The chemotherapy long-term effect on cognitive functions and brain metabolism in lymphoma patients

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***Aim*. A growing number of neuropsychological studies reported that chemotherapy may impair brain functions, inducing persistent cognitive changes in a subset of cancer survivors. The aim of this paper was to investigate the neural basis of the chemotherapy induced neurobehavioral changes by means of metabolic imaging and neuropsychological testing.**

***Methods*. We studied the resting brain [18F]FDG-PET/CT images of 50 adult cancer patients with diagnosis of lymphoma: 18 patients were studied prior and 32 after to chemotherapy. All patients underwent to a neuropsychological examination assessing cognitive impairment (tests for shifting attention, verbal memory, phonemic fluency), depression, anxiety and distress.**

***Results*. Compared to no chemotherapy patients, the treated group showed significant bilateral lower rate of glucose metabolism in prefrontal cortices, cerebellum, medial cortices and limbic brain areas. The metabolism of these regions negatively correlated with number of cycles and positively with post-chemotherapy time. The treated group showed a poorer performance in many frontal functions, but similar level of depression, anxiety and distress.**

***Conclusions*. Chemotherapy induced significant long-term changes in metabolism of multiple regions with a prevailing involvement of the prefrontal cortex. The observed cognitive dysfunctions could be explained by these changes. The recovery from chemotherapy is probably affected by treatment duration and by the time elapsed after its end. We speculated that the mechanism could be an accelerating ageing / oxidative stress that, in some patients at risk, could result in an early and persistent cognitive impairment.**

KEY WORDS: Neoplasms - Neuropsychology - Rest.

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Cognitive changes in cancer patients after adjuvant chemotherapy (CHT) treatments have been reported since the mid 1970s, with systematic research starting in the early 1990s. Since then, most but not all [1-3] neuropsychological studies on cancer survivors, having received adjuvant CHT, have reported cognitive impairments in multiple domains such as executive functions, learning, memory (especially working memory, while the retrieval of remote memories seems to be spared), attention, verbal fluency and speed of information processing.[4-10] Both prior meta-analyses [11, 12] and, more recently, longitudinal studies [13-16] have consistently shown that CHT induced cognitive impairments are small to moderate, involving mostly the cognitive functions subserved by frontal lobes.

Findings emerging from controlled longitudinal studies [13, 16-18] indicate that cognitive changes tend to fully resolve over time while cross-sectional studies suggest that they may persist for many years following completion of treatment, at least in a significant subset of patients.[19, 20]

Recent structural magnetic resonance imaging studies have provided consistent evidence that CHT can induce both gray and white matter changes which can be, at least partially, reversible. A CHT-related reduction of the gray matter volume [21] of brain structures

significantly correlated with attention/concentration and/or visual memory (such as the prefrontal, cingulate and parahippocampal cortex), and a loss of white matter integrity [21-26] has been shown by comparing CHT treated with untreated cancer patients. The reversibility of these changes, at least partial, was suggested by longitudinal examination of cancer patients, one study finding a significant increase of white matter volume from 6 to 12 months after CHT,[27] while another finding no gray and white matter volume differences 3 years after completion of CHT.[21] Three neuroimaging studies suggest, however, that CHT can induce long lasting adverse effects on brain functions. Using [15]O water PET during an activation short-term recall task, cerebral blood flow in specific regions of frontal cortex and cerebellum was significantly altered in breast cancer women investigated 5-10 years after receiving CHT.[28] Memory and planning fMRI tasks performed on a sample of breast cancer women recruited 3-5 years [29] and 9 years [30] after completion of CHT showed hypoactivation in some areas, especially in frontal cortex.

Besides, little is known about the mechanisms leading to these changes and how the brain tries to adaptively react. The recruitment of compensatory mechanisms aimed at overcoming the CHT induced structural and/or functional impairments has been suggested by a fMRI in pairs of 60-year-old identical twins discordant for breast cancer.[24] While performing an identical working memory task, the CHT treated twin showed, compared to the other, a greater spatial extent of activation in fronto-parietal dorsal attentional network.

The mechanisms for CHT induced cognitive changes are largely unknown; however, several hypotheses have been proposed, including blood brain barrier alterations, cytokines and hormonal deregulation, as well as a direct neurotoxicity of chemotherapic agents.[31]

The present study used brain resting state [18F] FDG-PET, combined with neuropsychological tests to assess relations between regional cerebral metabolic glucose rate (rCMRglc), cognitive performances and oncologic/therapeutic variables in lymphoma patients.

Materials and methods

Patients

Cancer patients were enrolled among those who were planned to undergo a whole-body [18F]FDG PET on a clinically routine basis for cancer staging or to monitor the disease after treatment.

Patients were considered eligible, after an accurate clinical examination, if they did not have neurological and psychiatric disorders or medications that could potentially alter neuropsychological performances and/or brain metabolism. Eligible patients gave written informed consent to participate in the project, which was approved by the ethical committee of San Giovanni Battista University Hospital, Turin.

Among 50 enrolled patients, 32 (age =45±16 years) had been previously treated with systemic CHT (7±9 months after completion) and 18 patients were not treated (No CHT, age =57±14 years). Within the CHT patients the majority (N.=22, 69%) had a non-Hodgkin's lymphoma (NHL) and 10 (31%) a Hodgkin's lymphoma (HL). All selected patients were evaluated and treated in the same Haematology Oncology Department. We created two subgroups from the CHT and No CHT total groups in order to obtain two groups of patients perfectly sex and age-matched, and eliminate serious confounding in a comparison analysis of the brain metabolism. The demographic and clinical characteristics are shown in Table I. The CHT group underwent to conventional standard-dose chemotherapy.

The ABVD (Adriamycin/Hydroxydaunorubicin/Doxorubicin, Bleomycin, Vinblastine and Dacarbazine) chemotherapy protocol (one of the most common CHT regimens for treating HL) was used in 28% (N.=9) of patients. The CHOP (Cyclophosphamide, Hydroxydaunorubicin, Oncovin/Vincristine, and Prednisone or Prednisolone) protocol (widely employed in the treatment of NHL) was used in 41% (N.=13) of patients. Second line treatments were used in the remaining 31% (N.=10) of patients.

In 56% of the cases (N.=18) the CHT has been associated with the monoclonal antibody Rituximab (54% of first-line treatment and 60% of second-line treatments).

The number of cycles of CHT ranged from 1 to 18 cycles with 44% (N.=14) of treatments consisting of less than 6 cycles, 44% (N.=14) 6-10 cycles and only 12% (N.=4) in more than 10 cycles. The time elapsed from the end of the treatment ranged from 1 week (recorded as 0 months) to about 3 years (35 months) with 38% (N.=12) of cases observed after 1 month or less since the end of the treatment, 41% (N.=13) between 2 and 12 months, 21% (N.=7) more then 12 months.

TABLE I.—*Clinical and demographic characteristics.*

Subgroups	No CHT (N.=18)	CHT (N.=32)	p	No CHT Mat (N.=14)	CHT Mat (N.=14)	p
Demographic						
Age [y]	57±14	45±16	0.01	52±10	52±10	1.00
Gender [M/F]	13/5	20/12	0.32	11/3	11/3	1.00
Education [y]	13±5	13±5	0.89	14±5	14±5	0.96
Lymphoma						
Type [HL/NHL]	2/16	10/22	0.12	2/12	2/12	1.00
Age at onset [y]	57±14	43±14	0.01	52±10	51±9	0.96
Disease Duration [mos]	2±2	23±48	0.02	2±2	12±11	<0.01
Chemotherapy						
Cycles Number [N.]	-	6±4	-	-	6±3	-
Post-CHT time [mos]	-	7±9	-	-	7±9	-
First-line Treatment [N.]	-	22	-	-	9	-
Second-line Treatment [N.]	-	10	-	-	5	-
Immunochemotherapy [N.]	-	18 (12/6)	-	-	10 (7/3)	-
Blood tests						
WBC [10^3/mL]	6.2±2.8	6.7±3.9	0.50	6.5±3.0	7.3±4.1	0.56
RBC [10^6/mL]	4.6±0.6	4.5±0.8	0.63	4.5±0.5	4.6±0.7	0.53
Hb [g/dL]	14.1±1.8	12.8±2.4	0.07	13.8±1.8	13.1±3.2	0.52
Anemia (Hb<12 g/dL) [N.]	3	11	0.01	2	3	0.71

CHT: chemoterapy; F: females; Hb: hemoglobin; HL: Hodgkin's lymphoma; M: males; Mat: matched for age, sex and education; mos: months; NHL: non Hodgkin's Lymphoma; RBC: red blood cells; WBC: white blood cells; y: years. First-line Treatment: ABVD (adriamycin [hydroxydaunorubicin], bleomycin, vinblastine, dacarbazine) or CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin [vincristine], prednisone or prednisolone). Immunochemotherapy: treatment plus immunotherapy (rituximab), in parenthesis first and second line. Values represent, when not otherwise specified, mean±standard deviation. Significance p. Two independent sample t test or p χ^2.

Neuropsychological examination

A neuropsychological examination was performed before the PET scanning preparation in a separate quite room, with a battery of neuropsychological and psychological tests, covering several domains (attention, memory, language, frontal functions), included: Mini Mental State Examination (MMSE), Trail Making Test B (TMT-B), Phonemic Fluency, Short Story Test, Hospital Anxiety and Depression Scale (HADS), Montgomery-Asberg Depression Rating Scale (MADRS), Distress Thermometer (DT).

PET scanning

In a quiet waiting room participants, lying in a supine position, were asked to refrain from moving and instructed "to keep their eyes closed, to not engage in any structured mental activity such as counting, rehearsing, etc., and to avoid falling asleep". They were then blindfolded and ear plugged and received intravenously about 4.5-5.5 MBq kg^{-1} of 2-deoxy-2-[18F]fluoro-D-glucose. About 30 minutes later PET/CT scan was performed by a Philips Gemini scanner (Philips Medical System, Cleveland, Ohio, USA). The brain scan acquisition time was of 20 minutes. Reconstructed brain images had a dimension of 128x128x90 voxels (2x2x2 mm^3). After the planned whole body [18F]FDG PET/CT examination was performed, the coronal, sagittal and transverse data sets were reconstructed using an 3D iterative technique (row action maximum likelihood algorithm, RAMLA-3D) and corrected with single scatter simulation (SSS).

Statistical analysis

[18F]FDG-PET brain images were preprocessed and voxel-based statistical analyses were performed using SPM8 (www.fil.ion.ucl.ac.uk/spm) running on MATLAB 7.5 software. All images were non linearly spatially normalized into the Montreal Neurological Institute (MNI) space and smoothed with an isotropic Gaussian kernel of 12 mm Full Width Half Maximum. Confounding effects of global activities differences were removed by normalizing the count of each voxel to the mean count of a standardized pontine region of interest (ROI) in order to avoid a biased normalization.[32] The pons was chosen on the basis of its relative stability and late involvement in neurodegenerative diseas-

es such as Alzheimer disease, a finding leading other investigators to use it as reference region. The ROI was a rectangular multislice region (x/x'=-8/8, y/y'=-32/-24, z/z'=-44/-34; MNI space) sampling 144 voxels on the central pontine region and manually drawn on the PET SPM template using the MRIcro application (http://www.sph.sc.edu/comd/rorden/mricro.html). Both ROI coordinates and dimensions were chosen to avoid low-counts background voxel sampling and to minimize the random noise effect. A previous careful visual inspection of the pons was conducted on each spatially normalized but non smoothed brain scan in order to detect metabolic changes which could alter the ROI measure. The same ROI was then employed on each spatial normalized and smoothed brain image and the pons mean voxel values (Y_p) sampled. Using the image calculation tool of SPM, the scaled voxel values (Y') of each brain was set at $Y' = (Y/Y_p)$ were Y was the non scaled ("raw") voxel value. Only voxel values greater than 80% of the whole brain mean MRglc were included in the analysis. All SPM results were thresholded at P<0.005 uncorrected for multiple comparisons, with an extent threshold cluster extent (Ke) of 25 voxels. Statistical inferences were performed by applying the Random Field Theory. Clusters with P≤0.05 corrected for multiple comparisons were considered as significant.

SPSS 13.0 was used for all other statistical analyses, P<0.05 was considered as significant.

Between groups rCMRglc comparison analyses were performed using a two independent samples t test after selecting 14 CHT and 14 No CHT patients exactly matched one by one (same sex and age) for a case-control design (Table I). Neuropsychological and psychological scores comparison were performed with a two independent samples t test for Matched groups raw scores (14 CHT *versus* 14 No CHT) and for total groups (18 CHT *versus* 32 No CHT) corrected scores (sex, age and education).

Since both animal [33, 34] and human studies suggested that CHT dose [9, 15] and number of CHT cycles (C),[19] as well as the time (T) elapsed since completion of the treatment [13, 16-18] can modulate the CHT effects on neurobehavior and brain metabolism, we tested this hypothesis on the whole CHT group (N.=32) with a General Linear Model (GLM) using age, gender, C and T as independent variables and rCMRglc as dependent variables.

To better investigate the possible mechanisms underlying the CHT induced changes we compared the age impact onto rCMRglc and test scores in the CHT and No CHT Matched groups, then a conjunction analysis between brain areas significantly correlated which age, C and T was performed (N.=32).

Finally, to link the neurobehavior with metabolic pattern we used a GLM with test scores, age and gender as independent variables and rCMRglc as dependent variable (N.=50).

Results

Comparison between No CHT and CHT groups

The total CHT and No CHT groups (Table II) differed in MMSE (P=0.04) and TMT-B (P=0.04) scores and showed a trend in Phonemic Fluency (P=0.08), but did not differ for depression self- (HADS-D) or hetero- (MARDS) evaluated, anxiety (HADS-A) or distress (DT, HADS-Tot).

The CHT and No CHT Matched groups did not differ (Table II) for any psychological (depression, anxiety, distress) or neuropsychological scores (MMSE, attention, fluency, memory, frontal functions). However a cluster of 3297 voxels involving bilaterally the anterior cingulate cortex (max Z=3.73, P corr. =0.03) and part of frontal cortices showed a lesser rCMRglc (Figure 1, Table III) in the CHT group.

Correlations with C, T and age

In the total CHT group, we observed a negative correlation between C and a bilateral fronto-temporal rCMRglc pattern (Figure 2). A similar pattern was positively correlated with T (Figure 2) and negatively with age (Figure 2). The conjoint analysis of the three correlations together gave a very large and significant cluster involving bilaterally the frontal cortices (Ke=13457, max Z=4.42, P corr. <0.01, Figure 2, Table III).

Comparison between age impact onto rCMRglc in No CHT and CHT groups

In the No CHT Matched group, age was negatively correlated with a large medial cluster involving cingulate cortex and cerebellum (Ke=8896, max Z=3.96, P corr. <0.01, Figure 3, Table III).

The CHT Matched group showed a similar pattern (Figure 3, Table III), but more extended, with two large clusters involving medial (Ke=11119, max

TABLE II.—*Neurobehavioral characteristics.*

Subgroups	No CHT (N.=18)	CHT (N.=32)	p	No CHT Mat (N.=14)	CHT Mat (N.=14)	P
Neuropsychological tests						
MMSE	27.6±1.4	26.7±1.5	0.04	28.4±1.3	28.1±1.8	0.63
TMT-B	71±37	100±52	0.04	84±24	97±52	0.40
Phonemic Fluency	36±9	30±12	0.08	38±8	33±11	0.21
Short Story IR	-	-	-	5±2	6±1	0.13
Short Story DR	-	-	-	6±2	6±1	0.69
Short Story Tot	10±3	10±3	0.96	11±3	12±1	0.43
Depression						
MADRS	10±5	8±7	0.40	9±6	8±7	0.68
HADS-D	4±3	4±4	0.90	4±3	4±3	0.86
Anxiety						
HADS-A	6±3	5±3	0.14	6±3	4±3	0.17
Distress						
DT	3±2	3±2	0.51	3±2	2±2	0.28
HADS-Tot	10±5	9±6	0.46	9±5	8±6	0.37

Raw scores for the Mat groups, corrected scores (age, sex and education) for the total groups. CHT: Chemotherapy; DR: delayed recall; DT: distress thermometer; HADS: Hospital Anxiety and Depression Scale; IR: Immediate Recall; Mat: matched for age, sex and education; MADRS: Montgomery-Asberg Depression Rating Scale; MMSE: Mini Mental State Examination; TMT-B: Trail Making Test B; Tot: total. Values represent, when not otherwise specified, mean±standard deviation. Significance p. Two independent sample t test.

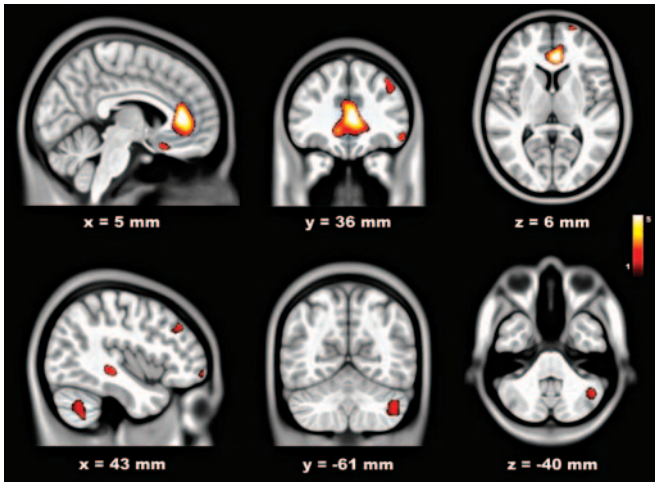

Figure 1.—Patterns of cortical CHT-induced rCMRglc changes. T-maps obtained by comparisons analysis between No CHT and CHT groups overlaid on canonical brain templates. Images are in neurological convention (left is left). Threshold P<0.005 uncorrected, Ke>25 for both rows, only for the fist row's cluster p corr≤0.05.

Z=4.32, P corr. <0.01), but also fronto-temporal left areas (Ke=6445, max Z=3.92, P corr. <0.01).

Correlation between test scores and rCMRglc

In the total sample of subjects no psychological or neuropsychological test significantly correlated (P<0.005) with the rCMRglc except for TMT-B, but the clusters disappeared if we applied a threshold correction for multiple comparison (the pattern was similar to that of the age negative correlation, data not shown).

Discussion

Some neuroimaging studies have shown that CHT could induce structural [21, 22, 25-27, 35] and functional [24, 28, 36] brain changes involving both the cortex and the white matter, with a prevailing involvement of the prefrontal cortex. However, the time course of such changes is less well consistently defined, with a study suggesting a complete recovery of the structural damage few years after the completion of the treatment [21], and others reporting a longer lasting functional impairment.[28, 29]

Our data strongly support a reversible, but long lasting model (at least after 6 months post-CHT) of CHT induced brain damage (Figures 1, 2, Table III), suggesting that chemotherapy induced cerebral glucose metabolic impairment could be transient and reversible over time (Figure 2), paralleling or even preceding the structural recovery of the CHT targeted brain regions. The neurobehavioral correlate of this metabolic impairment was the significant worsening of MMSE (P<0.05), TMT-B (P<0.05) and Flu-

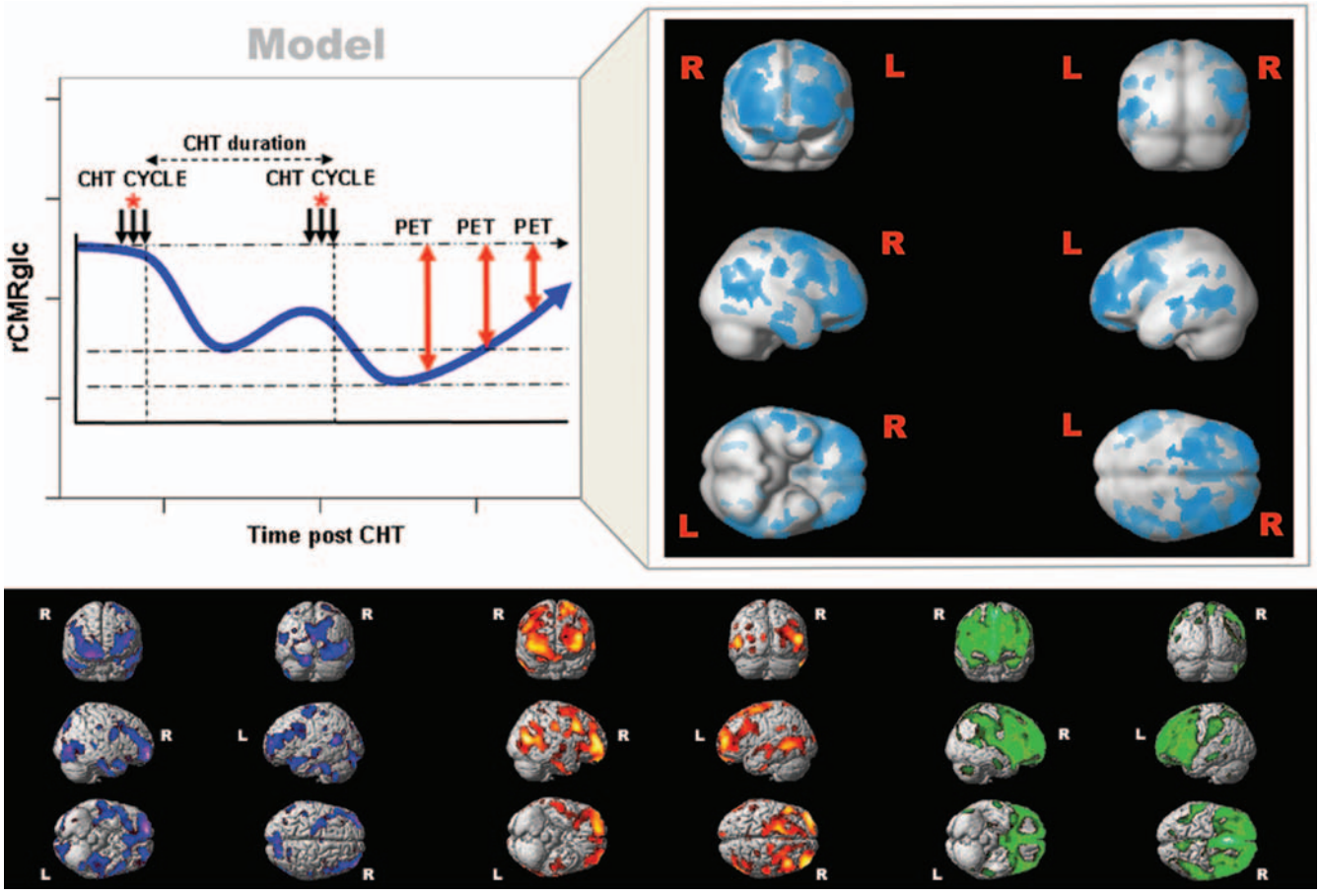

Figure 2.—Conjoint analysis of number of cycles, time elapsed after the therapy and aging. The whole group of patients having received chemotherapy showed a significant lowering of rCMRglc with the number of cycles C in the bilateral fronto-temporal cortices (in blue) and a recovering of the same areas rCMRglc with the time T elapsed after the therapy (in red). This pattern was also strongly negatively correlated with the age of the patients (in green). These findings are consistent with a time-dependent heuristic model of CHT-induced rCMRglc changes (on the upper-left). The model take in account moreover the possible cumulative neurotoxic effects of the CHT cycles (red asterisk). On the upper-right the common pattern of C, T and aging (in light blue) evidenced by a conjoin analysis (P<0.005 uncorrected, Ke>25).

ency (P<0.10) scores in the CHT groups (Table II). The results were significant only in the total CHT group as, probably in the Matched groups there was not enough power to reveal the effect (note that the differences between the Matched groups scores would be significant with a larger sample as in the total groups [Table II], we are in fact talking of a subtle subclinical impairment). These results are in agreement with findings emerging from controlled longitudinal neuropsychological studies [13, 16-18] indicating that cognitive changes are noticeable close to the end off-therapy, but tend to fully or partially resolve over one year.

However, the assumptions on the reversibility of brain metabolic and cognitive impairment must be taken with caution. Indeed, we cannot exclude that a subset of brain regions do not recover or recover only partially over time. Candidate regions could be medial areas that showed a long lasting metabolic impairment in the present study (ACC in the No CHT *versus* CHT comparison, Figures 1, 2, Table III), but not a linear recovery with post-CHT time (the frontal areas recovering were more lateral, Figure 2, Table III). We cannot exclude that these areas recover in a non linear, slower manner or only partially, so all these hypotheses are compatible with our analyses.

To gain more insights on the mechanisms underlying these chemotherapy related adverse ef-

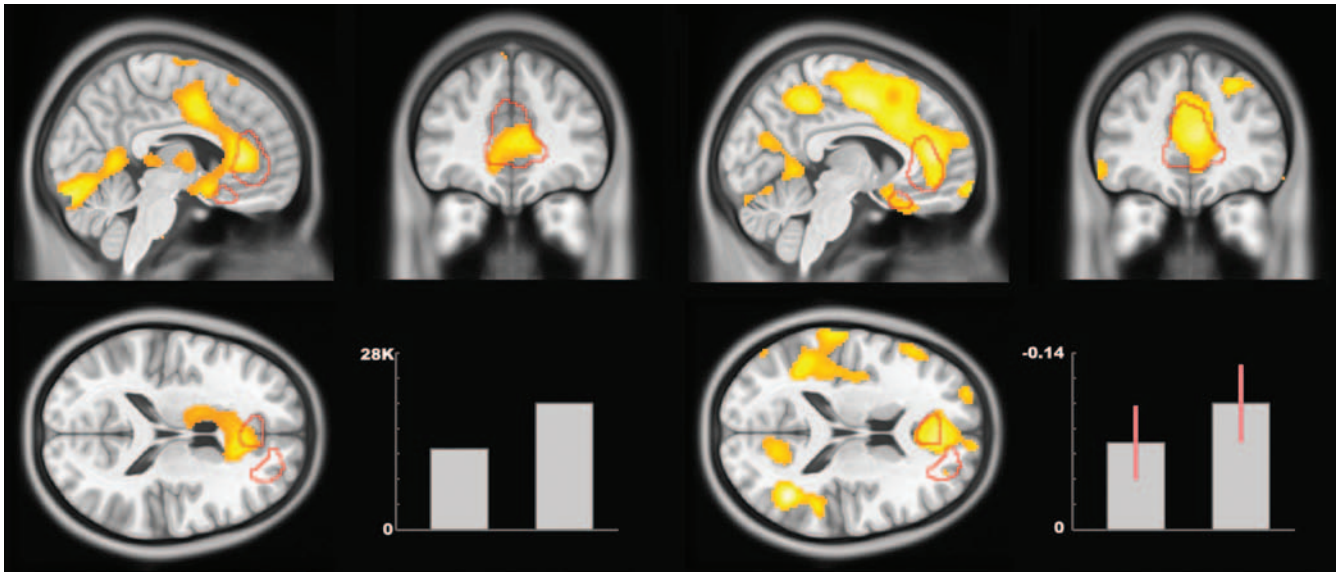

Figure 3.—Ageing in the No CHT (N.=14) and CHT (N.=14) groups. Compared to non treated patients (on the left), the rCMRglc of the medial cortices showed in the CHT patients (on the right) a more significant and negative association with age. The red outline shows the areas of significant CHT-induced lowered rCMRglc (Figure 1). The histograms represent (on the left) the number of significant age correlated voxel (P uncorrected <0.005) and the beta values (on the right) of the correlations inside the red outline. The CHT group showed both a greater number of voxels and a stronger negative correlation with age. Images are in neurological convention (left is left). Threshold P<0.005 uncorrected, Ke>25.

TABLE III.—*Voxel Based Analysis.*

Cerebral Region	BA	p corr.	Ke	Z	MNI Coordinates		
					x	y	z
Between subgroups comparison analysis (N.=28) Matched No CHT (N.=14) > CHT (N.=14)							
R ACC	24	0.03	3297	3.73	4	36	8
R Frontal Middle	46			3.58	26	48	16
L ACC	11			3.22	-10	36	-6
Negative correlation with age in No CHT Matched subgroup (N.=14)							
R ACC	25	<0.01	8896	3.96	4	34	8
R Cerebellum Crus 1				3.89	6	-84	-18
L MCC	24			3.60	0	4	40
Negative correlation with age in CHT Matched subgroup (N.=14)							
L MCC	24	<0.01	11119	4.32	-4	4	42
R ACC	32			3.92	6	44	12
R MCC	23			3.91	8	-8	50
L Frontal Inferior	45	<0.01	6445	3.92	-54	28	-2
L Temporal Pole	38			3.48	-44	14	-32
Conjoint analysis correlation with CHT Cycles + Time post-CHT + age in CHT subgroup (N.=32)							
L Frontal Middle	10	<0.01	13457	4.42	-38	60	14
R Frontal Middle	46			4.20	44	56	8
L Frontal Superior	11			3.71	-30	64	-6

Height threshold P=0.005 uncorrected for multiple comparisons; P corr.: P corrected for multiple comparisons;
ACC: Anterior Cingulate Cortex; BA: Brodmann Area; CHT: chemotherapy; Ke: cluster extent; L: left;
MCC: Middle Cingulate Cortex; R: right.

fects, we looked for a relationship between C and the cerebral glucose metabolism. The voxel-based correlation analysis evidenced a set of brain areas showing a significant negative association between C and the rCMRglc (Figure 2), which partially overlapped those uncovered by the post-CHT correlation analysis described above (Figure 2). These results therefore support a model in which the CHT induced brain damage appears to be related to C, in agreement with previous neuropsychological data [19] reporting a negative relationship between C and the cognitive performance. At this time we cannot discriminate between a pure dose dependency, a pure CHT duration dependency or a mixed/interaction form of dependency. The number of CHT cycles, in fact, could be thought as a mere proxy of either the above aspects, since an higher number of cycles could correlate with an higher dose, but also with a longer time of exposition. We cannot exclude that the number of cycles represent the number of times that the system came in contact with CHT and the complex cascade of events triggered by this exposition. So this repeated interaction per se (Figure 2) could be a factor guiding the changes and the adaptation mechanisms activated as a response by the system (*e.g.* cytokines production, stress system activation, immune system responses).

The pattern of CHT induced brain metabolic impairment, markedly characterized by a disproportionate involvement of frontal lobes (Figure 1, Table III), is reminiscent of that seen in aging [37-40] and some age-related neurodegenerative processes.[41] This was confirmed by our analysis on age negatively correlated pattern (Figure 2) and its large overlap with the previous C and T correlation patterns (Figure 2).

Oxidative DNA damage and decreased mitochondrial function are well established processes underlying brain aging changes,[42] findings leading Maccormick [43] to hypothesize that adverse effects associated with CHT might be related to acceleration of the ageing process. Inspired by this hypothesis we looked for differences in the correlations between age and the rCMRglc in the regions showing a lower glucose metabolism in the CHT and No CHT subgroups. This analysis showed that, compared to non treated patients, the CMRglc of medial cortices in CHT patients had a more negative and more widespread association with age (Figure 3, Table III), meaning that older subjects undergo a higher than expected CHT induced metabolic impairment. Taken together, these findings lead us to speculate that CHT induces ageing-like and/or accelerates ageing-related processes, such as oxidative stress and decreased mitochondrial function, which could lead to the rCMRglc reduction evidenced in patients receiving CHT.

The TMT-B score was the only neuropsychological measure showing significant correlations with rCMRglc ($P<0.005$), although not surviving to cluster multiple comparison correction. This probably because, among all the tests, it was the one more related to frontal functions and their decline with ageing. Noteworthy, the pattern was similar to the CHT induced pattern reinforcing the link between metabolic and neuropsychological alterations. A confounding effect on our results could be related to the anxiety status connected with the PET examination that may have influenced the neuropsychological setting, but to avoid the risk of drop out of patients, we choose not to separate sessions, however this limitation is overcome by the fact that this bias was equally distributed among groups.

Our data supported that the observed effect of CHT was not an indirect effect of the psychological status (distress, depression, anxiety) or of the chemotherapy induced bone marrow suppression, as the Matched groups did not differ for clinical mood or blood data (Table II).

Limitations

Obviously a longitudinal study could have an advantage in observing the evolution of metabolism over time, unfortunately, in a clinical setting it is complex to organize with patients highly emotionally and physically stressed. However, it could also have a disadvantage: the same patients after some months will have a longer disease duration and any metabolism difference could be related to a aging process. A potential limitation of the study is the heterogeneity of protocols treatment that could limit the possibility to assess CHT effects, for example, steroids could have a specific effect on brain metabolism, however the limited number of patients belonging to the different treatments subgroups did not consent to perform a meaningful statistical analysis.

Conclusions

This study evidenced significant chemotherapy related changes on glucose metabolism in multiple

brain regions, with a prevailing involvement of frontal lobes. Such metabolic changes appear to be positively related to the time elapsed from the end of the treatment suggesting that they are transient and rapidly reversible. A subset of these areas undergoes a metabolic impairment proportional to the number of CHT cycles while a subset, including the cerebellum and midline cortical regions, presents evidences of partial or delayed metabolic recovery.

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