Rehabilitationsmedizinische Behandlungsansätze: Kognitive Dysfunktion

Prof. Dr. O. Rick

Klinik Reinhardshöhe, Bad Wildungen

Interessenkonflikte

1. Anstellungsverhältnis oder Führungsposition
   Chefarzt Klinik Reinhardshöhe, Bad Wildungen
2. Beratungstätigkeit
   keine
3. Aktienbesitz
   keine
4. Honorare
   keine
5. Finanzierung wissenschaftlicher Untersuchungen
   keine
6. Gutachtertätigkeit
   keine
7. Andere finanzielle Beziehungen
   keine

Definition

Kurzfristige, langfristige oder dauerhafte Störung der

- ✓ Lernfähigkeit
- ✓ Gedächtnisleistung (insbes. Kurzzeitgedächtnis)
- ✓ Geschwindigkeit in der Gedankenverarbeitung (processing speed)
- ✓ Fähigkeit komplexe Aufgaben auszuführen (executive function)

Wefel und Schagen, Curr Neurol Neurosci Rep 2012

Inzidenz der kognitiven Dysfunktion

- ✓ 19-25% (78%) der Patienten nach Chemotherapie in objektivierbaren Testbatterien
- ✓ Bis 71% der Patienten nach eigenen Angaben 6 Monate nach der Chemotherapie
- ✓ Bis zu 20 Jahren nach der Krebstherapie
- ✓ Daten aus 53 Studien (inklus. 6 Meta-Analysen, 21 Längsschnittstudien)

Ahles et al., JCO 2012
Wefel und Schagen, Curr Neurol Neurosci Rep 2012

Pathophysiologie

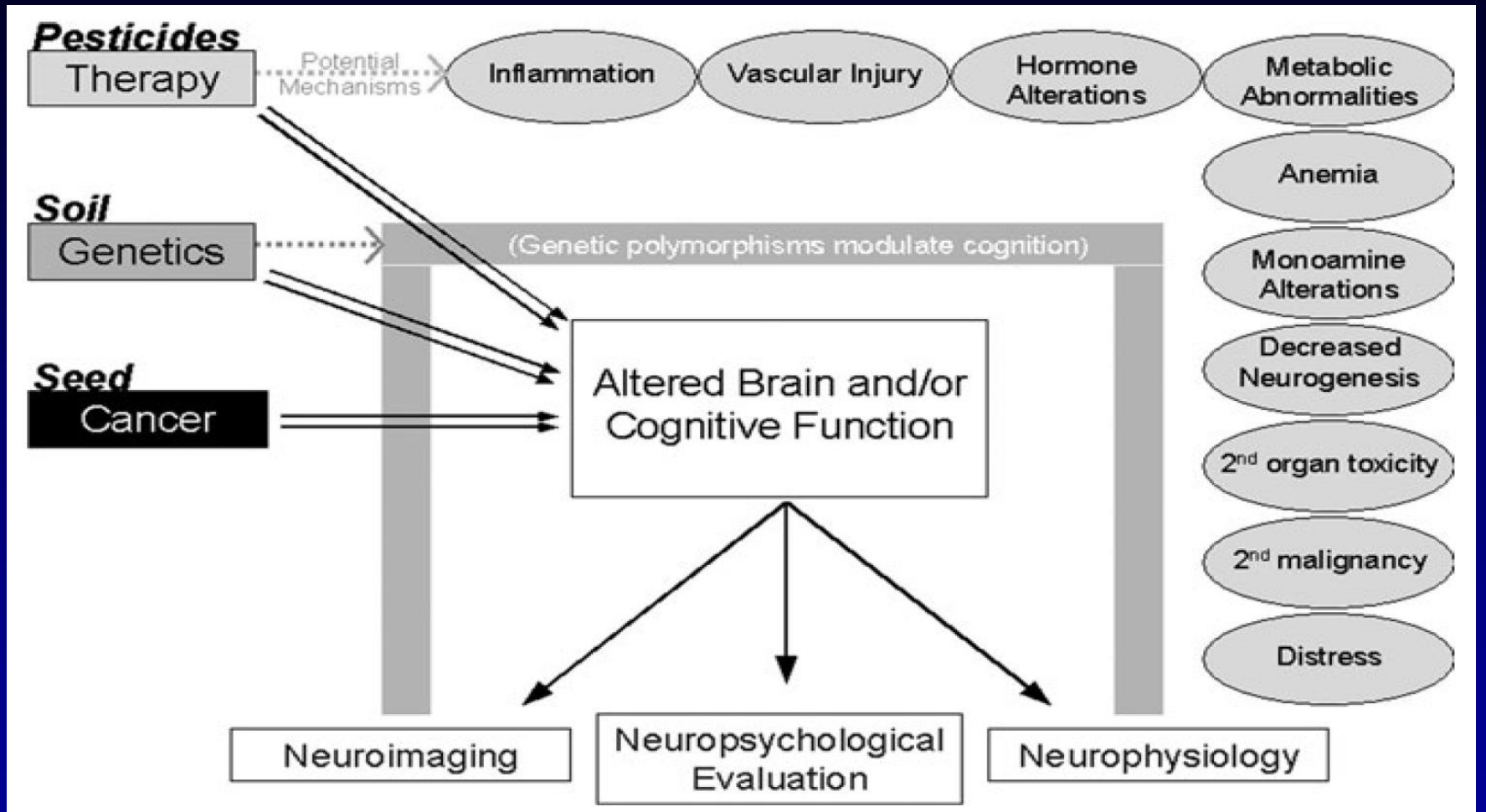


Figure 1. Postulated mechanisms of chemotherapy-associated cognitive changes.

Vardy et al., Ann Oncol 2008

Enflussfaktoren

Factors that Influence Cognitive Function in Patients with Cancer

Demographic	Psychological	Cancer therapy and cancer-related factors	Disease- and treatment-related symptoms
Years of education	Depression	Systemic therapies (ie, chemotherapy, hormonal therapy, biotherapy)	Anemia
General intelligence	Anxiety	Local therapies (ie, radiation therapy and surgery)	Fatigue
Age		Dose and duration of therapy	Pain
Gender		Concurrent therapies	Sleep disturbances
History of:		Direct delivery to central nervous system	
Neuropsychological disorder			
Psychiatric illness			
Developmental disorders			
Substance abuse			
Prior cancer therapy			

Bender und Thelen, Sem Oncol Nurs 2013

A meta-analysis of the effects of chemotherapy on cognition in patients with cancer

Kristy D. Hodgson [a,*], Amanda D. Hutchinson [b,c,1], Carlene J. Wilson [b,c,2], Ted Nettelbeck [a,3]

[a] *School of Psychology, University of Adelaide, Adelaide, SA, Australia*
[b] *Flinders Centre for Innovation in Cancer, School of Medicine, Flinders University of South Australia, SA, Australia*
[c] *Cancer Council South Australia, Eastwood, SA, Australia*

Effect size statistics associated with the eight cognitive domains defined by Lezak et al. (2004).[16]

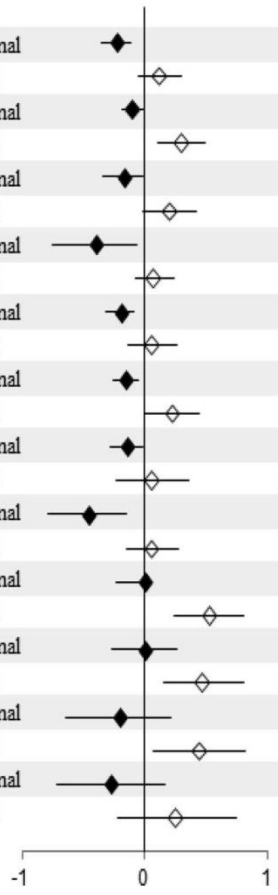
n= 997 davon 552 Pat.

Domain	*N* studies n=13	Effect size	95% Cllower	95% Clupper	Failsafe *N*
Executive function	6	−0.27[a]	−0.44	−0.09	0
Memory	12	−0.21[a]	−0.36	−0.07	0
Verbal function & language skills	9	−0.17[a]	−0.33	−0.00	0
Construction	9	−0.12	−0.28	0.04	0
Concept formation and reasoning	5	−0.10	−0.30	0.10	0
Perception	2	−0.06	−0.38	0.26	0
Orientation & attention	12	−0.02	−0.16	0.12	0

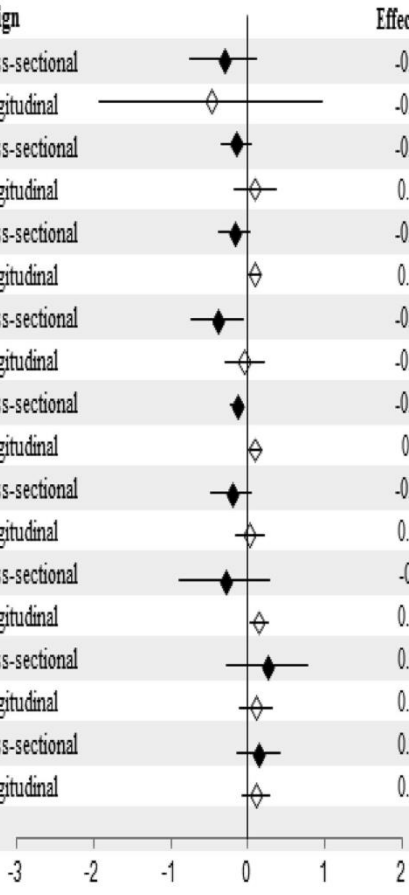
Hodgson et al., Cancer Treatment Reviews 2013

A Meta-Analysis of Cognitive Impairment Following Adult Cancer Chemotherapy

Cognitive function	Design	Effect size	CI lower	CI upper
MEMORY	Cross-sectional	-0.23	-0.35	-0.11
	Longitudinal	0.12	-0.05	0.3
Immediate	Cross-sectional	-0.1	-0.19	0
	Longitudinal	0.3	0.1	0.49
Delayed	Cross-sectional	-0.18	-0.34	-0.02
	Longitudinal	0.2	-0.02	0.42
Recognition	Cross-sectional	-0.4	-0.75	-0.06
	Longitudinal	0.07	-0.08	0.24
VERBAL	Cross-sectional	-0.2	-0.32	-0.09
	Longitudinal	0.06	-0.14	0.26
Immediate	Cross-sectional	-0.16	-0.26	-0.05
	Longitudinal	0.22	0	0.44
Delayed	Cross-sectional	-0.15	-0.28	-0.02
	Longitudinal	0.06	-0.23	0.36
Recognition	Cross-sectional	-0.47	-0.79	-0.15
	Longitudinal	0.05	-0.15	0.27
VISUAL	Cross-sectional	-0.1	-0.24	0.03
	Longitudinal	0.52	0.24	0.8
Immediate	Cross-sectional	0	-0.27	0.26
	Longitudinal	0.47	0.15	0.8
Delayed	Cross-sectional	-0.21	-0.64	0.21
	Longitudinal	0.44	0.07	0.81
Recognition	Cross-sectional	-0.28	-0.72	0.16
	Longitudinal	0.25	-0.22	0.74



Cognitive function	Design	Effect size	lower CI	upper CI
SPATIAL ABILITIES	Cross-sectional	-0.32	-0.76	0.11
	Longitudinal	-0.47	-1.92	0.96
ATTENTION	Cross-sectional	-0.14	-0.34	0.05
	Longitudinal	0.09	-0.18	0.37
Focused	Cross-sectional	-0.17	-0.38	0.03
	Longitudinal	0.09	0.01	0.17
Selective	Cross-sectional	-0.39	-0.73	-0.05
	Longitudinal	-0.04	-0.29	0.21
Capacity	Cross-sectional	-0.15	-0.23	-0.06
	Longitudinal	0.1	0.03	0.17
EXECUTIVE FUNCTIONS	Cross-sectional	-0.21	-0.49	0.05
	Longitudinal	0.02	-0.16	0.21
VERBAL ABILITIES	Cross-sectional	-0.3	-0.89	0.29
	Longitudinal	0.14	0.02	0.26
ARITHMETIC	Cross-sectional	0.11	-0.1	0.32
	Longitudinal	0.13	-0.15	0.42
MOTOR FUNCTIONS	Cross-sectional	0.25	-0.28	0.78
	Longitudinal	0.11	-0.07	0.29



Lindner et al., Neuropsychology 2014

Longitudinal Assessment of Chemotherapy-Induced Alterations in Brain Activation During Multitasking and Its Relation With Cognitive Complaints

Sabine Deprez, Mathieu Vandenbulcke, Ronald Peeters, Louise Emsell, Ann Smeets, Marie-Rose Christiaens, Frederic Amant, and Stefan Sunaert

- ✓ 18 Pat. mit Chemotherapie
- ✓ 16 Pat. ohne Chemotherapie
- ✓ 17 gematchte gesunde Probanden
- ✓ Mittels Multitasking Funktions-MRT untersucht zum Beginn der Therapie (t1) und 4-6 Monate danach (t2)

Deprez et al., JCO 2014

Longitudinal Assessment of Chemotherapy-Induced Alterations in Brain Activation During Multitasking and Its Relation With Cognitive Complaints

Sabine Deprez, Mathieu Vandenbulcke, Ronald Peeters, Louise Emsell, Ann Smeets, Marie-Rose Christiaens, Frederic Amant, and Stefan Sunaert

- ✓ Zu beginn war bei allen Pat. die kognitive Funktion vergleichbar
- ✓ Abnahme der kognitiven Funktion bei Chemo-Patienten (t1 zu t2), während Kontrollpatienten unverändert blieben
- ✓ Kein signifikanter Unterschied zwischen den Pat. mit oder ohne Chemotherapie

Deprez et al., J Clin Oncol 2014

Reduced Prefrontal Activation During Working and Long-Term Memory Tasks and Impaired Patient-Reported Cognition Among Cancer Survivors Postchemotherapy Compared With Healthy Controls

- ✓ Tumorpatienten (n= 15), 20% metastasiert
- ✓ Brust, Kolo-Rektal, Hodgkin, Leukämie, MM
- ✓ Gesunde Probanden (n= 14)
- ✓ Funktion-MRT-Kopf + Gedächtnis- und Aufmerksamkeitsarbeiten

Wang et al., Cancer 2016

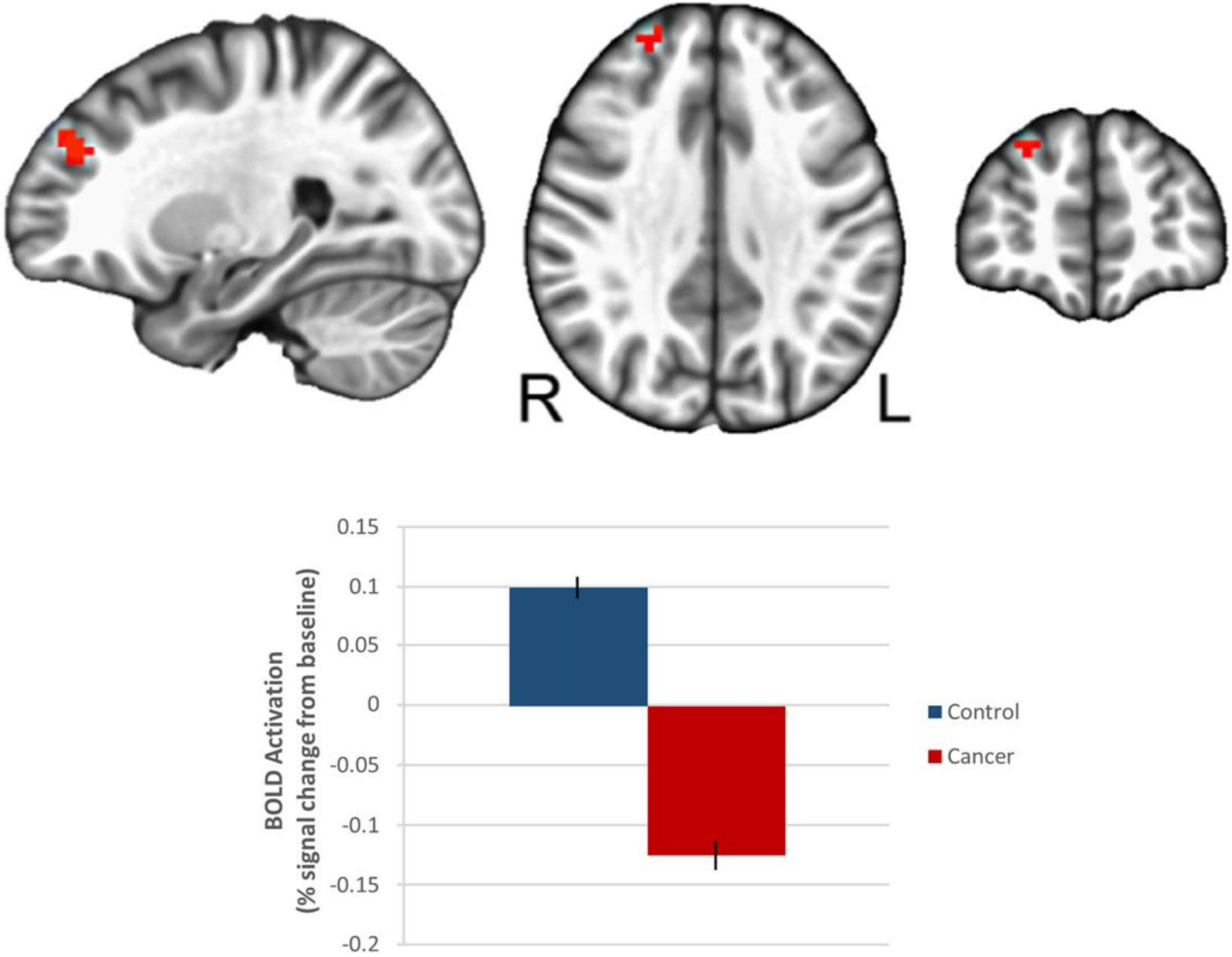


Figure 3. Between-group functional differences in the right (R) dorsolateral prefrontal cortex are illustrated for the n-back working memory task. Oncology patients had significantly decreased blood oxygen level-dependent (BOLD) activation in the right dorsolateral prefrontal cortex compared with controls. L indicates left.

Wang et al., Cancer 2016

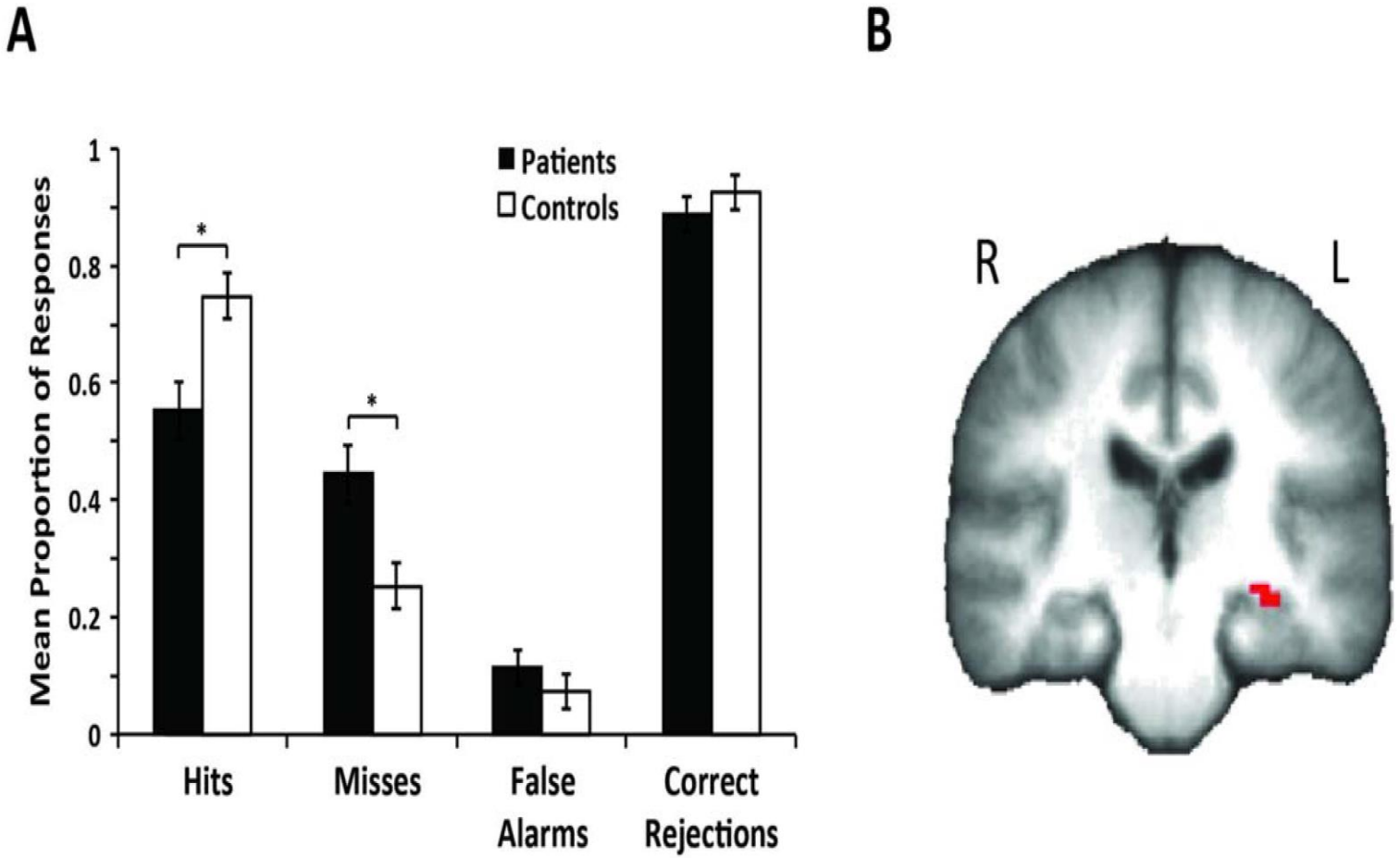


Figure 4. Between-group behavioral and functional differences are illustrated in the recognition task. (A) The proportions of hits, misses, false alarms, and correct rejections are illustrated for the visual recognition task. (B) Controls had increased activation when contrasting hits to correct rejections in the middle hippocampus (red area). Regions of increased activation that are not displayed also included the left lateral parietal cortex, the left fusiform gyrus, and the left lateral occipital cortex. Conversely, oncology patients had decreased activation compared with controls in the left hippocampus.

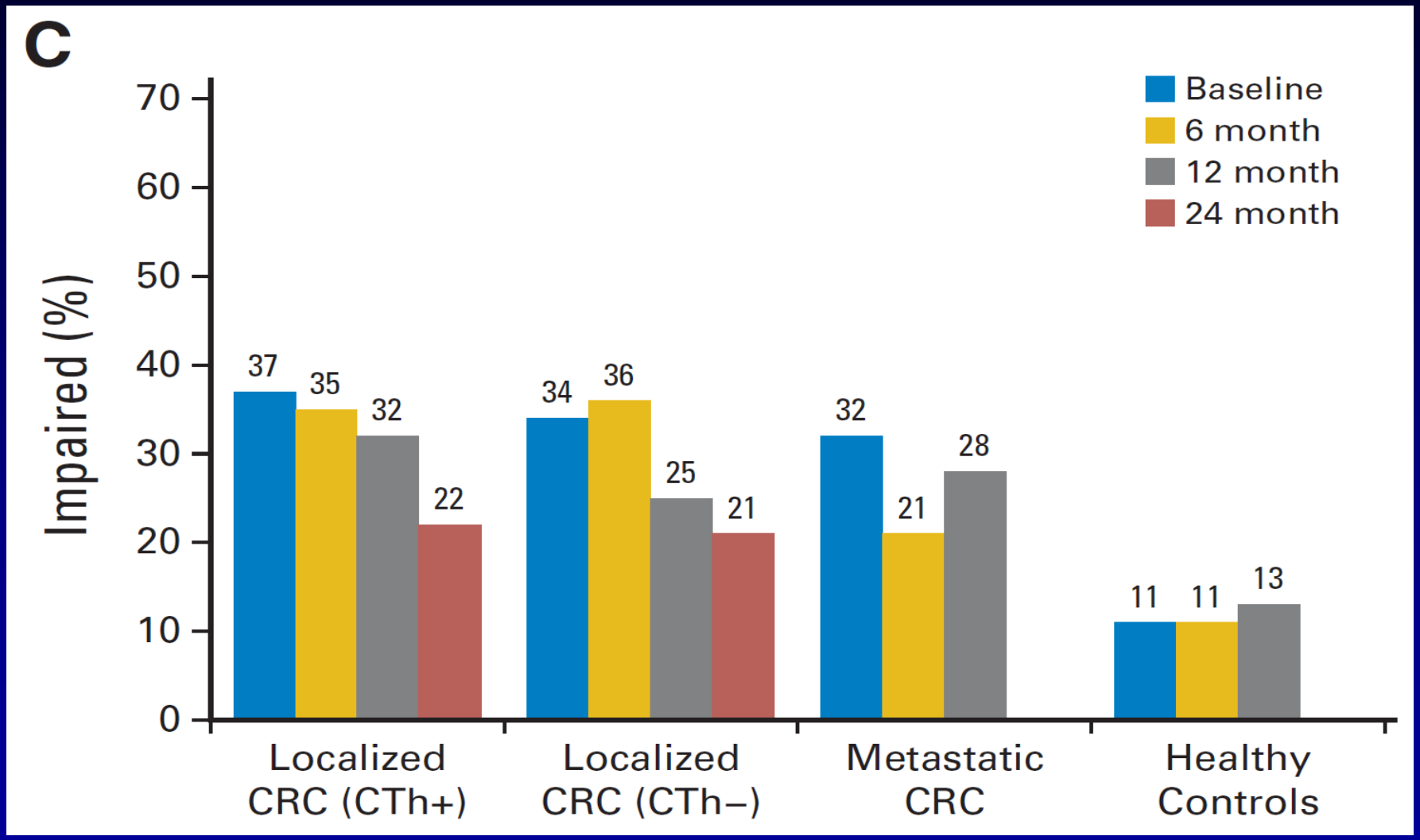
Wang et al., Cancer 2016

Cognitive Function in Patients With Colorectal Cancer Who Do and Do Not Receive Chemotherapy: A Prospective, Longitudinal, Controlled Study

- ✓ Stadium II-III + adjuvante Ctx (n= 173)
- ✓ Stadium I-II ohne adjuvante Ctx (n= 116)
- ✓ Stadium IV und Rezidive + Ctx (n= 73)
- ✓ Gesunde Probanden (n= 72)
- ✓ Neuropsychologische Testbatterien (CANTAB, FACT-F, FACT-CF, General-Health-Questionaire-12

Vardy et al., J Clin Oncol 2015

Cambridge Neuropsychological Test Automated Battery Test (CANTAB)

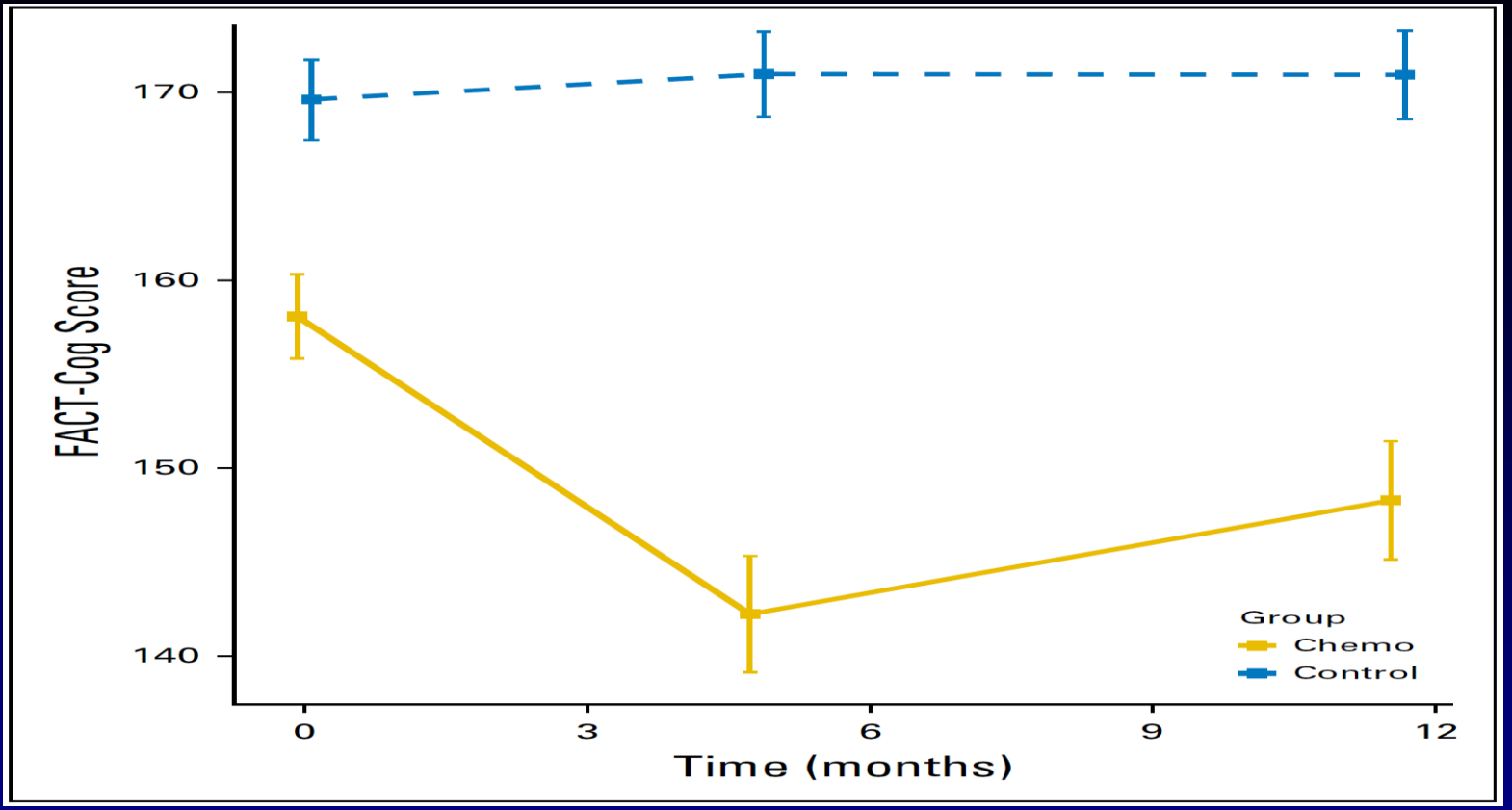


Vardy et al., J Clin Oncol 2015

Cognitive Complaints in Survivors of Breast Cancer After Chemotherapy Compared With Age-Matched Controls: An Analysis From a Nationwide, Multicenter, Prospective Longitudinal Study

- ✓ 581 Pat. mit nicht-metastasiertem Brustkrebs und Chemotherapie
- ✓ 364 gematchte gesunde Probanden
- ✓ FACT-Cog prä- und postchemotherapie und 6 Monate später

Janelsins 2017 et al., J Clin Oncol 2017



- ✓ Signifikante Korrelation zwischen FACT-Cog und Angst/Depression
- ✓ Kein signifikanter Einfluss der Tumortherapie

Janelsins 2017 et al., J Clin Oncol 2017

Therapeutische Optionen der Kognitiven Dysfunktion bei Krebspatienten

Evidence-Based Interventions for Cancer- and Treatment-Related Cognitive Impairment

Likely to Be Effective

- Cognitive training: group (Hassler et al., 2010; Poppelreuter et al., 2009; Von Ah et al., 2012)
- Cognitive training: individual (Gehring et al., 2009; Kesler et al., 2013; Miotto et al., 2013; Zucchella et al., 2013)

Von Ah et al., Clin J Oncol Nurs 2014

Evidence-Based Interventions for Cancer- and Treatment-Related Cognitive Impairment

Effectiveness Not Established

- Cognitive-behavioral training (Cherrier et al., 2013; Ferguson et al., 2007, 2012; Goedendorp et al., 2014; Locke et al., 2008; McDougall et a., 2011; Sherer et al., 1997)
- Electroencephalography or neurofeedback (Alvarez et al., 2013)
- Exercise (Baumann et al., 2011; Korstjens et al., 2006; Reid-Arndt et al., 2012; Schwartz et al., 2002)
- Meditation (Milbury et al., 2013)
- Mindfulness-based stress reduction (Hoffmann et al., 2012)
- Natural restorative environmental (Cimprich, 1993; Cimprich & Ronis, 2003)
- Qigong (Oh et al., 2012)

Von Ah et al., Clin J Oncol Nurs 2014

Evidence-Based Interventions for Cancer- and Treatment-Related Cognitive Impairment

Effectiveness Unlikely

- Gingko biloba (Attia et al., 2012; Barton et al., 2013)

Not Recommended for Practice

- Erythropoiesis-stimulating agents (Chang et al., 2004; Iconomou et al., 2008; Mancuso et al., 2006; Mar Fan et al., 2009; Massa et al., 2005; O'Shaughnessy, 2002; O'Shaughnessy et al., 2005)

Von Ah et al., Clin J Oncol Nurs 2014

Feasibility and efficacy of speed-feedback therapy with a bicycle ergometer on cognitive function in elderly cancer patients in Japan

- ✓ 78 Pat. mit Brust- und Prostatakrebs
- ✓ ≥ 65 Jahre
- ✓ Inhomogenes Kollektiv bez. Therapie + Stadium
- ✓ Ergometertraining 1x/Woche für 4 Wochen

  versus Warteliste
- ✓ Interventionsgruppe n= 38, Kontrolle n= 40

Miki et al., Psycho-Oncology 2014

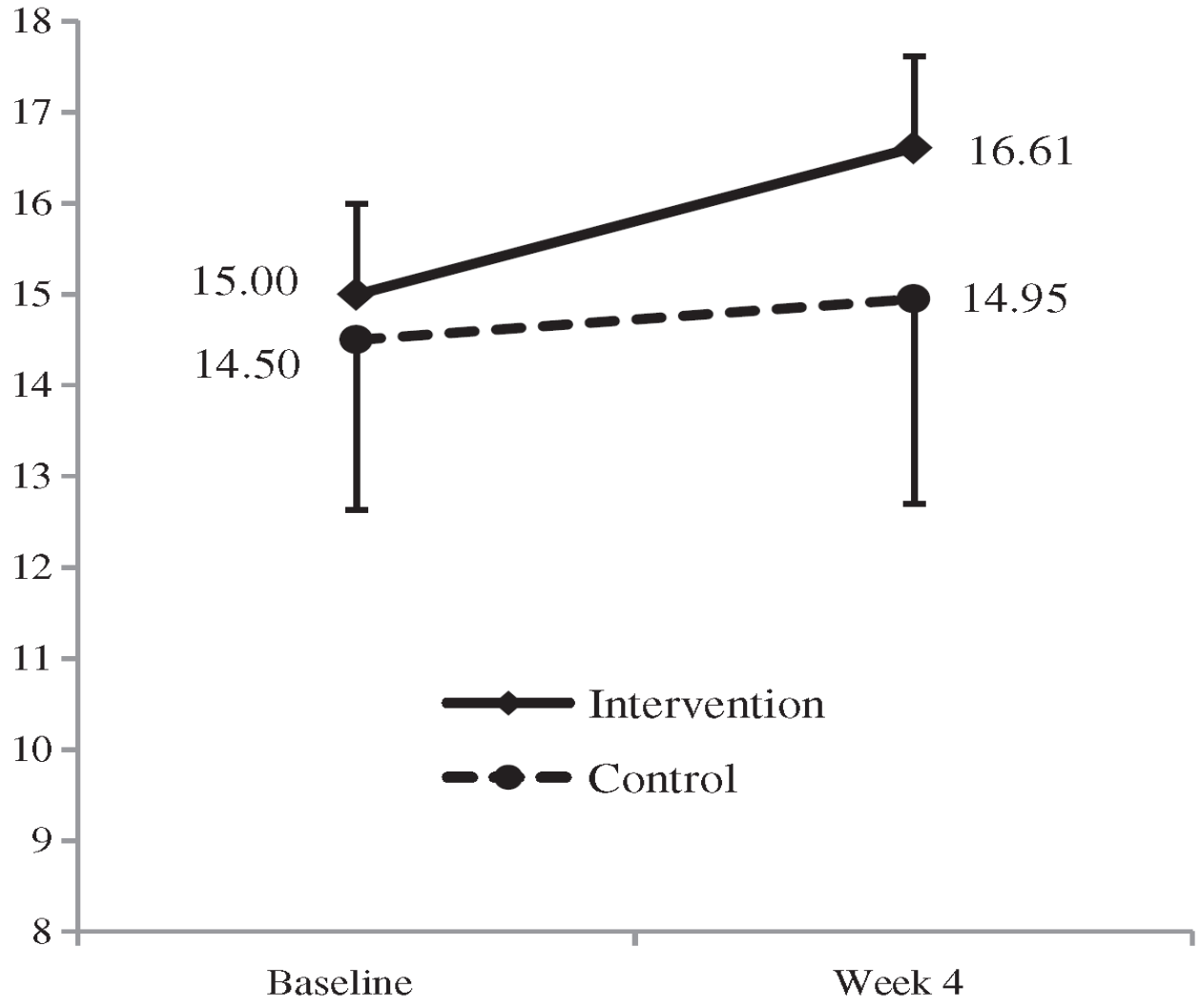


Figure 3. Change between the two groups in Frontal Assessment Batteryn (FAB) scores

Miki et al., Psycho-Oncology 2014

The Effectiveness of Psychosocial Interventions for Cognitive Dysfunction in Cancer Patients Who Have Received Chemotherapy: A Systematic Review

- ✓ 3109 Artikel gescreent
- ✓ 120 full-text Artikel
- ✓ 6 Artikel auswertbar für die Meta-Analyse

Hines et al., Worldviews on Evidence-Based Nursing 2014

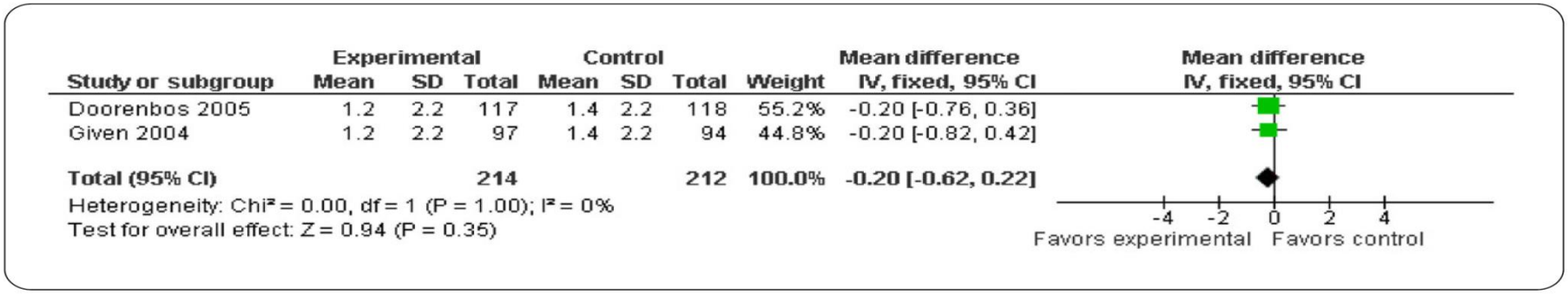


Figure 1. Cognitive behavioral intervention versus conventional care for inability to concentrate. Severity measured by 10-point Likert scale (10 weeks).

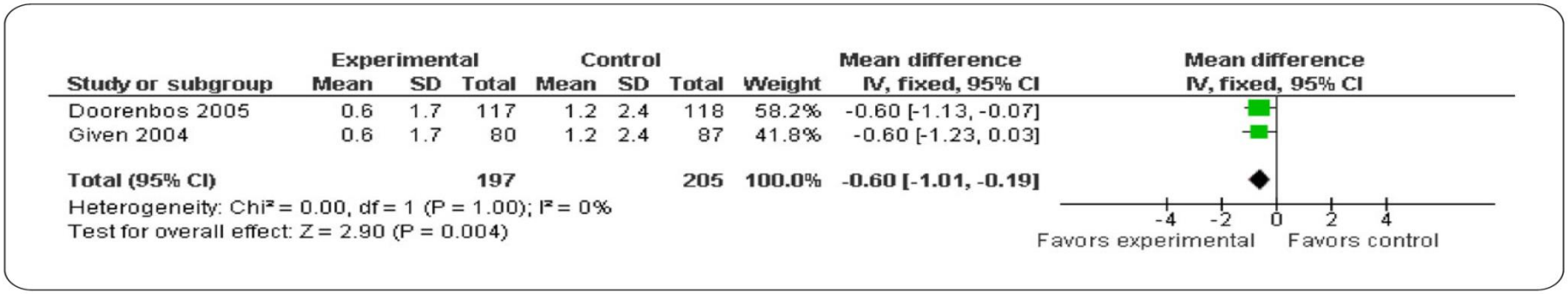


Figure 2. Cognitive behavioral intervention versus conventional care for inability to concentrate. Severity measured by 10-point Likert scale (20 weeks).

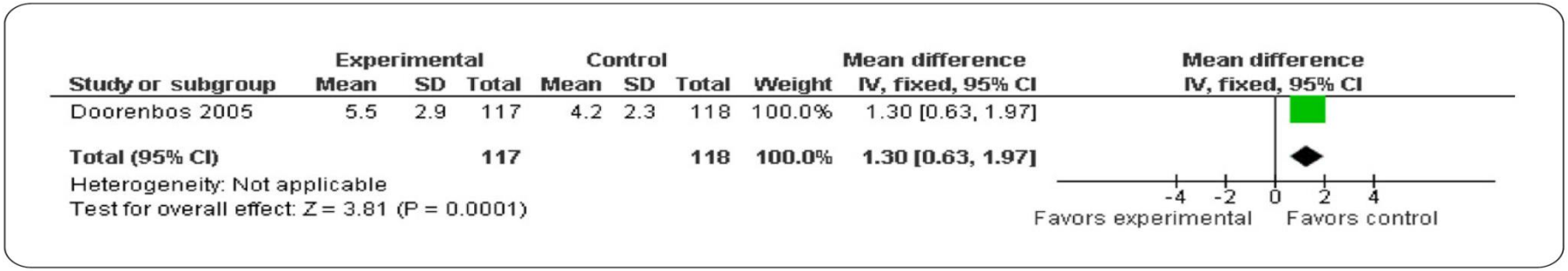


Figure 3. Cognitive behavioral intervention versus conventional care for inability to concentrate. Severity measured by 10-point Likert scale (32 weeks).

Hines et al., Worldviews on Evidence-Based Nursing 2014

Web-based cognitive training for breast cancer survivors with cognitive complaints—a randomized controlled trial

- ✓ Pat. mit Brustkrebs (n= 157)
- ✓ Pat. gaben eine kognitive Dysfunktion an
- ✓ Kein objektivierbarer Screening Test
- ✓ Web-basiertes kognitives Training (n= 94)
- ✓ 30 Trainingseinheiten über 6 Wochen
- ✓ Warteliste (n= 63)

Damholdt et al., Psycho-Oncology 2016

Table 2. Raw score-based descriptives, waitlist control group-based z-score conversions and MLM results for primary and secondary outcomes

	Baseline WLC (*N* = 63) eCogT (*N* = 94) M (SD)	Post-intervention WLC (*N* = 59) eCogT (*N* = 77) M (SD)	Follow-up WLC (*N* = 57) eCogT (*N* = 72) M (SD)	Time × group interaction effect *F*; *p* (day)
Primary outcome				
PASAT				
WLC	19.02 (9.88)	15.98 (11.54)	16.04 (10.66)	
eCogT	20.74 (12.37)	17.14 (12.66)	15.15 (10.90)	
eCogT-z	−0.175 (1.25)	−0.101 (1.10)	0.083 (1.02)	1.1; 0.334 (0.15)
Secondary outcomes				
CFQ raw scores				
WLC	46.38 (14.32)	38.63 (13.55)	38.79 (12.54)	
eCogT	44.97 (15.03)	36.62 (12.65)	35.81 (12.95)	0.2; 0.814 (0.07)
RAVLT total score trial I–V[a]				
WLC	48.59 (8.94)	49.33 (8.86)	51.96 (9.52)	
eCogT	48.23 (9.35)	50.94 (8.55)	54.68 (8.91)	
eCogT-z	−0.035 (1.05)	0.018 (0.97)	0.286 (0.94)	3.2; 0.043 (0.22)*
RAVLT recall[a]				
WLC	10.00 (2.54)	10.81 (2.44)	11.32 (2.49)	
eCogT	10.10 (2.97)	10.96 (2.84)	11.76 (2.39)	
eCogT-z	0.038 (1.17)	0.062 (1.17)	0.178 (0.96)	0.6; 0.520 (0.10)
Digit Span Forwards[b]				
WLC	8.10 (1.57)	8.25 (1.90)	8.11 (1.67)	
eCogT	8.47 (2.06)	8.86 (2.12)	9.04 (2.08)	
eCogT-z	0.234 (1.31)	0.320 (1.12)	0.560 (1.25)	1.6; 0.207 (0.18)
Digit Span Backwards[b]				
WLC	7.68 (1.76)	8.02 (1.79)	7.96 (1.96)	
eCogT	7.80 (1.67)	8.94 (2.05)	8.71 (1.95)	
eCogT-z	0.067 (0.95)	0.512 (1.13)	0.381 (0.99)	3.3; 0.040 (0.22)*

Damholdt et al., Psycho-Oncology 2016

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Damholdt et al., Psycho-Oncology 2016

Randomized controlled pilot trial of mindfulness-based stress reduction for breast and colorectal cancer survivors: effects on cancer-related cognitive impairment

- ✓ Pat. mit Brust- oder Darmkrebs (n= 71)
- ✓ Pat. gaben eine kognitive Dysfunktion an
- ✓ Kein objektivierbarer Screening Test
- ✓ MBSR über 8 Wochen (n= 35)
- ✓ Aufklärung und Beratung (ES) (n= 36)

Johns et al., J Cancer Surviv 2015

Dependent variables	MBSR $n=35$[a]	ES $n=36$[b]	Diff	SE diff	p value
Baseline (T1)					
AFI total ($\alpha=0.87$)	48.00	45.83	1.73	3.84	0.65
Effective action ($\alpha=0.83$)	44.88	43.05	1.86	4.23	0.66
Attentional lapses ($\alpha=0.64$)	51.71	47.27	3.61	4.65	0.44
Interpersonal effectiveness ($\alpha=0.78$)	51.56	51.17	−0.72	5.73	0.90
Post-intervention (T2)					
AFI total ($\alpha=0.88$)	64.64	52.28	12.57	3.54	0.001
Effective action ($\alpha=0.86$)	63.16	50.09	12.84	4.28	0.004
Attentional lapses ($\alpha=0.80$)	67.30	50.20	17.99	4.76	<0.001
Interpersonal effectiveness ($\alpha=0.78$)	65.54	59.50	6.99	4.26	0.106
6-month follow-up (T3)					
AFI total ($\alpha=0.90$)	64.83	55.21	8.90	3.75	0.021
Effective action ($\alpha=0.88$)	62.74	52.53	10.45	4.61	0.027
Attentional lapses ($\alpha=0.80$)	68.13	55.68	11.84	4.82	0.017
Interpersonal effectiveness ($\alpha=0.75$)	66.37	61.24	3.47	4.40	0.433

Johns et al., J Cancer Surviv 2015

Zusammenfassung

- ✓ Die Inzidenz und die Bedeutung der KD wurde lange unterschätzt
- ✓ Die KD ist ein multifaktorielles Geschehen mit einem morphologischen Korrelat
- ✓ Es findet sich eine signifikante Korrelation zwischen KD und psychischer Alteration
- ✓ Die Tumortherapie scheint eher eine untergeordnete Bedeutung zu haben (nicht „Chemo-brain“ sondern „Cancer-brain“)

Zusammenfassung

- ✓ Die therapeutischen Optionen sind allerdings rar und die Evidenzlage ist dünn
- ✓ Gewisse Effektivität haben:
  - Web/PC-basiertes kognitives Training
  - Psychotherapie
  - Achtsamkeitstraining, z.B. MBSR
  - Körperliche Aktivität
- ✓ Ein erheblicher Studienbedarf besteht

Vielen Dank für die Aufmerksamkeit

Prof. Dr. med. O. Rick
Klinik Reinhardshöhe, Bad Wildungen