Teriflunomide, cognition and MRI: a longitudinal study

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Introduction & Objectives

As cognitive impairment in multiple sclerosis (MS) is a frequent and disabling symptom, it is particularly important to identify treatments that have proven efficacy in this aspect of the disease. Several disease-modifying therapies for MS have been evaluated and shown to have a potential effect on cognition, but to date there is very little data with Teriflunomide (TRF), and its neurobiological correlates.

The objective is to explore the influence of TRF on comprehensive cognitive function and its MRI correlations (global and focal brain volume) in relapsing-remitting multiple sclerosis (RRMS) after two years of therapy.

Methods

Study design & population

1. Two assement timepoints

M0 (before TRF treatment)
MRI + Cognitive assessment

M24 (24 months TRF treatment)
Same MRI + Cognitive assessment

2. Two levels of analyses

24 patients with RRMS

Cognitive preserved patients n=15

Cognitive imparaired patients n= 9

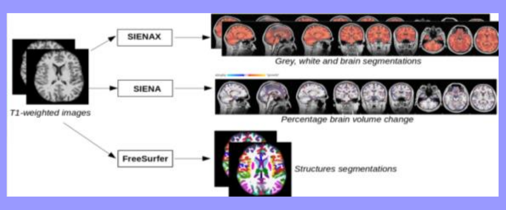
Evolution for all patients

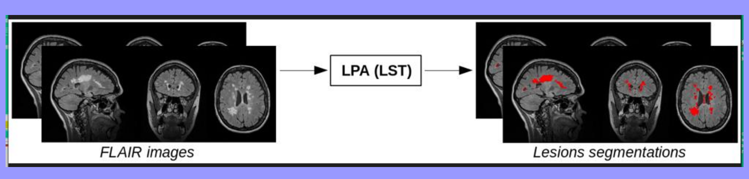
Group comparison (cognitive impairment if 4 or more subtests ≤ 10th percentile at baseline)

	All group	Preserved group	Impaired group	p-value***
	n =24	n=15	N=9	
Age*, in years	38.83 (8.75)	36.80 (8.39)	42.22 (8.71)	0.08
Years of education	14.29 (1.99)	14.13 (1.81)	14.56 (2.35)	0.60
Female/Male	14 / 10	9 / 6	5 / 4	0.86
Disease duration*	6.5 (6.45)	8.27 (6.94)	3.56 (4.45)	0.07
EDSS score**	1 (0 - 2.5)	1 (0 - 2.5)	1 (0 - 2)	0.98
TRF duration* in months	23.21 (2.72)	24 (0)	21.89 (4.26)	0.38

*mean (standard deviation); **median (range); EDSS = Expanded Disabillity Status Scale;
*** comparison between preserved versus impaired group

MRI analyses





Cognitive assesment: BCcogSEP

BCcogSEP is a French, short, comprehensive assessment test battery for patients with MS[1]. the PASAT test was removed from the analyses due to missing data (> 30%).

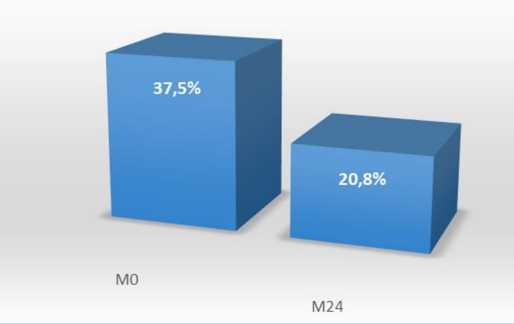
- **SRT** (verbal episodic memory) → Mean number of words, learning (%), delayed recall
- **10/36** (visuo-spatial memory) → Immediate and delayed recall
- **Digit Span** (auditory verbal working memory) → Direct and indirect
- **DSST/Code** (processing speed) → Number of correct answers in 1 min 30 sec
- **Crossed Tapping** (executiv function: shifting) → Number of errors
- **Go/no-go** (executiv function: Ihnibition) → Number of errors
- **Verbal fluency** (verbal initiation) → Number of words in 2 min for letter p and for animals

Performances are analysed in raw scores or residual score (= the difference between the expected and obtain scores, corrected for age, sex and education level)

Results

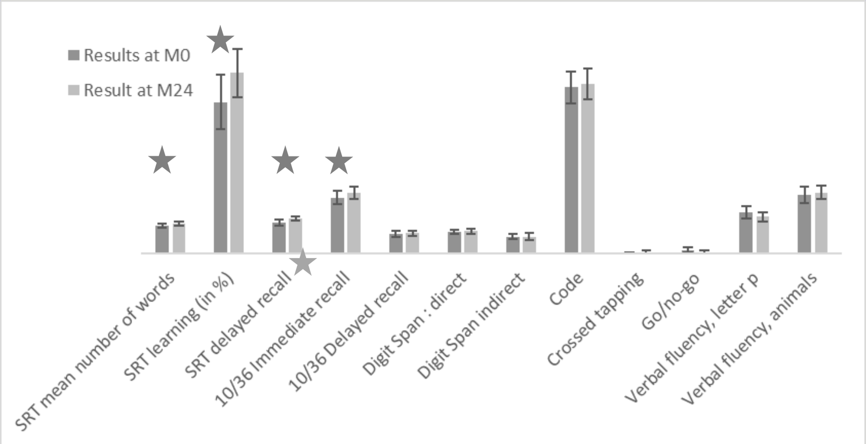
Evolution for all patients

1. Global cognitive impairment evolution



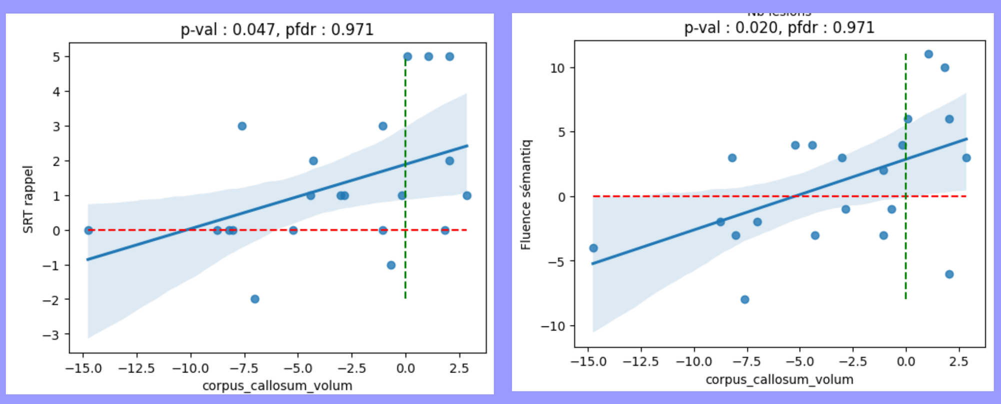
Percentage of patients with pathological BCcogSEP (4 or more subtests <10h perc) at inclusion (M0) and after two years of TRF treatment (M24)

2. Performance evolution for each test for all population



Comparison of mean raw scores between inclusion (M0) and after two years of TRF treatment (M24). ★ p<0.05

3. MRI correlation with cognition performance

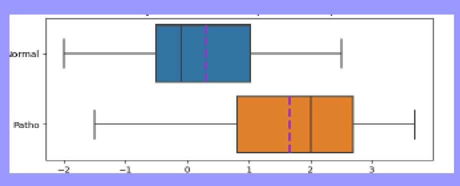


Corpus callosum volume correlates positively with SRT total recall evolution (links) and with semantic fuency evolution (right) . (we used residual scores for cognition)

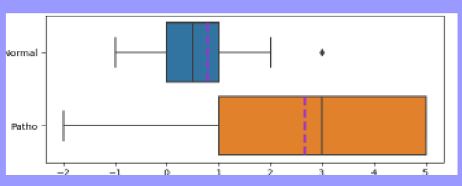
Group comparisons

Preserved Group | Impaired Group

1. Between group cognitive performance evolution



SRT test mean number of word (p=0.032)



SRT total recall (p=0.025):

The evolution of group performance differs only for SRT test. No other group differences in the other tests.

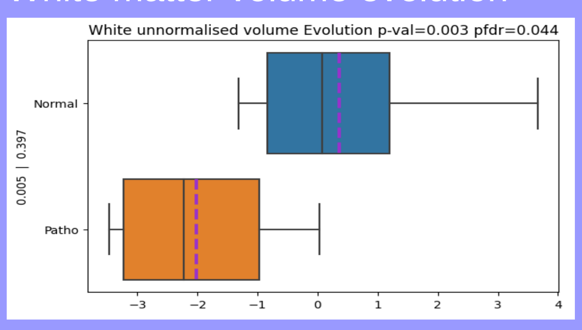
2. Intra-group analyses for cognition:

Impaired group
Improved at SRT mean number (p=0.013), learning (p=0.020), recall (p=0.01)
10/36 recall (p=0.033) GonoGo (p=0.024) _ No deterioration in any test

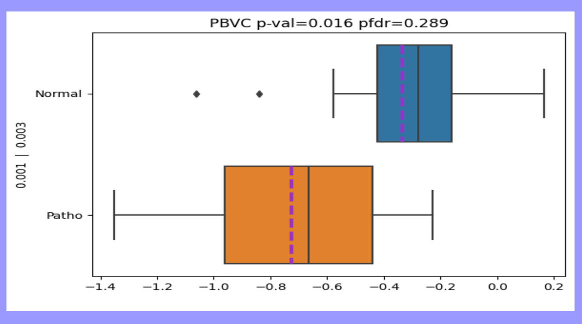
Preserved group
Improved at: SRT recall (p=0.025)_ No deterioration in any test

3. Between group MRI difference

White matter volume evolution



PBVC* volume evolution



Cognitive impaired group differ from preserved group at white matter volume evolution (p=0.003) and PBVC volume evolution (p=0.016) (lost of matter)

* PBCV for Pourcent Brain Volume Change

Conclusion

Results suggest that TRF treatment has a positive effect on cognitive functioning of RRMS patients, particularly those with cognitive impairment. Improvements are observed in verbal episodic memory for all patients but also in visuo-spatial memory and inhibition for patients with cognitive impairment. MRI analyses suggest a strong link between corpus callosum size and changes in cognitive performances. Patients with cognitive impairment are more likely to lose with matter and PBVC volumes. The patient's cognitive status appears to be an important factor to take into account for treatment choice .

1. Dujardin et al, 2004

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