

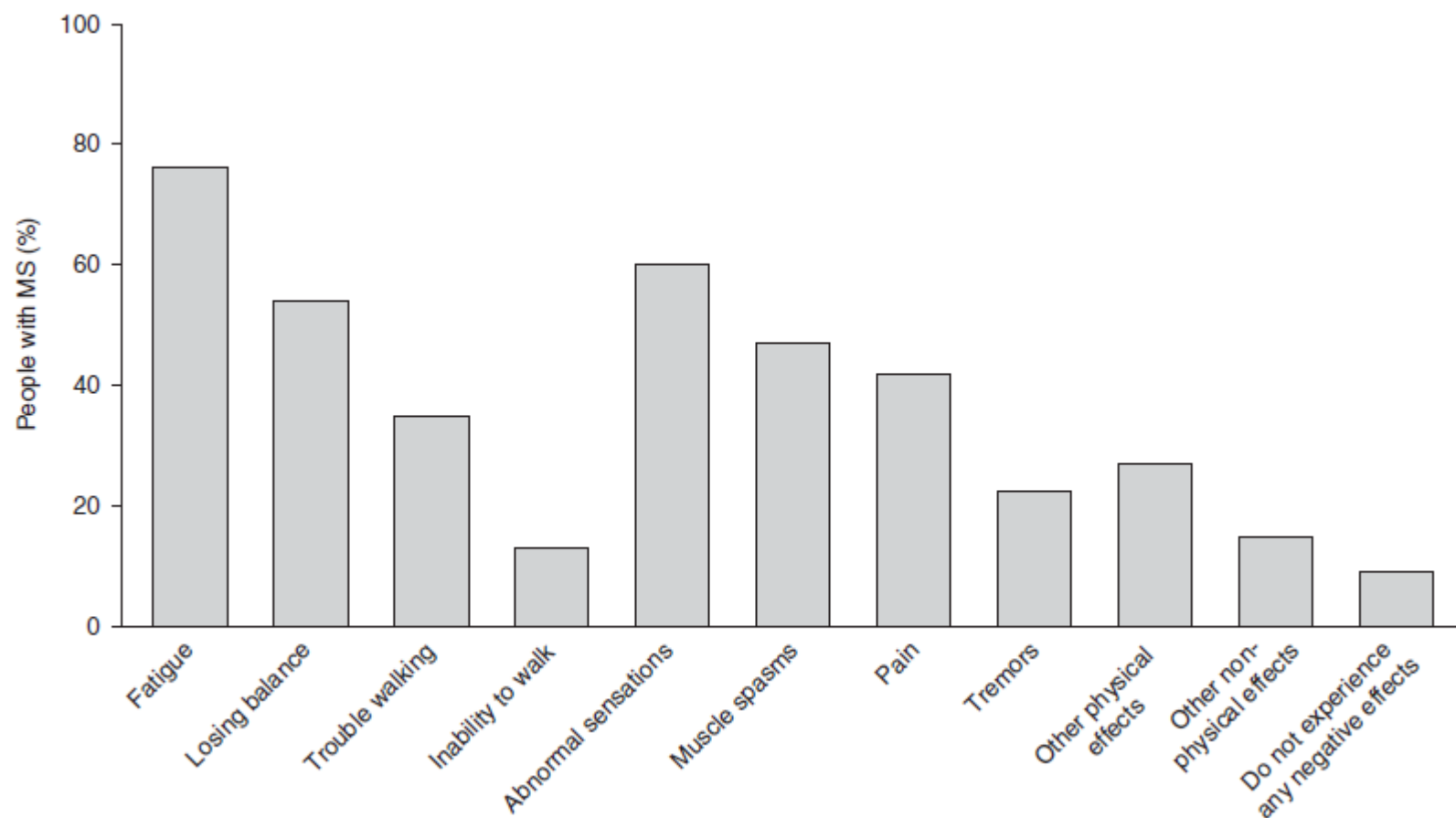
New perception of disability – including cognition, fatigue, pain and other impairments related to MS

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- **MS Relapse**
 - Draft Guideline states that “An accurate definition of relapse should be included in clinical trials” (lines 330-332).
- **MS Disability**
 - Not defined in the Guideline
 - Proposed definition*: a physical or mental handicap from MS that prevents a person from living a full, normal life or from holding a gainful job.
- **MS Impairments**
 - Not defined in the Guideline
 - Proposed definition*: a state of being diminished, weakened, or damaged from MS, mentally and/or physically (**Objective**)
- **MS Symptoms**
 - Not defined in the Guideline
 - Proposed definition*: any sensation or change in bodily or mental function experienced by a patient as a result of MS (**Subjective**)

* Personal adaptations from dictionary.com

Fig. 1. Multiple sclerosis (MS) symptoms experienced at least twice a week by people with MS (n= 1011; unweighted).



N.G. LaRocca, Patient 2011

THERE ARE MULTIPLE MS IMPAIRMENTS

1. Ambulatory
2. Cognitive
3. Visual
4. Bowel and Bladder
5. Balance
6. Sensory

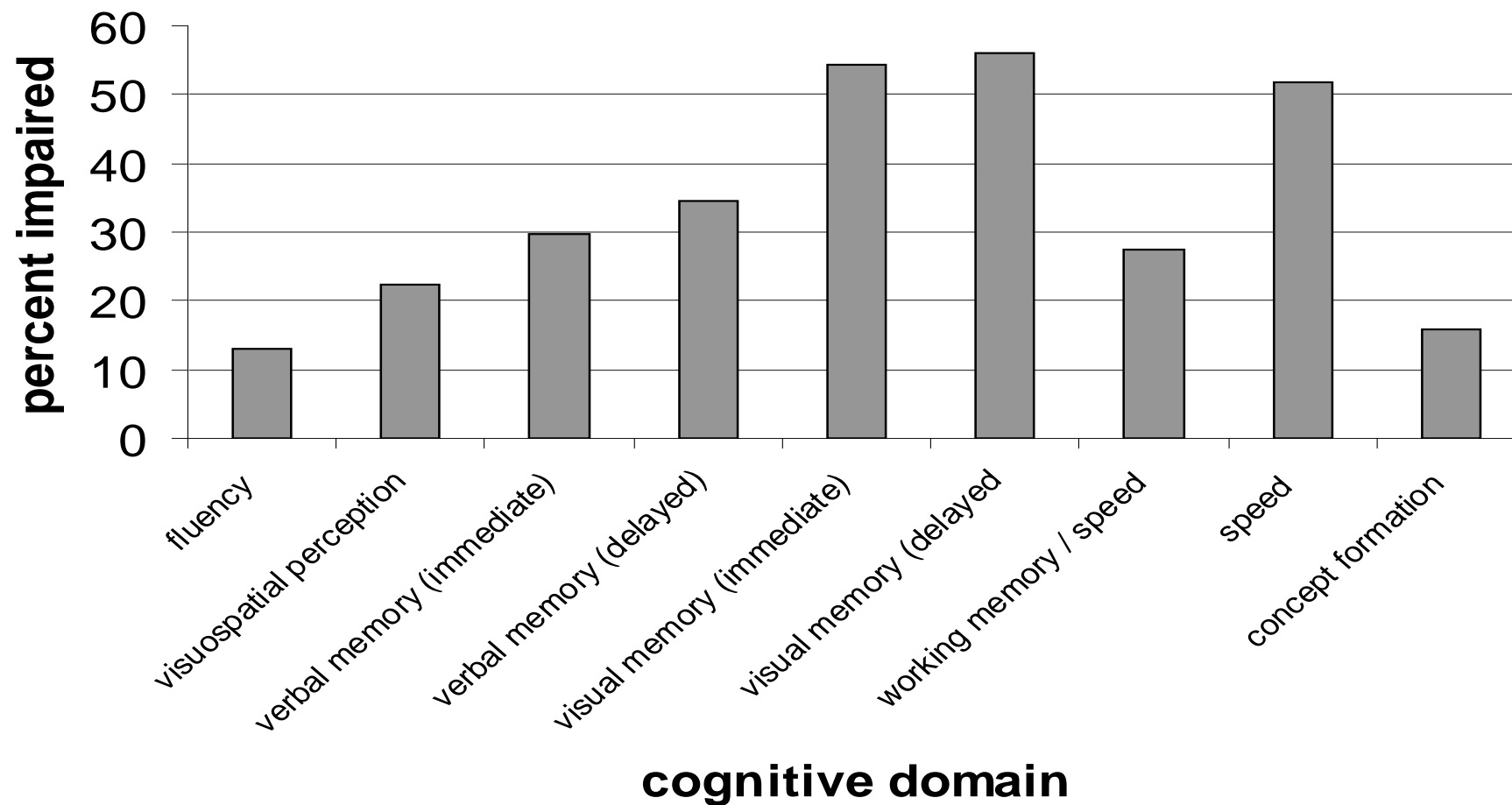
- A major consequence of MS is ambulatory impairment
 - Gait impairment results from weakness, spasticity, ataxia, loss of balance, fatigue, sensory loss, and cognitive impairment.
 - About half of people with MS require assistance with walking within 15 years.
 - Measurement of walking ability is a major component of instruments widely used for assessment of MS such as EDSS and MSFC.
 - Development of treatments and endpoints for Ambulatory Impairment Associated with MS should be encouraged.
 - The first symptomatic MS drug for improvement of walking in adult MS patients was conditionally approved in July 2011 (Fampyra®)
 - Its conditional approval reflects the need for clarity on acceptable endpoints for evaluation of ambulatory impairment associated with MS.

COGNITIVE IMPAIRMENT ASSOCIATED WITH MS (CIAMS)

- A major consequence of MS is Cognitive Impairment
 - Prevalence of 40-65%¹
 - 70-80% of SPMS subjects
 - 30-40% of RRMS subjects
 - High negative impact on employment and Activities of Daily Living
 - Begins early during the course of MS
- The two most affected cognitive domains are:
 - Information Processing Speed
 - Learning and Memory
- Cognitive Impairment Associated with MS (**CIAMS**) is an area of high unmet need
 - Current label enabling endpoints do not capture CIAMS
 - There are no treatments approved for CIAMS

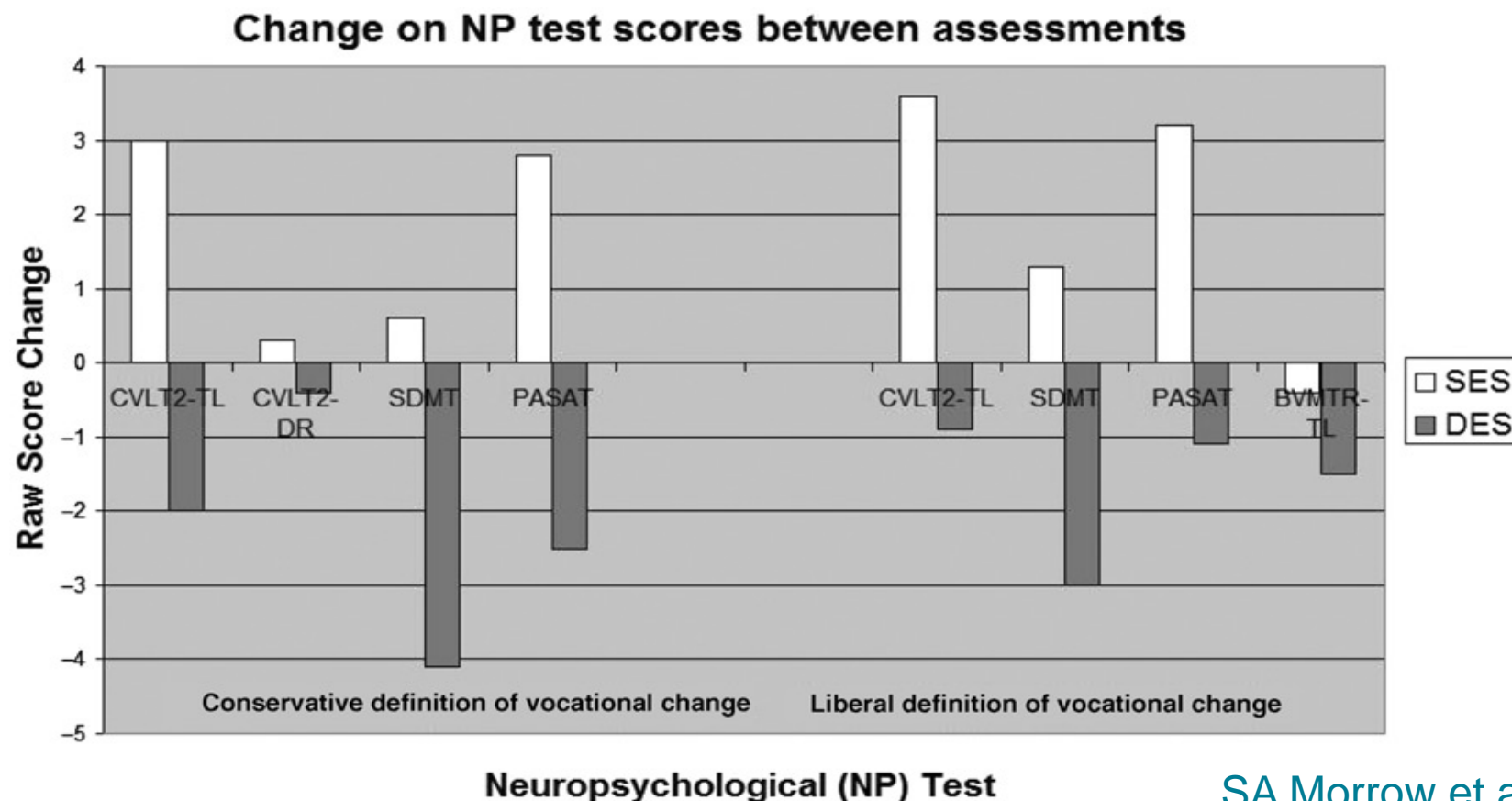
1. Amato et al. 2001; Deloire et al. 2006; Feinstein 2007; Rao et al. 1991

PREVALENCE OF DOMAIN IMPAIRMENT IN CIAMS



(Adapted from Benedict, et al., 2006)

CIAMS NEGATIVELY IMPACTS EMPLOYMENT



- Assessments were at least 12 months apart.
- SES=Stable Employment Status; DES=Deteriorated Employment Status; CVLT2=California Verbal Learning Test 2nd edition (TL=Total Learning, DR=Delayed Response); SDMT=Symbol Digit Modalities Test; PASAT=Paced Auditory Serial Addition Test

- A major consequence of MS is visual impairment
 - Visual impairment can result from a variety of pathological processes, including inflammation, demyelination, and axonal degeneration in the afferent visual pathway (retina, optic nerves, chiasm, tracts, and visual cortex)
 - The EDSS only measures full contrast central visual acuity, which is not sensitive to Visual Impairment Associated with MS (VIAMS).
 - Low contrast sensitivity is a better measure of VIAMS, yet it is not part of the EDSS, MSFC, or relapse severity assessments in MS
 - Measures of low contrast vision are predictive of “real-world” visual tasks, such as reading rate, facial recognition, and driving.
 - No drug has been approved for treatment of VIAMS

- Likely multifactorial (complex construct).
 - Our understanding of fatigue pathophysiology is limited (physical and cognitive impairment, medications, mood, pain, lack of sleep, anxiety, etc).
- Substantial contributor to decrements in quality of life and disability.
- High unmet need for treatments to treat MS fatigue.
- Need for acceptable endpoints
 - Majority of tools are self-report scales that measure perception of fatigue
 - Fatigability can be objectively measured by quantifying a decline during continuous performance
 - MS Community needs to agree on what PROs and/or objective tests should be used to measure treatment effects on MS fatigue

- Pain is a key symptom in MS
 - It is often linked to impaired quality of life and disability
 - Pain is an important therapeutic target for MS treatments
- Many features of pain associated with MS remain poorly understood.
 - There are several specific pain syndromes in MS
 - Headache, neuropathic limb pain, back pain, painful spasms, L'Hermitte sign, and trigeminal neuralgia.
- Various tools are available to measure pain in MS
 - All are patient reported
 - VAS, MPQ, McGill Pain Questionnaire, SF-36, MSQOL-54, and structured interviews
- There are regulatory accepted endpoints to measure pain treatments

- EFPIA agrees with the guideline that the EDSS does not address all functional systems relevant to MS
 - EDSS does not assess many relevant MS related impairments

- EFPIA recommendation
 - This focus needs broadening to include treatments for MS symptoms (lanes 106-109) (e.g. symptomatic therapies) and MS-impairments (lanes 236-238) (e.g. remyelination/reparative therapies)

- “MS is an inflammatory condition that damages the myelin of the Central Nervous System (CNS) and causes neurological impairment” (lines 77-78)
 - “The EDSS does not adequately assess upper limb function and cognitive impairment” (line 322)
 - Guideline needs to include other MS impairments beyond upper limb and cognitive impairment
- EFPIA submitted this wording for the proposed draft MS guideline
 - Many MS patients considered to have “benign” disease have important impairments not captured by the EDSS; this needs to be acknowledged in the guideline.

- EFPIA in agreement with the Guideline that
 - “Additional neurological rating scales, quantitative neuron-performance tests or patient and neurologist global opinion may be used as secondary measurements of disability” (lines 323-325).
- EFPIA feedback
 - The clinical development of medicinal products for the treatment of MS has focused mostly on physical consequences with little attention to the impact of the disease and its treatments on other functions (e.g. cognitive)
 - EMA should be open to discussions around new endpoints put forward by the larger MS community
 - The development and testing of treatments for MS impairments and symptoms should be encouraged.

- The guideline acknowledges the option to use various secondary efficacy endpoints based on other measures related to progression of disability (line 287)
 - **5.2.2. Secondary efficacy endpoints.** Other measures related to progression of disability supplementary to the measure chosen as the primary variable (e.g. neurological rating scales, measures of cognitive impairment, fatigue scales, ambulatory index) (lines 296-298)
- EFPIA feedback
 - The guideline should leave open the possibility that other measures of disability may be used as primary endpoint for specific impairments (e.g. *cognition could be a primary endpoint leading to a label saying that cognition is improved*).

- The guideline states that “Symptomatic treatment refers to all therapies applied to improve symptoms and complications caused by the disease e.g. fatigue, spasticity, ataxia, walking disability, weakness, bladder and bowel disturbances among others”.... while “treatment aimed to modify the course of the disease are aimed to prevent relapses and disability” (lines 112-115).
- The Guidance should recognize that DMTs may also lead to improvement in symptoms of MS beyond reducing relapses and disability progression.

- Coordinated Efforts of the MS Community including academia, industry, and regulators are needed to develop measurement tools that address specific MS symptoms and impairments.
- The same holds true for establishment of the clinically important changes for all newly approved measurement tools, whether subjective or objective.