A Meta-Analysis of the Sensitivity of Various Neuropsychological Tests Used to Detect Chemotherapy-Induced Cognitive Impairment in Patients With Breast Cancer

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Purpose/Objectives: To identify which neuropsychological tests have been used to evaluate chemotherapy-induced impairment in various domains of cognitive function in patients with breast cancer and to determine the sensitivity of each of the tests through estimation of effect size.

Data Sources: Original studies published from 1966–June 2006.

Data Synthesis: Although an array of neuropsychological tests are available to measure the various domains of cognitive function, information is lacking regarding the sensitivity and specificity of the tests to detect changes in cognitive function from chemotherapy.

Conclusions: This meta-analysis provides initial data on the sensitivity of some neuropsychological tests to determine chemotherapy-induced changes in cognitive function in patients with breast cancer.

Implications for Nursing: The identification of sensitive neuropsychological tests is crucial to further understanding of chemotherapy-induced cognitive impairments.

Key Points . . .

- ➤ Chemotherapy-induced impairments in cognitive function occur in some women with breast cancer.
- ➤ Meta-analysis is a quantitative approach that pools findings across studies to increase the power to detect significant effects if they exist.
- ➤ Detection of cognitive impairments requires neuropsychological tests that are valid, reliable, feasible, sensitive, and specific.
- ➤ Further studies are needed to determine the optimal neuropsychological tests to detect chemotherapy-induced cognitive impairments.

Impairment in cognitive function as a side effect of chemotherapy is a growing area of research as the numbers of patients with cancer who complain of difficulties in their abilities to remember, think, and concentrate increases (Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Cole, Scialla, & Bednarz, 2000; Cull et al., 1996). Impairment in cognitive function may adversely affect patients' return to normal life when treatment is completed. Survivors have complained about difficulties with multitasking at home and decreased performance at work. Increased awareness among cancer survivors and clinicians about chemotherapy's acute and chronic effects on cognitive function has resulted in a limited number of studies and points to the need for additional research.

An array of neuropsychological tests is available to measure the various domains of cognitive function. Healthcare professionals should consider numerous factors when selecting tests to measure each domain of cognitive function: (a) the specific cognitive domain to be measured, (b) the appropriateness of the test for the domain being studied, (c) the reliability and validity of the test and the availability of normative data for comparison, (d) the sensitivity and specificity of the test for a particular condition, (e) the availability of parallel forms when repeated measures are used, and (f) the feasibility of the instrument for clinical use (Lezak, Howieson, & Loring, 2004).

Although 13 studies that evaluated chemotherapy-induced cognitive impairments in patients with breast cancer were identified, how the specific neuropsychological tests used in the studies were chosen is not clear. Most studies stated that tests were chosen for their ability to measure a specific domain, evidence of reliability and validity, availability of parallel forms for longitudinal studies, or feasibility. However, a great deal of variability exists in the tests that were chosen to measure various domains of cognitive function. In addition,

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discrepancies exist in which cognitive domain that specific tests were purported to measure.

Specific information on the purpose, description, administration time, scoring, reliability, validity, normative data, and parallel forms is readily available for most neuropsychological tests. However, information regarding the sensitivity and specificity of neuropsychological tests to detect changes in cognitive function from chemotherapy is lacking. Lezak et al. (2004) defined sensitivity of a neuropsychological test as "the probability of correctly detecting abnormal functioning in an impaired individual" (p. 149) and specificity as "the probability of correctly identifying a normal individual or an individual from another clinical population intact with respect to the test under consideration (i.e., correct rejection of abnormality)" (p. 149).

Only one pilot study has evaluated the relative sensitivity of a number of neuropsychological tests to detect chemotherapy-induced cognitive impairments in a sample with breast cancer. Freeman and Broshek (2002) evaluated 15 neuropsychological tests and subtests based on their sensitivity to detect mild cognitive impairments in patients with head injuries. The sample in the cross-sectional study consisted of 17 patients with breast cancer, eight of whom were currently receiving standard-dose chemotherapy and nine survivors who had completed standard-dose chemotherapy treatment 6–12 months earlier. The authors hypothesized that patients who were currently receiving chemotherapy would have significantly poorer test scores than the survivors. Significant differences between the two groups were found on only 2 of the 15 neuropsychological tests. However, the findings were not in the hypothesized direction for both tests. Patients undergoing active cancer treatment demonstrated poorer performance on the visual construction subtest of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), whereas survivors demonstrated poorer performance on the Stroop test. Because impairments in cognitive function have been found in survivors as long as 10 years after chemotherapy (Ahles et al., 2002), a major limitation of the study was the use of a comparison group with potentially similar cognitive deficits to determine the sensitivity of various neuropsychological tests. In addition, cognitive impairment was found in some patients at baseline, prior to the initiation of chemotherapy (Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). An additional limitation of the study was a lack of baseline or prechemotherapy testing.

Another method that has been used to determine the sensitivity of neuropsychological tests is meta-analysis (Irwig et al., 1994; Zakzanis, 2001). Meta-analysis is a quantitative approach that is used to combine results from several studies with various sample sizes in an attempt to determine an effect size for a specific intervention or procedure (Glass, 1976; Lipsey & Wilson, 2001). A benefit of the approach is that pooling findings across studies increases the power to detect significant effects if they exist. Effect size is defined as the standardized index of the magnitude of the difference in the results across studies between the treatment and the comparison groups (Cohen, 1988). In addition, effect size provides information on the direction of a relationship. Meta-analysis has been suggested as a potentially useful tool for assessing the diagnostic accuracy of tests (Irwig et al.).

Only one meta-analysis was found that evaluated the sensitivity of various neuropsychological tests to detect diffuse brain damage in multiple patient populations (Chouinard & Braun, 1993). The sample consisted of 67 studies that used at least two neuropsychological tests to measure the same cognitive domain and provided evidence of a statistically significant difference in test scores between the clinical and control groups for at least one test.

Twenty-two neuropsychological tests were assigned to specific domains of cognitive function (e.g., attention and concentration, problem solving, speed of information processing, motor abilities, complex visual perception, constructional abilities, memory, language, executive function). Tests then were ranked within each study based on their ability to detect group differences. For tests that had several scores, only the score that found the greatest difference was used in the meta-analysis. Test rankings then were summed and divided by the total number of study comparisons to provide mean proportional rankings. Rankings were done so that smaller proportions indicated increased test sensitivity and larger proportions indicated decreased sensitivity. Although the meta-analysis (Chouinard & Braun, 1993) found differences in the sensitivity of several neuropsychological tests within specific domains of cognitive function, effect size was not calculated for each test. Because few studies provided means and standard deviations, the authors calculated z scores from the control groups and used them to rank tests in terms of sensitivity. Therefore, the rankings may be biased because sample sizes were not accounted for in the calculations.

Although the findings of the Chouinard and Braun (1993) meta-analysis represent a first step in determining the sensitivity of various neuropsychological tests to detect changes in cognitive function, they are not readily transferable to patients who are receiving chemotherapy for several reasons. First, many of the neuropsychological tests used in studies of chemotherapy-induced cognitive impairment were not included. In addition, the patient samples were heterogeneous (e.g., patients with normal aging, alcoholism, multiple sclerosis, Parkinson disease, HIV, Alzheimer disease, schizophrenia) and did not include patients with cancer. The focus of the meta-analysis was on patients with diffuse brain injuries, which may induce changes in cognitive function by different mechanisms than chemotherapy and result in impairments in different domains of cognitive function.

Two meta-analyses examined the nature and severity of cognitive impairments induced by chemotherapy in patients with breast cancer. Falleti, Sanfilippo, Maruff, Weih, & Phillips (2005) analyzed six studies that used 55 neuropsychological tests to measure various domains of cognitive function. Tests were assigned to one of six cognitive domains: attention, memory, motor function, executive function, spatial ability, or language. Negative effect sizes (i.e., chemotherapy resulted in deficits in cognitive function) ranging from negligible to moderate were found in each domain. Stewart, Bielajew, Collins, Parkinson, and Tomiak (2006) analyzed seven studies that used a total of 48 neuropsychological tests or subtests. Tests were grouped conceptually into eight cognitive domains: simple attention, working memory, short-term memory, long-term memory, speed of information processing, language, spatial skill, and motor abilities. Significant small negative effect sizes were found for every cognitive domain except attention. Because the effect size for each neuropsychological test that was used to measure the various domains of cognitive function was not provided in either

of the meta-analyses, it is not clear which tests were more sensitive to detect changes in cognitive function associated with chemotherapy.

Therefore, the purposes of the current meta-analysis were to identify which neuropsychological tests were used to evaluate chemotherapy-induced impairment in various domains of cognitive function in patients with breast cancer and to determine the sensitivity of each of the tests, used in at least two studies, through estimation of effect size.

Methods

Literature Search and Selection of Studies

A preliminary search was performed for original research reports published in English from 1966–June 2006 on the association between chemotherapy and cognitive impairments in patients with breast cancer. Five computerized databases were accessed (PubMed, PsycINFO, CogNet, CINAHL, and the Cochrane Database of Systematic Reviews). Unpublished sources were not considered. Key words used for the search were "breast cancer," "chemotherapy," "cognitive impairment," "cognitive deficits," "cognitive function," "antineoplastic agents," and "neuropsychological tests."

Several articles were listed in more than one database, and more than 150 citations were obtained. Abstracts from all of the research studies were reviewed to determine whether they met the following eligibility criteria: (a) original study data, (b) neuropsychological testing of patients with breast cancer who had received or were currently receiving chemotherapy, (c) valid and reliable neuropsychological tests with published standardized administration procedures, and (d) sufficient information reported (either by quantitative measurement or inferential statistics) on at least one test of cognitive function, to allow for the estimation of effect size. Reviews, commentaries, case reports, and meta-analyses were excluded.

Heterogeneous studies were excluded if they did not distinguish patients with breast cancer from those with other cancer diagnoses. The search was supplemented by a manual review of the bibliographies of all of the relevant studies and reviews. One additional study was found using that approach. Table 1 provides a summary of the 13 studies that met all of the eligibility criteria and their sample characteristics. Although each study used numerous tests to measure cognitive function, some of the tests were not used in two or more studies or information was not available on a specific test to calculate effect size. Only tests that were used in at least two studies were included in the meta-analysis; they are listed in Table 2.

Classification of Tests by Cognitive Domain

Prior to determining effect size for each of the neuropsychological tests, the researchers assigned each test to a specific cognitive domain. In some of the studies, several neuropsychological tests were used to measure more than one domain of cognitive function, but for the purposes of this meta-analysis, each test was assigned to a single domain to provide consistency in the evaluations. Although most of the domains were assigned using neuropsychological assessment references (e.g., Lezak et al., 2004; Spreen & Strauss, 1998), some were assigned using the guidance of the meta-analyses of chemotherapy-induced cognitive impairments in patients with cancer (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Falleti et al., 2005; Stewart et al., 2006).

Procedure

Johnson's (1993) DSTAT 1.10 meta-analysis software was used to calculate the standardized mean difference effect size (ES_{sm}) and the 95% confidence interval. Because small studies can overestimate effect size, the potential for bias was corrected by weighting the ES_{sm} for each test by the sample size and pooled variance (Hedges & Olkin, 1985). In addition, because some tests yielded several scores, average effect size was calculated for those tests (Lipsey & Wilson, 2001; Wolf, 1986). Effect sizes were calculated from standardized mean differences using the means and standard deviations reported for each neuropsychological test result. Approximately 79% of the effect sizes (n = 131) were determined using means and standard deviations. When means and standard deviations were not available, effect sizes were calculated from other reported statistics: p values (11%, n = 18) and t tests (10%, n = 17). Effect sizes were coded so that positive scores indicated better cognitive function and negative scores indicated poorer cognitive function.

Results

Effect sizes are interpreted as negligible if they are less than 0.20, small if they are 0.20–0.50, medium if they are 0.50–0.80, and large if they are greater than 0.80 (Cohen, 1988). A significance level of 0.05 is inferred when the 95% confidence interval does not cross zero (Shadish & Haddock, 1994). A total of 166 effect sizes were calculated from test results in the 13 studies, ranging from negligible to large. However, the average effect sizes for each test ranged from negligible to moderate and are summarized in Table 3.

Attention and Concentration

Attention is a cognitive function of the brain that enables a person to triage relevant inputs, thoughts, and actions while ignoring those that distract or are irrelevant (Gazzaniga, Ivry, & Mangun, 2002; Grober, 2002; Heilman, Valenstein, & Watson, 1997). Concentration is the ability to focus and sustain attention (Lezak et al., 2004). Four neuropsychological tests (d2 test, High Sensitivity Cognitive Screen [HSCS] attention subtest, and Wechsler Adult Intelligence Scale [WAIS] digit and spatial span subtests) were used in at least two studies to measure chemotherapy-induced impairments in attention and concentration. The digit span backward test produced the largest effect size, but none of the tests of attention and concentration produced a significant effect size.

Executive Function

Executive function refers to higher-order cognitive processes that include initiation, planning, hypothesis generation, cognitive flexibility, decision making, regulation, judgment, feedback utilization, and self-perception (Spreen & Strauss, 1998). Five neuropsychological tests (Booklet Category Test, Trail Making Test [TMT]-Part B, HSCS self-regulation and planning subtest, Stroop test, and WAIS similarities subtest) were used in at least two studies to measure chemotherapy-induced impairments in executive function. Although the Booklet Category Test produced the largest effect size, none of the tests of executive function produced a significant effect size.

Table 1. Characteristics of Studies Included in the Meta-Analysis

Study	Comparison and Sample	$\bar{X}$ Age (Years)	Staging and Treatment	$\bar{X}$ Time Since Treatment (SD)
Ahles et al., 1996	Within subjects (N = 20)	Not reported	Staging not reported. High-dose chemotherapy: 90% CTC, 10% cyclophosphamide/cisplatin/carmustine	Prior to bone marrow transplantation, one to three days after transplantation, and one month after transplantation
Ahles et al., 2002	Control: patients treated with local therapy; norms (N = 70)	Survivors: 60.6 (SD = 10.5)	**Survivors** Staging: 37% stage I, 54% stage II, 3% stage III, 3% stage IV, 3% regional Standard-dose chemotherapy—40% CMF, 40% CAF, 9% AC, 6% CMF plus vincristine/prednisone, 3% cyclophosphamide/carboplatin, 2% other	Survivors: 9.4 (4.5) years
		Control: 59.1 (SD = 10.7)	**Control group** Staging: 20% stage 0, 60% stage I, 14% stage I, 3% stage III, 3% unknown	Control: 9.9 (5.8) years
Bender et al., 2006	Within subjects; control: patients with ductal carcinoma in situ (N = 46)	Chemotherapy only: 40.1 (SD = 6.5)	**Chemotherapy only** Staging: 32% stage I and 68% stage II Standard-dose chemotherapy: 20% CMF, 40% AC, 40% AC plus a taxane	Chemotherapy only: within a week and one year after chemotherapy was completed
		Chemotherapy plus hormone-replacement therapy: 44.1 (SD = 3.5)	**Chemotherapy plus hormone-replacement therapy** Staging: 32% stage I and 68% stage II Standard-dose chemotherapy: 25% doxorubicin and a taxane, 33% AC, 42% AC plus a taxane	Chemotherapy plus hormone-replacement therapy: within a week and one year after chemotherapy was completed
		Control: 44.5 (SD = 4.2)	**Control group** Staging: 100% ductal carcinoma in situ	
Brezden et al., 2000	Control: healthy females (N = 107)	Current chemotherapy: median = 49 (range = 34–70)	**Current chemotherapy** Stage I or II (Exact percentages were not reported.) Standard-dose chemotherapy: 39% CMF and 51% FEC	Current chemotherapy: median three cycles of chemotherapy; range = two to eight cycles of chemotherapy
		Survivors: median = 46 (range = 26–61)	**Survivors** Stage I or II (Exact percentages were not reported.) Standard-dose chemotherapy: 52.5% CMF, 42.5% FEC, 5% other	Survivors: median = 25; range = 12–36+ months
		Control: median = 41.5 (range = 24–61)		
Castellon et al., 2004	Control: local treatment (N = 53)	Survivors: 46.8 (SD = 6.3) Control: 48.3 (SD = 4.0)	**Chemotherapy survivors** Stage I or II (Exact percentages were not reported.) Standard-dose chemotherapy: 41% CMF, 38% AC or doxorubicin added to CMF, 9% AC plus a taxane	Two to five years after diagnosis; exact time since chemotherapy was not reported.

(Continued on next page)

AC—doxorubicin and cyclophosphamide; CAF—cyclophosphamide, doxorubicin, and 5-fluorouracil; CMF—cyclophosphamide, methotrexate, and 5-fluorouracil; CTC—cyclophosphamide, thiotepa, and carboplatin; CTM—cyclophosphamide, thiotepa, and mitoxantrone; EC—epirubicin and cyclophosphamide; FEC—5-fluorouracil, epirubicin, and cyclophosphamide

Table 1. Characteristics of Studies Included in the Meta-Analysis *(Continued)*

Study	Comparison and Sample	$\bar{X}$ Age (Years)	Staging and Treatment	$\bar{X}$ Time Since Treatment (SD)
Donovan et al., 2005	Control: local treatment (N = 143)	Chemotherapy survivors: 52.3 (SD = 8.1)	**Chemotherapy survivors:** 18.3% stage 0 or I and 81.7% stage II Standard-dose chemotherapy: 56.7% AC, 16.7% AC plus paclitaxel, 13.3% CMF, 10% AC plus docetaxel, 3.3% doxorubicin and docetaxel	Chemotherapy survivors: 213.3 days after completion of external radiation therapy, exact time since chemotherapy not reported
		Control: 57.7 (SD = 9.1)	**Control** 95.2% stage 0 or I and 4.8% stage II	
Schagen et al., 1999	Control: stage I (N = 73)	Survivors: 47.1 (SD = 6.5)	Node positive (greater than stage I) (Exact staging was not reported.)	Survivors: 1.9 (1.0) years
		Control: 46.1 (SD = 5.2)	Standard-dose chemotherapy: CMF	Control: 2.4 (1.0) years
Scherwath et al., 2006	Control: local treatment only (N = 76)	Standard-dose chemotherapy survivors: 51.8 (SD = 8.6) High-dose chemotherapy survivors: 53.3 (SD = 7.1) Control: 54.6 (SD = 8.0)	High risk, greater than 10 nodes positive (Exact staging was not reported.) Standard-dose chemotherapy: EC followed by CMF High-dose chemotherapy: EC followed by CTM with stem cell support	Standard dose: 62.2 (22.7) months High dose: 61.6 (21.7) months
Shilling et al., 2005	Within and control: healthy females (N = 93)	Survivors: 51.1 (SD = 8.6) Control: 52.3 (SD = 5.8)	Early stage (Exact staging was not reported.) Standard-dose chemotherapy: 82% FEC, 3% CMF, 3% AC, 12% FEC followed by docetaxel or additional FEC	Four weeks after final chemotherapy treatment
Tchen et al., 2003	Control: healthy females (N = 200)	Current chemotherapy: median = 48; range = 27–60 Control: median = 47; range = 26–62	Staging was not reported. Standard-dose chemotherapy: 64% FEC, 11% CMF, 17% AC, 8% other	36% after third, 28% after fourth, 14% after fifth, 20% after sixth, and 2% after seventh cycle of chemotherapy
van Dam et al., 1998	Control: stage I (N = 104)	Standard-dose chemotherapy: 48.1 (SD = 6.8) High-dose chemotherapy: 45.5 (SD = 6.2)	Stage II, standard-dose chemotherapy: FEC High-dose chemotherapy: FEC followed by CTC	Standard-dose: 1.9 (1.1) years High-dose: 1.6 (0.8) years
		Control: median = 46.1 (SD = 5.2)		Control: 2.4 (1.0) years
Wefel et al., 2004	Within subjects (N = 18)	45.4 (SD = 6.7), range = 34–63	28% stage I and 72% stage II Standard-dose chemotherapy: CAF	Prior to chemotherapy and three weeks and one year after chemotherapy
Wieneke & Dienst, 1995	Norms (N = 28)	42 (SD = 6.7, range = 28–54)	Stage I and II (Percentages were not reported.) Standard-dose chemotherapy: 57% CMF, 29% CMF plus CAF, 14% CAF	6.6 (4.0); 0.5–12 months

AC—doxorubicin and cyclophosphamide; CAF—cyclophosphamide, doxorubicin, and 5-fluorouracil; CMF—cyclophosphamide, methotrexate, and 5-fluorouracil; CTC—cyclophosphamide, thiotepa, and carboplatin; CTM—cyclophosphamide, thiotepa, and mitoxantrone; EC—epirubicin and cyclophosphamide; FEC—5-fluorouracil, epirubicin, and cyclophosphamide

Table 2. Neuropsychological Tests Included in the Meta-Analysis and Assignment to Specific Domains

Tests by Cognitive Domain	Reference Support
Attention/concentration	
d2 test	Falleti et al., 2005; Spreen & Strauss, 1998
High Sensitivity Cognitive Screen (HSCS) attention subtest	Anderson-Hanley et al., 2003
Wechsler Adult Intelligence Scale (WAIS) digit span subtest	Anderson-Hanley et al., 2003; Falleti et al., 2005; Lezak et al., 2004; Stewart et al., 2006
WAIS spatial span subtest	Anderson-Hanley et al., 2003; Lezak et al., 2004
Executive function	
Booklet Category Test	Falleti et al., 2005; Lezak et al., 2004; Spreen & Strauss, 1998
HSCS self-regulation subtest	Anderson-Hanley et al., 2003
Stroop test	Anderson-Hanley et al., 2003; Falleti et al., 2005; Spreen & Strauss, 1998
Trail Making Test (TMT)-Part B	Anderson-Hanley et al., 2003; Falleti et al., 2005; Spreen & Strauss, 1998
WAIS similarities subtest	Anderson-Hanley et al., 2003; Falleti et al., 2005; Lezak et al., 2004
Information processing speed	
Fepsy binary choice subtest	Stewart et al., 2006
Fepsy visual reaction subtest	Stewart et al., 2006
Fepsy visual searching subtest	Stewart et al., 2006
Paced Auditory Serial Addition Test	Spreen & Strauss, 1998
TMT-Part A	Spreen & Strauss, 1998
WAIS digit symbol subtest	Anderson-Hanley et al., 2003; Stewart et al., 2006
Language	
Controlled Oral Word Association	Lezak et al., 2004; Spreen & Strauss, 1998; Stewart et al., 2006
HSCS language subtest	Stewart et al., 2006
Motor function	
Fepsy finger tapping test	Falleti et al., 2005; Stewart et al., 2006
Grooved pegboard	Anderson-Hanley et al., 2003; Falleti et al., 2005; Lezak et al., 2004; Spreen & Strauss, 1998; Stewart et al., 2006
Halstein-Reitan Neuropsychological Battery finger tapping subtest	Anderson-Hanley et al., 2003; Falleti et al., 2005; Lezak et al., 2004; Spreen & Strauss, 1998; Stewart et al., 2006
HSCS psychomotor subtest	Not listed in a reference
Visuospatial skill	
HSCS spatial subtest	Anderson-Hanley et al., 2003
Rey-Osterrieth Complex Figure Test (RCFT) copy	Anderson-Hanley et al., 2003; Falleti et al., 2005; Lezak et al., 2004; Spreen & Strauss, 1998; Stewart et al., 2006
WAIS block design subtest	Anderson-Hanley et al., 2003; Falleti et al., 2005; Lezak et al., 2004; Stewart et al., 2006
Verbal memory	
California Verbal Learning Test	Anderson-Hanley et al., 2003; Falleti et al., 2005; Lezak et al., 2004; Spreen & Strauss, 1998
HSCS memory subtest	Anderson-Hanley et al., 2003
Rey Auditory Verbal Learning Test	Anderson-Hanley et al., 2003; Falleti et al., 2005; Lezak et al., 2004; Spreen & Strauss, 1998
Wechsler Memory Scale (WMS) logical memory subtest	Anderson-Hanley et al., 2003; Falleti et al., 2005; Lezak et al., 2004; Spreen & Strauss, 1998; Stewart et al., 2006
Visual memory	
RCFT delayed recall	Anderson-Hanley et al., 2003; Falleti et al., 2005; Lezak et al., 2004; Spreen & Strauss, 1998; Stewart et al., 2006
WMS visual reproduction subtest	Falleti et al., 2005; Lezak et al., 2004; Spreen & Strauss, 1998; Stewart et al., 2006

Information Processing Speed

Information processing speed refers to the brain's ability to rapidly process simple and complex information (Freeman & Broshek, 2002). Because input of information may be tactile, auditory, verbal, or visual, this domain is inter-related with all of the other domains of cognitive function and may have a direct influence on people's ability to store such information into memory. Six neuropsychological tests (Fepsy binary choice, visual reaction, and visual searching subtests; Paced Auditory Serial Addition Test [PASAT]; TMT-Part A; and WAIS digit symbol subtest) were used in at least two studies to measure chemotherapy-induced impairments in information processing speed. Although the largest effect size was found with the PASAT and the visual reaction subtest of the Fepsy, none of the tests of information processing speed produced a significant effect size.

Table 3. Effect Sizes for Neuropsychological Tests Used in Studies of Chemotherapy-Induced Impairments

Test	Number of Studies	N	Effect Size	Lower 95% Confidence Interval	Upper 95% Confidence Interval
Attention/concentration					
d2 test	3	316	−0.399192	−0.898373	+0.100013
HSCS attention subtest	2	343	−0.184726	−0.540761	+0.171310
WAIS digit span subtest[a]	2	222	−0.348107	−0.782188	+0.072237
WAIS digit span forward	4	340	−0.023283	−0.542055	+0.495490
WAIS digit span backward	3	235	−0.448912	−0.961065	+0.063241
WAIS spatial span subtest	2	188	+0.008552	−0.442101	+0.459204
Executive function					
Booklet Category Test	2	46	−0.456752	−1.084876	+0.171314
HSCS self-regulation subtest	2	343	−0.258260	−0.615507	+0.008087
Stroop test	4	357	−0.021877	−0.492703	+0.448949
TMT-Part B	9	567	−0.125702	−0.606911	+0.370226
WAIS similarities subtest	2	46	+0.188273	−0.422259	+0.798805
Speed of information processing					
Fepsy binary choice subtest	2	211	−0.105302	−0.573555	+0.362945
Fepsy visual reaction subtest	2	211	−0.501889	−0.978857	+0.160956
Fepsy visual searching subtest	2	211	−0.055699	−0.523706	+0.412307
Paced Auditory Serial Addition Test	2	81	−0.538267	−1.107843	+0.031309
TMT-Part A	8	547	−0.299549	−0.766981	+0.191314
WAIS digit symbol subtest	7	523	−0.375823	−0.816644	+0.100617
Language					
COWA	8	557	−0.332899	−0.791787	+0.125989
HSCS language subtest	2	343	**−0.434461**	**−0.816900**	**−0.096861**
Motor function					
Fepsy finger tapping test	2	211	**−0.599585**	**−1.078915**	**−0.120254**
Grooved pegboard	3	87	**−0.955051**	**−1.684365**	**−0.225752**
HRNB finger tapping	2	213	+0.194945	−0.214320	+0.541522
HSCS psychomotor subtest	2	343	−0.282503	−0.640663	+0.107783
Visuospatial skill					
HSCS spatial subtest	2	343	−0.114439	−0.470401	+0.177954
RCFT copy	4	292	**−0.512445**	**−1.017514**	**−0.007376**
WAIS block design subtest	4	169	**−0.554656**	**−1.106400**	**−0.002912**
Verbal memory					
CVLT	4	216	−0.409361	−0.883348	+0.065488
HSCS memory subtest	2	343	**−0.453015**	**−0.813005**	**−0.093025**
RAVLT	4	328	−0.269487	−0.750206	+0.211232
WMS logical memory subtest	3	216	−0.409361	−0.883348	+0.344564
Visual memory					
RCFT delayed recall	7	514	−0.373973	−0.886677	+0.138735
WMS visual reproduction subtest	4	339	−0.194879	−0.625094	+0.235345

[a] Studies did not specify whether test was forward or backward.

COWA—Controlled Oral Word Association; CVLT—California Verbal Learning Test; HRNB—Halstead-Reitan Neuropsychological Battery; HSCS—High Sensitivity Cognitive Scale; RAVLT—Rey Auditory Verbal Learning Test; RCFT—Rey-Osterrieth Complex Figure Test; TMT—Trail Making Test; WAIS—Wechsler Adult Intelligence Scale; WMS—Wechsler Memory Scale

Note. Values that are bolded indicate significant effect sizes (p = 0.05).

Language

Language incorporates written and spoken communication when used to express thoughts. Impairments in language inhibit people's ability to communicate with others or to follow directions without needing repetitions and explanations. Language processing involves representing, comprehending, and communicating symbolic information, either written or spoken (Gazzaniga et al., 2002). Only two neuropsychological tests (HSCS language subtest and Controlled Oral Word Association) were used in at least two studies to measure chemotherapy-induced impairments in language. Only the language subtest of the HSCS produced a small but significant effect size (–0.43, p = 0.05).

Motor Function

Motor function relates to motor performance, such as speed, strength, and coordination. Four tests (Fepsy finger tapping test, grooved pegboard, HSCS psychomotor subtest, and Halstein-Reitan Neuropsychological Battery [HRNB] finger tapping subtest) were used in at least two studies to measure chemotherapy-induced impairments in motor function. Significant effect sizes were found for two of the tests of motor function. The grooved pegboard produced a large effect size (–0.90, p = 0.05), and the Fepsy finger tapping test produced a moderate effect size (–0.60, p = 0.05).

Visuospatial Skill

Visuospatial skill refers to the ability to process and interpret visual information regarding where things are situated in space (Spreen & Strauss, 1998). Three tests (HSCS spatial subtest, Rey-Osterrieth Complex Figure Test [RCFT] copy, and WAIS block design subtest) were used in at least two studies to measure chemotherapy-induced impairments in visuospatial skill. Significant moderate effect sizes were found for two of the tests of visuospatial skill (RCFT copy –0.51, p = 0.05; block design subtest of the WAIS –0.55, p = 0.05).

Verbal and Visual Memory

Memory is an outcome of learning that is created and strengthened by repetition (Gazzaniga et al., 2002). Memory infers the ability to acquire, store, and use new information (Grober, 2002). The most common types of memory are verbal and visual memory. Four tests (California Verbal Learning Test, HSCS memory subtest, Rey Auditory Verbal Learning Test, and Wechsler Memory Scale [WMS] logical memory subtest) were used in at least two studies to measure chemotherapy-induced cognitive impairments in verbal memory. Only the memory subtest of the HSCS produced a small but significant effect size (–0.45, p = 0.05). Two tests were used in at least two studies to measure chemotherapy-induced impairments in visual memory (RCFT delayed recall and WMS visual reproduction subtest). Although the largest effect size was found with the delayed recall of the RCFT, neither of the tests of visual memory produced a significant effect size.

Discussion

This meta-analysis is the first to evaluate the sensitivity of several neuropsychological tests to detect impairments in various domains of cognitive function induced by chemotherapy in patients with breast cancer. Results demonstrate that only six tests were sensitive to chemotherapy-induced impairment in four of the eight domains of cognitive function (i.e., language, motor function, visuospatial skill, and verbal memory). The most sensitive test was the grooved pegboard test, used to measure motor function. In addition, the Fepsy finger tapping test was found to be a sensitive measure in the same cognitive domain. Similarly, two tests used to measure visuospatial skill were found to be sensitive (RCFT copy and block design subtest of WAIS). Only one neuropsychological test was found to be sensitive to detect impairments in language (the language subtest of HSCS) and verbal memory (the memory subtest of HSCS).

Although some of the specific neuropsychological tests that were identified as sensitive in this study differed from those identified by Chouinard and Braun (1993), both studies provide some evidence for tests sensitive to impairment in the cognitive domains of language, motor function, and visuospatial skill in patients with diffuse brain injury and in those who received chemotherapy. Although the mechanisms of chemotherapy-induced cognitive impairments remain to be determined, some of the cognitive impairments identified in patients with diffuse brain injuries from congestive heart failure and chronic obstructive pulmonary disease are similar to those identified in patients with chemotherapy-induced cognitive impairments (Raffa et al., 2006). Because the current meta-analysis and the one performed by Chouinard and Braun identified different tests to measure most of the domains, one cannot determine whether the tests that were found to be sensitive in the analysis by Chouinard and Braun might be sensitive enough to detect changes induced by chemotherapy.

One limitation of the current study was the exclusion of unpublished studies that may not have been published because of negative findings, which would result in overestimation of effect sizes reported in this analysis. Given the limited number of studies on the effects of chemotherapy on cognitive function in patients with breast cancer, the results of this meta-analysis need to be interpreted with caution. Most of the neuropsychological tests used in the studies performed to date do not appear to be sensitive enough to detect changes in cognitive function. One explanation for the lack of significant findings is the relatively small number of patients studied to date, as well as the hetereogeneity of the study samples (e.g., various chemotherapy regimens, patients undergoing active treatment, cancer survivors at variable times after treatment). Another equally plausible explanation is that chemotherapy-induced changes in the various domains of cognitive function are time dependent or acute or chronic in nature. The detection of such changes, although dependent on the sensitivity of the neuropsychological test, is more dependent on the timing of test administration. Another possibility is that certain domains of cognitive function are not affected by chemotherapy. Lastly, chemotherapy-induced impairments in cognitive function may be so subtle that none of the currently used tests is sensitive enough to detect changes.

Conclusion

This meta-analysis provides initial data on the sensitivity of some neuropsychological tests to determine chemotherapy-induced changes in cognitive function in patients with breast cancer, but the limited number of studies makes drawing definitive conclusions difficult. Further investigation is needed to identify the instruments that are the most valid, reliable, sensitive, and specific for detecting chemotherapy-induced cognitive impairments, whether they are short term or persistent. In addition, carefully designed longitudinal studies with baseline measurements are needed to evaluate this potentially deleterious and devastating consequence of cancer treatment. The identification of sensitive neuropsychological tests is crucial to further understanding of chemotherapy-induced cognitive impairments. Increased awareness of this side effect of chemotherapy can guide nurses to monitor for its occurrence, as well as provide support to and advocate for patients.

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