

**Background:** Multiple sclerosis (MS) is a progressive disease of the central nervous system characterized by the production of widespread lesions, or plaques, in the brain and spinal cord. The widespread development of the plaques results in a broad range of symptoms, which include motor, cognitive and neuropsychiatric disorders.

Cognitive impairment is a common clinical feature of MS with prevalence rates ranging from 43% to 70%<sup>[1]</sup>. However the lower prevalence of cognitive impairment reported in population-based studies, ranging from 43% to 48%<sup>[2,3,4]</sup>, shows a possible overestimation of cognitive impairment in hospital-based studies.

The domains that are most often affected in patients with MS are information-processing speed, working memory and episodic memory; verbal fluency and executive functions can also be involved, but less frequently. General intelligence and central language abilities are relatively spared.

Progressive MS generally results in more severe cognitive impairment than does relapse-remitting MS<sup>[1]</sup>.

**Objectives:** The Republic of San Marino is one of the smallest republic in the world and its population is suitable to guarantee very accurate case collection. Moreover a previous study reported an higher prevalence of MS in this state than in continental Italy<sup>[5]</sup>.

The first aim of this study was to investigate the prevalence of Neurocognitive Disorder (NCD) in a well defined population-based cohort of MS patients in the Republic of San Marino.

A second aim of the study was to evaluate the characteristics of NCD in relapsing-remitting (RMS) and progressive (PMS) forms of MS.

**Materials:** The prevalence and characteristics of NCD were evaluated using a battery of neuropsychological tests which included tests of short and long term memory (both verbal and visual), information processing, attention, executive functions and visuo-constructive abilities. Each test was validated in the Italian population.

**Method:** An epidemiological survey to determinate the prevalence of MS in the Republic of San Marino has been previously carried out<sup>[6]</sup>; all these patients, plus every new case since the previous study, were called and enrolled. Seventy-three consecutive patients took part of the study. Inclusion criteria were the presence of defined MS according to the McDonald et al.<sup>[6]</sup> criteria. Exclusion criteria were the presence of any other neurologic, metabolic, psychiatric or learning disorders, other than MS that might have interfered with tests.

After careful checking of the inclusion and exclusion criteria the recruited sample consisted of 69 patients: 48 (69,56%) were affected by relapsing-remitting MS (RMS) and 21 (30,44%) by secondary or primary progressive forms of MS (PMS).

Since, as expected, age and disease duration differed between the two subgroups (PMS>RMS) we chose to introduce these factors as covariate in the analysis.

Demographic characteristics of the entire sample and of the two sub groups

	TOT	Subgroups		Differences between subgroups
		RMS	PMS	
n	69	48	21	
sex M/F	20/49	10/38	10/11	PMS>RMS
AGE in years M±SD	49,84 ± 13,97	45,17 ± 12,52	61 ± 10,37	PMS>RMS
Educational level in years M±SD	12,15 ± 3,95	11,89 ± 3,00	12 ± 5,59	ns
Disease duration (years since first symptom) M±SD	15,65 ± 10,66	13,26 ± 8,32	21,40 ± 13,45	PMS>RMS

**Results:** As shown in the pie graph, the prevalence of NCD (at least one cognitive deficit) was 31,88% in the whole population (22,92% in the RMS sub-group and 52,38% in the PMS sub-group).

The two-tailed t-test revealed a statistically significant difference between prevalence of NCD in the two sub-groups ( $T_{[67]}=-2,313$ ;  $p=0,027$ ).

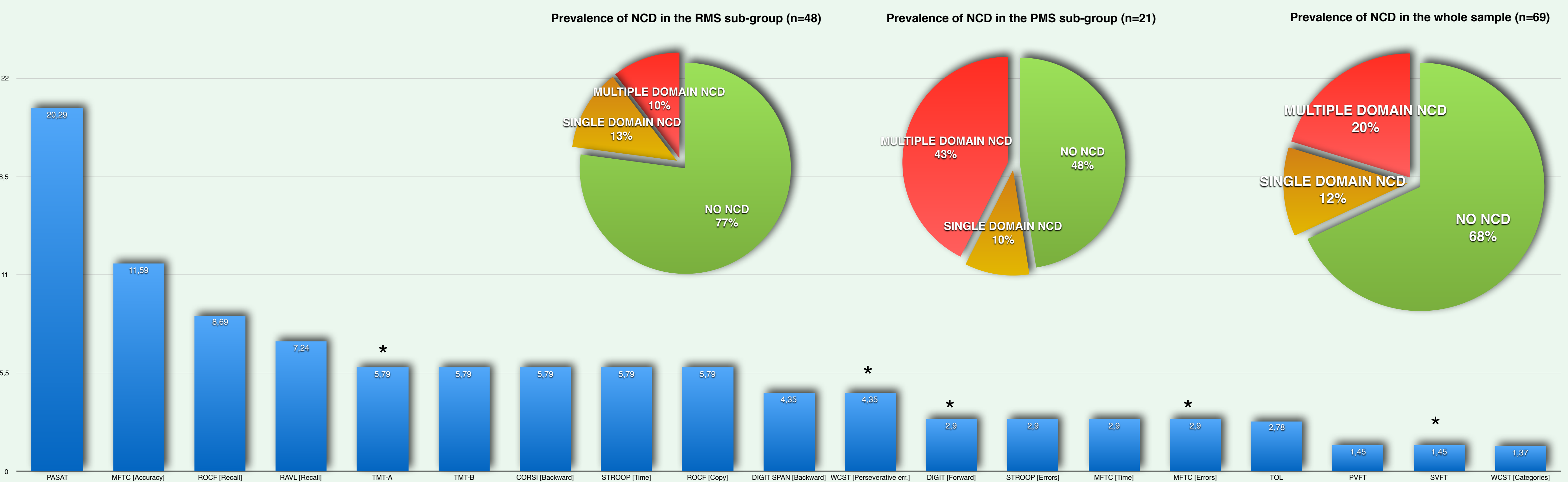
The confrontation of the two sub-groups revealed that among patients with NCD in the RMS sub-group 54,55% had a single-domain NCD and 45,45% a multiple-domain NCD, while in the PMS sub-group 81,82% had a multiple-domain NCD and only 18,18% had single-domain NCD.

The two-tailed t-test revealed a statistically significant difference between the prevalences of single and multiple domain presentation in the two sub-groups ( $T_{[67]}=-2,657$ ;  $p=0,013$ ).

The introduction of disease duration as covariate in the multivariate analysis did not change the results nor for the difference in prevalence of NCD in the two sub-groups ( $F_{[1,67]}=5,18$ ;  $p=0,026$ ) neither for the single or multiple domain presentation of NCD in the two sub-groups ( $F_{[1,67]}=7,49$ ;  $p=0,008$ ).

The most frequently impaired cognitive domain in the whole group was processing speed, followed by visual attention, visual and verbal long term memory.

The PMS subgroup performed worst than the RMS group in some tests of verbal short term memory, attention and executive functions (Marked with asterisks in the bar graph), while we found no group differences in other cognitive tests.



**Performance on neuropsychological tests (impaired in %) in the whole sample (n=69). Asterisks indicate statistically significant differences between the two subgroups (PMS worst than RMS).**  
PASAT=Paced Auditory Serial Addition Task; MFTC=Multiple Features Target Cancellation; ROCF=Rey-Osterrieth Complex Figure; RAVL=Rey Auditory Verbal Learning; TMT=Trail Making Test; Corsi=Corsi Blocks Test; WCST=Wisconsin Card Sorting Test; TOL=Tower of London Test; PVFT=Phonemic Verbal Fluency Test; SVFT=Semantic Verbal Fluency Test.

**Conclusion:** The Republic of San Marino offered a well defined cohort of patients for a population-based study of neurocognitive disorders in Multiple Sclerosis.

The prevalence of neurocognitive disorder in the Republic of San Marino is 31,88%, lower than one reported in previous population based studies ranging from 43% to 48%<sup>[2,3,4]</sup>.

The confrontation of relapsing-remitting and progressive MS patients revealed an higher prevalence of cognitive deficits for the second subgroup.

Moreover, among patients with neurocognitive disorder, patients with progressive forms of Multiple Sclerosis had an higher prevalence of multiple-domain presentation.

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