



HAL
open science

Sleep oscillations related to memory consolidation during aromatases inhibitors for breast cancer

S. Rehel, M. Duivon, F. Doidy, P. Champetier, P. Clochon, J.M. Grellard, C. Segura-Djezzar, J. Geffrelot, G. Emile, D. Allouache, et al.

► **To cite this version:**

S. Rehel, M. Duivon, F. Doidy, P. Champetier, P. Clochon, et al.. Sleep oscillations related to memory consolidation during aromatases inhibitors for breast cancer. *Sleep Medicine*, In press, 121, pp.210-218. 10.1016/j.sleep.2024.07.002 . hal-04639857

HAL Id: hal-04639857

<https://hal.science/hal-04639857>

Submitted on 9 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Copyright

Journal Pre-proof

Sleep oscillations related to memory consolidation during aromatases inhibitors for breast cancer

Rehel S., Duivon M., Doidy F., Champetier P., Clochon P., Grellard J.M., Segura-Djezzar C., Geffrelot J., Emile G., Allouache D., Levy C., Viader F., Eustache F., Joly F., Giffard B., Perrier J.

PII: S1389-9457(24)00320-4

DOI: <https://doi.org/10.1016/j.sleep.2024.07.002>

Reference: SLEEP 6142

To appear in: *Sleep Medicine*

Received Date: 21 May 2024

Revised Date: 28 June 2024

Accepted Date: 3 July 2024

Please cite this article as: Rehel S, Duivon M, Doidy F, Champetier P, Clochon P, Grellard J, Segura-Djezzar C, Geffrelot J, Emile G, Allouache D, Levy C, Viader F, Eustache F, Joly F, Giffard B, Perrier J, Sleep oscillations related to memory consolidation during aromatases inhibitors for breast cancer, *Sleep Medicine*, <https://doi.org/10.1016/j.sleep.2024.07.002>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2024 Published by Elsevier B.V.



1 Sleep oscillations related to memory consolidation during
2 aromatases inhibitors for breast cancer

3
4 Rehel S.¹, Duivon M.¹, Doidy F.¹, Champetier P.¹, Clochon P.¹, Grellard JM², Segura-Djezzar
5 C.^{3,4}, Geffrelot J.^{3,4}, Emile G.^{3,4}, Allouache D.^{3,4}, Levy C.^{3,4}, Viader F.¹, Eustache F.¹, Joly
6 F.^{2,3,4,5,6}, Giffard B.^{1,6*}, Perrier J.^{1*}

7
8 ¹ Normandie Univ, UNICAEN, PSL Université, EPHE, INSERM, U1077, CHU de Caen, GIP Cyceron,
9 Neuropsychologie et Imagerie de la Mémoire Humaine, 14000 Caen, France

10 ²Clinical Research Department, Centre François Baclesse, 3 avenue du Général Harris, Caen, France.

11 ³Institut Normand du Sein, Centre François Baclesse, Caen, France

12 ⁴Department of Medical Oncology, Centre François Baclesse, 3 Avenue du Général Harris, Caen, France.

13 ⁵INSERM, Normandie Univ, UNICAEN, U1086 ANTICIPE, Caen, France

14 ⁶ Cancer and Cognition Platform, Ligue Nationale Contre le Cancer, 14076, Caen, France

15 * Authors equally contributed to this work

16 Corresponding author: Joy Perrier

17 Neuropsychologie & Imagerie de la Mémoire Humaine

18 Unité de recherche 1077 INSERM-EPHE-UNICAEN, Pôle des Formations et de Recherche en

19 Santé (PFRS), 2 rue des Rochambelles F-14032 Caen Cedex CS 14032

20 Phone: +33(0) 2 31 56 83 83; E-mail: joy.perrier@unicaen.fr

21

22

Journal Pre-proof

1 **Summary**

2 Aromatase inhibitors (AIs) are associated with sleep difficulties in breast cancer (BC) patients.
3 Sleep is known to favor memory consolidation through the occurrence of specific oscillations,
4 i.e., slow waves (SW) and sleep spindles, allowing a dialogue between prefrontal cortex and
5 the hippocampus. Interestingly, neuroimaging studies in BC patients have consistently shown
6 structural and functional modifications in these two brain regions. With the aim to evaluate
7 sleep oscillations related to memory consolidation during AIs , we collected polysomnography
8 data in BC patients treated (AI+, n=17) or not (AI-, n=17) with AIs compared to healthy controls
9 (HC, n=21). None of the patients had received chemotherapy and radiotherapy was finished
10 since at least 6 months, that limit the confounding effects of other treatments than AIs. Fast and
11 slow spindles were detected during sleep stage 2 at centro-parietal and frontal electrodes
12 respectively. SW were detected at frontal electrodes during stage 3. Here, we show lower frontal
13 SW densities in AI+ patients compared to HC. These results concord with previous reports
14 about frontal cortical alterations in cancer following AIs administration. Moreover, AI+ patients
15 tended to have lower spindle density at C4 electrode. Regression analyses showed that, in both
16 patient groups, spindle density at C4 electrode explained a large variance of memory
17 performances. Slow spindle characteristics did not differ between groups and sleep oscillations
18 characteristics of AI- patients did not differ significantly from those of both AI+ patients and
19 HC. Overall, our results add to the compelling evidence of the systemic effects of AIs
20 previously reported in animals, with deleterious effects on cortical activity during sleep and
21 associated memory consolidation in the current study. There is thus a need to further investigate
22 sleep modifications during AIs administration. Longitudinal studies are needed to confirm these
23 findings and investigation in other cancers on this topic should be conducted.

24 **Keywords:** breast cancer; aromatases inhibitors; sleep; memory consolidation; frontal cortex

25

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26

1. Introduction

Breast cancer (BC) patients frequently complain about sleep disturbances and experience cognitive difficulties both before and after undergoing treatment (Lange et al., 2019; Otte et al., 2015; Perrier, Duivon, Rauchs, & Giffard, 2021). While most of previous studies predominantly focused on sleep problems following chemotherapy, endocrine therapy should also be considered as contributed factors to sleep difficulties in BC patients (Kwak, Jacobs, Haggett, Jimenez, & Peppercorn, 2020; Van Dyk, Joffe, & Carroll, 2021). Endocrine therapy is indicated for at least 5 years as adjuvant treatment for estrogen receptor-positive BC (75-80 % of patients), using aromatase inhibitors (AIs) for post-menopausal patients (Burstein et al., 2019). AIs are effective at reducing BC recurrence through downregulation of estrogen action by inhibiting synthesis of estrogens at a systemic level (Brueggemeier, 2004). Such downregulation of estrogens action can further impact several systems that are influenced by circulating estrogens, notably sleep (Dorsey, de Lecea, & Jennings, 2021). Indeed, sleep difficulties are prevalent among BC survivors under AIs treatment (Desai et al., 2013; García-Sánchez, Mafla-España, Torregrosa, & Cauli, 2022; Kwak et al., 2020; Savard et al., 2004), with deleterious effect on quality of life and treatment adherence (Kidwell et al., 2014; Smith et al., 2022). Our group recently highlighted that BC patients treated with endocrine therapy for 6 months, mainly with AIs, spent more time awake, with more movements at night than patients not treated with endocrine therapy (Martin et al., 2021). Based on these previous reports, one may expect sleep architecture modifications during AIs, with potential deleterious effects on memory processes.

1 Indeed, sleep is known to favor memory consolidation through the occurrence of
2 specific oscillations, i.e., slow waves (SW) and sleep spindles. Both oscillations have been
3 related to sleep-dependent memory consolidation through information transfer from
4 hippocampus to neocortex (Diekelmann & Born, 2010; Girardeau, 2023; Miyamoto, Hirai, &
5 Murayama, 2017; Ulrich, 2016). Spindles are the hallmark of sleep Stage 2 and SW are the
6 hallmark of sleep Stage 3. While SW are primarily generated at frontal electrodes (Dang-Vu et
7 al., 2005, 2010; Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004), sleep spindles are
8 occurring both at frontal (i.e., slow spindles) and centro-parietal (i.e., fast spindles) sites of the
9 scalp (Cox, Schapiro, Manoach, & Stickgold, 2017; Mölle, Bergmann, Marshall, & Born, 2011)
10 and are not represented by the same frequency bands. Fast spindle activity coincide with greater
11 activation in but also between the hippocampus and the cortex (Andrade et al., 2011; Bergmann,
12 Mölle, Diedrichs, Born, & Siebner, 2012; Schabus et al., 2007). Moreover, fast spindle density
13 is related to memory reactivation (Antony, Schönauer, Staresina, & Cairney, 2019; Cairney,
14 Guttesen, El Marj, & Staresina, 2018; Cowan et al., 2020). Through analyses of sleep
15 oscillations on central electrodes, our team has shown SW and spindle modifications in BC
16 patients (Duivon et al., 2022).

17 Aromatases are widely distributed in the brain, particularly in the hippocampus, and
18 estrogens' receptors are present in multiple brain regions, including the frontal, parietal cortices
19 as well as the hippocampus (Zwart, Terra, Linn, & Schagen, 2015). Studies in animals showed
20 that AIs did not affect frontal cortex integrity (Fester et al., 2012; Zhou et al., 2010) while
21 hippocampus plasticity, spine numbers and neuronal firing were impaired following AIs
22 administration (Gervais et al., 2019; Marbouti, Zahmatkesh, Riahi, & Sadr, 2020; Zhou et al.,
23 2010).

24 Knowing the role of sleep in memory consolidation, the potential impact of AIs on sleep
25 and the presence of both estrogens' receptors and aromatases in the hippocampus and in the

1 prefrontal and parietal cortices, we here argue that sleep-dependent memory consolidation
2 would be altered in BC patients treated with AIs. Liou and colleagues (Liou et al., 2019) have
3 indeed shown that, among postmenopausal BC survivors receiving AIs, insomnia and cognitive
4 impairment had a graded association, in which severity of perceived cognitive impairment
5 increases with insomnia severity. Still, modifications of sleep-dependent memory consolidation
6 during AIs administration is unknown, particularly in relationship with brain regions of interest,
7 such as hippocampus and frontal ones. We here focused on the effects of AIs on cortical sites
8 specifically related to SW and spindles activities (i.e., frontal and centro-parietal ones)
9 associated with memory consolidation.

10 **2. Materials & Methods**

11 **2.1. Participants**

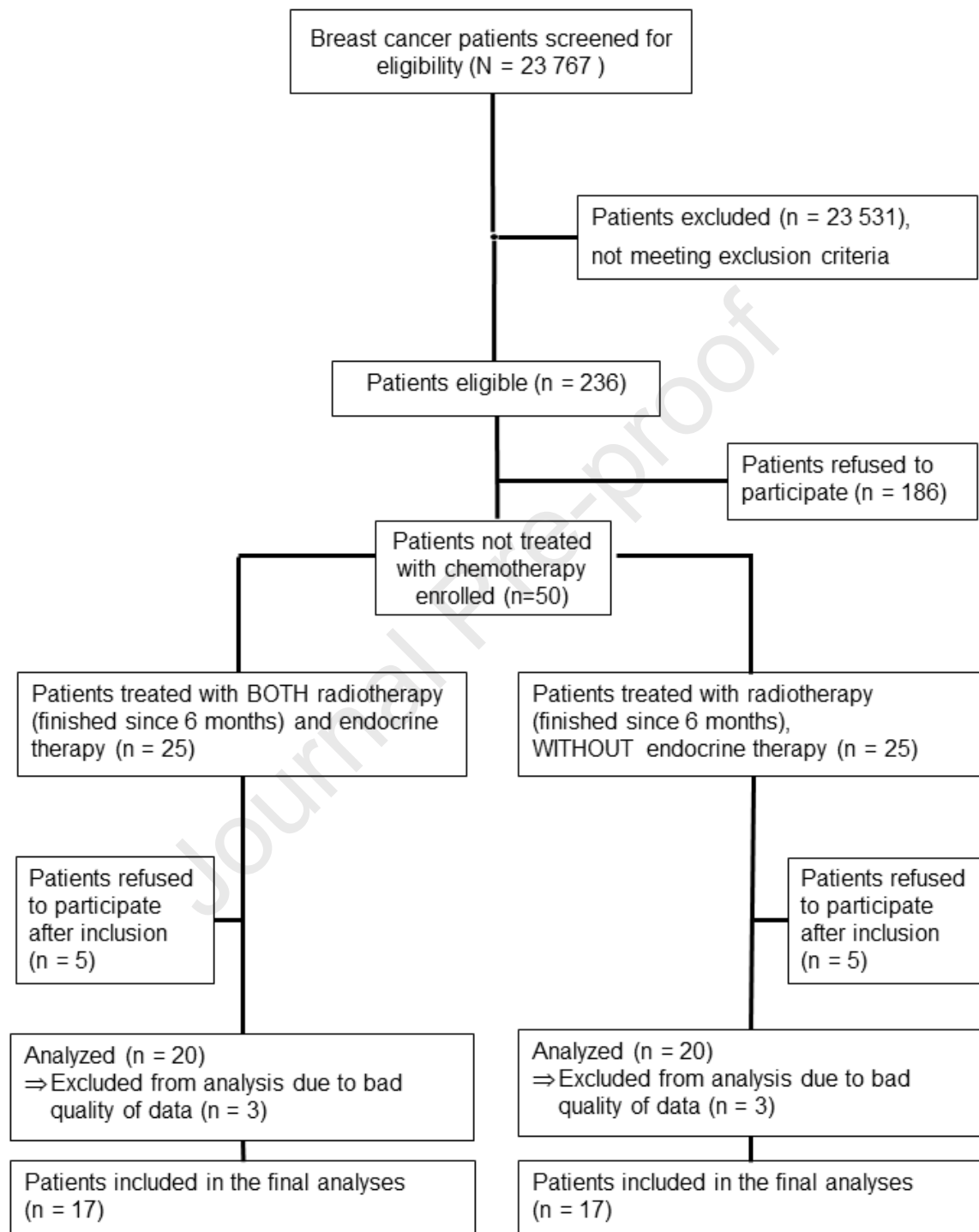
12 This work is part of the PROSOM-K study dedicated to evaluate the relationship between
13 memory and sleep quality in BC patients compared to healthy controls (HC). A detailed
14 description of this project is provided in the protocol paper (Duivon et al., 2018). Written
15 informed consent was obtained from each participant after a detailed presentation of the study,
16 and the PROSOM-K protocol was approved by the ethics committee (CPP Ile de France III;
17 n°ID-RCB: 2017-A02778-45; ClinicalTrials.gov Identifier: NCT03420105).

18 Patient inclusion criteria were: (i) age < 70 years old, (ii) no metastatic BC, (iii) already
19 undergone surgical or radiotherapy treatment, (iv) radiotherapy finished since at least 6 months
20 and no chemotherapy treatment, (v) menopausal status since at least 1 year at the time of
21 inclusion, (vi) no personality disorder and progressive psychiatric disorder, (vii) no
22 neurological sequelae, (viii) no drug or alcohol abuse, (ix) be a native French speaker, and (x)
23 have at least 7 years of education.

24 Inclusion criteria for HC were the same as for patients, but without history of cancer and
25 no cognitive impairment based on the Montreal Cognitive Assessment (score > 25; (Nasreddine
26 et al., 2005)). All participants were included between January 2018 and March 2020. Patients

1 were recruited by oncologists at the François Baclesse regional center (Caen, France), and HC
2 were recruited from the general population. We analyzed data from 17 BC patients treated with
3 both radiotherapy and AIs (named hereafter AI+), 17 patients with radiotherapy only (AI-) and
4 21 healthy women (HC) matched for age and education level. See Figure 1 for the consort
5 diagram of patients' recruitment.

Journal Pre-proof



1

2 *Figure 1: Consort flow diagram of patients' recruitment.*3 **2.2. Polysomnography recording and sleep architecture**

1 Participants underwent a full polysomnography (PSG) recording at home using a portable
2 device (Siesta®, Compumedics, Australia). Twenty electrodes were placed over different sites
3 of the scalp according to the international 10 – 20 system: prefrontal (FP1 | FP2), frontal (F3 |
4 F4 | F7 | F8 | Fz), central (C3 | C4 | Cz), temporal (T3 | T4), parietal (P3 | P4 | Pz), occipital (O1
5 | O2), ground and a bi-mastoid reference (M1 | M2), with impedance kept below 5 k Ω . This
6 montage also included an electrooculogram, an electrocardiogram and a chin electromyogram.
7 Respiratory movements, nasal pressure and oxygen saturation were recorded with thoracic and
8 abdominal belts, nasal and oral thermistors, and a finger pulse oximeter respectively. All
9 sensors were connected to the Compumedics Siesta sleep system and placed by a sleep
10 specialist (SP). The hardware EEG filter band pass was 0.15 – 121 Hz and the signal was
11 digitalized at a sampling rate of 256 Hz. PSG recordings and sleep stages (N1, N2, N3 and rapid
12 eye movement (REM) sleep) were visually scored in 30-s epochs by an electrophysiology
13 technician (SR) following the recommended standard criteria of the American Academy of
14 Sleep Medicine (AASM; (Berry et al., 2017)) using the Compumedics software system
15 (Compumedics ProFusion PSG Lite V4.5 version 468). The following sleep architecture
16 parameters were computed: total time in bed (TIB, min), total sleep time (TST, min), sleep
17 onset latency (defined as the time from lights out to the first epoch of sleep stage N2, SOL,
18 min), wake after sleep onset (WASO, min), sleep efficiency (defined as the ratio between time
19 spent asleep and time in bed; SE, %), percentage of time spent in each sleep stage according to
20 TST (N1, N2, N3 and REM sleep; %) and apnea-hypopnea index (AHI). Sleep apnea was
21 defined by a $\geq 90\%$ drop of nasal pressure for at least 10 seconds, whereas sleep hypopnea was
22 characterized by a $\geq 30\%$ drop of nasal pressure for a minimum of 10 seconds, associated with
23 an arousal or an oxygen desaturation of $\geq 3\%$.

24 **2.3. Sleep oscillation detection**

1 Automatic detection of spindles and SW was performed on all 4-s artifact-free epochs of sleep
2 stages N2 and N3, respectively. For this purpose, we used the open-source SpiSOP software
3 (www.spisop.org; RRID: SCR_015673), a custom made Matlab toolbox that utilizes Fieldtrip
4 ((Oostenveld, Fries, Maris, & Schoffelen, 2011), <http://fieldtrip.fcdonders.nl>). and that has
5 been previously used in several publications in the field (e.g. (Klinzing et al., 2016; Kurz et al.,
6 2021; Lecci et al., 2017)). SpiSOP documentation is available here:
7 www.spisop.org/documentation/. Standard settings that are defined in this documentation were
8 used and are based on the study of Mölle et al (Möller, Marshall, Gais, & Born, 2002).

9 As slow and fast spindle frequencies can vary across participants (Cox et al., 2017), we
10 firstly automatically determined slow and fast spindle frequency peaks based on the NREM
11 (Non-Rapid Eye Movement, sleep stages N2 and N3) power spectrum of each participant. Thus,
12 according to their expected power maxima, slow spindle peaks were identified on frontal
13 electrodes (F3, F4 and Fz) and ranged between 9 Hz and 12 Hz, and fast spindle peaks were
14 identified on central (C3, C4 and Cz) and parietal (P3, P4 and Pz) electrodes, at a range between
15 12 Hz and 15 Hz. SW were identified in the EEG recorded from all prefrontal and frontal
16 electrodes (FP1, FP2, F3, F4, F7, F8 and Fz) after bandpass-filtering the signal between 0.3 and
17 3.5 Hz. Then, events detected on artifacted epochs were manually rejected.

18 Parameters were computed for each oscillation on a 30-s window. We calculated the
19 number of detected spindles, their density (number of spindles per minutes of N2 sleep), mean
20 duration, mean amplitude (trough to peak potential), average oscillatory frequency, and
21 envelope for each participant and channel (F3, F4 and Fz for slow spindles, C3, C4, Cz, P3, P4
22 and Pz for fast spindles) during sleep stage N2. For SW, number of events, density (number of
23 slow waves per minute of N3 sleep), mean duration, mean amplitude, mean up-to-down slope
24 and mean down-to-up slope were analyzed for each participant and channel during sleep stage
25 N3.

2.4. Memory task

The memory task presented here is adapted from Rehel et al. (Rehel et al., 2019), and detailed presentation and scoring method is provided in Duivon et al. (Duivon et al., 2018). Briefly, participants had to learn 9 intentions (i.e. encoding) on a computer screen and had to recall these intentions after a 12-hour delay, which encompassed an overnight sleep period recorded by polysomnography. Each intention is scored between 0 and 6. We here retained the immediate recall retrieval score and the number of trials for encoding (i.e. before sleep recording) and the overall memory retrieval score (i.e. after the night of sleep), corresponding to a sleep-memory consolidation score, i.e. the number of intentions correctly recalled, which ranges from 0 to 54 (6 points by 9 intentions). Higher score indicates better memory performances.

2.5. Questionnaires

2.5.1. Sleep disturbances

Subjective sleep disturbances were assessed using the Pittsburgh Sleep Quality Index (PSQI; (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989)). The PSQI is a 19-item questionnaire measuring sleep habits and disturbances over the previous month. The global score ranges from 0 to 21. The Insomnia Severity Index (ISI; (Morin, Belleville, B elanger, & Ivers, 2011)) assessed severity of insomnia symptoms over the past two weeks. This questionnaire has 7 items, and a 5-point Likert scale is used to rate each item with answer options that range from 0 (no problem) to 4 points (very severe problem). Then, a total score ranging from 0 to 28 is yielded. Higher scores indicate worse sleep quality and greater sleep disturbances and insomnia.

2.5.2. Anxio-depressive factors, fatigue and well-being

Depressive symptoms were assessed with the Beck Depression Inventory (BDI; (Beck, Epstein, Brown, & Steer, 1988)), a 13-item scale with a total score ranging from 0 to 39. Anxiety levels were measured with the State-Trait Anxiety Inventory (STAI-B; (Spielberger, Sydeman, & Maruish, 1994)), which consists of 20 items evaluating how the participant usually feels (total

1 score ranges from 20 to 80). Higher values on both scales indicate higher levels of depression
2 and trait-anxiety symptoms.

3 Fatigue and well-being were assessed in BC patients only (AI- and AI+) using the
4 Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F; (Yellen, Cella, Webster,
5 Blendowski, & Kaplan, 1997)), a 13-item questionnaire (ranging from 0 to 52) and the
6 Functional Assessment of Cancer Therapy-General (FACT-G; (Cella et al., 1993)), a 27-item
7 questionnaire (ranging from 0 to 108). Higher scores in both questionnaires indicate lower
8 fatigue and greater well-being respectively.

9 **2.6. Statistical methods**

10 Statistical analyses were performed using JASP statistical software (version 0.16.1;
11 <https://www.jasp-stats.org/>) with statistical significance set at $p < 0.05$. ANOVA and ANCOVA
12 were followed by *post hoc* Tukey honestly significant difference tests where applicable.

13 Demographic characteristics (age and education level), levels of anxiety (STAI-B) and
14 depression (BDI), sleep questionnaires scores (PSQI and ISI) and AHI were compared between
15 groups using ANOVA. Memory scores were compared between groups using Type II
16 ANCOVA, controlling for age, education level, anxiety (STAI-B), depression (BDI) and AHI,
17 given the known effects of such variables on memory performances.

18 Sleep architecture and oscillation parameters were compared between groups using
19 Type II ANCOVA. Sleep variables were considered as dependent variables, group as
20 independent variable, and age, education level, anxiety (STAI-B), depression (BDI) and AHI
21 as covariates. For sleep oscillation parameters, analyses were performed on each electrode
22 separately.

23 Finally, we computed multiple backward stepwise regression in order to investigate the
24 association between memory score and sleep oscillation parameters in with group and sleep
25 oscillations parameter as explaining variables, accounting for age, education level, anxiety

1 (STAI-B), depression (BDI) and AHI, known to affect both sleep and memory. Only sleep
 2 oscillation parameters that differed between AI+ patients and either AI- patients or HC were
 3 considered in the regression model. In order to avoid autocorrelation effects between electrodes
 4 placed on the same cortical sites (e.g. frontal site with F3, F4), averaged values of electrodes
 5 were considered in the model and each sleep oscillation parameter was considered in a separate
 6 model.

7 3. Results

8 3.1. Participants' characteristics

9 Education level, anxiety and depression levels did not differ between groups, while a trend was
 10 observed for age ($p = 0.059$). See Table 1.

11 **Table 1** : Demographical, behavioral of participants and patients and clinical characteristics of patients.
 12

	AI- patients (n = 17)	AI+ patients (n = 17)	HC (n = 21)	ANOVA	Effect size
	M ± SD	M ± SD	M ± SD	p-values	η^2
Demographical characteristics					
Age (years)	59.65 ± 5.70	63.47 ± 4.42	62.62 ± 4.35	0.059	0.103
Education level (years)	12.31 ± 3.29	11.25 ± 3.38	11.76 ± 1.73	0.55	0.023
Behavioral characteristics					
Anxiety (STAI-B)	39.76 ± 9.88	39.41 ± 11.98	42.29 ± 9.30	0.64	0.017
Depression (BDI)	3.00 ± 2.32	3.88 ± 3.87	4.10 ± 3.24	0.56	0.022
Fatigue (FACIT-F)	38.00 ± 8.67	35.88 ± 11.94	NA	-	-
Well-being (FACT-G)	88.18 ± 12.69	81.41 ± 18.88	NA	-	-
Clinical characteristics					
Stage of the cancer, n (%)					
0	17 (100%)	2 (11.76%)	NA	-	-
I	0	11 (64.71%)	NA	-	-
IIA	0	4 (23.53%)	NA	-	-
Surgery, n (%)					

Breast-conserving surgery (lumpectomy)	15 (88.24%)	15 (88.24%)	NA	-	-
Mastectomy	3 (17.65%) *	2 (11.76%)	NA	-	-
Time since radiotherapy (months)	8.00 ± 4.08	8.20 ± 3.25	NA	-	-
Time since anti-aromatases therapy (months)	NA	7.00 ± 2.79	NA	-	-
Aromatase inhibitors					
Anastrozole, n (%)	NA	13 (76.47%)	NA	-	-
Exemestane, n (%)	NA	1 (5.88%)	NA	-	-
Letrozole, n (%)	NA	3 (17.65%)	NA	-	-

1 * One patient had a breast-conserving surgery and a mastectomy.

2 HC: Healthy Controls; AI-: breast cancer patients not treated with aromatase inhibitors; AI+: breast cancer patients treated with aromatase
3 inhibitors; STAI-B: State-Trait Anxiety Inventory; BDI: Beck Depression Inventory; FACIT-F: Functional Assessment of Chronic Illness
4 Therapy-Fatigue; FACT-G: Functional Assessment of Cancer Therapy-General; NA: Not Applicable. M: Mean; SD: Standard Deviation. Italic,
5 trend; bold, significant.

6 For all patients, radiotherapy was finished since at least 6 months. Age, education level, anxiety and depression were compared between all
7 groups with ANOVA, followed by *post hoc* Tukey honestly significant difference tests where applicable.

8 **3.2. Sleep questionnaires and architecture**

9 Groups significantly differed on subjective sleep disturbances (PSQI; $F(2, 52) = 3.44, p =$
10 0.039) and insomnia severity (ISI; $F(2, 52) = 4.00, p = 0.024$). AI+ patients reported greater
11 sleep complaints and more severe insomnia symptoms than HC. AI- patients did not differ from
12 both HC and AI+ patients. Sleep architecture parameters did not differ between groups. See
13 Table S1.

14 **3.3. Sleep oscillation parameters**

15 During sleep stage N2, fast spindle density measured on C4 electrode tended to differ between
16 groups ($F(2, 47) = 2.81, p = 0.070$), with AI+ patients tended to have lower fast spindle density
17 than HC ($p = 0.063$). AI- patients did not differ from both AI+ and HC.

18 During sleep stage N3, SW density on all prefrontal and frontal electrodes was lower in
19 AI+ patients compared to HC ($p < 0.02$ for all electrodes). AI- patients tended to differ from
20 HC at Fz electrode ($p = 0.07$). Patient groups did not differ significantly.

21 For ease of reading, only densities of both fast spindles and SW are depicted in Table 2 as other
22 results did not lead significant results (data not shown).

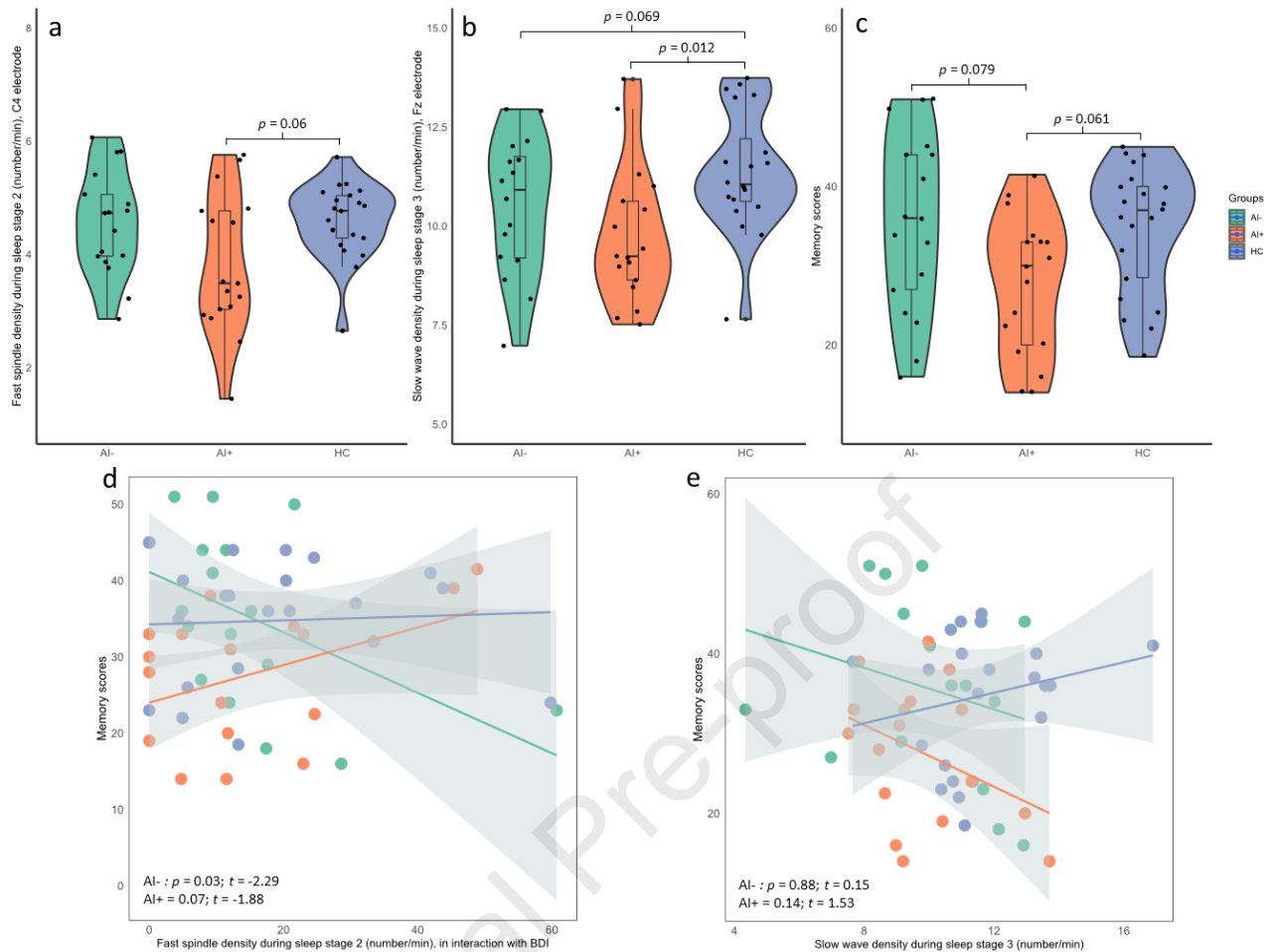
1 **Table 2:** Sleep oscillation densities during sleep stage N2 for spindles and during sleep stage N3 for slow waves.

	AI- patients (n = 17)	AI+ patients (n = 17)	HC (n = 21)	ANCOVA	Effect size	ANCOVA Post-hoc <i>p</i> -values		
	M ± SD	M ± SD	M ± SD	<i>p</i> -values	η ²	HC AI- vs AI+	HC vs AI+	AI- vs AI+
Fast spindle density detected during sleep stage N2 per minute								
C3	4.56 ± 1.06	3.97 ± 1.17	4.64 ± 0.73	0.21	0.05	-	-	-
C4	4.55 ± 0.91	3.82 ± 1.22	4.60 ± 0.66	0.07	0.09	0.87	0.06	0.24
Cz	4.54 ± 1.05	3.99 ± 1.08	4.65 ± 0.67	0.15	0.06	-	-	-
Slow wave density detected during sleep stage N3 per minute								
FP1	11.82 ± 2.74	10.97 ± 1.74	13.26 ± 2.03	0.005	0.16	0.11	0.004	0.53
FP2	11.82 ± 2.77	11.11 ± 1.85	13.20 ± 1.97	0.012	0.13	0.14	0.01	0.62
F3	10.02 ± 2.40	9.39 ± 1.47	11.20 ± 1.93	0.018	0.14	0.19	0.016	0.60
F4	9.84 ± 2.32	9.46 ± 1.54	11.11 ± 1.70	0.020	0.13	0.13	0.022	0.79
F7	10.65 ± 2.28	9.91 ± 1.66	11.65 ± 1.73	0.013	0.12	0.40	0.009	0.27
F8	9.83 ± 2.01	9.12 ± 1.55	10.94 ± 1.76	0.009	0.15	0.25	0.007	0.37
Fz	10.16 ± 2.27	9.77 ± 1.75	11.64 ± 1.91	0.009	0.16	0.069	0.012	0.84

2 HC: Healthy Controls; AI-: breast cancer patients without aromatase inhibitors; AI+: breast cancer patients with aromatase inhibitors; M:
3 Mean; SD: Standard Deviation; FDR: false discovery rate (correction for multiple comparisons). Comparisons of each parameter were realized
4 with analyses of covariance (ANCOVA) with age, education level and AHI as covariate. ANCOVA were followed by post hoc Tukey honestly
5 significant difference tests where applicable. Italic, trend; bold, significant.

6 See Figure 2a and b for fast spindle density at C4 electrode during stage 2 and SW density at

7 Fz electrode during sleep stage 3, respectively.



1

2 *Figure 2: Sleep oscillation densities, memory retrieval scores and their relationships. a and b, Sleep oscillation parameters*
 3 *were compared between groups using ANCOVA. Sleep variables were considered as dependent variables, group*
 4 *as independent variable, and age, education level, STAI-B, BDI and AHI as covariates. Analyses were performed*
 5 *on each electrode separately. a, Fast spindle density (number per minute) on C4 electrode during sleep stage 2*
 6 *across patients not treated (AI-) or treated (AI+) with aromatases inhibitors and healthy controls (HC). b, Slow*
 7 *wave density (number per minute) on Fz electrode during sleep stage 3 across patients not treated (AI-) or treated*
 8 *(AI+) with aromatases inhibitors and healthy controls (HC). c, Memory scores across patients not treated (AI-)*
 9 *or treated (AI+) with aromatases inhibitors and healthy controls (HC). Memory scores were compared between*
 10 *groups using ANCOVA, controlling for age, education level, BDI and STAI-B levels and AHI, given the known*
 11 *effects of such variables on memory performances. c and d, We computed multiple backward stepwise regression*
 12 *in order to investigate the association between memory score and sleep oscillation parameters, accounting for*
 13 *age, education level, BDI and STAI-B levels and AHI, known to affect both sleep and memory. Only sleep*
 14 *oscillation parameters that differed between AI+ patients and either AI- patients or HC were considered in the*
 15 *regression model. In order to avoid autocorrelation effects between electrodes placed on the same cortical sites,*
 16 *averaged values of electrodes were considered in the model i.e. for frontal site, averaged values were obtained*
 17 *using FP1, FP2, F3, F4, F7, F8 and Fz electrode values. c, Regression plot showing the relationship between*
 18 *memory score and fast spindle density at C4 during sleep stage 2 in interaction with BDI in all groups, with*
 19 *confidence interval in gray. d, Regression plot showing the relationship between memory score and slow wave*
 20 *density at Fz during sleep stage 3 in all groups, with confidence interval in gray.*

21

22

23

24

3.4. Memory performances

ANCOVA analyses on memory encoding performances (i.e. before sleep recording) did not reveal any significant group effect for the immediate cued recall scores ($F(2, 47) = 0.44, p = 0.65, \text{Eta}^2 = 0.02$), nor for the number of trials ($F(2, 47) = 0.60, p = 0.21, \text{Eta}^2 = 0.06$).

ANCOVA analyses on memory consolidation performances (i.e., retrieval scores after the night of sleep) yielded a significant group effect ($F(2, 47) = 3.41, p = 0.041, \text{Eta}^2 = 0.09$) with scores (Means \pm SD) as follows : AI- : 35.41 ± 11.33 ; HC: 34.76 ± 8.03 and AI+ : 27.71 ± 8.77 . See Figure 2c. Post hoc analysis revealed a trend towards lower memory performances in AI+ patients compared AI- patients ($p = 0.079$), and compared to HC ($p = 0.061$), while AI- and HC did not differ ($p = 0.99$).

3.5. Associations between sleep oscillation parameters and memory score in AI+ patients

Multiple linear regressions were conducted to predict memory retrieval score using groups and sleep oscillation parameter as predictors, accounting for covariables. Only sleep oscillation parameters that differed or tended to differ between AI+ and HC and/or AI- were considered in the model, i.e. fast spindle densities on C4 and SW densities on prefrontal and frontal regions. The final outputs are presented in Tables 3 and 4, respectively. Results indicate that 52% and 53% of the variance in memory retrieval score was explained by predictors in both models.

Both fast spindle density and BDI were negatively associated with memory retrieval score in all groups. In both patient groups, BDI was negatively associated with memory scores (trend for AI- and significant for AI+). In AI- patients, fast spindle density was associated with memory score in interaction with either AHI (trend, positive relationship) or BDI (significant, negative relationship). In AI+ patients, fast spindle density tended to predict memory retrieval score in interaction with BDI with a negative relationship. See Table 3 and Figure 2d.

1 SW density only tended to predict memory retrieval score in interaction with AHI in all
 2 groups, with a negative relationship. Regarding AI- patients, results revealed only a trend for
 3 significant relationship between SW density and memory score in interaction with STAI-B. See
 4 Table 4 and Figure 2e.

5 Overall, these results indicate significant prediction of memory retrieval score with fast
 6 spindle density in interaction with covariables in both patient groups, while SW density only
 7 tended to predict memory score in AI- patients and not in AI+ patients.

8 **Table 3:** Results from the stepwise regression analysis following backward selection of the model using fast
 9 spindle density during Stage 2 at the C4 electrode and groups as predictor accounting for covariables.

Predictors	Estimate	Standard Errors (SE)	t-values	p-values
Intercept	87.31	35.90	2.43	0.020
AI-	1.99	42.97	0.05	0.96
AI+	-64.68	35.93	-1.80	0.08
FS density on C4 during sleep stage N2	-13.99	7.29	-1.92	0.06
Education level	1.56	0.37	4.20	<0.001
AHI	0.33	1.52	0.22	0.83
Anxiety (STAI-B)	-0.15	0.12	-1.24	0.22
Depression (BDI)	-19.18	7.71	-2.49	0.02
FS density on C4 during sleep stage N2 * AI-	-0.26	8.85	-0.03	0.98
FS density on C4 during sleep stage N2 * AI+	10.53	7.72	1.36	0.18
AHI * AI-	-3.26	1.94	-1.68	0.10
AHI * AI+	-0.20	1.56	-0.13	0.90
BDI * AI-	17.15	8.71	1.97	0.06
BDI * AI+	17.20	7.90	2.18	0.04
FS density on C4 during sleep stage N2 * AHI	-0.04	0.33	-0.13	0.89
FS density on C4 during sleep stage N2 * BDI	4.02	1.59	2.52	0.02
FS density on C4 during sleep stage N2 * AHI * AI-	0.76	0.41	1.85	0.07
FS density on C4 during sleep stage N2 * AHI * AI+	0.03	0.35	0.09	0.93

FS density on C4 during sleep stage N2 * BDI * AI-	-4.05	1.77	-2.29	0.03
FS density on C4 during sleep stage N2 * BDI * AI+	-3.14	1.67	-1.88	<i>0.07</i>
R²	0.69			
Adjusted R²	0.52			
Residual standard error	6.812			
F(19, 35)	4.07			
AIC	226.20			

***p*-value of the model following backward selection <0.001**

1 Note: AI-: breast cancer patients without aromatase inhibitors; AI+: breast cancer patients with aromatase inhibitors; FS: Fast spindle; FS
2 Density – C4 during sleep stage N2: Fast spindle density on C4 electrode during sleep stage N2; STAI-B: State-Trait Anxiety Inventory; BDI:
3 Beck Depression Inventory; AHI: Apnea-Hypopnea Index; AIC: Akaike Information Criterion. Italic, trend; bold, significant.

4 **Table 4:** Results from the stepwise regression analysis following backward selection of the model using slow
5 wave density during Stage 3 at the frontal electrodes and groups as predictor accounting for covariables.

Predictors	Estimate	Standard Errors (SE)	<i>t</i>-values	<i>p</i>-values
Intercept	-101.80	112.20	-0.91	0.38
AI-	-86.91	186.20	-0.47	0.65
AI+	-358.20	253.90	-1.41	0.17
SW density on frontal regions during sleep stage N3	0.56	0.69	0.81	0.43
Age	1.85	1.55	1.20	0.25
Education level	4.80	3.96	1.21	0.24
Anxiety (STAI-B)	-1.29	1.03	-1.25	0.23
AHI	0.72	0.55	1.30	0.21
Depression (BDI)	0.74	2.59	0.29	0.78
SW density on frontal regions during sleep stage N3 * AI-	0.16	1.03	0.15	0.88
SW density on frontal regions during sleep stage N3 * AI+	2.85	1.86	1.53	0.14
Age * AI-	2.23	2.91	0.77	0.45
Age * AI+	6.29	4.23	1.49	0.15
Education level * AI-	3.50	5.27	0.66	0.51
Education level * AI+	5.32	5.56	0.96	0.35
STAI-B * AI-	-4.37	2.68	-1.63	0.12

STAI-B * AI+	-3.40	2.37	-1.44	0.17
AHI * AI-	3.40	2.17	1.57	0.13
AHI * AI+	-1.06	0.69	-1.52	0.14
BDI * AI-	-0.49	11.05	-0.05	0.96
BDI * AI+	14.53	7.91	1.84	0.08
SW density on frontal regions during sleep stage N3 * Age	-0.01	0.01	-1.05	0.31
SW density on frontal regions during sleep stage N3 * Education level	-0.01	0.02	-0.35	0.73
SW density on frontal regions during sleep stage N3 * STAI-B	0.01	0.01	1.11	0.28
SW density on frontal regions during sleep stage N3 * AHI	-0.01	0.00	-2.03	0.06
SW density on frontal regions during sleep stage N3 * BDI	0.00	0.02	0.00	1.00
SW density on frontal regions during sleep stage N3 * Age * AI-	-0.01	0.02	-0.73	0.48
SW density on frontal regions during sleep stage N3 * Age * AI+	-0.05	0.03	-1.53	0.14
SW density on frontal regions during sleep stage N3 * Education level * AI-	-0.01	0.03	-0.49	0.63
SW density on frontal regions during sleep stage N3 * Education level * AI+	-0.06	0.04	-1.63	0.12
SW density on frontal regions during sleep stage N3 * STAI-B * AI-	0.03	0.02	1.84	0.08
SW density on frontal regions during sleep stage N3 * STAI-B * AI+	0.02	0.02	1.57	0.13
SW density on frontal regions during sleep stage N3 * AHI * AI-	-0.01	0.01	-1.05	0.31
SW density on frontal regions during sleep stage N3 * AHI * AI+	0.01	0.01	1.72	0.10
SW density on frontal regions during sleep stage N3 * BDI * AI-	-0.01	0.07	-0.12	0.91
SW density on frontal regions during sleep stage N3 * BDI * AI+	-0.09	0.05	-1.73	0.10
R²	0.84			
Adjusted R²	0.53			
Residual standard error	6.812			

F(19, 35) 2.76

AIC 222.93

***p*-value of the model following backward selection** **0.011**

1 Note: AI-: breast cancer patients without aromatase inhibitors; AI+: breast cancer patients with aromatase inhibitors; SW: Slow wave; SW
2 density on frontal regions during sleep stage N3: Slow wave density on all frontal electrodes (FP1, FP2, F3, F4, F7, F8 and Fz) during sleep
3 stage N3; STAI-B: State-Trait Anxiety Inventory; BDI: Beck Depression Inventory; AHI: Apnea-Hypopnea Index; AIC: Akaike Information
4 Criterion. Italic, trend; bold, significant.

5 **4. Discussion**

6 With the aim to evaluate sleep-dependent memory consolidation during AIs BC, we computed
7 both SW's characteristics in prefrontal and frontal regions as well and spindle's characteristics
8 on centro-parietal electrodes. For this purpose, BC patients treated with AIs since at least 6
9 months were compared to BC patients not treated with AIs and healthy controls (HC). As a side
10 note, none of patients had received chemotherapy and radiotherapy (received by all BC patients)
11 was finished since at least 6 months. Knowing the effects of AIs on hippocampus physiology,
12 we expected spindle alterations on centro-parietal electrodes of the scalp (i.e., that allows a
13 dialogue between hippocampus and frontal areas) in patients treated with AIs. Here we showed
14 that, during Stage 2, fast spindle density on C4 electrode tended to be lower in AI+ patients
15 compared to HC. Moreover, during Stage 3, SW density was lower throughout frontal
16 electrodes in AI+ patients compared to HC. These results suggest lower memory reactivation,
17 and thus consolidation, during sleep in BC patients during AI treatment. In order to quantify
18 the variance in memory score explained by the oscillations' modifications during AI treatment,
19 we further conducted multiple regression analyses between sleep oscillation parameters and
20 memory retrieval score. Results showed that lower fast spindle density was related to lower
21 memory performance in both patient groups. Overall, our results add to the compelling evidence
22 of the systemic effects of AIs previously reported in animals (Gervais et al., 2019; Marbouti et
23 al., 2020; Zhou et al., 2010), both at the cerebral and behavioral levels.

24 In accordance with the role of both fast spindles and SW in memory consolidation
25 during sleep (Girardeau, 2023), we found that patients treated with AIs had both lower fast

1 spindles (trend) and SW (significant) densities, while only fast spindle density was negatively
2 related to memory performance. Such a relationship between fast spindle density and memory
3 performance concords with prior reports in HC about the beneficial role of sleep spindles on
4 later memory performance (Cowan et al., 2020; Lafortune et al., 2014). Previous findings have
5 suggested weakened or reversed memory consolidation processes in older population as
6 reflected by negative correlation between memory performances and sleep (Scullin, 2013). Our
7 results thus support recent hypotheses about premature brain aging in BC patients (Alfano et
8 al., 2017; Carroll et al., 2019; de Ruiter et al., 2023; Züst et al., 2023).

9 AIs have systemic effects and significantly impair hippocampus physiology (Gervais et
10 al., 2019; Marbouti et al., 2020; Zhou et al., 2010). Studies in animals have shown that AIs did
11 not affect frontal cortex integrity (Fester et al., 2012; Zhou et al., 2010) while hippocampus
12 plasticity, spine numbers and neuronal firing were impaired following AIs administration
13 (Gervais et al., 2019; Grassi et al., 2011; Marbouti et al., 2020; Zhou et al., 2010). In line with
14 such information, fast spindles, that are associated with hippocampal activity (Mölle et al.,
15 2011; Schabus et al., 2007), but not slow spindles differed between patients treated with AIs
16 and HC. In the current study, AIs probably impaired hippocampus activity leading to impaired
17 memory performance. Sleep spindles alone are sufficient to facilitate synaptic changes with
18 memory improvement after sleep (Wei, Krishnan, Komarov, & Bazhenov, 2018) that would
19 explain the lack of memory performance alterations in patients not treated with AIs. Apple and
20 colleagues (Apple et al., 2018) have found that hippocampal functional connectivity may be a
21 marker for compensatory mechanism in BC survivors having been treated with chemotherapy
22 and being currently treated with Tamoxifen that acts as a selective estrogen receptor modulator.
23 In line with such hypothesis, BC patients not treated with AIs may here have compensate
24 prefrontal alterations through higher hippocampal activity as reflected by the lack of significant
25 difference with HC in terms of both spindles' density and memory performance.

1 Moreover, SW density at frontal sites was lower in AI+ patients compared to HC,
2 suggesting impaired SW generation in the prefrontal cortex in BC patients receiving AIs. Both
3 white matter integrity (Menning et al., 2015) and functional connectivity hyperactivation
4 (McDonald, Conroy, Ahles, West, & Saykin, 2012; Scherling, Collins, Mackenzie, Bielajew,
5 & Smith, 2011, 2012) in prefrontal regions have been highlighted in BC patients before
6 chemotherapy, concurrently with lower cognitive performances (See (Sousa, Almeida, Bessa,
7 & Pereira, 2020), for review). Both surgery (i.e., anesthesia) and fatigue effects have been
8 proposed as mechanisms underlying such alterations. In the current study, given the time
9 between surgery and the assessment point, one may rather consider the effects of fatigue.
10 Indeed, cancer-related fatigue has been proposed as a possible mechanism underlying cancer-
11 related cognitive impairments through elevated levels of proinflammatory cytokines (Jenkins
12 et al., 2016). Such hypothesis requires further investigations.

13 One may consider limitations of the current study. First, our sample size is small, given
14 the difficulty to recruit BC patients with such specific inclusion criteria. Especially, results
15 related to fast spindle density did not reach significance and should be taken with caution.
16 Nonetheless, we were able to particularly focus only of AIs effects without other treatments
17 interfering with the results. Indeed, in the current study, none of the patients had received
18 chemotherapy and radiotherapy was finished since at least 6 months. Moreover, our groups of
19 patients were homogeneous and comparable in terms of cancer stages, treatments and
20 demographical characteristics that is rarely the case in previous studies in the field. In addition,
21 we considered cofounding variables, although not all, that could have interfered with results
22 (education level, anxiety, depression, sleep apnea). Both latter points are therefore strengths of
23 the current study and our results provides initial evidence of the potential deleterious effects of
24 AIs on sleep-related memory consolidation processes. Still, the cross-sectional nature of our
25 study does not allow for causal inference and our results cannot be applied to all cancer

1 populations. Nonetheless, the current patients' population account for a high proportion of
2 cancers. Regarding sleep assessment, the first-night effect was not controlled in this study.
3 However, our groups did not differ in terms of sleep latency nor for other sleep architecture
4 parameters that characterize first-night effect (Ding, Chen, Dai, & Li, 2022), except the number
5 of awakenings. Moreover, such an effect is expected to have been the same for all participants
6 in the current study. Finally, although we took sleep apnea index into account in our analyses,
7 we could not compute leg movements as a confounding factor, given that our PSG montage did
8 not include leg's electrodes. This parameter could have still influence sleep results and should
9 be consider un future studies. We believe that our results will pave the way to conduct such
10 studies in order to further help clinicians in decision to improve the risk-benefit balance with
11 beneficial effects on patients' quality of life.

12 To conclude, using fine-grained analyses of sleep oscillations related to memory
13 consolidation, we here showed lower frontal SW density, and, to a lesser extent lower centro-
14 parietal spindle density in patients treated with AIs compared to HC. Such modifications of
15 sleep oscillations explained a large variance of patients' memory performances. These results
16 concord with previous reports about frontal cortical alterations in cancer as well as
17 hippocampus physiology modifications following AIs administration. Overall, our results add
18 to the compelling evidence of the systemic effects of AIs previously reported in animals, with
19 deleterious effects on cortical activity during sleep and associated memory consolidation in the
20 current study. These findings illustrate the need for improving sleep in order to limit memory
21 difficulties in BC patients with potential beneficial effects on treatment adherence. Moreover,
22 these results highlight the need to limit adverse effects of AIs on sleep, either by using other
23 treatments, or by proposing sleep therapies along AI treatment. However, further studies using
24 longitudinal designs as well as others cancer populations are needed to confirm and precise
25 these findings.

1 **Authors' contribution:** SR: Roles/Writing - original draft and Writing - review & editing, Data
2 curation, Formal analysis, and Investigation; MD: Investigation, Writing - review & editing;
3 FD: Data curation, Formal analysis, Investigation, Validation; PCI and PCh: Software, Writing
4 - review & editing; PCI: Data Curation; JMG: Project administration; Resources; CS, JG, GE,
5 DA, CL and FV: Resources; FE and FJ: Conceptualization, Supervision, Writing - review &
6 editing; BG: Conceptualization, Methodology, Supervision, Project administration, Funding
7 acquisition, Writing - review & editing; and JP: Conceptualization, Methodology, Supervision,
8 Project administration, Funding acquisition, Validation, Formal analysis, Writing - review &
9 editing. All authors have critically revised the final version of the manuscript and have approved
10 its current version.

11 **Fundings:** This work was supported by the ARC foundation – for cancer research (2017-2020),
12 the French sleep society (SFRMS), the Région Normandie (Réseaux d'Intérêts Normands,
13 RIN), the Cancéropôle Nord-Ouest and the Ligue contre le Cancer – Normandie.

14 **Competing Interests:** The authors have nothing to disclose in relation with the current
15 manuscript.

16 **Data availability:** The data that support the findings of this study are available from the
17 corresponding author, JP, upon reasonable request.

18 **Acknowledgments:** We thank the clinical research department and the medical oncology
19 department of the Centre François Baclesse for their help in patient recruitment, especially
20 Marie Fernette and François Gernier, Sébastien Polvent for his help in sleep data collection, the
21 Interdisciplinary Center for Virtual Reality (CIREVE) in Caen (Normandy, France) for their
22 technical support, and all the participants for their active contribution to these results. The
23 Northwest Data Center (CTD-CNO) is acknowledged for managing the data.

24

1

2

Journal Pre-proof

1 **References**

- 2 Alfano, C. M., Peng, J., Andridge, R. R., Lindgren, M. E., Povoski, S. P., Lipari, A. M., ... Kiecolt-Glaser, J.
3 K. (2017). Inflammatory Cytokines and Comorbidity Development in Breast Cancer Survivors
4 Versus Noncancer Controls : Evidence for Accelerated Aging? *Journal of Clinical Oncology*,
5 35(2), 149-156. doi: 10.1200/JCO.2016.67.1883
- 6 Andrade, K. C., Spormaker, V. I., Dresler, M., Wehrle, R., Holsboer, F., Sämann, P. G., & Czisch, M.
7 (2011). Sleep spindles and hippocampal functional connectivity in human NREM sleep. *The*
8 *Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 31(28),
9 10331-10339. doi: 10.1523/JNEUROSCI.5660-10.2011
- 10 Antony, J. W., Schönauer, M., Staresina, B. P., & Cairney, S. A. (2019). Sleep Spindles and Memory
11 Reprocessing. *Trends in Neurosciences*, 42(1), 1-3. doi: 10.1016/j.tins.2018.09.012
- 12 Apple, A. C., Schroeder, M. P., Ryals, A. J., Wagner, L. I., Cella, D., Shih, P.-A., ... Wang, L. (2018).
13 Hippocampal functional connectivity is related to self-reported cognitive concerns in breast
14 cancer patients undergoing adjuvant therapy. *NeuroImage. Clinical*, 20, 110-118. doi:
15 10.1016/j.nicl.2018.07.010
- 16 Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety :
17 Psychometric properties. *Journal of consulting and clinical psychology*, 56(6), 893.
- 18 Bergmann, T. O., Mölle, M., Diedrichs, J., Born, J., & Siebner, H. R. (2012). Sleep spindle-related
19 reactivation of category-specific cortical regions after learning face-scene associations.
20 *NeuroImage*, 59(3), 2733-2742. doi: 10.1016/j.neuroimage.2011.10.036
- 21 Berry, R. B., Brooks, R., Gamaldo, C., Harding, S. M., Lloyd, R. M., Quan, S. F., ... Vaughn, B. V. (2017).
22 AASM Scoring Manual Updates for 2017 (Version 2.4). *Journal of Clinical Sleep Medicine:*
23 *JCSM: Official Publication of the American Academy of Sleep Medicine*, 13(5), 665-666. doi:
24 10.5664/jcsm.6576
- 25 Brueggemeier, R. W. (2004). Aromatase inhibitors : New endocrine treatment of breast cancer.
26 *Seminars in Reproductive Medicine*, 22(1), 31-43. doi: 10.1055/s-2004-823025

- 1 Burstein, H. J., Lacchetti, C., Anderson, H., Buchholz, T. A., Davidson, N. E., Gelmon, K. A., ... Griggs, J.
2 J. (2019). Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast
3 Cancer : ASCO Clinical Practice Guideline Focused Update. *Journal of Clinical Oncology*, *37*(5),
4 423-438. doi: 10.1200/JCO.18.01160
- 5 Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep
6 Quality Index : A new instrument for psychiatric practice and research. *Psychiatry research*,
7 *28*(2), 193-213.
- 8 Cairney, S. A., Guttesen, A. Á. V., El Marj, N., & Staresina, B. P. (2018). Memory Consolidation Is
9 Linked to Spindle-Mediated Information Processing during Sleep. *Current Biology: CB*, *28*(6),
10 948-954.e4. doi: 10.1016/j.cub.2018.01.087
- 11 Carroll, J. E., Van Dyk, K., Bower, J. E., Scuric, Z., Petersen, L., Schiestl, R., ... Ganz, P. A. (2019).
12 Cognitive performance in survivors of breast cancer and markers of biological aging. *Cancer*,
13 *125*(2), 298-306. doi: 10.1002/cncr.31777
- 14 Cella, D. F., Tulsky, D. S., Gray, G., Sarafian, B., Linn, E., Bonomi, A., ... Brannon, J. (1993). The
15 Functional Assessment of Cancer Therapy scale : Development and validation of the general
16 measure. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical*
17 *Oncology*, *11*(3), 570-579. doi: 10.1200/JCO.1993.11.3.570
- 18 Cowan, E., Liu, A., Henin, S., Kothare, S., Devinsky, O., & Davachi, L. (2020). Sleep Spindles Promote
19 the Restructuring of Memory Representations in Ventromedial Prefrontal Cortex through
20 Enhanced Hippocampal-Cortical Functional Connectivity. *The Journal of Neuroscience: The*
21 *Official Journal of the Society for Neuroscience*, *40*(9), 1909-1919. doi:
22 10.1523/JNEUROSCI.1946-19.2020
- 23 Cox, R., Schapiro, A. C., Manoach, D. S., & Stickgold, R. (2017). Individual Differences in Frequency
24 and Topography of Slow and Fast Sleep Spindles. *Frontiers in Human Neuroscience*, *11*. doi:
25 10.3389/fnhum.2017.00433

- 1 Dang-Vu, T. T., Desseilles, M., Laureys, S., Degueldre, C., Perrin, F., Phillips, C., ... Peigneux, P. (2005).
2 Cerebral correlates of delta waves during non-REM sleep revisited. *NeuroImage*, *28*(1),
3 14-21. doi: 10.1016/j.neuroimage.2005.05.028
- 4 Dang-Vu, T. T., Schabus, M., Desseilles, M., Sterpenich, V., Bonjean, M., & Maquet, P. (2010).
5 Functional neuroimaging insights into the physiology of human sleep. *Sleep*, *33*(12),
6 1589-1603. doi: 10.1093/sleep/33.12.1589
- 7 de Ruiter, M. B., Deardorff, R. L., Blommaert, J., Chen, B. T., Dumas, J. A., Schagen, S. B., ... McDonald,
8 B. C. (2023). Brain gray matter reduction and premature brain aging after breast cancer
9 chemotherapy : A longitudinal multicenter data pooling analysis. *Brain Imaging and*
10 *Behavior*. doi: 10.1007/s11682-023-00781-7
- 11 Desai, K., Mao, J. J., Su, I., DeMichele, A., Li, Q., Xie, S. X., & Gehrman, P. R. (2013). Prevalence and
12 risk factors for insomnia among breast cancer patients on aromatase inhibitors. *Supportive*
13 *Care in Cancer*, *21*(1), 43-51. doi: 10.1007/s00520-012-1490-z
- 14 Diekelmann, S., & Born, J. (2010). The memory function of sleep. *Nature Reviews. Neuroscience*,
15 *11*(2), 114-126. doi: 10.1038/nrn2762
- 16 Ding, L., Chen, B., Dai, Y., & Li, Y. (2022). A meta-analysis of the first-night effect in healthy individuals
17 for the full age spectrum. *Sleep Medicine*, *89*, 159-165. doi: 10.1016/j.sleep.2021.12.007
- 18 Dorsey, A., de Lecea, L., & Jennings, K. J. (2021). Neurobiological and Hormonal Mechanisms
19 Regulating Women's Sleep. *Frontiers in Neuroscience*, *14*. Consulté à l'adresse
20 <https://www.frontiersin.org/articles/10.3389/fnins.2020.625397>
- 21 Duivon, M., Perrier, J., Joly, F., Licaj, I., Grellard, J.-M., Clarisse, B., ... Giffard, B. (2018). Impact of
22 breast cancer on prospective memory functioning assessed by virtual reality and influence of
23 sleep quality and hormonal therapy : PROSOM-K study. *BMC Cancer*, *18*(1), 866. doi:
24 10.1186/s12885-018-4762-2

- 1 Duivon, M., Perrier, J., Segura-Djezzar, C., Joly, F., Rehel, S., Berthomier, C., ... Giffard, B. (2022).
2 Sleep-dependent memory consolidation in breast cancer : Use of a virtual reality prospective
3 memory task. *Frontiers in Neuroscience*, *16*, 908268. doi: 10.3389/fnins.2022.908268
- 4 Fester, L., Prange-Kiel, J., Zhou, L., Blittersdorf, B. V., Böhm, J., Jarry, H., ... Rune, G. M. (2012).
5 Estrogen-regulated synaptogenesis in the hippocampus : Sexual dimorphism in vivo but not
6 in vitro. *The Journal of Steroid Biochemistry and Molecular Biology*, *131*(1-2), 24-29. doi:
7 10.1016/j.jsbmb.2011.11.010
- 8 García-Sánchez, J., Mafla-España, M. A., Torregrosa, M. D., & Cauli, O. (2022). Adjuvant aromatase
9 inhibitor treatment worsens depressive symptoms and sleep quality in postmenopausal
10 women with localized breast cancer : A one-year follow-up study. *Breast (Edinburgh,
11 Scotland)*, *66*, 310-316. doi: 10.1016/j.breast.2022.11.007
- 12 Gervais, N. J., Remage-Healey, L., Starrett, J. R., Pollak, D. J., Mong, J. A., & Lacreuse, A. (2019).
13 Adverse Effects of Aromatase Inhibition on the Brain and Behavior in a Nonhuman Primate.
14 *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *39*(5),
15 918-928. doi: 10.1523/JNEUROSCI.0353-18.2018
- 16 Girardeau, G. (2023). Rôle des rythmes cérébraux dans la fonction mnésique du sommeil.
17 *médecine/sciences*, *39*(11), 836-844. doi: 10.1051/medsci/2023160
- 18 Grassi, S., Tozzi, A., Costa, C., Tantucci, M., Colcelli, E., Scarduzio, M., ... Pettorossi, V. E. (2011).
19 Neural 17 β -estradiol facilitates long-term potentiation in the hippocampal CA1 region.
20 *Neuroscience*, *192*, 67-73. doi: 10.1016/j.neuroscience.2011.06.078
- 21 Jenkins, V., Thwaites, R., Cercignani, M., Sacre, S., Harrison, N., Whiteley-Jones, H., ... Harder, H.
22 (2016). A feasibility study exploring the role of pre-operative assessment when examining
23 the mechanism of « chemo-brain » in breast cancer patients. *SpringerPlus*, *5*, 390. doi:
24 10.1186/s40064-016-2030-y

- 1 Kidwell, K. M., Harte, S. E., Hayes, D. F., Storniolo, A. M., Carpenter, J., Flockhart, D. A., ... Henry, N. L.
2 (2014). Patient-reported symptoms and discontinuation of adjuvant aromatase inhibitor
3 therapy. *Cancer*, *120*(16), 2403-2411. doi: 10.1002/cncr.28756
- 4 Klinzing, J. G., Mölle, M., Weber, F., Supp, G., Hipp, J. F., Engel, A. K., & Born, J. (2016). Spindle activity
5 phase-locked to sleep slow oscillations. *NeuroImage*, *134*, 607-616. doi:
6 10.1016/j.neuroimage.2016.04.031
- 7 Kurz, E.-M., Conzelmann, A., Barth, G. M., Renner, T. J., Zinke, K., & Born, J. (2021). How do children
8 with autism spectrum disorder form gist memory during sleep? A study of slow oscillation–
9 spindle coupling. *Sleep*, *44*(6), zsa290. doi: 10.1093/sleep/zsa290
- 10 Kwak, A., Jacobs, J., Haggett, D., Jimenez, R., & Peppercorn, J. (2020). Evaluation and management of
11 insomnia in women with breast cancer. *Breast Cancer Research and Treatment*, *181*(2),
12 269-277. doi: 10.1007/s10549-020-05635-0
- 13 Lafortune, M., Gagnon, J.-F., Martin, N., Latreille, V., Dubé, J., Bouchard, M., ... Carrier, J. (2014).
14 Sleep spindles and rapid eye movement sleep as predictors of next morning cognitive
15 performance in healthy middle-aged and older participants. *Journal of Sleep Research*, *23*(2),
16 159-167. doi: 10.1111/jsr.12108
- 17 Lange, M., Joly, F., Vardy, J., Ahles, T., Dubois, M., Tron, L., ... Castel, H. (2019). Cancer-related
18 cognitive impairment : An update on state of the art, detection, and management strategies
19 in cancer survivors. *Annals of Oncology*, *30*(12), 1925-1940. doi: 10.1093/annonc/mdz410
- 20 Lecci, S., Fernandez, L. M. J., Weber, F. D., Cardis, R., Chatton, J.-Y., Born, J., & Lüthi, A. (2017).
21 Coordinated infraslow neural and cardiac oscillations mark fragility and offline periods in
22 mammalian sleep. *Science Advances*, *3*(2), e1602026. doi: 10.1126/sciadv.1602026
- 23 Liou, K. T., Ahles, T. A., Garland, S. N., Li, Q. S., Bao, T., Li, Y., ... Mao, J. J. (2019). The Relationship
24 Between Insomnia and Cognitive Impairment in Breast Cancer Survivors. *JNCI Cancer*
25 *Spectrum*, *3*(3), pkz041. doi: 10.1093/jncics/pkz041

- 1 Marbouti, L., Zahmatkesh, M., Riahi, E., & Sadr, S. S. (2020). Inhibition of brain 17β -estradiol
2 synthesis by letrozole induces cognitive decline in male and female rats. *Neurobiology of*
3 *Learning and Memory*, 175, 107300. doi: 10.1016/j.nlm.2020.107300
- 4 Martin, T., Duivon, M., Bessot, N., Grellard, J. M., Emile, G., Polvent, S., ... Perrier, J. (2021). Rest
5 activity rhythms characteristics of breast cancer women following endocrine therapy. *Sleep*,
6 zsab248. doi: 10.1093/sleep/zsab248
- 7 Massimini, M., Huber, R., Ferrarelli, F., Hill, S., & Tononi, G. (2004). The sleep slow oscillation as a
8 traveling wave. *The Journal of Neuroscience: The Official Journal of the Society for*
9 *Neuroscience*, 24(31), 6862-6870. doi: 10.1523/JNEUROSCI.1318-04.2004
- 10 McDonald, B. C., Conroy, S. K., Ahles, T. A., West, J. D., & Saykin, A. J. (2012). Alterations in Brain
11 Activation During Working Memory Processing Associated With Breast Cancer and
12 Treatment : A Prospective Functional Magnetic Resonance Imaging Study. *Journal of Clinical*
13 *Oncology*, 30(20), 2500-2508. doi: 10.1200/JCO.2011.38.5674
- 14 Menning, S., de Ruiter, M. B., Veltman, D. J., Koppelmans, V., Kirschbaum, C., Boogerd, W., ...
15 Schagen, S. B. (2015). Multimodal MRI and cognitive function in patients with breast cancer
16 prior to adjuvant treatment—the role of fatigue. *NeuroImage. Clinical*, 7, 547-554. doi:
17 10.1016/j.nicl.2015.02.005
- 18 Miyamoto, D., Hirai, D., & Murayama, M. (2017). The Roles of Cortical Slow Waves in Synaptic
19 Plasticity and Memory Consolidation. *Frontiers in Neural Circuits*, 11, 92. doi:
20 10.3389/fncir.2017.00092
- 21 Mölle, M., Bergmann, T. O., Marshall, L., & Born, J. (2011). Fast and slow spindles during the sleep
22 slow oscillation : Disparate coalescence and engagement in memory processing. *Sleep*,
23 34(10), 1411-1421. doi: 10.5665/SLEEP.1290
- 24 Mölle, M., Marshall, L., Gais, S., & Born, J. (2002). Grouping of spindle activity during slow oscillations
25 in human non-rapid eye movement sleep. *The Journal of Neuroscience: The Official Journal of*

- 1 *the Society for Neuroscience*, 22(24), 10941-10947. doi: 10.1523/JNEUROSCI.22-24-
2 10941.2002
- 3 Morin, C. M., Belleville, G., Bélanger, L., & Ivers, H. (2011). The Insomnia Severity Index :
4 Psychometric Indicators to Detect Insomnia Cases and Evaluate Treatment Response. *Sleep*,
5 34(5), 601-608.
- 6 Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... Chertkow,
7 H. (2005). The Montreal Cognitive Assessment, MoCA : A brief screening tool for mild
8 cognitive impairment. *Journal of the American Geriatrics Society*, 53(4), 695-699. doi:
9 10.1111/j.1532-5415.2005.53221.x
- 10 Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2011). FieldTrip : Open source software for
11 advanced analysis of MEG, EEG, and invasive electrophysiological data. *Computational*
12 *Intelligence and Neuroscience*, 2011, 1:1-1:9. doi: 10.1155/2011/156869
- 13 Otte, J. L., Carpenter, J. S., Manchanda, S., Rand, K. L., Skaar, T. C., Weaver, M., ... Landis, C. (2015).
14 Systematic review of sleep disorders in cancer patients : Can the prevalence of sleep
15 disorders be ascertained? *Cancer Medicine*, 4(2), 183-200. doi: 10.1002/cam4.356
- 16 Perrier, J., Duivon, M., Rauchs, G., & Giffard, B. (2021). Le sommeil dans les cancers non cérébraux :
17 Revue de la littérature, mécanismes potentiels et perspectives pour mieux comprendre les
18 troubles cognitifs associés. *Médecine du Sommeil*, 18(2), 90-103. doi:
19 10.1016/j.msom.2020.12.002
- 20 Rehel, S., Legrand, N., Lecouvey, G., Laniepce, A., Bertran, F., Fleury, P., ... Rauchs, G. (2019). Effects
21 of Sleep and Age on Prospective Memory Consolidation : A Walk in a Virtual Museum. *Clocks*
22 *& Sleep*, 1(3), 332-351. doi: 10.3390/clockssleep1030028
- 23 Savard, J., Davidson, J. R., Ivers, H., Quesnel, C., Rioux, D., Dupéré, V., ... Morin, C. M. (2004). The
24 association between nocturnal hot flashes and sleep in breast cancer survivors. *Journal of*
25 *Pain and Symptom Management*, 27(6), 513-522. doi: 10.1016/j.jpainsymman.2003.10.013

- 1 Schabus, M., Dang-Vu, T. T., Albouy, G., Balteau, E., Boly, M., Carrier, J., ... Maquet, P. (2007).
2 Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement
3 sleep. *Proceedings of the National Academy of Sciences of the United States of America*,
4 *104*(32), 13164-13169. doi: 10.1073/pnas.0703084104
- 5 Scherling, C., Collins, B., Mackenzie, J., Bielajew, C., & Smith, A. (2011). Pre-chemotherapy differences
6 in visuospatial working memory in breast cancer patients compared to controls : An fMRI
7 study. *Frontiers in Human Neuroscience*, *5*, 122. doi: 10.3389/fnhum.2011.00122
- 8 Scherling, C., Collins, B., Mackenzie, J., Bielajew, C., & Smith, A. (2012). Prechemotherapy differences
9 in response inhibition in breast cancer patients compared to controls : A functional magnetic
10 resonance imaging study. *Journal of Clinical and Experimental Neuropsychology*, *34*(5),
11 543-560. doi: 10.1080/13803395.2012.666227
- 12 Scullin, M. K. (2013). Sleep, memory, and aging : The link between slow-wave sleep and episodic
13 memory changes from younger to older adults. *Psychology and Aging*, *28*(1), 105-114. doi:
14 10.1037/a0028830
- 15 Smith, K. L., Verma, N., Blackford, A. L., Lehman, J., Westbrook, K., Lim, D., ... Stearns, V. (2022).
16 Association of treatment-emergent symptoms identified by patient-reported outcomes with
17 adjuvant endocrine therapy discontinuation. *Npj Breast Cancer*, *8*(1), 1-13. doi:
18 10.1038/s41523-022-00414-0
- 19 Sousa, H., Almeida, S., Bessa, J., & Pereira, M. G. (2020). The Developmental Trajectory of Cancer-
20 Related Cognitive Impairment in Breast Cancer Patients : A Systematic Review of Longitudinal
21 Neuroimaging Studies. *Neuropsychology Review*, *30*(3), 287-309. doi: 10.1007/s11065-020-
22 09441-9
- 23 Spielberger, C., Sydeman, S., & Maruish, M. (1994). State-trait anxiety inventory and state-trait anger
24 expression inventory. The use of psychological testing for treatment planning and outcome
25 assessment. *Hillsdale, NJ, US: Lawrence Erlbaum Associates, Inc*, 292-321.

- 1 Ulrich, D. (2016). Sleep Spindles as Facilitators of Memory Formation and Learning. *Neural Plasticity*,
2 2016, 1796715. doi: 10.1155/2016/1796715
- 3 Van Dyk, K., Joffe, H., & Carroll, J. E. (2021). Sleep and endocrine therapy in breast cancer. *Current*
4 *Opinion in Endocrine and Metabolic Research*, 18, 165-170. doi:
5 10.1016/j.coemr.2021.03.007
- 6 Wei, Y., Krishnan, G. P., Komarov, M., & Bazhenov, M. (2018). Differential roles of sleep spindles and
7 sleep slow oscillations in memory consolidation. *PLoS Computational Biology*, 14(7),
8 e1006322. doi: 10.1371/journal.pcbi.1006322
- 9 Yellen, S. B., Cella, D. F., Webster, K., Blendowski, C., & Kaplan, E. (1997). Measuring fatigue and
10 other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT)
11 measurement system. *Journal of Pain and Symptom Management*, 13(2), 63-74. doi:
12 10.1016/s0885-3924(96)00274-6
- 13 Zhou, L., Fester, L., von Blittersdorff, B., Hassu, B., Nogens, H., Prange-Kiel, J., ... Rune, G. M. (2010).
14 Aromatase inhibitors induce spine synapse loss in the hippocampus of ovariectomized mice.
15 *Endocrinology*, 151(3), 1153-1160. doi: 10.1210/en.2009-0254
- 16 Züst, M. A., Mikutta, C., Omlin, X., DeStefani, T., Wunderlin, M., Zeller, C. J., ... Nissen, C. (2023). The
17 hierarchy of coupled sleep oscillations reverses with aging in humans. *The Journal of*
18 *Neuroscience: The Official Journal of the Society for Neuroscience*, JN-RM-0586-23. doi:
19 10.1523/JNEUROSCI.0586-23.2023
- 20 Zwart, W., Terra, H., Linn, S. C., & Schagen, S. B. (2015). Cognitive effects of endocrine therapy for
21 breast cancer : Keep calm and carry on? *Nature Reviews. Clinical Oncology*, 12(10), 597-606.
22 doi: 10.1038/nrclinonc.2015.124

23

24

25

Sleep oscillations related to memory consolidation during aromatases inhibitors for breast cancer

Rehel S.¹, Duivon M.¹, Doidy F.¹, Champetier P.¹, Clochon P.¹, Grellard JM², Segura-Djezzar C.^{3,4}, Geffrelot J.^{3,4}, Emile G.^{3,4}, Allouache D.^{3,4}, Levy C.^{3,4}, Viader F.¹, Eustache F.¹, Joly F.^{2,3,4,5,6}, Giffard B.^{1,6*}, Perrier J.^{1*}

¹ Normandie Univ, UNICAEN, PSL Université, EPHE, INSERM, U1077, CHU de Caen, GIP Cyceron, Neuropsychologie et Imagerie de la Mémoire Humaine, 14000 Caen, France

² Clinical Research Department, Centre François Baclesse, 3 avenue du Général Harris, Caen, France.

³ Institut Normand du Sein, Centre François Baclesse, Caen, France

⁴ Department of Medical Oncology, Centre François Baclesse, 3 Avenue du Général Harris, Caen, France.

⁵ INSERM, Normandie Univ, UNICAEN, U1086 ANTICIPE, Caen, France

⁶ Cancer and Cognition Platform, Ligue Nationale Contre le Cancer, 14076, Caen, France

* Authors equally contributed to this work

Corresponding author: Joy Perrier

Neuropsychologie & Imagerie de la Mémoire Humaine

Unité de recherche 1077 INSERM-EPHE-UNICAEN, Pôle des Formations et de Recherche en Santé (PFRS), 2 rue des Rochambelles F-14032 Caen Cedex CS 14032

Phone: +33(0) 2 31 56 83 83; E-mail: joy.perrier@unicaen.fr

Highlights

- Frontal slow wave density is lower during aromatase inhibitors treatment.
- Seemly, centro-parietal spindle density tend to be lower.
- Spindle density is related to memory performance.
- Aromatase inhibitors for breast cancer modify sleep-related memory consolidation
- Current patients' results confirm previous reports in animal models.

Journal Pre-proof

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Journal Pre-proof