Cognition and fatigue as major determinants of disability

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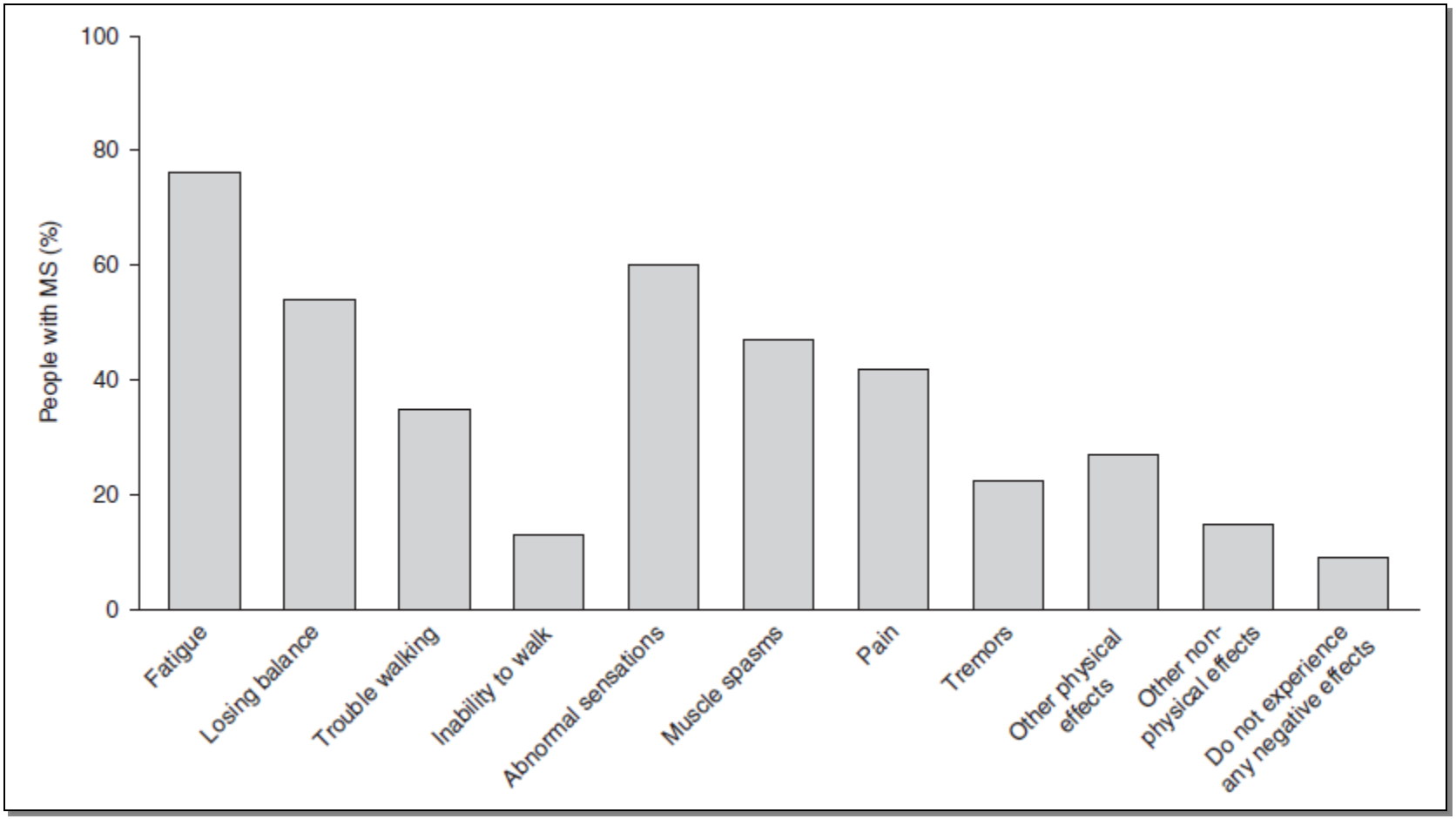
Disability in MS



LaRocca et al, 2011

Unemployment in patients with MS

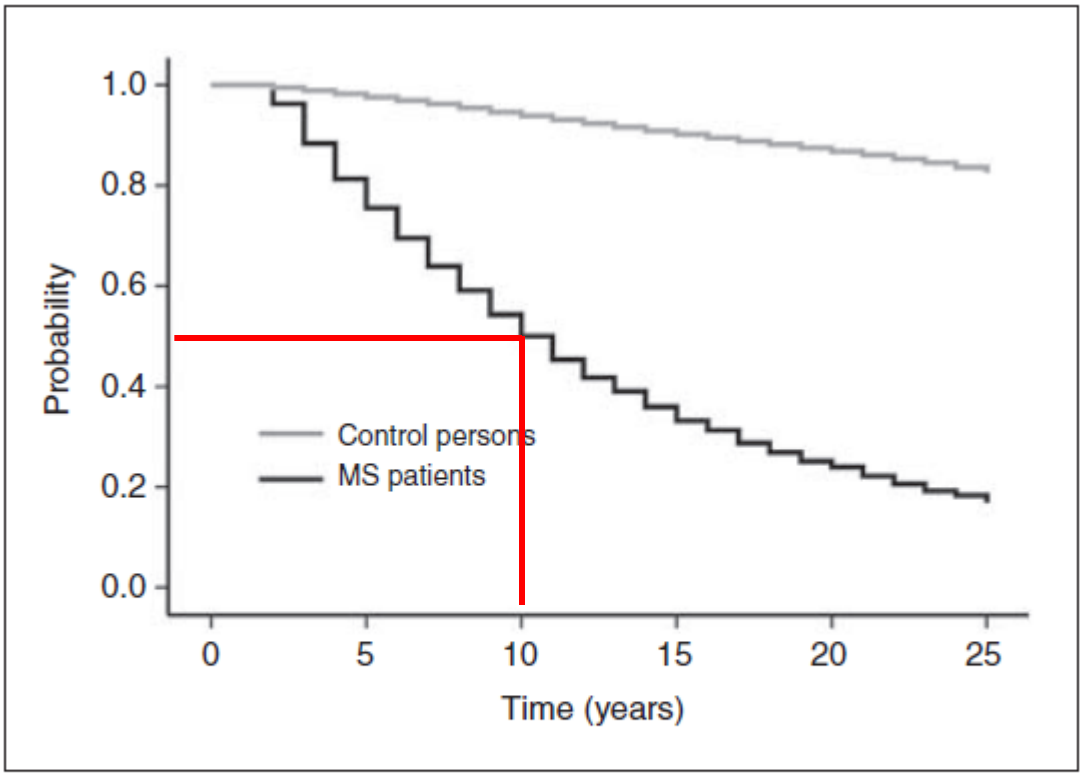


Figure 1. Probability of remaining in active employment after onset of multiple sclerosis. Key: grey, controls; black, patients.

Pfleger et al, 2010

Benign is MS ? Or missing the right measures ?

Benign multiple sclerosis

Cognitive, psychological and social aspects in a clinical cohort

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163 patients with "benign" MS (disease duration >15 years and EDSS <3.5):

- **45% cognitive impairment**
- **49% fatigue**
- **54% depression**

Amato et al, 2006

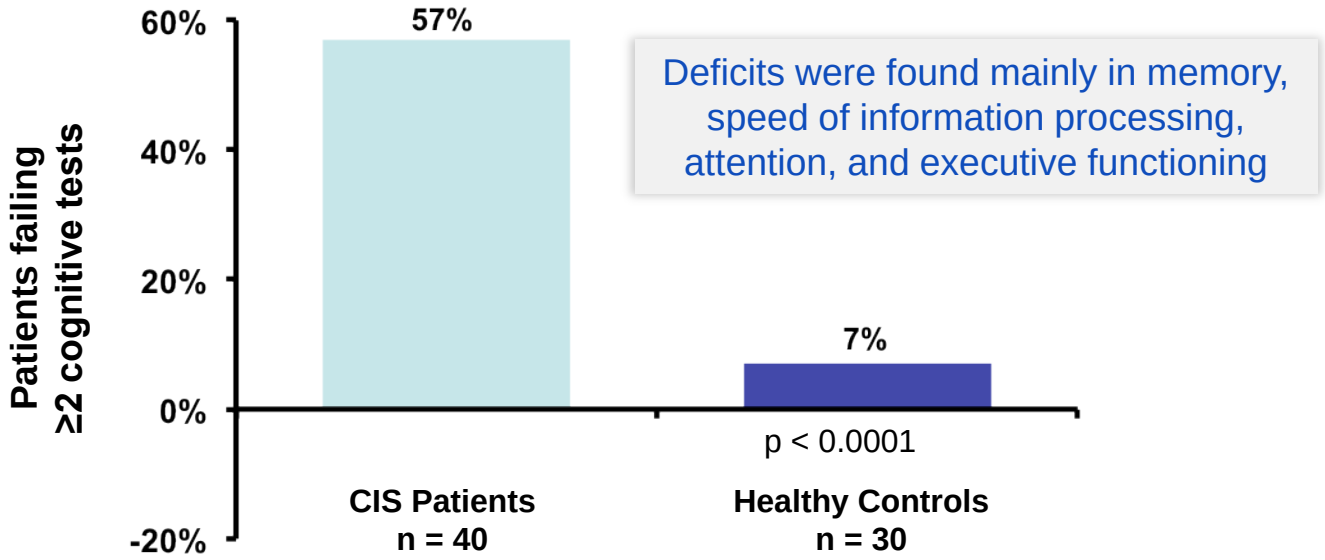
Cognition – background

- Cognitive impairment is an important predictor of healthrelated quality of life at all stages of multiple sclerosis (MS).[1]
- It reduces physical independence,[2] competence in daily activities,[3] coping,[4] symptom management,[5] medication adherence,[6] and rehabilitation potential.[7]
- Studies of large, unselected samples of MS patients have reported cognitive impairment prevalence rates between 40 and 70%.[8]
- Cognitive impairment can be found at all stages of the disease – CIS, RRMS, SPMS, PPMS.

1. Mitchell et al, 2005
2. Rao et al, 1991
3. Goverover et al, 2007
4. Ehrensperger et al, 2008
5. Vahter et al, 2009
6. Bruce et al, 2010
7. Langdon et al, 1999
8. Chiaravalloti et al, 2008

Impact of MS: Cognitive Functioning in the CIS Stage

Cognitive Test Performance in an Exploratory Study



40 untreated CIS patients who fulfilled the McDonald dissemination in space criterion compared to a cohort of 30 matched healthy controls. An extensive battery of neuropsychological tests was used to explore verbal and non-verbal memory, attention, concentration, speed of information processing, language and abstract reasoning. Cognitive impairment was present when at least 2 different neuropsychological tests were failed.

Feuillet et al, 2007

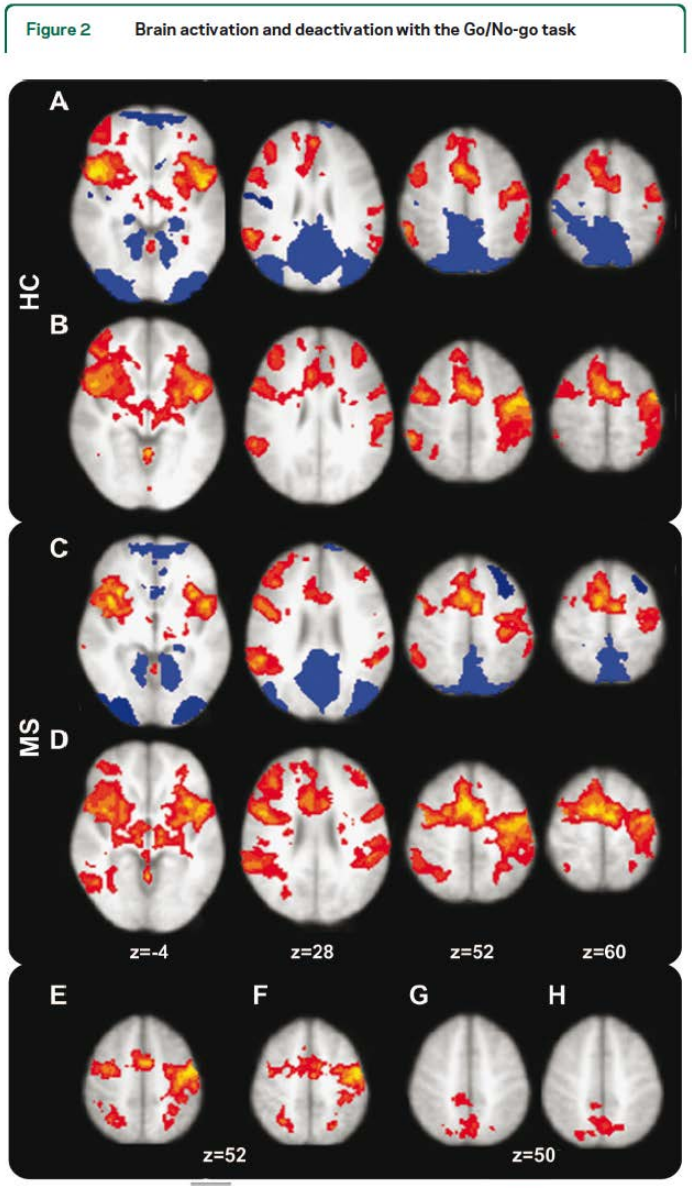
Cognition – pattern of deficits

- Over several years, MS patients' performance on tests of information processing speed declines more rapidly than on other cognitive tasks.[1]
- Detailed methodological investigations of performance on a range of cognitive tests point towards speed of processing as the unitary underlying deficit.[2]
- Information processing speed is reduced in MS patients, and the slowness is more pronounced on tasks that are explicitly timed, compared with normal participants.[3]

1. Denney et al, 2008
2. Denney et al, 2004
3. Denney et al, 2011

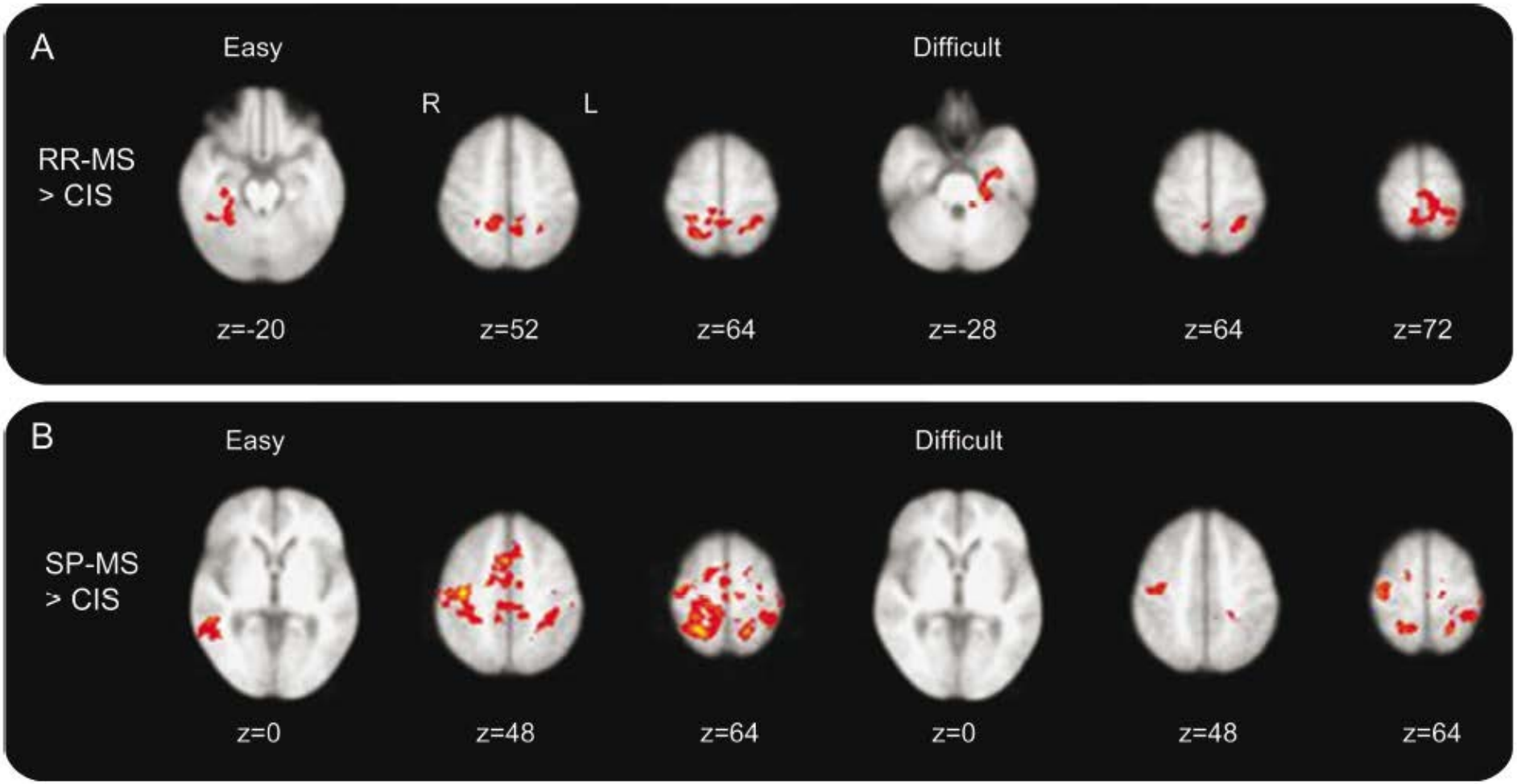
Cognition – activation patterns

- Using cognitive fMRI paradigms, adaptive changes of neuronal activation with progressing MS can be demonstrated.
- Once increased activation can no longer keep pace with the failing integrity of the cerebral cortex, cognitive performance plummets.
- Additional activations have been shown to increase across subtype cohorts from CIS to SPMS.



Loitfelder et al, 2011

Cognition – activation patterns



Loitfelder et al, 2011

Cognition – measurement

- Two cognitive batteries are particularly widely used in clinical and research settings, both having good psychometric properties and having been constructed to be relatively robust to the effects of other MS symptoms:
  - Brief Repeatable Battery of Neuropsychological tests (BRB-N).
  - Minimal Assessment of Cognitive Function in MS (MACFIMS).
- MS patients' self-report of cognitive impairments, although important clinically, is unlikely to be related to objective cognitive test performance, but rather linked to depression.
- Relatives' reports of patients' cognitive function are more likely to be reliable.

Cognition – information processing speed

- There are two widely used tests of processing efficiency and speed in MS:
  - the Paced Auditory Serial Addition Task (PASAT).
  - the Symbol Digit Modalities Test (SDMT, oral form).

- The tests have similar psychometric properties.
- There is evidence that the two tasks utilize slightly different cerebral networks, with the PASAT activating more frontal areas.

Cognition – memory

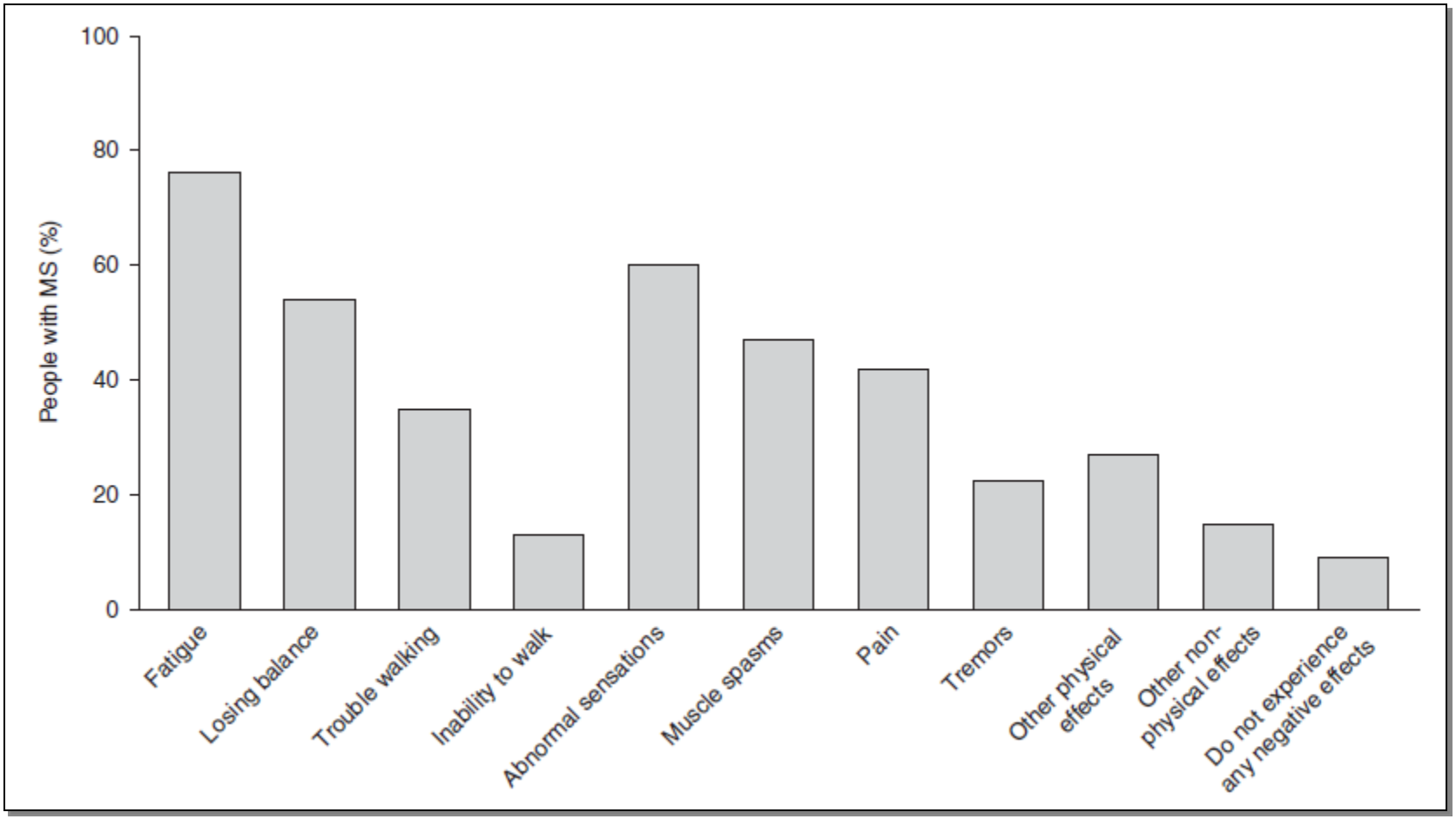
- MS patients are very likely to experience memory problems, with prevalence rates of 40–65% reported.
- The most usual tests of verbal memory are list learning tasks.
- A widely used test of verbal memory in clinical and research contexts is the California Verbal Learning Test-II (CVLT-II)

Cognition – unmet needs

- Cognition in MS is a priority for patients.
- Assessment tools are psychometrically sound and can be used effectively by a specialist neuropsychologist.
- Cognitive impairment is only loosely related to disease variables, but is more closely related to magnetic resonance variables, especially atrophy.
- Cognitive reserve modulates the adverse effects of MS pathology on cognitive function.
- Given the clinical relevance of cognition new endpoints should be defined or exisiting measures should be used as a primary endpoint to open avenues for new medicinal products for the treatment of MS.

Langdon et al, 2011

Disability in MS



LaRocca et al, 2011

Fatigue – background

- Fatigue is commonly reported in many neurologic illnesses, including multiple sclerosis, Parkinson disease, myasthenia gravis, traumatic brain injury, and stroke.
- Fatigue contributes substantially to decrements in quality of life and disability in these illnesses.

Table 1 Estimated prevalence of fatigue in selected neurologic illnesses

Population	Estimated prevalence, %
Multiple sclerosis	38–83[e51–e53]
Parkinson disease	28–58[12,20,32,e54]
Stroke	36–77[15,e55–e57]
Myasthenia gravis	75–89[14,e58,e59]
Postpolio syndrome	27–91[74,e60,e61]
Amyotrophic lateral sclerosis	44–83[16,e62]
Traumatic brain injury	45–73[e63,e64]

Kluger et al, 2013

Fatigue – background

- Fatigue is considered to be one of the main causes of impaired QoL among MS patients.[1]
- Fatigue is among the most common symptoms, reported by at least 75% of MS patients at some point in the disease course.[2,3]
- For many patients, fatigue is considered to be the single most debilitating symptom, surpassing pain and physical disability.[4]
- Fatigue imposes significant socioeconomic consequences, including loss of work hours and in some instances, loss of employment.[5]

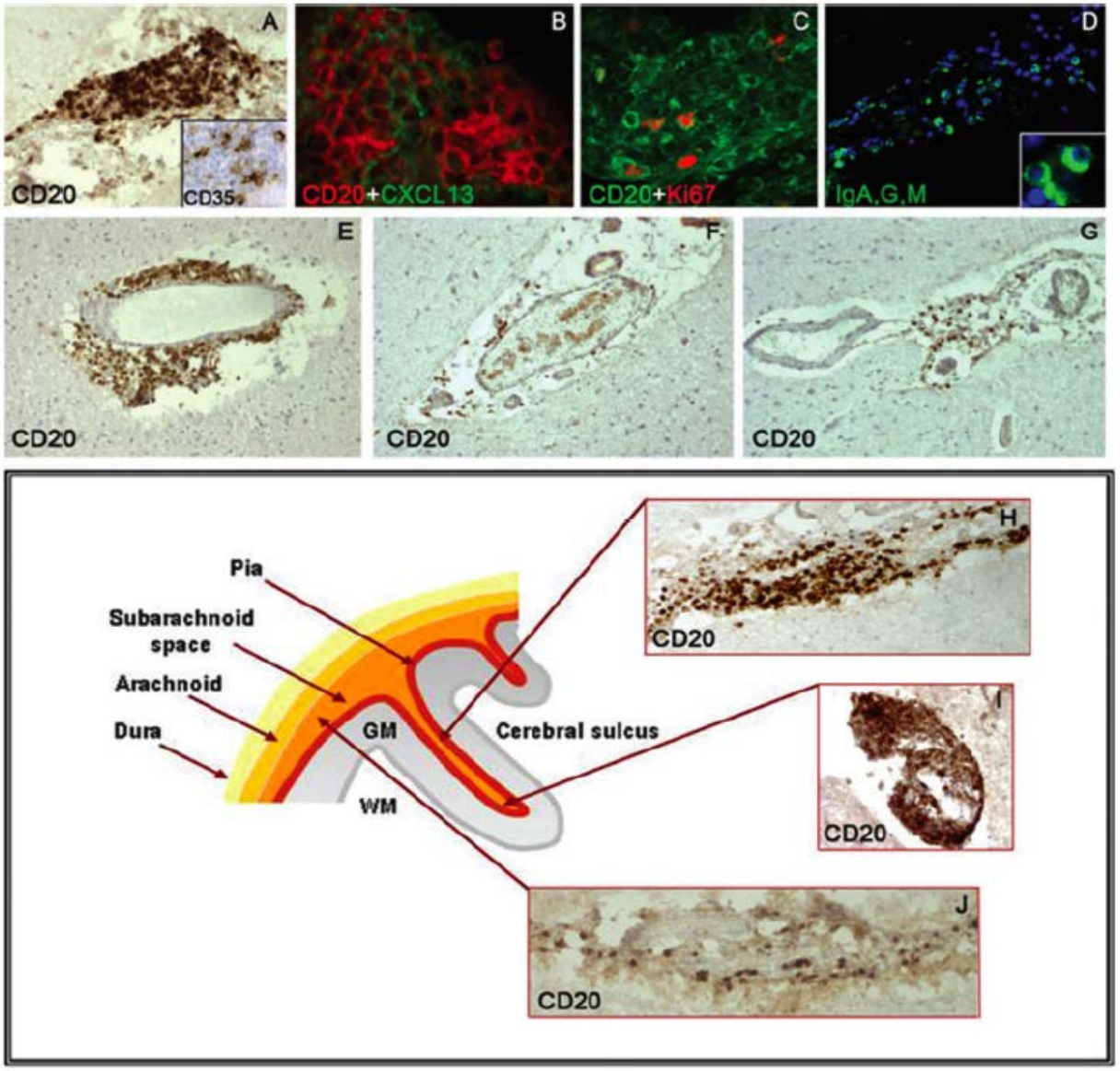
1. Krupp et al, 1988
2. Krupp et al, 2006
3. Lerdal et al, 2007
4. Janardhan et al, 2002
5. Smith et al, 2005

Fatigue – pathogenesis

- Proposed primary mechanisms of fatigue in MS involve the immune system or sequelae from CNS damage:
  - Proinflammatory cytokines
  - Cerebral lesions
  - Cortical atrophy
  - Hypothalamo-pituitary-adrenal axis dysfunction
  - Activation of neural circuits
  - Axonal damage

- There are no major demographic differences in MS patients with fatigue

Meningeal B cell follicels in MS



Magliozzi et al, 2007

Fatigue – measurement

- This analysis concludes that the FSMC and U-FIS represent the most robust scales for MS.

FSMC - Fatigue scale for motor and cognitive functions

U-FIS – Unidimensional fatigue impact scale

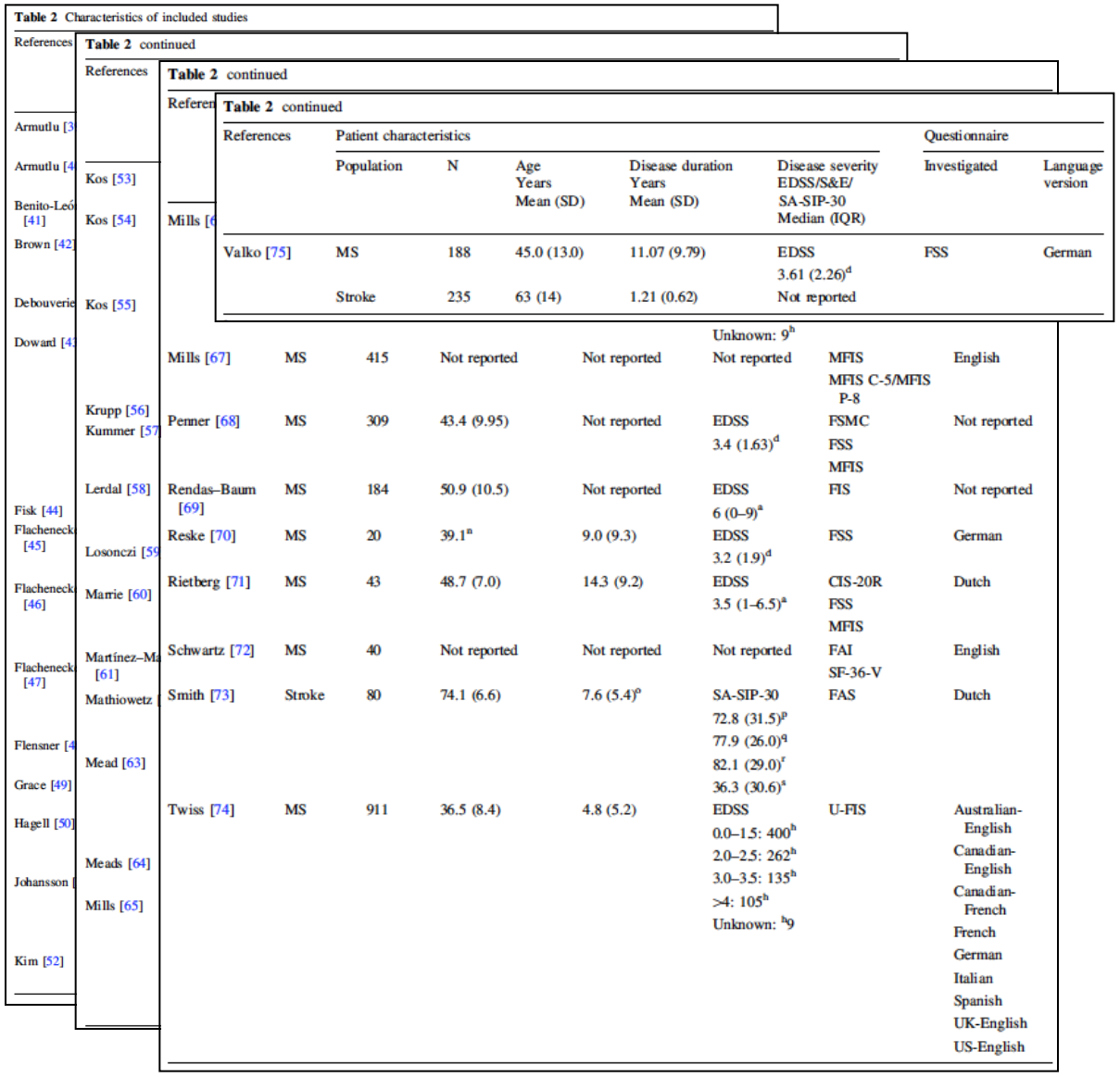


Table 2 Characteristics of included studies

Table 2 continued

Table 2 continued

Table 2 continued

References	Patient characteristics					Questionnaire	
	Population	N	Age Years Mean (SD)	Disease duration Years Mean (SD)	Disease severity EDSS/S&E/ SA-SIP-30 Median (IQR)	Investigated	Language version
Valko [75]	MS	188	45.0 (13.0)	11.07 (9.79)	EDSS 3.61 (2.26)[d]	FSS	German
	Stroke	235	63 (14)	1.21 (0.62)	Not reported		
Mills [67]	MS	415	Not reported	Not reported	Unknown: 9[h] Not reported	MFIS MFIS C-5/MFIS P-8	English
Penner [68]	MS	309	43.4 (9.95)	Not reported	EDSS 3.4 (1.63)[d]	FSMC FSS MFIS	Not reported
Rendas–Baum [69]	MS	184	50.9 (10.5)	Not reported	EDSS 6 (0–9)[a]	FIS	Not reported
Reske [70]	MS	20	39.1[a]	9.0 (9.3)	EDSS 3.2 (1.9)[d]	FSS	German
Rietberg [71]	MS	43	48.7 (7.0)	14.3 (9.2)	EDSS 3.5 (1–6.5)[a]	CIS-20R FSS MFIS	Dutch
Schwartz [72]	MS	40	Not reported	Not reported	Not reported	FAI SF-36-V	English
Smith [73]	Stroke	80	74.1 (6.6)	7.6 (5.4)[o]	SA-SIP-30 72.8 (31.5)[p] 77.9 (26.0)[q] 82.1 (29.0)[r] 36.3 (30.6)[s]	FAS	Dutch
Twiss [74]	MS	911	36.5 (8.4)	4.8 (5.2)	EDSS 0.0–1.5: 400[h] 2.0–2.5: 262[h] 3.0–3.5: 135[h] >4: 105[h] Unknown: [h]9	U-FIS	Australian-English Canadian-English Canadian-French French German Italian Spanish UK-English US-English

Elbers et al, 2012

Fatigue – taxonomy

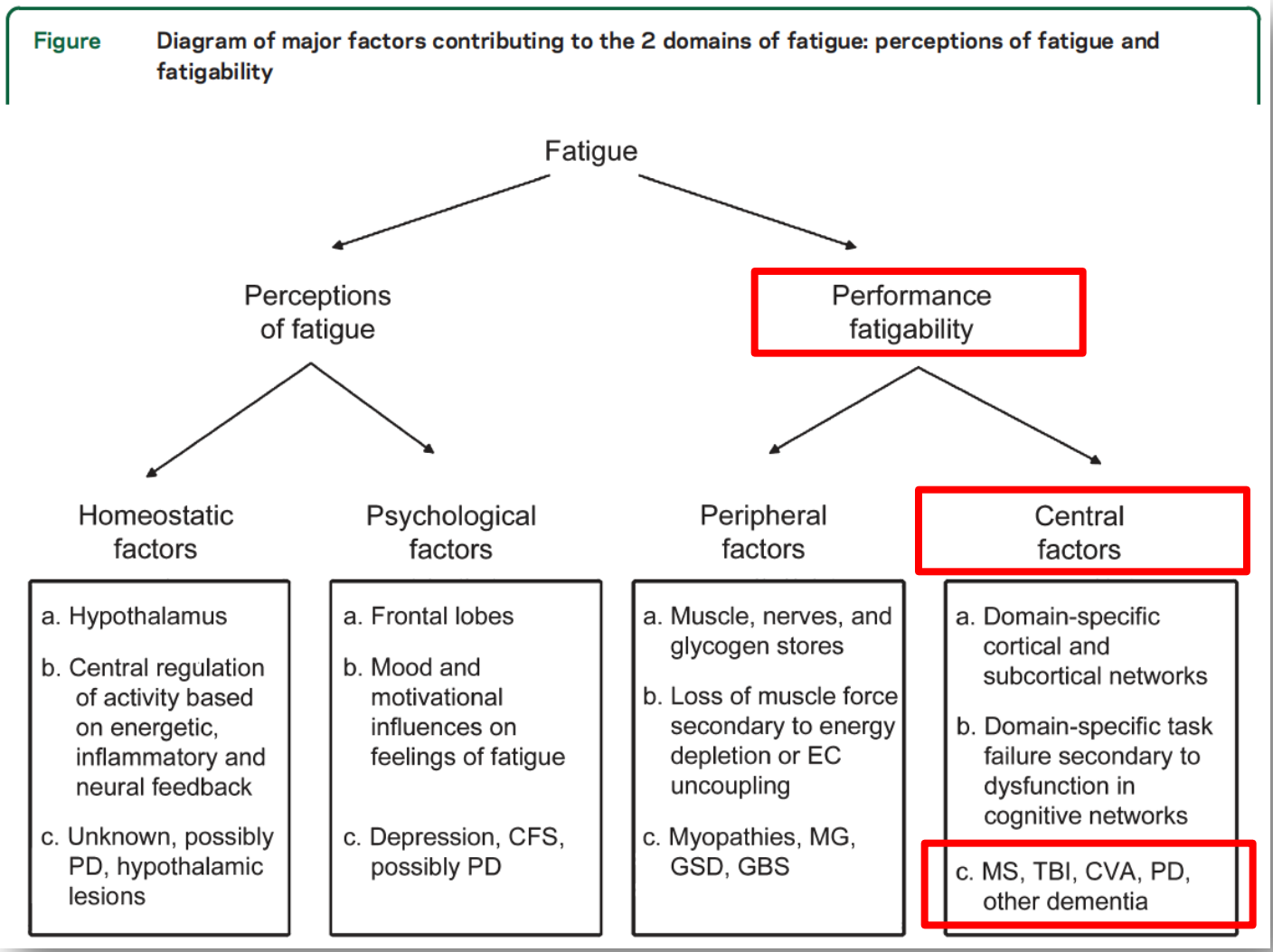
- The term “fatigue” is used without standard definitions or means of measurement.

- A unified taxonomy is needed to identify its distinct domains and to distinguish it from related phenomena.

- The following question could be addressed:
  1. Is this fatigue or a related phenomenon?
  2. Is the focus perception or performance?
  3. Is it clinically significant?
  4. Are there identifiable causal factors?
  5. Is there a particular domain of task performance affected?

Kluger et al, 2013

Fatigue – taxonomy



Kluger et al, 2013

Fatigue – unmet needs

- Objective tests to assess fatigue in MS and the impact of specific therapies need to be defined
- Fatigue is not captured by the EDSS, however, it represents a major component of disability in patients with MS.
- The EMA guidlines should acknowledge fatigue as a relevant disabling clinical symptom in MS patients.

Kluger et al, 2013

Summary

- MS is a disabling disease with a heterogenous clinical presentations.
- Our current primary endpoints addressing disability reflect only a small spectrum of the clinically relevant disabling symptoms.
- New measurements should be developed that can be implemented and will be accepted by regulators as relevant clinical endpoints in clinical studies.