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Catechol-O-Methyltransferase Gene Polymorphisms and the Risk of Chemotherapy-Induced Prospective Memory Impairment in Breast Cancer Patients with Varying Tumor Hormonal Receptor Expression

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCE 1 **Wen Li**
B 2 **Jingjing Zhao**
B 2 **Ke Ding**
E 3 **Herta H. Chao**
BC 4 **Chiang-Shan R. Li**
AG 2 **Huaidong Cheng**
AG 5 **Li Shen**

1 Cancer Hospital, Hefei Institutes of Physical Science, Chinese Academy of Sciences, Hefei, Anhui, P.R. China
2 Department of Oncology, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, P.R. China
3 Cancer Center, VA Connecticut Healthcare System, West Haven, CT, U.S.A.
4 Department of Psychiatry, Yale University School of Medicine, New Haven, CT, U.S.A.
5 Department of Radiation Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, P.R. China

* Wen Li and Huaidong Cheng contributed equally to this work

Corresponding Authors: Huaidong Cheng, e-mail: chd1975ay@126.com, Li Shen, e-mail: wangkai1964@126.com

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Background: Existing research evidence indicates that breast cancer patients have different degrees of cognitive dysfunction after chemotherapy, and polymorphisms in 3 genes (catechol-O-methyltransferase, COMT; apolipoprotein E, APOE; and brain-derived neurotrophic factor, BDNF) have been associated with cognitive impairment. However, the role of these 3 gene polymorphisms in modulating cognitive impairment in breast cancer survivors with varying hormonal receptor expression is not clear at present.

To explore the effects of genetic polymorphisms in BDNF, APOE, and COMT on the regulation of prospective memory impairments induced by chemotherapy in breast cancer patients with various expression levels of estrogen receptor (ER) and progesterone receptor (PR).





Material/Methods: A total of 232 patients with breast cancer (113 with ER-/PR- and 119 with ER+/PR+) were evaluated before and after chemotherapy for cognitive function, including prospective memory. Following previously published sequencing procedures, we assessed 6 single-nucleotide polymorphisms (SNPs), including BDNF (rs6265), APOE (rs429358, rs7412), and COMT (rs165599, rs4680, rs737865).

Results: The patients showed poorer prospective memory scores after chemotherapy than before chemotherapy. Furthermore, the ER-/PR- group showed poorer event-based prospective memory (EBPM) scores than the ER+/PR+ group ($z=-7.831$, $p<0.01$) after chemotherapy. The patients with the COMT rs737865G/G genotype, compared with those with the A/A and A/G genotypes, showed a linear EBPM performance ($\beta=1.499$, 95% confidence interval (CI)=1.017~2.211) and were less likely to have memory impairment. In contrast, APOE and BDNF polymorphisms did not influence cognitive performance.

Conclusions: The patterns of hormonal receptor expression may be related to prospective memory impairments induced by chemotherapy in breast cancer patients. Furthermore, the COMT polymorphism (rs737865) was linearly related to the extent of deficits in EBPM and may represent a potential genetic marker of risk for cognitive deficits triggered by chemotherapy in patients with breast cancer.

MeSH Keywords: **Breast Neoplasms, Male • Chemotherapy, Adjuvant • Cognitive Therapy • Polymorphism, Genetic**

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Background

Breast cancer is a frequently occurring malignancy among women, with an estimated 252 710 new cases in 2017 in the U.S. [1]. Chemotherapy can effectively treat patients with breast cancer. However, side effects in the long run, such as cognitive impairment, have been widely associated with chemotherapy [2]. Numerous studies have documented impairments in short- and long-term memory, cognitive processing speed, attention, executive function, and language function after chemotherapy [3,4]. Lasting for many years, chemotherapy-induced cognitive impairment (CICI) has been critically related to functional decline and impaired quality of life in patients with breast cancer [5–8].

One cognitive deficit is prospective memory (PM), which is the capability of memorizing things to be done at a certain time or place [9]. Prospective memory based on time (TBPM) and prospective memory based on event (EBPM) are distinguishable aspects of PM. In our previous study, we found PM impairments in breast cancer patients following chemotherapy. Also, patients with estrogen/progesterone receptor negative tumors (ER-/PR-) demonstrated significant deficits in EBPM but not TBPM [10,11].

Breast cancer is highly heterogeneous, with significant variations in histomorphology, immunophenotype, biological behavior, and therapeutic response. Molecular typing has distinguished breast cancer into luminal, HER-2 overexpression, basal-like, and normal breast-like subtypes [12]. A meta-analysis evaluated the variability of CICI in breast cancer patients [13]. For instance, our previous work showed heterogeneity among CICI in patients with breast cancer with various tumor hormone receptor expression profiles, with ER-/PR- but not ER+/PR+ showing deficits in EBPM after treatment with chemotherapy [10,14].

Previous studies have found that genetic polymorphisms in apolipoprotein E (APOE; rs429358 and rs7412), brain-derived neurotrophic factor (BDNF; rs6265), and catechol-O-methyl transferase (COMT; rs4680, rs165599, and rs737865) are associated with cognitive function [15–17]. COMT is an enzyme that catalyzes the O-methylation of catecholamines, a group of neurotransmitters central to cognitive functioning [18]. The COMT gene is an important gene for dopamine transport. Some research has found that the COMT gene is associated with cognitive function, including executive function of the prefrontal lobe, working memory, and attentional cognitive control [19]. An earlier study suggested a role of the COMT genotype in influencing cognitive function in survivors with breast cancer undergoing chemotherapy [20]. APOE is a polymorphic protein, and one study found that apolipoprotein gene polymorphisms are a significant risk factor for Alzheimer's disease [21]. Another study suggested that the APOE genotype, by itself and

combined with treatment, influenced memory, attention, verbal learning, and executive function in postmenopausal breast cancer patients [22]. BDNF is a neurotrophin, and BDNF plays an important role in nerve repair and survival, dendrite and axon growth, and long-term potentiation, which is closely related to cognitive function [23]. Breast cancer patients who were carriers of the BDNF Met allele were less likely to experience impaired verbal fluency [24].

The present study investigated PM impairments induced by chemotherapy in breast cancer patients with various expression levels of hormonal receptors, and characterized the influence of COMT, APOE, and BDNF polymorphisms on CICI.

Material and Methods

Participants

A total of 232 breast cancer patients, admitted to the Cancer Treatment Center of the Affiliated Second Hospital of Anhui Medical University from 2013 to 2015, were enrolled. They were separated into 2 groups according to tumor progesterone receptor (PR) and estrogen receptor (ER) expression, including 113 ER-/PR- patients and 119 ER+/PR+ patients. The Research Ethics Committee of the Second Affiliated Hospital of Anhui Medical University, China, issued the approval for this study. All participants provided written informed consent prior to the study.

Most of the subjects were right handed, and all subjects had more than 5 years of education and were eligible if they met the following criteria: 1) they had breast cancer, as diagnosed by immunohistochemistry and pathological diagnosis; 2) they had received standard-dose chemotherapy treatment with fluorouracil, cyclophosphamide, paclitaxel, and doxorubicin, rather than hormonal therapy; 3) they were of any age and had any pathological subtype; 4) they had a Mini-Mental State Examination (MMSE) score ≥ 24 ; 5) they had a Karnofsky performance scale (KPS) score ≥ 80 regarding general activities in daily life; and 6) they had unimpaired vision, hearing, and language. The exclusion criteria were as follows: 1) a history of treatment with a variety of combinations of chemotherapy, radiotherapy, and hormonal therapy; 2) distant metastasis or advanced cachexia; 3) psychiatric diagnoses (e.g., paranoid disorders, depression, or anxiety); 4) an alcohol or drug dependence history; 5) clinically diagnosed dementia; and 6) abnormalities including intracranial metastases in accordance with brain CT or MRI.

Neuropsychological tests

Several neuropsychological tests were performed for the assessment of normal memory and cognitive functions at baseline, prior to chemotherapy, and following 6 cycles of postoperative

adjuvant chemotherapy. For the assessment of visual spatial skills, language, calculation, short-term memory, and time and spatial orientation, the MMSE was administered. In the verbal fluency test (VFT), subjects were required to produce the names of as many animals as possible in 1 minute. For the measurement of short-term memory in the subjects, we employed a digit span test (DST) in which the subjects were required to recall the numbers read to them. The number of digits correctly recalled in serial order determined the total score.

Event-based prospective memory (EBPM) task

In the EBPM task, there were 32 Chinese cards with 12 Chinese words printed on each card; 2 of the words belonged to one category (small category), and the remaining 10 words belonged to another category (large category). The task of the subjects was to identify the 2 words belonging to the small category (target event). When seeing 2 specific animal words, the subjects were asked to knock on the table. The experimenter showed each card to the subject and then guided the subject to verbally answer the question at their speed. For each correct response to a target event (a total of 6 target events), we would give 1 point, for a total of 6 points. Two points were given for remembering to provide their telephone numbers when the test was done. By using a method similar to that developed by McDaniel et al., we recorded the subject's performance on the word-selection task. The EBPM task has a maximum score of 8 points.

Time-based prospective memory (TBPM) task

The TBPM task utilized 100 cards, with 12 two-digit numbers printed on each card. The subjects were asked to select the minimum and maximum numbers on the cards. We asked the subjects to tap the desk at 5-min intervals from the start of the session for 15 min. The subjects could monitor the time with a digital clock placed on their right shoulder. We recorded the exact time at which the subjects tapped the desk. When the clock showed 17 min, the task ended. If the subjects tapped on the desk between 10 s before and 10 s after the target time, 2 points were awarded. If the subjects tapped on the desk between 30 s before and 30 s after the target time, 1 point was awarded. The TBPM task had a maximum score of 6 points.

Genotyping

Peripheral blood was sampled intravenously, collected in sterile anticoagulation tubes, and incubated at -80°C until use. With the use of a blood genomic QIAGEN kit (Shanghai Genesky Bio-Tech Co, Ltd; Shanghai, China), we extracted genomic DNA from the peripheral blood. DNA samples were kept at -20°C . With the use of the improved multiplex ligase detection reaction (iMLDR) technique, we performed genotyping, supported by Shanghai Genesky Biotechnologies Inc. (Shanghai, China).

For each SNP, we distinguished the alleles with the use of different fluorescently labeled allele-specific oligonucleotide probe pairs. The prominent SNPs were distinguished by various extended lengths at the 3'-end. We established 2 negative controls: one in which the template was double-distilled water, and the other in which no primers were included with the DNA sample; the other conditions were all kept the same, on one plate. We designed duplicate tests, and the results were consistent. For verification of the results of the iMLDR technique, along with the use of Big Dye-terminator version 3.1 and an ABI3730XL automated sequencer (Applied Biosystems, Waltham, Massachusetts, USA), a random sample of up to 5% of the total sample DNA was directly sequenced.

Statistical analysis

The data here are reported as the mean \pm standard deviation (SD). Based on a one-way ANOVA and *t* test using SPSS (version 22.0, Chicago, IL, USA), we conducted statistical analysis. We calculated 95% confidence intervals (CIs) and odds ratios (ORs) by logistic regression. For non-normally distributed data, we conducted a Mann-Whitney U test. In addition, using chi-square (χ^2) tests, the frequencies of categorical variables (e.g., genotypes and alleles) were assessed. To analyze susceptibility to cognitive impairment, logistic regression was employed, and ORs and 95% CIs were calculated for the assessment of genetic effects. For individual SNP analyses, a general genetic model (dominant, recessive, additive models) was assumed, and the age, KPS score, years of education, and tumor pathology were adjusted. To characterize the associations between CICI and the COMT (rs737865) polymorphisms, we conducted linear regression. For all statistical tests, statistical significance was set at $p < 0.05$.

Results

Clinical data

Table 1 lists the 232 patients who satisfied the inclusion criteria, including 113 with ER-/PR- and 119 with ER+/PR+ breast cancer. Age (48.5 ± 10.7 vs. 48.9 ± 10.1 years, respectively) and education (10.0 ± 3.7 vs. 9.7 ± 4.1 years, respectively) were not significantly different between the 2 groups. In the ER-/PR- group, 104 patients had normal invasive carcinoma of the breast, 3 had special invasive carcinoma of the breast, and 6 had carcinoma *in situ*. In the ER+/PR+ group, 113 patients had nonspecial-type invasive breast cancer, 5 had carcinoma *in situ*, and 1 had microinvasive carcinoma.

Neuropsychological test, EBPM, and TBPM performance

Table 2 suggests that the MMSE scores decreased significantly from before to after chemotherapy (27.27 ± 1.57 vs. 26.65 ± 1.64 ,

Table 1. Basic clinical information.

Parameters	Groups (Mean±SD)	
	A (n=113)	B (n=119)
Age (years)	48.50±10.70	48.92±10.14
Education (years)	9.98±3.66	9.74±4.07
Pathological patterns	Non-special type invasive carcinoma of breast	104
	Special type invasive carcinoma of breast	3
	Carcinoma <i>in situ</i>	6
	Microinvasive carcinoma	0

Table 2. Neuropsychological performance before and after chemotherapy.

Task	Mean±SD	
	Before chemotherapy (n=232)	After chemotherapy (n=232)
MMSE	27.27±1.57	26.65±1.64*
DST	6.19±0.73	5.95±0.97**
VFT	11.48±1.52	9.96±2.13**
EBPM	2.72±1.01	2.00±1.19**
TBPM	4.98 ± 0.97	4.75 ±0.91*

* $p < 0.05$, ** $p < 0.01$. MMSE – Mini-Mental State Examination; DST – digit span test; VFT – verbal fluency test; EBPM – event-based prospective memory task; TBPM – time-based prospective memory task.

$p < 0.05$). Similarly, both DST and VFT scores decreased significantly from before (6.19±0.7 and 11.48±1.52, respectively) to after (5.95±0.97 and 9.96±2.13, respectively) chemotherapy. The EBPM and TBPM scores were also significantly decreased after chemotherapy: 2.72±1.01 vs. 2.00±1.19 ($p < 0.01$) and 4.98±0.97 vs. 4.75±0.91 ($p < 0.05$), respectively.

Neuropsychological test, EBPM, and TBPM performance: after vs. before chemotherapy

Table 3 expresses the cognitive impairment after chemotherapy in breast cancer patients with different hormone receptors. As shown in Table 3, the MMSE and TBPM scores increased slightly from before to after chemotherapy (ER-/PR-: 26.57±1.69 vs. 26.93±1.58; ER+/PR+: 4.73±0.89 vs. 4.77±0.93), showing little distinction ($p > 0.05$). In contrast, the DST, VFT, and EBPM scores increased remarkably from before to after chemotherapy; DST: (5.49±1.05) vs. (5.99±0.83), VFT: (8.89±1.84) vs. (10.97±1.90), and EBPM: (1.37±1.14) vs. (2.59±0.92). These differences were significant ($p < 0.01$).

The unit SNP loci analysis

The 6 polymorphisms of the COMT, APOE, and BDNF genes were all determined to be consistent with Hardy-Weinberg equilibrium for the 2 groups ($p > 0.05$), suggesting no interference of

inbreeding and population migration or other population genetic influences.

According to sequencing analysis (Table 4), the allelic distributions of COMT, APOE, and BDNF were not significantly different between the 2 groups ($p > 0.05$). In Table 5, the COMT rs165599 (dominant model: $\chi^2=4.876$, $p=0.027$) and rs737865 (recessive model: $\chi^2=4.380$, $p=0.036$) genotypic frequency distributions showed obvious differences. In addition, according to the results of the logistic regression analysis, the patients with the G/G (regulated, OR=2.019, 95% CI=1.097–3.717, $p=0.024$) genotype of COMT rs165599 had a notable increase in the likelihood of developing cognitive decline compared with the patients with the G/A and A/A genotypes. Compared with the patients with the G/A and A/A genotypes, the G/G genotype of COMT rs737865 exhibited a remarkably lower probability of developing cognitive decline (OR=0.519, 95% CI=0.272–0.991, $p=0.047$). The rs737865 polymorphism significantly increased the risk of CICI in recessive models (OR=2.888, 95% CI=1.096–7.612, $p=0.032$). When comparing the cognitive outcomes with the dominant models (OR=1.056, 95% CI=0.632–1.767, $p=0.834$) and additive models (OR=1.259, 95% CI=0.852–1.862, $p=0.248$), no significant associations were established for COMT (rs737865). Neither APOE (rs429358 and rs7412) nor BDNF (rs6265) showed any statistically notable distinctions between the 2 groups.

Table 3. Neuropsychological performance in patients with ER⁻/PR⁻ and ER⁺/PR⁺.

Task	Mean±SD	
	ER ⁻ /PR ⁻ (n=113)	ER ⁺ /PR ⁺ (n=119)
MMSE	26.57±1.69	26.93±1.58 [#]
DST	5.49±1.05	5.99±0.83 ^{**}
VFT	8.89±1.84	10.97±1.90 ^{**}
EBPM	1.37±1.14	2.59±0.92 ^{**}
TBPM	4.73± 0.89	4.77 ±0.93 [#]

[#] $p>0.05$, ^{**} $p<0.01$. MMSE – Mini-Mental State Examination; DST – digit span test; VFT – verbal fluency test; EBPM – event-based prospective memory task; TBPM – time-based prospective memory task.

Table 4. Sequencing of the 3 genes in the 2 groups.

SNP	COMT			APOE		BDNF
	rs4680	rs165599	rs737865	rs429358	rs7412	rs6265
CHR	22	22	22	19	19	11
Allele position	19951271	19956781	19930121	45411941	45412079	27679916
Ref allele	G	G	A	T	C	C
Alt allele	A	A	G	C	T	T
MAF	0.256	0.479	0.315	0.080	0.088	0.492
P for HWE	0.480	0.183	0.469	0.586	0.472	0.977
P^*	0.586	0.091	0.264	0.492	0.860	0.663

SNP – single-nucleotide polymorphism; CHR – chromosome; Ref allele – alleles in the *loci* on the reference sequence; Alt allele – the other (alternative) allele on the locus of the Ref allele; MAF – minor allele frequency (data from 1000 Genomes); HWE – Hardy-Weinberg equilibrium; P for HWE – p -value for HWE in 2 groups; P^* – p -value for allele frequency differences between the 2 groups.

The analysis of correlations between BDNF, APOE, and COMT gene polymorphisms and CICI

The analysis of the correlations between CICI (MMSE, DST, VFT, EBPM, and TBPM) and COMT (rs737865) indicated a marked association between the A/A genotype ($\beta=1.536$; 95% CI=1.02~2.313; $p=0.040$) and EBPM scores (Table 6). Specifically, the recessive model ($\beta=1.499$, 95% CI=1.017~2.211, $p=0.041$) was found to be slightly associated with EBPM.

Discussion

The present results showed (1) that ER⁻/PR⁻ patients performed more poorly on the DST, VFT, and EBPM tests following chemotherapy than ER⁺/PR⁺ patients; and (2) that the COMT rs737865 polymorphism was a candidate genetic marker of risk for CICI in patients with ER⁻/PR⁻ breast cancer, with a linear effect ($\beta=1.499$, 95% CI=1.017~2.211) on EBPM performance. To the best of our knowledge, these results are the first to demonstrate a link between COMT genotypes and CICI in breast cancer patients with a differential expression of hormonal receptors.

Memory impairment is a frequent cognitive adverse effect of chemotherapy [25], and may result in difficulties in everyday functioning and reduced quality of life in breast cancer patients [26,27]. Following our previous study documenting PM deficits [11], we replicated the finding here that patients with ER⁻/PR⁻ breast cancer experience worse chemotherapy-associated EBPM impairments than those with ER⁺/PR⁺ breast cancer [10].

Many studies have indicated important roles for estrogen and progesterone in cognitive functioning. Estrogen can promote synaptogenesis, regulate neurotransmission, prevent oxidative stress, and induce growth factor production [28,29]. Estrogen regulates the release of choline acetyltransferase (ChAT) and acetylcholine acetylase (AChE); thus, estrogen regulates cholinergic signaling central to learning and memory [30]. Studies have shown that the ER α estrogen receptor affects depression and cognitive dysfunction as well, and that ER α affects neuronal growth, neuroprotection, and cell signaling transcription [31,32]. ER α can effectively maintain hippocampal function. When E2 levels are low or high-affinity ER α is reduced, neuroprotection and synaptic function-related transcription are

Table 5. Genotype frequencies of SNPs of the 3 genes between the 2 groups.

SNP	Model	Genotype	ER-/PR-	ER+/PR+	P* (χ^2)	Logistic regression		
						OR (95% CI)	P**	
rs4680	Codominant	G/G	70	64	0.120	-		
		G/A	33	49		0.868	(0.521-1.448)	0.588
		A/A	10	6		1.842	(0.937-3.62)	0.076
	Dominant	G/G	70	64	0.208	1.403 (0.833-2.362) 0.204		
		G/A+A/A	43	55				
	Recessive	G/G+G/A	103	113	0.253	0.633 (0.232-1.723) 0.370		
A/A		10	6					
Additive	-	-	-	-	1.14 (0.757-1.716) 0.531			
rs6265	Codominant	T/T	23	30	0.664	1.10 (0.767-1.596) 0.586		
		T/C	59	57		0.834 (0.499-1.396) 0.490		
		C/C	31	32				
	Dominant	T/T	23	30	0.379	1.008 (0.567-1.792) 0.978		
		T/C+C/C	90	89				
	Recessive	T/T+T/C	82	87	0.926	1.29 (0.697-2.389) 0.418		
C/C		31	32					
Additive	-	-	-	-	1.097 (0.762-1.578) 0.618			
rs165599	Codominant	G/G	35	22	0.087	-		
		G/A	56	70		1.423	(0.967-2.093)	0.073
		A/A	22	27		1.418	(0.842-2.387)	0.190
	Dominant	G/G	35	22	0.027	2.019 (1.097-3.717) 0.024		
		G/A+A/A	78	97				
	Recessive	G/G+G/A	91	92	0.548	1.245 (0.664-2.335) 0.494		
A/A		22	27					
Additive	-	-	-	-	1.44 (0.979-2.118) 0.064			
rs737865	Codominant	A/A	58	60	0.098	-		
		A/G	48	43		1.641	(0.997-2.703)	0.052
		G/G	6	16		0.519	(0.272-0.991)	0.047
	Dominant	A/A	58	60	0.836	1.056 (0.632-1.767) 0.834		
		A/G+G/G	54	59				
	Recessive	A/A+A/G	106	103	0.036	2.888 (1.096-7.612) 0.032		
G/G		6	16					
Additive	-	-	-	-	1.259 (0.852-1.862) 0.248			
rs429358	Codominant	T/T	93	101	0.492	-		
		T/C	20	17		3.819e+004	(0-inf)	0.999
		C/C	0	1		2.01e-005	(0-inf)	0.999
	Dominant	T/T	93	101	0.597	0.813 (0.405-1.63) 0.559		
		T/C+C/C	20	18				
	Recessive	T/T+T/C	113	118	0.329	1.521e+009 (0-inf) 0.999		
C/C		0	1					
Additive	-	-	-	-	0.873 (0.448-1.703) 0.691			

Table 5 continued. Genotype frequencies of SNPs of the 3 genes between the 2 groups.

SNP	Model	Genotype	ER-/PR-	ER+/PR+	P* (χ^2)	Logistic regression	
						OR (95% CI)	P**
rs7412	Codominant	C/C	93	98	0.548	-	
		C/T	19	21		2.411e-005 (0-inf)	0.999
		T/T	1	0		4.511e+004 (0-inf)	0.999
	Dominant	C/C	93	98	0.992	1.033 (0.530-2.016)	
		C/T+T/T	20	21		0.923	
	Recessive	C/C+C/T	112	119	0.304	5.73e-010 (0-inf)	
T/T		1	0	0.999			
Additive	-	-	-	-	0.975 (0.521-1.856)	0.938	

* χ^2 – test of P values for SNP polymorphism distribution differences between 2 groups; ** P-value for logistic regression analysis; OR – odds ratio (OR); 95% CI – 95% confidence interval; Models – various genetic models that were defined as 1 (MM+Mm) versus 0 (mm) for dominant; 1 (mm) versus 0 (MM+Mm) for recessive; and 0 (mm) versus 1 (Mm) versus 2 (MM) for additive and codominant (M and m represent major and minor alleles, respectively).

impaired, resulting in memory impairment [33]. Progesterone is not only synthesized in the nervous system (brain, spinal cord, and peripheral nerves) but also affects the nervous system's function and structure. Progesterone is a typical neuroactive steroid, exerting its neurotrophic and protective effects by binding to receptors, and activating signal transduction pathways, which in turn influence the nervous system's function and structure [34,35]. Studies have shown that progesterone replacement therapy can delay apoptosis of nerve cells, reduce the volume of cerebral infarction, reduce experimental cerebral ischemic injury, promote the synthesis of myelin, and improve neurocognitive functions such as learning and memory [36-38]. A study on the relationship between physiological hormone cycles in animals and learning and memory abilities found that improvements in learning and memory were related to increases in estrogen and progesterone levels. When combined with estrogen, progesterone enhances estrogen's ability to improve learning and memory [39]. Progesterone receptors are widely expressed in the human brain and vital for cognitive function. In our study, patients with ER-/PR- breast cancer had more severe deficits in EBPM performance than patients with ER+/PR+ breast cancer.

Although the mechanisms underlying CICI remain unknown, according to preliminary evidence, genetic variations are likely to increase the extent of cognitive impairment. COMT polymorphisms are denoted as a valine (Val or G) and methionine (Met or A) substitution at codon 108/158. The activity of the COMT enzyme with the A/A genotype was 3- to 4-fold lower than that with the G/G genotype, resulting in reduced dopamine degradation [40]. The COMT Val158Met polymorphism has been shown to modulate the cognitive and symptom profiles in patients with schizophrenia, with more negative outcomes related to adverse childhood experiences in Met carriers [41].

Small and colleagues reported that COMT-Val+ carriers undergoing chemotherapy had worse performance on tests that required frontal cortical dopamine neurotransmission relative to COMT Met/A allele carriers after chemotherapy in breast cancer patients [20]. Our previous study showed that the COMT (rs165599) polymorphism influenced CICI in triple-negative breast cancer (TNBC) patients [14]. In this study, we observed that patients with ER-/PR- breast cancer had worse performance than patients with ER+/PR+ breast cancer on neuropsychological tests of cognitive function, including EBPM. This revealed that COMT (rs737865) genotypes (A/A), to a certain extent, can alter the changes in cognitive function that result following breast cancer treatment, especially on the EBPM task.

APOE ϵ 4 is associated with a decline in cognitive function, including Alzheimer disease [42-44]. Koleck et al. found that breast cancer patients with the APOE- ϵ 4 genotype showed deficits in executive function, attention, verbal learning, and memory after chemotherapy [22]. Here, we found that APOE (rs429358 and rs7412) showed no statistically significant differences between the 2 groups, which revealed that the expression of APOE may have nothing to do with the extent of CICI in breast cancer survivors with different expression levels of tumor hormonal receptors. The current study included 232 breast cancer survivors treated with standard chemotherapy regimens, among whom only 19 (8.19%) were over 65 years of age. Thus, the APOE polymorphisms may not have been related to cognitive decline in these breast cancer patients. Similarly, BDNF polymorphisms did not show a significant relationship with cognitive impairment in patients with breast cancer undergoing chemotherapy.

Table 6. Correlation analysis between COMT (rs737865) and CICI.

	Model	Genotype	B (95% CI)	P-value
MMSE	Dominant	A/A	1.078 (0.92~1.264)	0.351
		G/A+G/G		
	Recessive	A/A+G/A	0.971 (0.746~1.256)	0.830
		G/G		
	HOM	A/A	1.007 (0.767~1.319)	0.958
	HET	G/A	1.090 (0.920~1.292)	0.318
DST	Dominant	A/A	0.956 (0.73~1.25)	0.746
		G/A+G/G		
	Recessive	A/A+G/A	0.841 (0.532~1.329)	0.458
		G/G		
	HOM	–	0.843 (0.525~1.353)	0.478
	HET	G/A	1.004 (0.754~1.336)	0.979
VFT	Dominant	A/A	0.949 (0.84~1.072)	0.400
		G/A+G/G		
	Recessive	A/A+G/A	1.209 (0.977~1.496)	0.081
		G/G		
	HOM	A/A	1.168 (0.93~1.466)	0.181
	HET	G/A	0.910 (0.799~1.036)	0.153
EBPM	Dominant	A/A	1.117 (0.898~1.388)	0.321
		G/A+G/G		
	Recessive	A/A+G/A	1.499 (1.017~2.211)	0.041
		G/G		
	HOM	A/A	1.536 (1.02~2.313)	0.040
	HET	G/A	1.039 (0.826~1.306)	0.745
TBPM	Dominant	A/A	0.941 (0.707~1.253)	0.941
		G/A+G/G		
	Recessive	A/A+G/A	1.021 (0.627~1.663)	0.934
		G/G		
	HOM	A/A	1.002 (0.589~1.705)	0.994
	HET	G/A	0.959 (0.710~1.295)	0.783

HOM – homozygote; HET – heterozygote; beta – regression coefficient; 95% CI – 95% confidence interval

Limitations of the study

Finally, some limitations should be acknowledged. First, this study classified breast cancer into only 2 groups: an ER+/PR+ group and an ER-/PR- group, and failed to make comparisons with healthy controls. The expression of COMT, APOE, and BDNF gene polymorphisms in healthy women still needs

further research. The second limitation was that the experiment used the results of a subjective memory scale; objective cognitive tests could be further examined in future research. Third, the sample size of this experiment was small, making it a small-sample cross-sectional study that lacked a sufficient number of breast cancer patients for broad generalization. Fourth, this study focused only on the molecular

genetic changes and their relationship to memory impairments after chemotherapy in breast cancer patients. Specific brain regions related to memory impairment were not examined; imaging of brain function would be a good area for further study in the future.

Conclusions

In summary, we reported differences in chemotherapy-induced prospective memory impairments and genetic polymorphisms in patients with breast cancer with various expression patterns of hormonal receptors. The results suggest that the heterogeneity in CICI may be modified by the COMT (rs737865) polymorphism, which may alter the risk of cognitive impairment in patients with breast cancer with various expression patterns of tumor hormonal receptors.

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Ethics declarations

The Research Ethics Committee of the Second Affiliated Hospital of Anhui Medical University, China, issued the approval for this study.

Conflicts of interest

None.

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