

Coping with Chemobrain

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What is Chemobrain?

A broad term describing various cognitive problems related to chemotherapy

Now a more expansive term to describe cognitive changes related to cancer and cancer treatment

Imprecise term for a very complex and multifactorial process

Cancer Related Cognitive Impairment (CRCI) is a more comprehensive term

Cognitive Changes and Cancer

Previously dismissed because many chemotherapies do not penetrate the brain

- Radiation
- Surgery
- Hormonal therapy (tamoxifen), especially when combined with chemotherapy
- Supportive medications (corticosteroids, pain meds)
- Bone marrow transplant
- Mood disorder
- Disease itself
 - ~20-30% pre-treatment cognitive baseline lower

Chemotherapeutic agent	Drug category and mechanism
<i>Carmustine (BCNU)</i>	Alkylating agent
<i>Carmofur</i>	Antimetabolite
<i>Cisplatin</i>	DNA crosslinking agent
<i>Cyclophosphamide</i>	Alkylating agent
<i>Cytosine arabinoside (Ara-C)</i>	Antimetabolite
<i>Doxorubicin</i>	Anthracycline antibiotic; DNA intercalating agent
<i>5-Fluorouracil (5-FU)</i>	Antimetabolite
<i>Ifosfamide</i>	Alkylating agent
<i>Methotrexate</i>	Antimetabolite
<i>Paclitaxel</i>	Mitotic inhibitor
<i>Temozolomide</i>	Alkylating agent
<i>ThioTEPA</i>	Alkylating agent

Kaiser et al. Cortex 2014

	With PCD (n=1419)	Without PCD (n=1689)	p*
Surgery (%)	45.7	54.3	0.985
Radiation (%)	51.8	48.2	<0.000
Chemotherapy (%)	59.2	40.8	<0.000
Hormonal therapy (%)	61.3	38.7	<0.000
Current depression (%)	62.9	37.1	<0.000

PCD perceived cognitive dysfunction, SD standard deviation

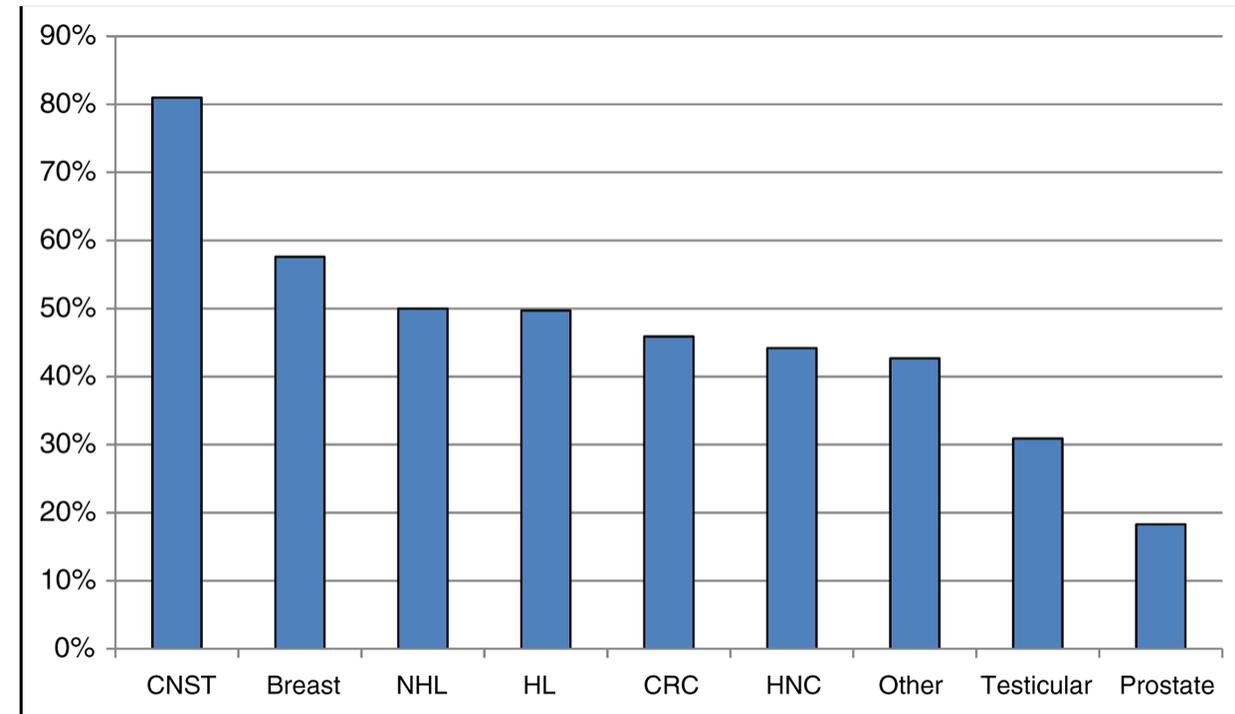
Schmidt et al. J Cancer Surviv 2016

Cognitive complaints are very common

Can affect up to **75%** of people **during treatment**, and up to **35%** after treatment

Improved cancer therapy has led to longer survival

Burden of disease and treatment-related survivorship issues has increased



One of the most problematic post-treatment symptoms

Mild to moderate symptoms can have profound impact on daily functioning and quality of life

Significant psycho-social impact when trying to resume work activities

Anxiety, uncertainty for the future

Many potential symptoms

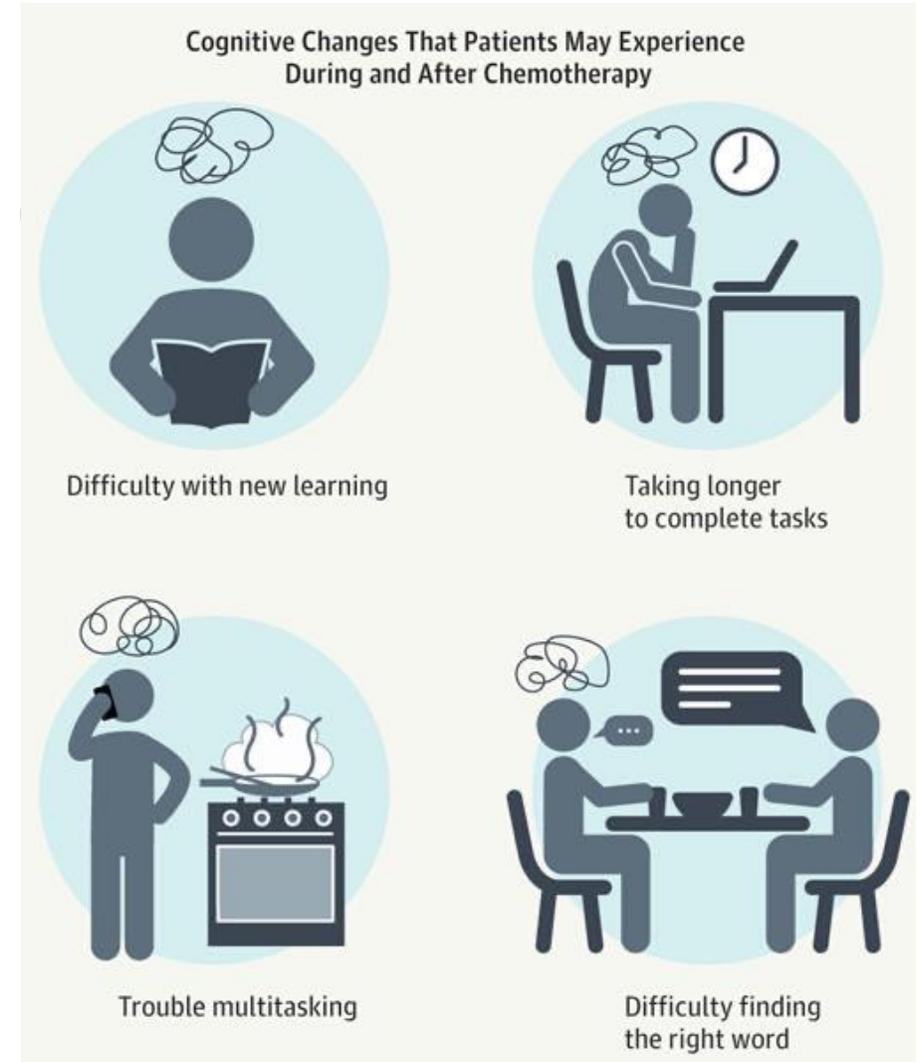
Difficulty processing information, slow mental processing (mental fog)

Poor attention span and concentration

Impaired short-term memory

Unable to multitask, plan, and organize

Difficulty finding words



Symptom intensity can vary greatly

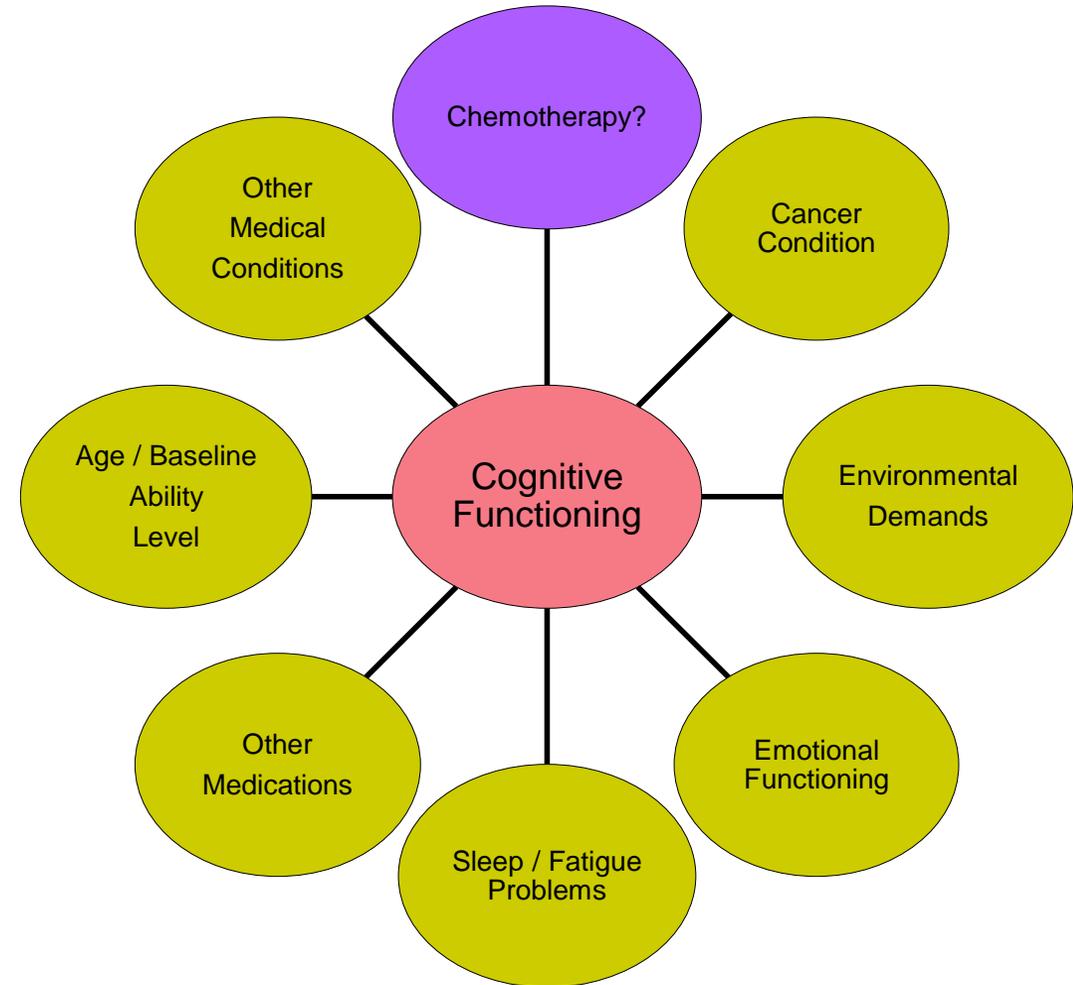
Many contributing factors

Symptoms can last for 6 months to several years

Usually, these symptoms slowly improve over 6-18 months

Sometimes can be chronic (~20-35%)

Often the degree of decline is mild



Common Cognitive Domains Affected

Learning and memory

Speed of mental processing

Attention

Executive functioning

Cognitive flexibility

Problem solving

Verbal fluency (response initiation and organization)

Discordant Findings Between Symptoms and Neuropsychiatric Testing

Symptoms are mainly subjective in nature

Many studies have not demonstrated significant objective cognitive impairments on neuropsychological testing

Objective cognitive impairment correlates poorly with severity of subjective symptoms

Neuropsychological tests do not always directly translate to a person's day to day function or consider contributing factors such as **fatigue, mood**, work and life demands

Emotional and Global Confounding Factors

Depression

Anxiety

Grief

Anger

Reduced Frustration Tolerance

Fatigue – physical / mental

No good comprehensive assessment yet

Diagnosis

No clear guideline for diagnosis

No imaging correlates

No specific lab tests

Rule out other potential contributing factors (anemia, electrolyte imbalances, sleep disturbances, fatigue, depression, previous brain surgery medications)

CRCI is Very Challenging to Study

Agreement on definition and characterization of CRCI as a clinical entity

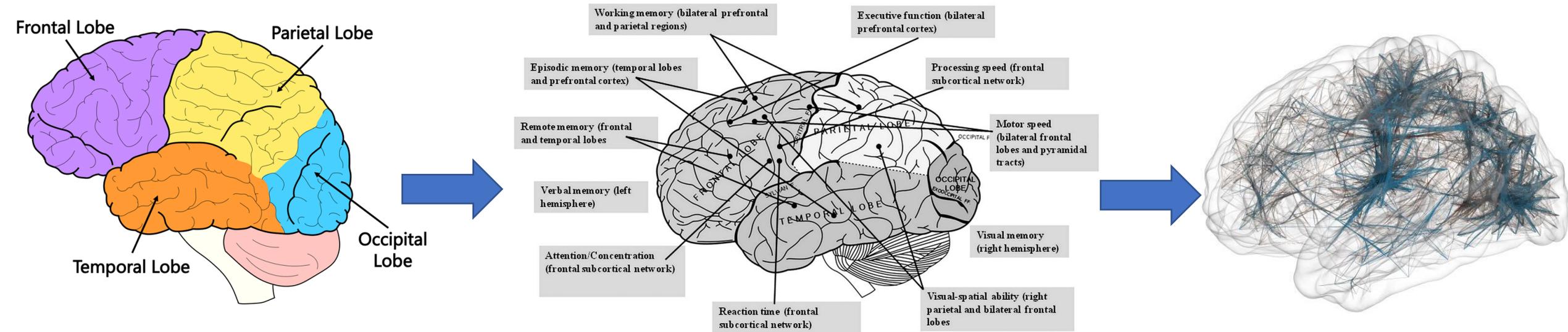
Different types of cancer and treatments

Different measurement scales used

How much of a decline is a decline?

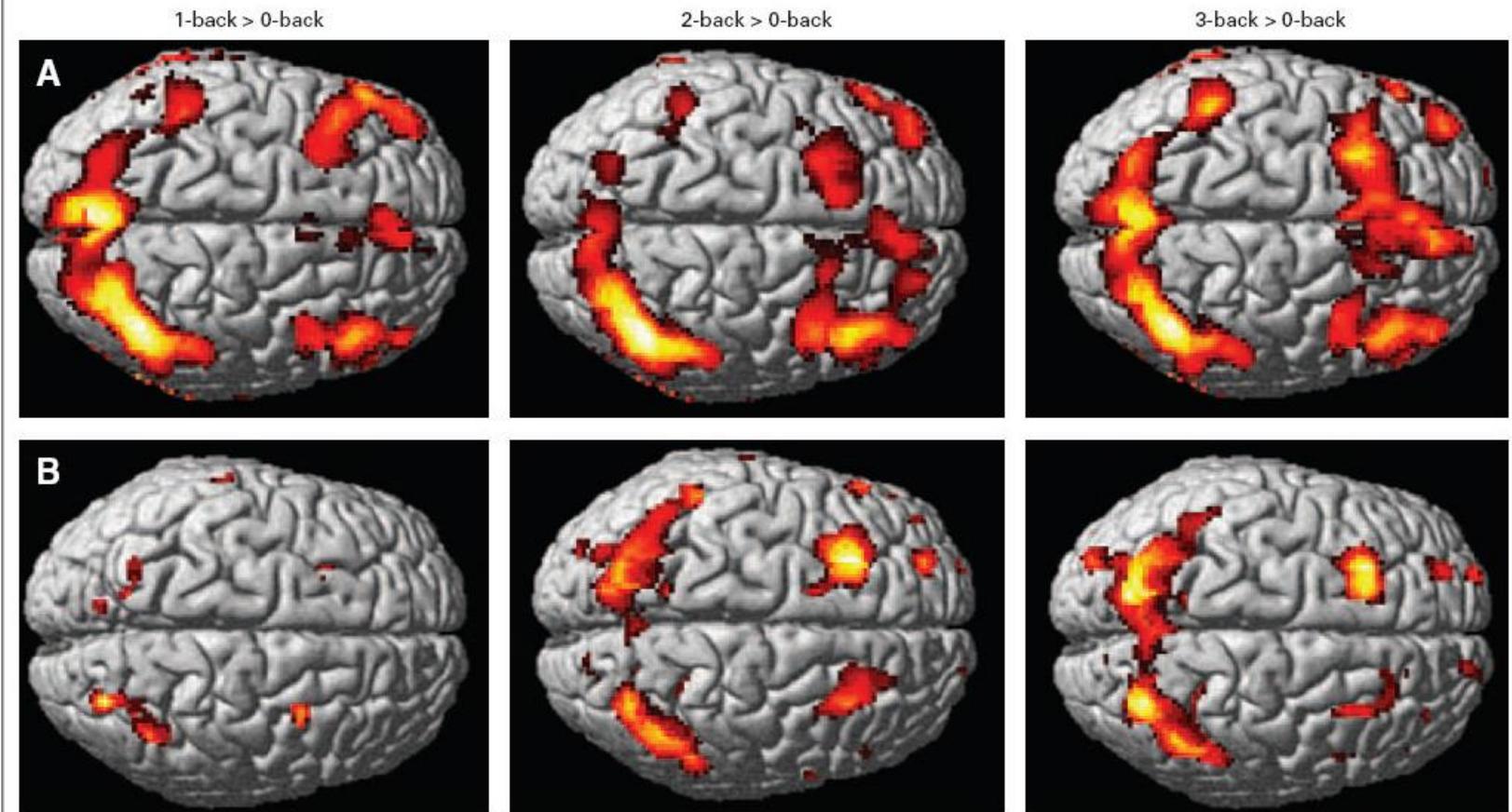
Patient differences (age, education level, cognitive reserve, etc)

Improving understanding of neurocognitive networks



Twin A – Breast cancer and treatment
(Doxorubicin, cyclophosphamide,
docetaxel, tamoxifen)

Twin B – No cancer



Biologic Basis of CRCI

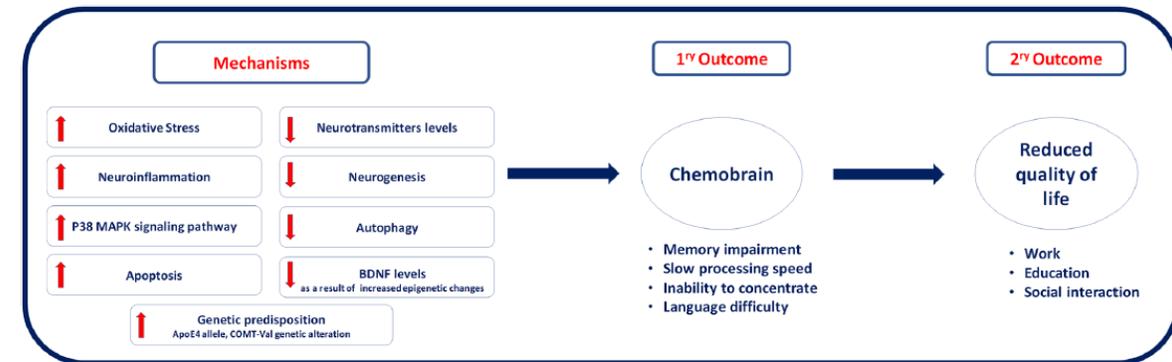
Underlying mechanism is not known - likely **multifactorial**

Inflammation and cytokine release from cancer and treatment

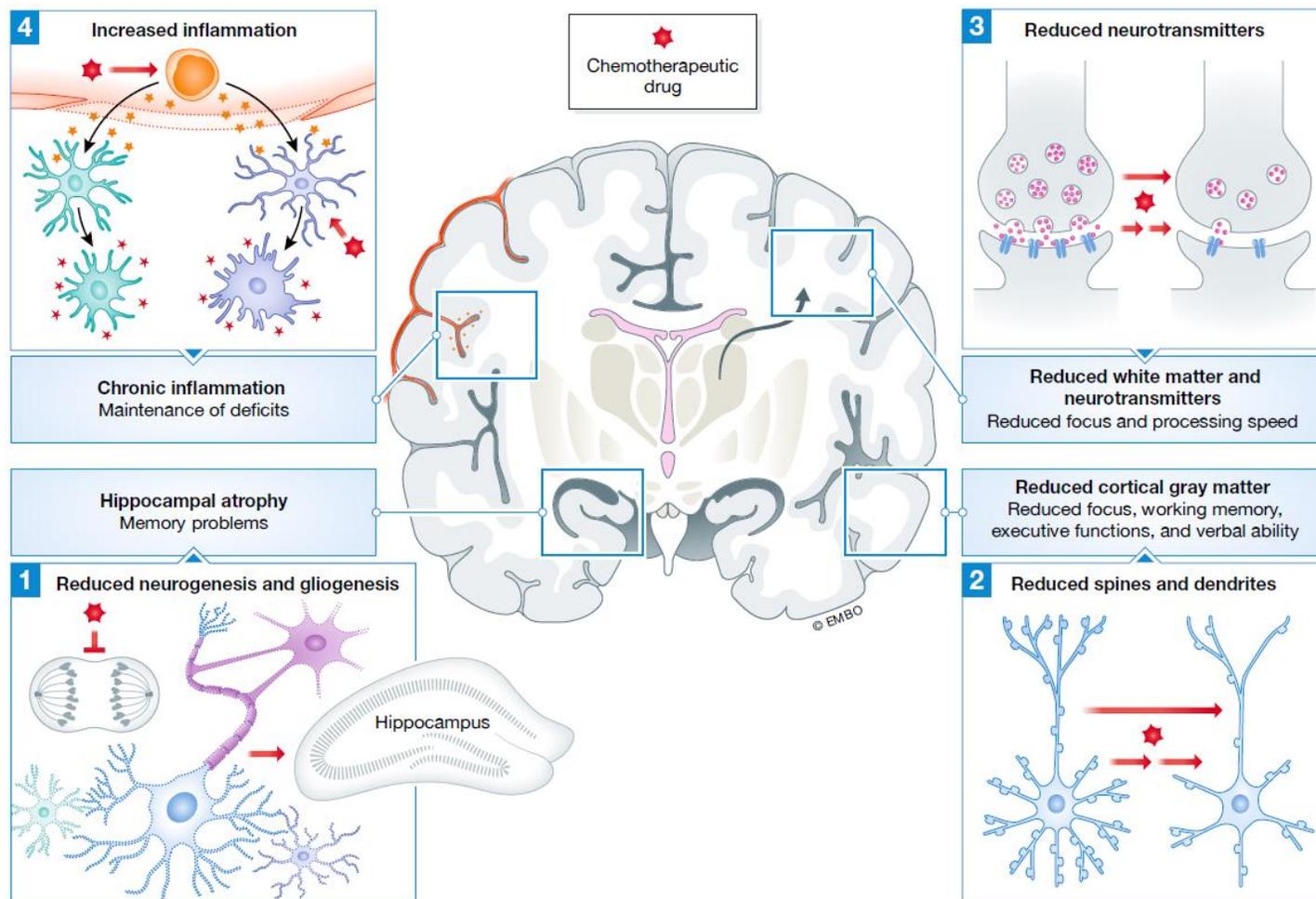
Oxidative stress can cause direct neural injury and inadequate repair

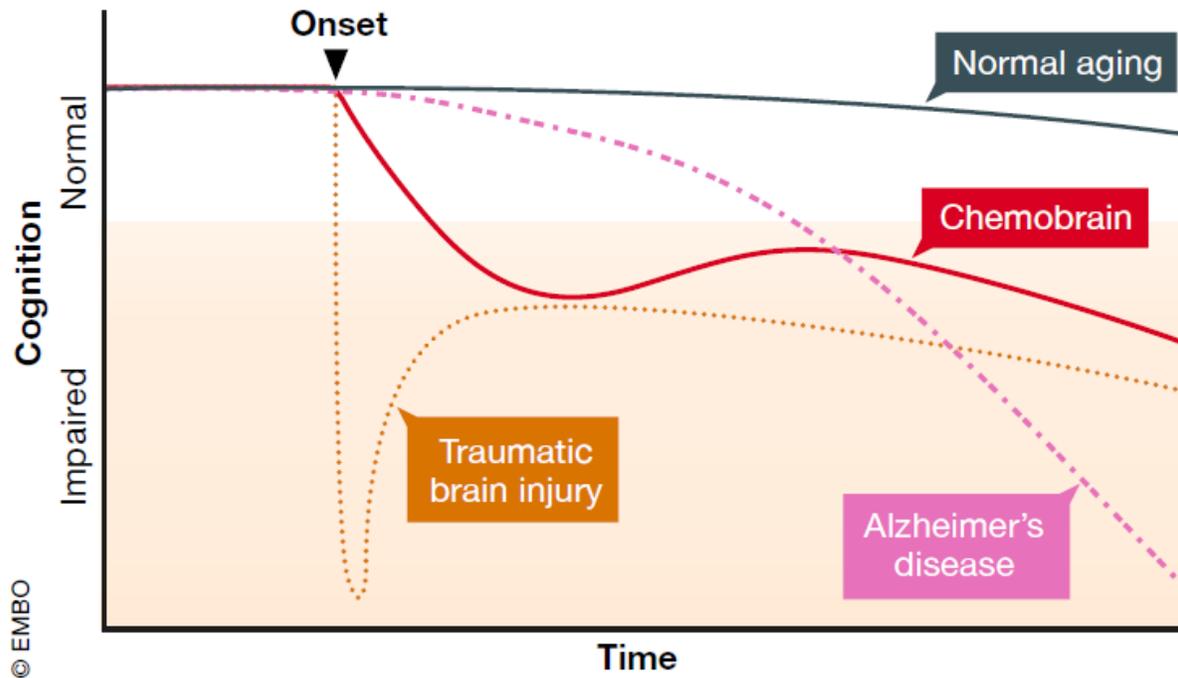
Decreased **neurotransmitter** production and secretion

Microvascular (blood vessel) damage

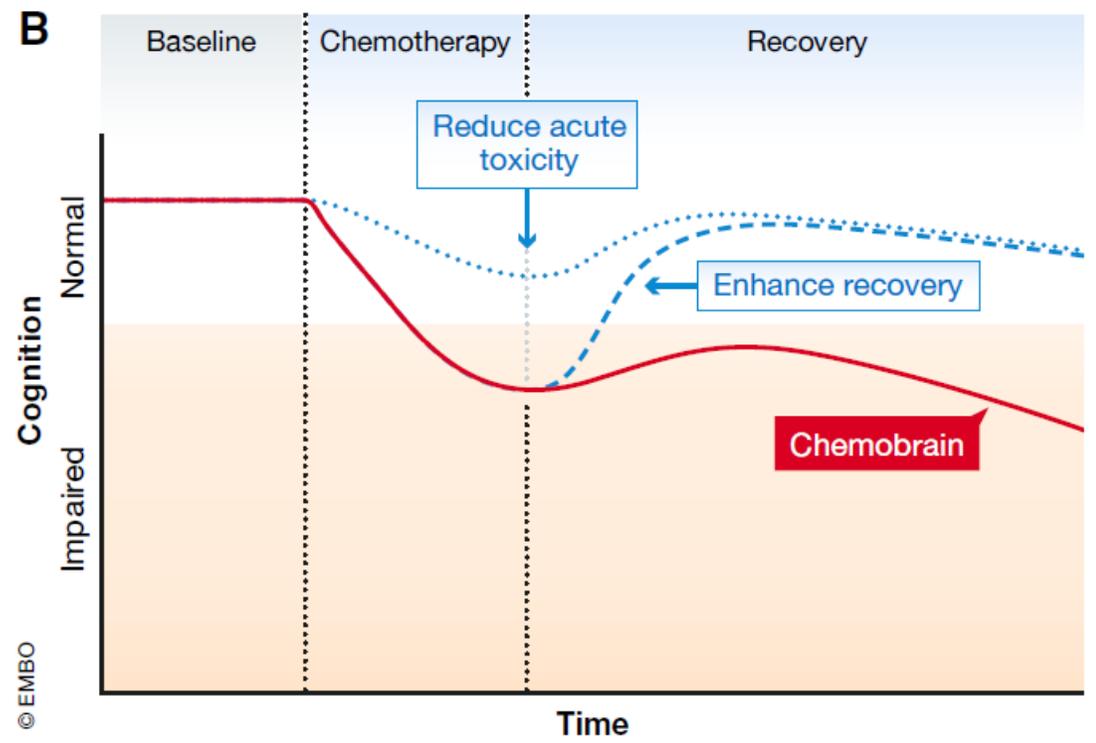


Learning from aging and neurodegenerative diseases





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Possible Risk Factors

Older age

- Accumulation of DNA damage
- Telomere shortening (implicated in organism life span and aging)
- Chronic inflammation
- Fewer stem cells for repair

Genetics

- *APOE4* - related to microvascular or neural repair processes and is associated with lower cognition in long-term survivors
- *COMT* - lower dopamine in frontal cortex and perform more poorly on cognitive testing

Cognitive Reserve

- Baseline IQ, educational level, prior brain injury/insults (TBI, stroke, general brain health)

Strategies to Manage

Given limited understanding and complex nature of the process there is no single pill or strategy

First thing to do is to tell your medical team

- Workup and rule out reversible causes of symptoms (anemia, electrolyte changes, thyroid dysfunction, vitamin deficiencies)
- Clean up medications if possible
- Identify factors to focus on (poor sleep, mood changes, pain)

Be mindful of potential difficulties and cut yourself some slack!

Compensatory strategies, lifestyle changes

- Keep a positive mind! Knowing symptoms are transient can help increase effort and desire to improve
- **DEVELOP A SYSTEM**
- Create new routines (easier said than done)
 - More deeply engrained than memories
 - New daily routines
 - Create a central place for essential things (phone, medications, wallet/purse, keys)
- Use memory aids (notebooks, phone notes, etc, **AVOID STICKIES**)
- Divide tasks up into smaller steps

Compensatory strategies, lifestyle changes

- Recognize things may take longer or be done differently
 - Pay more attention to new tasks, meeting new people, navigating new areas, etc
- Avoid multitasking
- Minimize distractions
- Take breaks
- Create checklists and priority lists
- Review your daily tasks at the end of the day

Memory Compensation

Acquisition

- Focus
- Ask for information to be delivered slowly, re-read, etc

Storage and Retrieval

- If possible, link new information to something meaningful
- Organize
- Mnemonics

Cognitive rehabilitation

- Ask your medical team about considering cognitive therapy via occupational or speech therapy
- Ask if detailed neuropsychological testing is indicated
- Keep the mind stimulated
 - Stay mentally active
 - Diverse and novel mental exercises
 - Socialize (hard to do with COVID-19)

Regular physical exercise

- Cardiovascular exercise can drive brain repair after injury
- Stimulates new neuron formation
- Facilitates connections between brain cells
- Low impact exercises like yoga, Tai Chi are good too!
- Can help decrease fatigue
- Also can reduce stress

Sufficient restorative sleep

- Sleep deprivation can damage neurons and prevent healing
- Poor sleep can cause daytime fatigue and impair cognitive function
- Sleep is important to organize the mind and consolidate memories
- Avoid stimulants before bed (caffeine, high sugar foods)
- Sleep hygiene - minimize exposure to bright lights (phone screens, TV) right before sleeping
- Meditation and relaxation techniques can be helpful
- Establish a regular bed time
- Try to get AT LEAST 6 hours of sleep

Good nutrition

- Balanced diet low in sugars, high in protein
- Diet high in antioxidants can be helpful in minimizing cancer therapy-related damage to brain cells
- Increase fruits and vegetables intake
- Multivitamin can't hurt

Engaging in positive and stress-reducing activities

- Many reasons to have stress during this time
- Try to focus on activities that give you pleasure
- Easier said than done

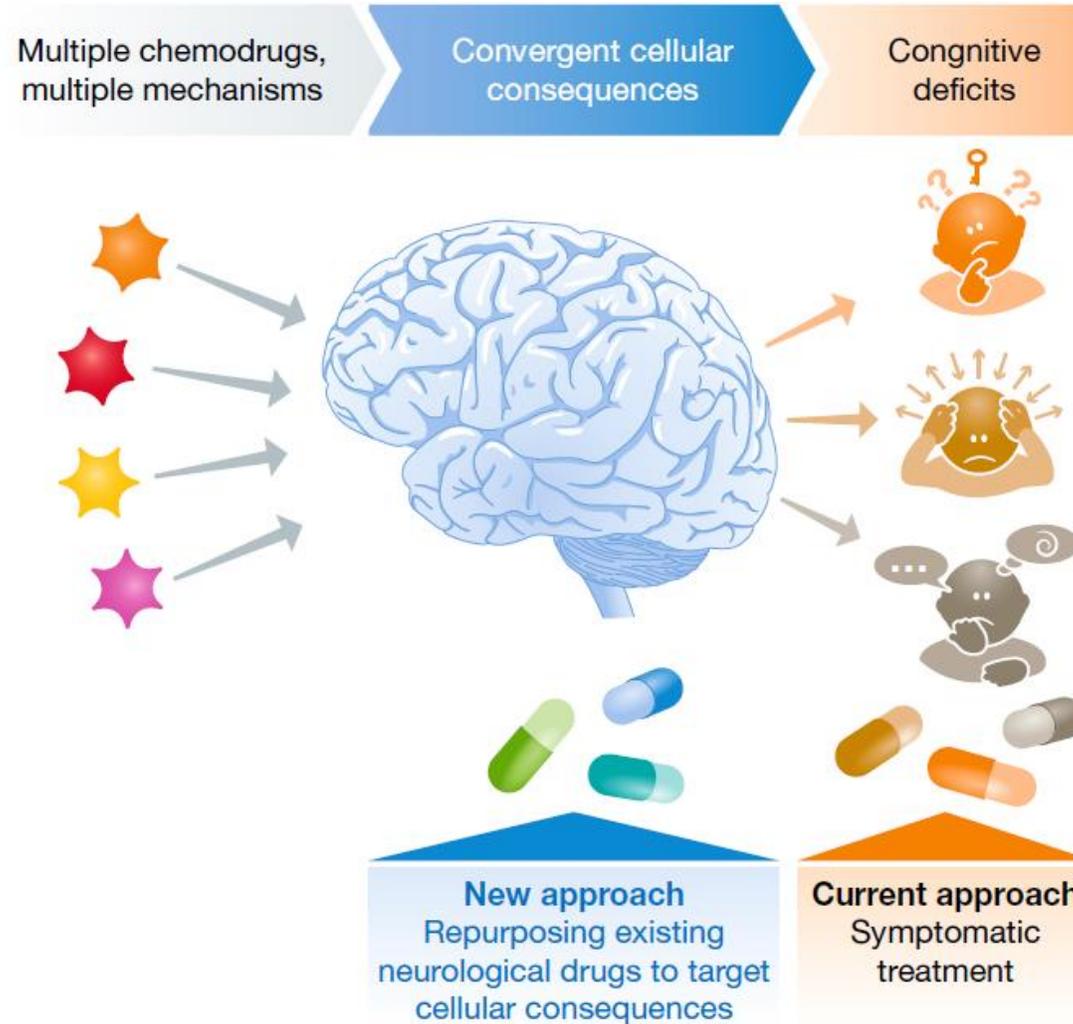
Psychological therapy

- Be proactive if mood is impacting day to day life
- Depression and anxiety can undermine cognitive health
- Often co-exists with diagnosis and treatment
 - Can be exacerbated by supportive drugs (corticosteroids)
- Supportive counseling can be helpful
- Medications can added if needed too

Drug therapy – limited options in general

- Neurostimulants such as methylphenidate (Ritalin) can improve cognitive function
 - Poorly designed studies have not shown significant benefit
- Modafinil (Provigil) or armodafinil (Nuvigil) can also help enhance cognitive function
- Neuroprotective drugs have not been well studied
 - Ginkgo biloba
 - Donepezil – drug used in dementia
 - Memantine – another dementia medication
 - Vitamin E – scavenges free radicals

Future Directions



Future Directions

Highly challenging given heterogeneity of symptoms and unclear causes

Repurpose other drugs being studied for neuroprotection in other conditions (dementia, TBI, stroke, MS)

Discovery and study drugs to **minimize oxidative stress** and **promote neurogenesis**

Improve neurotransmitter function

Target neuroinflammation

Identify more robust **risk factors**, imaging **biomarkers**

Patients with brain-directed cancer therapy

Lithium ⁵⁷	Protection against hippocampal neuron apoptosis	NCT01486459
Pioglitazone ⁵⁸	Anti-inflammatory, less oxidative neuron injury	NCT01151670
Ramipril ⁵⁹	Anti-inflammatory, less oxidative neuron injury	NCT03475186

Patients with systemic cancer therapy

Fluoxetine ⁶⁰	Protection of dividing cells in the hippocampus	NCT01615055
Docosahexaenoic acid ⁶¹	Functional recovery, reduction of microglia infiltration	NCT02517502
Ibuprofen ⁶²	Anti-inflammatory, less oxidative neuron injury	NCT03186638
Nicotine ⁶³	Glutamatergic neurotransmission	NCT02312934

Karschnia et al. Lancet Oncol 2019

Thank you for your time and attention!

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