

# Brain Matters: The Impact of CKD on Cognitive Function

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# Objectives

- Name and describe domains of cognitive function
- Discuss prevalence of cognitive impairment in CKD
- Identify specific domains of cognitive function impacted by chronic kidney disease (CKD)
- Explain nutrition and lifestyle approaches to protect cognitive function
- Identify strategies to use with patients who have mild cognitive impairment

# Cognitive Function

A general term used to describe many different functions including:

- Memory
- Perception
- Attention
- Processing speed
- Language skills
- Motor skills
- Executive Function



# Domains of Cognitive Function

- Memory

- Working memory – ability to hold information in consciousness for adaptive use. Includes maintenance of information and manipulation of information.
- Episodic/declarative/explicit memory – encodes, maintains, and retrieves information into and out of long-term memory.
  - Encoding – taking information from working memory and processing it for long-term storage.
  - Storage – retention of information after encoding.
  - Retrieval – recalling encoded information
- Procedural memory – memory for motor actions or skills (muscle memory)
- Semantic memory – long-term storage of verbal information.
- Prospective memory – the ability to remember to perform tasks in the future.

# Domains of Cognitive Function

- Perception – processes and integrates sensory information. Ability to recognize objects, sounds, and the intactness of the perceptual field.
- Attention:
  - Selective attention – process of attending to information that is relevant and important and ignoring nonrelevant information.
  - Sustained Attention/Vigilance – ability to sustain attention over time

# Domains of Cognitive Function

- Language Skills – ability to understand languages, access semantic memory, identify objects with a name, and respond to verbal instructions with behavioral acts.



# Domains of Cognitive Function

- Motor Skills – includes manual dexterity, motor speed, reaction time, and balance.
- Processing Speed – requires rapid performance of tasks ranging from simple to complex



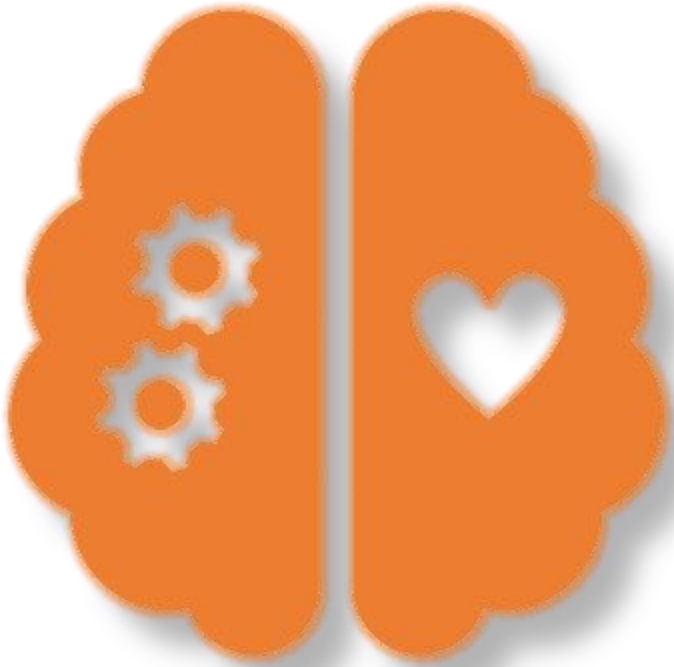


# Domains of Cognitive Function

- Executive Function
  - Set of processes that manifest control over other component cognitive abilities
  - Goal-directed behavior
  - Uses simpler cognitive functions for real-world adaptive success
  - Reasoning and problem-solving



# A Healthy Brain



Optimal capacity to function adaptively in the environment.

Competency across domains of “thinking, moving, and feeling.”

Absence of overt vascular or neurodegenerative injury

# Brain Health in Decline

3 out of 5 Americans will develop a brain disease in their lifetime.

- The brain begins showing cognitive decline as a person enters their 20's.
- Disorders associated with dementia are progressive, degenerative, and irreversible.



# Does this sound familiar...

You provide education to a patient during dialysis, or a clinic visit and set a goal for them to work on.

- At follow-up, patient shows no improvement, and you basically repeat the entire education.
- In some cases, pressing too hard to help the patient improve makes them defensive or upset.



# Is this patient...



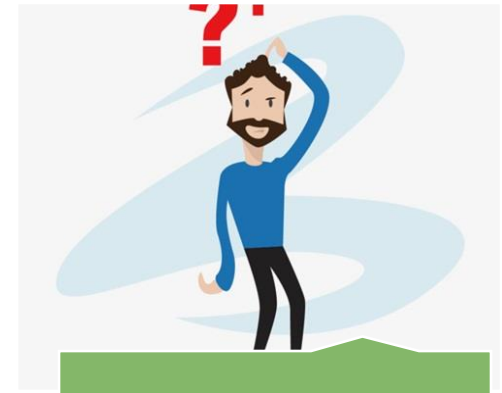
Non-Compliant



Unmotivated



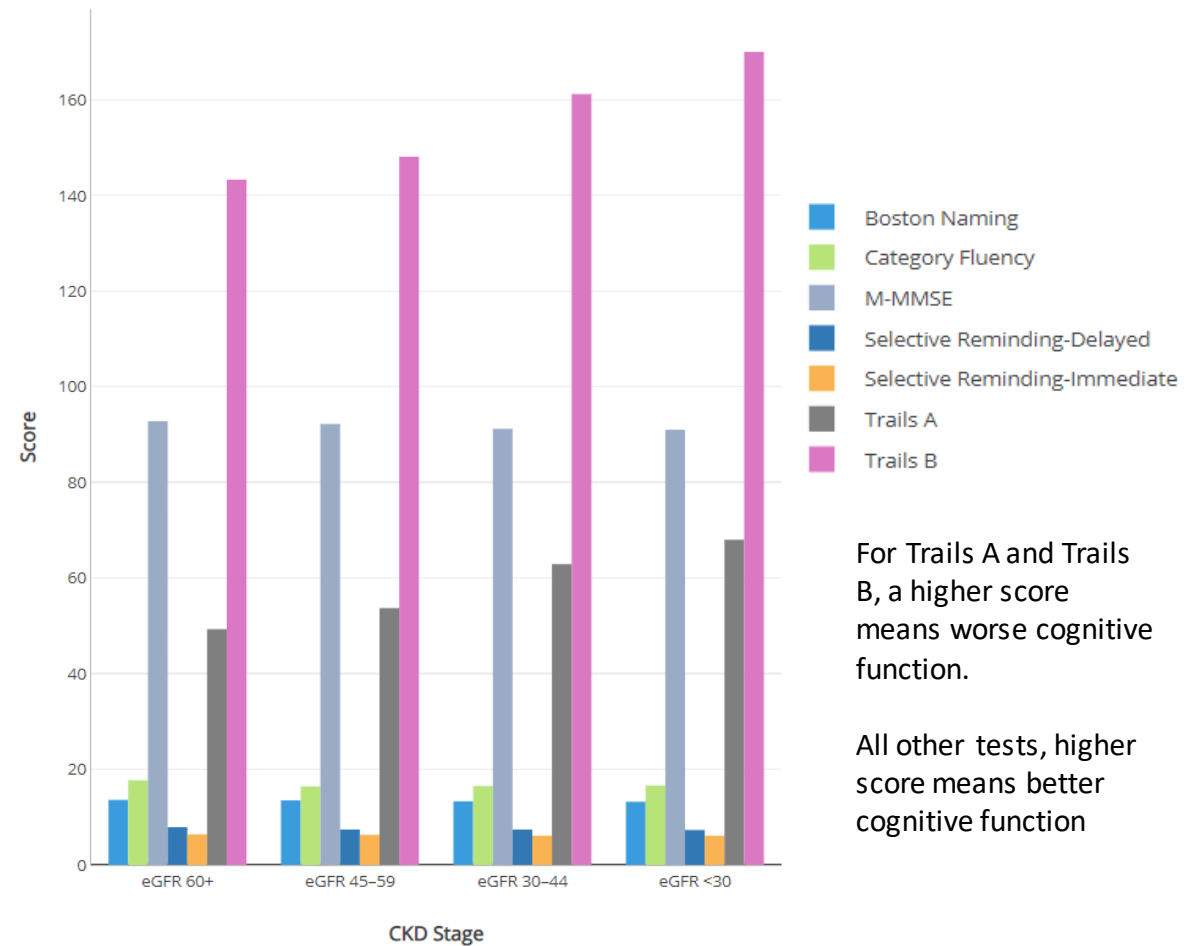
Stubborn



Health Illiterate

# Cognition and CKD

- Cognitive decline occurs early in CKD
  - Different domains change at different rates
  - Cognition worsens as eGFR declines
- In HD, >70-% of patients show impairment in as least 1 cognitive domain



Centers for Disease Control and Prevention. Chronic Kidney Disease Surveillance System—United States. website. <http://www.cdc.gov/ckd>



**Mild Cognitive Impairment (MCI)** - A condition in which individuals demonstrate cognitive impairment with minimal impairment of instrumental activities of daily living.

- ~46% of people with MCI develop dementia within 3 years.

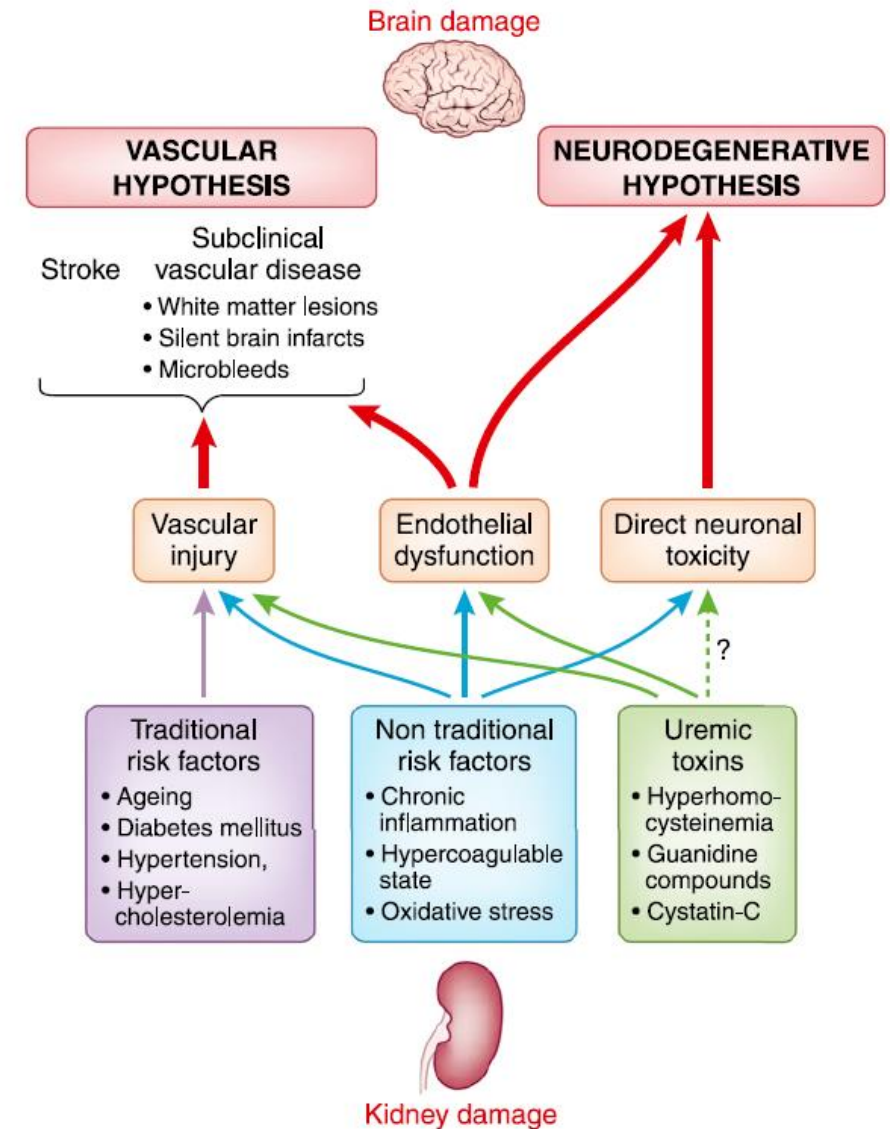
**Dementia** - a chronic or persistent disorder of the mental processes caused by brain disease or injury and marked by memory disorders, personality changes, and impaired reasoning.

## Vascular Hypothesis

- Kidneys and brain are both low-resistance end organs exposed to high volume blood flow which causes vascular damage
- Similar impairments seen in CKD and stroke:
  - Declines in executive function, psychomotor speed, and memory.

## Neurodegenerative Hypothesis

- Exposure to ACE inhibitors and/or uremic toxins cause damage within the brain leading to cognitive decline
  - Uremic guanidine is a neurotoxic agent



Bugnicourt, J. M., Godefroy, O., Chillon, J. M., Choukroun, G., & Massy, Z. A. (2013). Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. *Journal of the American Society of Nephrology*, 24(3), 353-363.



# General Risk Factors for Cognitive Decline

- Increased age
- Having a specific form of the APOE e4 gene
- Diabetes
- Smoking
- Hypertension
- High cholesterol
- Obesity
- Depression
- Lack of exercise
- Low education level
- Infrequent participation in mentally or socially stimulating activities

# Risk Factors Specific to CKD and ESRD

- Albuminuria
- Normalized brain tissue volume
- Hemoglobin levels
- Serum parathyroid hormone levels
- Uric acid levels
- Hyponatremia
- Poor nutrition and/or protein-energy wasting
- Functional impairment
- Anemia
- Acidosis
- Disturbed sleep
- Polypharmacy
- Duration of CKD

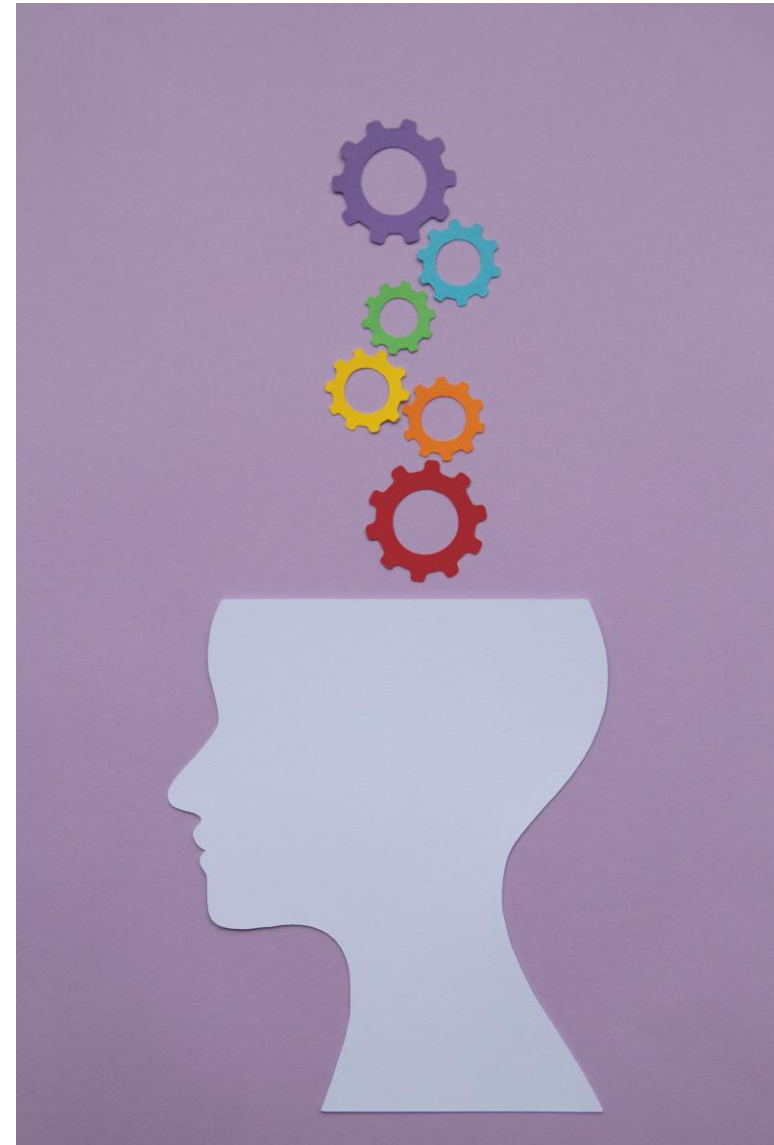
# Risk Factors in ESRD

Modality of dialysis may have an impact on severity of cognitive decline:

- Risk for mild cognitive impairment is lower in patients using peritoneal dialysis (PD) and in patients who avoid ever using a CVC
  - PD causes more gentle fluid shifts which may lead to less brain injury

# MCI and CKD

- Cognitive functions most impacted:
  - Memory
  - Learning
  - Attention
  - Processing and problem-solving
  - Self-control
    - Emotions
    - Depression



# MCI and CKD

- Memory, learning, attention, processing, and problem-solving all contribute to Health Literacy.
- **Health Literacy** = the cognitive and social skills that determine the motivation and ability to gain access, understand, and use information in ways which promote and maintain good health.
  - In CKD, this is suspected to be the first area of cognition to decline

# Symptoms of Mild Cognitive Impairment

- Increased forgetfulness including appointments and social engagements
- Losing train of thought
- Overwhelmed by decision making and/or understanding instructions
- More impulsive
- Poor judgment
- Depression
- Irritability
- Aggression
- Anxiety
- Apathy

	Mild Cognitive Impairment	Depression	Sleep Deprivation	Anemia
Forgetfulness	X	X	X	X
Impulsiveness	X			
Irritability	X	X	X	
Poor Judgement	X	X		
Apathy	X			X
Overwhelmed by decision making	X	X		
Depression	X	X	X	

# MCI vs Depression

- Prevalence of depression in dialysis patients estimated between 20-30%
- Depression can exist on its own or could be a result of MCI
- Depression in CKD is sometimes referred to as:
  - Pseudodementia
  - Functional Dementia
- After depression symptoms significantly improve, cognitive impairment often persists



# What this Means for Patients?

Patient will likely require assistance navigating care pathways, weighing treatment options, compiling advice from multiple sources, maintaining medication regimens, remembering appointments, etc.



# Ask Yourself...

**How can I offset or ease patient burden?**

**How can I accommodate CI to support patient participation?**

# Support Better Brain Health at All Stages



Screen for cognitive decline

MMSE

3MS

MoCA



Prevent, slow progression, or support new pathways

Promote neuroplasticity and neurogenesis



Adapt to accommodate cognitive impairment

Nutrition support

Resources

Education methods and materials


# Mini Mental State Examination (MMSE)

- 30-point test, ~10 minutes to administer
- The best-known and the most often used short screening tool for providing an overall measure of cognitive impairment in clinical, research and community settings.

## Mini-Mental State Examination (MMSE)

Patient's Name: \_\_\_\_\_ Date: \_\_\_\_\_

**Instructions: Ask the questions in the order listed.  
Score one point for each correct response within each question or activity.**

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		<b>TOTAL</b>

# Modified Mini Mental State Examination (3MS)

- 100-point exam, administered in ~15 minutes
- Modified from the MMSE
- Designed to be more sensitive to detect individuals with baseline MCI who would clinically convert to dementia

3MS MMSE		3MS MMSE	
5	DATE AND PLACE OF BIRTH Date: year _____ month _____ day _____ Place: town _____ state _____	5	NAMING (MMSE: Pencil Watch ) Forehead _____ Chin _____ 1 2 3 4 5 Shoulder _____ Elbow _____ Knuckle _____
3	REGISTRATION (No. of presentations: _____) SHIRT, BROWN, HONESTY (or: SOCKS, BLACK, MODESTY) (or: SOCKS, BLUE, CHARITY)	10	FOUR-LEGGED ANIMALS (10 seconds) 1 point ea.
7	MENTAL REVERSAL 5 to 1 Accurate _____ 2 1 or 2 errors/mistakes _____ 0 1 DIAGNOSIS 0 1 2 3 4 5	6	SIMILARITIES Arm-Leg Body part; limb; etc _____ 2 Less correct answer _____ 0 1 Laughing-Crying Feeling; emotion _____ 2 Other correct answer _____ 0 1 Eating-Sleeping Essential for life _____ 2 Other correct answer _____ 0 1
9	FIRST RECALL Spontaneous recall _____ 3 After "Something to wear" _____ 2 "SHOES, SHIRT, SOCKS" _____ 0 1 Spontaneous recall _____ 3 After "A color" _____ 2 "BLUE, BLACK, BROWN" _____ 0 1 Spontaneous recall _____ 3 After "A good personal quality" _____ 2 "HONESTY, CHARITY, MODESTY" _____ 0 1	5	REPETITION "I WOULD LIKE TO GO HOME-OUT" 1 or 2 missed/wrong words _____ 0 1 "NO IF'S ANDS OR BUTS" READ AND OBEY "CLOSE YOUR EYES" Obey without prompting _____ 3 Obey after prompting _____ 2 Reads aloud only (spontaneously or by request) _____ 0 1
15	TEMPORAL ORIENTATION Year Accurate _____ 8 Missed by 1 year _____ 4 Missed by 2-5 years _____ 0 2 Season Accurate or within 1 month _____ 0 1 Month Accurate or within 1 days _____ 2 Missed by 1 month _____ 0 1 Day of month Accurate _____ 3 Missed by 1 or 2 days _____ 2 Missed by 3-5 days _____ 0 1 Day of week Accurate _____ 0 1	5	WRITING (1 minute) (I) WOULD LIKE TO GO HOME-OUT (MMSE: Spontaneous sentence: 0 1) COPYING TWO PENTAGONS (1 minute) Each Pentagon 5 approximately equal sides _____ 4 4 5 unequal (>2:1) sides _____ 3 3 Other enclosed figure _____ 2 2 2 or more lines _____ 0 1 0 1 4 corners _____ 2 Not 4-corner enclosure _____ 0 1
5	SPATIAL ORIENTATION State _____ 0 2 County _____ 0 1 City (town) _____ 0 1 Hospital/office building/home? _____ 0 1	3	THREE-STAGE COMMAND TAKE THIS PAPER WITH YOUR LEFT-RIGHT HAND FOLD IT IN HALF, AND HAND IT BACK TO ME SECOND RECALL (Something to wear) _____ 0 1 2 3 (Color) _____ 0 1 2 3 (Good personal quality) _____ 0 1 2 3

# Montreal Cognitive Assessment (MoCA)

- 30-point test that can be administered in 10 minutes.
- Superior to MMSE for detecting MCI and early Alzheimer's dementia (AD).

NAME: \_\_\_\_\_  
Education: \_\_\_\_\_ Date of birth: \_\_\_\_\_  
Sex: \_\_\_\_\_ DATE: \_\_\_\_\_

**MONTREAL COGNITIVE ASSESSMENT (MOCA)**  
Version 7.1 Original Version

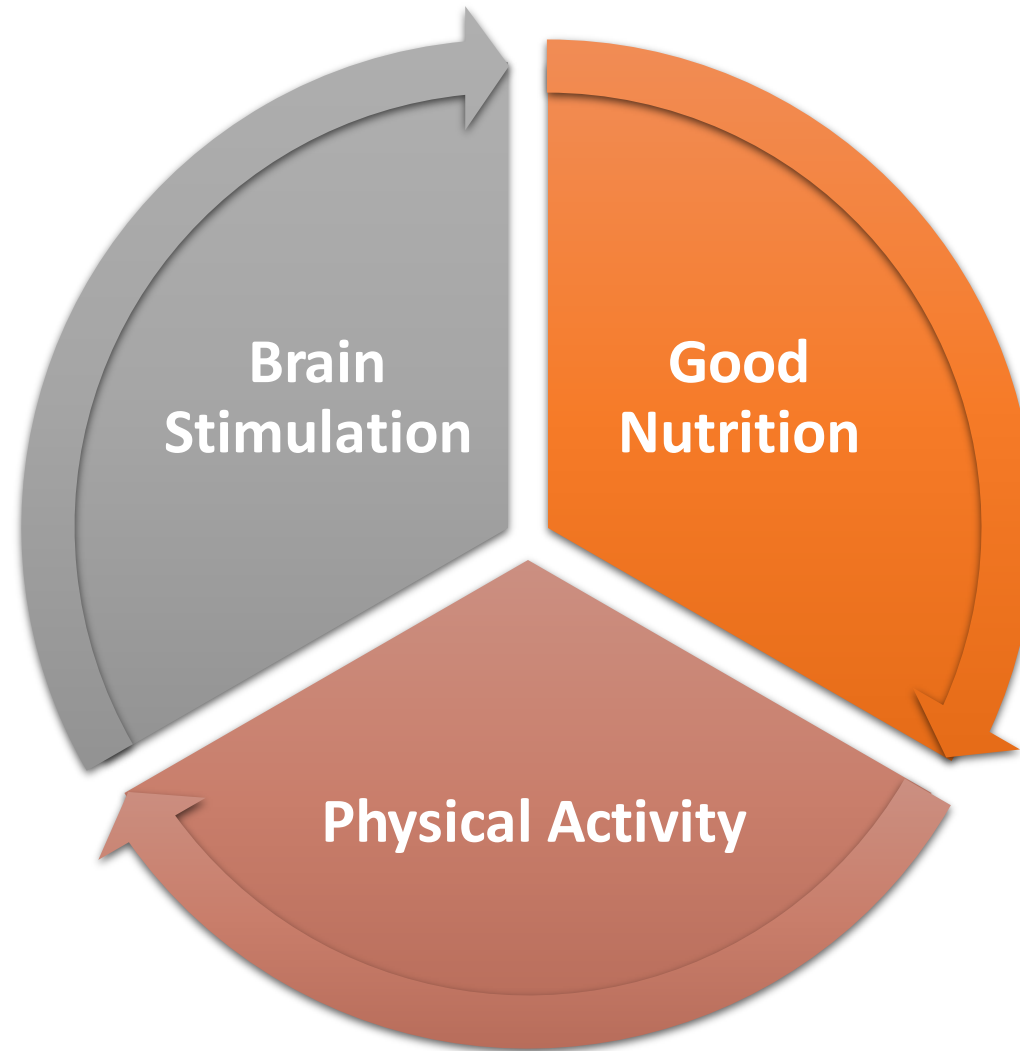
<b>VISUOSPATIAL / EXECUTIVE</b>		Copy cube	Draw CLOCK (Ten past eleven) (3 points)	POINTS																		
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			<input type="checkbox"/>																			
<b>MEMORY</b>		Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td></td> <td style="text-align: center;">FACE</td> <td style="text-align: center;">VELVET</td> <td style="text-align: center;">CHURCH</td> <td style="text-align: center;">DAISY</td> <td style="text-align: center;">RED</td> </tr> <tr> <td style="text-align: center;">1st trial</td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> <tr> <td style="text-align: center;">2nd trial</td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>		FACE	VELVET	CHURCH	DAISY	RED	1st trial	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2nd trial	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	No points
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<b>ATTENTION</b>		Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order <input type="checkbox"/> 2 1 8 5 4 Subject has to repeat them in the backward order <input type="checkbox"/> 7 4 2	<input type="checkbox"/>																			
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors <input type="checkbox"/> F B A C M N A A J K L B A F A K D E A A A J A M O F A A B		<input type="checkbox"/>																				
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<b>LANGUAGE</b>		Repeat: I only know that John is the one to help today. <input type="checkbox"/> The cat always hid under the couch when dogs were in the room. <input type="checkbox"/>	<input type="checkbox"/>																			
Fluency / Name maximum number of words in one minute that begin with the letter F <input type="checkbox"/> ____ (N ≥ 11 words)		<input type="checkbox"/>																				
<b>ABSTRACTION</b>		Similarity between e.g. banana - orange = fruit <input type="checkbox"/> train - bicycle <input type="checkbox"/> watch - ruler																				
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© Z.Nasreddine MD <a href="http://www.mocatest.org">www.mocatest.org</a> Normal ≥ 26 / 30		<b>TOTAL</b>		<input type="checkbox"/>																		
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Mahendran, R., Chua, J., Feng, L., Kua, E. H., & Preedy, V. R. (2015). The Mini-Mental State Examination and Other Neuropsychological Assessment Tools for Detecting Cognitive Decline. In *Diet and Nutrition in Dementia and Cognitive Decline* (pp. 1159-1174). Academic Press.

# Screening for Cognitive Impairment

- There are currently no recommendations regarding routine screening for cognitive impairment in CKD or ESRD.
- Viggiano et al -> Encourage the nephrologist to suspect cognitive impairment when the patient:
  - Reports forgetfulness and/or confusion about medications or appointments
  - Reports depression or altered sleep patterns
  - Is unable to answer questions without family member/caregiver assistance
  - Has a history of stroke or unexplained falls

# Reducing Risk and Slowing Progression





# Important Definitions

- Neuroplasticity
  - The ability of the brain to form and reorganize synaptic connections, especially in response to learning or following brain injury
  - Makes behavior change possible. New behavior = new pathway
- Neurogenesis
  - The process by which new neurons are formed in the brain

# Nutrition

- Typical Western diets high in fat and sugar have a direct negative impact on neurogenesis and neuroplasticity.
  - Increased inflammation and oxidative stress
  - Contributes to co-morbidities
  - Low fiber, high protein intake leads to gut dysbiosis
- Research has also found a connection between a typical Western diet and increased prevalence of depression



# Nutrition

Diets rich in plant-based foods, fish, and olive oil and limited in red meat, alcohol, and processed food have been implicated in supporting cognitive function, slowing progression of CKD, improving gut health, and reducing risk for depression.

- Examples include Mediterranean, Norwegian, and Japanese diets

# Mediterranean-Dash Intervention for Neurodegenerative Delay (MIND) Diet

- Lowered risk of Alzheimer's Dementia as much 53% in patients who strictly followed the diet and by 35% in who followed it moderately well.
  - Encourages 10 foods:
    - Leafy greens, all vegetables, berries, nuts, olive oil, whole grains, fish, beans, poultry, wine.
  - Discourages 5 foods:
    - Butter/margarine, cheese, red meat, fried food, pastries and sweets.

# Nutrition in Dialysis

## Fill in nutrition gaps whenever possible

- Prevent, slow, or reverse malnutrition and protein energy wasting
  - ONS and/or IDPN/IPN can improve nutrition status
    - Correct albumin
      - Low albumin linked to impaired cognition and functional capacity
      - Crucial for binding uremic toxins, anti-inflammatory and antioxidant effects, and correcting osmotic pressure in the vascular system.
- Correct vitamin and mineral deficiencies.

## Rotondi et al, 2023, *Association between Cognitive Impairment and Malnutrition in Hemodialysis Patients: Two Sides of the Same Coin*

- Purpose - Investigate whether cognitive impairment is associated with nutrition status in HD patients
  - Inclusion criteria:  $\geq 18$ yo, chronic HD  $\geq 3$  months
  - Exclusion criteria: major cognitive impairment or dementia based on DSM-5 diagnosis, presence of active CA, decompensated cirrhosis, severe heart failure, or intestinal malabsorption; medication that alters mental status
  - Data collected: ages, sex, level of education, comorbid conditions, dialysis vintage, BP, medications, BMI, MIS, 3-day food record, MoCA, blood markers – Hb, Ca, PO<sub>4</sub>, Mg, PTH, VitD, Alb, hsCRP, Tchol, Urea, bicarb
- MIS possible score 0-30, score  $\geq 8$  indicates malnutrition
- MoCA possible score 0-30, score  $< 26$  indicates cognitive impairment

## Rotondi et al, 2023, *Association between Cognitive Impairment and Malnutrition in Hemodialysis Patients: Two Sides of the Same Coin*

- 84 patients, 44M 40F, median age 75.8years, avg dialysis vintage 46 months
  - 3-day food record indicated average intake of 1.04g protein/kg/day and 24.92kcal/kg/day
  - Malnutrition identified in 34 patients (40%)
    - 80% of malnourished patients had MCI compared to 70% in the non-malnourished group
    - Cognitive domains most impacted – memory (100%), executive function (90%), and language (85%)
  - No difference in BMI or protein and energy intake between malnourished vs non-malnourished group

# Physical Activity and BDNF

- Brain-derived neurotrophic factor (BDNF)
  - Supports differentiation, maturation, and survival of neurons in the nervous system
  - Expressed in the central nervous system (CNS), gut, and other tissues
  - Decreased levels associated with neurodegenerative diseases with neuronal loss



# Physical Activity and BDNF

Exercise promotes synthesis of BDNF which modulates neural plasticity, promotes neurogenesis, and builds resilience to depressive disorders.

- Dose-dependent
- Single sessions can increase BDNF, results are amplified when exercise is consistent
- Best outcomes with moderate intensity aerobic exercise



# Exercise Intensity

## Target HR for Moderate Intensity

- 50% to about 70% of max heart rate
  - To estimate your maximum age-related heart rate, subtract your age from 220.
    - For example, for a 50-year-old person, the estimated maximum age-related heart rate would be calculated as  $220 - 50 \text{ years} = 170 \text{ beats per minute (bpm)}$ .
      - 70% maxHR:  $170 \times .7 = 119 \text{ bpm}$

## Talk Test

- If you can talk and sing without puffing at all, you're exercising at a low level.
- If you can comfortably talk, but not sing, you're doing moderate intensity activity.
- If you can't say more than a few words without gasping for breath, you're exercising at a vigorous intensity.

# Physical Activity and Dialysis Patients

- *Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial*, Manfredini et al, 2017
  - Duration of 6 months, N = 227
    - Control group n = 123 -> 102 HD, 21 CAPD
    - Exercise group = 104 -> 90 HD, 14 CAPD
  - Intervention:
    - 20 minutes of walking at low-to-moderate speed every second day with gradually increasing intensity.
  - Results:
    - Functional status improved in walking group, measure by 6-minute walking test and 5x sit-to-stand
    - Cognitive function and quality of social interaction showed statistically significant improvement in Exercise group compared to Control group

# Other Factors

- Social Engagement
  - Consider creative strategies during social distancing
- Mental Stimulation
  - Learning a new skill – language, music, dance, etc.
  - Exposure to new surroundings – travel, etc.
  - Brain games – need to switch it up to gain benefits
    - Online programs - BrainHQ, Lumosity
    - Sudoku, puzzles, etc.



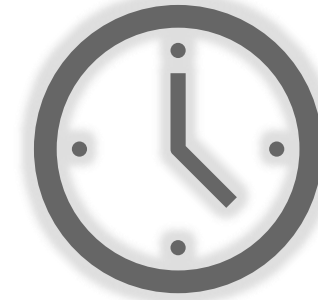
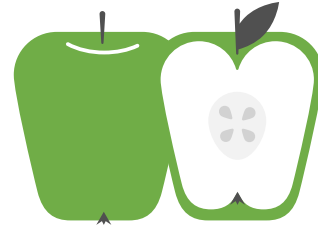
# Adapting Educational Approach



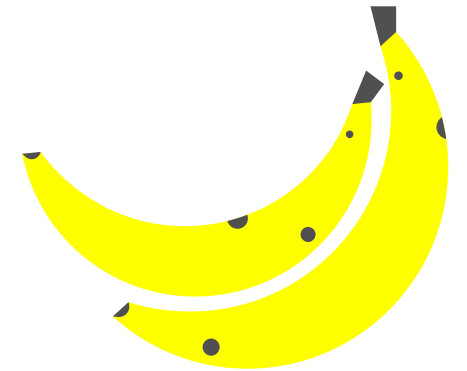
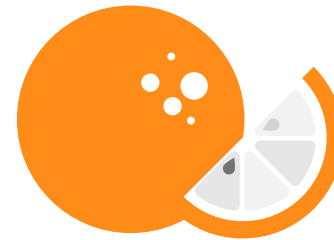
## Rely on Motivational Interviewing and Behavior Change Science

- Focus on truly meeting the patient where they are at, not where you want or expect them to be.
- Allow them the opportunity to exercise their brains through guided problem-solving.

# Education



- Know when to educate
  - Murray et al. determined cognitive performance is worst during hemodialysis session.
  - Best time to educate is shortly before dialysis or the day after dialysis.
- Use pictures, cartoons, and lots of **color** with text
- Provide large print visuals of diet plans





# Education

- Frame information as positive/negative or as do's/ don'ts
  - Avoid using numbers as numerical values are quickly forgotten thus carry little to no meaning
- Provide explicit descriptions of benefits with specific examples
  - MI tip -> tie in benefits that they specifically mention as motivating factors
- Provide infrastructure for them to find additional information
- Provide repeat education, instructions, and help set up reminders
  - Especially before decision making



# Education

## Strategy Training

- Treatment model that focuses on activation through performance of daily activities
- Keys to Strategy Training:
  - Self-selected goal
    - Individuals with cognitive impairment may learn best when given the opportunity to problem solve personally motivating goals or activities.
  - Self-evaluation of performance
  - Guided discovery
    - Allows individuals to decide what's effective and/or ineffective and then plan and modify as necessary
    - Use global strategy to engage in activities in organized and consistent format

# Education

- Recruit family members, caregivers, and community
  - Help with reminders
  - Receive education
- Focus on low-cost strategies



# Key Take-Aways

- Cognitive impairment is at least 2x more prevalent in CKD and ESRD than healthy age-matched controls.
- Cognitive decline begins at earlier stages of CKD than previously thought and is associated with worse outcomes including increased hospitalizations and mortality.
- Interventions should be geared towards:
  - Mitigating the risk of cognitive decline through a systems approach.
  - Adapting education, counseling, and medical nutrition therapy with consideration to cognitive impairment.

# Recommended Reading

- Rotondi et al, 2023 - Association between Cognitive Impairment and Malnutrition in Hemodialysis Patients: Two Sides of the Same Coin
- Drew et al. 2019 - Cognitive impairment in CKD: pathophysiology, management, and prevention.
- Manfredini et al. 2017 – Exercise on Dialysis: A Multicenter, Randomized Clinical Trial

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# Questions?





Thank you!

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