L'effetto della menopausa iatrogena precoce sulla funzione cognitiva

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- In recent years, breast cancer survival rates have significantly improved thanks to advances in diagnosis and treatment, but **potential late side effects of the treatment itself can negatively impact the quality of life of patients**.

- Many breast cancer survivors suffer from climacteric symptoms, such as vasomotor symptoms (hot flashes, night sweats, palpitations), vaginal dryness, sexual dysfunction, poor sleep and tiredness, osteoporosis, fertility problems and **neurological diseases**, including **cognitive dysfunction**.

- In particular, young women diagnosed with breast cancer have several issues and concerns, and are strongly affected by **symptoms of premature menopause and cognitive deterioration.**

About 40% of healthy women in the menopausal transition complain of forgetfulness: "brain fog"

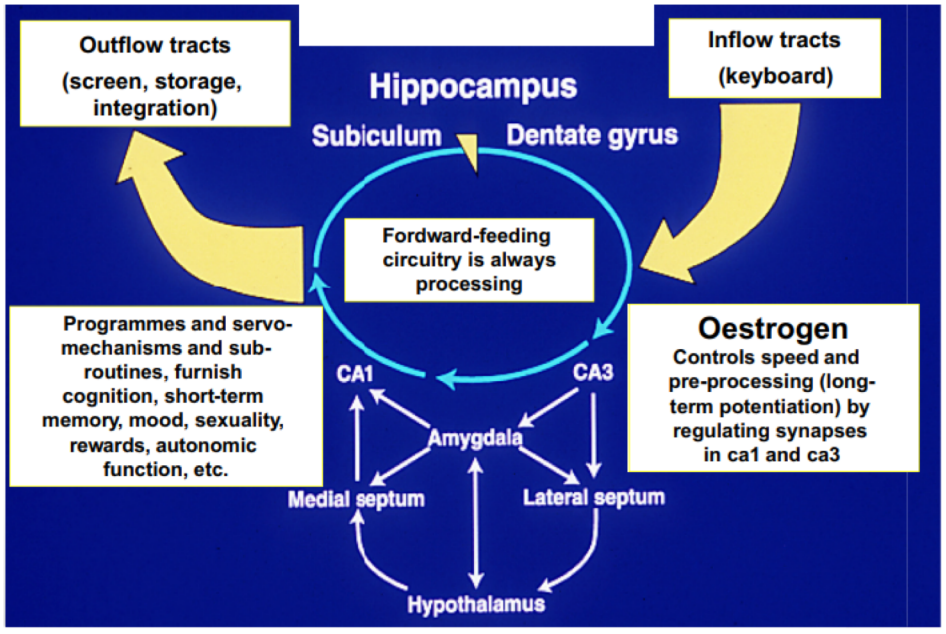
decrease in attention, memory, processing speed and other cognitive abilities interfering with their daily activities

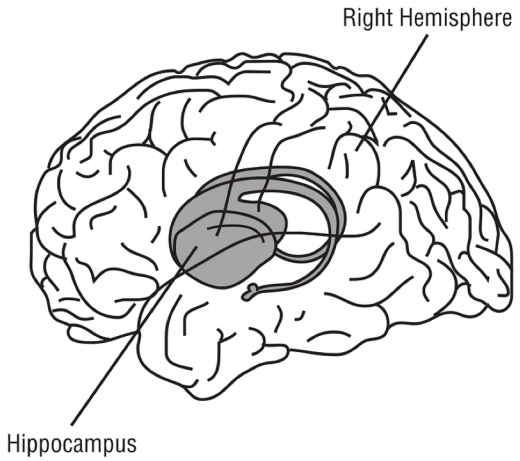
Maki et al., 2016

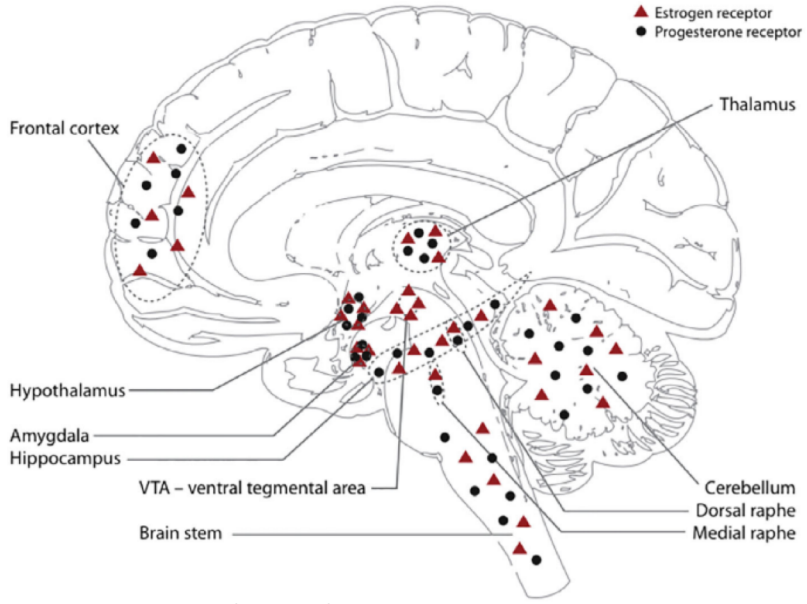
Sex hormones such as estrogen, progesterone and androgens play an important role in the modulation of brain functions and synaptic organization and plasticity,

affecting neurons, glia and microglia in many areas of the brain, including the hippocampus and limbic system

Silva et al., 2016







Boyle et al., 2020

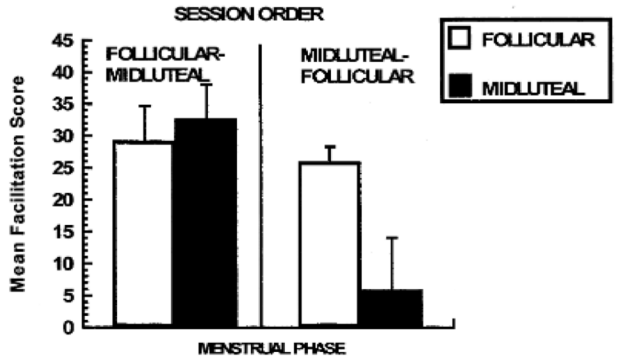
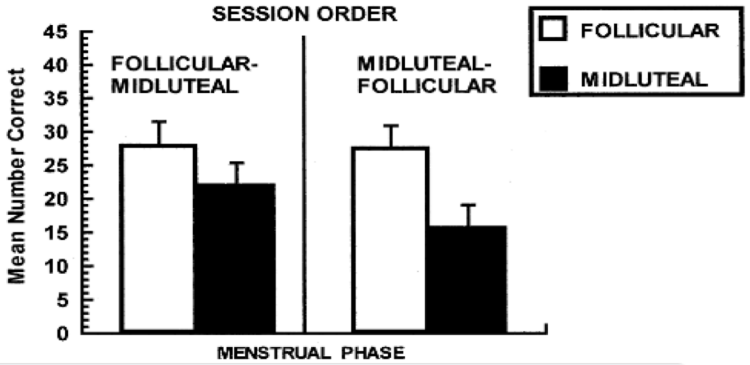
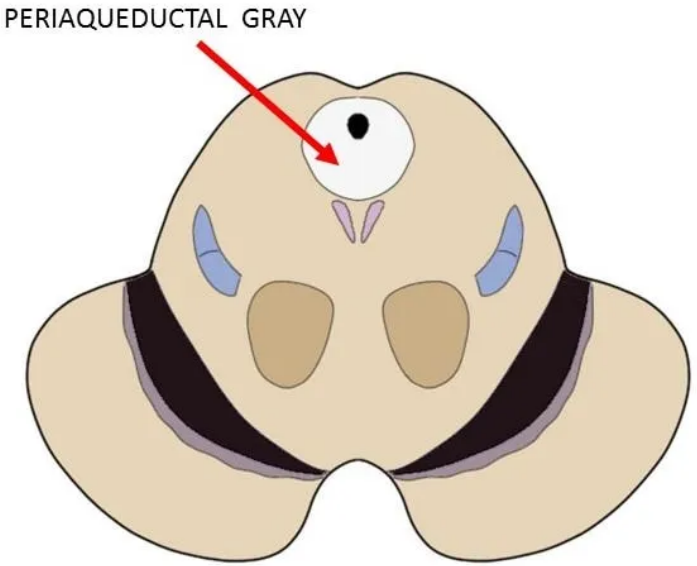


Fig. 1. Mean prime scores on the FOI test as a function of session order and menstrual cycle phase. Error bars are standard errors.



In premenopausal women the effect of estradiol on specific brain areas (hippocampus and temporal lobes) contributes to **memory performance**, improving **verbal fluency**, with differences observed between the follicular and luteal phase of the menstrual cycle, following the changes in estradiol circulating levels

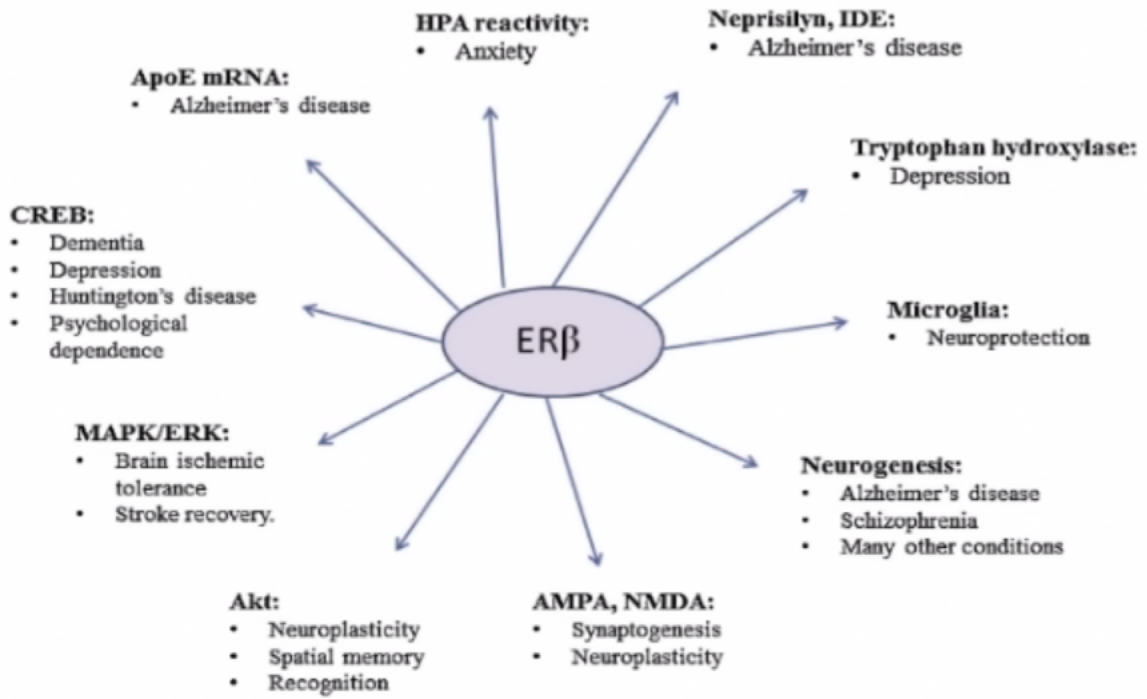
Maki et al., 2002; Maki et al., 2015



The decline in sex steroids, particularly estrogen, during the menopausal transition is associated with changes in eating behavior, metabolism and sleep, mood, sexuality, locomotor activity, immune response, memory and cognitive function.

Estrogen receptor beta has been found to be widely distributed in the female brain, especially in the hippocampus, amygdala and dorsal raphe nucleus

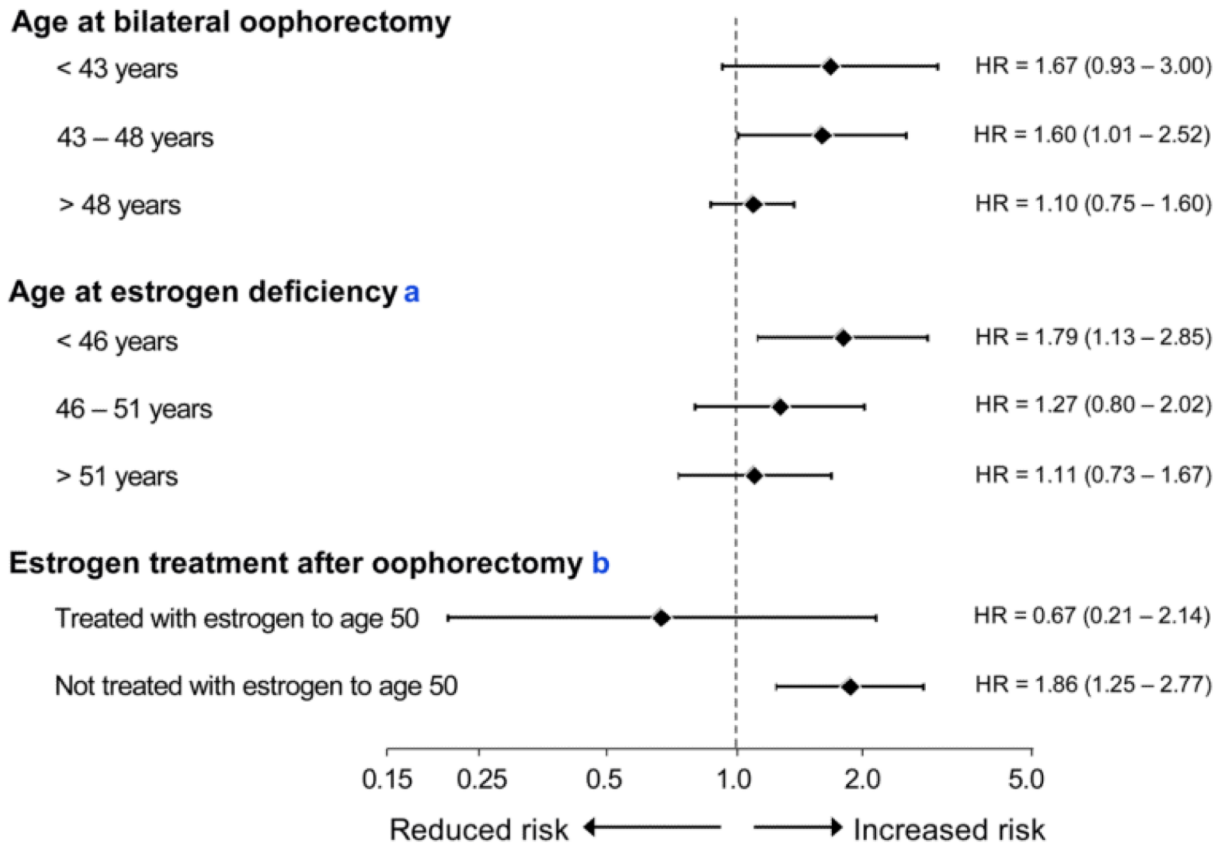
- protein expression of genes involved in neurological functions
- promotion of neurogenesis
- modulation of stress response
- neuroendocrine regulation
- neuroprotection against ischemia and inflammation
- reduction of anxiety and depression



Vargas et al., 2016

Estrogen improves the **formation of synapses on dendritic spines** in the hippocampus, increases cerebral blood flow and glucose metabolism, and acts as an **antioxidant**

Moreover, estrogen **increases choline acetyltransferase activity** in the basal forebrain and hippocampus, **reduces deposition of amyloid** in the brain, and **prevents cellular mitochondrial damage**

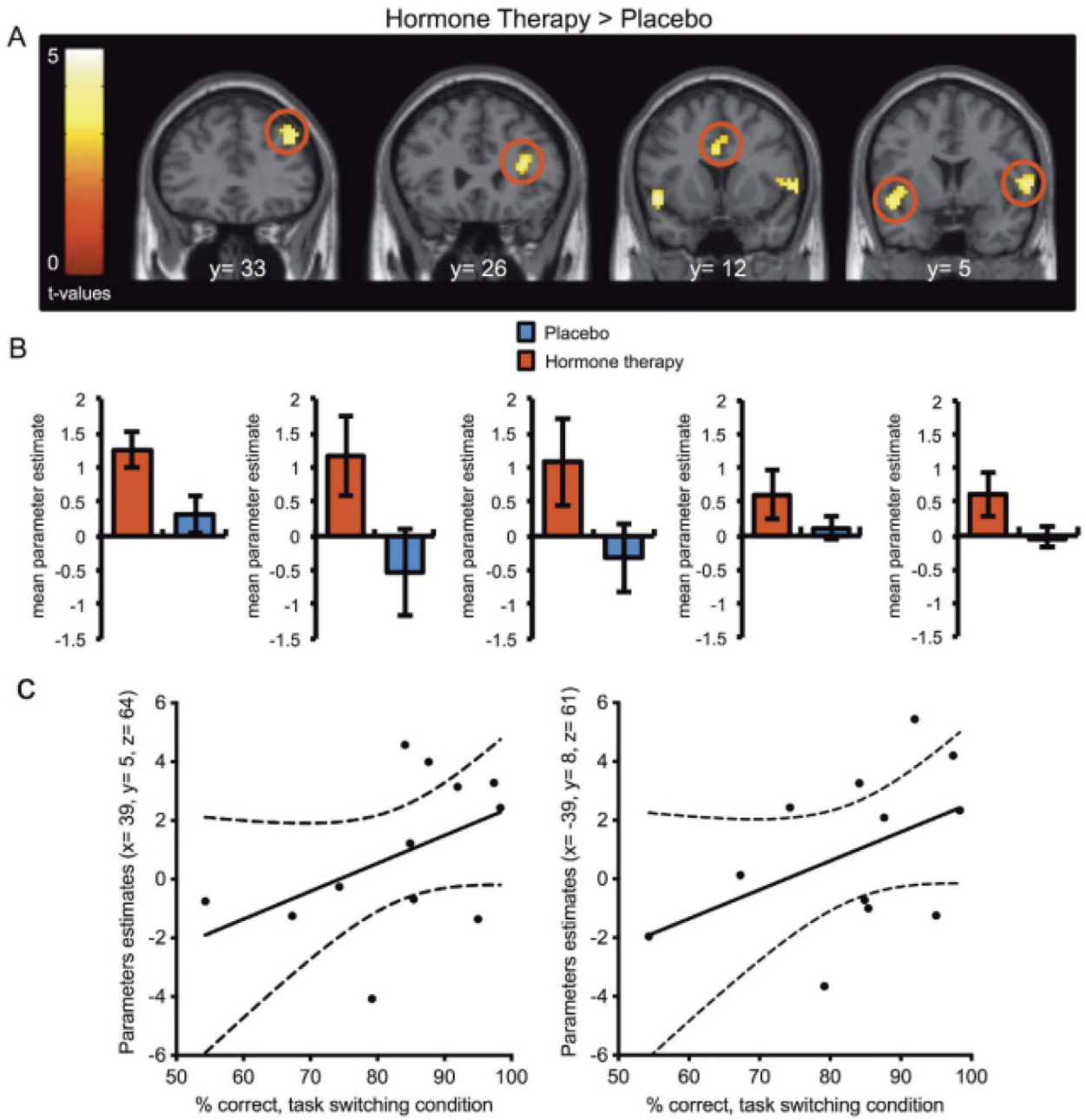


Rocca et al., 2012

One study used **task-fMRI** to assess cognitive control in early postmenopausal women to identify the effect that sequential 2 mg/ day oral 17β estradiol and then 100 mg oral progesterone or placebo would have on **dorsolateral prefrontal cortex (PFC) activity**

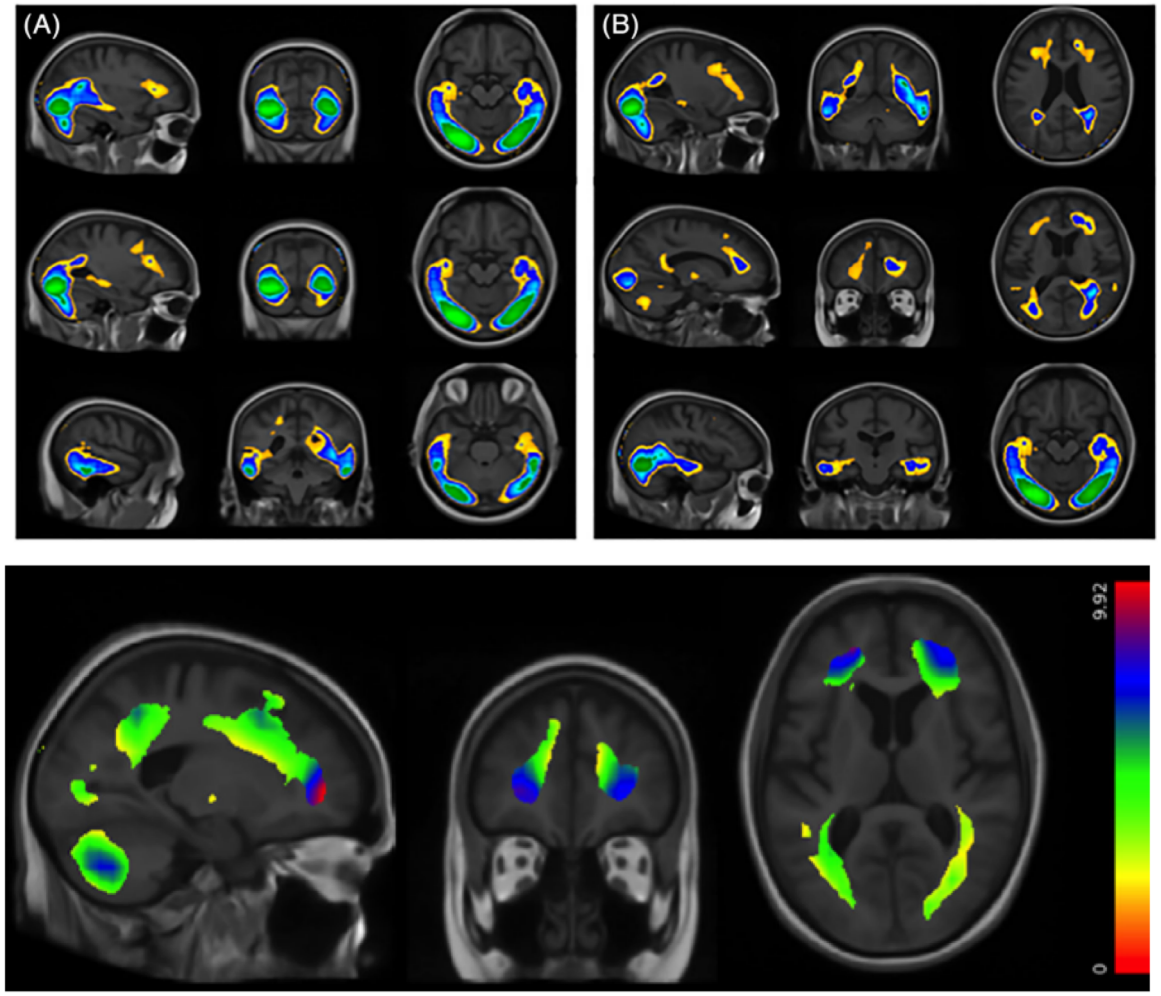
Increased activity of the dorsolateral PFC and better performance on the task switching task in women who were randomly assigned to HT compared to placebo.

Earlier initiation of HT had **greater benefits** to postmenopausal women

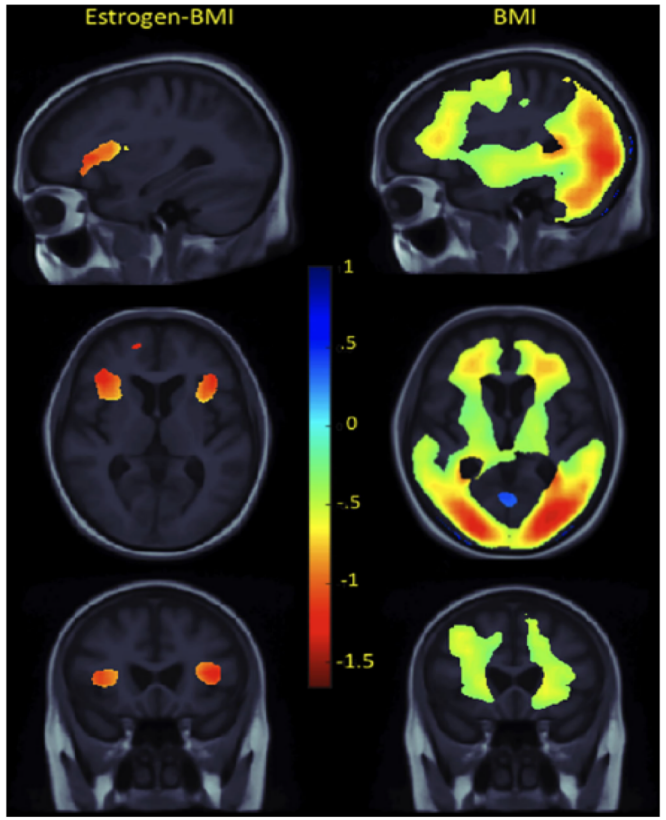


Girard et al., 2017

History of estrogen use in a large cohort of elderly women is associated **with larger gray and white matter volumes, in brain regions** relevant to cognitive function **including frontal, temporal, and parietal lobes**



the presence of BMI appeared to negate the positive impact of HT on the brain in isolated frontal regions of the brain



Boyle et al., 2020

In women who underwent **oophorectomy before the onset of menopause** for a non-cancer indication, unilateral and bilateral oophorectomy before the onset of natural menopause are associated with an increased risk of **cognitive impairment or dementia, with an age-dependent effect** *Rocca et al., 2007*

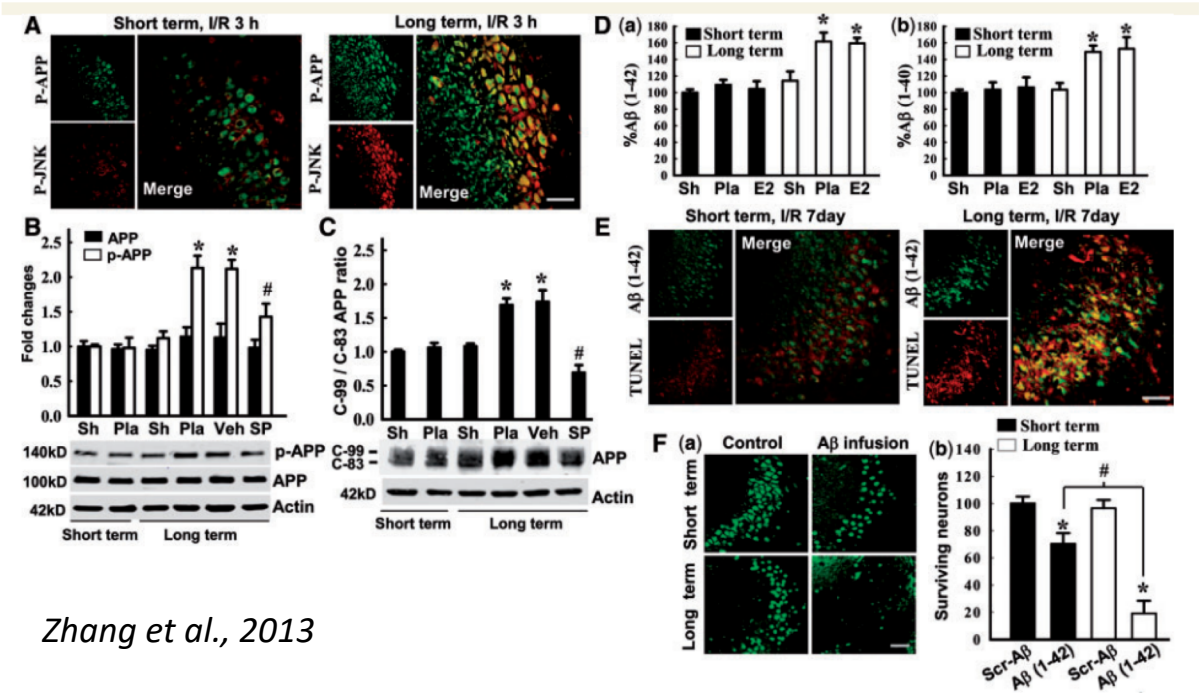
Premature menopause in animal models revealed that the most affected cerebral area is the hippocampus

→ hypersensitive to ischemic injury

→ induction of Alzheimer's disease-related proteins

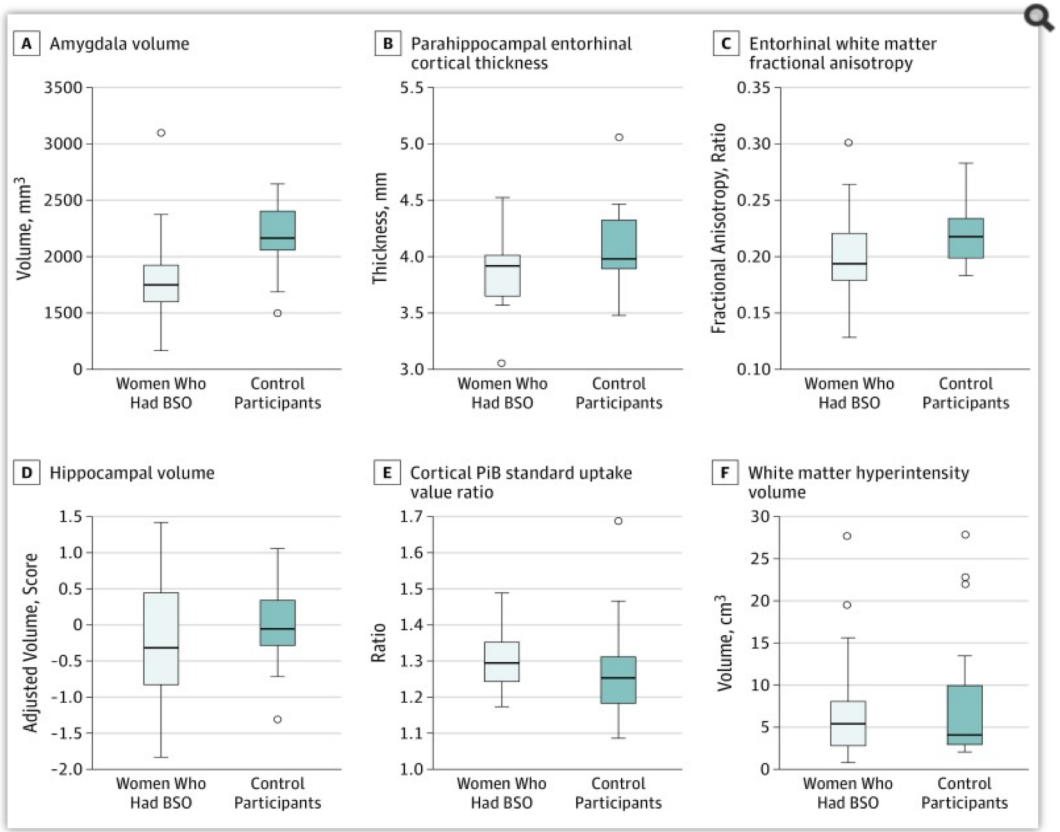
→ increase of amyloidogenesis

→ worsening of cognitive outcome



Zhang et al., 2013

Women who underwent bilateral oophorectomy show **increased β-amyloid deposition in the medial temporal lobe**



Zeydan et al., 2019

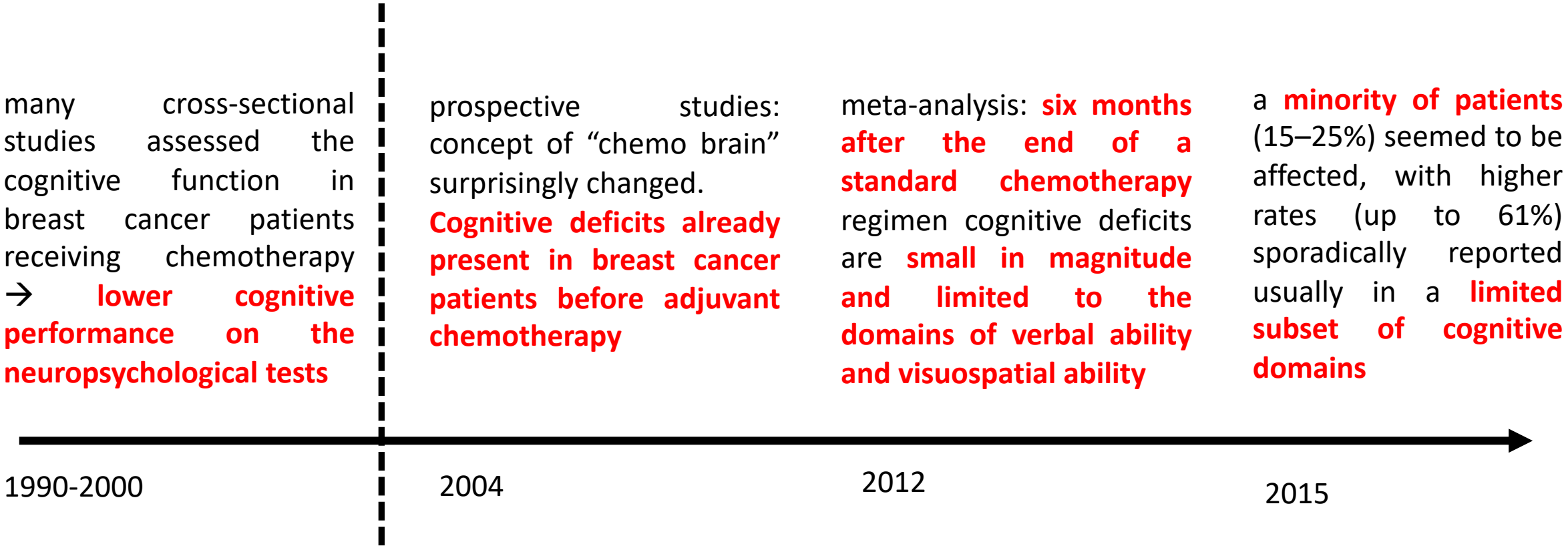
In **breast cancer patients**, systemic therapies (**chemotherapy and endocrine therapy**) contribute, **through different mechanisms**, to the onset of early menopause and the abrupt reduction of circulating estrogen levels, causing menopausal symptoms similar to those analyzed in women who undergo bilateral oophorectomy:

- vasomotor symptoms,
- vulvo-vaginal atrophy,
- sexual dysfunction and dyspareunia,
- musculoskeletal symptoms,
- neuropathy,
- fatigue,
- cognitive impairment,
- depression and anxiety

The role of adjuvant chemotherapy

Many premenopausal women diagnosed with breast cancer who received adjuvant chemotherapy complain of impaired memory, attention, speed of processing, word-finding, and other basic cognitive functions, in other words, “chemo fog” or “chemo brain”.

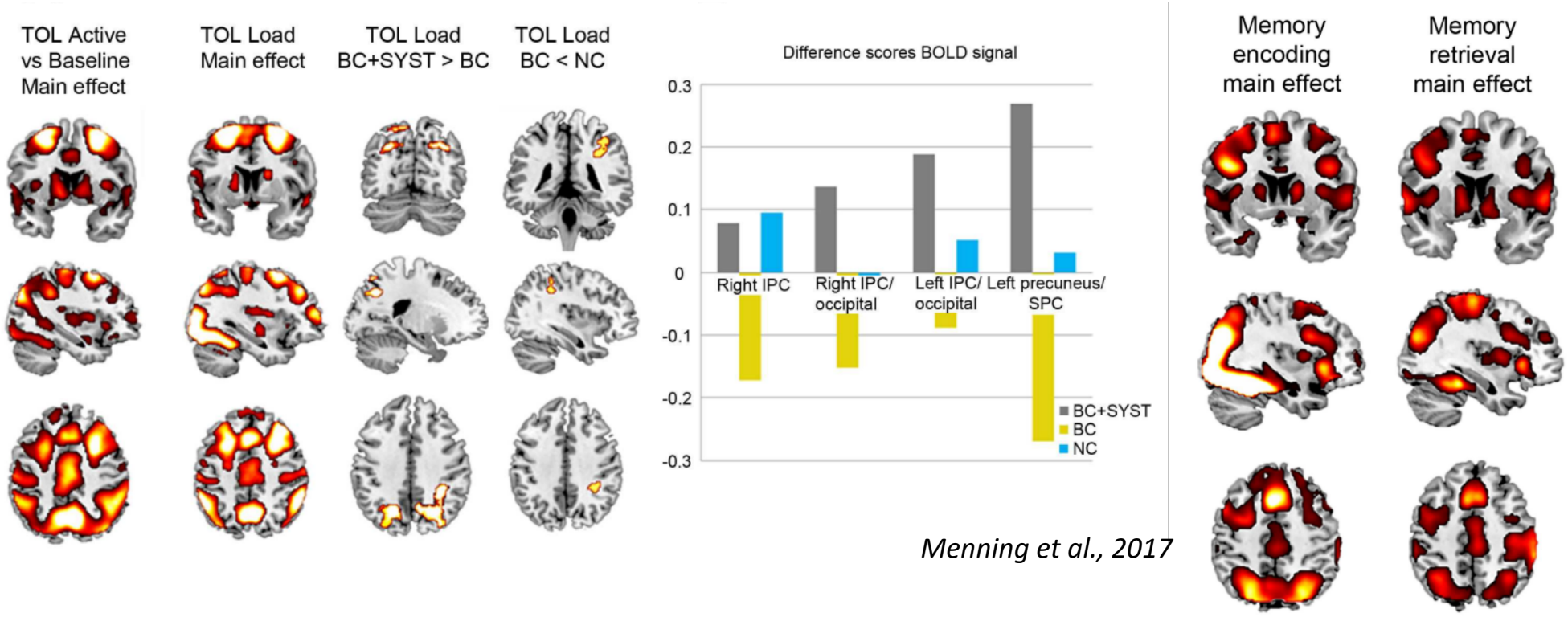
Hermelink et al., 2015; Raffa et al., 2006



fMRI and «chemo-brain»

Several studies using MRI documented both structural and functional brain differences between breast cancer patients treated with chemotherapy and control groups

regional hypoactivation and/or widespread brain activation during cognitive tasks
→ compensation for the dysfunction of areas relevant to the task by activation of additional brain areas



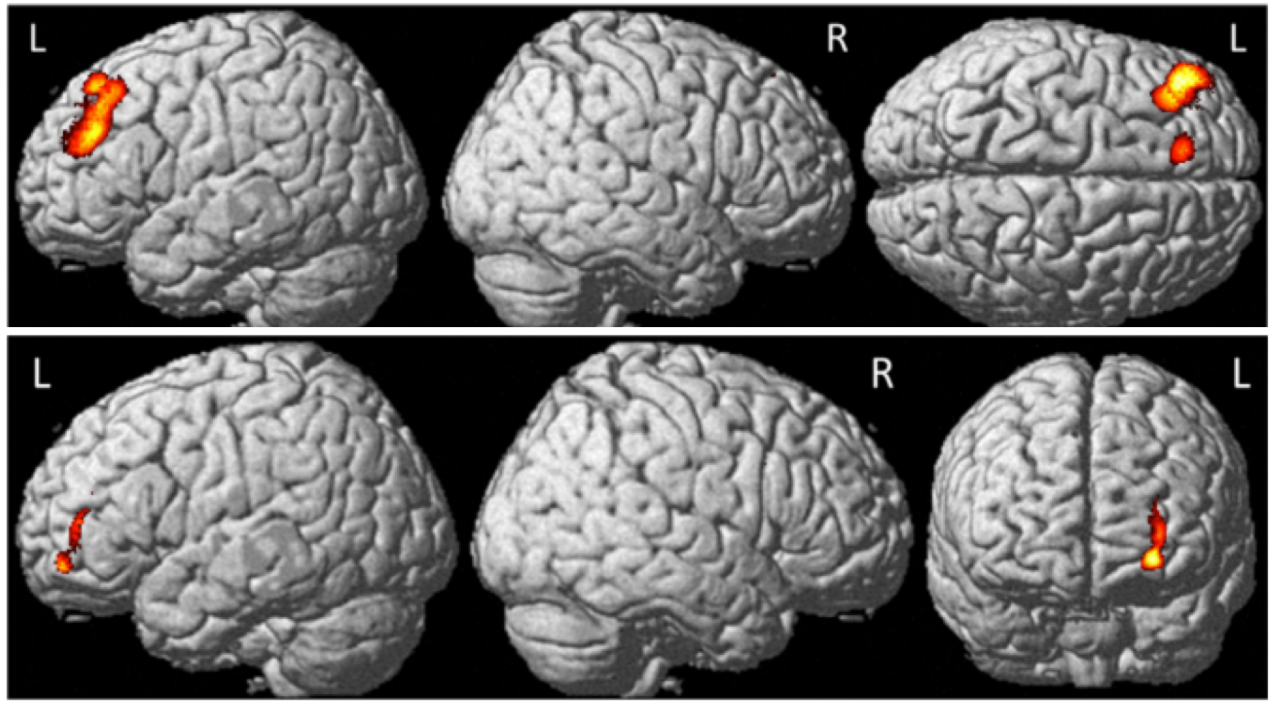
Menning et al., 2017

Parietal hyperactivation after systemic treatment in the context of stable levels of executive task performance → compensatory processing of hyperactivation to maintain adequate performance levels as response to decreased neural integrity

Structural MRI and «chemo-brain»

Structural differences in breast cancer survivors include reductions in gray matter volume, primarily in frontal structures and the hippocampus, and white matter integrity

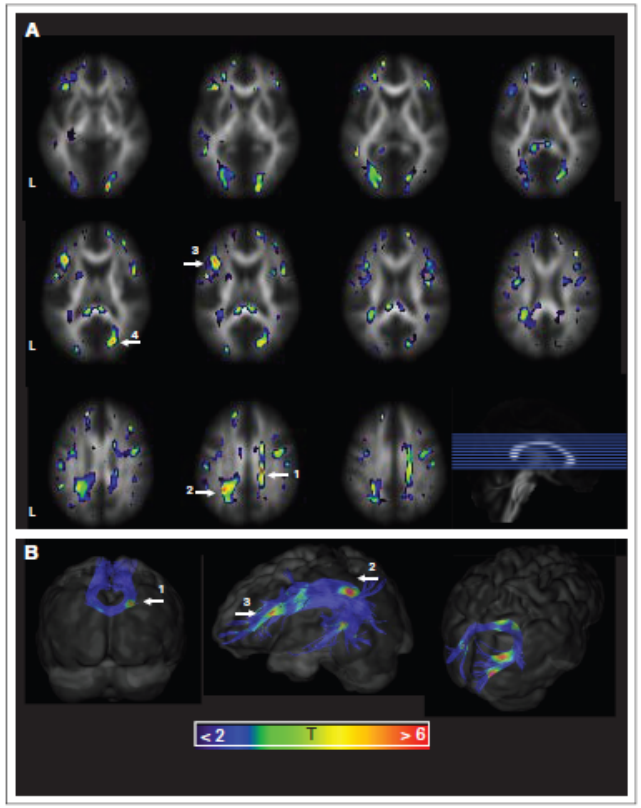
- **decrease in grey matter density one moth after chemotherapy, particularly in frontal regions**



- **Correlation between NPS test (executive functions) and grey matter density**

McDonald et al., 2012

- **decrease in FA** in chemotherapy-treated group in **frontal, parietal and occipital WM tracts**
- correlation between FA and NPS deficits

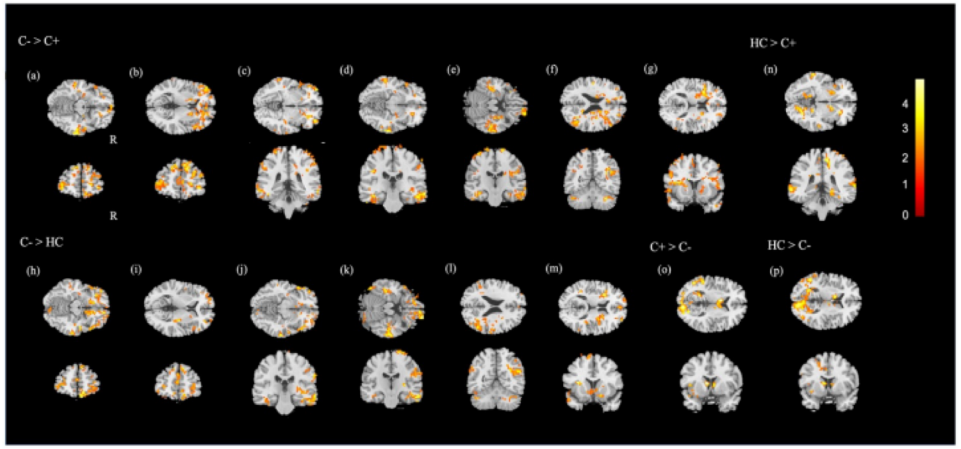


Deprez et al., 2011

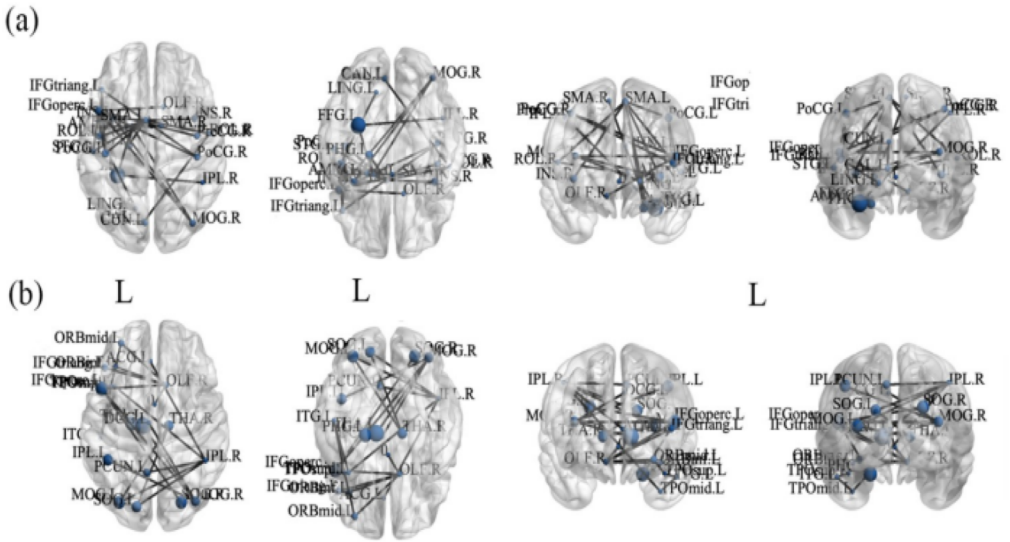
Chen et al., 2020

Functional connectome analysis to investigate functional changes among breast cancer survivors alterations were noted in various brain regions

The **C- group had hyperactivity in the PFC, bilateral middle temporal gyrus, right inferior temporal gyrus and right angular gyrus**.



Graph theoretical analysis demonstrated that the **C+ and C- groups were inclined toward regular and random networks, respectively**.



Subtle changes in both the cancer survivor groups patients diagnosed as having breast cancer **may have cerebral network alterations even before adjuvant chemotherapy initiation**

Chemo-brain: to be or not to be?

To date, the role of chemotherapy neurotoxicity in the onset of cognitive disease is still unclear

Many other factors may potentially affect the breast cancer patient's brain:

- endocrine therapy
- surgery
- radiotherapy
- biological factors, such as high cytokine levels
- psychological factors (women who receive chemotherapy have a more advanced cancer stage at diagnosis, worse prognosis and a greater psychological burden)
- study design, protocols, and sample size

The role of adjuvant endocrine therapy

**Given that the literature suggests a positive effect of estrogen on brain functioning,
it is possible that endocrine therapy in breast cancer patients, whose aim is to bring about estrogen deprivation,
might influence brain functioning and cognition**

In recent years, several studies have evaluated the impact of endocrine therapy on cognitive function in breast cancer patients and small prospective studies have found that initiation of endocrine therapy is associated with significant changes in neuropsychological performance

Table 6. Means and standard deviations of overall neuropsychological summary score and domain-specific summary scores for healthy group ($n = 28$) and matched hormonal subgroup ($n = 28$), and significance of ANCOVAs with age and education as covariates

	Healthy mean (SD)	Hormonal mean (SD)	Sig F
Overall	0.00 (0.31)	−0.24 (0.37)	0.01
Executive	0.01 (0.47)	−0.23 (0.37)	0.09
Language	0.01 (0.64)	−0.28 (1.16)	0.33
Motor	0.00 (0.98)	+0.22 (0.89)	0.42
Processing speed	0.00 (0.54)	−0.35 (0.58)	0.02
Verbal memory	0.00 (0.62)	−0.43 (0.82)	0.04
Visual memory	0.00 (0.75)	−0.27 (0.94)	0.11
Visuospatial	0.00 (0.98)	−0.39 (0.94)	0.16
Working memory	0.00 (0.46)	−0.11 (0.58)	0.52

SD, standard deviation; Sig F, significance of F of two- group ANCOVA

hormonal therapies (both tamoxifen and anastrozole) exert a subtle negative influence on cognition in breast cancer patients *Collins et al., 2008*

Extent of reliable change at T2 and T3

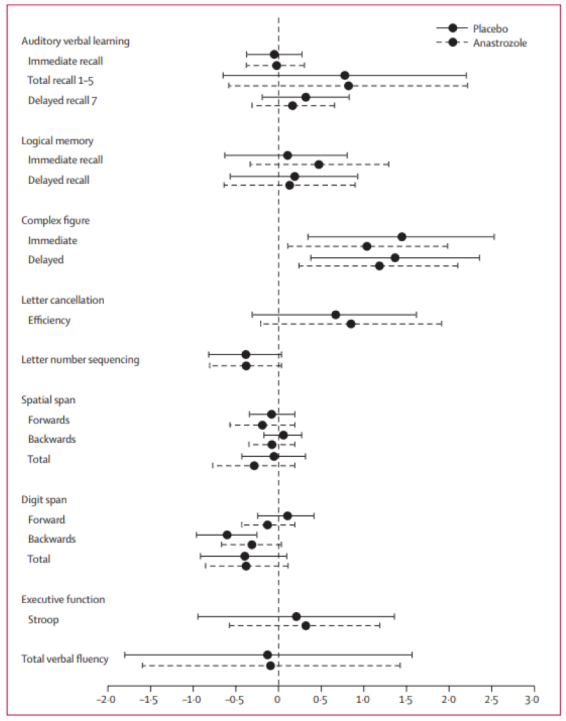
	T2			T3		
	Chemo	Nonchemo	Control	Chemo	Nonchemo	control
Decline on ⩾2 measures	17 20%	11 25.6%	9 18.4%	15 18.1%	6 14.3%	5 10.6%
Improve on ⩾2 measures	19 22.4%	7 16.3%	8 16.3%	27 32.1%	13 30.2%	7 14.6%

Patients who had experienced a treatment-induced menopause were more likely to show reliable decline on multiple measures at FU

Jenkins et al., 2006

TEAM (Tamoxifen and Exemestane Multicenter) neuropsychological performance in breast cancer patients approximately two years after tamoxifen or aromatase inhibitors

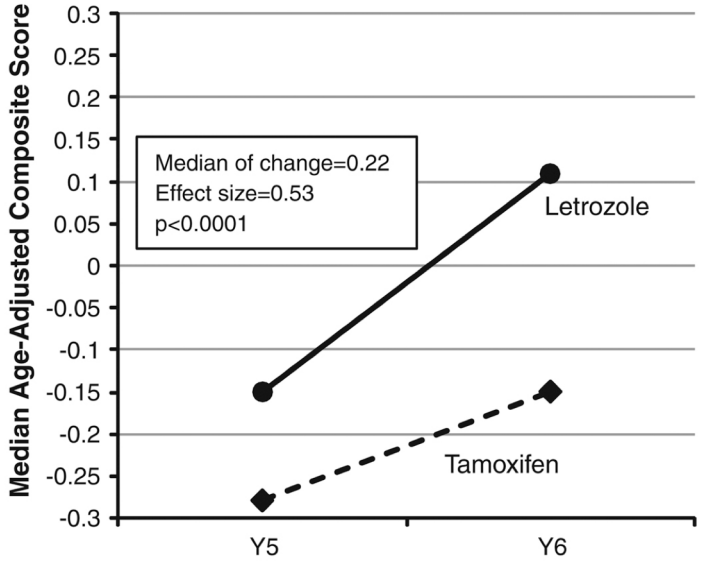
- Significantly greater memory complaints among breast cancer patients than healthy control participants, with no significant differences between tamoxifen or aromatase inhibitor
- Both groups **performed significantly worse** than healthy controls on **verbal fluency and information processing speed**
- After one year of treatment, **women randomized to tamoxifen showed statistically significantly lower functioning in verbal memory and information processing speed compared with those randomized to exemestane**



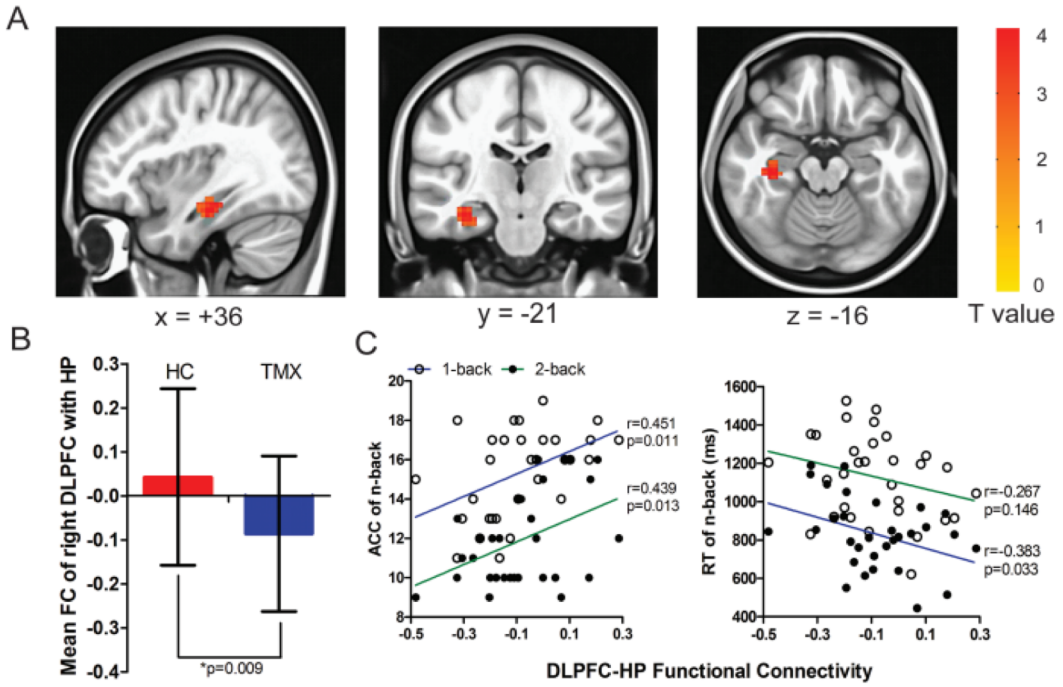
lack of impact of **anastrozolo** on cognitive function in a trial including postmenopausal women at high risk of breast cancer → **similar cognitive function after 2 years compared with those taking placebo**

Jenkins et al., 2008

postmenopausal women taking **letrozole** during 5 years of adjuvant endocrine therapy have **better global cognitive function than those taking tamoxifen**



Philips et al., 2011



Tamoxifen group vs placebo

→ **significant deficits in working memory and general executive function performance**

→ **significantly lower functional connectivity of the right dorsolateral prefrontal cortex with the right hippocampus** compared with the healthy controls

→ **significant** correlations in the tamoxifen group between the **functional connectivity strength of the dorsolateral prefrontal cortex with the right hippocampus and decreased working memory performance**

Chen et al., 2017

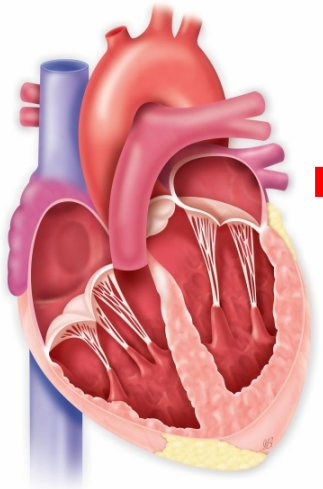
The role of VMS

- The relationship between vasomotor symptoms and cognitive impairment in breast cancer patients has not yet been demonstrated, but a correlation is likely to exist, as in **healthy menopausal women** (*Maki et al., 2020*)

- Many **non-hormonal treatments** of vasomotor symptoms have been proposed as methods that can contribute to improving cognition in breast cancer patients:

- **selective serotonin reuptake inhibitors (SSRIs)** and **selective serotonin-norepinephrine reuptake inhibitors (SSNRIs)** reduce the intensity and frequency of hot flashes by 20% to 65% *(Handley et al., 2015; Biglia et al., 2018; Biglia et al., 2007)*
- **anticonvulsant drugs**, such as gabapentin and pregabalin, decrease the frequency of climacteric symptoms by modulating thermoregulatory activity both in healthy menopausal women and in breast cancer survivors *(Hayes et al., 2011)*
- anti-hypertensive alpha-adrenergic agonist **clonidine** inhibits flushing by reducing peripheral vascular reactivity *(Sassarini et al., 2012)*
- purified **pollen** extract showed beneficial effects on vasomotor symptoms and insomnia in healthy women, probably deriving from the inhibition of serotonin uptake, with an SSRI-like mode of action; unfortunately, no data are available in women with breast cancer *(Winther et al., 2005)*
- **non-pharmacological methods**, such as acupuncture, yoga, breathing, hypnosis, diet and stellate ganglion block, can reduce climacteric symptoms both in healthy women and in breast cancer survivors *(Biglia et al., 2019)*

- high blood pressure
- higher lipids insulin resistant profile
- diabetes risk
- pro-inflammatory or pro-coagulant profile

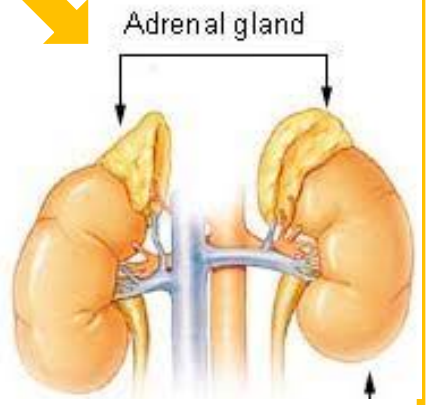


risk factor for dementia

VMS

•increased WMH in greater objectively-detected wake after sleep onset *(Thruston et al., 2019)*

•sleep disturbance negatively affects cognitive function during healthy aging *(Scullin et al., 2015)* and is associated with an increased risk of Alzheimer's *disease (Bubu et al, 2017)*



- elevated cortisol linked to decreases in memory and executive functioning, particularly in women *(McCormick CM et al., 2007)*
- reduction in blood flow to the brain (~5% reduction) *(Lucas et al., 2013)*

Conclusion

The cognitive impairment experienced by many breast cancer patients during and after treatments is multifactorial and related to:

- chemotherapy
- surgery,
- endocrine therapy,
- psychological factors,
- cancer itself
- VMS

- Its prevention and treatment are not yet clearly established

- Guidelines recommended that primary care clinicians ask breast cancer patients if they are experiencing cognitive difficulties, assess for reversible contributing factors of cognitive impairment, optimally treat when possible and refer patients with signs of **cognitive impairment for neurocognitive assessment and cognitive rehabilitation programs** *(Tepper et al., 2016)*

- Rehabilitation strategies play an important role and include group cognitive training, based on structured tasks or activities with the aim of improving cognition through practice by **strengthening neural pathways** and training compensatory strategies, such as interventions geared at improving, restoring or maintaining mental function through structured, repetitive practice of tasks posing a **mental challenge or requiring the person to problem solve** *(McCormick CM et al., 2007).*

Grazie per l’attenzione