

ORIGINAL ARTICLE

Plasticity in bilateral hippocampi after a 3-month physical activity programme in lung cancer patients

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Abstract

Background and purpose: Cancer treatments have deleterious effects on both brain structure and the cognition of lung cancer patients. Physical activity (PA) has beneficial effects on the cognition of healthy adults by eliciting brain plasticity, especially on the medial temporal lobe (hippocampus). Therefore, the aim was to study the neuroprotective effects of a 3-month PA programme (PAP) on the brain structure and cognitive performance of lung cancer patients.

Methods: Twelve patients (seven non-small-cell lung cancer [NSCLC] patients following chemotherapy, five small-cell lung cancer [SCLC] patients following chemotherapy and prophylactic cranial irradiation) agreed to complete the PAP and underwent baseline and 3-month (post-PAP) brain magnetic resonance imaging and neuropsychological evaluations (PAP group). Twelve lung cancer patients (seven NSCLC, five SCLC; non-PAP group) and 12 healthy sex-, age- and education-matched controls were recruited and completed two evaluations separated by the same amount of time. A region of interest voxel-based morphometry analysis focused on bilateral hippocampi was performed.

Results: Physical activity programme patients presented greater grey matter volume (GMV) across time in both hippocampi. Moreover, it was observed that SCLC patients in both the PAP and non-PAP groups presented a time-dependent GMV loss in bilateral hippocampi that was not significant in NSCLC patients. Importantly, the PA intervention decreased the magnitude of that GMV loss, becoming thus especially beneficial at the brain structural level for SCLC patients.

Conclusions: Our study demonstrates, using a neuroimaging approach for the first time, that PA is able to stop the deleterious effects of systemic chemotherapy and brain radiation on brain structures of the lung cancer population, especially in SCLC patients.

KEYWORDS

physical activity, lung cancer, chemobrain, radiation, cognitive impairment

INTRODUCTION

Cancer treatments including chemotherapy and cranial radiation (i.e., prophylactic cranial irradiation, PCI) have deleterious effects on the cognition of the lung cancer population. Mechanisms underlying

chemotherapy-induced cognitive deficits or chemobrain [1] have not yet been clearly elucidated [1]. Several etiopathogenic mechanisms have been proposed including disruption of the blood-brain barrier, cytokine-mediated inflammatory response, acceleration of aging by increased damage to DNA and extension of telomeres, as

well as individual genetic susceptibility. Previous studies observed that, 1 month after chemotherapy, small-cell lung cancer (SCLC) patients presented cognitive deterioration, especially in verbal fluency and visuospatial abilities, compared to healthy controls (HCs) [2,3]. These cognitive deficits were accompanied by changes in brain structure, especially located in the temporal lobe bilaterally [2], whose network also showed a compensatory hyperactivation during resting state [4].

Prophylactic cranial irradiation is the standard treatment in SCLC as an effective approach to overcome the high tendency to develop brain metastases associated with this type of cancer (10% of patients will present brain metastases at onset and nearly 50% during the course of disease [5]). Furthermore, it is known that cranial irradiation carries transient or permanent neurotoxic effects that can lead to subcortical dementia [6,7]. The pathophysiology underlying these radiation-induced toxic effects includes impairment of brain endothelial and oligodendrocyte progenitor cells, resulting in demyelination and late-onset white matter necrosis, decreases in hippocampal neurogenesis, changes in neuronal function (particularly, in synaptic plasticity) and neuroinflammatory responses [8]. Regarding lung cancer patients undergoing PCI, previous studies showed both short-term and long-term cognitive toxicity in SCLC survivors [9]. In the short term (3 months after PCI), SCLC patients presented a deterioration in verbal fluency that was accompanied by structural deficits (affecting grey matter in bilateral temporal regions and basal ganglia), thus increasing the previous damage already initiated by the chemotherapy [2]. In the long term (>2 years), up to 45% of SCLC survivors presented a cognitive deterioration that met dementia criteria in almost half of the cases (20%). These cognitive deficits were accompanied by chronic structural deficits in the basal ganglia bilaterally and in the corpus callosum. In addition, the severity of cognitive impairment positively correlated with the amount of damage in the microstructural organization of cerebral white matter [2,3,9].

Separately, physical activity (PA) in healthy adults has been demonstrated to improve certain aspects of cognition [10] as well as to protect against age-related cognitive decline [11], whilst being associated with changes in brain structural connectivity [12]. The effects of PA on cognition have been suggested to result from PA regulating the levels of brain derived neurotrophic factor, especially in medial temporal lobe regions (e.g., the hippocampus, HPC), which would elicit neuroprotective and learning-improvement effects [13,14]. The HPC, located in the medial part of the temporal lobe, is crucial for learning and memory functions [15–17]. The deterioration of this structure has been extensively observed in individuals with different types of dementia and cognitive impairment [18–20]. This previous evidence and suggested mechanisms point to PA utility as a potential therapeutic tool in the population at risk of cognitive decline.

Despite PA being used in several previous investigations with lung cancer patients, those reports were focused on PA effects on respiration, exercise capacity, quality of life and other health indicators [21,22] but, overall, evidence for benefits is scarce and still debated (see the review by Peddle-McIntyre et al., 2019 [23]). Further,

to date, no study has centred its efforts on investigating the potential neuroprotective effects of PA on the cognitive performance of these patients by applying neuroimaging approaches.

With the strong evidence provided by previous literature regarding the crucial role of the HPC on cognition and the sensitivity of this structure to both cancer treatments and PA, the aim was to study the structural characteristics and potential plasticity effects of a 3-month PA programme (PAP) on the bilateral HPC of lung cancer patients, as well as on their cognitive and neuropsychological performance and their quality of life. Moreover, the intention was to explore whether some differences may be present in this structure, at baseline or due to the effects of PA, depending on the cancer cellular type, so SCLC and non-SCLC (NSCLC) patients were compared, along with a matched HC group.

MATERIAL AND METHODS

Participants

Thirty-five patients (SCLC and NSCLC) enrolled in a large longitudinal study [3] were invited to participate in a 12-week PAP. Twelve of these patients (five SCLC, seven NSCLC) accepted and completed the PAP (PAP group). Another 12 patients from the longitudinal study, who matched the PAP group in age, sex, education, cancer cell type (five SCLC, seven NSCLC) and cancer treatment were included as non-PAP controls (non-PAP group). The inclusion criteria were as follows: (i) having a histologically proven diagnosis of lung cancer; (ii) aged 40–70 years; (iii) no severe concomitant illness, psychiatric disorder or magnetic resonance imaging (MRI) contraindication. Patients were excluded (i) if tests in serum were positive for onconeural antibodies (to exclude paraneoplastic encephalitis), (ii) if brain metastases were evidenced on MRI or (iii) if they showed disease progression.

Time-point 1 (T1) evaluation for SCLC patients here (PAP and non-PAP) corresponded to the temporal point 3 months after undergoing chemotherapy (platinum-based schedule) and 1 month after receiving cranial radiation (PCI, 25 Gy). For NSCLC patients, T1 assessment was performed after completion of chemotherapy (same platinum-based schedule). SCLC and NSCLC patients in both the PAP and non-PAP groups were re-evaluated once the PAP group finished the intervention, 3–4 months after T1 (time-point 2, T2). Moreover, 12 age-, sex- and education-matched HCs meeting the same inclusion and exclusion criteria (minus the cancer diagnosis) were included to control for changes due solely to time (i.e., HCs did not perform the PA intervention either). HCs underwent the same assessments separated by an equivalent amount of time as the patients. See Figure 1 for the study's timeline representation, and Table 1 for demographic information on the groups.

The current protocol was approved by the local ethics committee (protocol number PR157/11) and was in agreement with the Declaration of Helsinki. All participants received an explanation of the protocol and signed a written informed consent form.

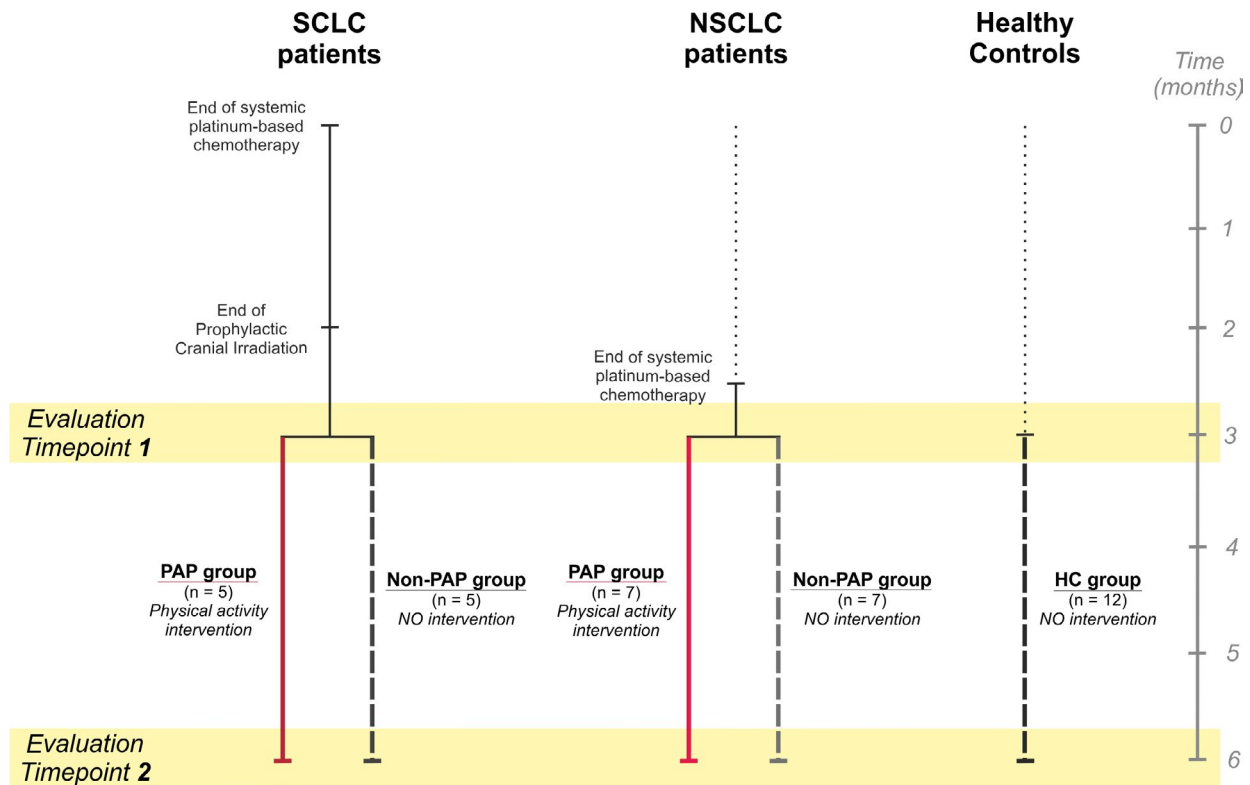


FIGURE 1 Schematic depiction of the evaluation and intervention timeline. The grey line on the right gives the time in months. Each cancer cell type group and the group of healthy controls are represented in different columns. The first 3 months give information about cancer therapy for the patients (solid lines) or the absence of it (dotted line) previous to the baseline evaluation T1. Yellow bars indicate the evaluation time-points 1 and 2. During the last 3 months, solid lines inform about the PA intervention (PAP group, counting both SCLC and NSCLC patients), whilst dashed lines represent the absence of PA intervention (i.e., the time between evaluation time-points for the non-PAP and HC groups). Abbreviations: NSCLC, non-small-cell lung cancer; PAP, physical activity programme; SCLC, small-cell lung cancer; T1, time-point 1

Physical activity programme

The PAP was especially developed for this experiment and consisted of a progressive programme of 2–4 days per week of unsupervised walking sessions and a weekly supervised cycling session [24–27]. Intensity and planned progression of the PAP was soft and slow, adapted to the performance and physical endurance of each patient, and guided by self-ratings of perceived exertion. Briefly, unsupervised walking sessions started with a recommended walking time of 12 min at a slow pace (first week), increasing up to 27 min at week 6 and intercalating 1 min at a more vigorous pace, and continued up to 30 min in week 12 with 10 of those minutes at a vigorous pace (see full protocol in Appendix S1, Appendix A). Supervised sessions followed three progressive cycling programmes, increasing total duration (15 min at weeks 1 and 2, 25 min in weeks 3–6 and 34 min in weeks 7–12) and increasing the amount of time at which cycling was performed at greater resistance (see Appendix S1, Appendix B).

During the first session, the protocol was explained to patients. Explanations included some warm-up and cool-down mobility and stretching exercises [26,28,29], and the Borg dyspnoea and tiredness scale [30]. A pedometer was also set with each patient's features to record the variables of interest from the unsupervised

walking sessions. In every session, heart rate, blood oxygen saturation (SAO_2) and dyspnoea/tiredness were frequently monitored. First and last sessions were also used to perform the pre- and post-PAP evaluation of the 6-min walking test (6 MWT [31–34]).

The output measures from the PAP to use in the subsequent statistical analyses included distance in the 6 MWT and levels at rest of SAO_2 , heart rate and breath ratio (i.e., number of breaths per minute).

Behavioural assessment: physical activity level, neuropsychological, depression and quality of life

To confirm the lack of baseline differences in PA levels between the two groups of patients, the Active-Q test [35], assessing the amount of physical activity/inactivity of an individual, was completed by all of them. In this questionnaire, high scores represent a greater level of PA.

On the other hand, at both T1 and T2 evaluations patients and controls completed an extensive neuropsychological battery in order to assess their IQ (vocabulary subtest from the Weschler Adult Intelligence Scale—III [36]), verbal memory and learning abilities (Rey's Auditory Verbal Learning Test, RAVLT), visuospatial abilities/memory (copy and delayed recall measures of the Rey-Osterreith

TABLE 1 Demographic and clinical information, and between-group differences

	SCLC		NSCLC		HCs (n = 12)	p value
	PAP (n = 5)	Non-PAP (n = 5)	PAP (n = 7)	Non-PAP (n = 7)		
Age (years) ^a	59.20 ± 3.27	57.80 ± 1.48	56.00 ± 6.33	62.29 ± 6.93	60.67 ± 6.93	n.s.
Gender ^b						
Male	3 (60%)	3 (60%)	6 (85.71%)	7 (100%)	9 (75%)	n.s.
Female	2 (40%)	2 (40%)	1 (14.29%)	0 (0%)	3 (25%)	n.s.
Education (years) ^a	8.00 ± 2.74	10.80 ± 5.72	9.43 ± 5.09	9.29 ± 3.73	9.42 ± 3.40	n.s.
KPS ^a	80.00 ± 10.00	84.00 ± 8.94	88.57 ± 6.90	87.14 ± 7.56	-	n.s.
PS ^a	1.40 ± 0.55	0.60 ± 0.55	0.86 ± 0.38	0.86 ± 0.38	-	n.s.
Tumour stage ^b						
Limited disease	2 (40%)	3 (60%)	-	-	-	
Extensive disease	3 (60%)	2 (40%)	-	-	-	
II B	-	-	-	1 (14.29%)	-	
III A	-	-	4 (57.14%)	-	-	
III B	-	-	2 (28.57%)	3 (42.86%)	-	
III C	-	-	1 (14.29%)	1 (14.29%)	-	
IV A	-	-	-	2 (28.57%)	-	
Chemo type ^b						
CDDP-based	4 (80%)	4 (80%)	7 (100%)	5 (71.43%)	-	n.s.
CBDCA-based	1 (20%)	1 (20%)	0 (0%)	2 (28.57%)	-	
Number of chemo cycles ^a	4.40 ± 0.89	4.80 ± 0.84	3.57 ± 0.79	3.86 ± 0.90	-	n.s.
Thoracic radiation ^b	5 (100%)	4 (80%)	7 (100%)	5 (71.43%)	-	n.s.

Notes:: Summary of demographics of the entire cohort, and disease and treatment-related characteristics of lung cancer patients. Mean and standard deviations are shown for mean age, years of education, KPS, PS and number of chemo cycles variables, whilst the number and percentage of cases is displayed for gender, tumour stage (classified according to Amin et al. [40]), chemotherapy type and thoracic radiation (informing about the number of patients who received thoracic radiation) variables.

Abbreviations: CBDCA, carboplatine; CDDP, cisplatin; Chemo, chemotherapy; HCs, healthy controls; KPS, Karnofsky Performance Scale; n.s., non-significant; NSCLC, non-small-cell lung cancer patients; PAP, physical activity programme; PS, Eastern Cooperative Oncology Group–ECOG Performance Status; SCLC, small-cell lung cancer patients.

^aMean ± SD.

^bn (%).

Complex Figure test, ROCF), verbal fluency (phonemic and semantic) and processing speed (Trail Making Test, TMT A and B). They also filled the Beck Depression Inventory (BDI) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core Questionnaire [37]. At the 3-month/post-PAP evaluation, different versions of the ROCF and the RAVLT, jointly with the phonemic and semantic verbal fluency tests, the TMT (A and B) and the BDI were administered.

Magnetic resonance imaging data

A T1-weighted sequence was obtained in a Siemens 3 T MRI scan and was preprocessed using the Computational Anatomy Toolbox 12 (CAT12, <http://www.neuro.uni-jena.de/cat/index.html#VBM>). See Appendix S1, Appendix B, for more details.

Preprocessed individual smoothed grey matter volume (GMV) images were included in a second-level analysis: a three-groups

(SCLC, NSCLC and HCs), two time-points (T1, T2) ANOVA full factorial design within SPM12, completed by applying a region of interest mask covering and restricting the analyses to bilateral hippocampi. After omnibus testing, pairwise *t* tests were performed at the group level to analyse within-group changes over time (T2–T1). Results were considered as significant at an uncorrected $p < 0.005$, with a cluster size of 100 consecutive voxels. When no post hoc test reached significance at the imaging level, GMV values from significant clusters within the hippocampi were extracted to investigate potential differences between the patients' groups.

Statistical analysis

Regarding behavioural measurements, in order to test both for pre-, post-PAP differences and between-group differences, a time-point (two: pre-, post-PAP) per group (three: PAP patients, non-PAP patients, HCs) mixed effects ANOVA was performed with these

variables. Also, a time-point (two) per group (two: PAP, non-PAP patients) repeated measures ANCOVA, with patients' pre-post weight difference as a control covariate, was carried out to check for differences in the PA level (i.e., Active-Q scores). Then, for exploring pre-post differences in PAP outcome measures, paired *t* tests between pre- and post-PAP values were carried out for those variables in the PAP group.

Grey matter volume values from the significant clusters obtained in the only significant voxel-based morphometry (VBM) result, the main effect of group (see Appendix S1, Appendix C, Table S1), were extracted and used in a second analysis to test for differences within the patient groups consisting of (i) a time-point (two: pre-, post-PAP) per group (two: PAP, non-PAP) mixed effects ANOVA to check for differences between PAP and non-PAP patient groups and (ii) a time-point (two: pre- and post-PAP) per group (two: PAP patients, non-PAP patients) per cell type (two: SCLC, NSCLC) mixed effects ANOVA to investigate the potential effects of cancer cell type in both groups of patients.

Finally, Spearman correlations were performed between the values for post-pre difference in behavioural variables and the GMV values of the significant hippocampal clusters from the VBM analysis (i.e., main effect of group comparison).

Analyses were performed using SPSS v.25 (released 2017, IBM SPSS Statistics for Windows, Version 25.0, IBM Corp.).

RESULTS

As shown in Table 1, our groups did not differ significantly in demographic or clinical variables.

Physical activity programme

Paired *t* tests found significant pre, post differences for distance in the 6 MWT ($t(10) = -2.43, p < 0.05$) and level of SAO₂ at rest ($t(9) = -2.45, p < 0.05$), such that values in both measures were greater post-PAP than pre-PAP. This suggests an improvement in cardiovascular resistance and breathing efficiency in patients undergoing our PAP. No significant results were observed for heart rate or breath ratio at rest. See Figure 2 for a depiction of these results and Appendix S1, Appendix C, Table S2 for more information.

Behavioural results

In line with previous reports [38,39], no significant main effect, pre-post or between-group difference was found for any of the neuropsychological, depression or quality of life measures.

Regarding the PA level (Active-Q score), no main effect of time (T2-T1 evaluations, $p = 0.061$) or time per group ($p = 0.096$) was found, meaning that there was no significant difference between patient intervention groups at either baseline or post-intervention.

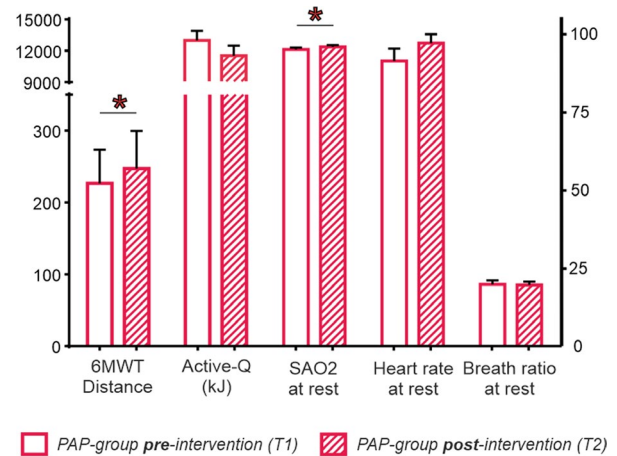


FIGURE 2 Results regarding the PAP outcome measures. This bar graph depicts the values pre- (T1) and post-PAP intervention (T2) in the PAP patient group, where it can be observed that there were significant differences at T2 in the distance walked in the 6 MWT and in the SAO₂ at rest. Note that the left y-axis corresponds to the first two variables from the left (i.e., 6 MWT and Active-Q) and the right y-axis scale corresponds to the other three variables (i.e., SAO₂, heart rate and breath ratio at rest). Abbreviations: 6 MWT, 6-min walking test; SAO₂, blood oxygen saturation; PAP, physical activity programme; T1, time-point 1; T2, time-point 2. Asterisks (*) mark significant differences at post-pre measurements at a p -value < 0.05

Neuroimaging results

Voxel-based morphometry ANOVA region of interest driven analysis showed a main effect of group ($F(2, 70) = 5.75, p < 0.005$, see Appendix S1, Table S1) in two clusters in the bilateral hippocampi, driven by the difference between HCs and the two groups of patients (see Figure 3).

Hence, in order to explore the potential differences between patient groups, a secondary analysis was performed with the GMV values extracted from the clusters in the bilateral hippocampi. A significant main effect of the intervention group was found in the time-point per group mixed effects ANOVA for the left HPC ($F(1, 22) = 4.47, p < 0.05$) so that the PAP group showed greater GMV across time compared to the non-PAP group (see Figure 4a1). Moreover, a significant time per intervention group interaction was also found for GMV in the left HPC ($F(1, 22) = 5.33, p < 0.05$), meaning that, in addition to starting with greater GMV, the PAP group showed an increase in GM after PAP intervention, whilst non-PAP patients showed a GMV decrease in this structure (see Figure 4b). For GMV in the right HPC, no significant main effect was found, and only a trend was observed paralleling the time-point per intervention group interaction ($p = 0.057$).

Lung cancer subtype

The same results were confirmed for the left HPC after including the cell type between-subject factor: there was a significant main

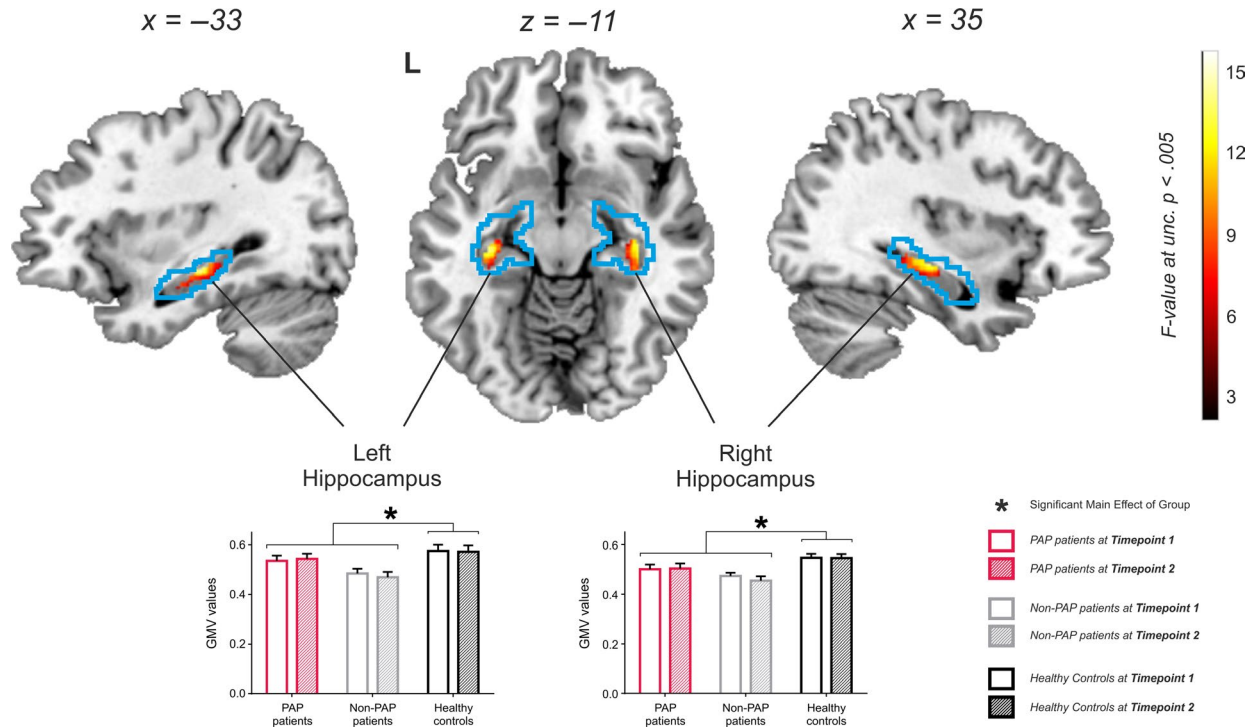


FIGURE 3 Voxel-based morphometry results for the main effect of group (imaging level, SPM). Depiction of the two significant clusters found within the bilateral region of interest applied in this analysis, covering left and right HPC. The warm-colour scale shows F values. Blue lines delineate the hippocampal region of interest used. Bar graphs in the lower panel show T1 and T2 values in GMV in the left and right HPC per group (PAP patient group in pink, non-PAP patient group in light grey, healthy controls in black); the significant main effect of group is marked with an asterisk (healthy controls greater than both groups of patients). Abbreviations: GMV, grey matter volume; HPC, hippocampus; L, left; PAP, physical activity programme

effect of patient group ($F(1, 20) = 4.562, p < 0.05$; see Figure 4a2) and a time-point per patient group interaction ($F(1, 20) = 5.414, p < 0.05$; see Figure 4b). Interestingly, by adding cancer cell type in the analysis several effects on the right HPC were observed: (i) a significant main effect of cell type ($F(1, 20) = 5.431, p < 0.05$) showing that NSCLC present greater GMV in the right HPC than SCLC across time (see Figure 4c2); (ii) a significant time-point per intervention group interaction ($F(1, 20) = 6.995, p < 0.05$) meaning that there was a significant loss of GMV in the non-PAP group at T2 independently of cell type (see Figure 4d); (iii) a significant time-point per cell type interaction ($F(1, 20) = 4.619, p < 0.05$) so that SCLC patients presented a significant loss of GMV at T2 across intervention groups (see Figure 4d); and (iv) a triple time-point per intervention group per cell type interaction ($F(1, 20) = 4.711, p < 0.05$) meaning that, within the non-PAP group, there was a significant loss of GMV in the right HPC at T2 only for the SCLC patients (see Figure 4d). See Appendix S1, Table S3, for more details regarding the neuroimaging results.

Correlations between neuroimaging and behavioural variables

No significant correlations were found between GMV values and PAP outcome measures.

However, GMV values at T1 in both left ($r = -0.493, p < 0.05$; Figure 5a1) and right ($r = -0.426, p < 0.05$; Figure 5a2) hippocampi negatively and significantly correlated with the T2-T1 difference in the Active-Q scores, meaning that those patients with greater GMV bilaterally at baseline started and ended the experiment with almost the same level of daily PA (smaller change in Active-Q scores). Also, GMV values at T1 in the left HPC negatively and significantly predicted the T2-T1 change in the performance of the ROCF tests, both for immediate copy ($r = -0.462, p < 0.05$; Figure 5b1) and delayed recall ($r = -0.493, p < 0.05$; Figure 5b2), and GMV values at T2 in the right HPC negatively and significantly correlated with the T2-T1 difference in performance in the delayed recall of the ROCF ($r = -0.439, p < 0.05$). These indicate that patients with greater GMV values in the left HPC at baseline and in the right HPC at T2 showed a maintenance of visuospatial and visual memory skills across time.

DISCUSSION

In the current study, the aim was to explore the potential neuroprotective effects of a 3-month PAP in a group of lung cancer patients that included both NSCLC and SCLC patients treated with chemotherapy \pm PCI. Behaviourally, the PAP showed effectiveness in general health indicators, since it improved patients' oxygen saturation at rest as well as resistance and velocity during walking. Moreover,

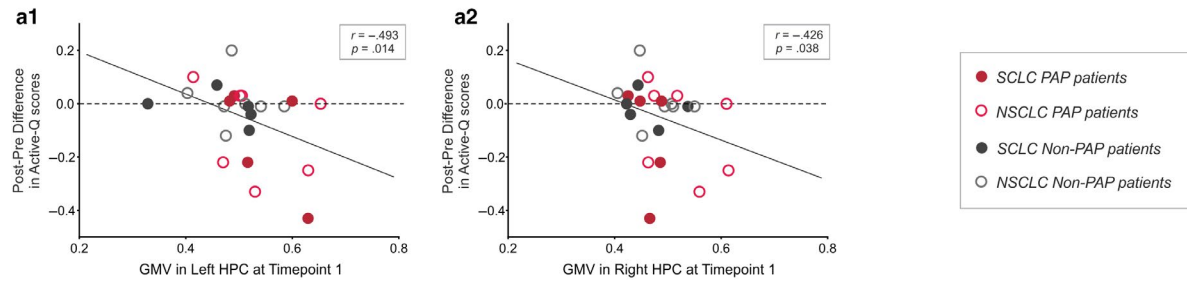
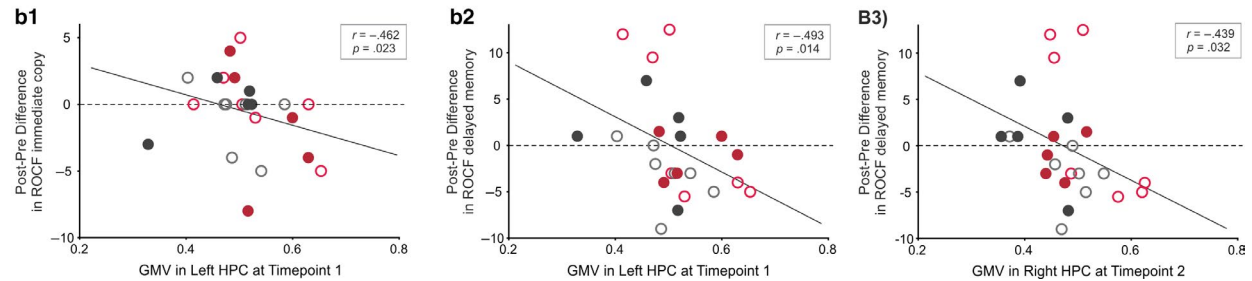
(a) Correlations between Hippocampal GMV values and PAP variables**(b) Correlations between Hippocampal GMV values and Neuropsychological variables**

FIGURE 5 Correlations between GMV values in the significant clusters within the HPC from the main effect of group contrast and the behavioural measures. (a) Correlations with the PAP-related measures: only significant correlations with the T2–T1 difference in the Active-Q score were found and are depicted. (b) Correlations with neuropsychological measures, specifically, with the score in the ROCF immediate copy and delayed memory recall. Abbreviations: GMV, grey matter volume; HPC, hippocampus; PAP, physical activity programme; ROCF, Rey–Osterrieth Complex Figure test; T1, time-point 1; T2, time-point 2

memory recall may suggest a link between plastic changes elicited by the PAP and patients' cognitive performance, which would support an important neurobehaviourally protective role for PA in these patients, since visuospatial abilities were described as altered after cancer treatment in this population, especially in SCLC patients [2,3].

Our study presents some limitations, which could be related, in most cases, to the small sample size and its inherent limited variability. First, a significant difference in GMV at baseline (T1) was observed between the PAP and the non-PAP patient groups, which may support a specific pre-disposition in the present sample for practising PA (i.e., patients with greater GMV in the left HPC seemed to be the ones most prompted to agree to participate in the PAP). However, the lack of behavioural and cognitive differences between the two groups at both evaluation time-points, and the lack of differences regarding the level of PA measured via the Active-Q test at baseline, do not support a selection bias. Finally, despite our PA intervention having a beneficial effect for general health and an impact on brain structure, the absence of significant differences between intervention groups in Active-Q scores at T2 suggests that our PAP was not intense enough to alter patients' PA routines. This may imply that the PAP might have needed a greater intensity or duration to be transferred to a usual everyday PA practice. Overall, despite the aforementioned limitations, our results suggest a beneficial effect of PA, since patients engaged in the intervention seem to maintain or increase the GMV values of bilateral HPC.

Findings for the PA intervention exposed here are modest but constitute a promising proof of concept, showing that some changes

may be elicited by PA interventions in lung cancer patients in key structures linked to cognitive performance (i.e., HPC), although some predispositions may be taking place as well. It is hypothesized that a PAP with greater duration and intensity might elicit more important and clearer effects, both at the brain and at the cognitive and quality of life levels. However, previous reports already pointed to the difficulty in obtaining measurable gains from PA interventions in this population [27,38].

As a conclusion, it has been found here that a 3-month PA intervention increases GMV in hippocampal structures in lung cancer patients. Also, it was observed that SCLC patients, independently of the group of study (PAP, non-PAP) or evaluation time-point, exhibited less GMV in hippocampal structures, which suggests a greater structural damage in this group (and goes in line with our previous reports). Most interestingly, our results suggest that SCLC patients may be the ones obtaining the greatest benefit from the PA intervention, thus proposing an important clinical implication. However, future studies are needed to validate these findings in larger cohorts.

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CONFLICT OF INTEREST

All authors declare not having any conflict of interest for the current work.

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DATA AVAILABILITY STATEMENT

Note that, although it is preferred that all the data discussed in the paper are available to the readers, the Institutional Research Ethics Board rules of the Hospital Universitari de Bellvitge need to be complied with, which means that only the data for those participants who agreed to secondary use of data in the consent form used in the experiment will be made available (after an anonymization process).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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