Cognitive Function in CFS: a measure of disability?

Gudrun Lange, PhD

Professor

Department of Physical Medicine and Rehabilitation, UMDNJ-NJMS

War Related Illness and Injury Study Center, Department of Veterans Affairs

Outline

- What do we know about cognitive function in CFS
  - from the patient’s perspective?
  - From the researcher’s perspective?
  - From the clinician’s perspective?
  - From the Social Security Administrations perspective?
- Bottom line

Cognitive Difficulties: Brainfog

Up to 85% of CFS patients complain of difficulties with attention, concentration and memory

- “I feel that my head is in a bag of cotton balls…”
- “I feel like I am loosing my mind…”
- “I have the brain of an 80 year old person and I am only 36…”

What “brainfog” does to me…

- 42-year old homemaker:
  - “…I used to cook exciting gourmet meals for my family, now I cannot follow the recipes in my cookbook anymore. When I’m up to it, I’m able to boil eggs. I feel useless sometimes and feel like a burden to my family.”

- 58-year old lawyer:
  - “…I still am a successful lawyer…by 11am I am so fatigued, I nap under my desk or in the bathroom. I prefer phone conferences to face to face meetings now, because I can make notes for myself. I have several volumes of memory books now, but my notes have become a lot spottier over the recent past. I used to deal with a number of cases at a time, now I am looking for excuses to avoid that. My boss has noticed that my performance has gone down and I’m afraid I’ll loose my job.”

Most commonly reported cognitive problems

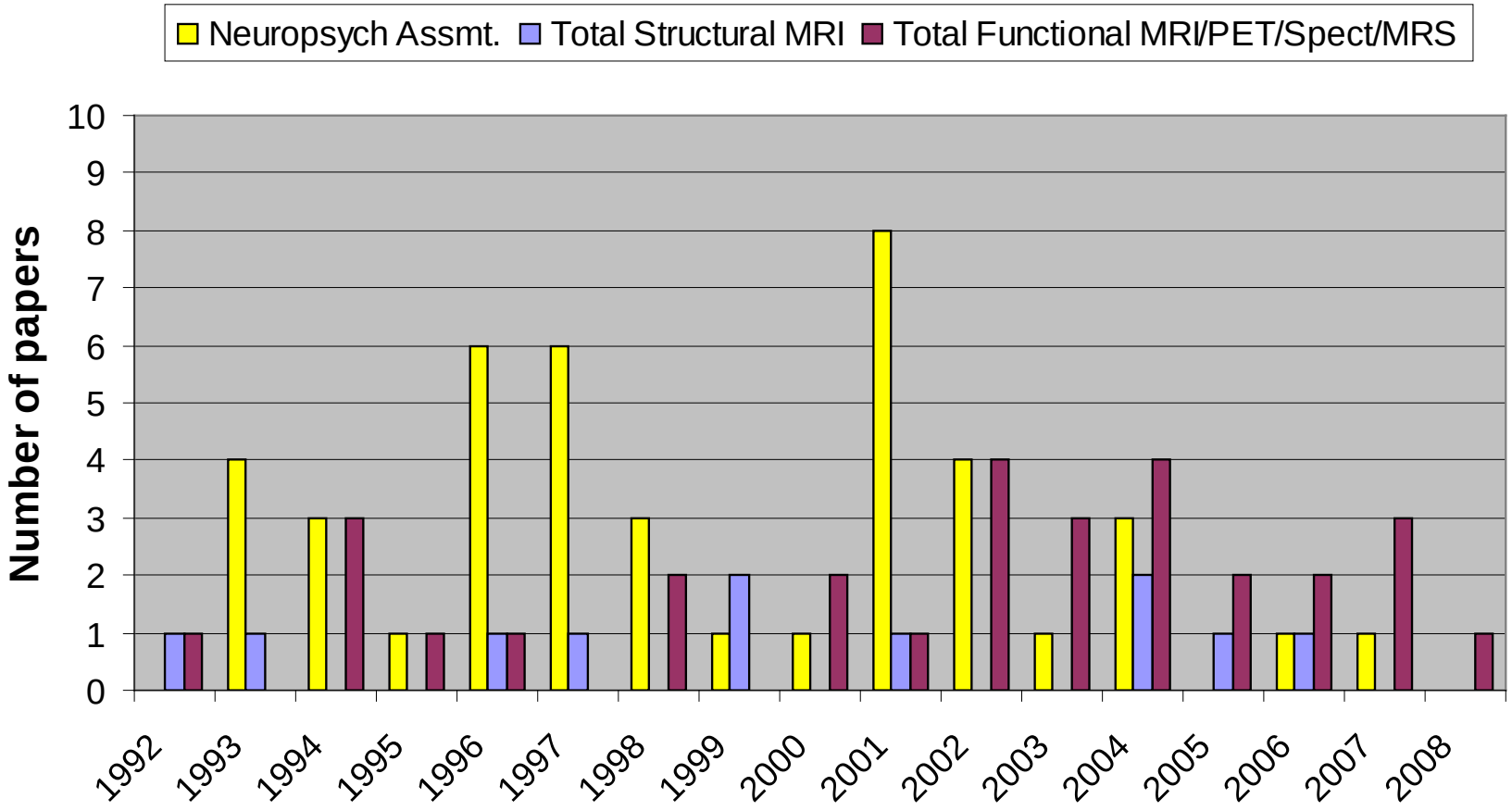
- Concentration and attention problems
  - “I have trouble reading a book, I have to read the same paragraph over and over again.”
- Memory difficulties
  - “I go shopping for food, once I get to the food store I cannot remember what I needed. I think I am dementing.”
- Word finding difficulties
  - “I am not going out anymore, I cannot keep up with the conversation, I cannot find the right words quickly, by the time I do, the conversation has moved on.”
- “Can’t think”
  - “I used to be so sharp, now I cannot figure out how to make a decision. I am so stupid now.”

Common Problem

- Mismatch between subjective and objective reports
  - Clinician and SSA “need” supporting “hard” findings to corroborate claim

- Difficult to aggregate disparate research findings
  - Increase in neuroimaging research
  - Decrease in neuropsychological research

16 Years of Investigation



Research pitfalls

- Different case definitions
  - SSA is using 1994 cased definition
- Stratification of CFS groups
  - Psych versus no psych
- Appropriate control groups
  - Physically unconditioned versus conditioned
- Wide array of self-report and neuropsychological assessment tools
  - Many non-standardized

Static Neuroimaging Studies: Brain lesions and brain volume

- When controlled for psych comorbidity
  - Some studies – no differences (Cope et al., 1996; Greco et al., 1997)

- Most prevalent findings (Buchwald et al., 1992; Natelson et al., 1993; Lange et al. 1999)
  - Non-specific, small white matter lesions in frontal lobe
    - Related to impairments in physical function (Cook et al., 2001)

  - Global loss of white matter (Lange et al., 2001)
  - Global loss of gray matter and in bilateral DLFC (Okada et al., 2004; DeLange et al., 2005)
    - linked to reduction in physical activity (DeLange et al., 2005)

Dynamic Neuroimaging Studies: Baseline Cerebral Blood Flow

- Measurement of Relative CBF
  - Limited since measured relative to another part of the brain
    - SPECT and PET

- Measurement of Absolute CBF
  - Actual blood flowing thru brain per unit time
    - Xe CT

Results: relative CBF

- Majority show reductions in CBF in CFS when controlled for psych comorbidity
  - Globally (Kuratsune et al., 2002; SPect: Schmaling et al., 2003)
  - Specifically in lateral frontal, medial temporal lobes, and brainstem (PET:Tirelli et al., 1994; SPect: Costa et al., 1995)
  - Anterior cingulate (SPect: Schmaling et al., 2003)
  - SPect and exercise challenge (Peterson et al., 1994)
    - No differences in cytokine production or CBF

Results: absolute CBF

- Measurement of cerebral distribution of Xenon gas
  - Confirmed cerebral hypoperfusion in CFS especially in left temporo-parietal region (Yoshiuchi et al., 2005)

Dynamic neuroimaging studies: Metabolic studies

- Positron Emission Tomography (PET):
  - Reduced Glucose in right medial frontal region, brainstem (Tirelli et al., 1998), anterior cingulate and orbitofrontal region (Siessmeier et al., 2003)
  - Reduced acetylcarnatine uptake in DLFC, occipital/parietal, frontal and medial temporal regions (Kuratsune et al., 2002)
    - Debated
  - Abnormalities in serotonergic neurotransmitter system across brain, specifically in hippocampus (Cleare et al., 2005) and anterior cingulate (Yamamoto et al., 2004)
  - Reduced SE molecule density in anterior cingulate (Yamamoto et al., 2004)
  - Reduced 5-HT(1A) receptor binding potential in hippocampus (Cleare et al., 2005)

Dynamic neuroimaging studies: Metabolic studies

- Magnetic Resonance Spectroscopy (MRS):
  - Increased choline resonance in left basal ganglia (Chaudhury et al., 2003) and occipital cortex (Puri et al., 2002)
  - NAA uptake decreased in right hippocampus (Brooks et al., 2000)
    - Suggestion of altered intra-membrane signaling?
  - Higher levels of ventricular spinal fluid lactate (Murrough et al., 2010)
    - Suggestion of lack of brain oxidization?

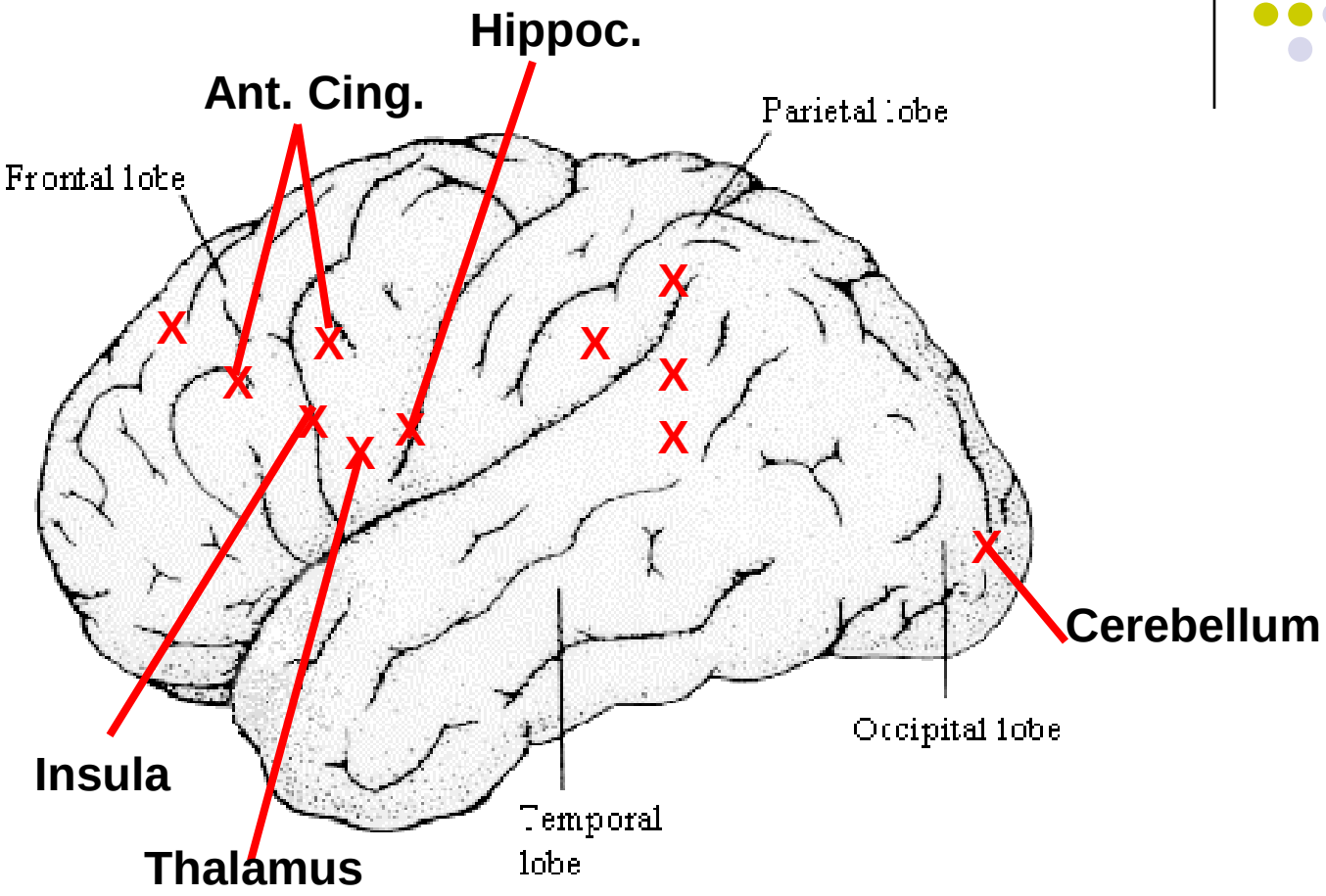
Dynamic neuroimaging studies: Functional studies

- Consistent findings when challenging the working memory system (Paced Auditory Serial Attention Test):
  - No differences in brain activity during simple condition
  - When task demands get more complex:
    - Involvement of anterior cingulate (Schmaling et al., 2003; Lange et al., 2005; Caseras et al., 2006; Cook et al., 2007), DLPC BA 45/46/10, and parietal regions BA 7/19/40 (Lange et al., 2005; Caseras et al., 2006; Cook et al., 2007), inferior medial temporal cortex BA 21/37 (Caseras et al., 2006; Cook et al., 2007),
  - When mental fatigue increases:
    - Hippocampus, Thalamus, cerebellum, insula (Cook et al., 2007)
  - When task load becomes greater:
    - Reduction in frontal and parietal brain regions (Caseras et al., 2006)

Dynamic neuroimaging studies: Functional studies

- CFS utilize more extensive regions of the verbal WM network
- CFS perform as accurately as Controls – behavioral performance is same as Controls
- CFS perform significantly slower than controls
- Implication of posterior attention system
- Implication of brain systems associated with ANS

Locations of brain neuroimaging findings



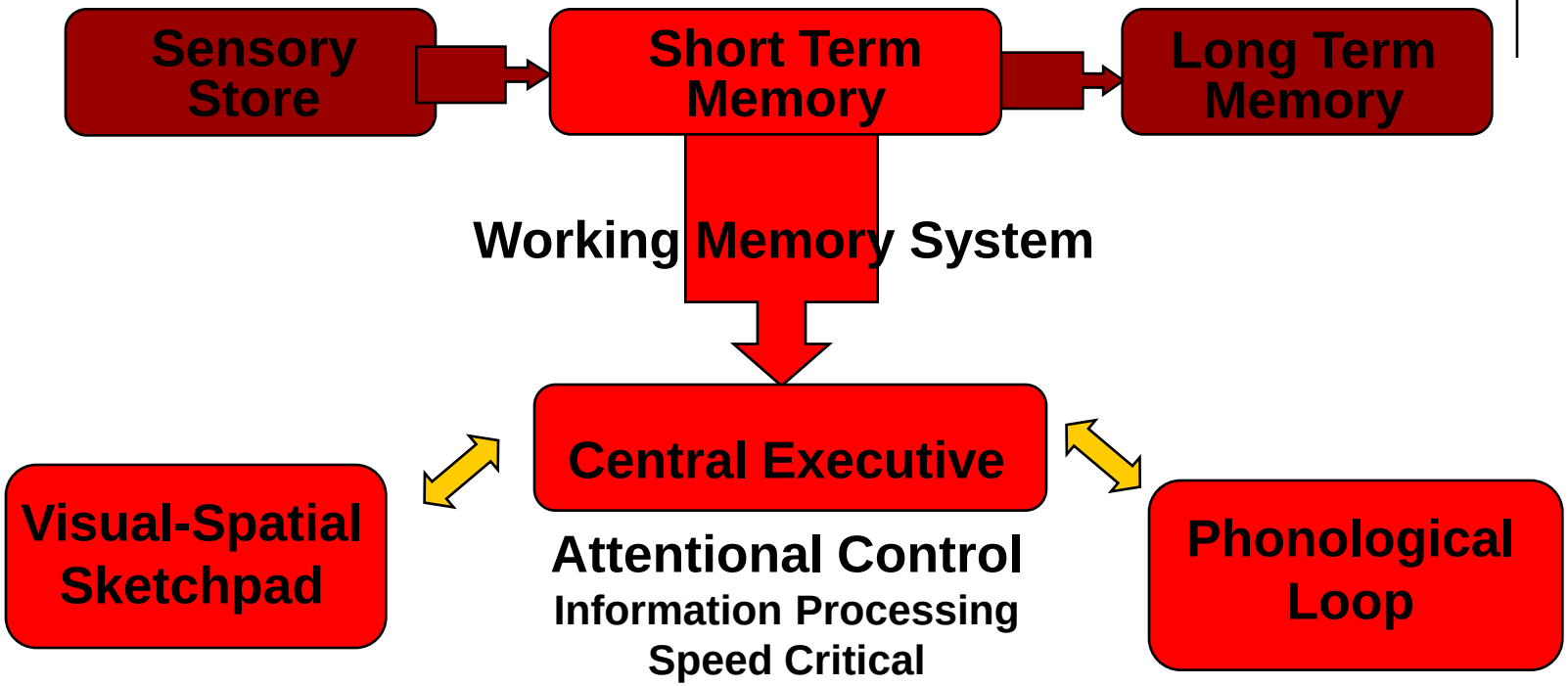
Neuropsychological Studies

- Isolated studies of cognitive function under
  - Immunological challenge
    - not different from controls (Arnold et al., 2002)
  - Noradrenaline challenge
    - Differences in “initial thinking time in planning tasks” (Moriss et al., 2002)
  - Exercise Challenge
    - No differences pre-and post max test (claypoole et al., 2001)
    - Diminished cardiovascular response to cognitive stress (LaManca et al., 2001)
  - Twin studies:
    - Suggest genetic link for cognitive performance (Mahurin et al., 2004)

Neuropsychological Studies

- Cognitive problems significantly more severe in CFS:
  - Without psychiatric overlap
  - Without Fibromyalgia
  - Sudden Onset
- Problems identified in:
  - Visual and verbal memory
  - Psychomotor function
  - Attention
- Most consistent finding:
  - Impaired information processing speed (e.g. Deluca et al., 1997; Busicchio et al., 2004; Buchwald et al., 2007)
  - Particularly complex information processing (e.g., Joyce et al., 1996; Dobbs et al., 2001; Chiaravallotti et al., 2003)

Information Processing Model of Memory



Storage and Encoding of Visual-spatial information

Two Subcomponents

Storage and Encoding of Auditory information

On neuropsychological exam:

- Patients are likely to show subtle and RELATIVE deficits in:
  - Efficient information processing
    - Decreased thinking speed
  - Ability to keep information “online”
    - Decreased amount of information for use available
  - Sequencing pieces of information and prioritizing their use
    - Decreased ability to make quick decisions

- Generally, NO decrease in overall intellectual function

On neuropsychological exam:

- RELATIVE information processing deficit can affect memory, language, motor, and executive function
- These “higher” cognitive functions are more “fragile” and prone to disturbance than “lower” cognitive functions
  - Less redundancy
- Automaticity of cognitive and motor function is often lost
- All of the above components are necessary for:
  - MULTI-TASKING
    - Important cognitive ability in today’s world
    - Necessary for many job functions
    - Considered by patients as a “severe” impairment

On neuropsychological exam:

- Decreased cognitive function identified relies on integrated brain networks
  - Difficult to pinpoint a specific brain region as “the” culprit

- Very difficult to identify and assess with available neuropsychological measures
  - Neuropsychologist performing exam HAS TO BE familiar with the nature and profile of cognitive abnormalities found in CFS
  - If not, neuropsychological evaluation performed may harm patient’s case

Social Security Disability Act

"…the Social Security Act (the Act) and our implementing regulations require that an individual establish disability based on the existence of a medically determinable impairment; i.e., one that can be shown by medical evidence, consisting of medical signs, symptoms and laboratory findings. Disability may not be established on the basis of an individual's statement of symptoms alone."

In English:

- A patient with CFS is not considered disabled simply because of having the symptoms consistent with the case definition of CFS

- A CFS patient has to show that symptoms are “severe enough” to result in “regular, predictable or sustained” limitations of even sedentary and light activities

  - “A case is won or lost based on the severity of your symptoms (limitations) and not on the CFS diagnosis. .. Winning a CFS disability case is now 10% documentation of the diagnosis and 90% documentation of impairments and limitations! Never lose sight of that crucial fact!“ (Disability lawyer)

Job of the Neuropsychologist

- Social Security Ruling, SSR 99-2p.; Titles II and XVI: Evaluating Cases Involving Chronic Fatigue Syndrome (CFS):
  - Self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities

- Neuropsychological evaluation is an integral part of a CFS patient's disability application

When is a cognitive finding severe enough?

- “If fatigue, pain, neurocognitive symptoms, or other symptoms are found to cause a limitation or restriction having more than a minimal effect on an individual's ability to perform basic work activities, the adjudicator must find that the individual has a ``severe'' impairment.”

- Writing a clear and informed neuropsychological report integrating the profile of clinical and research findings clearly is essential

Bottom line

- Patients perceive cognitive problems common in CFS as disabling
- Researchers provide interesting findings difficult to aggregate in support of disability claims
  - Functional neuroimaging is still experimental and often not accepted as evidence of cognitive impairment
- Clinicians need to be better educated about CFS to provide valid evaluations
  - Cost of neuropsychological evaluations is often a factor for patients
- SSA denies claims upon receipt of poorly argued and documented cognitive evaluation