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Journal

Brain Imaging and Behavior, 17(5)

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Publication Date

2023-10-01

DOI

10.1007/s11682-023-00781-7

Peer reviewed



Published in final edited form as:

Brain Imaging Behav. 2023 October ; 17(5): 507–518. doi:10.1007/s11682-023-00781-7.

Brain gray matter reduction and premature brain aging after breast cancer chemotherapy: a longitudinal multicenter data pooling analysis

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Author Contributions

The primary writing committee for this manuscript consisted of RLD, MBR, and BCM, who also conducted the data analyses. BC, BTC, JAD, KD, SD, BCM, PAN, MBR, AJS, SS, and SBS were responsible for obtaining funding and data acquisition for the original study cohorts. All authors contributed to manuscript writing and editing.

This study was presented in part at the International Cognition and Cancer Task Force (ICCTF) conference in Denver, CO in 2020.

Conflict of Interest

Sources of support for gathering and sharing the data analyzed for this paper include National Institutes of Health grants R03 AG045090, R01 NR010939, and R01 CA101318, Breast Cancer Research Foundation grant BCRF-9 2008–2016, Dutch Cancer Society grant 2009–4284, Research Foundation Flanders (FWO) grant G.048010N, and Stichting tegen Kanker. AJS has received support from Springer-Nature Publishing (Editorial Office Support as Editor-in-Chief, *Brain Imaging and Behavior*). All other authors declared no conflicts of interest that are relevant to the content of this article.

Compliance with Ethical Standards

Written informed consent was obtained from all participants as per protocols approved by the respective Institutional Review Board at each participating institution (City of Hope, Indiana University, KU Leuven, The Netherlands Cancer Institute, University of Michigan, and University of Vermont).

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Abstract

Brain gray matter (GM) reductions have been reported after breast cancer chemotherapy, typically in small and/or cross-sectional cohorts, most commonly using voxel-based morphometry (VBM). There has been little examination of approaches such as deformation-based morphometry (DBM), machine-learning-based brain aging metrics, or the relationship of clinical and demographic risk factors to GM reduction. This international data pooling study begins to address these questions. Participants included breast cancer patients treated with (CT+, n=183) and without (CT-, n=155) chemotherapy and noncancer controls (NC, n=145), scanned pre- and post-chemotherapy or comparable intervals. VBM and DBM examined GM volume. Estimated brain aging was compared to chronological aging. Correlation analyses examined associations between VBM, DBM, and brain age, and between neuroimaging outcomes, baseline age, and time since chemotherapy completion. CT+ showed longitudinal GM volume reductions, primarily in frontal regions, with a broader spatial extent on DBM than VBM. CT- showed smaller clusters of GM reduction using both methods. Predicted brain aging was significantly greater in CT+ than NC, and older baseline age correlated with greater brain aging. Time since chemotherapy negatively correlated with brain aging and annual GM loss. This large-scale data pooling analysis confirmed findings of frontal lobe GM reduction after breast cancer chemotherapy. Milder changes were evident in patients not receiving chemotherapy. CT+ also demonstrated premature brain aging relative to NC, particularly at older age, but showed evidence for at least partial GM recovery over time. When validated in future studies, such knowledge could assist in weighing the risks and benefits of treatment strategies.

Keywords

brain aging; breast cancer; chemotherapy; gray matter; magnetic resonance imaging (MRI)

Introduction

Cognitive problems frequently occur after chemotherapy for non-CNS cancers, at least partially attributable to neurotoxicity of chemotherapeutic regimens (Ahles & Root, 2018; Janelins, Kesler, Ahles, & Morrow, 2014; Lange, Joly, et al., 2019). Neuroimaging studies have reported gray matter (GM) reductions after chemotherapy in many brain regions, predominantly in cortex, particularly in the frontal lobes (Amidi et al., 2017; Amidi & Wu, 2019; Apple et al., 2017; Bergouignan et al., 2011; Chen et al., 2018; Conroy et al., 2013; Correa et al., 2013; Correa et al., 2017; de Ruiter et al., 2012; Henneghan et al., 2020; Hosseini, Koovakkattu, & Kesler, 2012; Inagaki et al., 2007; Jenkins et al., 2016; Kaiser, Bledowski, & Dietrich, 2014; Kesler et al., 2013; Koppelmans et al., 2012; Lepage et al., 2014; Li & Caeyenberghs, 2018; McDonald, Conroy, Ahles, West, & Saykin, 2010; McDonald, Conroy, Smith, West, & Saykin, 2013; McDonald & Saykin, 2013;

Mentzelopoulos et al., 2021; Niu et al., 2021; Simó et al., 2015; Sousa, Almeida, Bessa, & Pereira, 2020; Stouten-Kemperman, de Ruiter, Caan, et al., 2015; Stouten-Kemperman, de Ruiter, Koppelmans, et al., 2015; Yoshikawa et al., 2005). This is consistent with the importance of the prefrontal cortex for multiple aspects of cognitive functioning. However, most of these studies have been cross-sectional, lacking baseline assessments prior to systemic treatment. Longitudinal studies have baseline data, but typically have small sample sizes. Furthermore, studies often lack a disease-specific control group of chemotherapy-naïve patients, making it harder to attribute findings to chemotherapy exposure versus more general effects of the cancer disease process.

GM reductions after chemotherapy may resemble those observed with normal aging. This is consistent with evidence from clinical and preclinical studies that chemotherapy can have neurotoxic effects that mimic those underlying cellular aging (Henneghan et al., 2020; Koppelmans et al., 2012; Seigers, Schagen, Van Tellingen, & Dietrich, 2013). Machine-learning algorithms are particularly suited to capture the subtle and spatially heterogeneous morphological brain changes characteristic of brain aging. This provides a metric that estimates an individual's brain age based on neuroimaging data. For instance, an estimated brain age of 70 in a 60-year-old suggests 10 years of premature brain aging. This approach has demonstrated premature brain aging in disorders characterized by cognitive dysfunction (e.g., Alzheimer's disease, multiple sclerosis) (Boyle et al., 2021; Cole, 2018, 2020; Cole & Franke, 2017; Franke & Gaser, 2019; Franke, Gaser, Manor, & Novak, 2013; Gaser, Franke, Klöppel, Koutsouleris, & Sauer, 2013; Henneghan et al., 2020). One study to date has applied a brain aging algorithm approach to cancer patients. Breast cancer patients were evaluated pre-chemotherapy and on average one month and one year post-chemotherapy, and compared with noncancer controls. One month after completion of chemotherapy, breast cancer patients showed two years of premature brain aging compared to controls (Henneghan et al., 2020).

There is little knowledge on the trajectory of GM reductions after chemotherapy. Some research has shown lower GM compared to controls up to 20 years after treatment (Koppelmans et al., 2012). In contrast, several studies have reported partial recovery from GM reductions in the months to years after treatment (Conroy et al., 2013; Inagaki et al., 2007; Lepage et al., 2014; McDonald et al., 2010). One commonly used method is voxel-based morphometry (VBM), an automated technique for examination of GM density/volume on a voxel-by-voxel basis across the entire brain (Ashburner & Friston, 2000, 2001; Good et al., 2001). A related technique, deformation-based morphometry (DBM) (Ashburner et al., 1998), does not include a segmentation step and is less susceptible to variations in image quality (Schwarz & Kašpárek, 2011). Only one prior study has used DBM to examine brain volumetric changes after cancer and treatment (Blommaert et al., 2019). Several risk factors have also been reported for cognitive problems after chemotherapy, including older age (Ahles et al., 2010; Lange, Heutte, et al., 2019; Schilder et al., 2010); however, no prior work has described risk factors for GM reductions after chemotherapy.

In this study, an initiative of the International Cognition and Cancer Task Force (ICCTF) Neuroimaging Working Group, data from six centers in the USA and Europe were combined to investigate whether pre- to post-chemotherapy treatment neuroimaging changes

in breast cancer patients could be detected across an aggregated dataset using volume change metrics (VBM, DBM) and brain aging analyses. In addition to including patients who received chemotherapy (CT+), we included chemotherapy-naïve patients (CT-) and noncancer controls (NC). We expected GM reductions after chemotherapy that would be most prominent in cortical brain regions, and premature brain aging compared to chemotherapy-naïve patients and noncancer controls. We further evaluated whether these MRI indices of chemotherapy neurotoxicity were associated with time since treatment and whether older age was a risk factor.

Methods

Contributions

Invitations to participate were extended to attendees of ICCTF conferences via personal communications. Inclusion criteria were longitudinal high-resolution T1-weighted brain MRI data acquired at 3T in breast cancer patients who received chemotherapy (CT+) with one measurement prior to chemotherapy (baseline) and at least one measurement after chemotherapy (follow-up). Additionally, longitudinal data from breast cancer patients who did not receive chemotherapy (CT-), and noncancer controls (NC) were included as available. Information was gathered about available cognitive and behavioral data, but there was too much heterogeneity of measures among the cohorts for meaningful integration of those data. Approval of local Institutional Review Boards to participate or a waiver to provide anonymized data was required before data aggregation. Terms of access agreements were executed for each participating institution.

Data were contributed by four institutions from the USA (City of Hope, Indiana University, University of Michigan, and University of Vermont) and two from Europe (KU Leuven, Belgium, and The Netherlands Cancer Institute, the Netherlands). Some results from individual datasets were published previously (Blommaert et al., 2019; Chen et al., 2018; McDonald et al., 2013). Descriptions of participants, scanners, and acquisition parameters by institution are summarized in Supplementary Table 1. Anonymized data were securely uploaded to a high-performance computing server of Indiana University for analysis.

Volume change metrics

Locally developed MATLAB scripts (The MathWorks, Inc., Natick, MA), SPM12, and CAT12 were used to implement modulated VBM and DBM methods (see Supplementary Material) (Ashburner & Friston, 2000, 2001; Ashburner et al., 1998; Good et al., 2001). Statistical comparisons within and between groups and over time, including interaction analyses, were conducted using a full factorial model in SPM12, with factors of Group (three independent levels: CT+, CT-, NC) and Time (two non-independent levels: baseline and follow-up). Data acquisition site, age, and interscan interval were included as covariates for DBM and VBM. Intracranial volume (ICV) was additionally included for VBM. Overall significance was set at family-wise error (FWE) correction $P < 0.05$ to address multiple comparisons. Clusters were then considered significant at cluster-level $P_{\text{uncorrected}} < 0.05$. Mean values for clusters showing significant reduction in GM volume from baseline to follow-up in the cancer groups were extracted using MATLAB for post-hoc correlation

analyses. To evaluate overall GM loss and to account for the large interscan interval range we calculated annual GM loss by subtracting total GM volume (calculated in CAT12) at follow-up from total GM volume at baseline, divided by the interscan interval in years.

Brain age analysis

brainageR software (available on <https://github.com/james-cole/brainageR/releases/tag/1.0>, also see Cole et al. (Cole et al., 2017)) was used for generating brain-predicted age values at both timepoints. This involved using preprocessed brain volume images and comparing them to a machine learning model of brain aging trained on MRIs from healthy individuals (see Supplementary Material). Spearman's correlations of chronological age with brain age at baseline were used to assess the accuracy of brain age predictions. Between-group differences in brain aging ratio (brain age at follow-up minus brain age at baseline)/(age at follow-up minus age at baseline) were assessed with ANOVA, followed by paired comparisons, and considered significant at $P < 0.05$.

Correlation analyses

Spearman correlations evaluated associations between volume change metrics (annual GM loss, clusters showing GM volume reduction on VBM or DBM), and brain aging ratio, and between time since chemotherapy and age at baseline and volume change metrics (annual GM loss, significant VBM and DBM clusters) and brain aging ratio. To reduce the chance of type I error, $P < 0.01$ was considered statistically significant for all correlation analyses.

Results

Patient characteristics

At baseline participants were 50 years old on average and mean time between baseline and follow-up measurement (interscan interval) was 7.6 months. No significant differences were found for these variables between treatment groups. Annual GM loss was numerically larger for CT+ participants (Table 1). Duration of follow-up since chemotherapy was available for 181 out of 183 patients and was on average 3.8 months (range 0–15.0, SD 3.0). Chemotherapeutic regimens varied and consisted of alkylating agents and taxanes, with or without anthracyclines or antimetabolite agents (Supplementary Table 1).

VBM and DBM

The CT+ group (Table 2, Figure 1) showed volume reduction in left dorsolateral prefrontal cortex (DLPFC) and cerebellar GM from baseline to follow-up using VBM. DBM also showed volume reduction in left DLPFC, as well as additional reductions in right DLPFC and left anterior prefrontal cortex. The CT- group (Table 2, Figure 2) showed small clusters of volume reduction in right middle temporal and anterior prefrontal, left dorsal posterior cingulate, and left cerebellar GM from baseline to follow-up using VBM. Right anterior prefrontal cortex reduction was also evident using DBM. There were no regions where either cancer group showed significant volume increases, and no significant changes were seen in the NC group. Between-group interaction analyses were largely nonsignificant, though in one interaction NC showed relative reductions over time in left orbitofrontal cortex and right

putamen compared to CT+ (Table 2), due to a slight (nonsignificant) decline in NC and a slight (nonsignificant) increase in CT+.

Brain age analyses

Chronological age and brain age estimated at baseline showed correlations (r) of 0.77 (CT+), 0.79 (CT-) and 0.82 (NC, all P s<0.001, Supplementary Figure 1). Brain aging ratio was significantly different between groups ($P=0.035$). Post-hoc tests showed a significant difference between the CT+ and NC groups ($P=0.01$). Mean brain aging ratio was highest for the CT+ group (1.7), followed by the CT- (1.0) and NC (0.4) groups (Figure 3). The interscan interval for chemotherapy-treated patients was on average 7.5 months. As the brain age ratio was 1.7, this indicates longitudinal brain aging of 7.5 months*1.7=12.9 months, resulting in premature brain aging of (12.9-7.5)=5.4 months.

Associations between volume change metrics and brain age analyses

Annual GM loss was negatively correlated with brain aging ratio (i.e., a decline in GM was associated with an increase in brain aging ratio; CT+: $r=-0.44$, $P<0.001$, CT-: $r=-0.34$, $P<0.001$, NC: $r=-0.20$, $P=0.014$), indicating greater GM loss with greater brain aging. No significant correlations were found between brain aging ratio and VBM or DBM clusters showing significant change over time in the CT+ group. In the CT- group, there were significant negative correlations between brain aging ratio and VBM volume changes in the left dorsal posterior cingulate ($r=-0.26$, $P=0.001$), right middle temporal ($r=-0.24$, $P=0.003$), and right anterior prefrontal ($r=-0.22$, $P=0.006$) regions, indicating greater GM loss with greater brain aging.

Associations between time since treatment, age at baseline, and neuroimaging outcomes

Time since chemotherapy was positively correlated with annual GM loss ($r=0.21$, $P=0.004$) and negatively correlated with brain aging ratio ($r=-0.20$, $P=0.007$, Figure 4, upper panel), indicating that patients with longer time since treatment showed less GM loss and lower brain aging ratios. There were no significant correlations between time since treatment and VBM or DBM changes. Age at baseline was negatively correlated with annual GM loss in the CT+ group ($r=-0.35$, $P<0.001$), indicating greater GM loss with older age at baseline. This was not seen in CT- or NC ($r=-0.04$ and $r=-0.06$, respectively, P s>0.45). Age at baseline was positively correlated with brain aging ratio in the CT+ group ($r=0.27$, $P<0.001$, Figure 4, lower panel), indicating greater brain aging with older age. This was not seen in CT- or NC ($r=0.12$ and $r=-0.05$, respectively, P s>0.16). The only significant correlation between age at baseline and VBM or DBM clusters showing change over time was a positive correlation in the CT- group ($r=0.24$, $P=0.003$) for the left cerebellar VBM cluster, suggesting older patients showed less volume loss in this region over time.

Discussion

This study represents the first implementation of a large multicenter neuroimage pooling strategy assessing alterations in cerebral structure after breast cancer chemotherapy. Within one year after chemotherapy completion patients showed reduced GM volume and premature brain aging. Volume change (VBM and DBM) analyses showed bilateral GM

To evaluate the validity of a machine-learning-based brain age measure as a global measure for premature brain aging, we determined associations with annual GM loss (averaged across brain GM). In all three groups, annual GM loss showed a highly significant association with the brain aging ratio, indicating that greater GM loss is associated with greater premature brain aging. This confirms the validity of brain aging ratio as a general as opposed to brain region-specific marker of chemotherapy-induced premature brain aging. Of note, annual GM loss was not significantly higher in chemotherapy-treated patients than those who did not receive chemotherapy or noncancer controls. This suggests that the brain aging ratio may be a more sensitive measure for chemotherapy-associated neurotoxicity than GM volume. Voxel-wise analyses and brain age estimations likely provide complementary methods to measure neurodegenerative consequences of cancer treatment. Whereas voxel-based methods provide a well-established approach to assess regional changes in brain tissue suggestive of neurotoxicity, brain age estimations may provide a global assessment of brain health that is more sensitive than measurements of overall tissue reduction. Since the algorithm is trained on multiple scanners, it might be more stable across different imaging protocols and scanners.

The large variation in time since chemotherapy completion allowed us to investigate time since treatment effects, although still within a relatively short timeframe. Time since chemotherapy was positively associated with annual GM loss and brain aging ratio, both indicating that the extent of premature brain aging decreased over time in the timeframe covered in the current study (up to 455 days after chemotherapy). We therefore found no support for the accelerated aging hypothesis, which proposes that age-associated declines after cancer follow a steeper slope than those without a cancer history (Ahles, Root, & Ryan, 2012). In contrast, our findings seem to be more compatible with partial recovery after chemotherapy-induced brain aging. This is in agreement with studies in breast cancer patients that found partial recovery from chemotherapy associated GM reductions; two studies found partial recovery one year versus one month post-chemotherapy (Lepage et al., 2014; McDonald et al., 2010), whereas one study found GM reduction one year, but not three years after chemotherapy (Inagaki et al., 2007). Another VBM study similarly showed a positive correlation between GM density and time since chemotherapy (Conroy et al., 2013). These findings suggest that some recovery from chemotherapy-associated GM reduction occurs.

An important topic in the study of cancer and cognition is whether some patients are at risk for cognitive decline after receiving chemotherapy. Several studies point to older age as a risk factor (Ahles et al., 2010; Lange, Heutte, et al., 2019; Schilder et al., 2010). We observed that age at chemotherapy treatment was significantly associated with both annual GM loss as well as brain aging ratio; the older a patient was before receiving chemotherapy, the more GM loss and the higher the brain aging ratio after chemotherapy. Importantly, these associations were not observed in the other two groups. This may point to an underlying mechanism for older age as a risk factor for chemotherapy-associated cognitive problems.

There are limitations to the current study, most inherent to a retrospective data pooling project. Clinical and treatment variables (e.g., disease characteristics, chemotherapy, radiotherapy, and endocrine treatment regimens/doses) were not gathered consistently across

sites, and so could not be included in analyses. Similarly, we could not include cognitive or behavioral data, as there was insufficient overlap between measures used in the different independent cohorts. We therefore could not assess whether decreases in GM or degree of premature brain aging were associated with cognitive or behavioral change. The maximum time since chemotherapy completion was 15 months, but 75% of the MRI data were acquired within 6 months after chemotherapy, limiting interpretation of results over 6 months post-chemotherapy. Although all MRIs were T1-weighted high-resolution scans acquired on 3T scanners, MRI protocols and scanners varied, which could contribute to differences in image inhomogeneity and contrast distribution. Importantly, the brain age algorithm was also trained on MRI scans acquired with different protocols from different vendors. While brain age is a promising biomarker, in the currently applied algorithm it is unclear how variables are being combined to make predictions. There was also variability in the applied chemotherapeutic regimens, although most patients received alkylating agents and taxanes, with or without anthracyclines or antimetabolite agents. Overall, sample heterogeneity may have contributed to the lack of significant interaction effects. Strengths of the present study include the large sample size, the wide age range of participants, the wide range in time intervals between measurements, the longitudinal nature of the data, and the inclusion of both disease-specific and noncancer control groups.

Conclusions

We found that breast cancer chemotherapy is associated with frontal and cerebellar GM decline and premature brain aging within one year after treatment. Our findings suggest that some recovery occurs over time, and that older age is a risk factor for chemotherapy-associated premature brain aging. When validated in future studies with longer follow-ups, ideally with harmonized scan protocols, such knowledge could be used for tailored patient education, early cognitive interventions, and in weighing the risks and benefits of treatment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors wish to posthumously acknowledge the contributions of John D. West, MS to this research.

Funding Sources

Sources of support for gathering and sharing the data analyzed for this paper include National Institutes of Health grants R03 AG045090, R01 NR010939, and R01 CA101318, Breast Cancer Research Foundation grant BCRF-9 2008–2016, Dutch Cancer Society grant 2009–4284, Research Foundation Flanders (FWO) grant G.048010N, and Stichting tegen Kanker.

Data Availability Statement

Inter-institutional terms of access agreements enacted for the purposes of this data pooling study do not permit resharing of the study data. Those interested on obtaining data could

contact the individual participating institutions, and the corresponding author can facilitate reasonable such requests.

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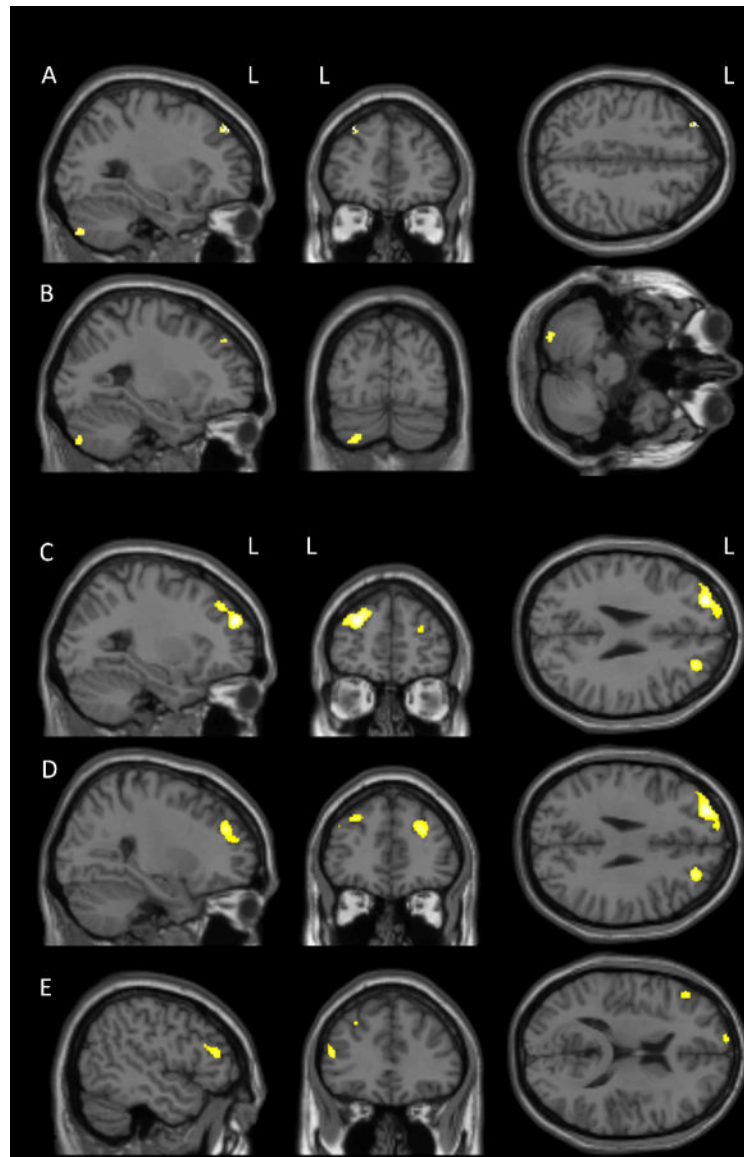


Figure 1.

Gray matter volume reduction from baseline to follow-up in breast cancer patients treated with chemotherapy (CT+ group) as seen on voxel-based morphometry (VBM) in A) left dorsolateral prefrontal cortex and B) left cerebellum, and on deformation-based morphometry (DBM) in C) left anterior prefrontal cortex, D) right dorsolateral prefrontal cortex, and E) left dorsolateral prefrontal cortex (overall FWE-corrected $p < 0.05$, cluster-level $p_{\text{uncorrected}} < 0.05$).

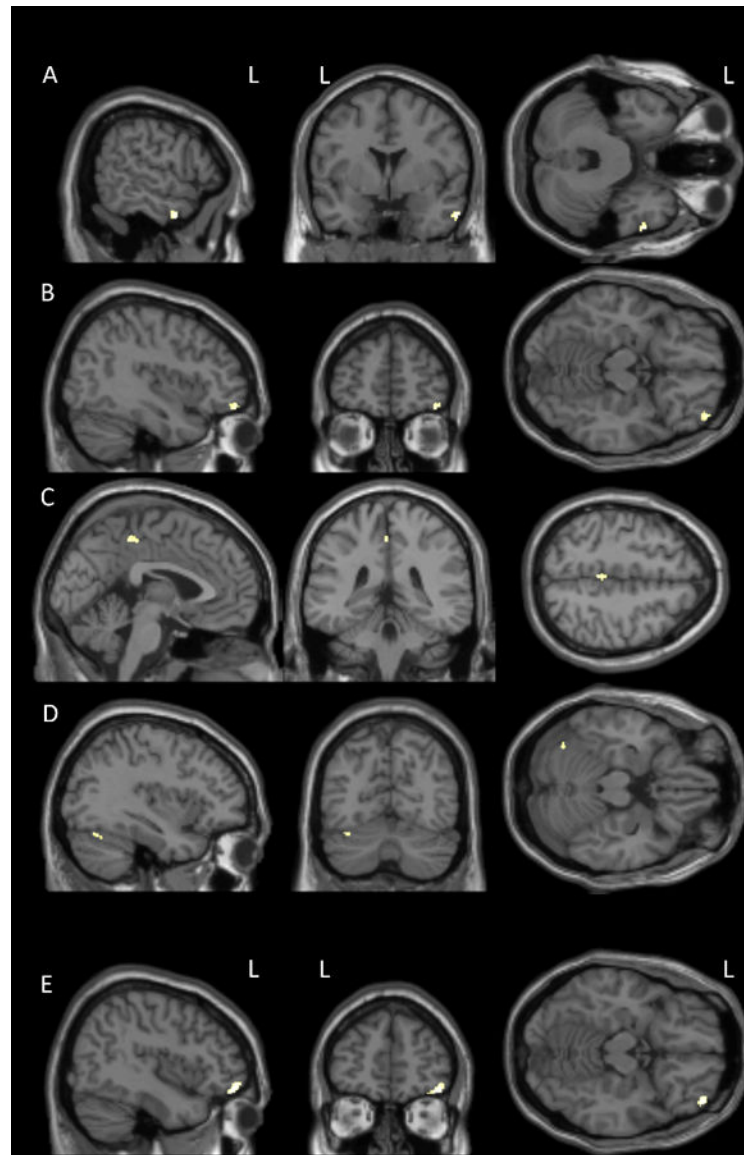


Figure 2. Gray matter volume reduction from baseline to follow-up in breast cancer patients not treated with chemotherapy (CT- group) as seen on voxel-based morphometry (VBM) in A) right middle temporal gyrus, B) right anterior prefrontal cortex, C) left dorsal posterior cingulate cortex, and D) left cerebellum, and on deformation-based morphometry (DBM) in E) right anterior prefrontal cortex (overall FWE-corrected $p < 0.05$, cluster-level $p_{\text{uncorrected}} < 0.05$).

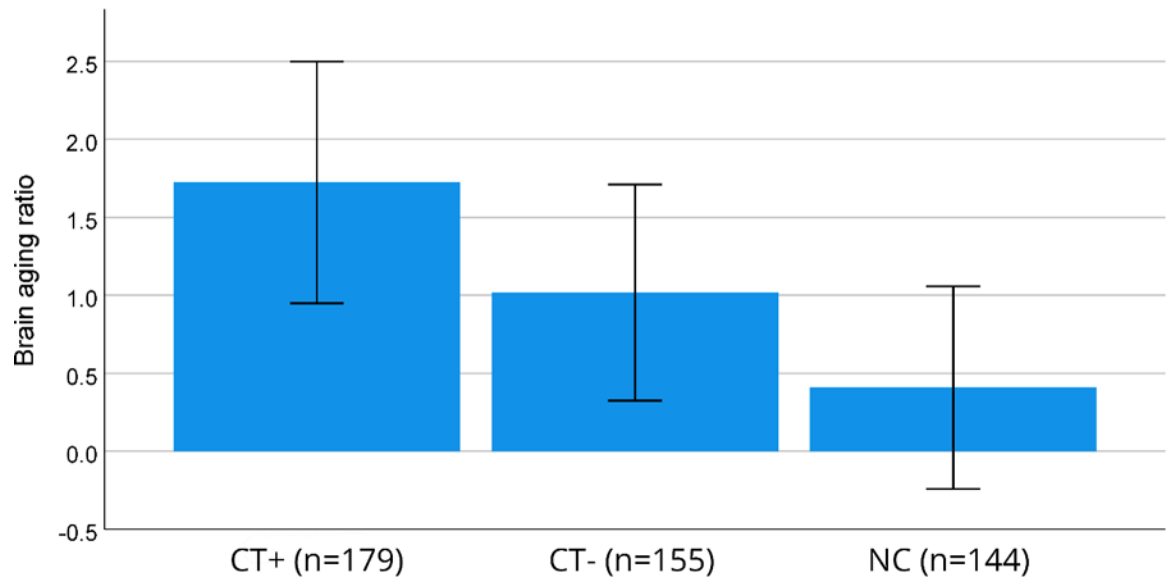


Figure 3. Brain aging ratio per group, defined as longitudinal brain aging/chronological aging. Error bars show SEM.

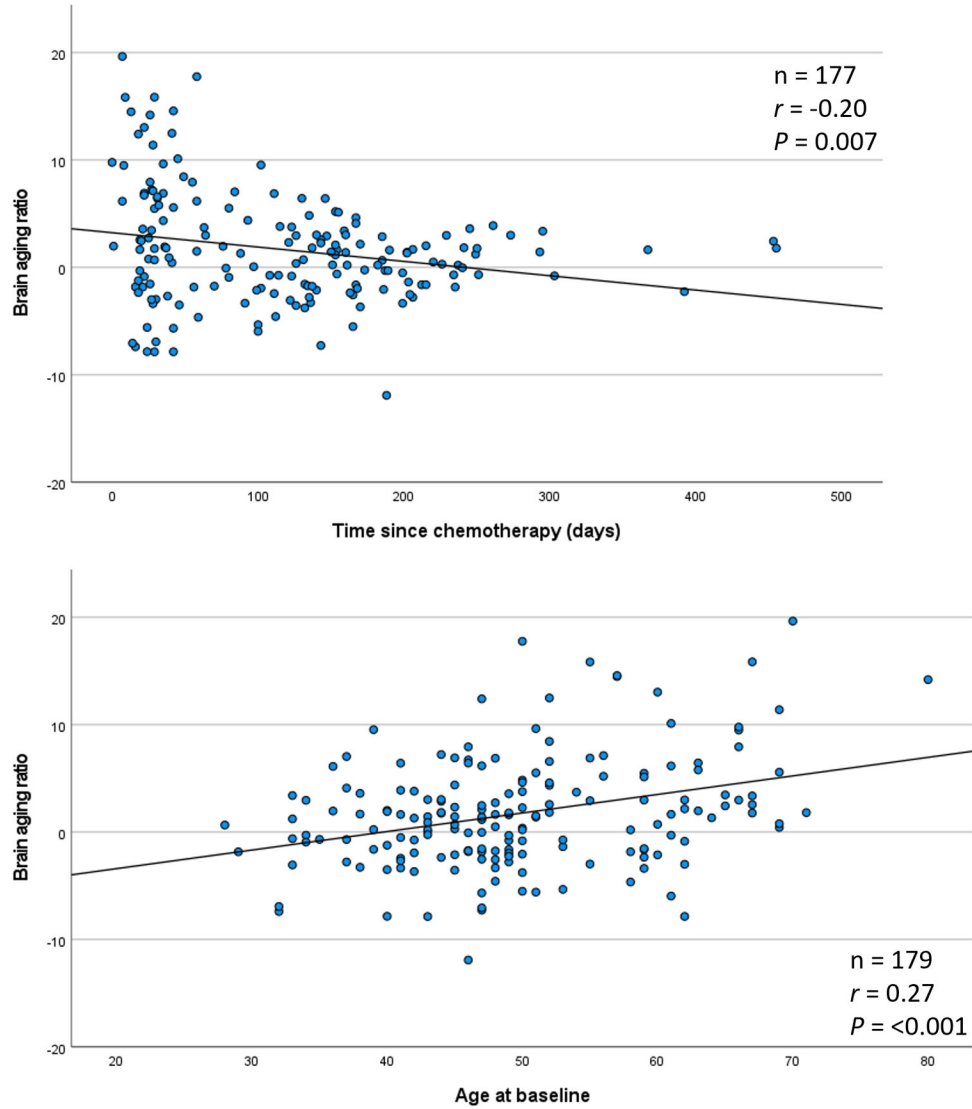


Figure 4. Upper panel: correlation of time since chemotherapy with brain aging ratio. Lower panel: Correlation of age at baseline with brain aging ratio in patients treated with chemotherapy.

Table 1.

Participant Characteristics

	CT+ (n=183)	CT- (n=155)	NC (n=145)	<i>P</i>
Age	49.9 (10.1)	51.5 (8.9)	49.7 (10.8)	0.24
	Range 28–82	Range 30–75	Range 20–78	
Breast cancer stage				
0	0 (0%)	39 (25.2%)		
I	52 (28.4)	98 (6.2%)		
II	86 (47.0%)	16 (10.3%)		
III	28 (15.3%)	0 (0%)		
Missing	17 (9.3%)	2 (1.3%)		
Interscan interval (months)	7.5 (3.4)	7.8 (3.3)	7.6 (3.6)	0.73
	Range 2.4–23.1	Range 2.1–18.7	Range 3.0–26.7	
Annual gray matter loss (ml/year)	-9.2 (32.2)	-4.4 (23.1)	-5.5 (26.2)	0.24

Values are mean (SD); CT+=Breast cancer patients treated with chemotherapy; CT-=Breast cancer patients treated without chemotherapy; NC=Healthy controls with no cancer diagnosis. Significance of group differences was assessed with ANOVA.

Table 2.

VBM and DBM Results

MNI peak (x,y,z)	Cluster level		k	Z	Brain region
	$P_{\text{FWE-corrected}}$	$P_{\text{uncorrected}}$			
VBM CT+ Baseline > Follow-up					
-28 45 44	0.002	0.030	46	6.19	Left dorsolateral prefrontal cortex (BA9)
-26 -80 -44	<0.001	0.004	90	5.04	Left cerebellum
VBM CT- Baseline > Follow-up					
60 2 -32	0.001	0.013	63	5.56	Right middle temporal gyrus (BA21)
40 52 -15	0.002	0.039	41	5.30	Right anterior prefrontal cortex (BA10)
-2 -38 51	0.002	0.032	45	5.17	Left dorsal posterior cingulate cortex (BA 31)
-36 -68 -21	0.001	0.015	61	5.07	Left cerebellum
DBM CT+ Baseline > Follow-up					
-27 51 27	<0.001	<0.001	1565	6.31	Left anterior prefrontal cortex (BA10)
27 42 28	<0.001	0.003	367	5.50	Right dorsolateral prefrontal cortex (BA9)
-48 34 15	0.002	0.042	149	5.14	Left dorsolateral prefrontal cortex (BA46)
DBM CT- Baseline > Follow-up					
44 50 -15	0.002	0.047	141	5.10	Right anterior prefrontal cortex (BA10)
DBM NC reduction from Baseline to Follow-up Relative to CT+					
-15 42 -18	0.001	0.020	202	5.54	Left orbitofrontal cortex (BA11)
24 12 -9	0.001	0.015	224	5.47	Right putamen

MNI=Montreal Neurological Institute coordinates; FWE=Family-wise error; k=cluster extent; VBM=Voxel-based morphometry; DBM=Deformation-based morphometry; BA=Brodman Area; CT+=Breast cancer patients treated with chemotherapy; CT-=Breast cancer patients treated without chemotherapy; NC=Healthy controls with no cancer diagnosis