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Self-reported chemotherapy-related cognitive impairment compared with cognitive complaints following menopause

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Abstract

Objective: Cancer-related cognitive impairment (CRCI) is commonly reported following the administration of cancer treatment. Current longitudinal studies, primarily in women with breast cancer, suggest that up to 35% to 60% of patients exhibit persistent CRCI (pCRCI) following completion of chemotherapy. Complaints of subjective cognitive decline (SCD) are also commonly reported by women during and following the menopause transition in noncancer patients. Although the majority of evidence for cognitive difficulties in cancer patients and survivors is attributed to chemotherapy, there is growing evidence to suggest that menopausal status can also influence cognitive function in cancer patients.

Methods: Given that menopausal status may be contributing to pCRCI, we compared a group of primarily postmenopausal women with pCRCI to 2 groups of postmenopausal women: women who endorse menopause-associated SCD (maSCD+) and women who do not (maSCD−) to explore the similarities/differences between maSCD and pCRCI and the potential role of menopause in pCRCI.

Results: Persistent CRCI participants report more severe SCD symptoms than women after natural menopause, despite being on average 2.5-year postchemotherapy, supporting previous findings that CRCI can persist for months to years after completing treatment. Persistent CRCI participants not only endorsed greater SCD but also exhibited objective performance differences. In addition, pCRCI participants endorsed significantly greater menopausal symptoms compared with either maSCD group. Results were not related to menopausal status prior to chemotherapy or current endocrine therapy use.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conclusions: These results suggest that while menopausal symptoms may contribute to SCD experienced by cancer patients after chemotherapy, they do not fully account for pCRCI.

Keywords

cancer; chemotherapy-related cognitive impairment; menopause; oncology; subjective cognitive decline

1 | BACKGROUND

Cancer-related cognitive impairment (CRCI) is commonly reported following the administration of cancer treatment.[1] Current longitudinal studies suggest that up to 75% exhibit cognitive decline during treatment, 35% to 60% exhibit persistent cognitive decline following completion of chemotherapy,[2] and research suggests that CRCI can persist for months to years after finishing treatment.[3] This persistent CRCI (pCRCI) can have profound consequences upon quality of life, including occupational and social functioning.[4] The American Cancer Society defines CRCI as increased forgetfulness, trouble concentrating and remembering details, difficulty with multitasking, word finding, and taking longer to finish tasks.[5] Although changes across various domains on objective testing have been reported for CRCI, effects have been reported most prominently in the domains of attention, working memory, executive function, and processing speed.[6] Severity of CRCI is typically mild to moderate in nature, such that impairments experienced would not typically qualify for a diagnosis of mild cognitive impairment (MCI)[7] or dementia; however, even subtle impairments in cognitive functioning can greatly impact quality of life.[2]

Complaints of cognitive dysfunction are also commonly reported by women during and following the menopause transition in noncancer patients[8] and may be related to the decline in circulating estrogen levels.[9] The transition from premenopausal to postmenopausal status is associated with cognitive difficulties in learning and memory.[10] For example, approximately 60% of middle-aged women reported cognitive changes in the Seattle Midlife Women's Health Study,[11] and 42% of postmenopausal women reported a negative change in cognition in the Study of Women Across the Nation.[12] There is also increasing evidence that subjective cognitive decline (SCD), even with normal performance on objective neuropsychological tests, is associated with an increased risk for developing late-life cognitive decline and Alzheimer disease in female noncancer patients.[13] In addition to naturally occurring menopause, surgically induced menopause has been found to be detrimental to cognitive functioning, particularly on verbal memory tasks,[14] as well as being associated with fewer improvements with practice compared with age-matched women who underwent a natural menopause.[15] Although not universally agreed upon,[16] it has been suggested that chemotherapy-induced menopause might have similar effects on cognitive functioning.[17]

Although the majority of evidence for cognitive difficulties in cancer patients and survivors is attributed to chemotherapy, there is growing evidence to suggest that menopausal status and/or endocrine therapy can also influence cognitive function in cancer patients.[1] Case studies in breast cancer reveal that cognitive difficulties can vary among patients who

received the same course of chemotherapy, suggesting that this could be related to menopausal status.[18] The effect of menopause may be particularly relevant for breast cancer patients since adjuvant endocrine therapy for hormone-receptor positive (HR+) breast cancer, which account for approximately 70% to 75% of breast cancers,[19] has been shown to impact cognitive function, either alone or in combination with chemotherapy.[20] For example, neuroimaging research in breast cancer patients has shown that changes in the patterns of brain activity from prechemotherapy to postchemotherapy treatment varies according to pretreatment menopausal status.[21] Given that there is a question of how much menopause contributes to the pCRCI phenotype in women, we compared a group of primarily postmenopausal women with subjective pCRCI with 2 groups of postmenopausal women without a history of cancer: women who endorse subjective complaints after menopause (menopause-associated SCD [maSCD+]) and women who do not (maSCD) to explore the similarities and differences between SCD following chemotherapy and SCD following menopause. This comparison is unique because the majority of CRCI research has compared cancer patients with completely healthy controls. While our maSCD− group serves as a healthy control group, the addition of a comparison group of otherwise healthy women without a history of cancer who also endorse SCD (maSCD+ group), to our knowledge, has never been previously examined.

2 | METHODS

2.1 | Participants

This study included data from 63 total participants who were recruited for 2 separate studies conducted by the same principal investigator: a pCRCI study and a maSCD study; pCRCI participants were recruited as part of a clinical trial () evaluating the effect of transdermal nicotine to improve subjective pCRCI in breast cancer, ovarian cancer, and lymphoma patients; MaSCD study participants were recruited as part of a larger study examining the ability of estrogen to enhance cholinergic-related cognitive function.[22] Only screening and baseline (pretreatment) data are presented for both studies.

A total of 36 women were recruited and screened for the pCRCI study. Of this sample, 24 cancer (breast cancer = 20), ovarian cancer = 1, lymphoma = 3) patients completed both a screening and baseline visit and were included in the current analysis. Twelve were excluded because they did not meet inclusion/exclusion criteria. The pCRCI study was conducted at Vanderbilt University. The maSCD study was conducted at both Vanderbilt University and University of Vermont. A total of 53 healthy, postmenopausal women were recruited and screened for the maSCD study. Of this sample, 39 women completed both a screening and baseline visit and were included in the current analysis. Fourteen were excluded because they did not meet inclusion/exclusion criteria. Both studies were performed in accordance with the recommendations of University of Vermont and Vanderbilt University Institutional Review Boards with written informed consent from all participants.

2.2 | Inclusion and exclusion criteria

Both studies had very similar exclusion criteria, which allowed for the comparison between studies. Both studies excluded for (1) smokers (no nicotine use within the last 5 years), (2)

any active neurologic and/or psychiatric disease, history of significant head trauma followed by persistent neurologic deficits, or known structural brain abnormalities, (3) current major depression or another major psychiatric disorder as described in DSM-5, (4) any history of alcohol or substance abuse or dependence, and (5) any significant systemic illness or unstable medical condition, which could lead to difficulty complying with the protocol. Exclusion criteria for the maSCD participants included all of the above criteria for the pCRCI study with the following additional criteria: (1) use of hormone therapy during the last year, (2) a history of breast cancer, and (3) and a history or presence of severe menopausal symptoms.

Differences in inclusion criteria for the 2 studies were as follows:(1) pCRCI study participants were required to be between 35 to 80 years of age, been diagnosed with noninvasive or invasive breast cancer, ovarian cancer, or lymphoma, undergone chemotherapy treatment within the last 1 to 5 years, endorsed pCRCI subjective complaints; (2) maSCD study participants were required to be between 50 to 60 years of age, and postmenopausal (ie, without menses for 1 y and without surgically induced menopause).

2.3 | Screening measures

Both studies shared similar screening measures. Participants were screened to exclude individuals with evidence of clinically significant cognitive impairment or dementia. To rule out the presence of current mood disorders, all participants were psychiatrically assessed using the Beck Depression Inventory Scale[23] (BDI; score ≤ 9). The menopause symptom checklist[24] (modified from Sherwin[25]), a 60-item self-report rating inventory, was used to assess frequency of menopausal symptoms in the last 4 weeks. The Cognitive Complaint Index (CCI)[26] was used to operationalize both study participants as having subjective complaints (see Vega et al[27] for details). The CCI was chosen as the screening measure to operationalize breast cancer patients as having subjective complaints because previous research has shown that CCI score correlates with underlying neurodegenerative changes even when unaccompanied by deficits on formal testing,[26] and it has been used in previous studies by Newhouse et al looking at cognitive complaints in postmenopausal women.[28]

2.4 | Outcome measures

2.4.1 | Behavioral—For both the pCRCI study and maSCD study, a CCI score was calculated as the percentage of all items endorsed. For the pCRCI study, participants were required to have endorsement of at least 20% of all items to be considered as having chemotherapy-related subjective complaints[26] (n = 24). For the maSCD study, participants were categorized in the maSCD+ group (n = 16) if they endorsed more than 20% of the items on these questionnaires. Conversely, participants were categorized in the maSCD− group (n = 23) if they endorsed less than 20% of items on the CCI. The maSCD study, like the pCRCI study, also targeted women who had cognitive complaints; however, they were not required to have a specific score on the CCI for study entry. Only after the screening visit were women sorted into the maSCD+ and maSCD− groups based off their CCI score. Beck Depression Inventory scores were calculated according to Beck et al,[23] with higher scores indicating more severe depressive symptoms. The Menopause Symptom Checklist

(MSC) score was calculated according to Newhouse et al,[24] with higher scores indicating greater menopausal symptoms.

2.4.2 | Cognitive—The 2 studies shared similar cognitive testing batteries enabling comparison of the datasets. These cognitive domains included tests of simple attention and verbal episodic memory. Only baseline data are included from each study.

The critical flicker fusion (CFF) task[29] was used as a test of attention/vigilance. The outcome variable for CFF is frequency (Hz) for ascending and descending trials. The choice reaction time (CRT task[30]) was used as a measure of attention and psychomotor speed. Outcome variables on the CRT included the mean and median processing reaction time (time from stimulus onset to initiation of movement), the mean and median motor reaction time (time from initiation of movement to stimulus termination), and mean and median total reaction time, with lower scores indicating better performance. The Buschke selective reminding task (SRT)[31] was used to assess immediate and delayed memory recall. Participants are read a list of 16 words and must immediately recall the list across 8 trials. Upon completing the immediate recall portion of the SRT and after a 20-minute delay, participants are asked to complete a single delayed recall trial. See Supporting Information for more details regarding all cognitive tasks.

2.4.3 | Data analysis—One-way analyses of variance (ANOVAs) were performed using IBM SPSS Statistics for Mac, version 24 (IBM Corp, Armonk, New York) to evaluate group differences between pCRCI study participants and maSCD study participants (categorized as either maSCD+ or maSCD−) on behavioral and cognitive outcome measures. Correlations between behavioral and cognitive measures were performed using Pearson product-moment correlations. For correlation analyses, CCI was analyzed as a continuous variable. The alpha level for rejection of the null hypothesis was set at $P < .05$. All behavioral analyses and the SRT analysis included data from all 63 participants. Three participants from the maSCD− group failed to complete the CRT and CFF and were therefore excluded from those analyses. Tukey honestly significant difference was used to look at pairwise differences. All pairwise comparisons are FDR corrected for multiple comparisons.

3 | RESULTS

3.1 | Demographics

Demographics for each group are shown in Table 1. There was no difference in mean age between groups. The mean ages for each group are as follows: maSCD+ = 56.75, maSCD− = 56.04, and pCRCI = 54.21. A total of 14 pCRCI participants were currently on endocrine therapy (tamoxifen n = 7, aromatase inhibitors = 7); pCRCI participants were an average of 2.5 (±1.84) years postchemotherapy.

3.2 | Behavioral

See Table 2 for all behavioral ANOVA results. There was a statistically significant difference between pCRCI, maSCD+, and maSCD− groups in CCI score. Post hoc analyses revealed that pCRCI participants had a higher mean CCI score (mean = 0.4466, $P < .001$) compared

with both maSCD+ (mean = 0.275) and maSCD− (mean = 0.088) group (Figure 1A). Additionally, the maSCD+ group had a higher mean CCI score compared with the maSCD− group ($P < .001$). There was a statistically significant difference between pCRCI, maSCD+, and maSCD − groups on the MSC score. Post hoc analyses revealed that the pCRCI (mean = 27.88, $P < .001$) group had a higher mean MSC score compared with the maSCD− (mean = 12.96) group, but not the maSCD+ (mean = 21.00) group (Figure 1B). There was statistically significant difference between pCRCI, maSCD+, and maSCD− groups on BDI. Post hoc analyses revealed that pCRCI participants (mean = 4.92, $P < .01$) and the maSCD+ group (mean = 5.13, $P < .001$) both had a higher mean BDI score compared with the maSCD − (mean = 1.83) group (Figure 1C). There was no significant difference between pCRCI participants who received endocrine therapy and those who did not on any behavioral measure (see Table S1). There was also no significant difference between pCRCI participants based on menopausal status prior to chemotherapy on any behavioral measure (see Table S2).

3.3 | Cognitive

Results for CRT descriptive statistics and ANOVA results are shown in Table 2. There was a statistically significant difference between pCRCI, maSCD+, and maSCD− groups for CRT median processing reaction time. Post hoc analyses revealed that pCRCI participants had a higher median processing reaction time (mean = 467.08 ms) compared with both maSCD+ (mean = 399.84 ms, $P < .05$) and maSCD− (mean = 405.30 ms, $P < .05$) groups (Figure 1D). However, there was no significant difference between groups on CRT median motor reaction times or CRT median total reaction time. Both CFF and SRT results are included in Table S3. There was no significant difference between groups on any CFF or SRT mean variables. There was no significant difference between pCRCI participants who received endocrine therapy and those who did not on any cognitive measure (see Table S1). There was also no significant difference between pCRCI participants based on menopausal status prior to chemotherapy on any cognitive measure (see Table S2).

3.4 | Relationship between behavioral and cognitive outcome measures

Pearson correlation coefficient results are shown in Table S4. Scatter plots for significant correlations are shown in Figure 2. There was a significant positive association between the following behavioral outcome measures: MSC score and CCI score (Figure 2A), BDI score and MSC score (Figure 2B), and BDI score and CCI score, (Figure 2C). Cognitive Complaint Index score was also significantly positively associated with CRT median processing reaction time (Figure 2D).

4 | CONCLUSIONS

Persistent CRCI participants report more severe SCD symptoms than women after natural menopause, despite being on average 2.5-year postchemotherapy, supporting previous findings that CRCI can persist for months to years after finishing treatment.[3] Persistent CRCI participants not only endorsed greater SCD on the CCI but also exhibited objective performance differences. Persistent CRCI participants were slower on the processing reaction time component (time from stimulus onset to initiation of movement). This finding

supports previous research in breast cancer patients that also found evidence of cognitive impairment on attention and processing speed.[3,6] In addition, pCRCI participants endorsed significantly greater menopausal symptoms on MSC compared with the maSCD− group, but not the maSCD+ group. Results were not related to menopausal status prior to chemotherapy or current endocrine therapy use.

These results suggest that although menopausal symptoms may contribute to some of the SCD experienced by cancer patients after chemotherapy, they do not fully account for pCRCI. This suggests, at least in women, that menopause is only one component of pCRCI. The effects of cancer and chemotherapy treatment on brain function are likely multifactorial, and a number of biological mechanisms, in addition to menopause, have been suggested to play a role in the development of CRCI. These possible mechanisms for CRCI, including blood brain barrier damage, neurotoxic cytokines, DNA damage, oxidative stress, reduced synaptic plasticity, altered growth factor levels, and impaired hippocampal neurogenesis, [32,33] likely overlap with hormone changes following menopause, suggesting possible additive effects.

Neuroimaging studies have identified structural changes in the brain after chemotherapy in gray and white matter,[6] providing support for an anatomical basis to explain the functional impairments reported by cancer patients. In addition to structural brain changes, chemotherapy has also been shown to decrease task-related brain activation in regions of the parietal lobe that were involved in planning and episodic memory.[34] In a prospective longitudinal study, decreased working memory-related brain activity in the frontal lobes was seen 1 month after chemotherapy that partially recovered 1 year later.[35] Studies examining the effects of chemotherapy on functional connectivity have revealed disrupted connectivity in frontal, temporal, and striatal brain regions and increased subjective complaints in executive functioning and memory difficulties compared with controls. These findings suggest a relationship between network connectivity and subjective reports of cognition in breast cancer patients' 5-year postchemotherapy compared with healthy controls.[36] Longitudinal studies in breast cancer patients have revealed decreased functional connectivity 1 month after chemotherapy that partially returned to baseline at 1 year in the dorsal attention network.[37] In addition, increased memory complaints were noted at 1 month and 1 year of postchemotherapy. These findings suggest a detrimental effect of chemotherapy on brain functional connectivity that is related to selfassessment.[37] Thus, the impact of chemotherapy on network connectivity through its disruption of gray matter integrity and/or white matter connectivity may contribute to the functional impairments or subjective complaints endorsed by cancer patients during and after chemotherapy.

Although we did not obtain any neuroimaging in the pCRCI study, an functional magnetic resonance imaging study of working memory examining a subset of maSCD participants used in the current study[22] found that women with substantial postmenopausal cognitive complaints showed greater cortical activity (measured via BOLD signal) during working memory performance than women without such complaints despite equivalent performance, suggesting that cognitive complaints may indicate increased neural effort, perhaps as a form of compensation. In addition, resting-state functional connectivity analyses conducted using the maSCD participants[27] indicated a positive correlation between the executive control

network and cognitive complaint score, weaker negative functional connectivity within the frontal cortex, and stronger positive connectivity within the right middle temporal gyrus in postmenopausal women who report more cognitive complaints, supporting previous findings suggesting that high levels of cognitive complaints may reflect changes in brain connectivity. Although speculative, the performance deficits observed in this study may indicate long-term changes in reduced processing efficiency as a result of chemotherapy in pCRCI. These findings suggest that cortical connectivity changes or compensation may be responsible for the symptoms of maSCD and pCRCI.

4.1 | Study limitations

Although the pCRCI sample was primarily postmenopausal at the time of study (measured by Follicle-stimulating hormone (FSH) levels), 2 women included in the pCRCI sample were considered premenopausal, potentially increasing variability. However, analyses were repeated without the 2 premenopausal pCRCI participants, and the results remained unchanged. Additionally, a group of cancer patients that had undergone chemotherapy who do not endorse pCRCI would have been an informative comparison group. In addition, due to the small sample sizes of these groups, many of the reported effects should be considered preliminary. Finally, since the current study sample included participants recruited from 2 different studies, the cognitive and behavioral assessments that the two studies had in common were few; therefore, only limited comparisons could be made between groups.

This study also has several strengths. The majority of CRCI research has compared cancer patients with completely healthy controls. While our maSCD− group serves as a healthy control group, the addition of a comparison group of otherwise healthy women without a history of cancer who also endorse SCD, to our knowledge, has never been previously examined. Both studies had similar ages between groups and no differences based on age were found on any behavioral or cognitive measures. Finally, the correlation of a subjective measure of cognitive functioning (CCI) with objective test performance differences provides support that subjective complaints that persist following chemotherapy are indicative of attention and psychomotor changes.

4.2 | Clinical implications

There is increasing evidence that SCD, even with normal performance on objective neuropsychological tests, is associated with an increased risk for developing late-life cognitive decline and Alzheimer disease in female noncancer patients.[13] This is of particular importance to older cancer patients due to the age-associated increase in the risk for dementia. Increasing evidence suggests that older patients are more susceptible to cognitive decline associated with chemotherapy and adjuvant endocrine therapies for breast cancer than younger patients.[38] Additionally, age appears to interact with cognitive reserve, a predictor of future cognitive decline, to increase risk for cognitive decline following chemotherapy.[38] Thus, the persistence of a significant level of cognitive complaints in pCRCI or maSCD may indicate that such patients are at increased risk for late life cognitive impairment. The question of why some cancer patients experience persistent CRCI for years following completion of chemotherapy when others do not and whether these individuals are at higher risk for age-related cognitive decline will require further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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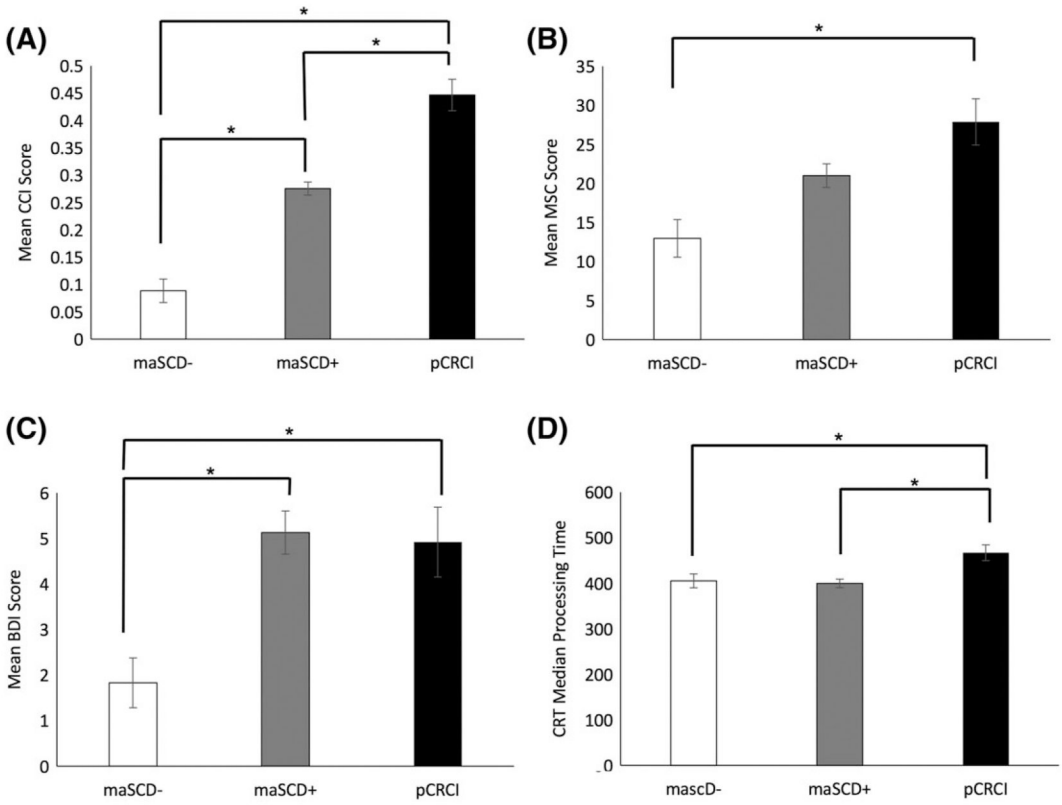

FIGURE 1.

Bar graphs showing significant analysis of variance results. A, Group differences in mean (±SE) Cognitive Complaint Index (CCI) score. B, Group differences in mean (±SE) Menopause Symptom Checklist (MSC) score. C, Group differences in mean (±SE) Beck Depression Inventory (BDI) score, and D, group differences in choice reaction time (CRT) median processing reaction time (±SE). For all graphs, groups are distinguished by the following colors: pCRCI (black), maSCD+ (gray), and maSCD− (white). Asterisks indicated significant pairwise differences between groups, $*P < .05$. All pairwise comparisons are FDR corrected for multiple comparisons

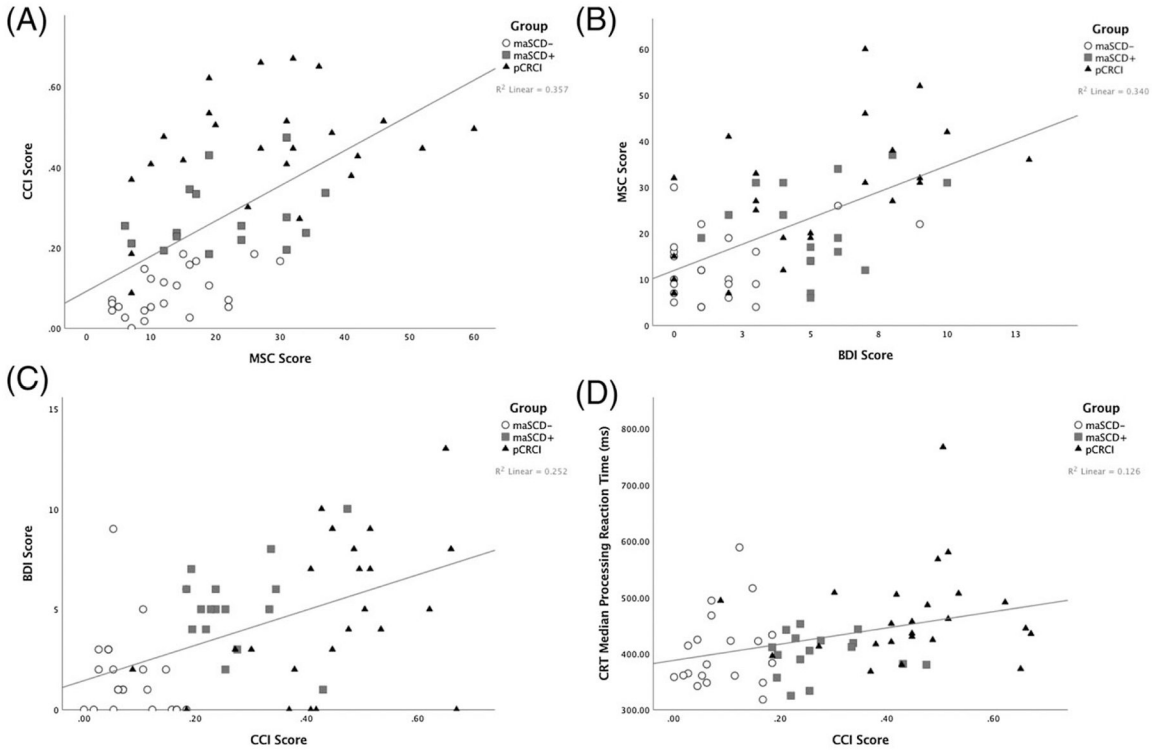

FIGURE 2.

Scatterplots showing significant correlations between cognitive and behavioral measures. A, Correlation between Menopause Symptom Checklist (MSC) score and Cognitive Complaint Index (CCI) score. B, Correlation between Beck Depression Inventory (BDI) score and MSC score. C, Correlation between CCI score and BDI score; D, correlation between CCI score and choice reaction time (CRT) task median processing reaction time (in millisecond). For all graphs, groups are distinguished by the following colors: pCRCI (black triangles), maSCD+ (gray squares), and maSCD− (white circles)

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TABLE 1

pCRCI and maSCD participant demographic

		pCRCI (n = 24)	maSCD+ (n = 16)	maSCD− (n = 23)
Age in years (mean ± SD)		54.21 ± 9.38	56.75 ± 2.70	56.04 ± 2.94
Years since completed chemotherapy (mean ± SD)		2.50 ± 1.84	…	…
Cancer type	Breast	20	…	…
	Lymphoma	3		
	Ovarian	1		
Current endocrine therapy	Premenopausal	14	…	…
	Postmenopausal	10		
Menopausal status prior to chemotherapy	Premenopausal	13	…	…
	Postmenopausal	11		
Current menopausal status	Premenopausal	2	16	23
	Postmenopausal	22		

Abbreviations: maSCD, menopause-associated subjective cognitive decline; pCRCI, persistent cancer-related cognitive impairment.

TABLE 2

pCRCI and maSCD behavioral and CRT descriptive statistics and ANOVA results

		N	Mean	Std. Dev	Std. Error	Minimum	Maximum	ANOVA Result
CCI score	maSCD+	16	0.28	0.09	0.02	0.18	0.47	$F(2,60) = 70.73$, $P < .0001$
	maSCD−	23	0.09	0.06	0.01	0.00	0.18	
	pCRCI	24	0.45	0.14	0.03	0.09	0.67	
Age	maSCD+	16	56.75	2.70	0.67	51.00	60.00	$F(2,60) = 0.927$, $P = .401$
	maSCD−	23	56.04	2.95	0.61	50.00	60.00	
	pCRCI	24	54.21	9.38	1.92	38.00	73.00	
BDI score	maSCD+	16	5.13	2.19	0.55	1.00	10.00	$F(2,60) = 8.70$, $P = .001$
	maSCD−	23	1.83	2.27	0.47	0.00	9.00	
	pCRCI	24	4.92	3.75	0.77	0.00	13.00	
MSC score	maSCD+	16	21.00	9.63	2.41	6.00	37.00	$F(2,60) = 10.63$, $P < .0001$
	maSCD−	23	12.96	7.25	1.51	4.00	30.00	
	pCRCI	24	27.88	14.50	2.96	7.00	60.00	
CRT median processing reaction time	maSCD+	16	399.84	37.42	9.35	325.00	452.50	$F(2,57) = 6.21$, $P = .004$
	maSCD−	20	405.30	68.26	15.26	318.00	588.50	
	pCRCI	24	467.08	84.53	17.26	368.00	767.00	
CRT median motor reaction time	maSCD+	16	394.06	85.67	21.42	257.00	585.50	F (2,57) = 0.98, $P = .380$
	maSCD−	20	358.20	64.12	14.34	273.00	523.50	
	pCRCI	24	376.65	79.58	16.24	243.50	637.50	
CRT median total reaction time	maSCD+	16	801.84	111.35	27.84	584.50	1046.50	$F(2,57) = 2.22$, $P = .118$
	maSCD−	20	770.80	120.61	26.97	633.50	1115.00	
	pCRCI	24	852.79	148.62	30.34	642.50	1414.00	

Abbreviations: ANOVA, analysis of variance; BDI, Beck Depression Inventory; CCI, Cognitive Complaint Index; CRT, choice reaction time task; maSCD, menopause-associated subjective cognitive impairment; MSC, Menopause Symptom Checklist; pCRCI, persistent chemotherapy-related cognitive impairment.