DEMENTIA 2022

Robert Bender, MD
Broadlawns Medical Center

I have no financial relationships to disclose.

OBJECTIVES

Know and understand:

- The risks for and causes of dementia
- The evaluation of patients with dementia
- How to plan behavioral and pharmacologic treatment strategies to minimize the personal, social, & financial impacts of dementia
- How to refer patients and caregivers to available community resources

TOPICS COVERED

- Epidemiology and Societal Impact
- Risk Factors and Prevention
- Assessment and Differential Diagnosis
- Differentiating Types of Dementia
- Treatment and Management
- Resources

WHAT IS DEMENTIA?

- Describes in general several disorders that cause significant decline in one or more areas of cognitive functioning severe enough to result in functional decline
- Progressive and disabling
- *Not* an inherent aspect of aging
- Different from normal cognitive lapses

THE EPIDEMIOLOGY OF DEMENTIA

- 6%–8% of people ≥65 yr have Alzheimer dementia (AD)
  - ➢ Prevalence doubles every 5 yr after age 60
  - ➢ Nearly 45% or more of those aged 85+ have AD
- Vascular dementia is thought to cause an estimated 15%–20% of cases and often coexists with AD — “mixed dementia”
- Dementia with Lewy Bodies (DLB) is second most common cause in people over 65

Etiology

- Normal Pressure Hydrocephalus
- Traumatic Brain Injury
- Drug or alcohol related dementia
- Vascular Dementia
- Autoimmune related dementia

THE IMPACT OF DEMENTIA

Economic

- $604 billion annually for direct costs of medical and social care and informal care
- Medicare, Medicaid, private insurance provide much of the direct costs — remaining costs with families and/or caregivers ($220.2 billion in US)

Emotional

- Direct toll on patients
- Nearly half of caregivers suffer psychological distress, especially depression, and have more physical health issues

ETIOLOGY

- Alzheimer disease
  - ➢ Amyloid plaques/oligomers
  - ➢ Tau neurofibrillary tangles
- Lewy body and Parkinson dementia
  - ➢ Cytoplasmic α-synuclein inclusion bodies
- Frontotemporal dementia
  - ➢ Tau or ubiquitin proteins

RISK FACTORS FOR DEMENTIA

Protective Factors

Definite: unknown

Possible

- NSAIDs
- Antioxidants
- Intellectual activity
- Physical activity
- Statin

Risk Factors

Definite

- Age
- Family history
- *APOE4* allele
- Down syndrome
- Depression
- Hypertension
- Hearing loss

Possible

- Head trauma
- Fewer years of formal education
- History of depression
- Cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, obesity)

Hearing Loss and Dementia Risk

- In a study from Johns Hopkings, Dr. Lin and colleagues tracked 639 adults for 12 years and found that:
- Mild hearing loss doubled risk
- Moderate hearing loss tripled the risk
- Severe hearing loss increased the risk 5 fold

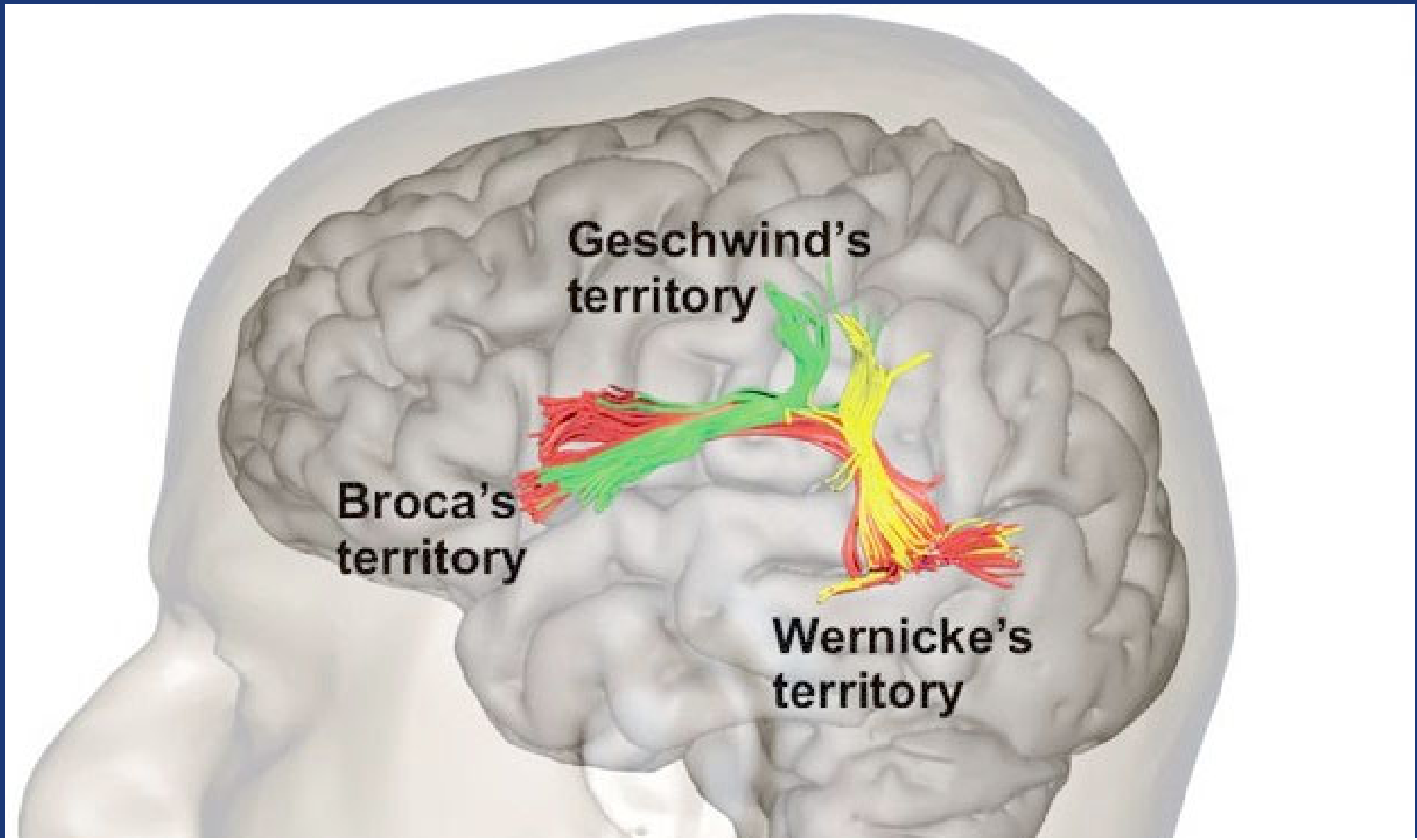
GRS Teaching Slides

Hearing Loss and Changes in the Brain

- Hearing loss seems to shrink some parts of the brain responsible for auditory response.
- Hearing loss is associated with loss of nerve cells in areas of the brain responsible for hearing
- With hearing loss, we see less activity in the brain when patients concentrate on complex sentences
- Speech comprehension goes down.f

The Arcuate Fasciculus

- The Intelligence Highway



The Arcuate Fascuculus

- The Intelligence Highway
- Key language areas shown in the previous slide only become active when language is turned into meaning
- Listening to language in Wernicke's area and Gerscwind's territory signifying that sounds are being turned into meaning.
- Broca's are is involved in listening as well because understanding words involves to some extent articulating them "in your head".

THE GENETICS OF DEMENTIA

Early onset (<60 years old)

- Amyloid precursor protein (APP)
- Presenilin proteins (PS1 and PS2)

Late onset

- Apolipoprotein E gene (*APOE 2/3/4*) — chromosome 19
  - ➢ *APOE4* — two alleles confers greatest risk, decreasing age of onset in dose-related fashion
  - ➢ *APOE2* — protective
- Genome-wide association studies have identified other genes that confer risk of AD

ASSESSMENT: HISTORY

Ask both the patient and a reliable informant about the patient's:

- Date of onset of current condition, chronology and nature of symptoms
- Medical history
- Current medications & medication history
- Patterns of substance use or abuse
- Living arrangements

ASSESSMENT: PHYSICAL

Examine:

- Neurologic status
- Mental status
- Functional status (direct observation or informant report)
- General physical exam

Include:

- Quantified screens of cognitive function
  - ➢ For example, Folstein's MMSE, Mini-Cog, SLUMS, MoCA
- Neuropsychologic testing when presentation is atypical or if results are confounded by a high level of education or subtle changes

SCREENING INSTRUMENTS FOR EVALUATING COGNITION (1 of 2)

Name	Items/ Scoring	Domains assessed	Web link (accessed May 2015)
Mini-Cog	2 items Score = 5	Visuospatial, executive function, recall	http://geriatrics.uthscsa.edu/tools/MINICog.pdf
SLUMS	11 items Score = 30	Orientation, recall, calculation, naming, attention, executive function	http://medschool.slu.edu/agingsuccessfully/pdfsurveys/slumsexam_05.pdf
MoCA	12 items Score = 30	Orientation, recall, attention, naming, repetition, verbal fluency, abstraction, executive function, visuospatial	www.mocatest.org

SCREENING INSTRUMENTS FOR EVALUATING COGNITION (2 of 2)

Name	Items/ Scoring	Domains assessed	Web link (accessed May 2015)
Folstein MMSE	19 items Score = 30	Orientation, registration, attention, recall, naming, repetition, 3-step command, language, visuospatial	For purchase: www.minimental.com
Functional Activities Questionnaire	10 items Score = 30	Informant based, executive functioning, activities of daily living, attention, concentration, memory, home safety	www.healthcare.uiowa.edu/familymedicine/fpinfo/Docs/functional-activities-assessment-tool.pdf

ASSESSMENT: LABORATORY

Routine

- CBC
- Na+, Ca++
- BUN/Cr
- Fasting glucose
- RPR
- TSH
- Vitamin B_{12} level
- Folic acid
- Liver function

Optional (based on clinical exam and suspicion)

- Liver function
- Folic acid
- Homocysteine/methylmalonic acid
- Urinalysis / Toxicology
- CSF analysis
- HIV testing
- Autoimmune panel in csf and serum

ASSESSMENT: BRAIN IMAGING

Consider imaging when:

- Onset occurs at age <65 years
- Symptoms begin suddenly or progress rapidly
- There is evidence of asymmetric or focal neurologic deficits
- Clinical picture suggests normal-pressure hydrocephalus
- Patient has had recent fall or other head trauma

Consider:

- Noncontrast CT head scan
- MRI
- Positron emission tomography (PET) when diagnosis remains uncertain

NORMAL AGING

- Mild decline in memory
- Requires more effort and time to recall new information
- Decline does not impair functioning
- New learning is slower but still occurs
  - Usually well-compensated with lists, calendars, other memory supports

Differential Diagnosis

- Drugs, developmental syndrome, delerium
- Emotional problems
- Metabolic dysfunction
- Endocrine disorder
- Nutritional problem, degenerative neurologic disorder
- Trauma, Tumor
- Infection, inflammation, ischemia
- Anoxia, autoimmune disease, arrhythmia, anemia
- Social, sensory, spiritual isolation, seizure disorder
- PLUS: pain, low urine or stool output

MILD NCD/MCI

- MCI: Subjective complaint of decline in at least one cognitive domain: noticeable and measurable
- No impairment in independent living
- 9.4 to 14.3/1000 person-years convert to Alzheimer disease; higher in amnestic MCI
- ~50% with amnestic MCI maintain stable level of impairment or return to normal cognitive status in 3–5 yr

ALZHEIMER DISEASE

- Onset: gradual
- Cognitive symptoms: memory impairment core feature with difficulty learning new information, language, visuospatial
- Motor symptoms: rare early, apraxia later
- Progression: gradual, over 8–10 yr on average
- Lab tests: normal
- Imaging: possible global atrophy, small hippocampal volumes

VASCULAR DEMENTIA

- Onset: may be sudden/stepwise
- Cognitive symptoms: depend on anatomy of ischemia, but dysexecutive deficits and slowing common
- Motor symptoms: correlates with ischemia
- Progression: gradual or stepwise with further ischemia
- Lab tests: normal
- Imaging: cortical or subcortical changes on MRI

DEMENTIA (OR NCD) WITH LEWY BODIES

- Onset: gradual
- Cognitive symptoms: memory, visuospatial, hallucinations, fluctuating symptoms
- Motor symptoms: parkinsonism
- Progression: gradual, but faster than AD
- Lab tests: normal
- Imaging: possible global atrophy

FRONTOTEMPORAL DEMENTIA

- Onset: gradual, usually age <60
- Cognitive symptoms: executive, disinhibition, apathy, language, +/- memory
- Motor symptoms: none (rare genetic forms associated with ALS)
- Progression: gradual but faster than AD
- Lab tests: normal
- Imaging: atrophy in frontal and temporal lobes

Drug or Alcohol Related Dementia

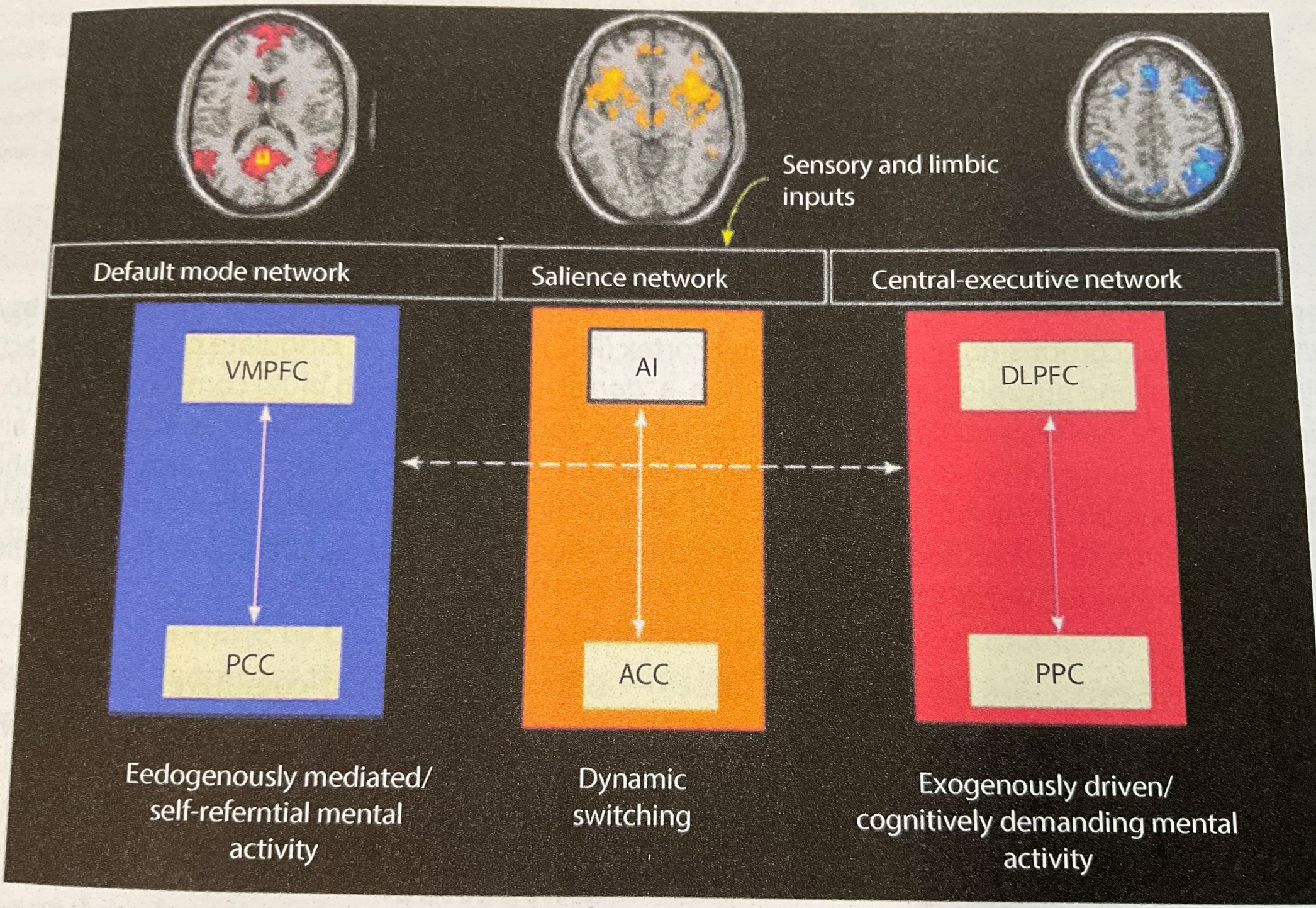
- H and P
- Physical stigmata
- Dopamine burn out syndrome
- History of Werniche's or Korsakoff syndromes

Autoimmune Disorders

- Lupus
- Sjorgen's disease
- Autoimmune process attacking specific receptors in the brain e.g. NMDA receptors

Decision Making

- This area is important in the overall evaluation of patients with dementia of any cause.
- Our colleagues from research centers around the world have done a great job in describing the centers of the brain that play an important part in our ability to make cogent decisions.


Sensory and limbic inputs
Default mode network
Salience network
Central-executive network
VMPFC
PCC
AI
ACC
DLPFC
PPC
Eedogenously mediated/ self-referntial mental activity
Dynamic switching
Exogenously driven/ cognitively demanding mental activity

DELIRIUM VS. DEMENTIA

- Delirium and dementia often occur together in older hospitalized patients
- The distinguishing signs of delirium are:
  - ➢ Acute onset
  - ➢ Cognitive fluctuations throughout the course of a day
  - ➢ Impaired consciousness and attention
  - ➢ Fluctuating levels of alertness
  - ➢ Altered sleep cycles

➢ Search for underlying dementia once delirium cleared

DEPRESSION VS. DEMENTIA (1 of 2)

- The symptoms of depression and dementia often overlap.
  - ➢ Presents diagnostic challenges

- Patients with primary dementia commonly experience symptoms of depression, and may minimize cognitive losses

DEPRESSION VS. DEMENTIA (2 of 2)

- Patients with primary depression are generally unlike those with dementia in that they:
  - ➢ Demonstrate ↓ motivation during cognitive testing
  - ➢ Express cognitive complaints that exceed measured deficits
  - ➢ Maintain intact language and motor skills
- ~50% presenting with reversible dementia and depression progress to dementia within 5 yr

THE GENERAL PROGRESSION OF DEMENTIA (1 of 2)

Stage 1: No cognitive impairment

Unimpaired individuals experience no memory problems, and none is evident to a health care professional during a medical interview.

Stage 2: Very mild cognitive decline

Individuals at this stage feel as if they have memory lapses, especially in forgetting familiar words or names or the location of keys, eyeglasses, or other everyday objects. However, these problems are not evident during a medical examination or apparent to friends, family, or coworkers.

Stage 3: Mild cognitive decline

Early-stage Alzheimer disease can be diagnosed in some, but not all, individuals. Friends, family, or coworkers begin to notice deficiencies. Problems with memory or concentration may be measurable in clinical testing or discernible during a detailed medical interview.

Stage 4: Moderate cognitive decline (mild or early-stage Alzheimer disease)

At this stage, a careful medical interview detects clear-cut deficiencies. The affected individual may seem subdued and withdrawn, especially in socially or mentally challenging situations.

THE GENERAL PROGRESSION OF DEMENTIA (2 of 2)

Stage 5: Moderately severe cognitive decline (moderate or mid-stage Alzheimer disease)
Major gaps in memory and deficits in cognitive function emerge. Some assistance with day-to-day activities becomes essential.
Stage 6: Severe cognitive decline (moderately severe or mid-stage Alzheimer disease)
Memory difficulties continue to worsen, significant personality changes may emerge, and affected individuals need extensive help with customary daily activities.
Stage 7: Very severe cognitive decline (severe or late-stage Alzheimer disease)
This is the final stage of the disease when individuals lose the ability to respond to their environment, to speak, and ultimately to control movement.

PRIMARY GOAL OF TREATMENT

To enhance quality of life and
maximize functional performance by
improving or stabilizing cognition, mood, and behavior

NONPHARMACOLOGIC MANAGEMENT (1 of 2)

- Cognitive rehabilitation
- Supportive individual and group therapy
- Physical and mental activity
- Regular appointments every 3–6 months
- Family and caregiver education and support
- Attention to safety
  - ➢ Need for supervision, wandering, driving etc.

NONPHARMACOLOGIC MANAGEMENT (2 of 2)

- Environmental modification
  - ➢ Supportive strategies such as clocks, calendars, to-do list, visual clues, simple and compassionate communication style
  - ➢ Structure activities to match patient abilities

PHARMACOLOGIC MANAGEMENT

- *Treatment should be individualized*
- Cholinesterase inhibitors: donepezil, rivastigmine, galantamine
- Memantine
- Other cognitive enhancers
- Antidepressants
- Psychoactive medications
- Aducanumab

CHOLINESTERASE INHIBITORS (1 of 2)

- Slow breakdown of acetylcholine
- Clinical trials demonstrate modest delay in cognitive decline compared with placebo in AD
- GI side effects common
  - ➢ Mitigated by slow titration curve
  - ➢ Maximum dosing of donepezil 23 mg/day creates significant side effects without evidence of improving global function
- No evidence of difference in efficacy among drugs

CHOLINESTERASE INHIBITORS (2 of 2)

- Use in other dementias
  - ➢ Widespread use in vascular dementia *not* recommended
  - ➢ Attention and behavioral disturbances in Lewy body dementia can *benefit* from treatment
  - ➢ Rivastigmine is *FDA-approved* for mild to moderate dementia in Parkinson dementia
  - ➢ Treatment in frontotemporal dementia may *worsen* agitation

MEMANTINE

- Neuroprotective effect is to reduce glutamate-mediated excitotoxicity
- Modest *benefit* on cognition, ADLs, and behavior in AD
- Limited effect on cognition and no evidence to support widespread use in vascular dementia
- FDA-approved for moderate to severe AD
- Common adverse events: constipation, dizziness, headache

OTHER COGNITIVE ENHANCERS

- Vitamin E (α–tocopherol) may lower rate of functional decline, but no evidence of cognitive improvement in AD
  - ➢ The clinical efficacy and safety of vitamin E has yet to be fully established
- Selegiline may lower rate of functional decline, but no evidence of cognitive improvement in AD
- Ginkgo biloba offers no benefit in slowing cognitive decline in MCI

SYMPTOM MANAGEMENT (1 of 2)

- Psychoactive medications
  - Behavioral disturbances best managed nonpharmacologically, eg, reducing overstimulation, environmental modification
  - When meds are required, target symptoms should be identified, and therapy selected accordingly
- Antidepressants
  - Depressed mood, low appetite, insomnia, fatigue, irritability, agitation
  - *Possibly* effective for disinhibition and compulsive behaviors associated with frontotemporal dementia
  - Caution: falls and anticholinergic effects that may worsen confusion (ie, paroxetine)

SYMPTOM MANAGEMENT (2 of 2)

- 1st/2nd-generation antipsychotics
  - ➢ Limited evidence of efficacy and increased risk of all-cause mortality in dementia
  - ➢ Should be used with caution in targeting delusions, hallucinations, paranoia, and irritability — frequently attempt to taper off
- Valproic acid and carbamazepine
  - ➢ Possible options, but with limited evidence and increased risk of mortality
- Benzodiazepines and anticholinergic medications should be *avoided*

RESOURCES FOR MANAGING DEMENTIA (1 of 2)

- Specialist referral to:
  - ➢ Geriatric psychiatrist
  - ➢ Neurologist
  - ➢ Neuropsychologist
- Social worker
- Physical therapist
- Nurse
- Pharmacist

RESOURCES FOR MANAGING DEMENTIA (2 of 2)

- Attorney for will, conservatorship, estate planning
- Community: neighbors & friends, aging & mental health networks, adult day care, respite care, home-health agency
- Organizations: Alzheimer's Association, Area Agencies on Aging, Councils on Aging
- Services: Meals-on-Wheels, senior citizen centers

CHOOSING WISELY®

- Don’t prescribe cholinesterase inhibitors for dementia without periodic assessment for perceived cognitive benefits and adverse gastrointestinal effects.
- Don’t use antipsychotics as first choice to treat behavioral and psychological symptoms of dementia.

SUMMARY (1 of 2)

- Dementia is common in older adults but is *not* an inherent part of aging
- AD is the most common type of dementia, followed by vascular dementia and dementia with Lewy bodies
- Evaluation includes history with informant, physical & functional assessment, focused labs, & possibly brain imaging

SUMMARY (2 of 2)

- Primary treatment goals: enhance quality of life and maximize function by improving cognition, mood, behavior
- Treatment may involve both medications and nonpharmacologic interventions
- Community resources should be used to support patient, family, caregivers

CASE 1 (1 of 3)

- A 65-year-old man comes to the office with his wife because she is concerned about his memory. He is a retired engineer.

- His wife offers examples of recent uncharacteristic mistakes that he has made in their finances.
  - ➢ He forgot to pay the mortgage several months ago.
  - ➢ In the grocery store, his credit card was denied for missed payments.

- The patient describes his experience.
  - ➢ Balancing accounts feels more effortful and takes longer than it had in the past.
  - ➢ He feels overwhelmed by distractions.
  - ➢ He is frequently unable to find keys and other objects.
  - ➢ He is often unable to recall names of acquaintances until minutes or hours later.

CASE 1 (2 of 3)

Which one of the following is most likely to indicate pathologic neurologic decline?

A. Taking longer to complete routine tasks
B. Forgetting to pay mortgage and credit card bills
C. Having a complaint about memory
D. Experiencing difficulty retrieving names

CASE 1 (3 of 3)

Which one of the following is most likely to indicate pathologic neurologic decline?

A. Taking longer to complete routine tasks

B. Forgetting to pay mortgage and credit card bills

C. Having a complaint about memory

D. Experiencing difficulty retrieving names

CASE 2 (1 of 4)

- A 73-year-old man has memory problems that are increasingly evident to his wife, and he has had several unexplained falls.
- Neuropsychiatric history
  - ➢ Seven years ago he began to have impaired smell, altered taste, and fitful sleep with recurrent dream enactment.
    - Symptoms have progressed.
    - The dream enactments wake his wife at night.
  - ➢ Fluctuating cognitive dysfunction and bilateral arm tremors developed.
  - ➢ For several years, he has had hallucinations of children in the room. The hallucinations do not frighten him.
    - The hallucinations worsened when he was hospitalized for a UTI last year.
    - Neuroleptic agents were administered, but his condition deteriorated and he required restraints for several hours.
  - ➢ Behavioral interventions have been unsuccessful.

CASE 2 (2 of 4)

- History: hypertension, hyperlipidemia, diabetes, urinary incontinence, constipation
- MRI of the brain shows mild white matter changes.

CASE 2 (3 of 4)

Which one of the following medications should NOT be considered for this patient?

A. Clonazepam
B. Donepezil
C. Fludrocortisone
D. Haloperidol
E. Rivastigmine

CASE 2 (4 of 4)

Which one of the following medications should NOT be considered for this patient?

A. Clonazepam
B. Donepezil
C. Fludrocortisone
D. Haloperidol
E. Rivastigmine

CASE 3 (1 of 2)

Which one of the following is true regarding the risk of prescribing psychotropic medications to patients with dementia?

A. First- and second-generation antipsychotics increase both morbidity and all-cause mortality.

B. Second-generation antipsychotics do not increase morbidity and all-cause mortality.

C. First-generation antipsychotics do not increase morbidity and all-cause mortality

D. First- and second-generation antipsychotics increase morbidity but not all-cause mortality.

CASE 3 (2 of 2)

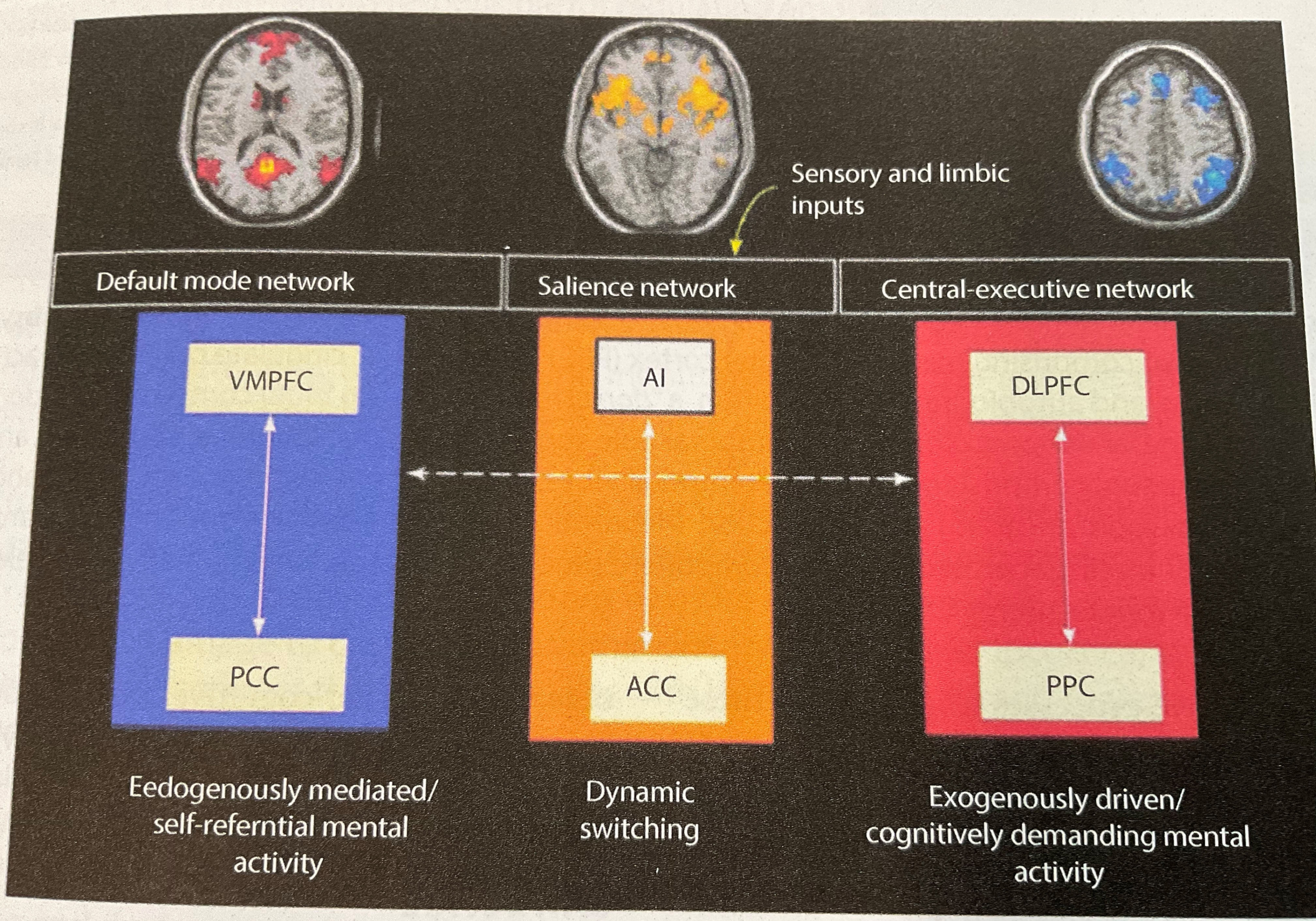
Which one of the following is true regarding the risk of prescribing psychotropic medications to patients with dementia?

A. First- and second-generation antipsychotics increase both morbidity and all-cause mortality.

B. Second-generation antipsychotics do not increase morbidity and all-cause mortality.

C. First-generation antipsychotics do not increase morbidity and all-cause mortality

D. First- and second-generation antipsychotics increase morbidity but not all-cause mortality.


Sensory and limbic inputs
Default mode network
Salience network
Central-executive network
VMPFC
PCC
AI
ACC
DLPFC
PPC
Eedogenously mediated/ self-referntial mental activity
Dynamic switching
Exogenously driven/ cognitively demanding mental activity