Evaluation of adaptive cognitive function in Multiple Sclerosis Patients Using Functional Transcranial Doppler

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Abstract: Background: Functional Transcranial Doppler (fTCD) is an efficient reliable method for detecting cerebral lateralization; however very few studies were interested in its application in multiple sclerosis (MS) clinical settings. **Objective:** Our purpose was to investigate whether lateralization index for language is altered in multiple sclerosis patients using fTCD and its relation to adaptive cognitive functions. **Methods:** The study recruited 20 multiple sclerosis patients and 20 healthy control subjects matched for age, sex and handedness. Using fTCD lateralization index for language was calculated in both groups. To assess clinical disabilities due to MS, we used Multiple Sclerosis Function Composite (MSFC), Expanded Disability Status Scale (EDSS) and the Edinburgh Handedness Inventory (EHI). **Results:** Multiple sclerosis patients showed more bilateral activation for language tasks compared to controls ($P < 0.001$). Lateralization index in patients showed high significant correlation with the disease duration (P value < 0.01). Functional TCD lateralization index revealed a significant correlation with the PASAT scores (P value <0.05), however it showed no correlation Timed Waked Test TWT or the nine Hole Peg Test (9HPT). In addition there was no significant correlation of fTCD lateralization index with either the EDSS or the Edinburgh Handedness Inventory scores. **Conclusion:** Functional transcranial Doppler should be more entertained in investigating cognitive dysfunction in multiple sclerosis patients. It may offer a future promising tool for diagnosing and following up treatment and rehabilitation effects.

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1. Introduction

Functional recovery in MS is achieved and sustained through remyelination, resolution of inflammation and functional reorganization. After stroke, functional reorganization relies on molecular and cellular mechanisms to induce changes in systems-level functional responses, which are the proximal effectors of of perception, action and cognition in the undamaged hemisphere **(1)**. Evidence across brain systems supports a similar adaptive role for functional reorganization in MS despite widespread pathology. Functional reorganization accompanying recovery in this disease limits the negative effect of damage on behavior Interestingly, the distribution of reorganization can alter a previously lateralized function to a certain hemisphere. For example, the distribution of activity in motor tasks changes toward increased ipsilateral hemisphere (unaffected) activation as the disease progresses, sometimes even in simple motor tasks. A persistent recruitment of the sensorimotor cortex on the ipsilateral hemisphere is associated with poor clinical recovery **(2)**.

Literature reviewing revealed the usage of fTCD in multiple sclerosis very few studies, in spite of the fact that multiple sclerosis has been extensively investigated using conventional TCD. Functional TCD was largely investigated in evaluation of other neurological diseases, e.g. stroke, migraine**,** epilepsy, along with psychiatric disorders such as schizophrenia, and autism. Our interest is based upon the fact that most multiple sclerosis lesions are perivenular, so the disease could have a vascular (venular) pathogenetic origin. Recent data suggests that these changes are found with increased prevalence in MS but with modest sensitivity/specificity for the disease **(3)**. Despite the clear involvement of the cerebrovascular system in multiple sclerosis, it shows - at least from theoretical point of view- no direct biasing to flow velocities at the basal arteries of the brain, which form the basis for fTCD. Testing the applicability of fTCD in MS patients, as a measure for altered functional organization, could help in the ever-demanding functional assessment and maybe even the expected outcome for MS patients.This study was trying to answer two main questions; whether lateralization index measured by fTCD is affected in MS patients? And are fTCD parameters correlating with clinical functional scales?

2. Subjects and methods

The study was carried out on forty subjects, of whom 20 patients had multiples sclerosis and 20 were

healthy control subjects. Inclusion criteria incorporated patients with definite MS according to revised Mcdonald criterion 2010 and having relapsing remitting or secondary progressive patterns. Exclusion criteria comprised other clinical types of MS (primary progressive, progressive relapsing, benign MS), MS patients with focal lesions at critical language areas on MRI, Patients with other neurological or medical diseases affecting cognitive function, inability to insonate through the temporal window due to bone thickness or bone defects and age above 45 or below 18 years. To assess for different clinical effects of MS, we conducted the following clinical scales to all patients; [1] Edinburgh Handedness Inventory (EHI) **(4),** a measurement scale used to assess the dominance of a person's right or left hand in everyday activities. [2] Multiple Sclerosis Function Composite (MSFC) scale **(5)** which is three parts scale measures different disability domains in MS patients; (a) The Timed Waked Test (TWT), measures ambulation disability, (b) 9 Hole Peg Test (9HPT), measures the arm function, (c) Paced Auditory Serial Addition Test (PASAT), measures the cognitive disability. [3] Expanded Disability Status Scale (EDSS) **(6)**, a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time. Edinburgh Handedness Inventory was also applied to all control subjects. To assess for language lateralization inex we applied simultaneous bilateral functional Transcranial Doppler sonography (fTCD) to all 40 subjects to record blood flow velocities (FV) in the anterior, middle, and posterior cerebral arteries as a way for close coupling between regional cerebral blood flow changes and neural activation. Determination of hemispheric language dominance by fTCD was performed as subjects were seated in front of a computer screen where, 5 seconds after a cueing tone, a letter was presented for 2.5 seconds Subjects silently had to find as many Arabic words as possible starting with the displayed letter. To control the performance of the task, subjects were instructed to report the words after a second auditory signal 15 seconds after presentation of the letter. All words had to be reported within a 5-second time period. Afterward, a relaxation period of 60 seconds was given. Then the next letter was presented in the same way. Letters were presented in random order. No letter was displayed more than once. Relative FV changes from repeated presentations of letters (on the average 20 runs) were averaged time-locked to the cueing tone. Differences in the velocity changes in the two MCAs in every patient were statistically evaluated by the Wilcoxon test for each time point.

3. Results

The patients group included 8 males (40%) and 12 females (60%) with mean age was 30.9 years. The control group showed a closely matching age and sex. Both patients and control had completed the Edinburgh Handedness Inventory (EHI), both groups showed relative similarity, with Patient's mean score 85.0 and control mean score 83.0. Lateralization index for language using the fTCD was done for both groups, there was a significant difference being lower in patients group ($p<0.001$) (table 1).

Table 1: Summary of results for both patients and controls

	Patients (N=20)	**Control (N=20)**	**p-value**
Age (Ys) (mean ± SD)	30.95 ± 6.07	31.10 ± 6.7	p =0.94
Sex N (%)	Female=12 (60)	Female= 11(55)	P=0.76
Disease Type	RR*=13 SP*= 7	-	-
Disease Duration (Ys) (mean ± SD)	4.3 ± 2.1	-	-
EHI* (mean ± SD)	85.0 ± 13.5	83.0 ± 15.6	p =0.67
EDSS* (mean ± SD)	3.925 ± 1.9213	-	
MSFC* total score (mean ± SD)	0.830 ± 0.09	-	
fTCD*, Lateralization index (mean ± SD)	1.3650 ± 0.16631	4.2775 ± 1.07882	p < 0.001

*RR=Relapsing remitting, SP=Secondary progressive, EHI= the Edinburgh Handedness Inventory, EDSS Expanded Disability Status Scale = MSFC= Multiple Sclerosis Function Composite, fTCD=Finctional Transcranial Doppler.

Table 2: Summary of MSFC Scores

Test (MSFC)	**Mean ± SD**
The Timed Waked Test (TWT)	7.1±1.832
9 Hole Peg Test (9HPT)	22.6±4.272
Paced Auditory Serial Addition Test (PASAT)	40.1±9.760
MSFC total score	0.83± 0.092

A significant difference was found in the lateralization index values between patient subgroups (relapsing remitting or secondary progressive) with p-value of less than 0.05 for all parameters (Table 3).

Table 3: Functional scales and fTCD lateralization index for both MS types.

Variable (mean)	RR-MS	SP-MS	p Value
Disease Duration (Y)	4 years	6 years	0.033
EDSS Score	2.7	6.2	0.043
MSFC total score	0.842	0.811	0.029
fTCD lateralization index	1.42	1.26	0.042

In the control group, a significant positive correlation exists between handedness score and lateralization index (P value 0.01), while there were The in contrast showed no significant correlation in the patient group, neither for the whole group nor for a disease subtype (p>0.05) (Figure 1).

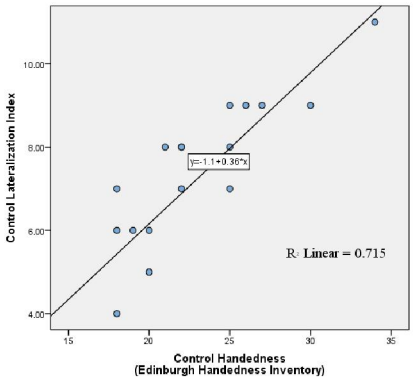

Figure 1: Correlation between handedness score and lateralization index in control group

Correlations between lateralization index measured by fTCD and different functional scales demonstrated that there is no significant correlation with the EDSS or total MSFC mean scores. However on doing correlations with the MSFC subscales we found a significant correlation between the PASAT mean scores and the lateralization index mean values (P value <0.016) (Figure 2).

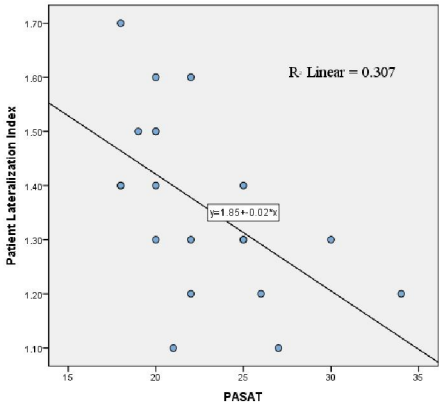

Figure 2: Correlation between lateralization index and PASAT (sub component of MSFC)

In addition, a highly significant correlation (P value < 0.01) was found between the disease duration and the lateralization index (Figure 3).On the other hand, disease phase or sex did not affect the significant relationship found between duration and lateralization index.

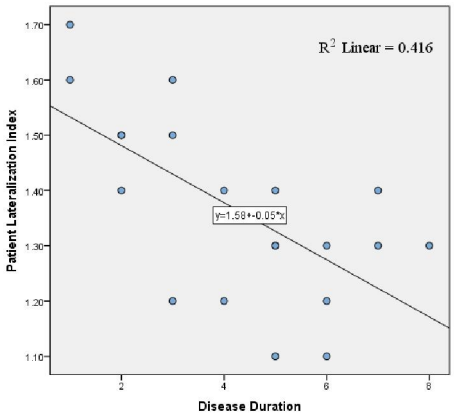

Figure 3: Correlation between lateralization index and disease duration

4. Discussion

In the current study, functional Transcranial Doppler (fTCD) for language lateralization was compared between 20 Multiple Sclerosis (MS) Patients, and 20 healthy subjects (control) matched for both age and sex. The study clearly shows the remarkable change in lateralization of language in multiple sclerosis patients compared to the control group. Lateralization index was significantly lower in patient group (reflecting bilateral hemispheric activation) compared to control group (higher lateralization index values reflects left hemispheric activation). Handedness assessment was done by Edinburgh Handedness inventory to closely match the handedness between the two groups. This inventory is used in our study for objective neuropsychological assessment of lateralization for hand function. Despite both groups showed relatively similar mean scores at the Edinburgh Handedness inventory, fTCD for language differed markedly. All multiple sclerosis patients studied showed bilateral hemispheric activation for the language task in contrast to the control group. A comparable difference was found as

well between relapsing remitting and secondary progressive subgroups, being lower at secondary progressive subgroup. This indicates more profound affection than the relapsing remitting phase of the disease. These findings reflect the existence of neuroplasticity mechanisms reflecting the plasticity of the adult human brain. This has been amply documented by several studies during the past few years **(1)**, **(7)**, **(8)**. The neuroplasticity that takes place in response to pathological lesions may reduce the functional consequences of these lesions and thus prevent or reduce the clinical expression of the symptoms **(9)**. It was recently suggested, on the basis of fMRI studies, that cortical reorganization processes of this kind might prevent the expression of acute symptoms (relapses) and slow down the gradual aggravation of the natural evolution of the disease **(10)**.

Interestingly, the study showed that fTCD language lateralization index in multiple sclerosis patients had no correlation with clinical functional scales such as the EDSS and MSFC in general. This finding supports the recently proposed MS disease progression hypothesis by **Schoonheim et al**, which suggests that initial structural damage causes brain hyperactivation, which results in low disability and cognitive preservation, but after this hyperactivation peaks, progressive cognitive impairment and disability ensue **(11)**. While this hypothesis elegantly describes the general mechanism of altered brain activation observed in MS patients, it also illustrates the lack of specific mechanisms that may prevent development of disability in patients, especially in patients who follow a milder course **(12)**.

In the view of the previous hypothesis by **Schoonheim et al (11)**, the lack of significant correlation between fTCD lateralization index and clinical functional scales, inferring that the bilateral hemispheric activation is a compensatory "hyper activation" that leads to functional clinical improvement. This has been shown by different recent fMRI studies **(13)**.

The bilateral hemispheric activation as an adaptive compensatory mechanism for language is not unique to multiple sclerosis, it is well known at different neurological disorders, as in stroke **(14)**, and brain tumors **(15)**. However, the early appearance of this mechanism as shown in the current study and the lack of apparently focal lesions in MRI at critical language areas reflects the diffuse and wider spread nature of the disease than the focal lesions detected in conventional MRI.

Quantitative magnetic resonance techniques almost invariably demonstrate abnormalities in the normal appearing brain tissue, being white matter, or gray matter. While the exact origin of the changes remains elusive, these abnormalities seem to occur, to a certain degree, independently of the focal lesions. In the normal appearing white matter, a wide variety of quantitative magnetic resonance techniques show subtle, but definite abnormalities in multiple sclerosis patients, and may even be already present at presentation **(16)**.

Eshaghia et al, showed in a longitudinal study for atrophic and degenerative changes in MS that there was a clear early correlation with disease duration irrespective of the focal lesions **(17)**. Our study showed a similar early correlation for disease duration with neuroplasticity and functional adaptive changes for a certain function (language). It is tempting to speculate that neuroplasticity and adaptive changes run in parallel with the continuous degenerative changes occurring in MS patients. However, this speculation should be translated to longitudinal studies comparing MRI parameters for brain volume, white matter involvement and grey matter volume with the fTCD parameters would offer a better insight for this issue **(18)**.

A subset of MSFC, the Paced Auditory Serial Addition Test PASAT, showed a significant correlation with the fTCD lateralization index. A possible interpretation, is that EDSS and the subcomponents of MSFC that are related mainly to motor functionality, did not show a significant relationship, in contrast to the PASAT (the pure cognitive subcomponent) which showed a significant relationship. PASAT is one of the cognitive tests that demonstrate early affection in multiple sclerosis patients as it tests the processing speed, which is heavily dependent on white matter integrity. The authors of an interesting study using PASAT procedures on patients in the early stage of Clinically Isolated Syndrome (CIS) established that compensatory functional activation do occur compared to control. This activation occurred both quantitatively (more activation at the expected sites) and topographically (activation of new areas compared to control) **(19)**.

In the light of the study of **Audoin et al**, earlier affection of PASAT and fTCD lateralization index (our study) provides an insight for the early affection of cognitive processing in MS patients **(19)**. In fact, other functions like motor functions shows early affection as well **(20)**. The fTCD lateralization index for language did not show a correlation with the functional scales that test motor functions (MSFC hand and walking tests, and the EDSS), so the results should be interpreted cautiously. An explanation for such finding may be due to affection of the motor functions by focal lesions at other critical sites such as the spinal cord and the corticospinal tract. These lesions would increase the disability significantly

leaving the reminder of the brain systems at a relatively better function.

In conclusion, fTCD provides valuable information –in coincidence with functional cognitive scales- about ongoing adaptive brain mechanisms through objectively assessed lateralization index values. Hence, fTCD could be a valuable, practical and easily applied tool considered in following up disease status and progression, rehabilitation and disease modifying drugs effects for multiple sclerosis patients.

Further validation of our results should be obtained through a longitudinal study at different populations multiple sclerosis patients for following up the changes in lateralization index in with the evolution of time. A future application for comparing fTCD lateralization index with fMRI for language tasks may also be a worse thought for more confirmation of the results and more accurate spatial localization of cerebral activation.

Reference

1. Cramer SC. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Ann Neurol* 2008 Mar;63:272-287.
2. Tomassini V, Matthews PM, Thompson AJ, et al. Neuroplasticity and functional recovery in multiple sclerosis. *Nat Rev Neurol* 2012 Nov 5;8:635-646.
3. Baracchini C, Gallo P. Prevalence, sensitivity, and specificity of chronic cerebrospinal venous insufficiency in MS. *Neurology* 2011 Nov 22;77:e124-e125.
4. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971 Mar;9:97-113.
5. Cutter GR, Baier ML, Rudick RA, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain* 1999 May;122 (Pt 5):871-882.
6. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983 Nov;33:1444-1452.
7. Bosnell RA, Kincses T, Stagg CJ, et al. Motor practice promotes increased activity in brain regions structurally disconnected after subcortical stroke. *Neurorehabil Neural Repair* 2011 Sep;25:607-616.
8. Filippi M, Riccitelli G, Mattioli F, et al. Multiple sclerosis: effects of cognitive rehabilitation on structural and functional MR imaging measures--an explorative study. *Radiology* 2012 Mar;262:932-940.
9. Pelletier I, Sauerwein HC, Lepore F, Saint-Amour D, Lassonde M. Non-invasive alternatives to the Wada test in the presurgical evaluation of language and memory functions in epilepsy patients. *Epileptic Disord* 2007 Jun;9:111-126.
10. Pelletier J, Audoin B, Reuter F, Ranjeva J. Plasticity in MS: from Functional Imaging to Rehabilitation. *Int MS J* 2009 Apr;16:26-31.
11. Schoonheim MM, Geurts JJ, Barkhof F. The limits of functional reorganization in multiple sclerosis. *Neurology* 2010 Apr 20;74:1246-1247.
12. Schoonheim MM, Hulst HE, Landi D, et al. Gender-related differences in functional connectivity in multiple sclerosis. *Mult Scler* 2012 Feb;18:164-173.
13. Colorado RA, Shukla K, Zhou Y, Wolinsky JS, Narayana PA. Multi-task functional MRI in multiple sclerosis patients without clinical disability. *Neuroimage* 2012 Jan 2;59:573-581.
14. Thulborn KR, Carpenter PA, Just MA. Plasticity of language-related brain function during recovery from stroke. *Stroke* 1999 Apr;30:749-754.
15. Kosla K, Pfajfer L, Bryszewski B, Jaskolski D, Stefanczyk L, Majos A. Functional rearrangement of language areas in patients with tumors of the central nervous system using functional magnetic resonance imaging. *Pol J Radiol* 2012 Jul;77:39-45.
16. De Groot CJ, Bergers E, Kamphorst W, et al. Post-mortem MRI-guided sampling of multiple sclerosis brain lesions: increased yield of active demyelinating and (p)reactive lesions. *Brain* 2001 Aug;124:1635-1645.
17. Eshaghi A, Bodini B, Ridgway GR, et al. Temporal and spatial evolution of grey matter atrophy in primary progressive multiple sclerosis. *Neuroimage* 2014 Feb 1;86:257-264.
18. Dutta R, Trapp BD. Pathogenesis of axonal and neuronal damage in multiple sclerosis. *Neurology* 2007 May 29;68:S22-S31.
19. Audoin B, Au Duong MV, Malikova I, et al. Functional magnetic resonance imaging and cognition at the very early stage of MS. *J Neurol Sci* 2006 Jun 15;245:87-91.
20. Rocca MA, Valsasina P, Ceccarelli A, et al. Structural and functional MRI correlates of Stroop control in benign MS. *Hum Brain Mapp* 2009 Jan;30:276-290.