Age Associated Cognitive Decline and Mild Cognitive Impairment (MCI)

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Disclosures

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Objectives

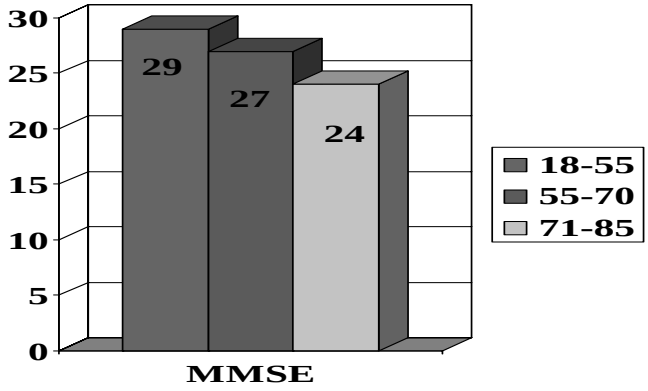
- Rationale for Neuropsychological Assessment
- Neuropsychological Evaluation in Growing Older
  - Age appropriate decline in cognitive function
  - 'Abnormal' aging
    - Dementias
    - Mild Cognitive Impairment
- Neuropsychology Crucial?
- Conclusions
- Future Directions

Rationale for Neuropsychological Assessment

- Aging and Brain disorders manifested by changes in cognitive and behavioral function
  - Dementia is decline in previously acquired cognitive and behavioral abilities which leads to deficits in ability to function
  - Mild Cognitive Impairment is 'abnormal' decline in cognitive function greater than expected for age.
- Neuropsychological assessment is only way to measure alterations in cognitive and behavioral function.

Normal Aging

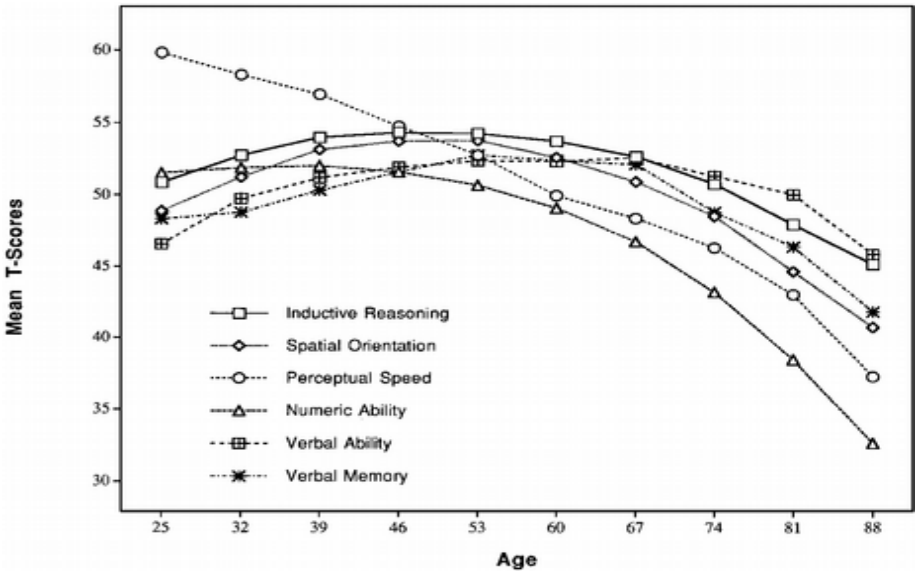
- **Extensive Data indicate aging is associated with cognitive decline**



Normal Aging

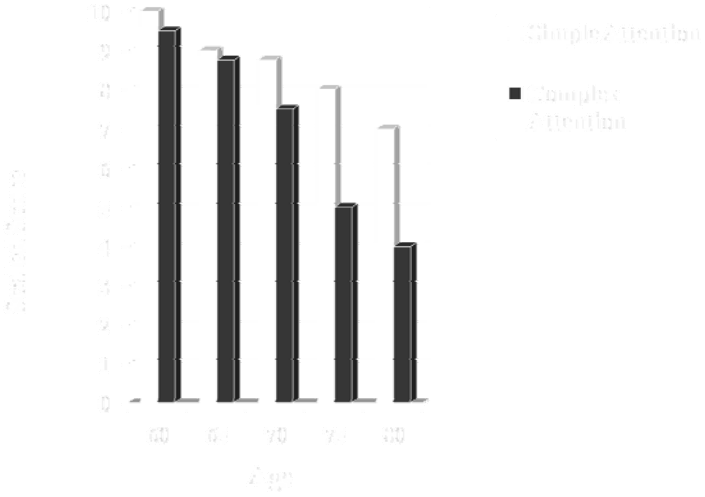
- **What, When and How Much cognitive decline occurs with aging varies:**
  - Numerical ability/arithmetic and processing speed
    - beginning about age 25
  - Memory (Episodic or Declarative)
    - Late 30's or 40's perhaps as late as 50's to 60's
      - Seattle study found about age 53
  - Reasoning, verbal ability, and Visuoperceptual skills
    - Beginning in 50's and 60's
  - Word knowledge, vocabulary, word reading
    -Stable into late adulthood (70's+)

Longitudinal change in cognition with normal aging

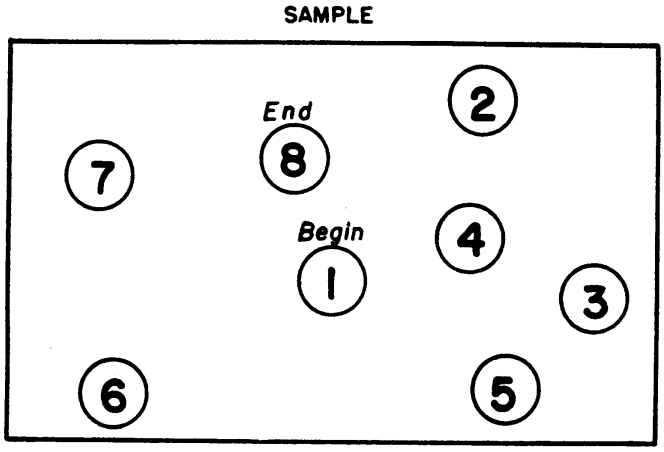


From Schaie (1996)

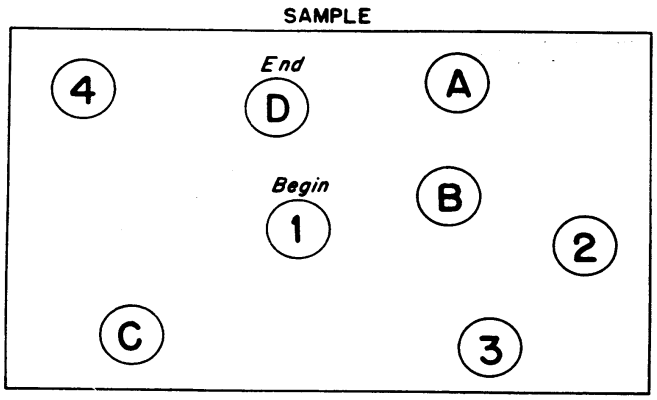
Cognitive Changes in Normal Aging: Simple Attention and Complex Attention



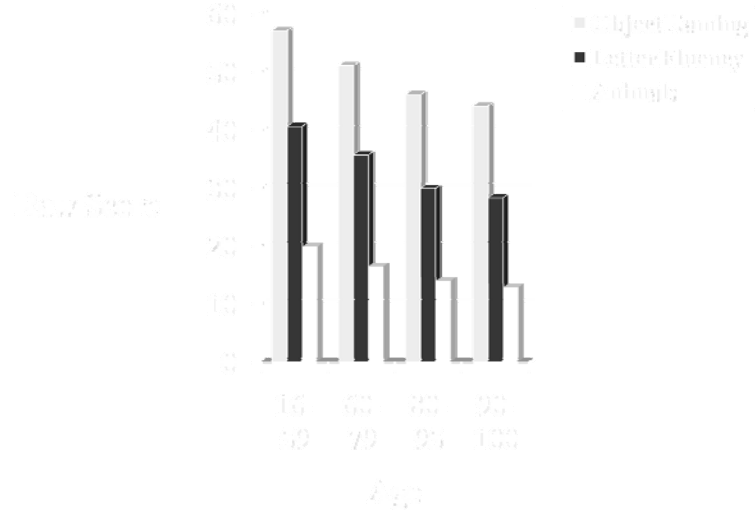
Attention: Simple Task



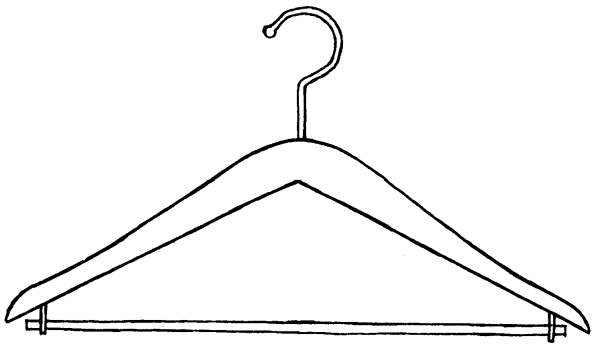
Attention / Processing Speed: Difficult Task



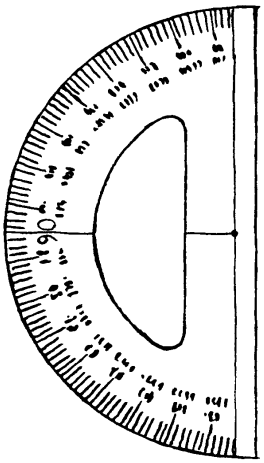
Cognitive Changes in Normal Aging
Language



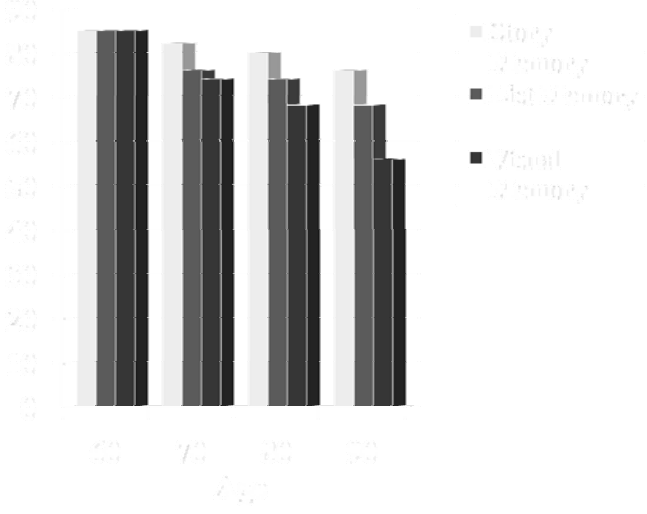
Object naming:
Easy Item



Object Naming: Difficult Item



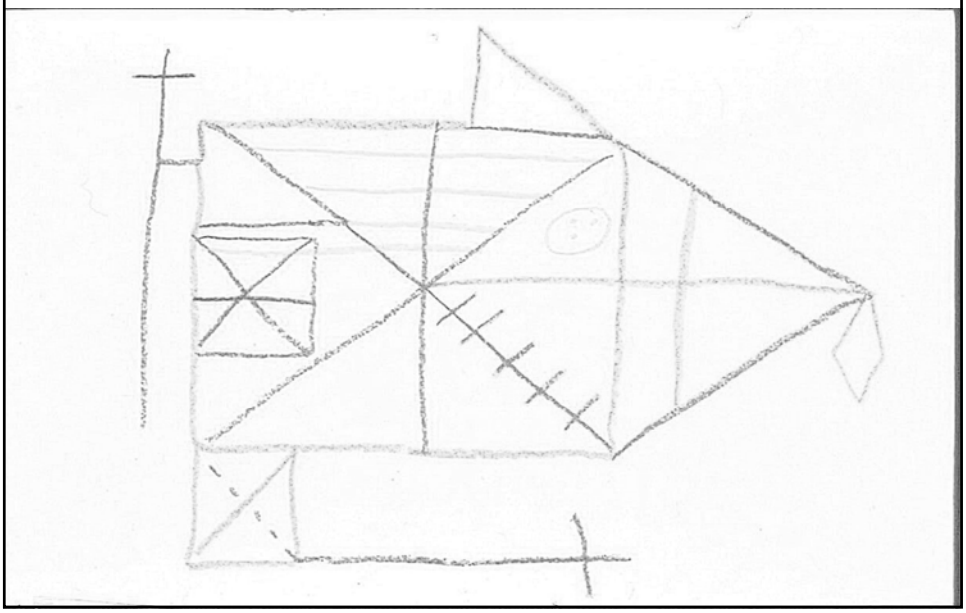
Cognitive Changes in Normal Aging Memory



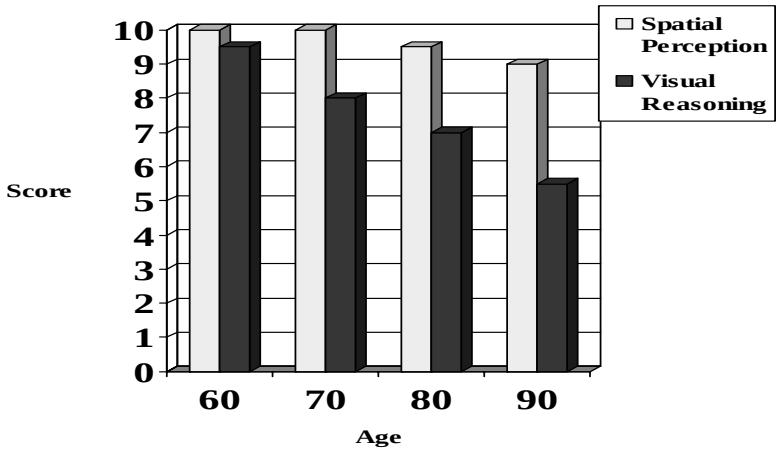
Verbal Memory

- Bat
- Cannon
- Chair
- Floor
- Orange
- Mayor
- Bus
- Play
- Corner
- Salad
- Lever
- Square

Visual (non-verbal) memory



Cognitive Changes in Normal Aging: Visuoperceptual/Visual Reasoning



Visuospatial Perception: Spatial Perception

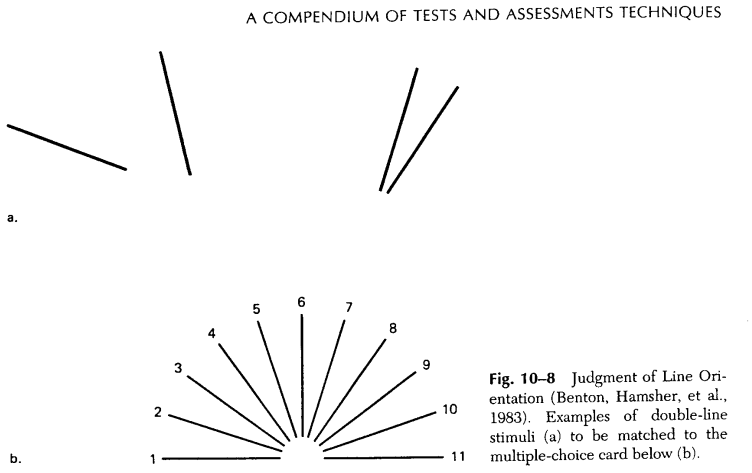
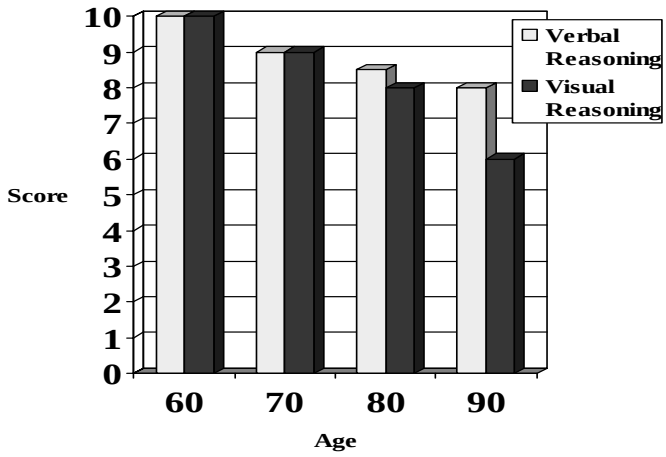


Fig. 10–8 Judgment of Line Orientation (Benton, Hamsher, et al., 1983). Examples of double-line stimuli (a) to be matched to the multiple-choice card below (b).

Cognitive Changes in Normal Aging: Reasoning



Verbal Reasoning

Easy

- **Wood and Coal**

Hard

- **Platypus and Stork**

Objectives

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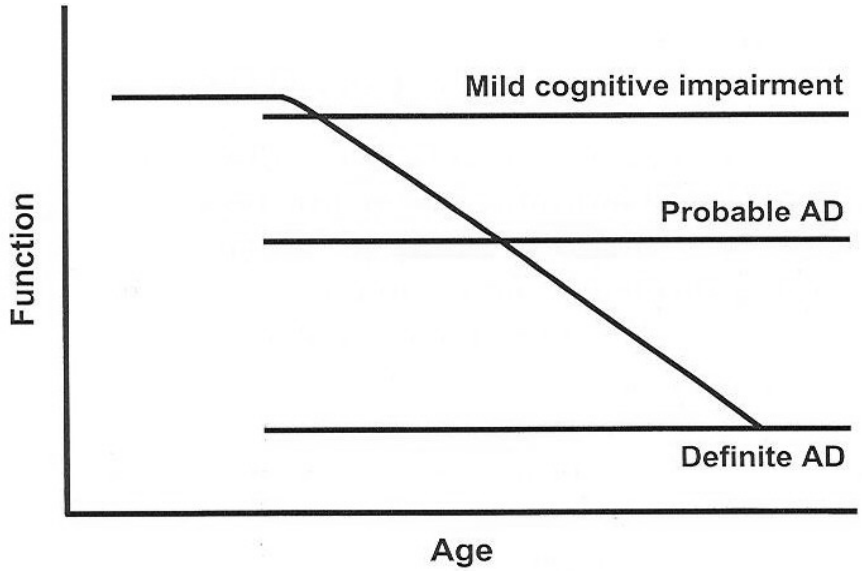
Cognitive Decline: Dementia and Mild Cognitive Impairment

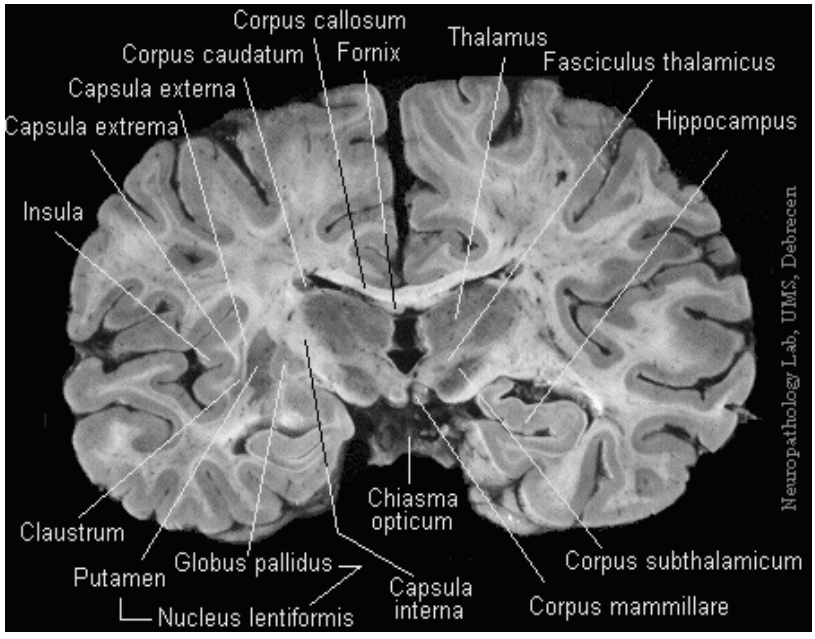
- **Extensive terms and research to defining where normal aging stops and pathology begins**
  - Age-appropriate memory Impairment (AAMI)
  - Senility
  - Benign semnescent forgetfulness
  - Cognitive Impairment – No Dementia (Canada)
  - Mild Cognitive Disorder
  - Mild Cognitive Impairment (MCI)
  - Mild Neurocognitive Disorder
  - Questionable dementia
- **Defining 'Impairment'**

Theoretical Progression from normal to dementia

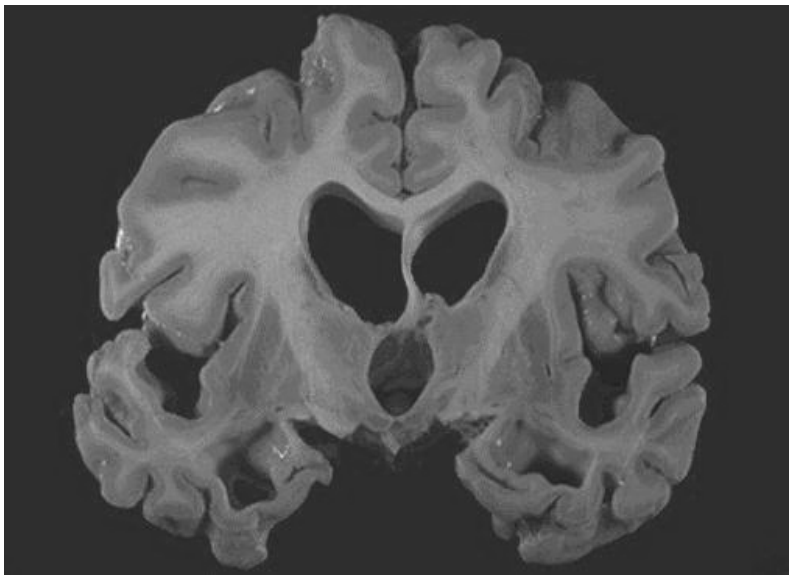


From Petersen, 2003

Gross Pathology: Normal Coronal View



Gross Pathology: Alzheimer's Disease



How to define where pathology begins?

Defining Impairment: Dementia

- Dementia is broadly defined as a decline in cognitive function from a previous level of ability severe enough to interfere with work, school, social activities, etc. that is not due to delirium or encephalopathy
- DSM-IV TR defines dementia more specifically as requiring a deficit in memory and at least one other cognitive deficit
  - e.g., Aphasia, Agnosia, Apraxias, executive functions

  AND
  - Impairment in ability to work, attend school, complete ADLs, etc.
- How to measure memory loss and cognitive or behavioral impairment

Identifying Cognitive Impairment

- Methods to define impairment in neuropsychological function for dx of dementia
  - Clinical interview with pt (and collateral source)
  - MMSE
  - Clinical Dementia Rating scale (CDR)
  - Neurologic/neurobehavioral exam
  - Clinical neuropsychological evaluation
- Structure of CNS does NOT allow for dx of dementia
  - MRI, CT, PET study can NOT identify cognitive impairment for dx of dementia

When is Impaired Actually Impaired

- **Threshold for impairment can vary from diagnostician to diagnostician**
- When is MMSE score impaired?
  - MMSE score 25/30?
  - MMSE score 23/30?
  - MMSE score 18/30?
- Neuropsychological criteria for defining impairment
  - < 16th percentile (<1.0 SD below average = possible impairment)
  - < 7th Percentile (<1.5 SD below average = MCI)
  - 2nd Percentile (<2.0 SD below average = dementia)

Neuropsychologic Profile of Dementias

- **So-called 'cortical' dementias**
  - Memory loss (impaired recall without benefit of recognition cues) with other cortical findings such as agnosias, aphasias, and/or apraxias.
    - Prototype is Dementia of Alzheimer's type
- **So-called 'subcortical' dementias**
  - slowed processing speed, with deficits in attention, memory (poor spontaneous retrieval but intact recognition), visuospatial skills, and executive functions (initiation, planning, behavioral apathy).
    - Prototype is Vascular dementia or Parkinson's disease dementia

Alzheimer's Disease

- Early deficits
  - Early and profound impairment in memory
    - Deficient consolidation and rapid forgetting
      - Retention rate over 20-30 minutes < 50 %
  - Attention/working memory intact
  - Social withdraw (common early)
  - Verbal fluency (semantic < phonemic) and dysnomia
  - Visuoconstructional apraxia
  - Executive function (impulsivity, indifference, poor insight)
- Later stage deficits
  - IQ, attention, behavioral apathy, agitation, delusions

Vascular Dementia

- Early deficits
  - Memory impaired
    - Poor spontaneous recall, but recognition intact
  - Attention (divided attention/working memory)
  - Visuoperceptual/Visuoconstructional apraxia
  - Executive function (reasoning, sequencing, apathy)
  - Verbal fluency (semantic > phonemic)
  - Social withdraw, depression
  - Focal neurological deficits
- Later stage deficits
  - IQ, agitation, delusions

Lewy Body Dementia

- Early deficits
  - Early and profound impairment in Attention
    - Immediate memory/working memory impaired
  - Visuoperceptual/Visuoconstructional apraxia
  - Executive function (reasoning, sequencing, poor insight)
  - Fluctuating mental status, visual hallucinations
  - Memory not severely impaired
- Later deficits
  - Memory, IQ, language/speech, agitation, delusions

Frontotemporal Dementia

- Early deficits (considerable variability)
  - Executive function (impulsivity, reasoning, sequencing, apathy, disinhibition, poor insight)
  - Behavioral/Mood (Early and profound changes)
  - Attention (divided attention/working memory)
  - Verbal fluency (phonemic < semantic) naming deficits
    - Primary progressive aphasias have early and profound language deficits
  - Memory (mild deficits only)
- Later deficits
  - Memory, IQ, visuoperceptual, agitation, echolalia, mutism, stimulus bound behaviors

Objectives

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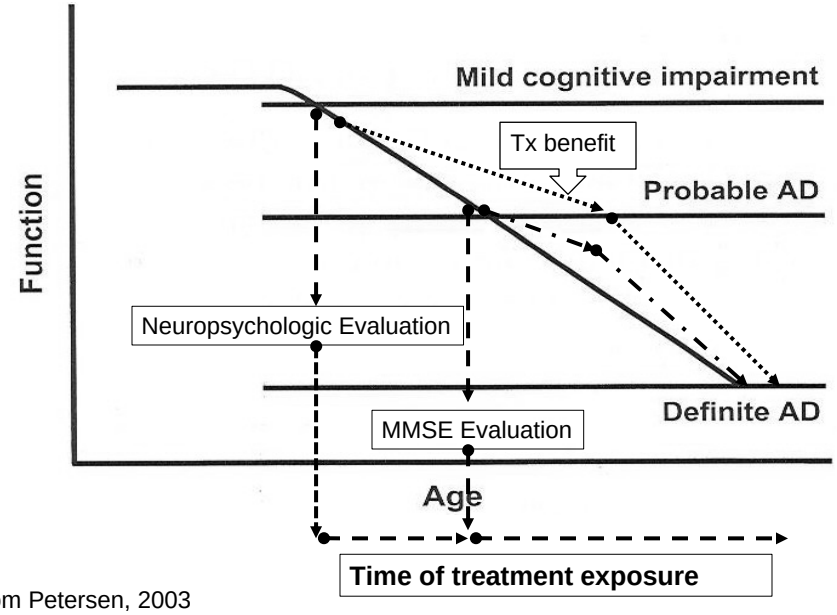
Mild Cognitive Impairment (MCI)

- Term to describe Pts with cognitive impairment, but do NOT meet diagnostic criteria for dementia
- Peterson et al. (Mayo Clinic) defined MCI as:
  - Subjective memory complaint
  - Objective memory deficit compared to age-matched peers (1.5 or more standard deviations below average)
  - Otherwise cognitively intact
  - Otherwise intact daily functioning
    - Patient may use adaptations for memory loss
  - Not demented

Who Cares? Why MCI is Important

- Earliest cut-point distinguishing normal aging from abnormal aging
  - Controversy
    - Unique disease entity? OR
    - Prodromal state representing initial stages of disease?
- MCI increases risk to develop dementia
  - Annual progression of healthy community living older adults (aged 55+) to dementia is about 1-2 % per year
  - Annual progression from MCI to dementia is 10-15%
- MCI first clinical point to initiate treatment?

Theoretical benefit for various rates of early detection



From Petersen, 2003

Advances: Diagnostic Criteria

- Dropped need for subjective memory complaint
- Different measures and cut-offs
  - Original required only one measure within a domain to be ≤ -1.5 SD below peers
    - (e.g., if one of 2 memory scores ≤ -1.5 SD = MCI)
  - 'comprehensive' require 2 (or more) measures within a domain to be < -1.0 SD below peers
  - 'liberal' require only one score fall < -1.0 SD below peers
  - 'conservative' requires 2 (or +) measures within a domain < -1.5 SD below peers

Advances: Diagnostic Subtypes

- Single Domain MCI
  - Amnestic MCI (aMCI-s)
    - The "original" with memory ≤ -1.5 SD below demographically-matched peers.
  - Non-amnestic MCI (naMCI-s)
    - Non-memory domain (e.g., language, attention, etc.) ≤ -1.5 SD below peers.
- Multiple Domain MCI
  - Multidomain amnestic MCI (aMCI-m)
    - Memory + another domain ≤ 1.5 SD below peers
  - Multidomain nonamnestic MCI (naMCI-m)
    - 2 or more nonmemory domain < -1.5 SD below peers

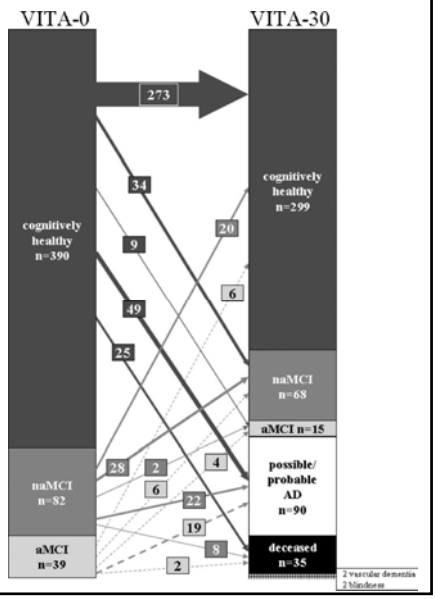
Why MCI Subtype Important? Predict Different Dementias?

- Each dementia may have distinct MCI:
  - aMCI-s ⇨ AD
  - aMCI-m ⇨ AD or Vacular dementia (VaD)
  - naMCI-s ⇨ FTD or Lewy Body dementia (DLB)
  - naMCI-m ⇨ VaD or DLB
- Early data:
  - MCI subtypes **not** consistent conversion to distinct dementias, BUT
    - aMCI-s and multiple domain MCI greater risk for AD

Progression of Aging

Fisher et al., Neurology 2007;68: 288-291

- Healthy
  - 273 (70%) ⇨ healthy
  - 34 (9%) ⇨ naMCI
  - 9 (2%) ⇨ aMCI
  - 49 (13%) ⇨ AD
  - 25 (6%) ⇨ mortality
- Amnestic MCI
  - Healthy = 15%
  - Dementia = 49%
- Non-amnestic MCI
  - Healthy = 24%
  - Dementia = 27%



Progression Rate: MCI to _____

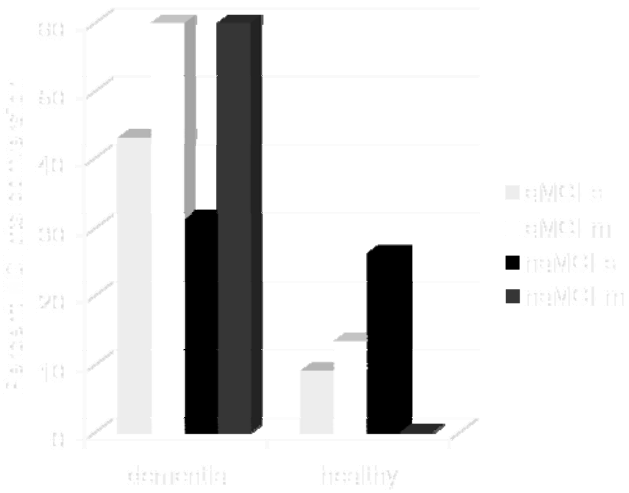
- Dementia
  - Annual conversion rates
    - Low = 2 % per year
    - High = 31 % per year
    - Mean = 10-15 % per year
- Cognitively Healthy (revert to healthy status)
  - Study period (1.7 to 6 years)
    - Low = 15 %
    - High = 44 %
  - Annual conversion rate

    Mean = 8-11 % per year

Conversion Rate: MCI subtypes

Busse et al. Neurology 2006; 67: 2176-2185

- Dementia
  - aMCI-m=60%
  - naMCI-m=60%
  - naMCI-s=31.3%
- Cognitively Healthy
  - naMCI-s=26.3%
  - naMCI-m=0%



MCI and Dementia: Risks and Protective Factors

- Progression to Dementia less likely if
  - Non-amnestic MCI-single domain (naMCI-s)
  - Minimal cerebrovascular disease
    - No stroke, diabetes, heart disease, smoking, HTN, hyperlipdemia
  - Mild to moderate ETOH intake
  - Exercise
  - High “cognitive reserve”
    - May account for lack of association between severity of brain pathology and clinical symptoms
    - High academic achievement, premorbid IQ, occupational attainment, leisure activities
  - No psychiatric symptoms (anxiety, amotivation, or depression)

When to Refer for Neuropsychologic Evaluation?

- Assessment of neuropsychological function crucial for diagnosis and management of dementias and MCI
  - However, assessment sensitivity and specificity needs vary depending upon issue
    - To distinguish patient neuropsychological function as normal or grossly abnormal, clinical neuropsychologic eval. **NOT** needed.

Neuropsychology Crucial?

- Detailed neuropsychologic eval assists:
  - Differential diagnosis
    - Dementia vs. pseudodementia
    - Differential diagnosis of dementias
    - Identify subtypes of MCI
      - Amnestic MCI versus non-amnestic MCI
  - Treatment planning
    - Allow early detection to start treatment
      - Different dementia/MCI subtypes may = different tx
    - Monitor treatment effectiveness of cognitive deficits
    - Determining care needs (placement)
  - Determining competency/functional capacity

Bottom Line

- Distinguishing normal aging from abnormal is complex
  - Inter-individual variations in normal aging
    - Cognitive progression within neuropsychological domains occurs at different rates
      - Processing speed and reaction time decline first
      - Language (word knowledge, reading) most resillant
    - Cognitive progression likely affected by numerous biological and environmental variables
  - Intra-individual variability in cognitive functions important to consider
    - 30 % of individuals will have a score < 5th %ile on comprehensive neuropsychological evaluation.
  - Criteria used to distinguish normal aging from abnormal aging better identified
    - Common standard is MCI

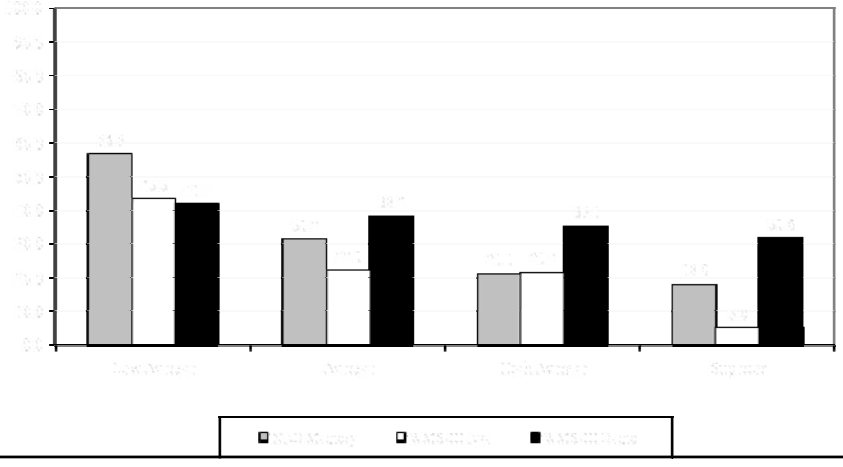
Bottom Line

- MCI useful diagnosis
  - Often used criteria to Diagnose MCI
    - Score on neuropsychological measure < -1.5 SD below the mean of healthy peers
  - Increases likelihood of progression dementia
    - 10-15 % progress from MCI to dementia per year
  - Subtypes of MCI proposed
    - Amnestic MCI (single or multiple domain)
    - Non-amnestic MCI (single or multiple domain)
  - MCI represents early clinical point to start treatment
    - Increase exposure/power of any intervention?

Questions

Cognitive function varies within individuals

- Percent of healthy individuals with at least one memory score < 5th %ile

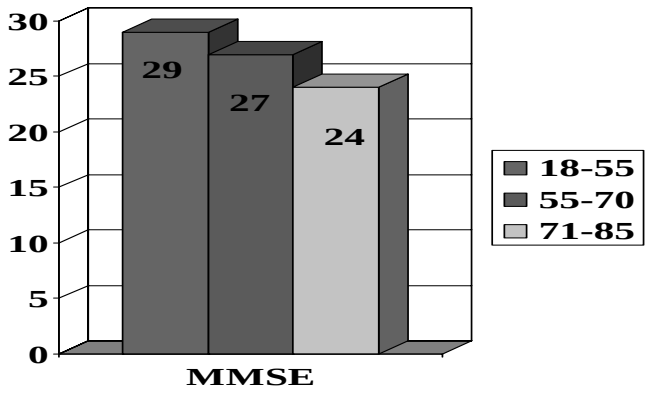


Defining Cognitive Impairment: Dementias

- Neuropsychological deficits should follow known neuropathological disease patterns
  - Distinguish pseudodementia from dementias
- Neuropsychological deficits vary between dementias
  - AD has more profound memory deficits than Frontotemporal dementia
- Within a dementia syndrome, considerable inter-individual variability
  - One pt with AD may exhibit more language dysfunction while another may exhibit more visuospatial deficits

Normal Aging

- **Average MMSE score by age**



Parkinson's Disease Dementia

- Early deficits
  - Information processing/Psychomotor speed
  - Executive function (reasoning, sequencing, apathy, disinhibition)
  - Attention (divided attention/working memory)
  - Visuoperceptual/visuoconstructional
  - Verbal fluency (phonemic < semantic) and naming deficits. Hypophonia, micrographia, dysarthria.
  - Memory (poor spontaneous recall, intact recognition)
- Later deficits
  - Memory, IQ, attention (basic)

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Historical Overview of Neuropsychology

- Origins of Neuropsychology
  - **Relationship to Behavioral Neurology**
    - **Functional Anatomical Correlation**
    - **Cortical Localization/Lateralization**
  - Relationship to Psychology
    - Normative comparisons
    - Quantifying Brain Functions

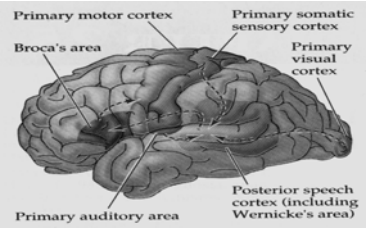

Figure 25.1 Diagram of the major brain areas involved in the comprehension and production of language. The primary sensory, auditory, visual, and motor cortices are indicated to show the relation of Broca's and Wernicke's language areas to the less specialized areas that are nonetheless involved in the comprehension and production of speech.

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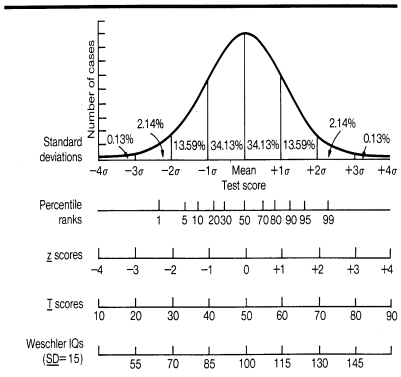
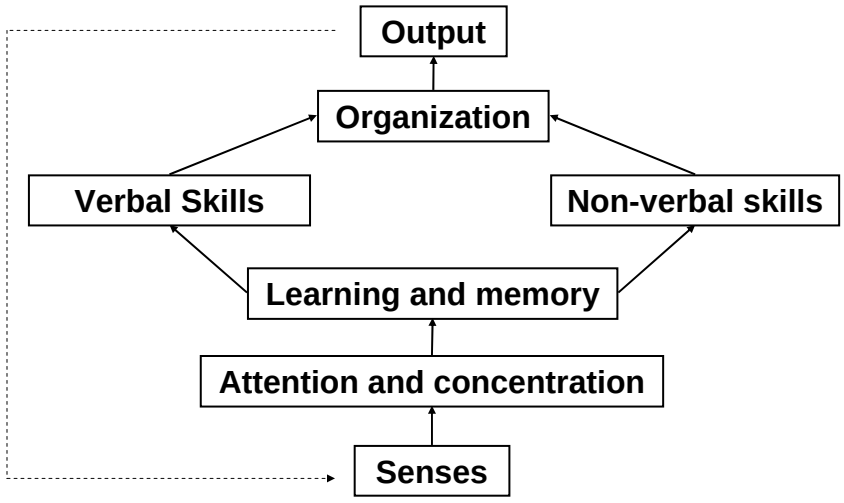


Neuropsychological Evaluation: Fundamentals

- Assessment of Brain-Behavior Relationships
  - Identify and quantify presence (or absence) of neuropsychological deficits
- Assumptions for Evaluation
  - Brain dysfunction affects behavior
  - Behavior changes can be associated with particular brain processes/areas/neurological syndromes
  - Assessment can be reliable
  - Assessment can be valid
  - Assessment affects diagnosis/treatment

Brain Organization



Baker GA. *personal communication, 2008*

Neuropsychological Evaluation Methods

- MMSE
- Clinical observations
  - Neurological exam
- Self-report
- Collateral (spouse) report
- Neuropsychologic Eval.
  - Intelligence
  - Attention/Processing Speed
  - Language
  - Memory
  - Visuoperceptual
  - Abstraction/Problem solving
  - Personality/Behavior

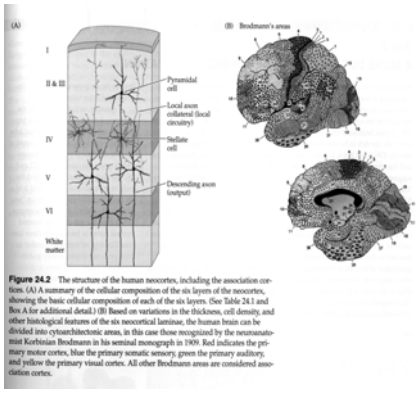
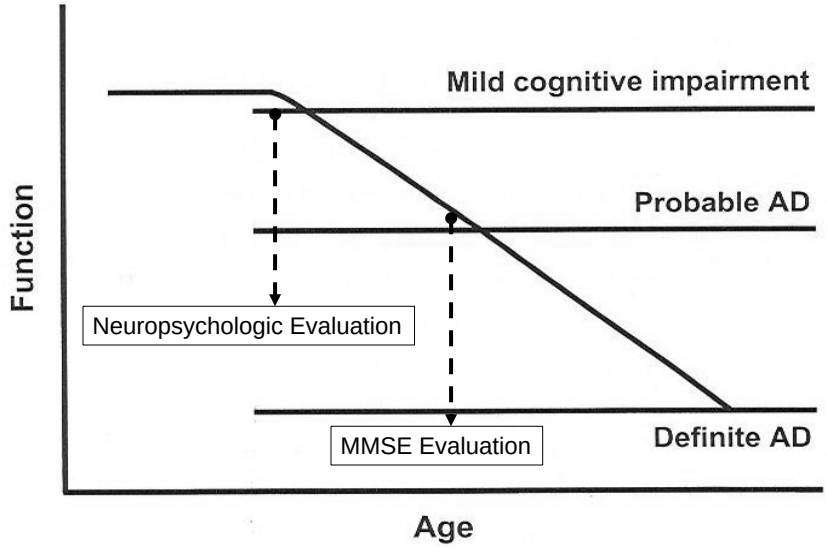


Figure 24.2 The structure of the human neocortex, including the association cortices. (A) A summary of the cellular composition of the six layers of the neocortex, showing the basic cellular composition of each of the six layers. (See Table 24.1 and Box A for additional detail.) (B) Based on variations in the thickness, cell density, and other histological features of the six neocortical laminae, the human brain can be divided into cytoarchitectonic areas, in this case those recognized by the neuroanatomist Korbinian Brodmann in his seminal monograph in 1909. Red indicates the primary motor cortex, blue the primary somatic sensory, green the primary auditory, and yellow the primary visual cortex. All other Brodmann areas are considered association cortex.

Neuropsychology Crucial? (continued)

- Detailed neuropsychologic assessment assist in:
  - Early detection allow for early start of treatment
  - Identification of MCI subtype may lead to different treatment
    - Progression of amnestic MCI to dementia higher
    - Progression of non-amnestic MCI to dementia low

Temporal Detection of Mild Cognitive Impairment



From Petersen, 2003

Clinical Neuropsychological Evaluation: Benefits

- **Neuropsychologic (cognitive and behavior) is:**
  - Systematically measured across multiple domains
    - Memory, language, attention/executive, visuoperceptual, mood
  - Assessed using reliable and validated tools:
    - Score obtained in Seattle same as Tampa
  - Referenced (compared against):
    - Healthy demographically matched peers
    - Individual level based on premorbid expectations
  - Threshold for impairment can be adjusted for individual needs
    - Research vs. clinical vs. medicolegal

Diagnostic Value of Neuropsychological Evaluations

- Define severity/type of cognitive impairment/dementia
- Distinguish Dementia from pseudodementia
- Differential diagnosis of dementias
- Diagnose Mild Cognitive Impairment
- Identify pts needs for accommodation/adaptations
- Identify pts at risk to live alone, drive, make decisions, etc.
- Evaluate for effectiveness of therapies or to track progression of disease
- Predict mortality
  - Individuals with greater intra-individual variability in cognitive function at greater risk for death (Shipley et al. 2006; MacDonald et al. in press)
    - Simple and choice reaction time mean & variability
    - Verbal memory

Severity/Type of Cognitive Impairment

- Neuropsychological evaluation can quantify cognitive deficits AND strengths
  - Describe severity (mild vs. profound) of deficits
  - Describe cognitive and behavioral strengths
- Neuropsychological deficits vary between dementias
  - AD has more profound memory deficits than Frontotemporal dementia
- Variable clinical presentation within a dementia disease (e.g., inter-individual variability)
  - One pt with AD may exhibit more language dysfunction while another may exhibit more visuospatial deficits

When ‘impaired’ is not impaired: Depression/pseudodementia

- Neuropsychological evaluation effective at distinguishing dementia from pseudodementia
  - Performance within and across neuropsychological profile not consistent with functional neuroanatomy or known neuropsychological pathology
    - Patients with dementia tend to provide false positive errors on memory tests
    - Patients with pseudodementia give more false negatives (“I don’t know.”)
    - Fluctuation of scores within a neuropsychological domain
    - Failure on symptom validity tests/tests of task engagement
      - Passed by individuals with mild/moderate dementia