ii) cognitive function using the Symbol Digit Modalities Test (SDMT) [16], (iii) fatigue using the 7-item Fatigue Severity Scale (FSS) [17] and the 21-item Modified Fatigue Impact Scale (MFIS) [18], (iv) anxiety and depression using the 14-item Hospital Anxiety and Depression Scale (HADS) [19], and (v) excessive daytime sleepiness using the 8-item Epworth Sleepiness Scale (ESS) [20].

Transcranial magnetic stimulation

The TMS paradigm performed in this study was previously described (for details see [21,22]). Briefly, patients were seated in a quiet room in a comfortable chair and wore a cap that enables to mark and optimize coil repositioning during the experiment. Motor evoked potentials (MEP) were collected via a pair of adhesive pre-gelled surface electrodes (Ref. 9013S0242, Natus-Dantec, Skovlunde, Denmark) placed over the right first dorsal interosseous (FDI) muscle in a tendon-belly montage. Signals were acquired (sampling rate: 5kHz), filtered (20 Hz - 2 kHz bandwidth) and amplified (50–500 μ V/division) using Phasis II machine (EsaOte, Florence, Italy). The level of contraction in the target muscle was controlled by visual and auditory feedback.

First, the resting motor threshold (rMT) which reflects the biophysical properties of neural membrane was determined on a fully relaxed FDI muscle. This corresponds to the minimal stimulator intensity necessary to produce MEP (≥ 50 μ V) in 5 of 10 trials. This was followed by the assessment of the contralateral cortical silent period (CSP) and interhemispheric inhibition (IHI).

CSP is a neurophysiological parameter that reflects inhibitory processes within the spinal cord

and the motor cortex [21,22]. It implies an early spinal component and a late cortical component, and is mediated by GABAergic neurotransmission. Whilst patients exert tonic voluntary contraction of the target muscle, single TMS pulses were delivered at 140% of rMT. CSP was measured on highly-magnified superimposed traces from the end of the MEP till reoccurrence of electromyographic activity. For the rMT and CSP, a MagPro X100 stimulator (MagVenture (Mag2Health), Farum, Denmark) was used, and pulses were delivered through a circular coil (MC125, MagVenture, Denmark).

The interhemispheric inhibition (IHI), a parameter reflecting the transcallosal GABA-mediated inhibitory activity, was also assessed in this study. It was obtained at complete muscle rest using two figure-of-eight coils (70mm coil type P/N 9925–00; Magstim) connected via a Bistim module to two Magstim 200 stimulators as previously described [22]. A paired-pulse paradigm was applied using suprathreshold stimuli (interstimulus intervals: 8, 10 and 12 ms), the adopted intensity of both pulses was that yielding MEP with a peak-to-peak amplitude of 1 mV. For each interval, IHI was calculated using the following formula: $IHI = 100 - (100 \times \frac{\text{MEP amplitude in response to double-pulse}}{\text{MEP amplitude in response to test pulse}})$. Afterwards, the mean (IHI_{mean}) and maximal (IHI_{max})

IHI obtained for the three intervals was studied [21].

For each parameter (CSP and IHI obtained at each interval), 4 trials were performed and averaged online in each patient.

Statistical analyses

SPSS was used to perform statistical analysis (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp). The normality of data distribution was tested using Kolmogorov-Smirnov test and the homogeneity of variance was checked using Levene test. Group comparison was performed using Mann-Whitney test or Student t test for

quantitative data and Fisher's exact test for qualitative data. In the whole cohort, Spearman's or Pearson's correlation and Benjamini-Hochberg false discovery rate (FDR) corrections were applied to assess the relationship between TAS scores and all measures (i.e., clinical, sociodemographic, neuropsychological and neurophysiological data) ($q=0.05$). The significance level was set at 0.05. Data are presented as mean \pm SD.

Results

Corticospinal excitability data

Compared to patients with low alexithymia scores, those with high alexithymia scores had significantly shorter CSP (145.27 ± 77.26 ms vs. 81.87 ± 45.72 ms, respectively; $p=0.019$), but they did not differ with regards to rMT or IHI (**Table 1**).

Sociodemographic, clinical and neuropsychological data

The means of TAS scores in low alexithymia and high alexithymia groups were respectively 43.00 ± 8.45 and 61.92 ± 5.32 . Low alexithymia and high alexithymia groups did not significantly differ with regards to sociodemographic and clinical data, namely age (54.13 ± 12.13 vs. 56.42 ± 11.86 years, respectively), gender ($n=8$ women/ $n=7$ men vs. $n=4$ women/ $n=8$ men, respectively), education (14.47 ± 1.92 vs. 13.50 ± 1.98 years, respectively), relationship status ($n=10$ in a relationship vs. $n=7$ in a relationship, respectively), disease type ($n=7$ PP/ $n=8$ SP vs. $n=6$ PP/ $n=6$ SP, respectively), EDSS score (5.73 ± 1.24 vs. 6.33 ± 0.49 , respectively), immunotherapy ($n=7$ treated/ $n=8$ untreated vs. $n=5$ treated/ $n=7$ untreated, respectively), duration of the disease (12.87 ± 6.06 vs. 12.58 ± 6.12 years, respectively) and duration of the progressive phase (8.60 ± 6.22 vs. 8.42 ± 7.49 years, respectively).

In addition, no significant group differences were observed in scores of HADS_{anxiety} (low alexithymia: 4.80 ± 3.28 vs. high alexithymia: 5.75 ± 3.47), HADS_{depression} (low alexithymia: 5.40 ± 3.48 vs. high alexithymia: 7.17 ± 3.07), MFIS (low alexithymia: 45.93 ± 13.59 vs. high alexithymia: 55.58 ± 17.05), FSS (low alexithymia: 50.13 ± 9.01 vs. high alexithymia: $47.92 \pm$

13.40), ESS (low alexithymia: 5.27 ± 4.30 vs. high alexithymia: 3.17 ± 2.55), and SDMT (low alexithymia: 44.93 ± 13.64 vs. high alexithymia: 38.17 ± 14.04).

Correlation analysis

Regarding the neurophysiological evaluation, a significant inverse correlation was found between TAS scores and CSP duration ($r=-0.59$, $p=0.001$).

Among the sociodemographic variables, a significant inverse correlation was found between TAS scores and years of education ($r=-0.48$; $p=0.012$).

On the clinical and neuropsychological evaluation, TAS scores were significantly directly correlated with MFIS scores ($r=0.39$; $p=0.048$) and tended to inversely correlate with SDMT scores ($\rho = -0.34$; $p=0.080$).

After applying correction for multiple comparison, the only remaining significant correlation was between TAS scores and CSP duration ($p_{\text{FDR adjusted}} = 0.015$).

To test the relationship between alexithymia and CSP while controlling for education and fatigue, a stepwise linear regression analysis was performed after checking the assumptions. TAS score was the dependent variable. Independent variables were MFIS score and years of education (step 1) and CSP (step 2). CSP duration significantly contributed to the variance in TAS scores ($\beta=-0.489$, $p=0.002$).

Discussion

This study offers, for the first time, insights into the neurophysiological mechanisms of alexithymia in progressive MS. Compared to patients with low alexithymia scores, those with high alexithymia scores exhibited a reduced CSP. In addition, in the whole cohort, TAS scores were significantly correlated with CSP duration, years of education, and fatigue scores, and tended to correlate with SDMT scores.

Neurophysiological data

The present data suggest an association between alexithymia and CSP. The fact that CSP reflects GABAergic activity, such a relationship may be interpreted as a defective GABAergic transmission in MS patients with high alexithymia. The results of the present study replicate the findings of a previous one done in patients with borderline personality disorder [5]. Such results suggest a dysfunction of GABAergic interneurons in the motor cortex in relation with alexithymia. One may hypothesize that this could involve other GABAergic interneurons such as those of the corticolimbic system, a finding that may explain affective manifestations [5].

Regarding IHI, neither a group difference nor a correlation was found with regards to alexithymia. Based on the interhemispheric deficit model, the hypothesis of this work was to observe an altered interhemispheric transfer (i.e., IHI) in relation with alexithymia in MS [4]. Unlike the present work, one neuropsychological study suggested a defective interhemispheric transfer at the basis of alexithymia [23]. Such a discrepancy between both studies might be attributed to differences in the outcomes (i.e., neuropsychological [23] vs. neurophysiological variable), the adapted alexithymia scale (Beth Israel Questionnaire [23] vs. TAS), and the cohorts' clinical and sociodemographic characteristics.

Another TMS study documented a reduced IHI among students with high alexithymia scores [6]. The differences in the recruited cohorts (healthy students [6] vs. patients with progressive MS) may explain the divergence in outcomes. In fact, IHI is mediated by transcallosal excitatory pathways that travel to the other hemisphere to exert their inhibitory action on the opposite corticospinal tract via GABAergic interneurons [7]. The corpus callosum is frequently altered by MS pathological processes [24]. Therefore, one may hypothesize that, in this study, the corpus callosum - and subsequently the IHI- is severely affected and could no more serve to differentiate between individuals with high and low alexithymia (floor effect).

Sociodemographic, clinical and neuropsychological data

Patients with high and low alexithymia did not differ regarding sociodemographic data, a finding that is in line with part of the available literature [1,23]. However, the current work has shown links between alexithymia and some variables (i.e., education level and fatigue) although these relationships did not pass the statistical correction.

First, alexithymia was associated with lower education, a finding that is consistent with some [25], but not all MS studies (for reviews see [1]). Individuals with higher education might have better language skills to verbalize their feelings, rendering them less alexithymic than those with lower education. In addition, in MS, education was suggested as a proxy for cognitive reserve [26], and might have a role in mediating the manifestations of alexithymia.

Second, a correlation was found between alexithymia and MS fatigue which may suggest common substrates or bidirectional interaction between both symptoms (for review see [1]). For instance, recent evidence suggests interoceptive failure in the pathophysiology of alexithymia and fatigue [27,28].

In addition, a nonsignificant trend toward correlation was found between TAS and SDMT scores. Similarly, other MS studies did not find significant association between alexithymia and cognitive measures [2,23]. Moreover, no significant association was found between alexithymia and anxiety/depression which is consistence with some, but not all MS studies (for reviews see [1]). As some authors propose, alexithymia, depression and anxiety should be considered as overlapping, yet distinct constructs [29]. Finally, since poor sleep quality has been reported in the context of alexithymia [30], excessive daytime sleepiness was evaluated in the current work, but did not correlate with alexithymia. Only few available reports have addressed this issue, but none was done in MS. Alexithymia was found to be linked with sleep in one study using subjective measures (i.e., Pittsburg sleep quality index [31]), and in one of two other studies employing a polysomnographic evaluation [30,32].

Limitations and perspectives

It is worth noting some limitations. First, one should acknowledge the exploratory nature of the study and the small sample size. Hence, the results should be considered as preliminary. Second, the cross-sectional design of the study constitutes another limitation. Long-term follow-up would be of interest to observe parallel changes in alexithymia and TMS measures. Third, the current work focused on progressive MS. Since progressive types are mainly characterized by neurodegeneration, future works may consider similar evaluation in patients with relapsing-remitting MS. Therefore, the current results merit to be addressed in a large cohort of MS patients with different disease types and judge the utility of CSP in assessing alexithymia in this whole population.

Fourth, a limitation might arise from the adopted assessment tools. Cognition was evaluated using the SDMT which is a sentinel test widely used for cognitive screening in MS [33]. Since the relationship between alexithymia and cognitive variables is supported by some studies in healthy and clinical populations, employing neuropsychological batteries would provide a thorough assessment of the neuropsychological correlates of alexithymia in MS. The same applies to sleep quality whose evaluation was limited to a single scale. Admitting the frequency of sleep symptoms in MS, future works may benefit from an in-depth assessment of sleep. As for the neurophysiological evaluation, it focused on few variables; therefore, including other corticospinal excitability parameters might enhance the current knowledge on the matter. For instance, a more comprehensive neurophysiological evaluation may include measures of intracortical inhibitory and facilitatory circuits (e.g., intracortical inhibition and facilitation). Using other parameters to explore the callosal fibers, like interhemispheric facilitation and ipsilateral corticospinal silent period, could provide different insight on the interhemispheric hypothesis. Moreover, combining physiological measures with MRI techniques would enable a simultaneous evaluation of structural and functional correlates of alexithymia. Furthermore,

it would be of interest to include neuroimmune evaluation since central (i.e., cerebrospinal fluid levels of interleukin-8) and peripheral (i.e., serum levels of interleukins-6 and -8, and tumor necrosis factor- α) inflammatory markers were found to be associated with alexithymia in other clinical populations [1].

Conclusion

This study offers insights into the neurophysiological mechanisms of alexithymia in MS. Reduced GABAergic transmission, as reflected by short CSP, seems to be associated with alexithymia in this population. Our findings warrant further investigation in large-scale longitudinal studies.

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Table 1. Neurophysiological patients' data

	Low alexithymia group (n=15)	High alexithymia group (n=12)	P value (Student t test)
rMT (%)	58.93 ± 12.84	61.50 ± 16.82	0.657
CSP (ms)	145.27 ± 77.26	81.87 ± 45.72	<u>0.019</u>
IHI _{mean} (%)	-0.25 ± 39.29	-8.22 ± 34.67	0.587
IHI _{maximal} (%)	25.41 ± 31.98	13.50 ± 29.36	0.329

Values are expressed as mean ± SD. CSP: Cortical Silent Period; IHI: Interhemispheric Inhibition; rMT: resting Motor Threshold. P<0.05 are underlined.