Nature and Extent of Cognitive Dysfunction in Cancer Survivors

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How prevalent is cognitive dysfunction in cancer survivors?

- 1/3 to 2/3 of patients report cognitive dysfunction (Joly et al., 2010)
- May be as high as 70% of survivors (Boykoff, et al. 2009)
- Frustrating
- Upsetting
- frightening

Survivor Perspective

- "you have to fight to make yourself remember numbers, words, places that you go. Sometimes I would leave the house to go somewhere and I really couldn't remember how to get there… it almost made me break down because of the fact that you think you are losing your mind"

Boykoff et al. 2009)

Impact of Dysfunction

- Diminished independence
- Limited ability to manage responsibilities
- Difficulty or inability to return to work or previous position/level of responsibility
- Early retirement
- Avoidance of social situations or reducing participation in social conversations
- Strain on family, friends

Boykoff et al. 2009)

Responses from Medical Community

- Lack of acknowledgement to denial from medical community of the existence of cognitive dysfunction
- Agreement that cognitive impairment exists but stating that 'everything will be fine'
- Attributing changes to age, menopause
- Lack of knowledge on how to manage symptoms

Boykoff et al. 2009)

FACT-Cog

- My memory is as good as it has always been
- I have forgotten names of people soon after being introduced
- Words I wanted to use seemed to be on the "tip of my tongue"
- My mind is as sharp as it has always been
- My thinking is as fast as it has always been
- I have had trouble finding the right word(s) to express myself
- I have walked into a room and forgotten what I meant to get or do there
- I have been able to bring to mind words that I wanted to use while talking to someone
- I have tried to do things (like writing lists or keeping a calendar) so these problems would not interfere
- I have had trouble forming thoughts
- I have had to use written lists more often than usual so that I would not forget things

Jacobs et al. (2007)

FACT-Cog

- Hematopoetic stem cell transplant N= 101
- Age= 52 years, Ed= 13.8
- F.u. 6 – 12 months post transplantation
- FACT-cog and neuropsych assessment
  - No relationship between FACT-cog and neuropsych results (except for other noticed)

Cognition and Breast Cancer studies

- Early studies indicated cognitive impairments might be very common (Reid- Arndt, 2006)
- Attention and Memory
  - Cross sectional
  - Self-report
  - Small sample sizes, selective sample sizes
  - Brief batteries, no baseline
- Self reported impairments correlate with subjective reports of distress more than objective performance deficits, both prior to and after chemotherapy (Cimprich et al, 2005 & Vandam et al, 2004)
- Restricted conclusions

Cognition and Breast Cancer studies

- Attention and processing speed (digit span, digit symbol)
- Visual and verbal memory (WMS-LM, RVLT)
- Executive Functions (Trails B, Stroop)
- Meta-analysis indicated largest effects were for verbal memory and executive functions (c. Anderson-Hanley et al., 2003)

Areas of Cognitive Domain

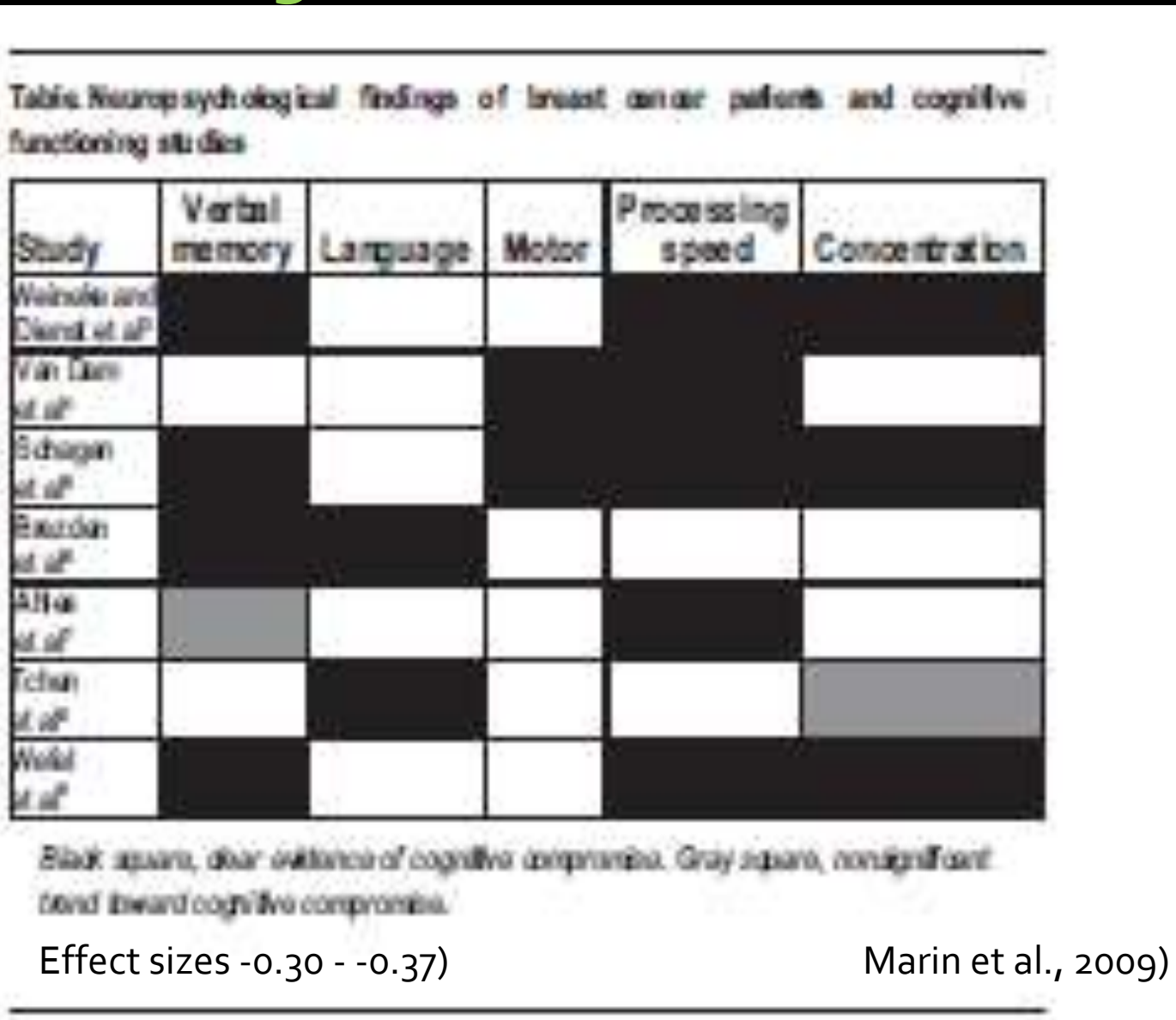


Table. Neuropsychological findings of breast cancer patients and cognitive functioning studies

Study	Verbal memory	Language	Motor	Processing speed	Concentration
Weinstein and Dierkes et al[a]					
Van Dam et al[b]					
Schagen et al[c]					
Brezden et al[d]					
Allen et al[e]					
Tchen et al[f]					
Wefel et al[g]					

Black squares, clear evidence of cognitive compromise. Gray squares, nonsignificant trend toward cognitive compromise.

Effect sizes -0.30 - -0.37) Marin et al., 2009)

Cognition and Breast Cancer studies

Duration ?

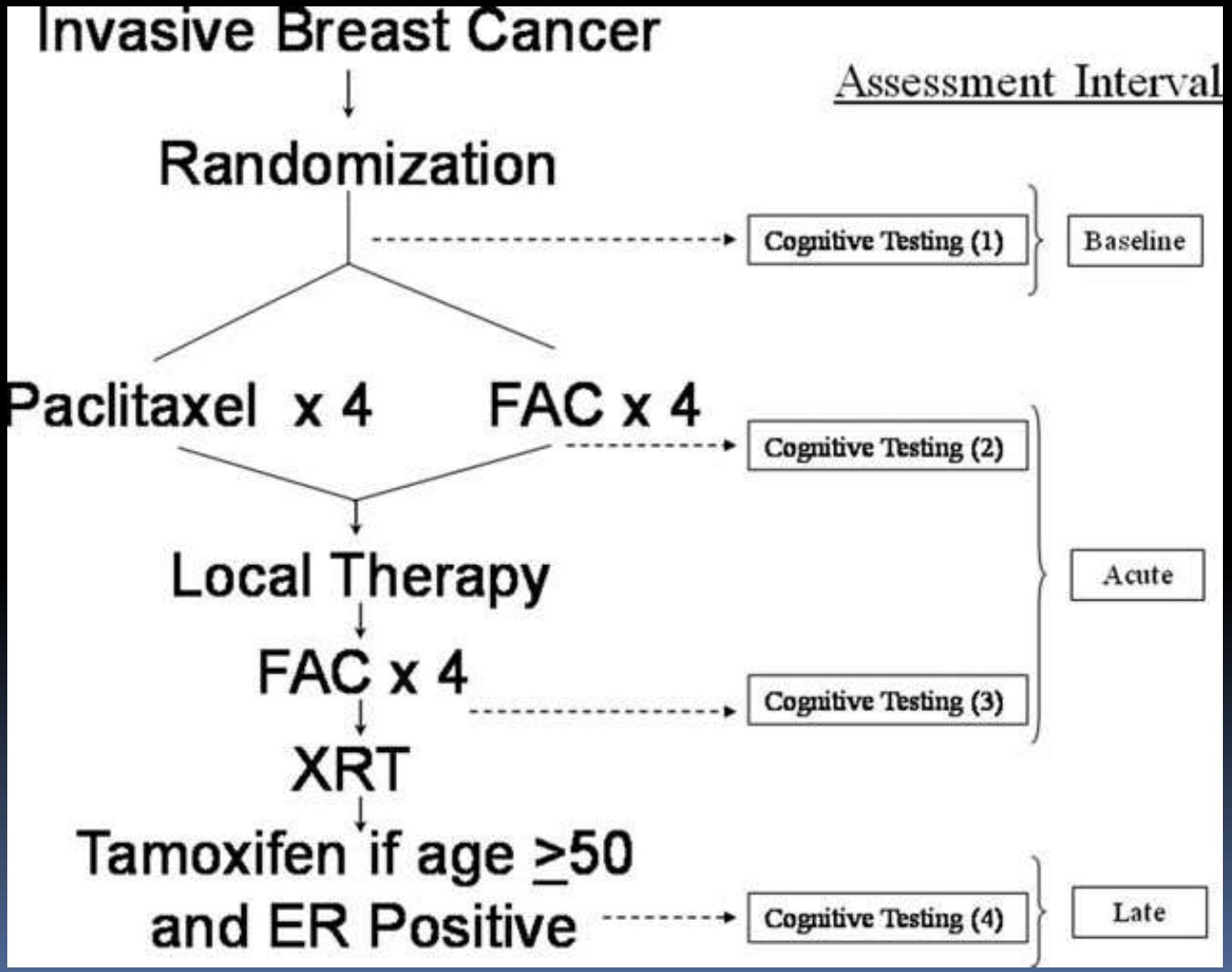
- Some studies indicate continued cognitive impairments 5 – 10 years post chemotherapy (e.g. forgetfulness, increased distractibility, problems concentrating) (Ganz et al, 2002; Ahles et al., 2002)
- Other studies indicate that cognitive impairments noted 2 years post treatment were no longer present 4 years post-treatment (Schagen et al, 2002)

Baseline Assessment

- 35 % of breast cancer patients (N=84) evaluated after needle biopsy or surgery prior to chemotherapy demonstrated cognitive impairments (Wefel et al., 2004)
- A subsequent longitudinal study (N=18) of breast cancer patients found 33% of patients with cognitive impairment prior to chemo, 61% at 6mos post chemo., 50/50 decline/improve at 18 months (Wefel et al., 2010)

Cognitive Impairment in Breast Cancer

N=42



Wefel et al., 2010

Cognitive Impairment in Breast Cancer

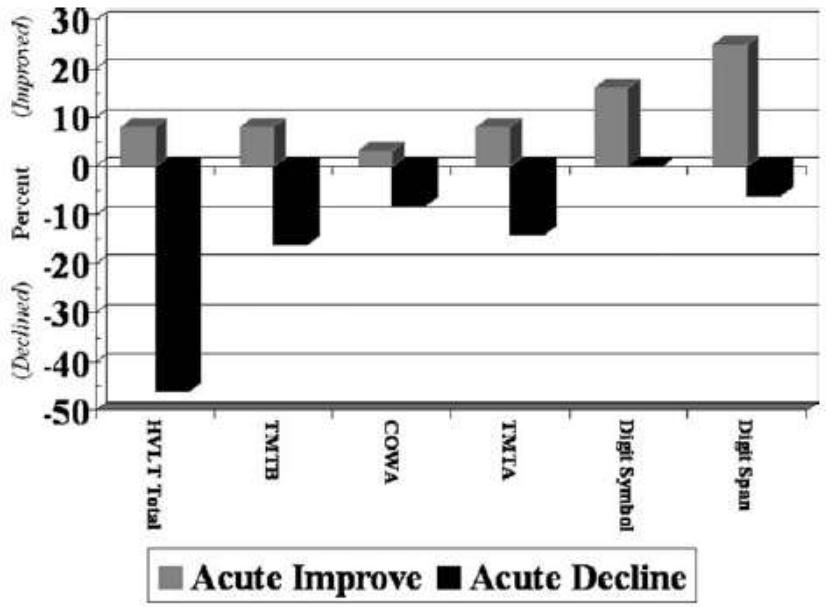


Figure 3. The frequency of acute treatment-related changes in cognitive function based on the practice effect adjusted reliable change index is depicted.

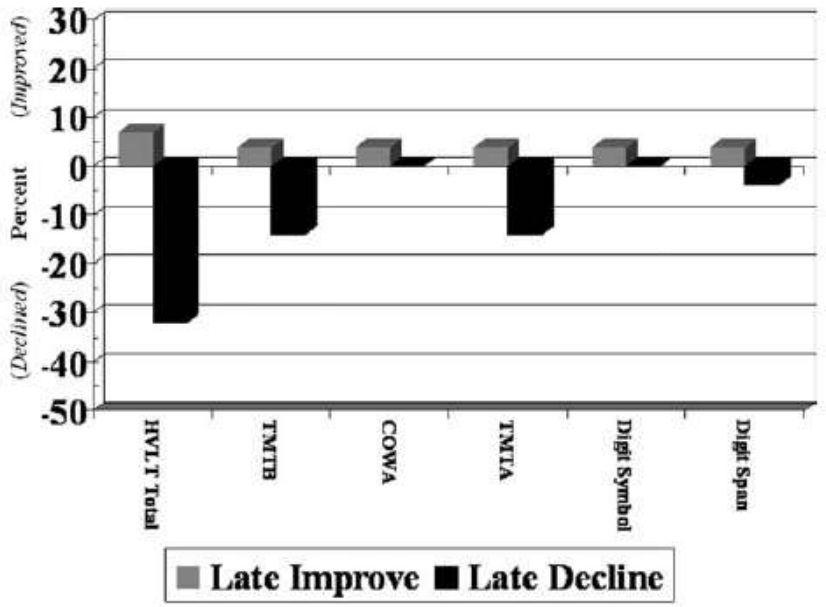


Figure 4. The frequency of late emerging changes in cognitive function based on the practice effect adjusted reliable change index is depicted.

Wefel et al.,2010

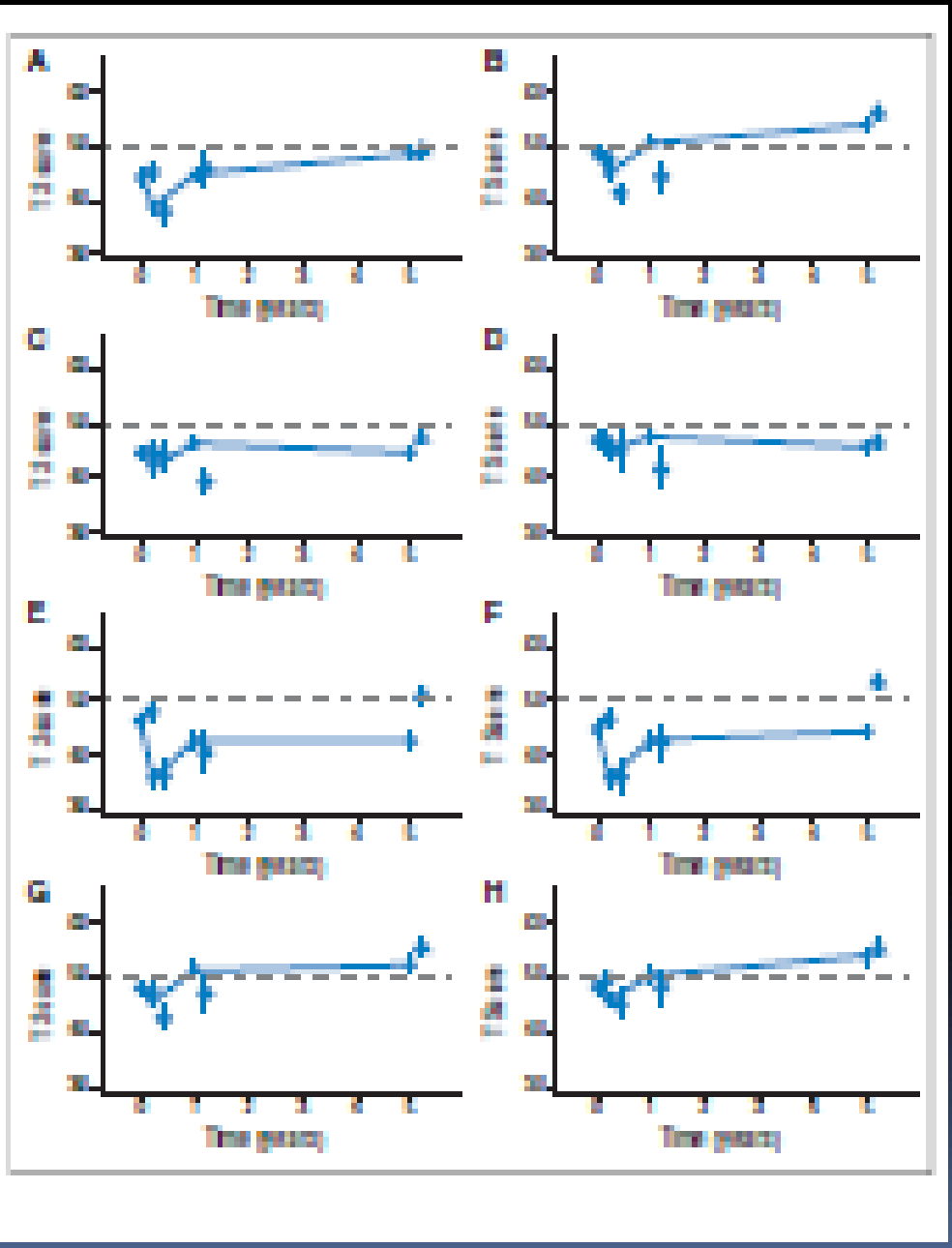
Duration of cognitive impairment?

Duration of cognitive impairment?

- Uknown-
- Some studies suggest lasting impairments for many years- up to 20 years
- Study of N=1,300 (18mos) N=1,059 (36 mos) Chinese women BCA, mid 50s: logical memory, verbal fluency, stroop.
  - Improvements observed at 18mos and 36 mos post treatment. Older age, lower ed assoc. with less improvement on verbal fluency. (Zheng,2014)

Duration of cognitive impairment?

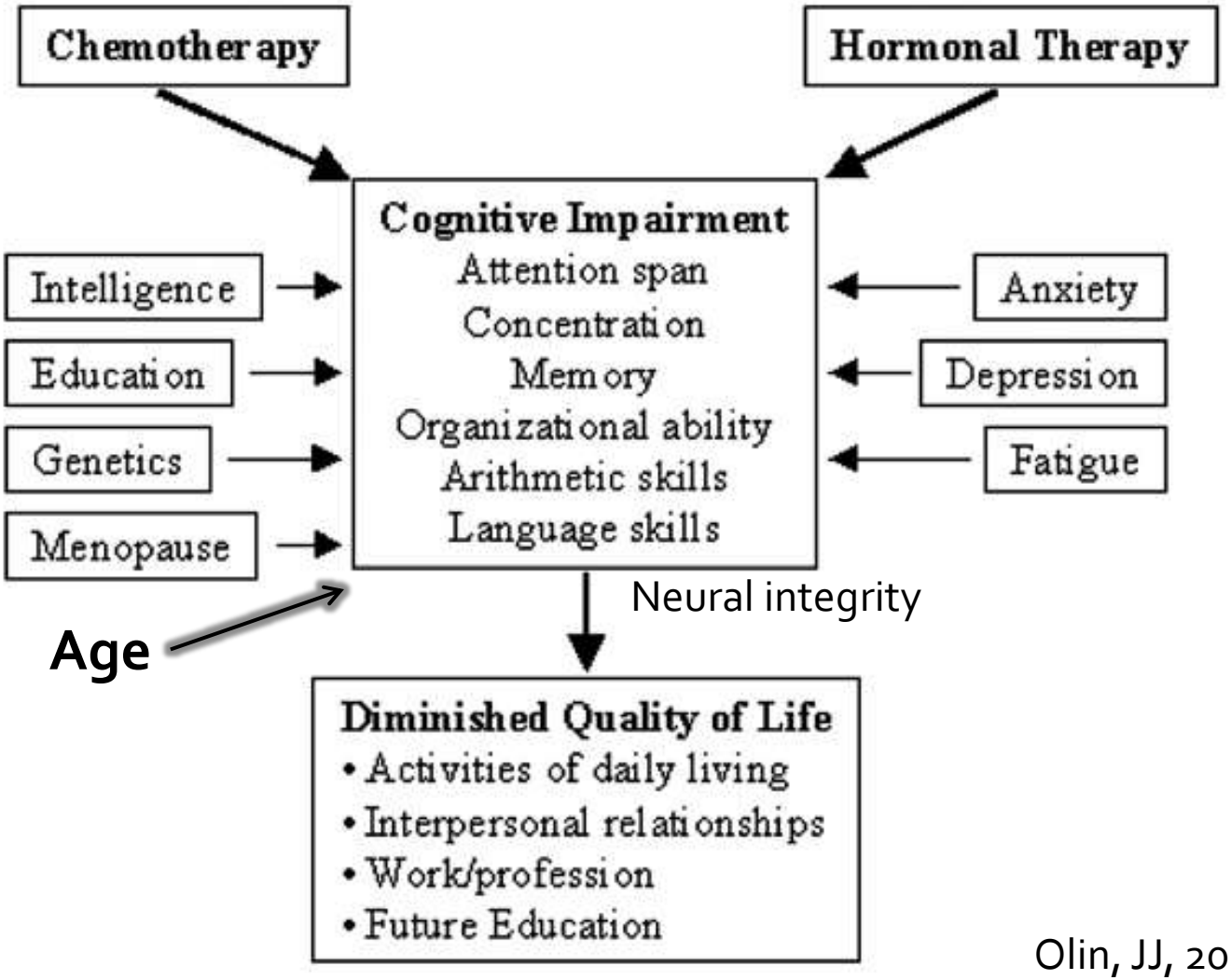
- Neurocognitive function of Hematopoetic cell transplantation -followed for 5 years
  - N=92 survivors tested 80 days, 1 and 5 years post-transplant with controls tested at same intervals
  - Follow up patients continued to show improvement up to 5 years post transplant in all areas except for motor dexterity and a small effect for verbal recall



A. COWAT
B. DSST
C. HVLT
D. HVLT- delay
E. Grooved Pegboard dom.
F. Grooved Peg. Non-dom
G. Trails A
H. Trails B

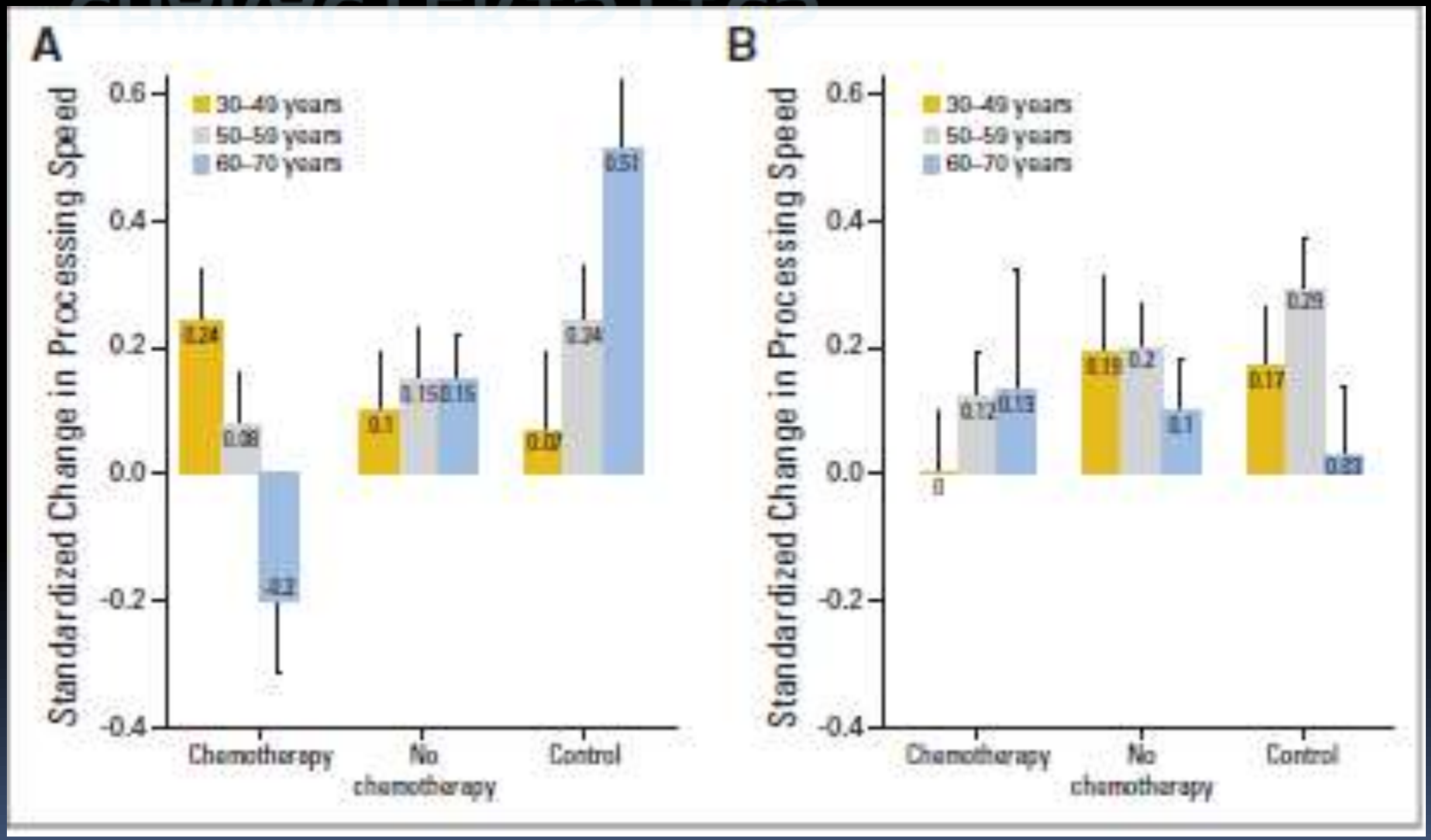
Syrjala et. al, 2011

Variables to be considered



Olin, JJ, 2001)

PRE-MORBID/ BASELINE CHARACTERISTICS



N= 39 control, N=46 chemotherapy, N=64 no chemo)

(Ahles et al., 2010)

Impairment of cognitive function in Breast cancer: High Dose vs Standard Dose

Table 6. Percentage of patients with deviant neuropsychologic test scores

No. tests failed (impairment determination)†	Treatment group* CTC (n = 34) No. (%)‡	FEC (n = 36) No. (%)	Control (n = 34) No. (%)
0–2 (not impaired)	23 (68%)	30 (83%)	31 (91%)
≥3 (impaired)	11 (32%)	6 (17%)	3 (9%)
		Chi-squared test:	$P = .043$§

Van Dam et al., 1998

Table 1
Summary of animal research investigating the effect of chemotherapeutic treatment on cognition.

First author	Cytostatic(s)	Animals[a]	Cognitive assessment	Cognitive outcome	Comments
Alkylating agents					
Konat	Cyclophosphamide + doxorubicin	Female Sprague-Dawley rats (10 months old)	Passive avoidance + open field	Impaired passive avoidance learning	No effect on anxiety behavior
Lee	Cyclophosphamide or 5-fluorouracil	Female Fischer-344 rats (young seven months and aged 18 months)	MWM + Stone 14-unit T-maze	No impairment	Transient improvement in MWM and Stone 14-unit T-maze seven to nine weeks post treatment
Macleod	Cyclophosphamide + doxorubicin	Female ovariectomized Sprague-Dawley rats (eight weeks old)	Cued and contextual fear conditioning	Impaired contextual fear memory	No effect on cued-fear or acquisition of fear response
Mondie	thioTEPA	Male C57BL/6J mice (five weeks old)	NOR + OLR	Impairment in NOR and OLR	No effect on depressive behavior
Reiriz	Cyclophosphamide	Male CF1 mice (70–90 days old)	Step-down inhibitory avoidance	Impaired inhibitory avoidance	No effect on anxiety behavior
Yang	Cyclophosphamide	Male ICR mice (8–10 weeks old)	Passive avoidance + NOR	Impaired passive avoidance learning Impaired NOR	
Cisplatin and analogues					
Fardell	Oxaliplatin + 5-fluorouracil	Male Sprague-Dawley rats (nine weeks old)	MWM + NOR + fear conditioning	Impairment in MWM, NOR and contextual fear memory	No impairment in cued-fear memory
Antimetabolites					
Elbeltagy	5-Fluorouracil	Male Lister-hooded rats (150–170 g)	Fear conditioning + OLR	Impairment in recall of fear conditioning memory and OLR	
Foley	Methotrexate + 5-fluorouracil	Male Swiss-Webster mice (20–35 g)	Operant conditioning	Combined MTX + 5-FU impair acquisition and retrieval of an operant response	No impairment due to MTX 5-FU failed to impair operant conditioning except at high doses
Gandal	Methotrexate + 5-fluorouracil	Male C57BL/6Hsd mice (seven to eight weeks of age)	Contextual fear conditioning + NOR	No impairment in NOR	Increased freezing during test of fear conditioning
Li	Cytosine arabinoside	Male Sprague-Dawley rats (200–250 g)	MWM	Impairment in remote recall of MWM	No impairment in MWM learning or recent recall
Li	Methotrexate	Male Long-Evans rats (12 weeks old) and young female and male Long-Evans (two weeks old)	NOR + OLR	Impaired OLR	No impairment in NOR + open field activity
Madhyastha	Methotrexate	Male Wistar rats (four months old)	Conditioned avoidance test	Impaired conditioned avoidance learning and memory	No effect on anxiety behavior
Mustafa	5-Fluorouracil	Male Lister-hooded rats (200–250 g)	OLR	Subtle impairment in OLR	
Seigers	Methotrexate	Male Wistar rats (three months old)	MWM + NOR + contextual fear conditioning	Impairment in MWM and NOR after MTX When trained prior to MTX treatment, impairment in MWM and fear conditioning memory	
Sieklucka-Dziuba	Methotrexate	Male and female Albino Swiss mice (20–25 g)	Passive avoidance task	Impaired passive avoidance learning	
Stock	Methotrexate	Male and female Sprague-Dawley rats. MTX treatment at 17 days old. Behavioral testing at 80 days old	Appetitive Pavlovian discrimination + conditioned taste aversion	No impairment in either appetitive or aversive conditioning	
Yanovski	Methotrexate	Male and female Lewis-inbred rats. MTX treatment at 16–17 days age. Behavioral testing at 12–14 weeks old	Conditioned emotional response + conditioned taste aversion	Impaired conditional emotional response learning Impairment in conditioned taste aversion acquisition	
Winocur	Methotrexate + 5-fluorouracil	Female BALB/C mice (approximately two months old)	Spatial MWM, cued memory, discrimination learning, NMTS, dNMTS	Impairment in spatial MWM, NMTS and dNMTS	No impairment in cued memory or discrimination learning
Topoisomerase interactive agents					
Liedke	Doxorubicin	Male Wistar rats (180–350 g)	Inhibitory avoidance conditioning	Impairment of memory retention	
Sieklucka-Dziuba	Doxorubicin	Male and female Albino Swiss mice (20–25 g)	Passive avoidance task	No impairment	
Antimicrotubule agents					
Boyette-Davis	Paclitaxel	Male Long-Evans rats	Five choice serial reaction time task	No impairment	

Abbreviations – MTX: methotrexate; 5-FU: 5-fluorouracil; NOR: novel object recognition; MWM: Morris water maze; OLR: object location recognition; NMTS: non-matching to sample; and dNMTS: delayed non-matching to sample.
[a] Age and weight of animals where provided.

Animal Studies on effects Of Chemotherapeutic agents On cognition

(methotrexate, paclitaxel, 5-fluorouracil, cyclophosphamide)

Most but not all studies show Impairments in learning and memory

Seigers & Fardell (2011)

Mechanisms of Action

- Neurogenesis- cytostatics inhibit cell division
- Oxidative stress- (carboplatin, cyclophasphamide) and antioxidants block cog. Impairments when co-admin (Konat, 2008)
- 5-FU decreases myelin sheaths (speed of information processing)
- Inflammation – cytokines (MTX activates microglia, but no BZ receptor activity despite cog. Impairment) (Siegers, 2010)
- Blood flow – anti-angiogenic effect of cytostatic agents

Hippocampal blood vessel density decrease: methotrexate

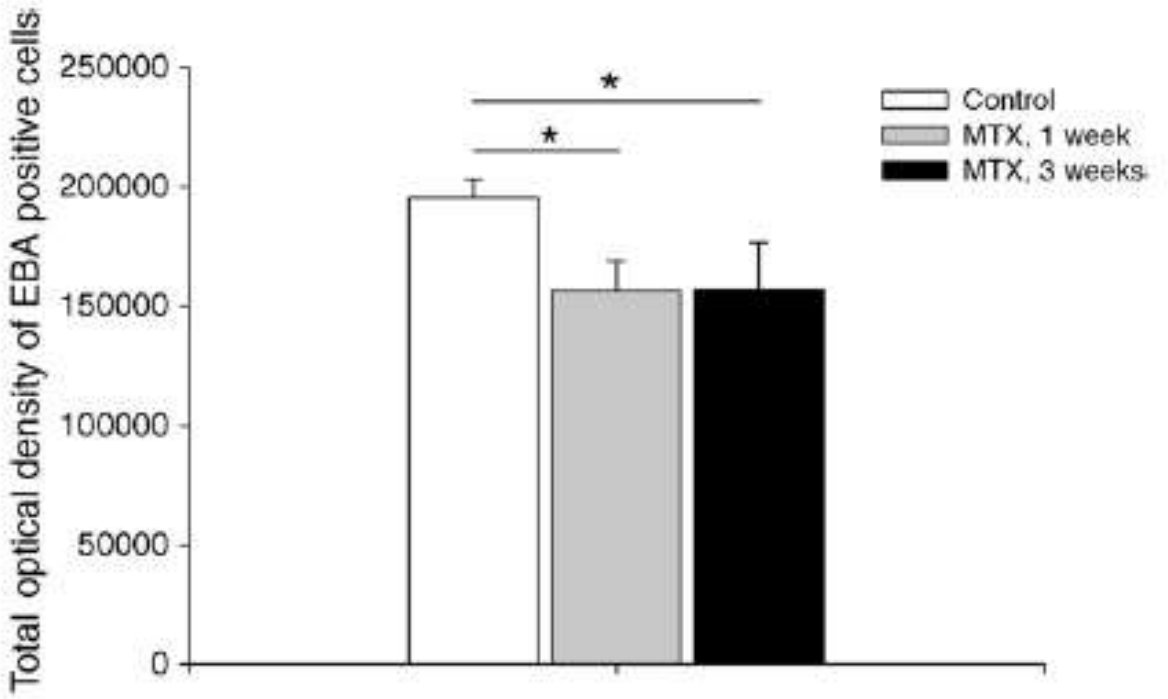


Fig. 2. Optical density of EBA-positive blood vessels in the dentate gyrus of the hippocampus of control rats (open bar, $n = 12$); animals treated with MTX, sacrificed 1 week after treatment (grey bar, $n = 8$); and animals treated with MTX, sacrificed 3 weeks after treatment (black bar, $n = 8$). One-way ANOVA revealed a significant group effect ($F_{2,26} = 3.747$, $P < 0.05$). Post-hoc test revealed that blood vessel density was significantly decreased in both MTX-treated groups (sacrificed 1 week or 3 weeks after treatment, $P < 0.05$).

(Seigers et al., 2010)

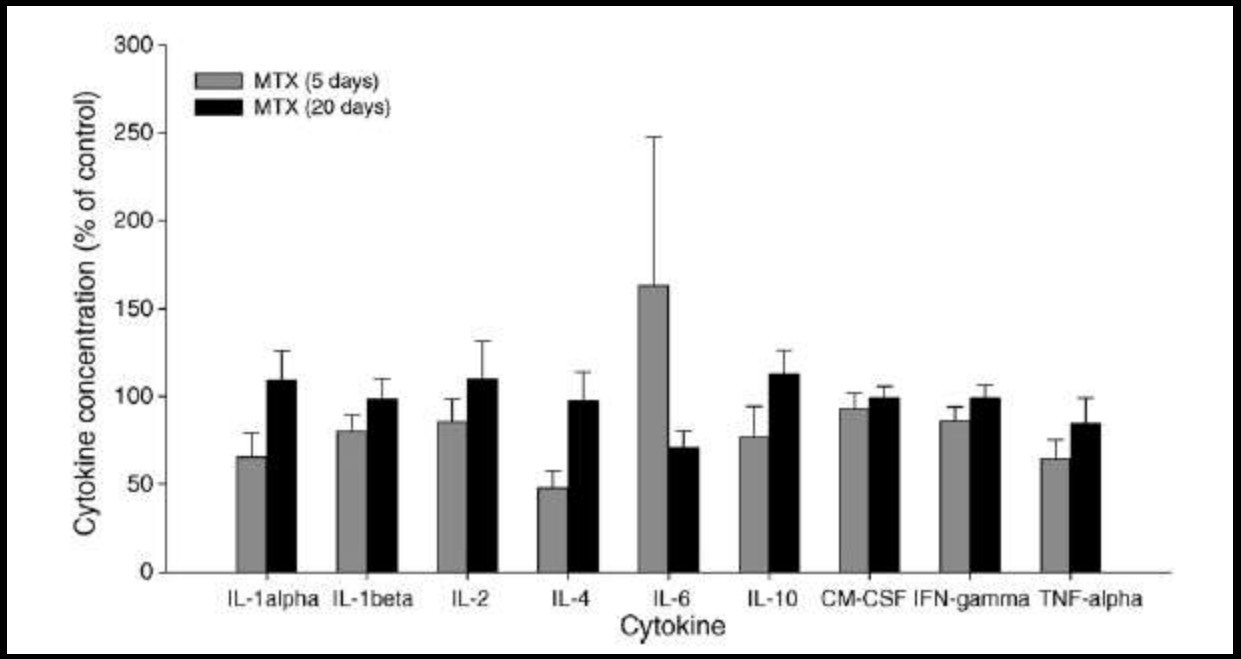


Fig. 10. Cytokine levels in hippocampal tissue from animals sacrificed 5 days after treatment with MTX (dark grey bar, $n = 8$), and 20 days after treatment with MTX (closed bar, $n = 8$). The cytokine levels of animals treated with MTX are represented as percentage of controls. MTX did not suppress the levels of any cytokine measured 5 days or 20 days after treatment compared to the levels in control animals.

FDG Altered frontal, cerebellar, BG, activity in Breast Cancer Survivors 5-10 yrs Post chemo

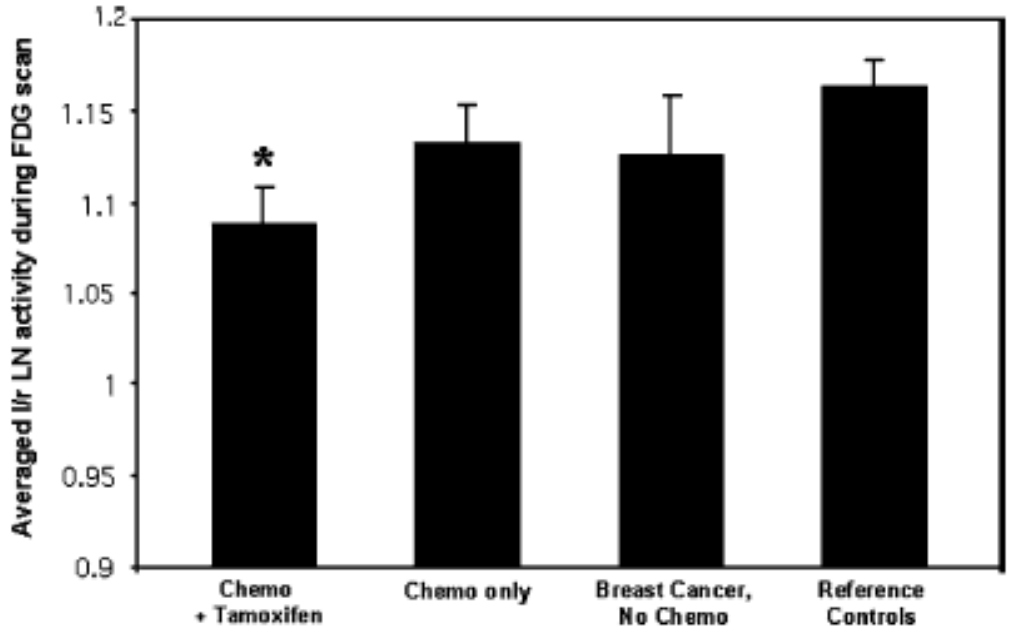
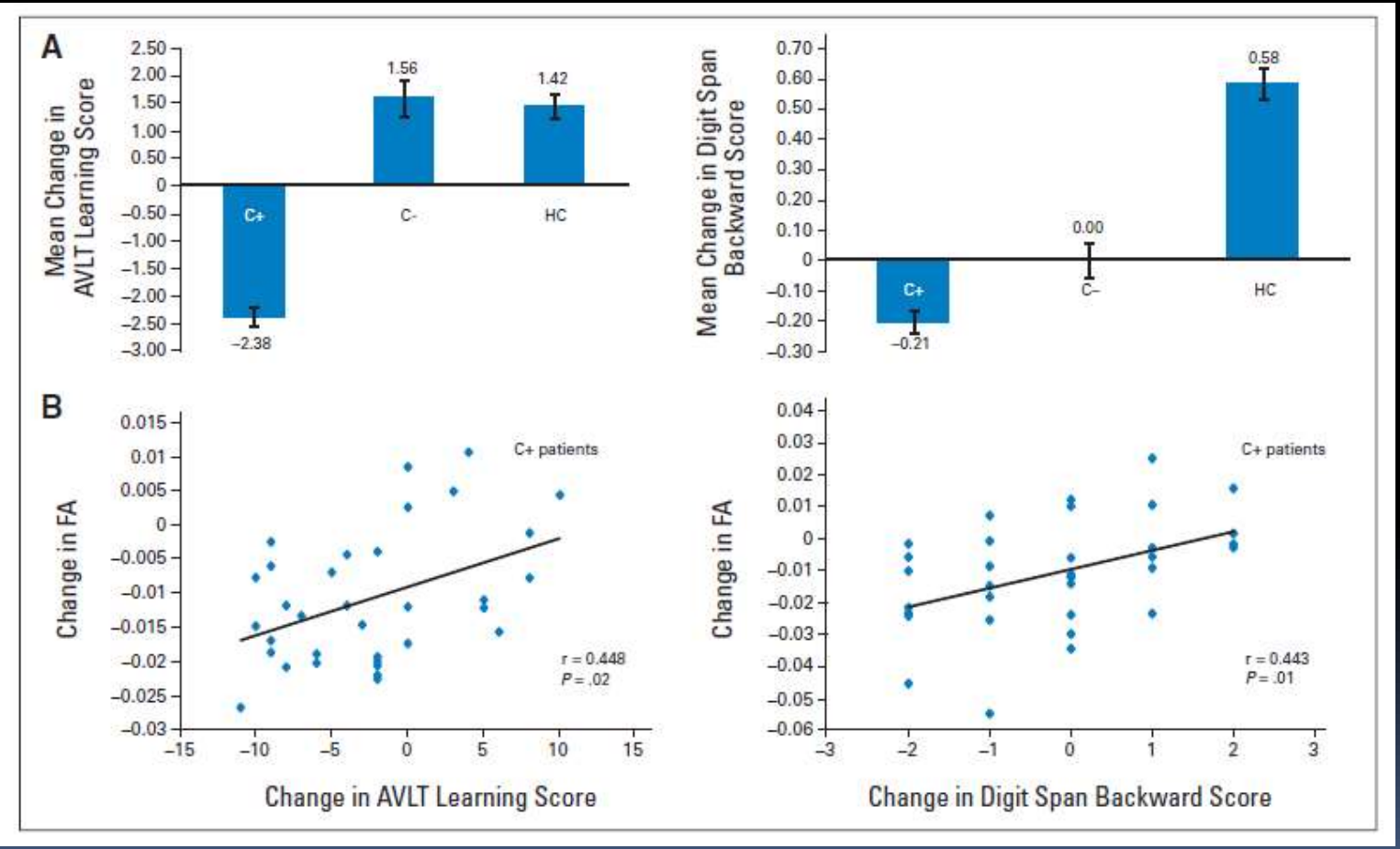


Fig. 3 Level of metabolism in lentiform nuclei (normalized to whole-brain activity) measured in subjects undergoing chemotherapy + tamoxifen therapy tended to be lower (by 7–8%, $P < 0.01$) than the level seen in all other control groups, including those subjects who received chemotherapy without tamoxifen, as well as those who received no chemotherapy for their breast cancer, and a reference group without chemotherapy or breast cancer

Silverman et al. 2006

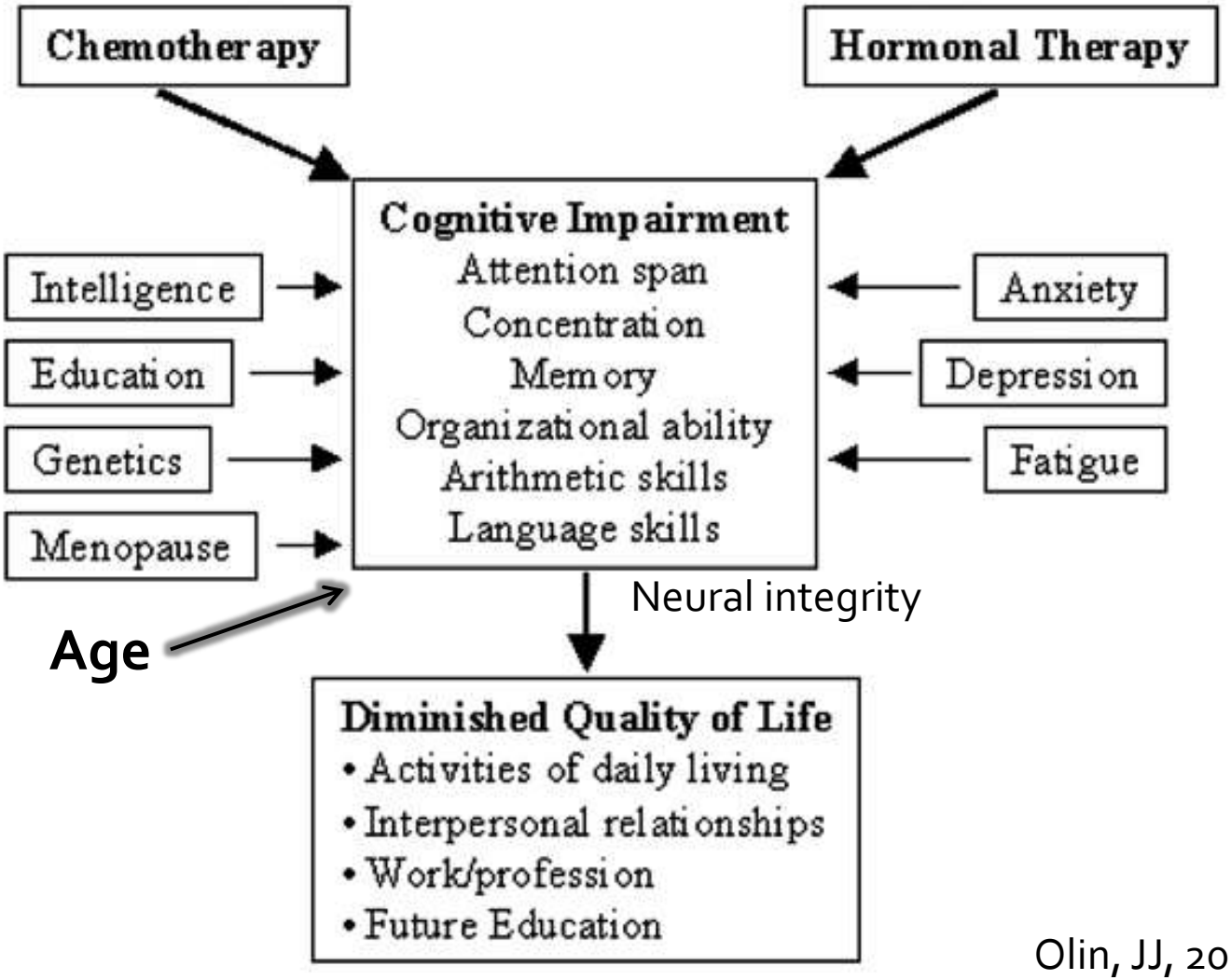
Pre/Post Chemotherapy Changes in White matter (DTI) in BCa



Parietal superior longitudinal fasiculus

Deprez et al. 2012

Variables to be considered



Olin, JJ, 2001)

Fatigue

- 75-96% of patients suffer from chemotherapy induced fatigue
  - Tiredness despite adequate rest or sleep
  - Lasts well beyond treatment period
  - Most common symptom
- Strong association between fatigue and perceived cognitive impairment
- Lack of association between fatigue and objective assessment

Anxiety & Depression

- Depression incidence in cancer patients (6% to 50%)
  - Depression rates generally improve (i.e. decrease) following treatment
  - Only patients with ongoing symptoms demonstrate high levels of depression
- Studies do not find an association between objective cognitive performance and depression/anxiety
- Studies do find an association between subjective perception of cognitive impairment and depression/anxiety

Hormone effects

- Pre-mature menopause
  - Human studies demonstrating cognitive changes associated with lack of estrogen
  - Animal studies showing impact on neuronal growth, branching & cognition with hormone withdrawal
- Hormone treatment
  - Aromatase inhibitors (anastrozol, letrozole,exmestane)
  - SERMS (tamoxifene, raloxifene)
  - Prostate cancer (androgen deprivation)

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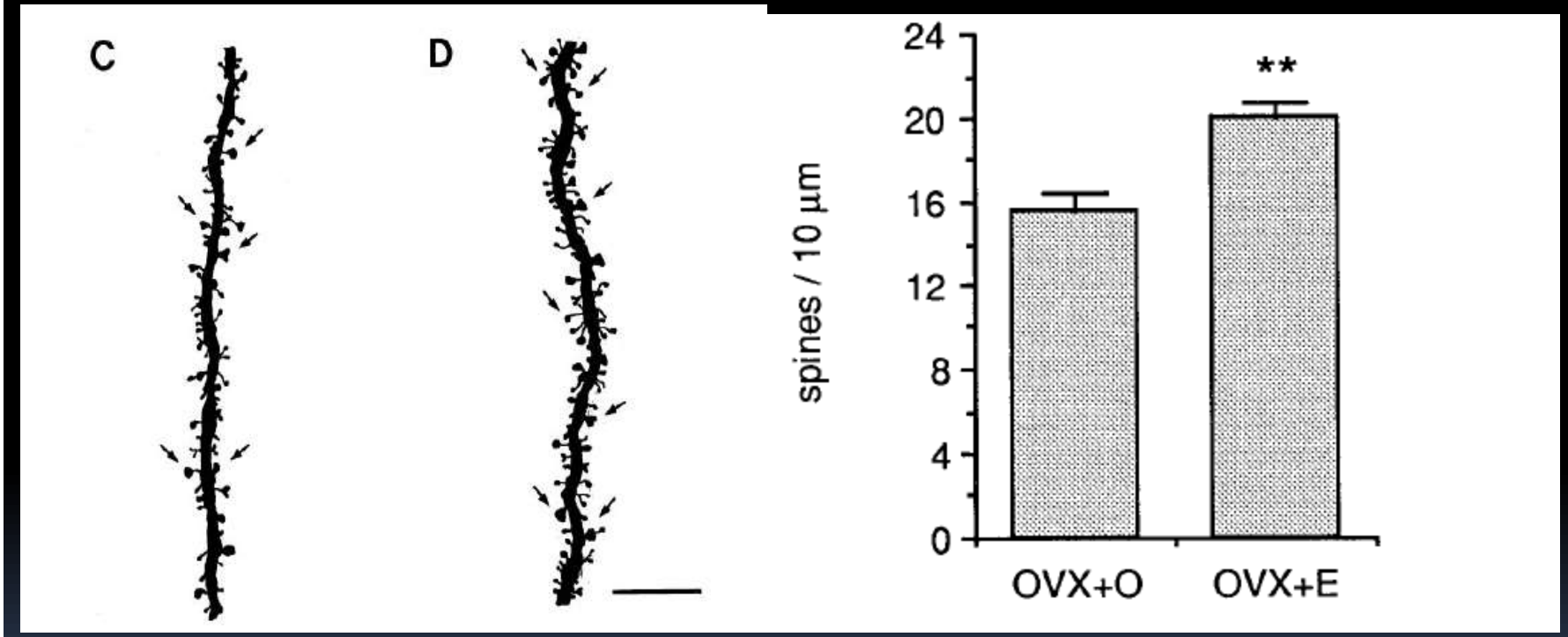
Cognitive changes with Endocrine therapy in Breast Cancer: SERMS

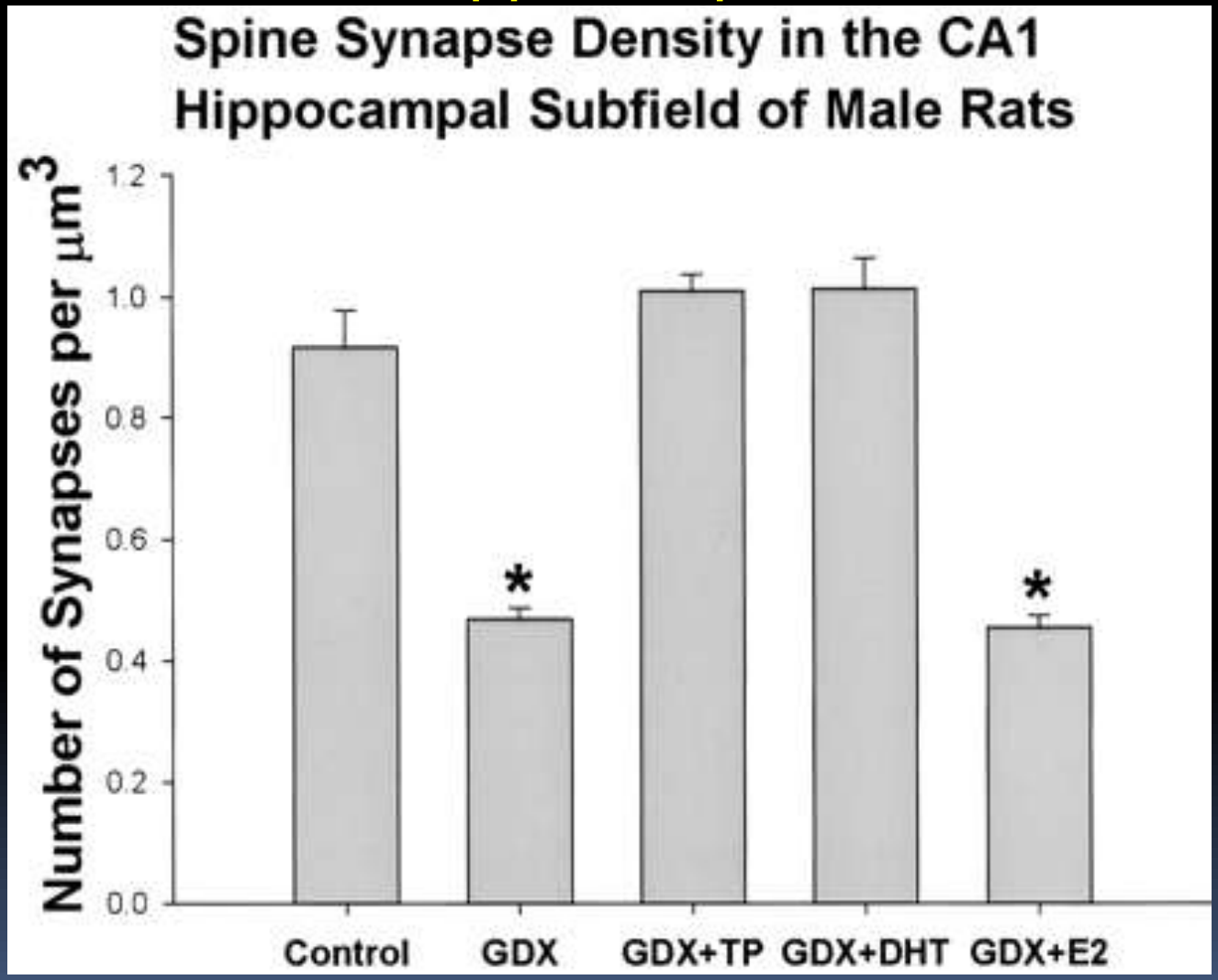
- MORE N=7478 No effect on cog. Fxn
  - Raloxifene, placebo
- CoSTAR N=1498 Cog. Testing similar in both groups
  - Tamoxifene, raloxifene
- P-1 N=13,388 little difference between groups
  - Tamoxifen, placebo
- TEAM & BIG studies show decline with tamoxifen

Estradiol increased spine synapse density



Wooley et al., 1997

Post GDX- Testosterone maintains synapses in hippocampus



Leranth et al., *J. Neurosci*. 2003

Cognitive changes with Endocrine therapy in Breast Cancer: AIs

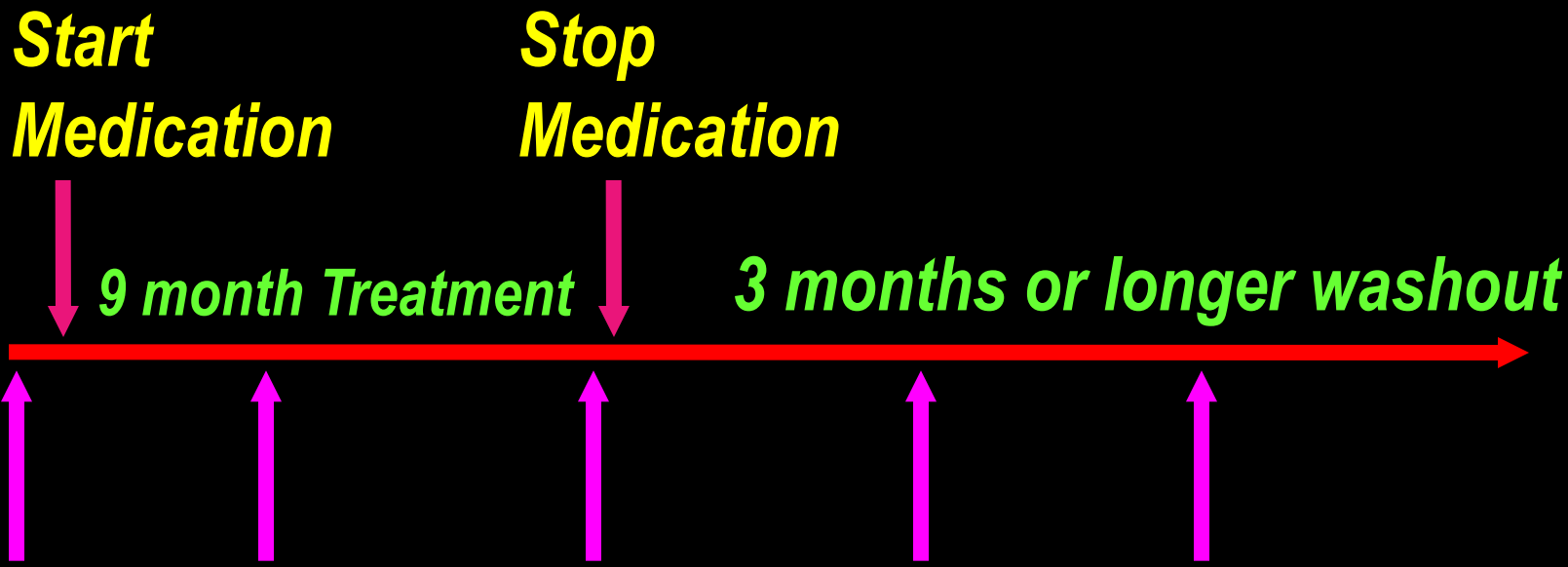
- Greater cognitive decline has been shown with anastrozole as compared to tamoxifen
- Lesser cognitive decline with exmestane and letrozole
- Studies vary with regard to sample size, methods

Intermittent Androgen Suppression (IAS)

Combined treatment:

- LHRH (GnRH) agonist – leuprolide acetate 7.5 mg IM injection every 4 weeks
  - Inhibits LH/FSH secretion from the pituitary
- Flutamide 250mg p.o. three times daily
  - Androgen receptor antagonist –competes w/ T/DHT for AR
- IAS cycles androgen withdrawal (6-9 months) with an "off treatment" period
- Treatment is reinstated as the prostate specific antigen (PSA) reaches a threshold

Study Design



Baseline Cognitive Testing & PET

Month 1 Cognitive Testing

Month 9 Cognitive Testing & PET

Month 12 Cognitive Testing

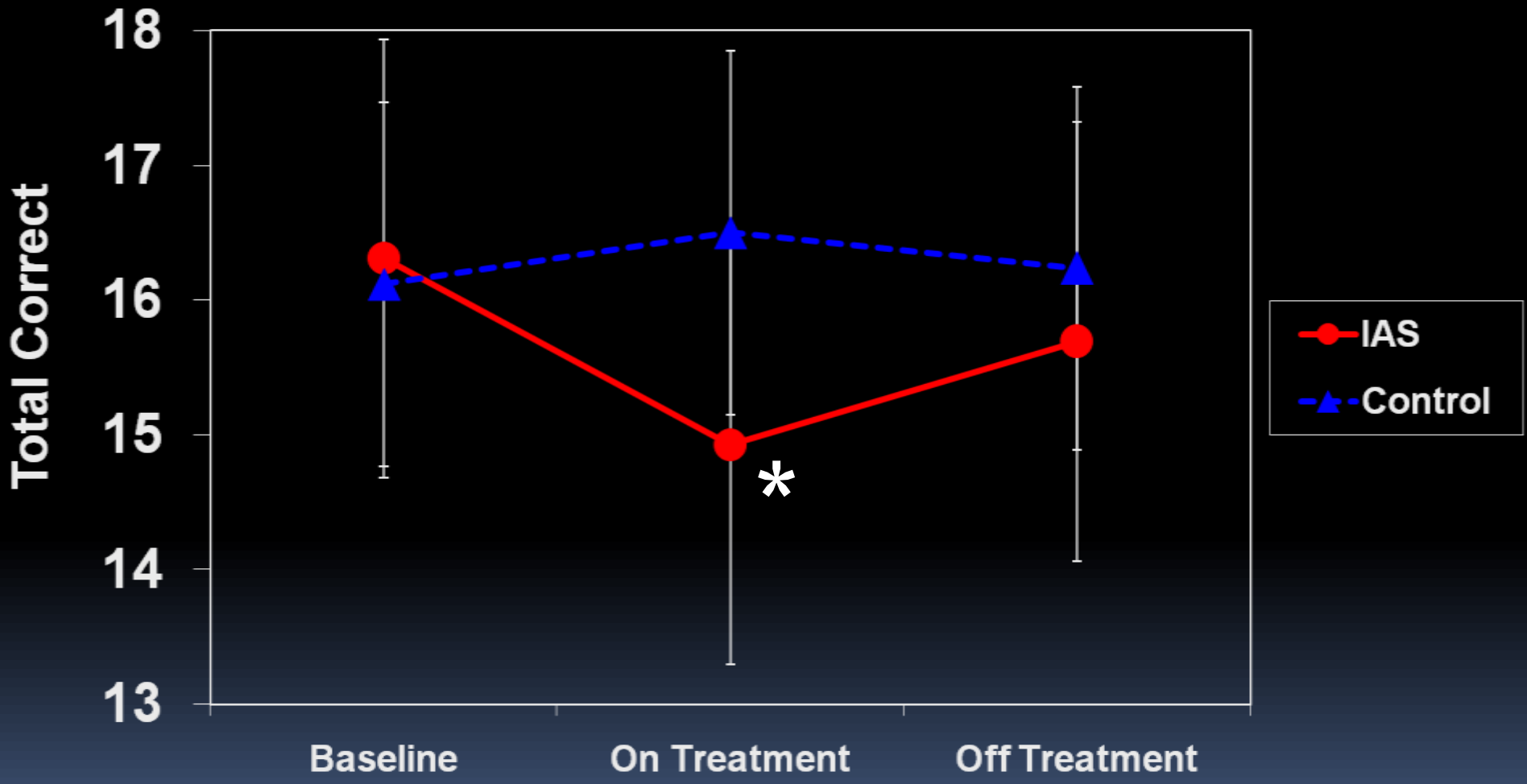
Re-start Medication If PSA rises

Pre-Baseline Cognitive Testing

Cognitive Battery

- Verbal memory- paragraph recall, proactive interference word list
- Spatial Memory- Route test
- Spatial abilities- Block design, Mental Rotation
- Executive Functions- verbal fluency, Stroop, SOPT

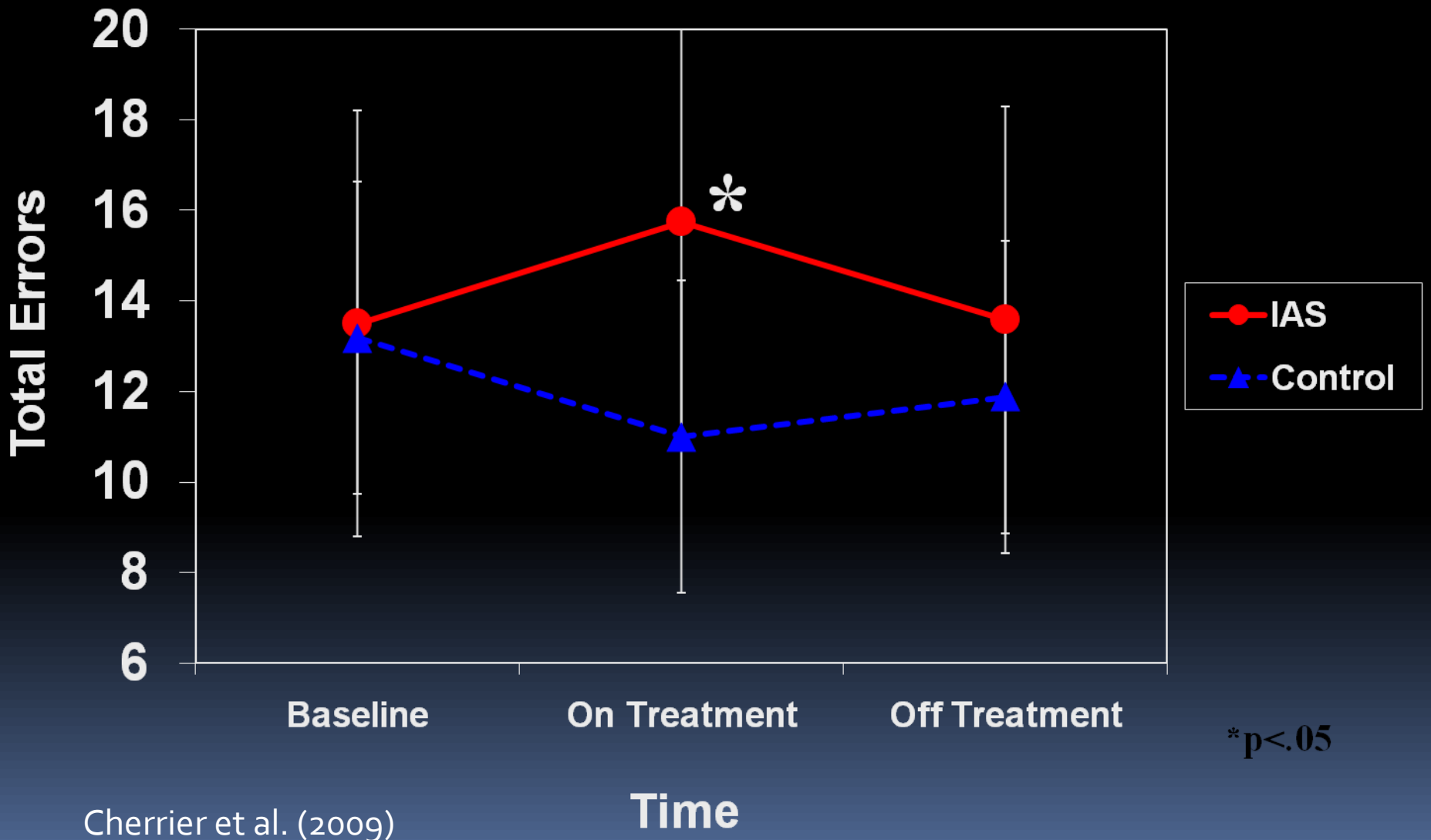
Mental Rotation



Cherrier et al. (2009)

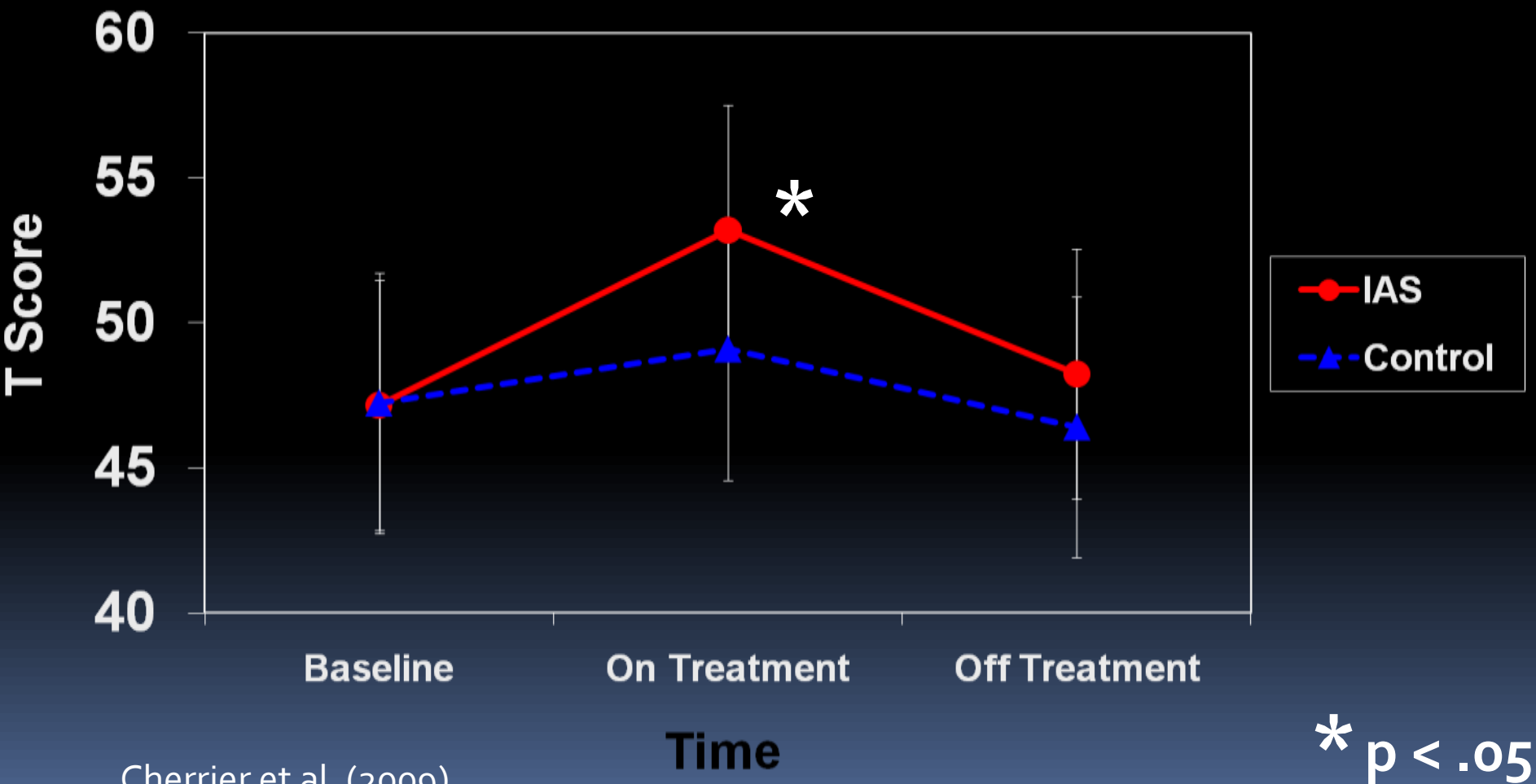
* $p < .05$

Self Ordered Pointing Task



Cherrier et al. (2009)

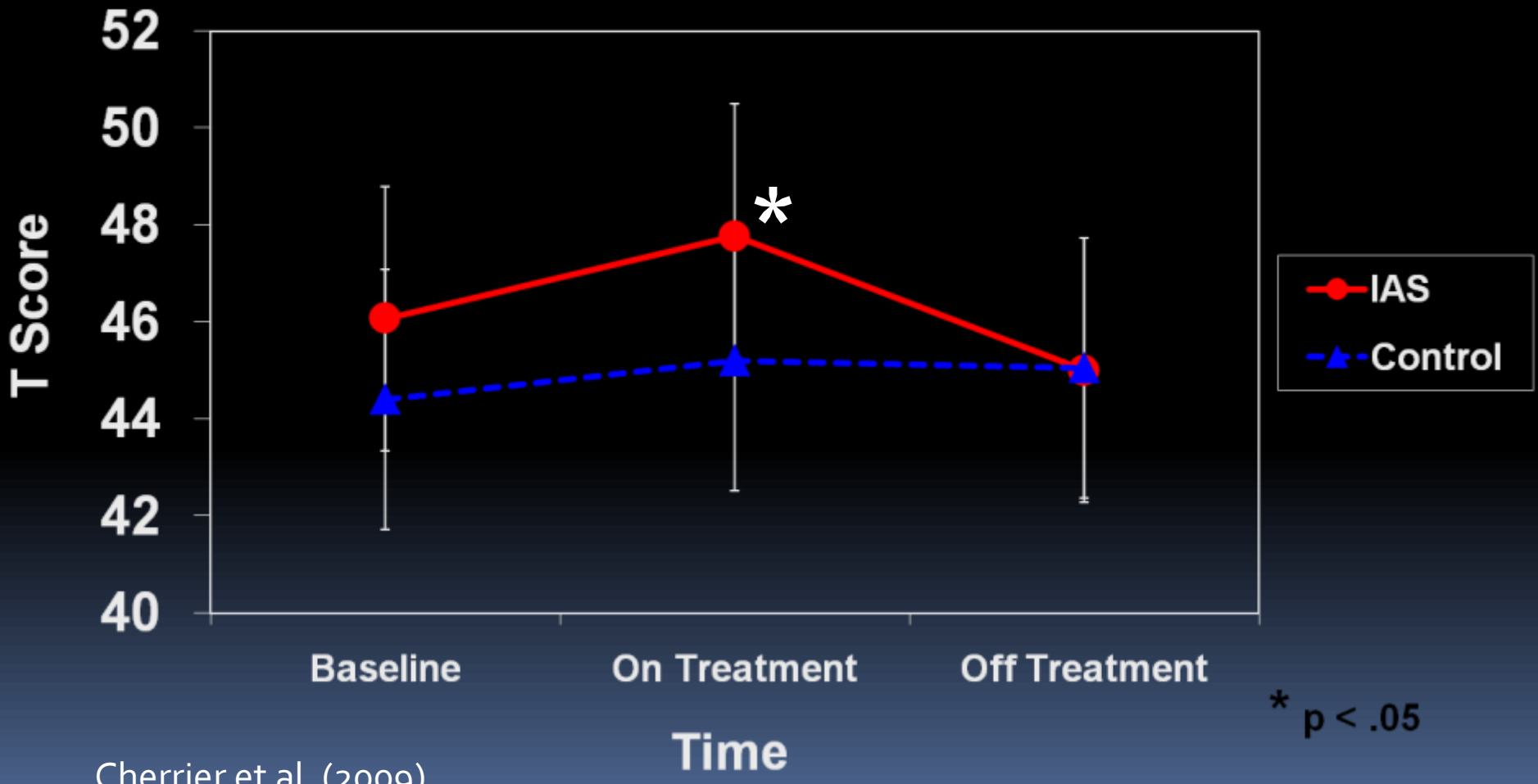
Profile of Moods State: Fatigue-Inertia



Cherrier et al. (2009)

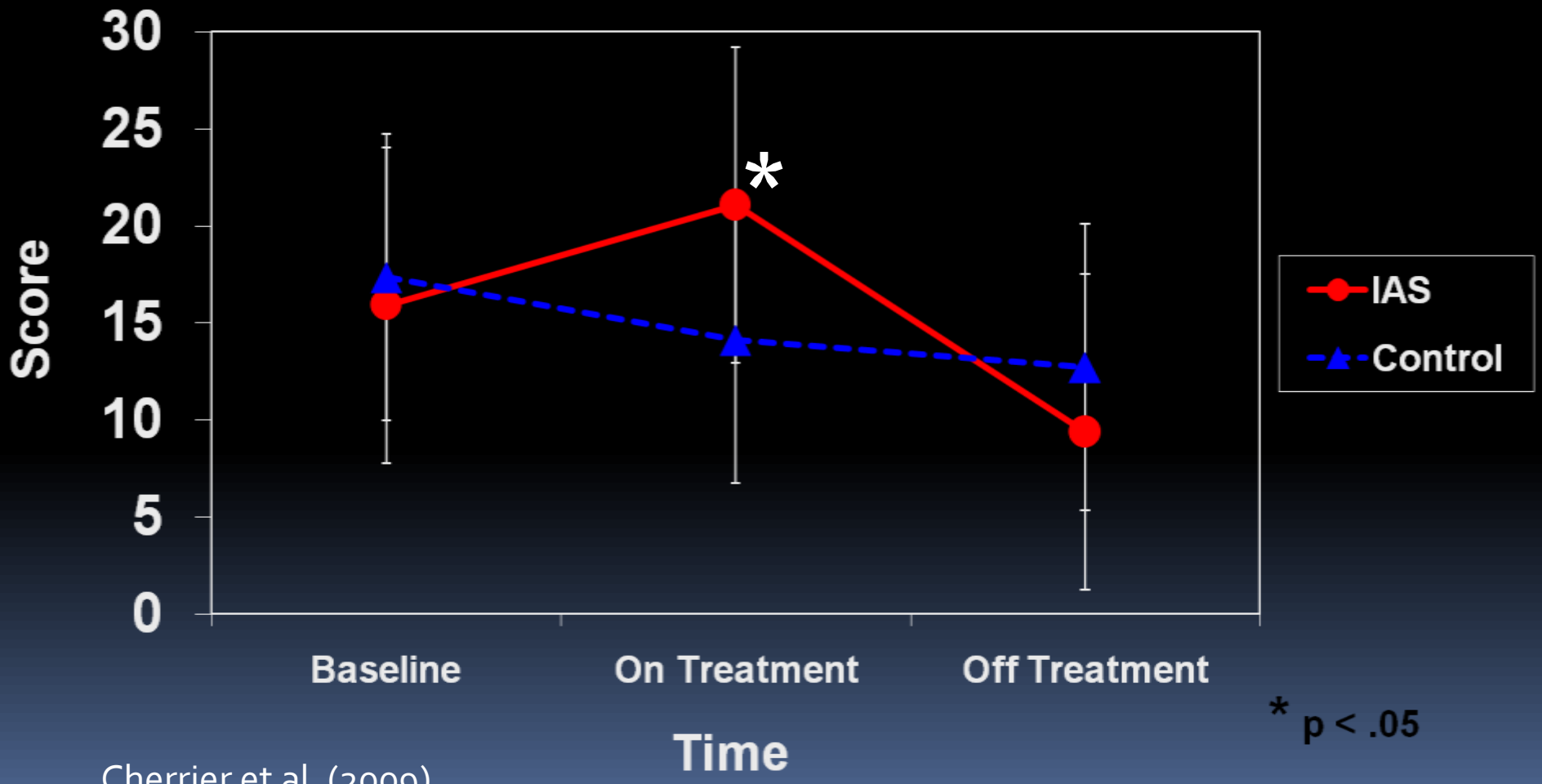
* $p < .05$

Profile of Moods State: Depression



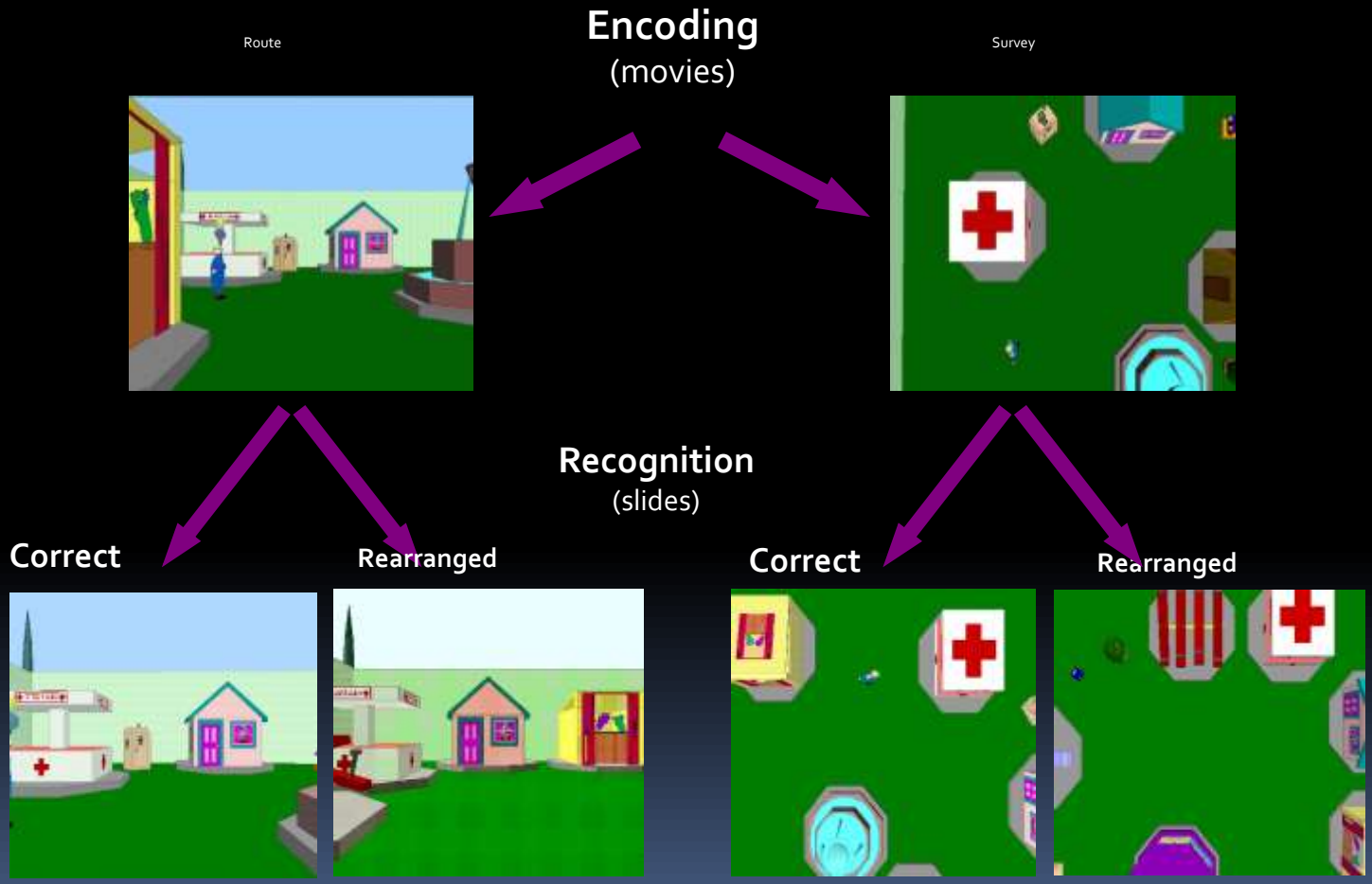
Cherrier et al. (2009)

Visual Analog Scale: Irritability



Cherrier et al. (2009)

Environmental Memory Task



Shelton et al, 2002, 2007)

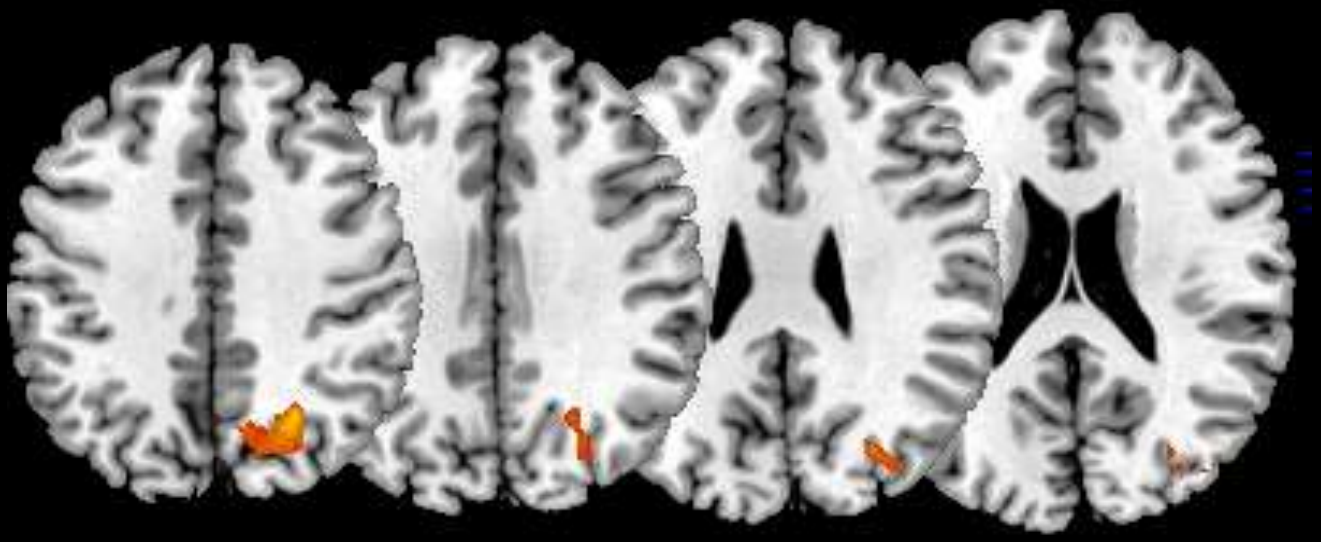


Fig. a (left) Region of reduced
Activation during Tx
Compared to baseline

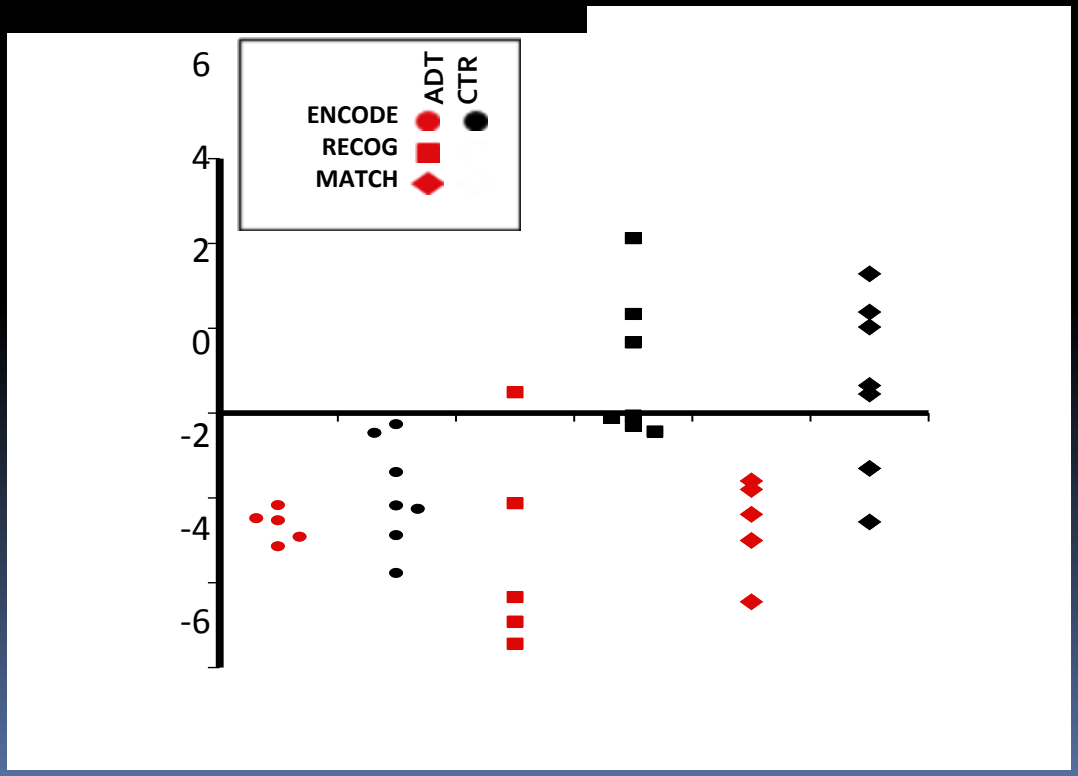
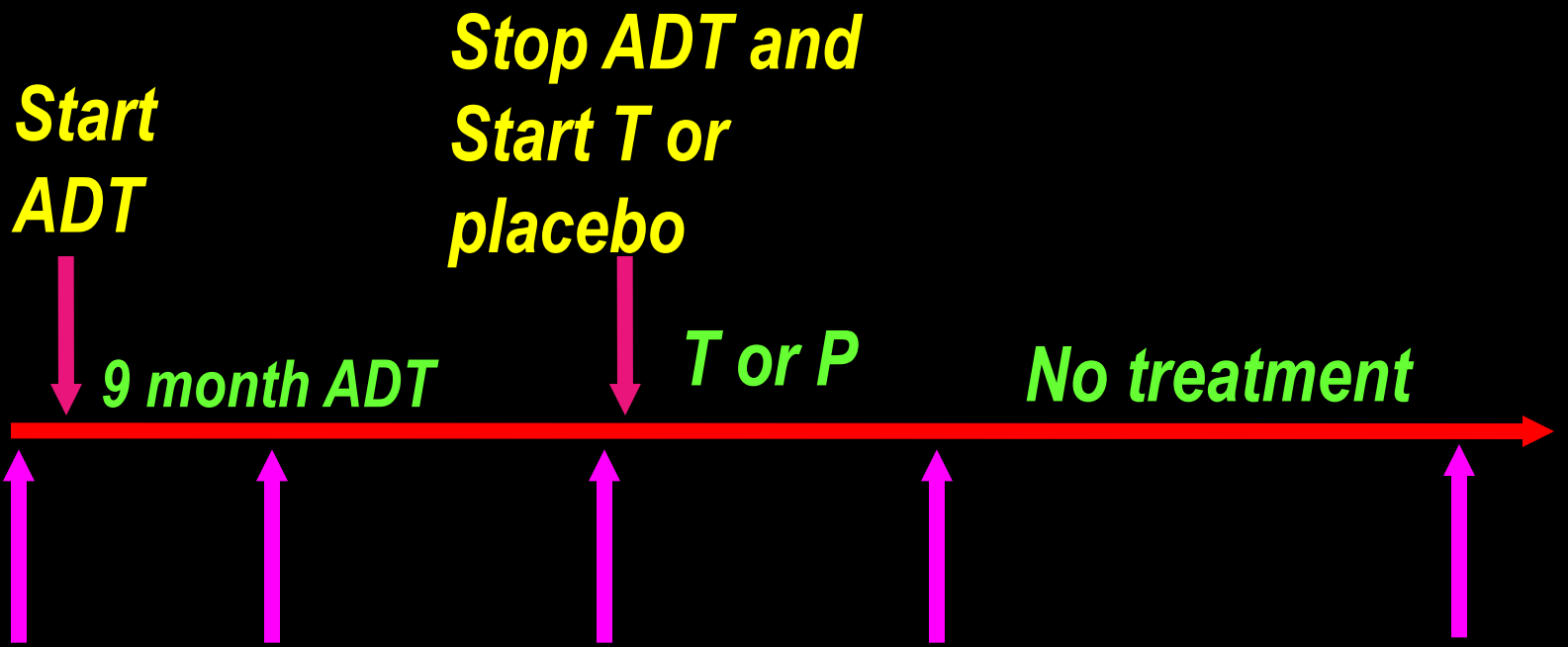


Fig. b (right) Difference scores (time2 – time1) for
Mixed effects GLM Z scores. Neg = decrease
Pos= increase
Encode- environmental memory Task
Recog- environmental memory Task
Match- mental rotation task

(Cherrier et al., 2009)

SCORE: Study Design



Baseline Cognitive Testing

Month 1 Cognitive Testing

Month 9 Cognitive Testing

Month 10 Cognitive Testing

Month 15 Cognitive testing

Pre-Baseline Cognitive Testing

How to treat cognitive dysfunction?

- Are there any other obvious medical or health conditions that can be addressed or treated?
  - Anxiety , Depression, fear of recurrence
  - Diabetes, heart disease, BMI/weight
  - Alcoholism, drug use, smoking
  - Sleep, sleep apnea, fatigue, anemia
- Psychosocial factors that need to be addressed? Stress
  - Work/life balance?
  - What was the previous baseline

Research findings on treatments:

- Very few published studies on interventions or methods to prevent or treat cognitive dysfunction in cancer
  - Historical literature in brain injury/rehabilitation
  - Other neurological disorders- multiple sclerosis, dementia/MCI, epilepsy
  - Childhood cancers

Pharmacological interventions

- Psychotropic medications
  - Depression
  - Avoid anti-anxiety medication (Benzodiazepines)
- Cognitive Enhancers
  - Cholinesterase inhibitors & AD medications
  - Gingko
- Statins & anti-inflammatory
- Stimulants- ADHD
  - Methylphenidate study neg. for BC (lower et al., 2009)
- Eythropoeitin (evidence neg for cancer)
- Vitamins

Modafinil

- Medication for 'narcolepsy' improves attention and alertness, unique CNS stimulant
- Advanced cancer patients N=28 with high fatigue, 4 days on placebo vs modafinil then crossover (Lundorff et al., 2009)
  - Psychomotor speed & sequencing (TMT) improved as well as depression and drowsiness
- BC patients with fatigue N=68 22 months post tx, four weeks on modafinil then cross over to m or placebo (Kohli et al., 2009)
  - Improved on a computerized test of attention and memory

Cognitive Rehabilitation

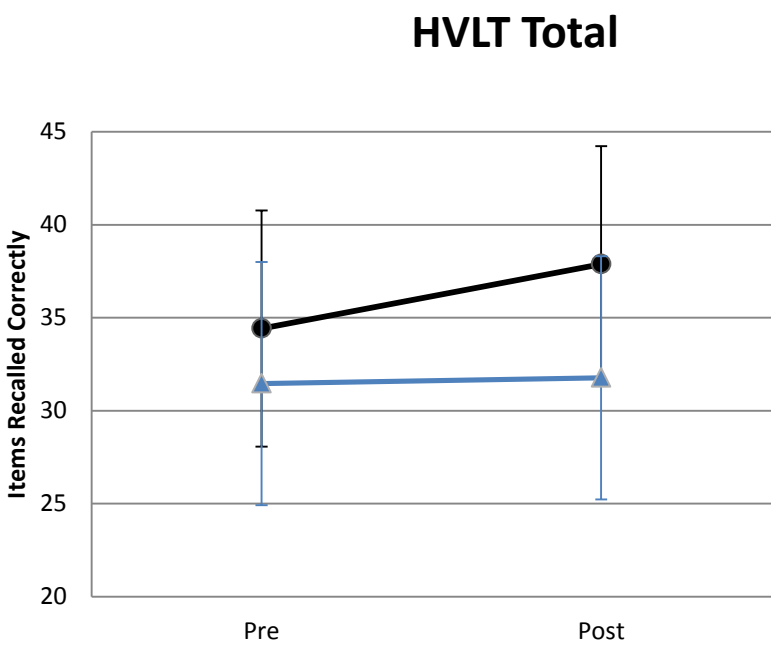
- Some evidence of intervention success in children (Butler et al.)
- Memory and Attention Adaption Training (MAAT)
  - N=29 BC three years post Tx , complaints of memory and attention problems (Ferguson, 2007)
  - 4 individual monthly visits with phone contact (education, relaxation, schedule, workbook)
  - Improvement in self report and Neuropsych measures post TX, & 2 and 6 months f.u.

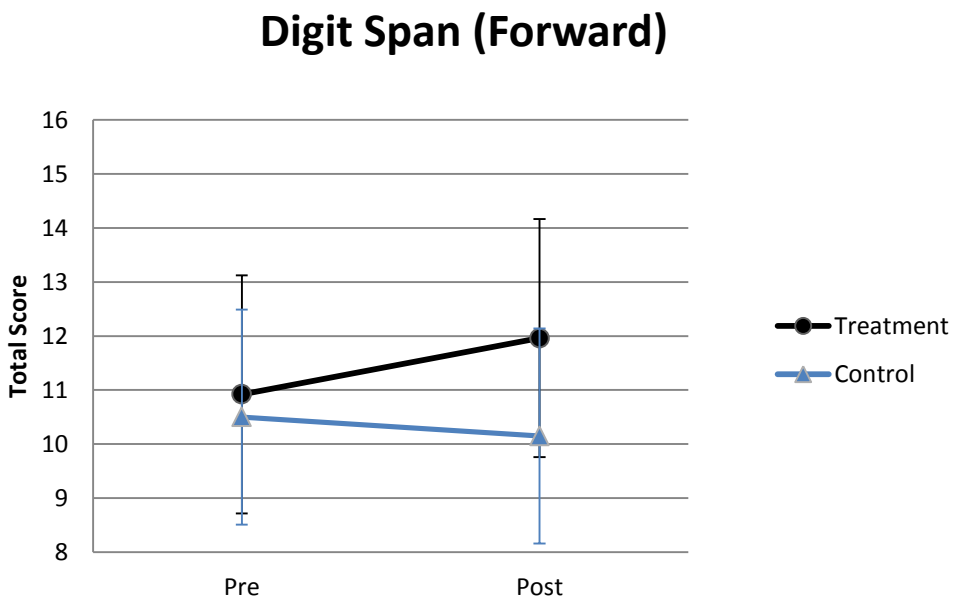
CARES study

- Currently enrolling cancer patients
  - 1yr or more post treatment (no transplant)
  - Stable on medications (serms/ais ok)
  - Not currently undergoing treatment for ca
  - Able to undergo cognitive testing

  - Pre-Tx evaluation 7 weeks of Tx, post Tx evaluation

Pre/Post Cognitive Changes

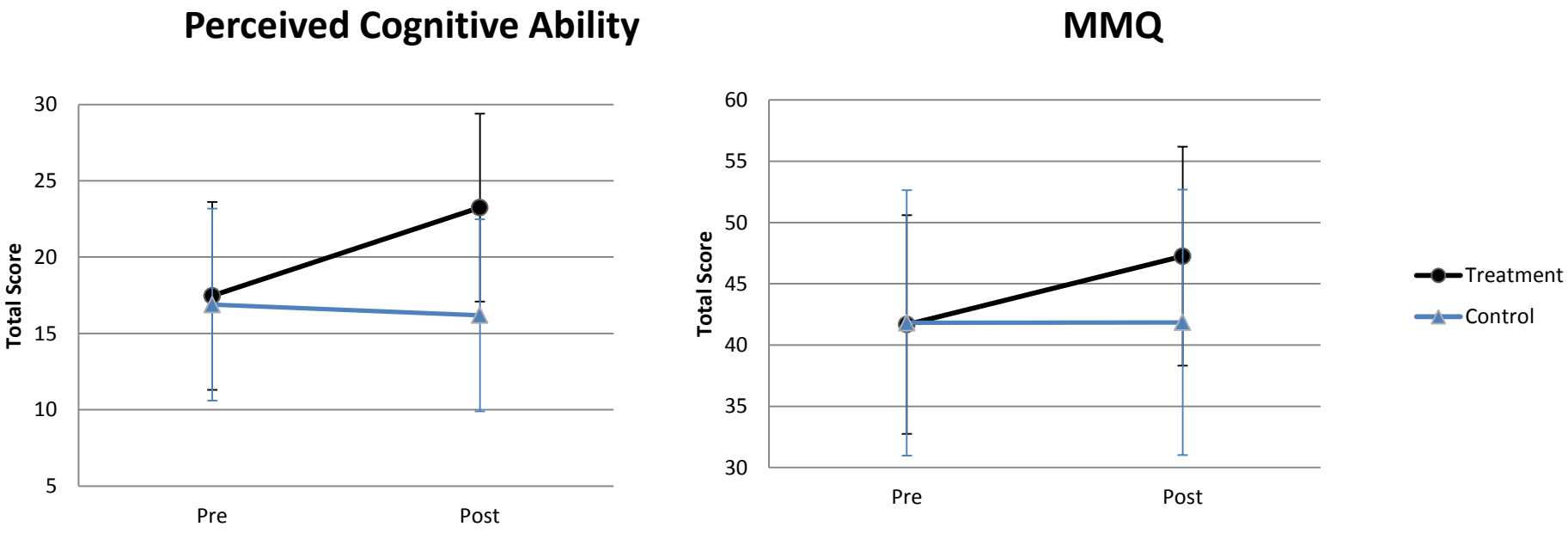




significant improvement on verbal memory and attention (working memory) compared to baseline ($p<.05$) and compared to control (interaction effect) $p<.05$)

Cherrier et al., 2014

Pre/Post Questionnaire Changes



Participants in the treatment group endorsed significant improvement on all subscales of the FACT-cog and increased use of cognitive strategies compared to baseline ($p<.05$) and compared to control (interaction effect) $p<.05$)

Cherrier et al., 2014

BOOST: Post Treatment Questionnaire

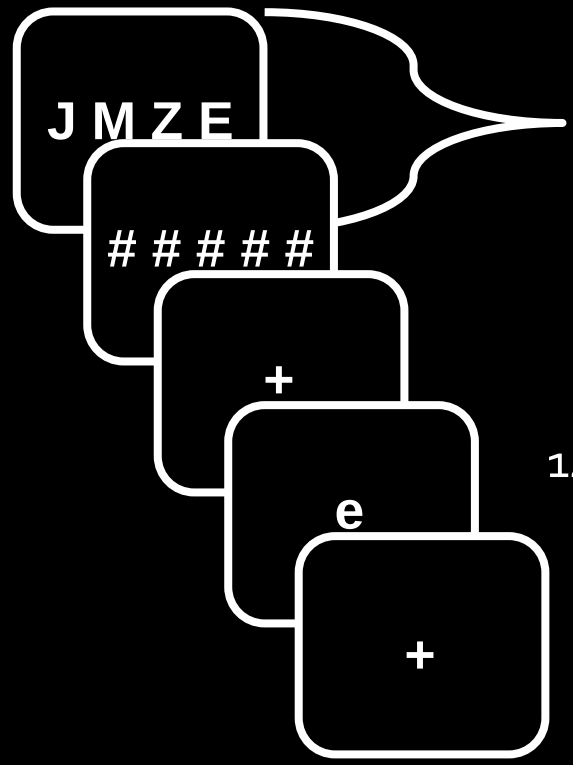
1=strongly disagree 5=strongly agree

4	Better understanding of how memory and attention work
5	More confident about trying new solutions to address memory and attention difficulties
4	Learned new solutions for dealing with daily memory failures
4	My ability to remember information has improved
4	Overall I am better able to cope with cognitive difficulties
4	I enjoyed working and learning in a group setting
1	I would prefer to have online/computerized training
1	This treatment could be more effective using a computer format

Cherrier et al., 2014

Working Memory Task

Memory Set
2500 ms
Mask
100 ms
Maintenance
1400 ms
Probe
500 ms
Fixation
1500 ms



3 Item **5 Item** **7 Item**

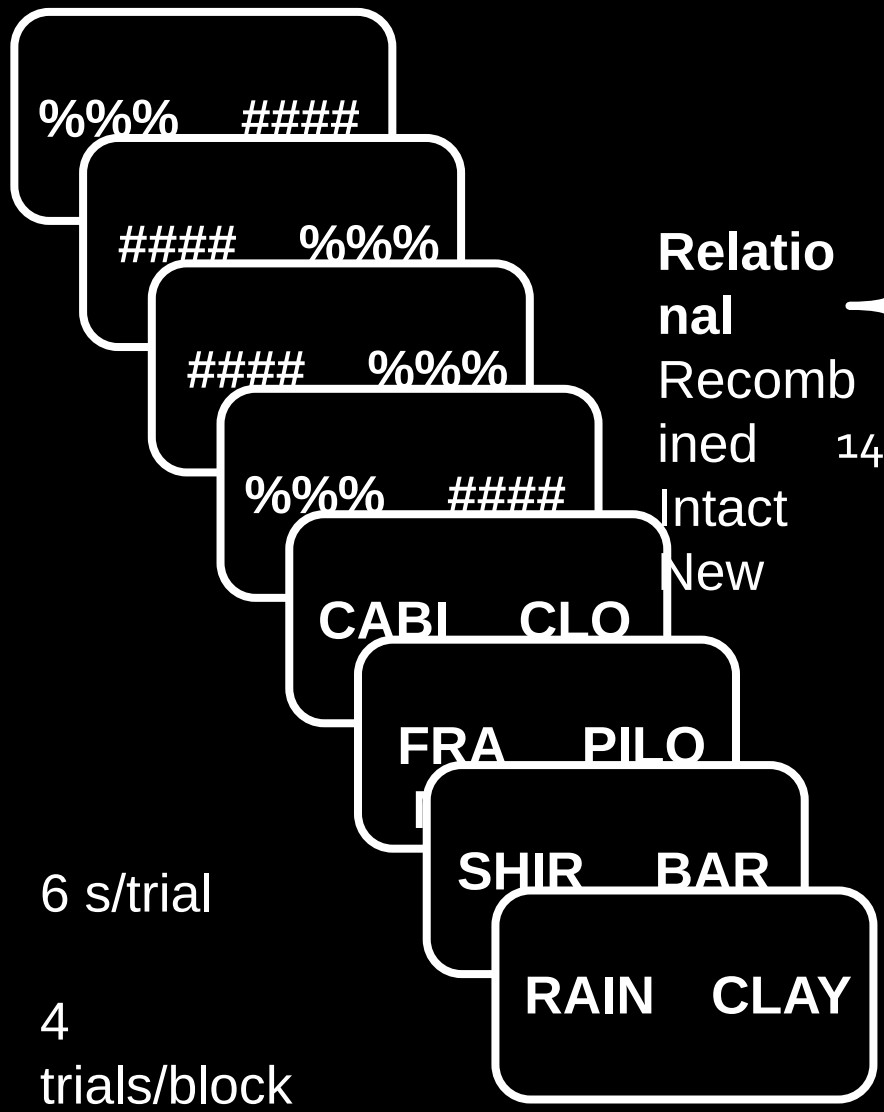
Memory Load

14.45 trials/block

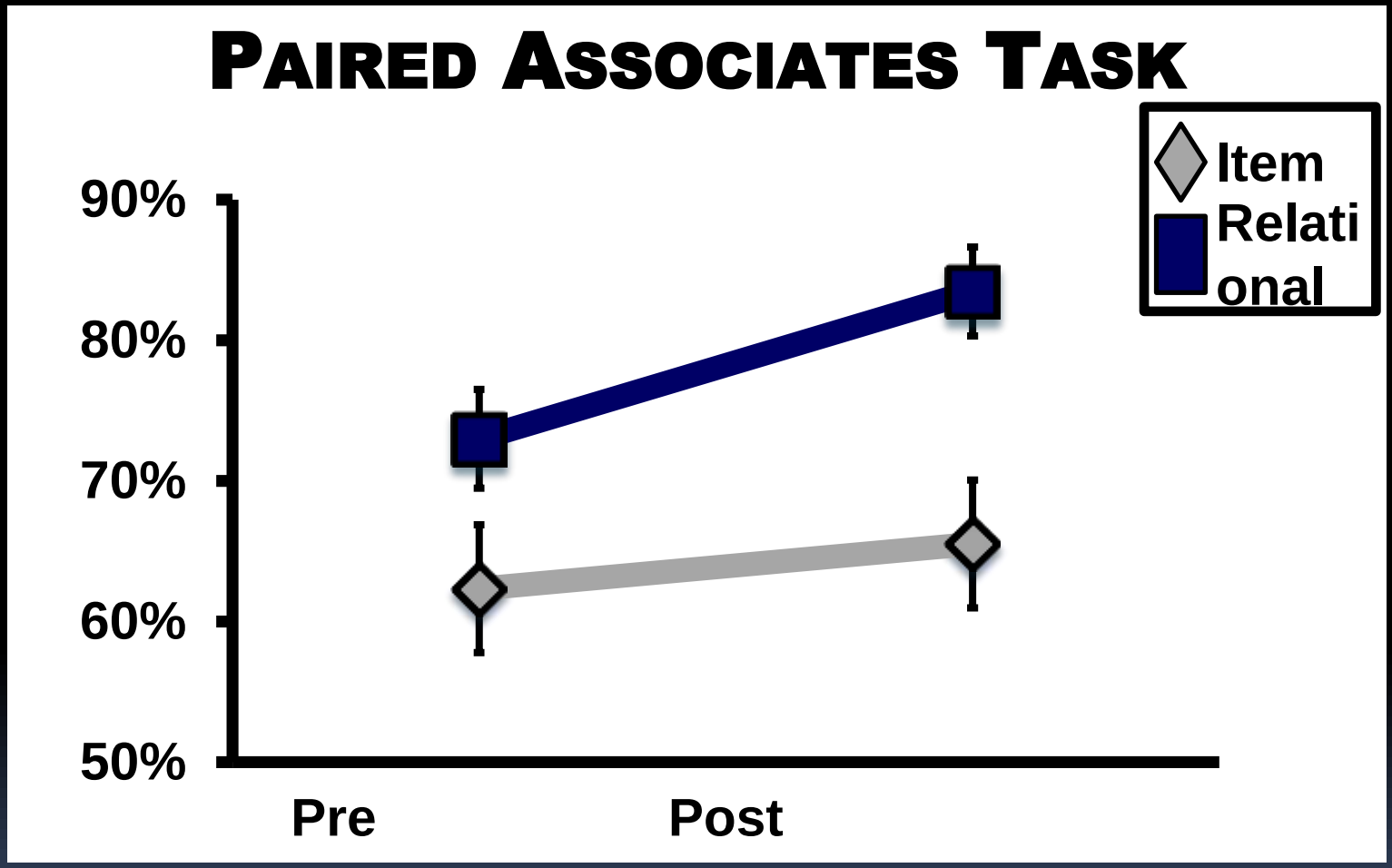
24 s/block

17 blocks/run

Paired Associates Task



In scanner responses:

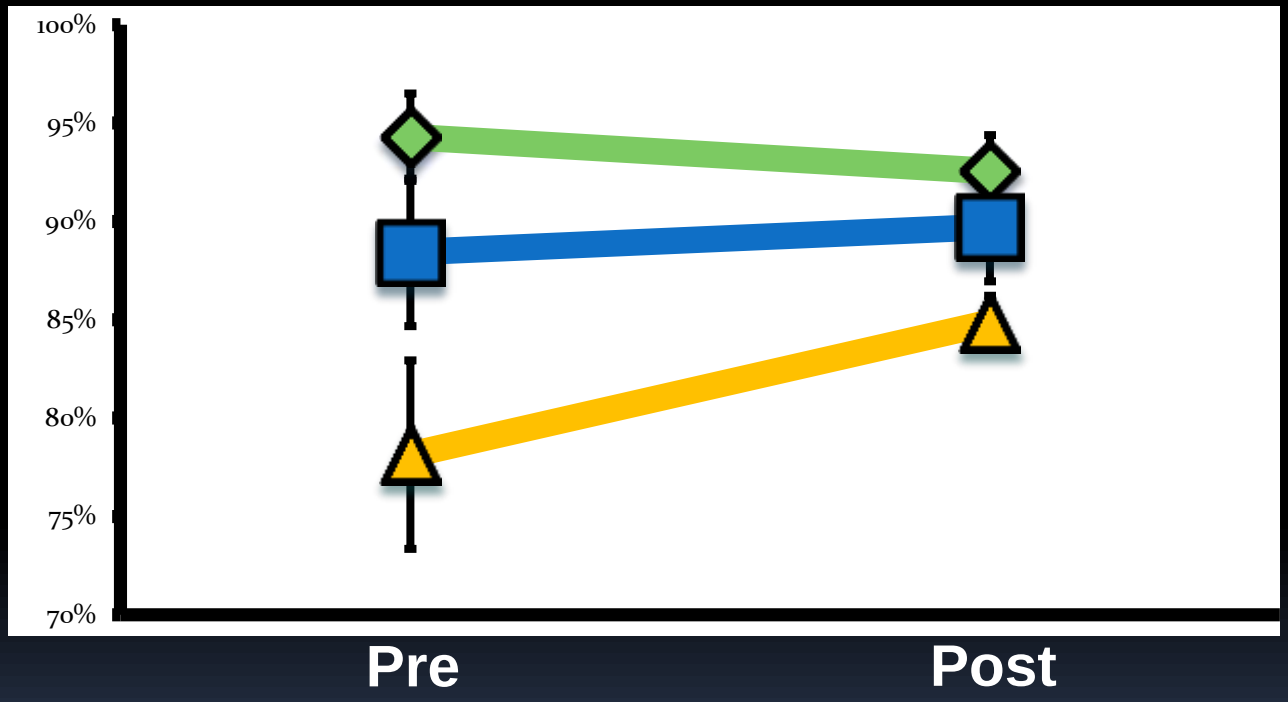


Trained participants showed a significant improvement in accuracy in the Relational condition ($p<.001$), but not in the Item condition ($p=.67$) of the Paired Associates task.

Cherrier et al., 2014

In scanner responses:

Working Memory Task



Participants also showed a non-significant improvement in accuracy within higher-load, but not lower-load trials in the Working Memory Task.

Cherrier et al., 2014

Other interventions

- Exercise
  - Exercise improves cognition in older adults and those with mild memory impairments (Baker et al., 2010, Liu-Ambrose, 2010; Davis, 2010)
  - Exercise may improve fatigue, pain, and overall health and quality of life in cancer survivors and those undergoing treatment (McTiernan, 2004; Denmark-Wahnefried et al, 2003)
- Increases regional capillary density, neural metabolic capacity, BDNF

Other interventions

- Meditation- alert, restful state
- Requires focused attention, increased sense of control
  - Used to help with chronic pain, anxiety, depression, smoking cessation
  - Eeg studies have found neurophysiological modulations associated with meditation practice
  - fMRI studies have shown brain activation changes with increasing meditation practice
  - Improvements in attention, cognitive flexibility
  - An option for mobility restricted or challenged patients

Biegler et al., 2009

Summary:

- 50 – 70% patients experience subjective cognitive complaints – related to anxiety, depression, other physical symptoms
- 10 – 30% objectively measured impairments
- Patients can improve over time , including years post treatment
- Pre-morbid factors should be taken into consideration
- Cognition can be accurately measured with norm based tests

Summary:

- Causes of cognitive dysfunction are likely multi-factorial
- Interventions (targeted) can be effective