

ORIGINAL ARTICLE

Cognitive impairment in patients with melanoma before adjuvant immune checkpoint inhibitor therapy and associations with brain gray matter, *catechol-O-methyltransferase* genotype, and psychological factors

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Abstract

Background: Cancer-related cognitive impairment (CRCI) is a significant concern in patients with cancer but understanding its prevalence and risk factors in patients with malignant melanoma (MMPs) remains limited. This study explores CRCI via a multifaceted approach integrating neurobiological, genetic, and psychological assessments.

Methods: Cognitive functioning across multiple domains was assessed via neuropsychological tests in 47 MMPs before adjuvant immune checkpoint inhibitor therapy, compared with 53 matched healthy controls (HCs). Self-reported cognitive complaints, brain gray matter (GM) properties, *catechol-O-methyltransferase* (COMT) genotype, and psychological and behavioral factors were evaluated. Between-group differences were analyzed with *t*-tests and χ^2 tests, and associations were explored with correlation analyses. GM properties were assessed in a subset of 23 MMPs and 47 HCs.

Results: MMPs exhibited significantly lower cognitive functioning across multiple tests (all $p < .05$), with a high CRCI prevalence (68.1% vs. 26.4% in HCs). MMPs reported higher fatigue, anxiety, and insomnia severity and poorer sleep quality and quality of life (all $p < .01$). Self-reported cognitive complaints in MMPs were associated with some cognitive test scores (all $p < .05$), fatigue ($p < .001$), and anxiety ($p = .045$). GM analyses revealed a smaller left cuneus volume in MMPs and significant associations between MMPs' processing speed and cortical thickness (right precentral and left inferior parietal regions) and between delayed verbal memory and right postcentral GM volume (all $p < .01$).

This trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT04565769).

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Conclusions: These findings underscore the need for comprehensive assessments in MMPs to better understand and address CRCI. A multifaceted approach would provide valuable insights that could inform future interventions and improve patient outcomes and quality of life.

KEYWORDS

cancer, cancer-related cognitive impairment (CRCI), *catechol-O-methyltransferase* (COMT), magnetic resonance imaging, melanoma, psycho-oncology, side effects

INTRODUCTION

Evidence suggests that cancer-related cognitive impairment (CRCI) is highly prevalent among patients with non-central nervous system (non-CNS) cancers.¹ Up to 75% of patients with cancer or survivors demonstrate CRCI at some point during their disease trajectory (before, during, or after treatment),² yet research has predominantly focused on breast cancer and chemotherapy effects.³ A recent systematic review noted that few studies have investigated CRCI in patients with malignant melanoma (MMPs),⁴ which indicates a need for more CRCI research in the MMP population. Melanoma has been increasing over the last few decades,^{5,6} with an estimated 510,000 new cases and 96,000 deaths by 2040.⁷ The management of melanoma has been revolutionized with the introduction of immune checkpoint inhibitors (ICIs) and targeted therapies, which has led to significantly improved survival.^{8–11} Given the extended survival rates and younger age at diagnosis compared to other cancers,¹² MMPs are expected to return to daily activities, including work, which could be impaired by cognitive deficits. If unidentified and unmanaged throughout the cancer and treatment trajectory, cognitive impairment can negatively affect daily functioning and the ability to work,^{13,14} with consequences for well-being, quality of life, health behaviors, and distress levels.¹⁵

Research into non-CNS tumors, such as melanoma, has yet to fully explore their effects on cognitive function independent of treatment. The mechanisms linking peripheral tumors to CNS-induced cognitive and behavioral changes remain elusive. Still, they undoubtedly involve a complex interplay between the immune system, genetic factors, host behavior, and psychosocial state.¹⁶ Various psychological and biological factors may affect cognitive function in patients with cancer. Previous research has, for example, indicated a negative correlation between distress and neuropsychological functioning in different cancer populations.¹⁷ The present study explores such psychological factors, including anxiety, depression, fatigue, and sleep disturbances, which are known to correlate with cognitive functioning in patients with cancer.

Various biological factors have also been suggested as risk factors for CRCI.² One potential biological risk factor is the *catechol-O-methyltransferase* (COMT) gene. The Val158Met (rs4680) variant in COMT may influence dopamine levels, possibly by predisposing Val carriers to CRCI.^{18,19} A growing body of studies have also used

neuroimaging techniques to investigate the underlying neural substrate of CRCI in patients with cancer.²⁰ However, a better understanding of the mechanisms of CRCI and the relationships between CRCI and neuroimaging biomarkers is still needed. Magnetic resonance imaging (MRI) has the potential to noninvasively assess structural brain properties that may underlie CRCI and potentially identify neuroimaging biomarkers for early detection or prediction of cognitive dysfunction in patients with CRCI.^{2,21} Nonetheless, the available research has mainly been undertaken in breast cancer populations, which has yielded mixed results.²² No studies have focused on neuroimaging markers of CRCI in MMPs, which has left a gap in our understanding of whether structural brain changes contribute to cognitive impairments in this population.

Given the scarcity of knowledge about CRCI and underlying factors in untreated MMPs, this report's primary research questions—based on baseline data analyses from a longitudinal study—were as follows. What is the prevalence and nature of CRCI in newly resected MMPs before initiation of systemic treatment, and are key psychological, neurobiological, and genetic factors associated with CRCI in this population? Thus, the study's objectives were (1) to investigate baseline cognitive performance (including the prevalence of CRCI) and self-reported cognitive complaints in newly diagnosed MMPs referred for adjuvant ICI treatment and compare with age-, education-, and gender-matched healthy controls (HCs); (2) to compare psychological outcomes related to the quality of life in MMPs and HCs and explore potential associations with cognitive outcomes; (3) to compare structural brain gray matter (GM) properties in MMPs and HCs and explore potential associations with cognitive outcomes; and (4) to explore possible associations of cognitive outcomes with the COMT (rs4680) polymorphisms.

MATERIALS AND METHODS

The study was preregistered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT04565769)²³ and approved by the Regional Scientific Ethical Committee (registration number 1-10-72-71-20). The study is reported in accordance with guidelines for observational cross-sectional studies (Strengthening the Reporting of Observational Studies in Epidemiology).²⁴ Data were collected and stored in accordance with Danish Data Protection Agency guidelines.

Recruitment and procedures

MMPs scheduled for adjuvant ICI treatment at the Department of Oncology, Aarhus University Hospital (AUH), were consecutively recruited from June 2021 to October 2023 (National Committee on Health Research Ethics trial registration number 1-10-72-71-20). Inclusion criteria included a confirmed malignant melanoma diagnosis scheduled for adjuvant ICI treatment at AUH. Exclusion criteria included insufficient Danish language proficiency, age <18 years, previous systemic cancer treatment (ICI, chemotherapy, or anti-hormonal treatment), neurodegenerative disease (e.g., dementia), substance abuse, progressive psychiatric disease (e.g., schizophrenia), other conditions causing cognitive impairment, and the use of a pacemaker (only excluded for the MRI scans). HCs matched for age, education, and gender were recruited locally. All participants were scheduled to be assessed at four time points: after resection but before any further treatment (baseline to T1), 8 weeks later during ICI treatment (T2), 24 weeks after baseline during ICI treatment (T3), and approximately 12 weeks posttreatment (T4). All assessments included questionnaires, tests of neuropsychological functioning, and blood sampling. At T1 and T3, participants underwent a structural MRI scan. Assessments were obtained on the same day at all time points, and MRI scans were obtained before or after neuropsychological tests. Informed consent was obtained from all participants at enrollment.

Although the longitudinal study includes comprehensive assessments across four time points, the current report presents baseline data only.

Questionnaires

Questionnaires included sociodemographic factors (e.g., educational status and income) and health behavior outcomes (e.g., exercise and alcohol consumption). Patient-reported outcome measures (PROMs) were obtained for commonly reported symptoms, including depression and anxiety,²⁵ fatigue,²⁶ sleep quality,^{27,28} sickness behavior,²⁹ quality of life,³⁰ and self-reported cognitive complaints.³¹ For further details, see Table 1.

Neuropsychological assessment

Cognitive function was assessed via a battery of neuropsychological tests shown to be sensitive to the effects of cancer and its treatment (approximately 45 min). The selection of tests was based on recommendations from International Cognition and Cancer Task Force (ICCTF) guidelines³⁴ and a recent publication suggesting the use of a broader range of cognitive tests in oncology populations.³⁵ For details regarding the test battery, see Table 2.

MRI

MRI was conducted with a 3T Philips scanner at the Danish Centre for Particle Therapy at AUH to examine brain structural properties without the use of contrast. Three scan sequences were collected: (1) a high-resolution T1-weighted structural scan of brain GM and white matter (WM); (2) a diffusion/kurtosis-weighted scan for assessment of WM microstructure properties; and (3) a fluid attenuated inversion recovery sequence for assessment of cerebral infarctions. Each MRI scan took approximately 30 min in total. This report focuses on GM structural changes.

Biological assessments

Blood (10 mL) was collected for the assessment of inflammatory immune markers (not reported in the present article) and one selected gene variation (*COMT*). Blood samples were drawn before neuropsychological testing to minimize test-related effects. The samples were preprocessed according to marker-specific procedures and pipetted into the appropriate tubes at the Department of Clinical Biochemistry (AUH). Samples were stored at -80°C before being analyzed at the Department of Molecular Medicine (AUH). Genomic DNA was extracted from the blood samples by standard methods, and *COMT* genotyping was performed with a flanking primer. Information about *COMT* Val158Met (*rs4680*) is explained in detail in Supplementary Materials.

Statistical analysis

A sample of 42 MMPs and 42 HCs was deemed necessary on the basis of an a priori power calculation estimating the sample size for the detection of a 2 (group) $\times$ 4 (time) effect on cognitive function corresponding to a small effect size of 0.3 (Cohen *d*) with $\alpha = 0.05$ and statistical power $(1 - \beta) = 0.90$. To account for potential dropout, we ended up including 47 MMPs and 53 HCs in the final sample. The present analyses were only concerned with the cross-sectional comparison of MMPs and HCs at baseline.

All statistical analyses were conducted with IBM SPSS Statistics for Windows, version 29.0.1.0.³⁶ Descriptive statistics were used to characterize sociodemographic, clinical, psychological, and behavioral variables. Hospital Anxiety and Depression Scale (HADS) depression and anxiety subscales, fatigue, insomnia, and sleep quality were analyzed with clinical cutoffs: scores of 8–21 indicated mild to severe symptoms of anxiety/depression,³⁷ <30 for severe fatigue,²⁶ and >15 for clinical insomnia,³⁸ and >5 for poor sleep on the Pittsburgh Sleep Quality Index.²⁸ Between-group differences were examined with *t*-tests and χ^2 tests.

Group differences in cognitive performance were tested with unadjusted *t*-tests and analyses of covariance (ANCOVAs) adjusted

TABLE 1 Demographic, clinical, and psychological characteristics of study participants.

Characteristics	MMPs (N = 47)	HCs (N = 53)	p	BCa 95% CI
Demographic variables				
Gender, No. (%)				
Women	18 (38.3)	24 (45.3)		
Men	29 (61.7)	29 (54.7)		
Age, mean (SD), years	61.40 (14.76)	58.23 (14.28)	.28	−2.592 to 8.948
Education, mean (SD), years	14.10 (2.96)	15.14 (2.45)	.06	−2.10 to 0.04
Premorbid intelligence (WAIS-IV), mean (SD)	14.85 (4.36)	16.23 (4.49)	.124	−3.13 to 0.39
Occupational engagement, No. (%)				
Yes	23 (48.9)	18 (33.9)		
No	24 (51.1)	35 (66.1)		
Income, 100.000 DKK	4.17 (2.32)	4.38 (2.17)	.65	−1.10 to 0.68
Marital status, No. (%)				
Married/cohabiting	32 (68.1)	44 (83.0)		
Divorced/not cohabiting	15 (31.9)	9 (17.0)		
Health behaviors				
Exercise, h/week	8.11	8.21	.93	−2.43 to 2.24
Alcohol consumption, drinks/week	5.34	6.77	.23	−3.80 to 0.93
Smoking (yes), No. (%)	3 (6.4)	1 (1.9)		
Clinical variables				
Melanoma stage, No. (%)				
IIIA	3 (6.38)			
IIIB	21 (44.7)			
IIIC	17 (36.2)			
IIID	2 (4.26)			
IV	4 (8.51)			
Known primary tumor, No. (%)				
Yes	42 (89.4)			
No	5 (10.6)			
Psychological symptoms, mean (SD)				
Anxiety (HADS) ^a	3.64 (3.76)	1.87 (1.93)	.003**	0.60 to 2.94
Depression (HADS) ^a	1.70 (2.93)	0.85 (1.38)	.061	−0.04 to 1.75
Fatigue (FACIT) ^b	43.13 (7.32)	48.58 (3.32)	<.001**	−7.67 to −3.24
Sleep quality (PSQI) ^c	5.48 (3.72)	3.81 (2.48)	.009**	0.42 to 2.91
Insomnia (ISI) ^d	5.96 (4.92)	3.64 (3.45)	.007**	0.65 to 3.99
Sickness behavior ^e	4.43 (4.34)	2.34 (2.01)	.002**	0.77 to 3.40
QOL (EORTC QLQ-C30) ^f				
Summary score	87.67 (11.70)	96.35 (4.37)	<.001**	−12.10 to −5.25
Global health status	75.89 (18.89)	88.52 (10.10)	<.001**	−18.56 to −5.06
Cognitive complaints, mean (SD)				
Self-reported impairment (PAOFI) ^g , total	25.30 (15.85)	18.68 (12.84)	.023*	0.92 to 12.32
Motor/sensory perceptual	7.4 (3.36)	6.38 (2.29)	.07	−0.103 to 2.16

TABLE 1 (Continued)

Characteristics	MMPs (N = 47)	HCs (N = 53)	p	BCa 95% CI
Language	18.43 (5.96)	15.60 (4.55)	.009**	0.73 to 4.91
Memory	19.72 (6.30)	18.79 (5.26)	.42	−1.36 to 3.22
Higher level cognitive and intellectual functions	13.74 (4.34)	11.89 (3.61)	.022*	0.28 to 3.44
<i>COMT genotype (rs4680)</i>				
Gene variation, No. (%)				
Heterozygous (Val/Met)	21 (46.7)	30 (56.6)		
Homozygous (Met/Met)	14 (31.1)	18 (34.0)		
Wild type (Val/Val)	10 (22.2)	5 (9.4)	.210	

Abbreviations: BCa 95% CI, bias-corrected and -accelerated bootstrapped 95% confidence interval for the difference between means; *COMT*, catechol-O-methyltransferase; DKK, Danish kroner; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; HADS, Hospital Anxiety and Depression Scale; HCs, healthy controls; ISI, Insomnia Severity Scale; MMPs, patients with malignant melanoma; PAOFI, Patient's Assessment of Own Functioning Inventory; PSQI, Pittsburgh Sleep Quality Index; QOL, quality of life; SD, standard deviation.

^aOn the HADS, higher scores indicate higher levels of anxiety and/or depression,²⁵ reported as total scores on the depression and anxiety subscales separately.

^bOn the FACIT fatigue scale, higher scores indicate lower levels of fatigue (Webster, 2003),³² reported as a total raw score.

^cOn the PSQI, higher scores indicate higher levels of sleep disturbance,²⁸ reported as the global PSQI score, which is a sum of seven component scores.

^dOn the ISI, higher scores indicate higher levels of insomnia,²⁷ reported as the total score of the scale.

^eOn sickness behavior, higher scores indicate higher levels of sickness behavior, reported as the total score of the scale.

^fOn the EORTC QLQ-C30, higher scores indicate higher health-related quality of life,³⁰ reported as the summary total score and global health score on the basis of transformed scores for each scale or question.

^gOn the PAOFI, higher scores on subscales are indicative of poorer perceived cognitive functioning (Bell, 2013),³³ reported as raw scores on each scale and the total.

* $p < .05$ (two tailed).

** $p < .01$ (two tailed).

for age and premorbid cognitive functioning (objective 1). Assumptions of normality and homoscedasticity of the *t*-tests were checked with the Shapiro–Wilk and Levene tests, with the Welch *t*-test applied when an assumption was violated. ANCOVA assumptions were assessed by inspecting residuals and testing for normality. Effect sizes (Cohen *d*) were calculated for cognitive outcomes (Table 2). Neuropsychological performance was assessed with individual tests that were grouped into cognitive domains for organizational purposes (Table 2). A *z* score was calculated for each cognitive outcome with the mean $\pm$ SD scores of the HCs, and were not aggregated within each domain. A global composite score (GCS) representing overall cognitive performance was calculated for each participant as the average of the participant's *z* scores. Following ICCTF guidelines,³⁴ participants were classified as demonstrating clinically significant cognitive impairment if they scored at or below -2 SDs (*z* score, ≤ -2) on one neuropsychological test or at or below -1.5 SDs (*z* score, ≤ -1.5) on two neuropsychological tests (objective 1). The frequency of cognitive impairment was compared to normative probability curves, which suggested approximately 28% impairment with a battery of 12 tests.³⁹ A composite symptom load score (averaging *z* scores for anxiety, depression, fatigue, sleep quality, and insomnia severity on the basis of the HC group) was included as a covariate in sensitivity analyses of cognitive performance and cognitive complaints (objectives 1 and 2). Statistical significance was set at $p < .05$.

For neuropsychological test outcomes that exhibited significant between-group differences, we used both individual test scores and GCSs to explore associations with psychological and behavioral outcomes as well as cognitive complaints. The Pearson correlation test was used to explore these associations (objective 2).

General linear models (GLMs) examined the interaction effects of group $\times$ genotype (Val/Val, Val/Met, or Met/Met) on the GCS, as well as of cognitive performance on specific tests (attention, working memory, and executive function) (objective 4). Information about analyses of volumetric and cortical thickness can be found in Supplementary Materials (objective 3).

RESULTS

As illustrated in Figure 1, the study included 47 patients with resected stage III–IV melanoma referred for adjuvant treatment with ICIs. This cohort comprised 29 men (age range, 22–79 years) and 18 women (age range, 22–76 years), which yielded a participation rate of 60%. MMPs had undergone surgical resection within the previous 12 weeks. The HCs consisted of 53 participants, which included 29 men (age range, 26–78 years) and 24 women (age range, 23–76 years). There were no significant between-group differences (MMPs vs. HCs) on background variables. However, MMPs reported higher levels of anxiety, fatigue, sleep difficulties, insomnia severity, and

TABLE 2 Neuropsychological test scores and impairment rates by group.

Cognitive domain	Neuropsychological test	Raw score, mean ± SD			t- test, p	Adjusted p ^a	BCa 95% CI	Effect, Cohen d	z score, mean ± SD			Cognitive impairment: z ≤ 1.5, No. (%) ^a		
		MMPs	HCs						MMPs	HCs		MMPs	HCs	p
Attention and working memory	WAIS-IV digit span, total correct	22.68 ± 4.52	25.51 ± 4.24	.002**	.009**	−4.57 to −1.09	.65	−0.67 ± 1.07	0.0 ± 1.00	12 (25.5)	2 (3.8)	.002**		
	PASAT	43.17 ± 11.22	48.92 ± 9.97	.011*	.002**	−10.09 to −1.43	.55	−0.58 ± 1.12	.0005 ± 1.00	12 (28.6)	1 (1.9)	<.001**		
Processing speed	WAIS-IV coding, correct	53.43 ± 16.95	66.54 ± 13.50	<.001**	<.001**	−19.22 to −6.99	.86	−0.97 ± 1.13	−.0001 ± 1.00	20 (43.5)	2 (3.8)	<.001**		
	TMT-A, s	37.55 ± 16.44	30.74 ± 11.74	.018*	.046*	1.20 to 12.44	.48	−0.58 ± 1.40	0.0004 ± 1.00	7 (15.6)	6 (11.3)	.538		
Verbal learning and memory	HVLT-R immediate, total score	22.55 ± 5.09	26.60 ± 4.49	<.001**	<.001**	−5.95 to −2.15	.85	−0.90 ± 1.13	0.008 ± 1.00	14 (29.8)	2 (3.8)	<.001**		
	HVLT-R delayed recall, total score	7.83 ± 1.99	9.21 ± 2.15	.001**	.01**	−2.20 to −0.55	.66	−0.64 ± 0.93	−0.001 ± 1.00	6 (12.8)	1 (1.9)	.033*		
Visual learning and memory	BVMT-R immediate, total score	19.21 ± 8.33	23.25 ± 6.75	.01*	.031*	−7.03 to −1.04	.54	−0.60 ± 1.23	−0.0007 ± 1.00	16 (34)	4 (7.5)	<.001**		
	BVMT-R delayed recall, total score	7.47 ± 3.28	9.36 ± 2.43	.002**	.006**	−3.03 to −0.75	.66	−0.78 ± 1.35	−0.0006 ± 1.00	16 (34)	4 (7.5)	<.001**		
Verbal fluency	COWAT, animals, correct	22.64 ± 6.18	26.13 ± 6.34	.006**	.05*	−5.98 to −1.00	.56	−0.55 ± 0.97	0.0003 ± 1.00	6 (12.8)	6 (11.3)	.824		
	COWAT letters (S), correct	13.28 ± 6.05	17.58 ± 5.48	<.001**	.002**	−6.6 to −2.02	.75	−0.79 ± 1.00	0.0009 ± 1.00	15 (31.9)	3 (5.7)	<.001**		
Executive function	TMT-B, s	85.20 ± 34.02	74.77 ± 38.87	.17	.60	−4.41 to 25.27	.28	−0.27 ± 0.88	0.00 ± 1.00	4 (8.9)	0 (0)	.03		
	WAIS-IV matrix, correct	14.66 ± 4.38	17.75 ± 3.90	<.001**	.002**	−4.74 to −1.45	.75	−0.79 ± 1.12	0.0012 ± 1.00	11 (23.4)	4 (7.5)	.027*		

Note: For outcomes violating test assumptions, p values from corresponding alternate tests are reported.

Abbreviations: BCa 95% CI, bias-corrected and -accelerated bootstrapped 95% confidence interval for the difference between means; BVMT-R, Brief Visuospatial Memory Test-Revised; COWAT, Controlled Oral Word Association Test, phonemic (S) and semantic (animals) examinations; HVLT-R, Hopkins Verbal Learning Test-Revised; HCs, healthy controls; MMPs, patients with malignant melanoma; PASAT, Paced Auditory Serial Addition Test; SD, standard deviation; TMT-A/B, Trail Making Test, part A/B; WAIS-IV, Wechsler Adult Intelligence Scale, version 4.

^aANCOVAs adjusted for age and premorbid cognitive functioning.

*p < .05 (two tailed).

**p < .01 (two tailed).

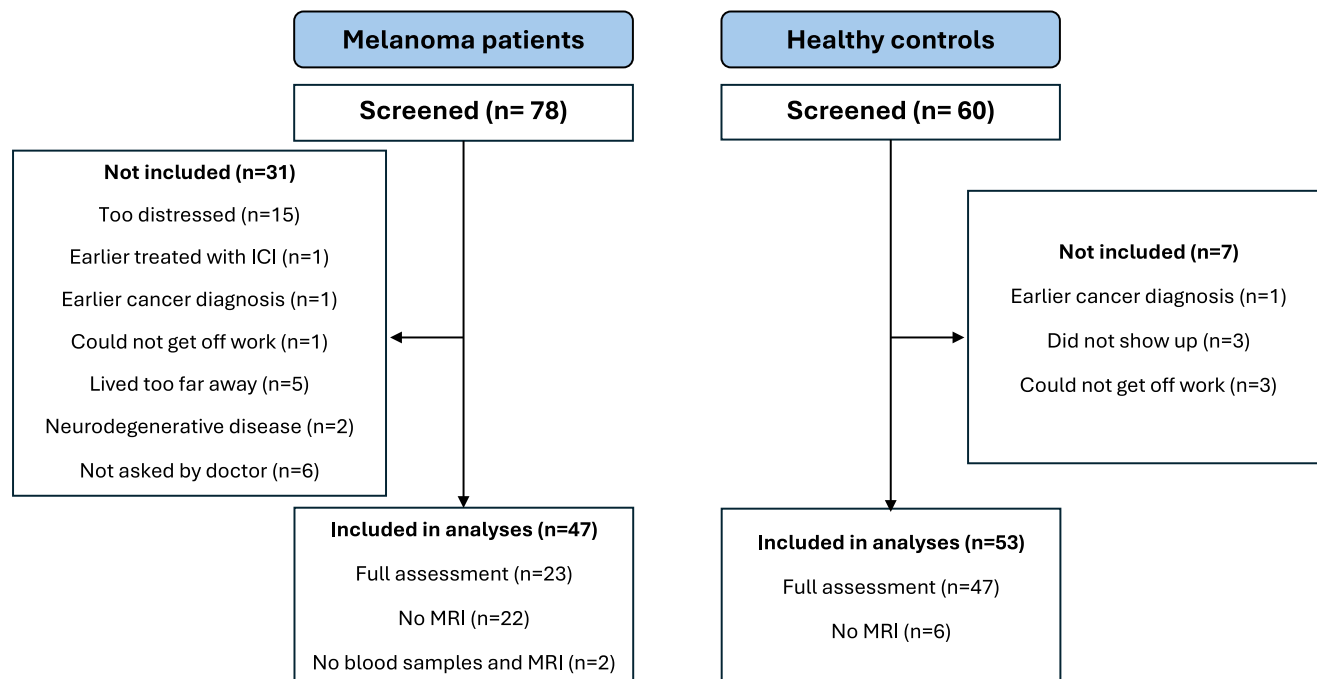


FIGURE 1 Study flow diagram. ICI indicates immune checkpoint inhibitor; MRI, magnetic resonance imaging.

sickness behavior and a lower quality of life than HCs (all $p \leq .001-.009$). Specifically, four MMPs (8.5%) had mild to severe symptoms of depression, whereas none in the HC group did ($p = .045$). For anxiety, five MMPs (10.8%) and one HC (1.9%) reported mild to severe symptoms ($p = .096$). Regarding fatigue, three MMPs (6.4%) and none of the HCs reported severe symptoms ($p = .10$). Clinical levels of insomnia were observed in four MMPs (8.5%) and none of the HCs ($p = .045$). Additionally, 21 MMPs (45.7%) compared to 13 HCs (24.5%) reported poor sleep quality ($p = .035$). Participants' demographic, clinical, and psychological characteristics are shown in Table 1.

Cognitive performance, CRCI prevalence, and associations with PROMs

At the group level, MMPs scored significantly lower than HCs on 11 of 12 neuropsychological tests (all $p < .05$), with moderate to large effect sizes noted across all cognitive domains (Table 2). These differences remained statistically significant after adjustment for age and premorbid intelligence. Mean GCS was significantly lower in MMPs (M, -0.68 ; SD, 0.79) than in HCs (M, -0.0032 ; SD, 0.58) ($t[98] = -4.94$; $p < .001$). Clinically significant cognitive impairment was present in 68.1% of MMPs, which exceeded the prevalence in HCs (26.4%) ($\chi^2[1] = 17.41$; $p = .001$) and the expected probability of 28% ($p < .01$). Frequencies of test-specific impairments for $z < -1.5$ are presented in Table 2. Among MMPs, 23.4% ($n = 11$) exhibited impairment in one domain, 19.1% ($n = 9$) in two domains, 8.5% ($n = 4$) in three domains, and 29.8% ($n = 14$) in four or more domains. A correlation was found between the fatigue total score and Trail

Making Test, part A (TMT-A) ($r = -0.320$; $p = .029$) when examining associations between PROMs and neuropsychological test results, with MMPs scoring lower than HCs. Including the composite symptom load as a covariate in the analyses of between-group differences in cognitive performance, they maintained statistical significance for almost all neuropsychological outcomes (all $p < .03$), which included the differences in GCSs ($p < .001$). Only TMT-A was reduced to nonsignificance ($p = .061$).

Cognitive complaints

Significant differences in self-reported cognitive complaints (Patient's Assessment of Own Functioning Inventory [PAOFI] total scores) were found between MMPs (M, 25.30 ; SD, 15.85) and HCs (M, 18.68 ; SD, 12.84) ($t[98] = 2.30$; $p = .023$) (Table 1). Differences between groups were also significant for the subscales of language ($p = .009$) and higher level cognitive and intellectual functions ($p = .022$). After adjusting for the composite symptom load, all outcomes remained statistically significant (all $p < .03$). Among MMPs, self-reported cognitive complaints were significantly correlated with several neuropsychological test results. The PAOFI total score was correlated with animal fluency ($r = -0.34$; $p = .02$), which indicated that more complaints were linked to poorer performance. The motor/sensory subscale of the PAOFI was marginally associated with the Wechsler Adult Intelligence Scale, version 4 (WAIS-IV) digit span ($r = -0.29$; $p = .05$). The language subscale was associated with the WAIS-IV digit span ($r = -0.43$; $p = .003$), Paced Auditory Serial Addition Test (PASAT) ($r = -0.41$; $p = .007$), animal fluency ($r = -0.44$; $p = .002$), lexical fluency ($r = -0.36$; $p = .012$), and GCS ($r = -0.43$;

$p = .003$). Additionally, the PAOFI (total) score was significantly correlated with HADS anxiety ($r = 0.29$; $p = .045$) and Functional Assessment of Chronic Illness Therapy fatigue ($r = 0.44$; $p < .001$).

Brain GM properties and associations with cognitive performance

Significant between-group differences (MMPs vs. HCs) in GM volume were observed in one region after applying the clusterwise correction for multiple comparisons in FreeSurfer (i.e., correction threshold of 3.0; $p < .001$; clusterwise probability): the left cuneus (cluster size, 458.872 mm²; Montreal Neurological Index coordinates

$x = -11.1$, $y = -71.7$, and $z = 17.0$; $p = .0004$) (Figure 2). No significant differences were found between groups in cortical thickness.

For neuropsychological tests where MMPs scored significantly lower than HCs, potential associations with volumetric and cortical thickness in both the left and right hemispheres were explored. We found no associations between the area showing volumetric difference (the left cuneus) and any neuropsychological test scores. However, we observed statistically significant associations between WAIS-IV coding and cortical thickness in the right precentral cortex, TMT-A and cortical thickness in the left inferior parietal cortex, and Brief Visuospatial Memory Test–Revised, delayed recall and volume in the right postcentral cortex in MMPs (Table 3; Figure 3). These associations were not found in the HC group. No statistically



FIGURE 2 Brain gray matter properties between groups (patients with malignant melanoma vs. healthy controls). Between-group differences in gray matter volume in the left cuneus are shown in yellow.

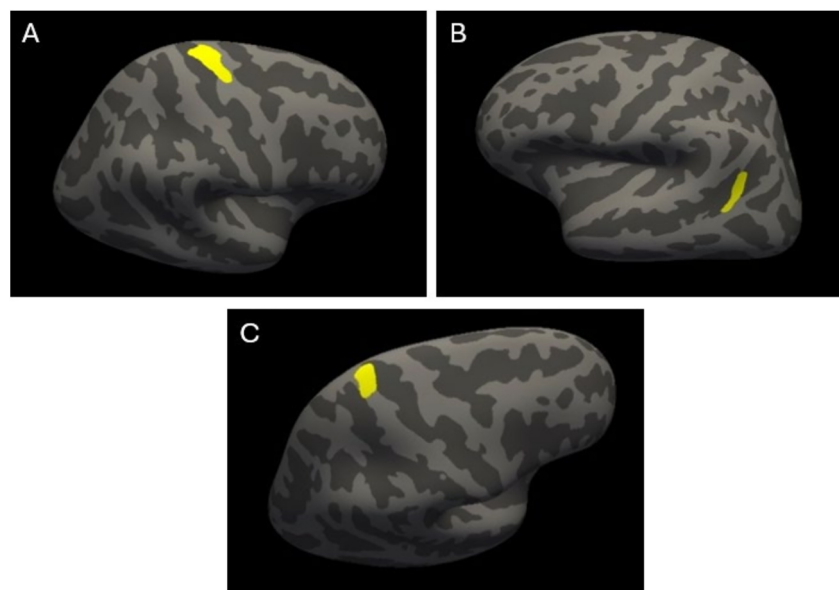


FIGURE 3 Brain gray matter properties associated with cognitive performance in MMPs. (A) Cortical thickness in the right precentral cortex, shown in yellow, associated with WAIS-IV coding in MMPs. (B) Cortical thickness in the left inferior parietal cortex, shown in yellow, associated with TMT-A in MMPs. (C) Volume in the right postcentral cortex, shown in yellow, associated with BVMT-R delayed recall in MMPs. BVMT-R delayed recall indicates Brief Visuospatial Memory Test–Revised, delayed; MMPs, patients with malignant melanoma; TMT-A, Trail Making Test, part A; WAIS-IV, Wechsler Adult Intelligence Scale, version 4.

TABLE 3 Cortical thickness and volume showing significant correlations with scores of neuropsychological tests among patients with melanoma.

Neuropsychological test	Corrected <i>p</i>	Cluster size, mm ²	MNI coordinates			Structures
			x	y	z	
BVMT-R delayed recall	.0201	226.65	10.4	−35.8	66.3	Volume in right postcentral cortex
TMT-A	.01435	212.37	−39.0	−54.0	16.0	Thickness in left inferior parietal cortex
WAIS-IV coding	.00040	387.34	16.5	−23.4	66.0	Thickness in right precentral cortex

Abbreviations: BVMT-R delayed recall, Brief Visuospatial Memory Test–Revised, delayed; MNI, Montreal Neurological Index; TMT-A, Trail Making Test, part A; WAIS-IV, Wechsler Adult Intelligence Scale, version 4.

significant correlations were identified between self-reported cognitive complaints (the PAOFI total score) and GM properties.

Genotypes and cognitive performance

The frequencies of *COMT* risk allele carriers did not differ between groups (Table 1). GLMs showed no gene-by-group interaction effects (MMPs vs. HCs) on overall cognitive performance as measured by the GCS ($F[2,92] = 1.99$; $p = .14$; mean, 0.95) or by individual test scores on the WAIS-IV digit span total ($F[2,92] = 0.49$; $p = .62$; mean, 0.54), PASAT ($F[2,87] = 0.30$; $p = .74$; mean, 0.35), TMT, part B ($F[2,89] = 0.401$; $p = .67$; mean, 0.37), or WAIS-IV matrix ($F[2,92] = 0.56$; $p = .575$; mean, 0.35).

DISCUSSION

In this study, resected MMPs referred for adjuvant immunotherapy demonstrated statistically significant cognitive impairment compared to HCs by scoring significantly lower on 11 of 12 neuropsychological tests. Additionally, MMPs had a statistically significantly lower GCS and a higher prevalence of clinically significant cognitive impairment as defined by the ICCTF criteria (68.1%) compared with HCs (26.4%) and normative expectations (28%).

Objective 1 was to investigate baseline cognitive performance, including CRCI and self-reported cognitive complaints, in newly resected MMPs. CRCI is mainly studied in the context of treatment-related CRCI; however, a review of pretreatment CRCI reported an estimated prevalence of 30%.¹⁶ Our findings do not align with the 30% but with previous baseline studies of cancer populations with testicular^{40,41} and ovarian cancer⁴² that demonstrated high levels of CRCI before the initiation of systemic treatment (58%–72.4%). This suggests that CRCI is present in a substantial proportion of MMPs before the start of systemic treatment, which is consistent with reports on pretreatment CRCI in other cancer populations.

MMPs exhibited statistically significantly higher levels of cognitive complaints compared to HCs (objective 1), particularly on the PAOFI total scores and subscales of language and higher level cognitive and intellectual functions. Interestingly, although self-reported cognitive complaints are usually not correlated with

cognitive test performance,^{16,43} the PAOFI showed medium to large associations with cognitive test performance.⁴⁴ In our study, we also observed associations between neuropsychological tests and self-reported cognitive complaints in MMPs: the PAOFI total score was statistically significantly associated with animal fluency, the motor/sensory subscale of the PAOFI was marginally associated with the WAIS-IV digit span, and the language subscale of the PAOFI was associated with the WAIS-IV digit span, PASAT, animal fluency, lexical fluency, and GCS. These associations, ranging from small to medium, indicated that higher levels of self-reported cognitive complaints were linked to lower cognitive test performance. This suggests some alignment between patients' perceptions of cognitive function and actual performance. Although relying solely on self-reported complaints as a proxy for cognitive tests is not advisable, the incorporation of both measures is recommended. However, the clinical significance of these correlations should be interpreted with caution because of the small to medium strength of these associations, which may limit their practical impact on patient care decisions.

MMPs reported statistically significantly higher levels of anxiety, fatigue, sleep difficulties, insomnia, and sickness behavior, and a lower level of quality of life compared to HCs. These findings align with previous research involving MMPs⁴⁵ and other cancer populations.^{46,47} Despite these differences, clinically meaningful symptom levels were only observed at the group level in relation to sleep difficulties, with MMPs scoring just above the threshold for poor sleep.²⁸ This underscores that although MMPs experienced more psychological and behavioral symptoms than HCs as a group, the symptoms did not necessarily reach clinically significant levels. However, at the individual level, more MMPs reported clinical levels of depression, anxiety, fatigue, insomnia, and poor sleep compared to HCs. Ongoing discussions concerning CRCI in patients with cancer—particularly whether it arises primarily from adverse effects of treatment or the psychological distress related to a cancer diagnosis—remain unresolved.¹⁶ Apart from fatigue, no associations were found between cognitive test results and psychological distress symptoms in the present study (objective 2). Overall symptom load did not account for between-group differences in cognitive performance.

From a clinical perspective, integrating neuropsychological testing with patient-reported complaints is essential for personalized care. Our results emphasize that self-reported cognitive complaints are linked with psychological symptoms, such as anxiety and fatigue,

which may influence patients' perceptions of their cognitive function. This result is consistent with previous findings showing cognitive complaints to be linked with other distress symptoms and a lower quality of life.^{48,49} Appropriate treatment targets in this situation include addressing distress (e.g., anxiety and depression) that may benefit both the distressing symptoms and the perceived cognitive complaints. There has been a concerted effort to enhance the understanding of self-reported cognitive complaints, their relationship to cognitive function and psychosocial stressors, and brain-based biomarkers.^{50,51} Given the multifactorial nature of etiology and biology, there is a compelling need for additional transdisciplinary research endeavors.

Objective 3 was to compare structural GM properties in MMPs and HCs and explore potential associations with cognitive outcomes. CRCI has been associated with brain changes in regions primarily associated with memory, executive function, and attention.^{20,52} Our study found statistically significant volumetric differences in the left cuneus region between MMPs and HCs before systemic treatment. Although the cuneus region is involved in visual processing,⁵³ we found no associations between this area and impairments in visual tasks. However, brain structures can be affected by psychological stress,⁵⁴ which several MMPs also experienced in the present study. Moreover, we found associations between brain areas and cognitive performance. Such associations may reflect the involvement of attention and executive functions supported by specific areas of the brain,^{55,56} as well as the involvement of distributed neural networks underlying cognitive functions.^{57,58} In summary, the observed volumetric differences and correlations between brain areas and cognitive performance provide novel insights into the neural underpinnings of CRCI in MMPs before treatment. Further research is needed to elucidate the exact mechanisms driving these findings and their implications for patient care and management.

Objective 4 was to explore possible associations between cognitive outcomes and the *COMT* (rs4680) polymorphisms. The *COMT* gene has previously been studied for its role in cognitive function.²² Although previous research has suggested links between *COMT* gene variation and CRCI, particularly in patients with breast cancer,¹⁹ our study did not find significant risk-by-group interactions between *COMT* variation and cognitive performance in MMPs. This suggests that *COMT* may not be a significant risk factor for CRCI in this population, although future research is warranted.

To our knowledge, the present study is the first to investigate possible neurobiological and genetic mechanisms for CRCI in newly diagnosed, recently resected MMPs referred for adjuvant ICI treatment via assessments of cognitive function, psychosocial factors, and biomarkers of GM and *COMT* genotype. The inclusion of an age-, education-, and gender-matched HC group strengthens the study design. However, some limitations should be addressed in future studies. First, the focus on newly diagnosed MMPs referred for adjuvant ICI treatment may restrict generalizability to other patient populations with melanoma or different types of cancer. Second, some of the null findings may be attributed to type 2 errors due to

insufficient statistical power because the sample size was determined for the prospective study on the basis of the primary outcome of neuropsychological test performance. Third, recruiting patients from a single hospital and controls from the local community may introduce selection bias and limit generalizability. Last, we did not apply corrections for multiple comparisons to the neuropsychological tests because of the interdependence of cognitive measures and the exploratory nature of the study.

In conclusion, in this study, MMPs demonstrated significant cognitive impairment across multiple domains compared to HCs, even before adjuvant immunotherapy. MMPs also showed significant overall cognitive impairment and elevated self-reported cognitive complaints compared to HCs. Objective cognitive impairments were accompanied by alterations in brain structure and increased psychological distress. Our findings underscore the importance of early cognitive evaluation in MMPs, and highlight the need for further research into the underlying mechanisms and tailored interventions addressing both cognitive and psychological aspects from the outset. By identifying cognitive impairment early, there is an opportunity to address these issues proactively, which would potentially improve the quality of life and treatment outcomes for patients with melanoma. Our study contributes to a growing body of evidence underscoring the complexity of CRCI and the need for continued research in this area.

AUTHOR CONTRIBUTIONS

Josefine T. Danielsen: Conceptualization; investigation; funding acquisition; writing—original draft; methodology; validation; visualization; writing—review and editing; software; formal analysis; project administration; data curation. **Robert Zachariae:** Conceptualization; methodology; validation; writing—review and editing; supervision; resources; data curation. **Henrik Schmidt:** Conceptualization; investigation; methodology; validation; writing—review and editing; project administration; supervision; resources; data curation. **Jesper F. Kallehauge:** Conceptualization; software; methodology; writing—review and editing; supervision; resources; data curation. **Julie K. Thomsen:** Investigation; methodology; visualization; writing—review and editing; software; formal analysis; data curation. **Jeffrey S. Wefel:** Conceptualization; methodology; validation; visualization; writing—review and editing; supervision; resources. **Lisa M. Wu:** Conceptualization; investigation; methodology; validation; visualization; writing—review and editing; data curation; supervision; resources. **Ali Amidi:** Conceptualization; writing—original draft; methodology; validation; visualization; writing—review and editing; software; formal analysis; data curation; supervision; resources.

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CONFLICT OF INTEREST STATEMENT

Robert Zachariae reports consulting for AstraZeneca, Johnson & Johnson, and Pfizer and holding stock with Novo Nordisk. Jeffrey S. Wefel reports consulting for GT Medical Technologies, Vanquish Oncology, Astellas Pharma, Bayer HealthCare Pharmaceuticals, Novocure, Intra-Cellular Therapies, and Juno Therapeutics. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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SUPPORTING INFORMATION

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

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