



**CATÓLICA**  
**INSTITUTO DE CIÊNCIAS DA SAÚDE**

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LISBOA · PORTO

**THE ROLE OF COGNITIVE RESERVE in moderating THE  
COGNITIVE EFFECTS OF CHEMOTHERAPY in BREAST  
CANCER**

Dissertação apresentada à Universidade Católica Portuguesa para obtenção  
do grau de mestre em Neuropsicologia

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Por

Maria Isabel Fernandes Manica

Lisboa, 2021



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**O PAPEL DA RESERVA COGNITIVA na moderação dos EFEITOS  
COGNITIVOS DA QUIMIOTERAPIA no CANCRO DE MAMA**

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Maria Isabel Fernandes Manica

Sob Orientação de: Raquel Lemos, PhD e Maria Vânia Nunes, PhD

Lisboa, 2021

## **Abstract**

The effect of cancer treatments in cognition has been a matter of scientific debate for several years. An early identification of risk/protective factors that may interact with this cognitive impact could lead to better quality of life during and after oncological treatments. Cognitive reserve is a factor mostly known in the neurodegenerative context as a moderating factor between brain pathology and its clinical manifestations. Although already studied in the oncological context, there is no record that a more comprehensive assessment model for Cognitive Reserve has been used. CRIq is a socio-behavioral questionnaire that estimates an individual's level of cognitive reserve by collecting information related to their entire adult life.

The main objective of this work is to assess the differences in cognitive functioning, through the neuropsychological performance, before treatment and six months after its beginning, as well as to understand the role of cognitive reserve as a moderator factor of these possible changes.

Thirty-two women diagnosed with early breast cancer and indicated for chemotherapy treatment were recruited. Results showed a significant relationship between cognitive reserve and cognitive functioning prior to chemotherapy, but this effect was not seen at 6 months. There were no cognitive changes between the two moments; however, there was an improvement in performance in three cognitive measures at six months compared to the first assessment. Other cognitive reserve factors may interact with cognitive functioning than those assessed in the CRIq and practice effects may have been involved in the cognitive performance improvement.

## Resumo

O efeito dos tratamentos oncológicos sobre a cognição é um assunto em debate científico há vários anos, contudo continua a ser pouco consensual entre a comunidade científica. A caracterização cognitiva destes doentes e a identificação de fatores de risco/protetores que possam interagir com este efeito lateral poderão levar à promoção de uma melhor qualidade de vida durante e após os tratamentos. A reserva cognitiva é um fator conhecido no contexto neurodegenerativo como um fator moderador entre a patologia cerebral e as manifestações clínicas da mesma. Apesar de estudada em contexto oncológico, não existe registo de que um modelo de avaliação mais abrangente de Reserva Cognitiva tenha sido utilizado. A CRIq, é um questionário sociocomportamental que estima o nível de reserva cognitiva de um indivíduo através da recolha de informação relativa a toda a sua vida adulta.

Assim, o objetivo principal deste trabalho é o de avaliar diferenças no funcionamento cognitivo, através do desempenho na avaliação neuropsicológica, antes e seis meses após o início do tratamento oncológico, bem como compreender o papel da reserva cognitiva enquanto fator moderador destes efeitos.

Trinta e duas mulheres com diagnóstico de cancro da mama precoce e com indicação para tratamento com quimioterapia foram recrutadas. Os resultados evidenciaram uma relação significativa entre a reserva cognitiva e o funcionamento cognitivo previamente ao início da quimioterapia, mas este efeito não se manteve aos 6 meses. Não se verificaram alterações cognitivas entre ambos os momentos, contudo, verificou-se uma melhoria de desempenho entre os dois momentos em três medidas cognitivas. Os resultados sugerem que outros fatores de reserva cognitiva poderão interagir com o funcionamento cognitivo que não os avaliados na CRIq e que o efeito de prática poderá também estar envolvido na melhoria de desempenho observada.



*“Aqueles que passam por nós, não vão sós. Deixam um pouco de si, levam um pouco de nós.”*

*In O Príncipezinho, Antoine de. Saint Exupéry*

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O que sabe a fim, é frequentemente um início.

Uma eterna aprendiz

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## 1.Introduction

Cancer is often described as the “disease of the century” and the growing number of cases lead to broader options for treatment. However, as pharmacological treatments become more available, the concern about the impact of these ones on the quality of life and cognitive functioning of these patients has also increased. Cognitive complaints are frequent among cancer patients, especially after the treatment and the impact of these ones on their quality of life is significant. Taking this into account, studying this phenomenon becomes extremally relevant not only to understand the mechanisms behind it but also to identify possible risk factors that can be assessed and previously managed, promoting a better quality of life during and after the disease (Vannorsdall, 2017, O’Farrell et al., 2013, Wefel & Schagen,2012).

One of the major factors described in the literature as a protector of the development of cognitive deficits respects the construct proposed by Stern (2002) designed as *Cognitive Reserve*. This construct emerges from the verification of an indirect link between the cognitive insult and its clinical manifestations, and it proposes that combined genetics and principally lifetime stimulation could help to cope with brain pathology Stern (2002, 2009, 2020). In the oncological context, cognitive reserve through some of its determinants (education and premorbid IQ) has been studied as a possible moderator factor between treatments and cognitive changes (Amidi et al., 2015, Menning et al.,2016, Pierrer et al., 2020, Syarif et al., 2019). Since these changes appear to only affect a sample of cancer patients, a greater CR could help cope with the cognitive challenges impose by the treatments (Ahles et al., 2010, Mandelblatt et al., 2018; Janelains et al., 2018).

To this date and to our knowledge, no study has been carried involving a more global assessment of cognitive reserve, particularly through socio-behavioral questionnaires.

The purpose of this investigation is to study the cognitive changes in a sample of breast cancer patients undergoing chemotherapy longitudinally and analyzed the role of cognitive reserve in the development of those same changes. In other words, the main goal is to understand if Cognitive Reserve is a moderator factor, that could help breast cancer patients to cope with the brain challenges imposed by chemotherapy.

## **2. Literature Review**

### **2.1. Cancer Related Cognitive Impairment (CRCI)**

The progress in pharmacological treatments has permitted to increase the life expectancy of oncological patients. At the same time, there is a growing concern about the long-term consequences of the disease and its treatments, especially in cognitive functioning and quality of life (Vannorsdall, 2017, O'Farrell et al., 2013, Wefel & Schagen, 2012).

The subjective experience of cognitive difficulties within this population, in the absence of primary central nervous system (CNS) pathology, has led to a wave of studies that try to find a connection between oncological treatments and cognitive impairment (Boykoff, 2009, Vannorsdall, 2017, Wefel & Schagen, 2012). The term first used to describe this deterioration on cognition associated with cancer treatment was *chemobrain* or *chemofog* and it was proposed by the patients (Wefel et al., 2004, O'Farrell et al., 2013, Sousa et al., 2020). This condition englobes a range of symptoms such as memory loss, inability to concentrate, and difficulty thinking (Brezden et al., 2000; Schagen et al., 2000; Wieneke et al., 1995, Boykoff, 2009).

For non-CNS cancers, chemotherapy does not represent a direct risk of neurotoxicity because it is believed to not crossing the blood-brain barrier (Boykoff, 2009). For this reason, for some time this phenomenon has been attributed to psychological variables (O'Farrell et al., 2013) devaluing a possible biological mechanism. However, currently,

it is believed that it results from a set of factors/mechanisms, including psychological and biological factors (Vannorsdall, 2017, Ahles & Saykin, 2007).

Literature about *chemobrain* is increasing significantly comprising, possible mechanisms and risk factors for its development and concerns different cancer locations. Breast cancer patients represent the majority of chemobrain studies since prevalence and survivorship rates are high, and they also present a good prognosis expecting to return to daily basis life following the treatment (O'Farrell et al., 2013, Ahles et al., 2010; Jansen et al., 2011; Menning et al., 2016; Mandelblatt et al., 2018; Janelins et al., 2018; Perrier et al., 2020)., However, there is also evidence of cognitive impairments after chemotherapy in testicular cancer (PEDERSEN et al., 2009; Schagen et al., 2008), gastric cancer (Oh & Moon, 2019; Kim et al., 2016), hematological cancer (Wouters et al., 2016; Krolak et al., 2016; Trachtenberg et al., 2018; Sharafeldin et al., 2018), and lung cancer (Kusmierek et al., 2020).

Nevertheless, the term *chemobrain* quickly became redundant in the sense that it attributes chemotherapy as the only reason for these cognitive changes. Now there is an understanding that cognitive impairment results from a combination of factors (biological and psychological factors, genetics, among others) (Pierre, 2010), where treatment represents one possibility. Thus, the term currently used is *Cancer Related Cognitive Impairment* (CRCI) (Vannorsdall, 2017), not only because of the multiplicity of factors involved in the development of these cognitive changes but also, due to the importance of evaluating all of these patients to promote a better quality of life and healthy aging (Wefel et al., 2011).

In terms of incidence of CRCI, there are substantial differences according to the type of study, the measures used to assess cognitive changes and the cut-off to be considered as representing a deficit (Ahles, 2012, Wefel et al., 2011). In cross-sectional studies with

breast cancer survivors, it was found that between 17% to 75% of women experienced cognitive changes from 6 months to 20 years after chemotherapy (Ahles, 2012; Wefel, 2012). In longitudinal studies, about 69% of participants showed cognitive dysfunction (Wefel, 2012). Other studies also found percentages between 15% to 25% of deficits in follow-up assessments. Notwithstanding, some studies did not find any cognitive deficits or changes after cancer treatments (Ahles, 2012, Debes et al., 2010; Mehlsen et al., 2009; Collins et al., 2009), and others even find an improvement in some cognitive domains like verbal and visual memory (Cérrulla et al., 2018; Conroy et al., 2013), processing speed (Lepage et al., 2014), attention and executive functions (Cérrulla et al., 2018). The improvement found on some of these studies were justified by the impact of practice effects, defined as an improvement in test performance as a result of prior exposure to the testing materials (Duff, 2012).

The incidence of CRCI also varies according to the measures used to assess cognition. On one hand, there are self-reported questionnaires that measure subjective cognitive experience, and on the other hand, there are objective cognitive measures that allow for a quantification of the deficit. Regarding the first type of measures, in longitudinal studies, half of the patients reported cognitive decline at some point during the treatment (Ahles et al., 2018). In one study, with a sample of hematological cancer patients, almost 35% reported concentration difficulties, and about 52% reported memory changes six months after the end of chemotherapy (Cull et al., 1995). Ten years after chemotherapy, the survivors continued to report difficulties in the attentional domain (Ahles et al., 2012). More recently, a study done by Janelins et al. (2017), showed a similar percentage for subjective cognitive difficulties, varying between 37% to 58%. In short, the major domains reported by patients as representing changes are attention, multitasking, and nomination (Cull et al., 1995). Regarding the second type of measures, through objective

measures of the deficits, more precisely with the performance of patients in neuropsychological assessment tests (Ahles et al., 2018), even though the performance on these tests also indicates cognitive changes in attention, executive functions, processing speed and memory, although still significant, they are more subtle (Ahles et al., 2018, Billiet et al., 2018, Biglia et al., 2012, Jenkins et al., 2006, Amidi et al., 2017, Chen et al., 2017). In the more recent longitudinal study, using objective measures, the authors found that patients' performance on computerized measures of attention and executive functions as well on traditional verbal fluency to be declined when compared with healthy controls (Janelsins et al., 2018).

The experience of these cognitive changes can be different among patients and dependent on the phases of the treatment and of life. Even though there are some fluctuations between the affected domains, there is a core of cognitive abilities that are more sensitive to cancer and their treatments, namely learning and memory, attention, processing speed, and executive function (eg.: working memory), measured by objective neuropsychological instruments (Pierre, 2010; Vannorsdall, 2017; Asher & Myers, 2015, Kusmirek et al., 2020, Ahles et al., 2018, Wefel et al., 2018, Joly et al., 2015). These deficits suggest the involvement of frontal cortical and subcortical regions (Schagen, 2013; Wefel et al., 2011). The severity of these changes varies between mild and moderate, especially when compared with common neurological diseases (eg., stroke, dementia) (Ahles et al., 2018). The changes, particularly from those who are within the limits of global cognitive ability, can be noticed by the patient and/or others. For example, individuals with less cognitive resources feel that even the smallest change leaves them below the expectation to properly perform their daily basis (Vannorsdall, 2017; Asher & Myers, 2015).

The cognitive deficit pattern varies across patients and survivors in terms of severity. In some cases, milder or moderate deficits are described, translating into a higher effort to concentrate or remembering but without implications on basic daily living activities or quality of life. On the contrary, there are other cases where the deficit is severe and consequently affects daily functioning. The severity can be influenced by multiple factors like personal characteristics, the biology of the tumor, the treatment and social support (Pierre, 2010).

In longitudinal studies and as previously explained, the incidence and frequency of the deficits vary according to the population being studied, the assessment measures used, and the definition of deficit. Most of the patients show pre- and post-treatment effects, however, a minority never show any cognitive change (subjective or objective) (Hardy, 2018).

Approximately 20% to 40% of the cancer patients show cognitive deficits at the time of cancer diagnosis (previously to any treatment). Cognitive changes at baseline have been related to the emotional response to the diagnosis and treatment, which can include stress, fatigue, and humor changes (Vannorsdall, 2017). Besides the cognitive reports, some studies using neuroimaging have demonstrated structural and functional differences in this population even before treatment, especially in the frontal lobe (Vannorsdall, 2017). In a sample of breast cancer patients, 33% showed deficits before any treatment (Wefel et al., 2004). Similarly, Ahles et al. (2008), also verified that in the same type of population with early stages of cancer (I to II), there was evidence that patients had a lower performance in reaction time tests and a higher probability of worst general results. During the treatment, there is evidence that 65% to 75% of oncological patients developed changes in cognition (Vannorsdall, 2017). In mild forms of cognitive deficit, the rate of cognitive impairment tends to stabilize during the first six months after treatment. In

those who have severe deficits the expected recovery time is about 2 years after the treatment (Vannorsdall, 2017). Wefel (2010) found that a third of patients show persistent cognitive deficits one year after the end of the treatment.

There is also evidence of late effects of chemotherapy (>5 years). In a systematic review, Koppelmans et al., (2013) suggests that they can persist for 5 to 21 years after the treatment. Ahles et al. (2002), found that lymphoma and breast cancer patients scored lower in verbal memory and psychomotor function tasks 5 years after the treatment. In the same way, Koppelmans et al. (2012) reported declines in verbal memory, processing speed, executive functions, and psychomotor speed in unilateral breast cancer patients 21 years after the diagnosis. In longitudinal studies involving neuropsychological assessments, the main domains affected were attention and executive functioning, however, a minor sample of patients also showed a higher risk for long-term memory dysfunction (Koppelmans et al., 2012). Wefel et al. (2010), in a sample of 196 cancer patients, verified that 71% of patients had worse performance when compared with the control group seven months after the end of treatment and this percentage decreases to 61% in a late assessment after treatment (7.7 months after chemotherapy).

There is also evidence of changes in neuroimaging studies, including decreased grey matter volume and white matter integrity (McDonald et al., 2013; Koppelmans et al., 2014, Ruiters et al., 2012); hyperactivation of frontal areas (McDonald et al., 2012) and changes in the neural networks' organization (Bruno et al., 2012).

In what concerns to the underlying mechanisms, cancer-related cognitive impairment has been associated with multiple factors, including genetic predisposition, failure of the blood-brain barrier integrity, neurotoxicity from the treatment, DNA damage, reduction of hormonal levels (estrogen and testosterone), the effects of the cytokines in the brain, microvascular obstruction, and brain tissue infiltration (Pierre, 2010). There are also some

explanations based on the psychological status of the patient (fatigue, depression, and anxiety as a consequence of the diagnosis) (Pierre, 2010).

The differences in the cognitive complaints experienced by cancer patients, and the failure in establishing a direct link between the treatments and the effects on cognition, lead to the need of identifying possible risk factors that could be the basis for CRCI (Ahles 2012, 2018). The risk factors that were identified until now can be part of several categories: biological/genetic factors, demographic factors, social factors, psychological factors, factors related to the lifestyle of the patient and with the treatment (Ahles 2012, 2018).

The presence of the APOE e4 allele, a well-known risk factor for Alzheimer's Disease (AD), is related to a worst survivor's performance in tasks of visual memory and spatial ability (Ahles et al., 2003). The presence of the COMT-Vall allele was associated with the worst performance in attention, motor speed, and verbal fluency task in comparison with survivors that have the COMT-Met allele (Cole et al., 2015; Small et al., 2011; Vannorsdall, 2017).

Regarding the risk factors associated with the treatment itself, exposure to higher doses, a cumulative effect of chemotherapy multi-agents or the combination of different treatments, and the intraarterial administration are associated with a higher risk of neurotoxicity (Wefel, 2012; Schagen, 2013; Vannorsdall, 2017).

At a sociodemographic level, age is the most studied risk factor (Ahles et al., 2018). Older age is associated with a higher risk for cognitive impairment and with a higher predisposition to clinical conditions involving cognition. In cancer, age works as a moderator factor of the treatment effects in cognition. Older age results in more cognitive domains affected or more extensively (Vannorsdall, 2017).

More recently, cognitive reserve (CR) has been identified as a differential factor in the development of cognitive dysfunction (Vannorsdall, 2017). In other clinical conditions like AD, a lower CR is associated with a higher impact on cognitive function, or on the other side higher CR leads to less severe and delayed clinical manifestations, cognitive effects, and functional impairment of this disease. As so, high CR is a protective factor against some neurodegenerative or demyelinating diseases. On the other hand, low CR can be a risk factor for the development and severity of clinical manifestations of some neurological diseases (Stern, 2002). In CRCI, the studies performed until now focus on low CR as a risk factor for cognitive impairment after cancer treatments. In this clinical context studies generally use education as a proxy of CR, showing that fewer years of education are associated with a higher impairment after cancer treatments (Perrier et al., 2020; Trachtenberg et al., 2018; Galvin et al., 2019; Sharafeldin et al., 2018; Syarif et al., 2019, Wazqar et al., 2019).

## **2.2 Cognitive Reserve (CR)**

The concept of reserve emerges from the verification of an indirect link between the cognitive insult and its clinical manifestations. This means that it appears to exist a disconnection between the lesion level and its consequences and that lesions do not always result in clinical symptomatology. Having this in mind, Stern (2002) proposed that *cognitive reserve*, acquired through lifetime stimulation, could help to cope with brain pathology, being a moderator factor of this link.

The concept of reserve, as proposed by Stern (2002), can be explained by different theoretical models, depending on the inclusion of the brain as part of an active or passive process. In this regard, there are two main categories of models: Passive Models and Active Models. The first one explains reserve in terms of the amount of lesion that can be sustained until it reaches the limit where a clinical expression is seen. On the other

hand, the second one tries to understand reserve as the responsible for cognitive tasks execution differences (Stern, 2002).

The Passive Models of Reserve are based on the concept of brain reserve (BR), which is determined by quantifiable/ neurobiological factors like brain volume or the number of synapses (Stern, 2002, 2009). This concept implies that some people cope better with pathology before clinical and cognitive manifestations due to individual variation in brain structure (Stern et al., 2020). Illustratively, this means that individuals with a higher brain volume can sustain a bigger brain insult before the clinical deficits appear, i.e., their neural substrate is capable of maintaining a normal functioning up to a certain limit. This applies to the clinical manifestation of the disease but also to the severity of that same manifestation. These models assume the existence of a fixed cutoff point from which everyone will have functional symptoms (Stern, 2002). More recently, the concept of brain maintenance (BM) had emerged helping to explain how life experience can shape BR. BM reflects the idea that the brain is moldable according to life experience and lifestyle besides genetics. It is defined as the “reduced development of age-related brain changes and pathology over time based on life experience and genetics” (Stern et al., 2020). BR is the status of the brain at a point in time and BM is the process of maintaining the brain, meaning that a better BM can sustain a higher BR (Stern et al., 2020).

According to the assumptions of these passive models, they can be classified as quantitative since it is assumed that a specific brain lesion will have the same impact on everyone (Stern, 2002). Briefly, all individuals have the same amount of brain reserve, and a brain insult can be sufficient or insufficient to exhaust that capacity. Thus, this category of models does not include individual characteristics about the cognitive process or about task execution, no foresees potential qualitative differences between different types of lesions (Stern, 2002). On the other hand, the Active Models of Reserve are based

on the idea that the brain tries to deal with lesions through a preexistent cognitive process or a compensatory process. According to these models, we can talk about two expressions of reserve: Neural Reserve and Compensatory Mechanisms/ Compensation (Stern, 2002, 2009; Stern et al., 2020).

Neural Reserve can be understood as a process of recruiting neural networks or cognitive means that are less vulnerable to the disruption after an insult, thus giving prevalence to the preexistent process. This process is the same used by healthy individuals in solving more complicated tasks. Unlike passive models, this concept includes interindividual differences in cognitive processing and is based on functional brain processes (networks of brain regions associated with performing a task and their pattern of interactions). Compensation, on the other side, refers to the use of neural networks and brain structures that are not frequently required, to compensate for the damages of the lesion (Stern, 2002, Stern, 2009; Stern et al., 2020). There are changes in the cognitive processing to deal with the lesion manifestations (Stern, 2009).

Stern (2002) refers that a combination of these two model approaches can better describe his proposal of the reserve concept.

As previously mentioned, the concept of CR emerges with the purpose of explaining a recurrent situation in clinical practice in which patients with the same brain lesion had different clinical manifestations, with no direct relationship between the two (Stern, 2002). That said, what is being described in the literature is that CR can help explain that differences in cognitive and functional abilities through the notion that cognitive processes may adapt to pathology, presenting, therefore, different degrees of vulnerability to the brain insult itself (Stern et al., 2020). The ability of the cognitive mean at the basis of a certain task supports the disruption and continues to operate effectively. This can

also translate into the ability to use different paradigms that relate to unusual approaches to certain problems when the usual is no longer available (Stern, 2002).

CR is not fixed and immutable, it results from a certain combination of cognitive stimulant activities (intelligence, education, occupation, physical exercise among others) (Stern, 2009; Stern et al., 2020) that can be beneficial in all life stages (Stern, 2002). This combination of activities covary and foresees the development of CR during the individual whole life, and they are usually named CR proxies (Stern, 2009, Stern et al., 2020). These socio-behavioral indices attempt to represent experiences that contribute to the development of CR, and they do not imply any specific functional mechanisms (Stern et al., 2020).

CR proxies reflect life experiences and include education or literacy level, hobbies and leisure activities, socioeconomic status (SES), occupation, premorbid ability, among others (Stern, 2009; Stern et al., 2020).

### **2.3. Cancer Related Cognitive Impairment and Cognitive Reserve**

In the oncological context, CR has been indicated as a risk/protective factor for the development of cognitive impairment during cancer treatments (Ahles et al., 2010). Similarly, to what happens in other conditions like Alzheimer's disease or others resulting from brain insults, a lower CR is related to poorer cognitive performance outcomes. This means that individuals with less CR are more vulnerable to develop clinical manifestations after a brain insult or disease. The same rationale is being now applied to CRCI (Ahles et al., 2010).

The literature investigating the moderator factor of CR in CRCI uses proxies of the cognitive reserve as the index of this ability. The proxies used are mainly education (years of education or high education vs low education) and premorbid ability (higher premorbid ability vs lower premorbid ability) (Vannorsdall, 2017).

Regarding education, Janelsins et al. (2018) found that a lower education level, explained a worst result at baseline in Wide Range Achievement Test (WRAT) 3<sup>rd</sup> Version - reading score; higher levels of anxiety and depression were also predictors for cognitive decline in a breast cancer sample. In another study, 86% of breast cancer patients experienced a certain degree of decline in executive functions, and the variables that most interacted with cognitive decline were education, along with other sociodemographic and clinical risk factors (Syarif, 2019). Pierrer et al. (2020) also found that breast cancer patients with higher education levels had a better performance in verbal episodic memory recall, higher anxiety scores, and hippocampal atrophy one month after chemotherapy compared with those less educated.

Premorbid ability is usually assessed through irregular words reading questionnaires like the National Adult Reading Test (NART) (Amidi et al., 2015; Gonzalez et al., 2015; Lycke et al., 2016; Wouters et al., 2016) or WRAT (Mandelblatt et al., 2018; Janelsins et al., 2018). Ahles et al. (2010) studied the interaction between age, CR (measure with WRAT-3), and chemotherapy. Older patients, with lower baseline WRAT-3 reading scores and who have been exposed to chemotherapy had lower performance on processing speed tasks (Ahles et al., 2010). There was also a significant interaction between the WRAT-3 reading subscore and language tasks (Ahles et al., 2010). Menning et al. (2016), found that 16% of participants undergoing chemotherapy showed cognitive decline six months after ending the treatment in comparison with 4% of other breast cancer participants. Chemotherapy patients had a lower premorbid ability, worse physical condition, and less social functioning at baseline.

Besides the breast cancer population, there are also other studies trying to find an interaction between CR determinants and CRCI in other cancer types (Amidi et al., 2015; Gonzalez et al, 2015; Lycke et al., 2016 Trachtenberg et al., 2018; Galvin et al., 2019).

Amidi et al., (2015) verified in a sample of testicular cancer survivors assessed between 2 to 7 years after the treatment (chemotherapy, radiotherapy, and/or surgery) that they had impairment in 9 of the 12 neuropsychology tests applied. This represents that 62% of the sample had a cognitive deficit. The only predictor of these deficit was the NART score, usually used as a premorbid ability measure.

Despite the common practice of using CR proxies to determine the level of reserve in the context of research, this may not reflect the concept of CR properly (Kartschmit et al., 2019). Since it is a theoretical construct, its measurement poses several challenges and sometimes depends on subjective measures that may not capture the whole construct. The proposed methods for quantification of CR can be included in the residual approach, the functional imaging approach, or more indirect measurements approaches. The residual approach tries to explain the current level of cognitive reserve based on the variance in cognitive performance that can't be explained according to demographic variables or brain measures. The functional imaging approach focus on the identification of possible brain networks underlying CR (Kartschmit et al., 2019).

Considering the complexity of this construct and its varied determinants, other indirect ways of obtaining a CR index have been proposed, namely through socio-behavioral proxies' indicators (education, occupation, leisure activity) or through standardized questionnaires. These questionnaires include several CR proxies. They also have a predefined score, which allows comparisons between different studies (Kartschmit et al., 2019).

The **Cognitive Reserve Index questionnaire (CRIq)** estimates the CR of an individual through the collection of information regarding their entire adult life (Nucci et al., 2012).

This questionnaire was built based on the CR concept proposed by Stern (2009). It was developed by Nucci et al. (2012) and is now under the process of validation to the Portuguese Population.

The CRIq includes demographic data and 20 items grouped into three sections: education, working activity, and leisure time. Each one of these sections provides a subscore: CRI-Education, CRI-Working Activity, and CRI-Leisure Time (Nucci et al., 2012). CRI-Education corresponds to the years of education plus other courses (minimum of six months). CRI-Working Activity is the result of the years of working activity multiplied by the cognitive complexity of the job. CRI-Leisure Time is the result of the number of years of activity for which frequency was often/always plus the score related to the number of children. In the end, a global index of cognitive reserve is also obtained – CRI (Nucci et al., 2012).

This questionnaire should be applied as a semi-structured interview and preferably to the individual of interest. The only exception is when the person is not cognitively healthy, and in that case, this should be applied to somebody that is informed about the habits of the subject (Nucci et al., 2012).

A series of studies support the construct validity of the CRIq in clinical populations. For example, Milanini et al. (2016) found that the CRI was associated with a lower risk of cognitive impairment in patients with HIV. Fenu et al. (2018) also found, in Multiple Sclerosis Patients, a significant association between measures of cognitive assessment and CRIq scores. In the same way, Volpi et al. (2017) found that a higher CRI was associated with a lower probability of having Mild Cognitive Impairment. CRIq was also tested for convergent validity, being moderately associated with the score of vocabulary test of WAIS-III (Kartschmit et al. 2019; Nucci et al., 2012)

Regarding CRCI, there is no study to date using this questionnaire.

Although several studies corroborate the idea that chemotherapy can be in fact associated with the cognitive deficits in cancer survivors, there are others that refute this idea or do not fully prove it (Hermelink et al., 2007; Jenkins et al. 2006), so this issue is far from being consensual. That said, the main aim of this study is to assess the cognitive effects of chemotherapy in women diagnosed with breast cancer and to understand the role of cognitive reserve in the development and the severity of these effects. The following hypothesis are proposed for this study:

Hypothesis 1: There are cognitive changes resulting from chemotherapy, which are more evident in the following domains: Executive Functions, Memory, Attention and Processing Speed.

Hypothesis 2: The Cognitive Reserve acts as a protective/risk factor in the development and severity of these cognitive changes, therefore, subjects with less cognitive reserve show more cognitive changes and/or more severe.

Hypothesis 3: Validation of Cognitive Reserve Index Questionnaire for the group undergoing chemotherapy.

### **3. Methods**

#### **3.1. Participants**

Women with early breast cancer, stages I–III, were recruited as part of a multicentre clinical pilot study - BOUNCE (Predicting Effective Adaptation to Breast Cancer to Help Women to BOUNCE Back) and Champalimaud-Helsinki cognitive function study (H20202 Project number 777167) conducted at the Breast Unit of the Champalimaud Foundation Clinical Centre. We recruited a cohort of patients from the chemotherapy (CT) arm of the Cognitive Study. In this undergoing study the main inclusion criteria were Women with early breast cancer and ER+ disease, with indication for curative treatment with systemic CT, with a regimen including anthracyclines and taxanes (N=32),

and local treatment with surgery (breast cancer conservative surgery or mastectomy and axillary assessment) and/or radiation therapy.

To guarantee that the participants at the CT group were cognitively integrated, a group of healthy volunteers (V) was recruited during the current study. The groups were paired according to sociodemographic variables (age and education).

The major purpose of the study was to detect cognitive changes between 2 assessment moments (before and 6 months after the start of the treatment). The recruitment of healthy volunteers was only to assure that the clinical group did not present any cognitive impairment pretreatment, as a precondition to the experimental study. That said, the results from the comparison of the cognitive performance between the CT group and the healthy volunteers are presented in this section and not on the results section as usual.

Demographical characteristics of the population are shown in **Table 1**. No statistically differences were found on age ( $U=504.5, p=0.871$ ) or education level ( $U=472.0, p=0.58$ ) between the two groups. To assure that the experimental group did not present any impairment before the treatment, we compare the performance of the CT group with the performance of healthy volunteers on neuropsychological measures. Data were analyzed with Mann-Whitney Test ( $U$ ). No differences were found at baseline (M0) between the CT and V groups on any of the neuropsychological measures as described in **Table 2**. When analyzing the 3 subscales of cognitive reserve, there were also no differences between the two groups (CRI-Education:  $U = 481, p= 0.68$ ; CRI-Working Activity:  $U =400 p= 0,13$ ; CR-Leisure Time:  $U = 507 p= 0,95$ ) at baseline.

Participants from both groups were excluded for the following criteria: refusal to sign informed consent, presence of distant metastases, history of another malignancy or contralateral invasive breast cancer within the last five years except cured basal cell carcinoma of skin or carcinoma in situ of the uterine cervix, history of early-onset (i.e.,

before 40 years of age) mental disorder (i.e., schizophrenia, psychosis, bipolar disorder, diagnosis of major depression) or severe neurologic disorder (i.e., a neurodegenerative disorder, dementia), major surgery for severe disease or trauma which could affect patient's psychosocial wellbeing (for example, major heart or abdominal surgery) within 4 weeks prior to study entry or lack of complete recovery from the effects of surgery, treatment for any major illness in the last half-year, pregnancy or breastfeeding at the time of recruitment, non-fluency in Portuguese and basic education outside of Portugal. In addition to the previous criteria, women in the clinical group were also excluded if they present other diagnosed concomitant diseases such as clinically significant (i.e., active) cardiac disease (e.g., congestive heart failure, symptomatic coronary artery disease, or cardiac arrhythmia not well controlled with medication) or myocardial infarction within the last 12 months.

### **3.2. Measures**

#### *Neuropsychological measures*

Participants who underwent chemotherapy treatment completed a longitudinal objective neuropsychological assessment of cognitive function at 2 time-points (T0-baseline; T1-after 6 months). As explained in the methods section, and shown in table 2, the presence of the healthy volunteer's group was justified to ensure that the CT group did not have cognitive changes at baseline and so they only did a single neuropsychological assessment.

The neuropsychological assessment battery consisted of cognitive tests, that were selected by a panel of experts for its validated availability in Portuguese language and corrected normative data and following the International Cognition and Cancer Task Force Recommendations (ICCTF) (Wefel et al., 2011):

1) *Auditory Verbal Learning Test (AVLT) A and B (2)*, which assesses different aspects of learning and verbal memory. The test includes five immediate recall trials that provide information about the acquisition and learning processes, a delayed evocation trial, and a recognition trial which allows exploring different aspects of retention.

**Table 1.**

*Population Demographic Characteristics*

	CT N = 32	V N= 32	<i>U</i>	<i>p</i> -value
<b>Age</b>				
Mean	49.75	49.44		
S.D.	7.70	7.63		
Median	48	49.50	504.50	0.92
Interquartile Range	[43.25, 55.75]	[42.25, 55.75]		
<b>Education (Years)</b>				
Mean	16.69	16.50		
S.D.	3.97	3.14		
Median	17	17	472.00	0.58
Interquartile Range	[13.75, 19]	[13, 18]		
Abbreviations: CT- Chemotherapy Group, V –Healthy Volunteers, S.D. Standard Deviation				
Note: U = Mann Whitney Test				

In the immediate recall trials, the examiner reads aloud a list of 15 words and asks the participant to say as many words as possible that she can remember from the list. This procedure is carried out 5 consecutive times. After 20/30min the examiner asks the test-taker again to remember as many words as possible from the first list (Delayed Recall

test). Last, the examiner presents a new list of words, that includes the words presented in the first one and others. In this trial, it is asked to the participant to say “Yes” or “No” according to these criteria (The word read was on the first list of words, or no?) (Cavaco et al., 2015).

The scores for each of the five immediate recall tests and the delayed recall test correspond to the number of target words retrieved from the list of 15 possible words. The maximum score for each one of these trials is 15. The score for the recognition trial corresponds to the number of target words correctly identified (the correct answer was Yes) plus the number of non-target words correctly identified (the correct answer was No). The maximum score is 30 (Cavaco et al., 2015).

The test scores are useful for distinguishing between memory deficits that are attributable to recovery versus storage problems (Cavaco et al., 2015).

Besides these direct scores, this test allows having some index's: *Total Learning* (TL), *Learning Over Trail* (LOT), and *Long-Term Percent Retention* (LTPR). TL corresponds to the total number of words remembered from trial one to trial five. LOT is the score of TL adjusted to the first trial of immediate recall. LTPR is the score of the delayed recall trial expressed as the proportion of trial 5 ( $100 \times (\text{Delayed Recall Score} / \text{Immediate Recall Score Trial 5})$ ) (Cavaco et al., 2015).

2) *Trail Making Test A and B (TMT-A, TMT-B)* (Cavaco et al, 2013): TMT is used to assess divided attention, processing speed, and cognitive flexibility. It consists of two parts (Part A and Part B): Part A assesses attention, visual demand, the speed of coordination between vision and the upper motor function and information processing (Cavaco et al, 2013) and, Part B, assesses divided attention, memory, and executive functions, namely the ability to change or maintain a rule - cognitive flexibility (Cavaco et al, 2013).

Test A consists of joining 25 numbers consecutively as quickly as possible (1-2-3-4 -...) and Test B consists of consecutively joining numbers in ascending order and letters in alphabetical order, alternating the sequence (1-A-2-B-3-C ... except the letter K) as quickly as possible (Cavaco et al, 2013).

For each one of the trials, the examiner registers the time that the participant took to complete the task. Besides these direct measures, it is possible to calculate other three derived scores namely the time difference between both task (TMT-B – TMT-A), the ratio score (TMT-B / TMT-A), and the score expressed in proportion (TMT-B – TMT-A/ TMT-A) (Cavaco et al, 2013). The other two derived scores were explored, namely the sum TMT A + TMT B and multiplication TMT A x TMT B /100 (Cavaco et al, 2013).

3) *Stroop Colour Word Test* (Golden & Freshwater, 1978; Portuguese Adaptation from Fernandes, 2013), assesses selective attention, cognitive flexibility, and the ability to inhibit and resist interference from external stimuli, that is, it assesses the extent to which the person is able to keep an objective in mind while simultaneously suppressing a more intuitive and familiar response. The test consists of three parts with three different stimulus cards, each containing 100 items, distributed in five columns. In the first part, the reading words test (W), the words “Red”, “Green” and “Blue” are printed in black ink and the individual has to read the words as quickly as possible for 45 seconds; in the second part, the naming test (C), there are 100 “XXX” items printed in red, green and blue ink, the aim is to name the colors as quickly as possible for 45 seconds; the third part, the interference test (WC), the words of the first card are printed with the colors of the second card and the subject's task is to name the color with which the word was printed as quickly as possible for 45 seconds. The total score for each one of the tasks is the number of words/ colors identified. Interference is calculated using the following formula:  $WC - WC'$ , in which the  $WC'$  (estimated interference), is calculated using the

formula:  $WC' = [C \times W] / (C + W)$  (Fernandes, 2013). A score greater than 0 is indicative of high resistance to interference (Fernandes, 2013).

4) *Wechsler Adult Intelligence Scale (WAIS-III) Letter Number Sequencing* (Wechsler, 2008) allows for assessing auditory working memory and attention. It comprises a set of 7 items with three trials each, in which the participant task is to repeat the sequences of letters and numbers that the examiner reads aloud, sequencing the numbers, first, in ascending order and then the letters, alphabetically. The length of the sequences varies between a number and a letter, and four numbers and four letters. The scores correspond to the number of trials correctly answered. The test ends after 3 incorrect trials on the same item. The maximum score is 21 (Wechsler, 2008).

5) *Wechsler Adult Intelligence Scale (WAIS-III) Coding subtest* (Wechsler, 2008) measures attention and processing speed, as well as short-term non-verbal memory and visual perception. In this sub-test, the subject is given an exercise sheet with a symbol key associated with numbers from 1 to 9. Subsequently, a sequence of numbers is given and the participant is requested to draw the corresponding symbol under each of the numbers. The test ends after 120 seconds and the correct symbols that the subject draws during that time are counted. The test requires visual scanning and tracking within the copy of symbols paired with numbers, thus, lower scores also indicate learning ability deficits (Wechsler, 2008).

6) *Verbal Fluency Test* (Cavaco et al., 2013) assesses verbal functioning as well as semantic and working memory. The test consists of two tasks: 1) semantic fluency in which the participant is asked to name animals for 60 seconds, and 2) phonemic fluency which consists of three trials (1min each), and where the participant is asked to produce the largest number of words, except names (e.g. Bernardo and Belgium) starting with a specific letter - "M", "R", and "P". The raw scores correspond to the number of total

words per trial, and the total words per type of fluency being assessed (raw score for semantic fluency is the number of total words in the first trial and the raw score for phonemic fluency is the sum of all the words from the 3 last trials (Cavaco et al., 2013). We also used the *TeLPI test*, *Teste de Leitura de Palavras Irregulares (5)*, which is a Portuguese irregular word reading test to estimate the premorbid intellectual ability. The test is composed of a card with 46 printed irregular words and the participant is asked to read them aloud. The correctly said words are then summed and a TeLPI raw score enables to estimate verbal IQ accounting for years of education (Alves et al., 2012). The TeLPI test was only performed at T0 (after diagnosis) because IQ ability is a stable measure over time.

7) *Montreal Cognitive Assessment (MoCA)* (Freitas et al., 2011): It is a brief instrument designed for the screening of mild cognitive impairment. It consists of a one-page test, and it assesses eight cognitive domains, namely, attention, visuospatial abilities, executive functions, memory, language, concentration, working memory, and orientation (temporal and spatial). This was only applied to the healthy volunteers as a screening measure for cognitive impairment. None of the healthy volunteers were excluded based on their result on MoCA.

### *Questionnaires*

In addition to the neuropsychological assessment protocol and to determine the influence of CR on the development and severity of these cognitive changes, it was used the Cognitive Reserve Index Questionnaire (CRIq). CRIq estimates the CR of an individual through the collection of information regarding their entire adult life (Nucci et al., 2012). The CRIq includes demographic data and 20 items grouped into three sections: education, working activity, and leisure time. Each one of these sections provides a subscore: CRI-Education, CRI-Working Activity, and CRI-Leisure Time (Nucci et al., 2012). CRI

Education corresponds to the years of education plus other courses (minimum of six months). CRI-Working Activity is based on a five-level scale of the cognitive complexity and responsibility associated with a job (low skilled manual work, skilled manual work, skilled non-manual, professional occupation, and highly responsible or intellectual occupation), and the raw score for this section is the result of the years of a working activity multiplied by the cognitive complexity of the job. CRI-Leisure Time is the result of the number of years of activity for which frequency was often/always plus the score related to the number of children ( $5 \times \text{number of children} + 10$ ) (Nucci et al., 2012). Since this questionnaire is not validate for the Portuguese population, we will be using the raw scores for each one of these sections.

The data collection of chemotherapy group was already undergoing at the time this project (cognitive reserve) was presented. As so, a new consent form was submitted to the ethics commission and presented to the clinical group

### **3.3. Statistical Analyses**

Data was collected and processed via Excel (Microsoft Corp, Redmond, W A, USA), and was analyzed by using the SPSS software version 26 (SPSS, Inc., Chicago, IL, USA).

Since one of the major purposes of this study was the validation of CRIq to the oncological population, we explored some psychometric properties, such as the reliability, using the Cronbach's alpha Coefficient as well as the concurrent validity using the estimated QI's measured with TeLPI.

As almost all of the data collected significantly deviated from the presupposes of parametric statistics methods (normal distributions and homogeneous variances verified with the Shapiro-Wilk and Levene homogeneity tests respectively) we opted to use nonparametrical statistical methods for intragroup comparisons.

Results with  $p < 0,05$  were considered statistically significant.

Descriptive statistics were used for the sample's characterization (results were presented in the methods section).

To analyze the differences in neuropsychological measures between the first timepoint assessment and the second timepoint assessment on the CT group, we used a Wilcoxon Test ( $Z$ ) for related samples.

The relationship between CT cognitive reserve subscales scores and the performance on the neuropsychological measures was analyzed using the Spearman correlation coefficient, in the two assessment moments.

Analyses were performed using all available data. Missing data was not common, except for a single participant of the CT group in the Digit Symbol Task and in the TeLPI.

**Table 2.***Comparison between CT and V on neuropsychological measures on M0*

		CT	V	U	<i>p</i> -value
Auditory Verbal Learning Test (AVLT)	Delayed Recall				
	Mean (SD)	11.25 (2.60)	11.69 (2.15)		
	Median [IQR]	12 [9.25, 13]	12 [10, 13]	467.50	0.55
	Total Learning				
	Mean (SD)	54.84 (7.40)	55.88 (5.40)		
	Median [IQR]	54 [51, 61.75]	55 [50, 59]	503.50	0.91
	Learning Over				
	Trail	17.5 (6.80)	19.25 (6.10)		
	Mean (SD)	16.50 [11.25, 22.75]	19.50 [14.25, 23.75]	420.50	0.22
	Median [IQR]				
	Long Term				
	Percent Retention	87.42 (16.90)	86.87 (10.20)		
	Mean (SD)	86.67 [75.89, 100]	86.67 [78.09, 93.21]	510.00	0.98
	Median [IQR]				
	Recognition				
Mean (SD)	29.59 (0.76)	29.56 (0.70)			
Median [IQR]	30 [29, 30]	30 [29, 30]	487.00	0.68	
Trail Making Test	A				
	Mean (SD)	31.66 (6.00)	33.81 (11.50)		
	Median [IQR]	30.5 [28, 36]	31 [25, 40]	495.50	0.99
	B				
	Mean (SD)	72.06 (19.70)	66.9 (23.60)		
	Median [IQR]	68 [60, 78.75]	60 [50, 82]	395.50	0.12
(B-A)					
Mean (SD)	40.41 (19.00)	33.10 (18.20)			

	Median [IQR]	37 [29.50, 51]	34 [20, 41]	407.50	0.16
	(B/A)				
	Mean (SD)	2.33 (0.60)	2.04 (0.60)		
	Median [IQR]	2.35 [1.80, 2.88]	1.90 [1.70, 2.88]	386.50	0.09
	(B-A/A)				
	Mean (SD)	1.33 (0.60)	1.24 (1.10)		
	Median [IQR]	1.35 [0.80, 1.88]	1 [0.70, 1.50]	416.50	0.20
	(A+B)				
	Mean (SD)	103.7 (22.20)	100.7 (32.30)		
	Median [IQR]	100.5 [91, 111.25]	93 [82, 110]	410.50	0.17
	(AxB/100)				
	Mean (SD)	23.12 (9.10)	24.20 (16.00)		0.44
	Median [IQR]	21.20 [17.28, 26.90]	19.52 [13.64, 26.50]	454.50	
Color Word Stroop Test	Word				
	Mean (SD)	94.59 (12.23)	94.34 (12.63)		
	Median [IQR]	95 [85.75, 102.75]	94.50 [87.25, 100]	509.50	.97
	Color				
	Mean (SD)	68.81 (8.04)	64.78 (13.53)		
	Median [IQR]	68 [62.25, 72]	66.50 [57.75, 74]	439.50	.33
	Color Word				
	Mean (SD)	41.25 (8.70)	38.78 (7.96)		
	Median [IQR]	40 [37.25, 46.75]	39 [32.25, 42.75]	425.00	.24
	Interference				
	Mean (SD)	1.5 (8.19)	-0.03 (7.60)		
	Median [IQR]	0.94 [-2.62, 7.42]	-1 [-6.75, 6.75]	442.50	.35

Verbal Fluency (VF)	Animals				
	Mean (SD)	22.38 (4.90)	22.94 (4.92)		
	Median [IQR]	22 [18, 26.75]	23[20, 25.75]	471.00	0.58
	Letter M				
	Mean (SD)	12.22 (3.40)	12.84 (3.27)		
	Median [IQR]	12 [10, 14]	13[10, 15]	451.00	0.41
	Letter R				
	Mean (SD)				
	Median [IQR]	11.31 (3.50)	12.03(3.45)		
		12 [9, 14]	12 [10.25, 14]	445.50	0.37
Letter P					
Mean (SD)					
Median [IQR]	13.53 (3,50)	13.38 (3.69)			
	3.54 [11, 16.5]	12.50 [11, 16]	495.50	0.82	
Total					
Mean (SD)	37.06 (8.60)	38.25 (8)			
Median [IQR]	37.50 [29, 43.25]	37.50 [34, 44]	476.00	0.63	
Digit Symbol	Mean (SD)	78.06	71.78 (14.25)		
	Median [IQR]	78 [68, 84]	69 [60.75, 81.75]	358.50	0.59
Letter and Number	Mean (SD)	9.94 (1.80)	9.13 (2.71)		
	Median [IQR]	10 [9, 11]	9 [7.25,10]	415.50	0.19
Palavras Irregulares	Words				
	Mean (SD)	41.77 (3.10)	42.16 (3.09)		
	Median [IQR]	43 [40, 44]	43 [40.25, 44]	456.00	0.58
	IQ				
Mean (SD)	122.14 (8.10)	122.97 (8.14)			
Median [IQR]	125.40[115.40,128.00]	124 [118, 127]	460.50	.63	

Teste de Leitura de	VIQ				
	<i>Mean (SD)</i>	122.14 (21.34)	124.94 (6.83)		
	<i>Median [IQR]</i>	127.9 [116.90, 131.20]	126 [119, 129]	461.50	0.64
	RIQ				
	<i>Mean (SD)</i>	113.37 (17.99)	116,63 (4.87)		
	<i>Median [IQR]</i>	117.85[110, 119.90]	117 [114, 120]	475.00	0.77
Cognitive Reserve Index Questionnaire (CRI $\alpha$ )	Education				
	<i>Mean (SD)</i>	18.87 (4.41)			
	<i>Median [IQR]</i>	18.5 [16.50, 23.50]	-	-	-
	Working Activity				
	<i>Mean (SD)</i>	119.35 (52.5)			
	<i>Median [IQR]</i>	120 [85, 155]	-	-	-
	Leisure Time				
	<i>Mean (SD)</i>	244.51 (93.06)	-	-	-
	<i>Median [IQR]</i>	210 [175, 290]			

Abbreviations: U= Mann Whitney Test, IQ : Intelligence Quotient, VIQ : Verbal Intelligence Quotient,

RIQ: Realization Intelligence Quotient; CT - Chemotherapy group, V - Healthy Volunteers

## 4. Results

### Sample characterization

Thirty-two women undergoing chemotherapy were recruited from Champalimaud Clinical Center, aged between 36 and 63 years with 6 to 25 years of education. Demographical characteristics of the population are shown in **Table 1**.

### Cognitive Performance at baseline

As described on **Table 2** was not found any cognitive impairment at baseline.

### Cognitive Reserve at baseline

CR was assessed using the CRIq subscales. For each subscale was calculated the mean (SD) and the CT group was classified as having low, on average or high CR in each one of these subscales. Low CR corresponds to scores at least 1 SD below the mean, High CR corresponds to the scores at least 1 SD above the mean and on average corresponds to the values within the mean ( $\leq 1SD$  – Low CR;  $\geq 1SD$  – High CR;  $[1SD < M < 1SD]$  - On Average). The distribution of level of CR in breast cancer sample is described in **Table 3**.

**Table 3.**

*Characterization of the breast cancer sample in terms of level of CR for each subscale of CRIq*

	CRI-Education			CRI-Working Activity			CRI-Leisure Time		
	L CR	A CR	H CR	L CR	A CR	H CR	L CR	A CR	H CR
n	4	20	8	4	26	2	2	25	5
%	12.5	62.5	25	12.5	81.3	6.3	6.3	78.1	15.6

Abbreviations: CRI- Cognitive Reserve Index, LCR- Low cognitive reserve, ACR- On average Cognitive Reserve, HCR- High Cognitive Reserve; ACR: LCR: At least 1SD below mean, HCR: At least 1 SD above mean.

### CRIq Psychometric Properties

The internal consistency reliability of CRIq was estimated using Cronbach's alpha. The index of internal consistency was 0.74 for the CT group (the alpha increased marginally to 0.75 if the item "Voluntary Work" was deleted), confirming a good reliability of the test when used to examine Portuguese women with breast cancer.

We also tested for concurrent validity using a measure of premorbid ability validated for the Portuguese population, TeLPI. A significantly positive correlation was found between the estimated IQ ( $\rho=0.49, p < 0.01$ ), estimated VIQ ( $\rho= 0.50, p<0.01$ ) and RIQ ( $\rho=0.45, p=0.01$ ) and the CRI-Education subscale in the CT group. No other significant correlation was found for TeLPI estimated IQ's and CRI-Working Activity or CRI-Leisure Time.

As expected, we also found a significant positive correlation between CRI-Education and Years of Education ( $\rho= 0,57, p < .001$ ) and between CRI-Working Activity and CRI-Leisure Time with age ( $\rho= 0,45, p= .009$ ;  $\rho= 0,54, p<0.01$ , respectively).

### Correlation between Cognitive Performance and Cognitive Reserve at baseline

Considering the relationship between the cognitive performance (using the neuropsychological tests) and cognitive reserve at baseline the following significant negative correlations were found (**Table 4**): TMT-A and CRI-Leisure Time ( $\rho = -0.42, p=0.01$ ), TMT BxA and CRI-Leisure Time ( $\rho = - 0.43, p= 0.02$ ), TMT B + A and CRI-Leisure Time ( $\rho = -0.43, p= 0.02$ ), Semantic Verbal Fluency (Animals) and CRI-Education ( $\rho = -0.36, p= 0.04$ ). A positive significant correlation was found between the Phonological Verbal Fluency (Letter R) and CRI-Leisure Time ( $\rho = 0.60, p < 0.01$ ).

## Differences between Baseline (M0) and M6

### - Cognitive Performance

Comparisons within the CT group for the neuropsychological measures over the time (M0 and M6) showed significant differences only on two derived scores of TMT, namely, the sum of A+B ( $Z = -2.25, p = 0.03$ ), and multiplication  $A \times B / 100$  ( $Z = -2.20, p = 0.03$ ) and on the Color Task of Color Word Stroop Test ( $Z = -2.04, p = 0.04$ ). Nevertheless, as shown in **Table 5**, these differences are due to an improvement in performance.

### - Cognitive Reserve (CRIq)

Since we did not observe any negative changes between both assessments, we analyzed CR as a protective factor on the development of cognitive impairment during chemotherapy. We started by analyzing the correlation between the cognitive status at M6 (through neuropsychological measures) with the subscales of CRIq. We did not find any significant correlation between these two variables at this timepoint.

In order to investigate if the level of cognitive reserve (high vs low) has influenced the performance in the subtests where an improvement was found (TMT sum A+B, TMT multiplication  $A \times B / 100$  and Color Task from the Color Word Stroop Test) we did the following analysis:

Considering the change in the neuropsychological performance a new variable called “Improvement” was created. Patients were classified in a dichotomous way depending on whether there has been an improvement in their performance from M0 to M6 or not.

For the cognitive reserve level, we calculated the mean (SD) of each CRIq subscale (for a reference on descriptive see **Table 2**) and compared individually each patient with this value, as described in the previously topic “Cognitive Reserve at baseline ( $\leq 1SD$  – Low CR;  $\geq 1SD$  – High CR;  $[1SD < M < 1 SD]$  - On Average).

The percentage of patients that improved in the neuropsychological tests is described in **Table 6**.

In TMT A+B, 68,8% of the clinical sample had a better performance on M6 and in TMT AxB/100 this value was of 65,5%. In both these measures, more than 50% of these patients showed a CR (in all subscales) at or above the mean. In the Color Task from the Stroop Test, 28,1% of the clinical sample had a better performance on M6 when compared with M0, and only 3,1% of this percentage had a lower cognitive reserve on 2 of the subscales of CRIq (CRI-Education, CRI-Working Activity).

**Table 4**

*Significant Correlations for CRIq Subscales and TMT-A, TMT(BXA), TMT (B+A/A), Verbal Fluency Animals and Letter R*

Variable	n	CRI-Education		CRI-Working Activity		CRI-Leisure Time	
		Rho	p-value	Rho	p-value	Rho	p-value
TMT -A	32	-	-	-	-	-0.41*	0.02
TMT (B x A)	32	-	-	-	-	-0.43*	0.02
TMT (B + A / A)	32	-	-	-	-	-0.43*	0.02
VF (Animals)	32	-0.40*	0.04*	-	-	-	-
VF (R)	32	-	-	-	-	0.60**	<0.01

*Abbreviations:* CRI = Cognitive Reserve Index (Questionnaire), TMT=Trail Making Test , VF = Verbal Fluency

*Note :* Significant Spearman Correlation = \* p<0.05 ; \*\* p<0.01

**Table 5.**

Comparison of the performance on neuropsychological measures at baseline and M6 for the CT group

		<i>M0</i>	<i>M6</i>	<i>Z</i>	<i>p-value</i>
Auditory Verbal Learning Test (AVLT)	Delayed Recall				
	<i>Mean (SD)</i>	11.25 (2.60)	11.97 (2.10)		
	<i>Median [IQR]</i>	12 [9.25,13]	12 [11, 14]	-1.89	0.59
	Total Learning				
	<i>Mean (SD)</i>	54.84 (7.40)	55.53 (7.40)		
	<i>Median [IQR]</i>	54 [51, 61.75]	56.50 [51, 61]	-0.70	0.48
	Learning Over Trail				
	<i>Mean (SD)</i>	17.5 (6.80)	18.81 (6.20)		
	<i>Median [IQR]</i>	16.50 [11.25, 22.75]	20 [14.30, 23.80]	-0.69	0.49
	Long Term Percent Retention				
	<i>Mean (SD)</i>	87.42 (16.90)	90.82 (13.48)		
	<i>Median [IQR]</i>	86.67 [75.89 ,100]	91.99 [83.30, 100]	-1.25	0.21
Recognition					
<i>Mean (SD)</i>	29.59 (0.76)	29.31 (1.10)			
<i>Median [IQR]</i>	30 [29, 30]	30 [29, 30]	-1.08	0.28	
Trail Making Test (TMT)	A				
	<i>Mean (SD)</i>	31.66 (6.00)	29.66 (6.72)		
	<i>Median [IQR]</i>	30.5 [28, 36]	28 [25, 31.80]	-1.72	0.96
	B				
	<i>Mean (SD)</i>	72.06 (19.70)	66.31 (15.20)		
	<i>Median [IQR]</i>	68 [60, 78.75]	66 [54, 74.50]	-1.91	0.56
	(B-A)				
	<i>Mean (SD)</i>	40.41(19.00)	36.7 (15.40)		
<i>Median [IQR]</i>	37 [29.50, 51]	36.50 [24.80, 47.80]	-1.21	0.22	

	(B/A)				
	<i>Mean (SD)</i>	2.33 (0.60)	2.3 (0.60)		
	<i>Median [IQR]</i>	2.35 [1.80, 2.88]	2.4 [1.80, 2.78]	-0.18	0.86
	(B-A/A)				
	<i>Mean (SD)</i>	1.33 (0.60)	1.3 (0.60)		
	<i>Median [IQR]</i>	1.35 [0.80, 1.88]	1.4 [0.80, 1.78]	-0.18	0.86
	(A+B)				
	<i>Mean (SD)</i>	103.7 (22.20)	95.97 (17.68)		
	<i>Median [IQR]</i>	100.5 [91, 111.25]	95,50 [83.3, 105.3]	-2.25	0.03*
	(AxB/100)				
	<i>Mean (SD)</i>	23.12 (9.1)	19.84 (7.07)		
	<i>Median [IQR]</i>	21.20 [17.28, 26.88]	18,12 [15.4, 23.3]	-2.20	0.03*
Color Word Stroop Test	Word				
	<i>Mean (SD)</i>	94.59 (12.23)	95.91 (11.88)		
	<i>Median [IQR]</i>	95 [85.75, 102.75]	95.50 [88.25, 102]	-1.43	0.15
	Color				
	<i>Mean (SD)</i>	68.81 (8.04)	66.63 (8.10)		
	<i>Median [IQR]</i>	68 [62.25, 72]	66 [61,71]	-2.04	0.04*
	Color Word				
	<i>Mean (SD)</i>	41.25 (8.70)	40.97 (8.16)		
	<i>Median [IQR]</i>	40 [37.25, 46.75]	40.50 [36.25, 46]	-0.96	0.49
	Interference				
	<i>Mean (SD)</i>	1.5 (8.19)	1.75 (6.80)		
	<i>Median [IQR]</i>	0.94 [-2.62, 7.42]	2.01 [-2.07, 6.69]	-0.99	0.3

Verbal Fluency (VF)	Animals				
	<i>Mean (SD)</i>	22.38 (4.90)	22.16 (4.68)		
	<i>Median [IQR]</i>	22 [18, 26.75]	22 [19, 25]	-0.39	0.70
	Letter M				
	<i>Mean (SD)</i>	12.22 (3.40)	12.74 (3.78)		
	<i>Median [IQR]</i>	12 [10, 14]	12 [10, 15]	-0.60	0.51
	Letter R				
	<i>Mean (SD)</i>	11.31 (3.50)	12.06 (3.25)		
	<i>Median [IQR]</i>	12 [9, 14]	12 [9, 14]	-1.14	0.25
	Letter P				
<i>Mean (SD)</i>	13.53 (3.50)	13.77 (4.33)			
<i>Median [IQR]</i>	3.54 [11, 16.50]	13 [11, 16]	-0.20	0.85	
Total					
<i>Mean (SD)</i>	37.06 (8.60)	38.58 (10.20)			
<i>Median [IQR]</i>	37.50 [29, 43.25]	38 [32, 44]	-1.01	0.31	
Digit Symbol	<i>Mean (SD)</i>	78.06 (12.20)	77.44 (13.87)		
	<i>Median [IQR]</i>	78 [68, 84]	76,50 [68, 86.25]	-0.38	0.70
Letter and Number Sequencing	<i>Mean (SD)</i>	9.94 (1.80)	9.59 (1.95)		
	<i>Median [IQR]</i>	10 [9, 11]	10 [9, 11]	-0.83	0.41

Abbreviations: Z= Wilcoxon Test

Notes: \* p<0.05

**Table 5.**

*Percentage of Participants who Improved from M0 to M6 distributed for each level of CR*

	CRI-Education			CRI-Working Activity			CRI-Leisure Time			Total <sup>1</sup>
	Low CR Average	On	High CR	Low CR Average	On	High CR	Low CR Average	On	High CR	
TMT - AxB/100	9,4	40,6	15,6	9,4	56,3	0	6,3	50	9,4	65,6
TMT - AB	12,5	40,6	15,6	9,4	59,4	0	6,3	53,1	9,4	68,8
Stroop C	3,1	15,6	9,4	3,1	18,8	6,3	0	25,0	3,1	28,1

Abbreviations: CR = Cognitive Reserve, CRI=Cognitive Reserve Index (questionnaire), TMT=Trail Making Test, C = Color  
<sup>1</sup> Total Percentage of Improvement

Note: All results are presented as Percentage

## 5. Discussion

CR has been identified as one of the possible predictors of cognitive functioning after the oncological treatments, especially, after chemotherapy (Vannorsdall, 2017). However, to date and as far as we know, there is not any study that considered a broader model of CR including more than one proxy simultaneously in the CRCI context. In fact, the most used CR assessment technique is related to the estimation of years of education and/or premorbid ability exclusively (Janelsins et al., 2018; Syarif, 2019; Amidi et al., 2015; Gonzalez et al., 2015; Lycke et al., 2016; Wouters et al., 2016). Having this in mind, the use of a more comprehensive model of CR assessment like the CRIq is extremely relevant on the context of CRCI. It should enable to determine not only if other sociobehavioral factors could interact with the development and severity of the cognitive changes observed after treatment, but also to identify other risk/protective factors for CRCI.

Because of that, one of the major aims of this study was to validate the CRIq, as a measure of cognitive reserve, in the oncological population (women with breast cancer).

In our study, the CRIq showed a good overall reliability (internal consistency) when used to assess Portuguese women with breast cancer.

We also analyzed the concurrent validity through the correlation with the estimated IQ's from TeLPI. A significant correlation was only found with the CRI-Education subscale score. Usually, pre-morbid IQ is used as a proxy of CR, however, contrarily to what could have been expected, our results did not prove it. This means that using premorbid ability as a proxy of cognitive reserve should not translate into a global measure of CR, and so that result should be interpreted carefully.

Additionally, we analyzed the association between years of education with CRIq, and as expected, the two variables were strongly correlated, namely, with CRI-Education. We

also verified a significant correlation of Age and CRI-Working Activity and CRI-Leisure Time. Since these two subscales are dependent on the years in which a profession or activity was performed (Nucci et al., 2012) it would be expected that as age increases, the score of these two scales would also increase.

The sample recruited in this study was not large enough to perform a factor analysis, to assess construct validity, and so we only analyzed reliability and concurrent validity.

CRCI is the currently term used to describe the cognitive difficulties that oncological patients experiencing during and after the treatments (Vannorsdall, 2017; Wefel et al., 2011) and there is a substantial evidence that these complaints are related with objective cognitive impairment (Ahles et al., 2018, Janelins et al., 2018). Up to 65% to 75% of patients develop changes in cognition during the treatment, especially in attention, executive functions, processing speed and memory that varies between mild to moderate in terms of severity (Pierre, 2010; Vannorsdall, 2017; Asher & Myers, 2015). That said, one of the major purposes of this study was to investigate the cognitive changes resulting from chemotherapy and so we assessed a sample of breast cancer patients before the start of the treatment and six months after this one started (Wefel et al., 2011).

At baseline, the breast cancer sample was compared with a healthy volunteers group equivalent in gender, age, and years of education, to establish if cognitive impairment was present (Wefel et al., 2011). The breast cancer sample recruited showed an overall high level of years of education, that it is not representative of the Portuguese population. In order to control this phenomenon, a group of volunteers matched for educational level and age, was recruited. The objective of this group was to assess the cognitive performance at baseline to ensure no cognitive impairment before treatment.

However, unlike other previous studies where 20% to 40% of the sample presented cognitive deficits before treatment (Vannorsdall, 2017; Wefel et al., 2014; Ahles et al. 2008), in our study the CT group presented a similar performance to the healthy volunteers on all neuropsychological measures, confirming no cognitive impairment pre-treatment.

We also assessed the breast cancer patients six months after the first evaluation and compared the performance between the two moments. The only significant differences found between this two moments were on the two derived scores from TMT (A+B and AxB/100) that provide indices of overall cognitive function and not only executive functioning (Cavaco et al., 2013) and in the performance of the Color Task from the Color Word Stroop Test. The differences found were due to an improvement on the cognitive performance and not due to an impairment, not confirming our first hypothesis proposed. Although this was not what we were expecting, there are other studies that also reported the lack of cognitive impairment after chemotherapy when compared to the performance pre-treatment (Hermelink et al., 2017; Jenkins et al., 2016).

We propose two possible scenarios for the results found. The first one is related with the limitations of neuropsychological tests, more precisely related with the practice effects and the second one is related with CR and will be explained forward on this discussion. The guidelines from the ICCTF recommended that longitudinal studies with repeated evaluations using objective measures should be conducted to detect changes in cognition throughout the whole treatment process (Wefel et al., 2011). However, a repeated administration of these tests has an associated practice effect (Cerulla et al., 2018). This represents a source of variability in test scores that are not attributable to a real change in the individual's cognition but that are instead due to learning the task. This effect has been already studied in CRCI, where significant improvements in a second (9 weeks) and

in a third (1 year) assessment moments were found not to be realistic, because, when these scores were corrected using appropriated statistical methods, most of the task's performances showed to be impaired (Cerulla et al.,2018). In a study carried by Cerrulla (2018), the tasks that showed a higher improvement between evaluations were essentially measures of executive functioning like the TMT and the Semantic Fluency, and also related to memory domain (i. e., the WAIS-III Logical Memory subtest and the Rey Complex Figure). We believe that our results may be due to a practice effects.

This is a problem when conducting longitudinal evaluations, and in this context where the deficits are so subtle, sometimes they can go unnoticed and be masked by limitations of the cognitive tasks (eg.: practice effects), especially when the sample size is not large.

As explained in the Literature Review section, CR has been identified as one of the possible predictors of cognitive functioning after the oncological treatments (Vannorsdall, 2017). However, CR construct can be expressed in two ways depending on whether a brain insult had occurred or not (Stern, 2002, 2009, Consentino & Stern, 2013). For healthy subjects, cognitive reserve is related with the execution of more complicated cognitive tasks using for that purpose preexisting neural networks. It is expected that an individual with a higher CR, will use more efficiently the neural networks when performing a cognitive task (Stern, 2002, 2009, Consentino & Stern, 2013).

Using CRIq, we assessed the level of cognitive reserve of our breast cancer sample and found that at least 60% of the sample presented a level of CR in or above the mean. We also found that CR is associated with some cognitive measures at baseline, proving that it is related with cognitive performance. The neuropsychological measures that were

more related with CR (TMT-A, TMT BxA, TMT B+A, Phonological Verbal Fluency Letter R) are more related with the executive function domain.

The fact that our sample had a level of CR mostly above the mean could explain the lack of impairment across all cognitive domains before chemotherapy. Nevertheless, previous studies have shown the presence of cognitive impairment is already before starting the oncological treatments (Wefel et al., 2014; Ahles et al., 2008) that are corroborated with neuroimaging reports where structural and functional brain differences were found (Vannorsdall, 2017).

Although the mechanism by which chemotherapy acts on cognitive functioning is not yet defined (Pierre, 2010), CR seems to play an important role in the cognitive changes reported so far. When a brain insult occurred, CR acts as a compensatory mechanism, i.e., alternative neural networks are recruited in order to compensate for the damage in the commonly used ones maintaining the normal cognitive functioning (Stern, 2002; Stern, 2009; Stern et al., 2020). For that, we studied the role of CR in the cognitive functioning during the treatment process.

In our breast cancer sample, we only evidence changes in some of the neuropsychological measures used at M6 (the sum TMT A+B, the multiplication  $A \times B / 100$  and the Color Task from Color Word Stroop Test) we still analyzed if cognitive functioning at this timepoint was related with CR. No significant correlation was found.

Notwithstanding, CR results from the combination of cognitive stimulant activities throughout the life span including those assessed by CRIq but also others (such as genetics, literacy, bilingualism, physical exercise), meaning that other factors contributing to CR can be more relevant at this phase of the treatment than the one's we assessed. Although CRIq is based on the definition of CR proposed by Stern (2002) (Nucci et al., 2012), the theoretical construct itself imposes several limitations on its

assessment and so subjective and indirect assessment approaches like the CRIq may not capture the global construct. As a result, the CR could not be related to the changes observed, not necessarily meaning that it is not relevant, but because there are other determinants that are more important at a given time than others.

Finally, and since the changes observed at M6 were due to an improvement in performance and not an impairment as expected, we analyzed if high levels of CR could be a protective factor and could consequently justify the improvements seen. The purpose of this subjective analysis was to verify if those who had improved during the treatment were also those with higher cognitive reserve, calling up to this model the concept of neural compensation.

For that, we classified the patients as having high, on average or low cognitive reserve and which of them showed a better performance between the first and second evaluations in the tasks where significant differences were found. More than 50% of the patients who showed improvements had a CR on average or higher (in all subscales) for the TMT derived scores (sum A+B and multiplication  $A \times B / 100$ ) and 25% of those who showed an improvement on the Color Task of the Color Word Stroop Test were also classified as having higher values of CR. So, although CR was not related with cognitive performance at this timepoint, we verified that the patients who improved had in fact a higher CR level. In this case, it appeared that CR is protecting these patients from developing cognitive deficits at M6, using, for that, alternative neural networks, to compensate the one's damaged indirectly by oncological treatments. This is the second explanatory scenario that could possibly justify for the results found when comparing cognitive performance at M0 and M6.

Despite the discussion of two possible scenarios for the lack of cognitive impairment found (practice effects and compensatory mechanism), these are not incompatible. Practice effects assumes that a certain improvement in performance could be explained by the previous exposures, since some tests are susceptible to learning (Duff, 2012). Cognitive reserve, and more precisely, neural reserve, postulates that individuals with higher levels of CR will solve tasks more efficiently and more capably, and so, learning the task is a way to do it better (Consentino & Stern, 2013). In our study, we cannot exclude the possibility that these two approaches, could have occurred simultaneously.

Generally, a higher level of CR would imply a better cognitive performance. However, in our study, the semantic verbal fluency (animals) task showed to be negatively correlated with the education subscale of CRIq, showing that more years of formal education were related with a lower production of words belonging to the animal category. This is not consistent with what is expected for this cognitive task, where more years of education should be related with a better performance (Cavaco et al., 2013). Nevertheless, a possible explanation would be that the scores were not adjusted for age, since some of the older participants have more years of education. As explained by Cavaco et al. (2013), it is expected that the older the person is, the less words it will be producing in one minute. Moreover, of the education distribution is not normal in our sample, with a great proportion of individuals with a tendency 17 years of education. As such, this is not a realistic correlation because there are not enough participants less educated to have a fair comparison between these two groups (more years of education vs less years of education).

## **5.1. Limitations**

The present study presents several limitations that could explain the unexpected results. The first and probably the major one is related with the sample size, since our clinical sample was small (N=32). Also, a recurrent issue in the clinical center where this sample was recruited, has to do with the fact that the population is highly educated therefore preventing a comparison between different levels of education and also not enabling to understand the impact of cognitive reserve in cognitive performance.

While we had included a cohort of healthy volunteers, comparisons could only be made at baseline, and not on follow-up assessments, as recommended by ICTFF (Wefel et al., 2011). Since the healthy volunteers only performed baseline assessment, was not possible to use statistical methods (e.g.: Reliable Change Index) to control for practice effects.

CRIq is a sociobehavioral questionnaire to measure CR; however, as already mentioned this scale does not represent the whole construct and this could have impacted the results found. Having studied other determinants of CR could have been useful to understand if some play a more important role in a given treatment time than the one's studied.

Lastly, we did not analyze or control the presence of affective disturbances that could also have impacted the cognitive complaints. An interaction between the cognitive performance and affective disturbances could better predict the direction and severity of CRI.

## **5.2. Further research direction**

Further developments should include increasing the clinical sample size and addressing other possible factors, like psychological distress. Also, it would be important to have a standardized sample including more representative education levels as well as balanced CR levels thus enabling more powerful statistically comparisons.

Future also comprises follow-up visits of the control group at the same timepoints of patients. This will be important not only to detect possible cognitive changes between the clinical group and the healthy group at the same timepoints, but also to control for normal cognitive status fluctuations and for practice effects.

Furthermore, although CRIq proved to be a relevant tool; in future studies, other CR assessment approaches should be addressed.

## **6. Conclusion**

Contrary to the evidence, our results do not demonstrate cognitive changes in the CT group before the treatment, suggesting that cognitive reserve may play an important role in cognitive functioning both in breast cancer patients and in healthy subjects.

We also verified, contrarily to what we expected, that there is no significant impairment between pre- and post-chemotherapy and that CR was not related to the cognitive status at this second point. However, we have seen that individuals with higher CR present better performances at the follow-up visit when compared to baseline. An improvement in this performance could be explained by two possible scenarios: the first is related with possible practice effects in neuropsychological tests, and the second presupposes that CR could play an important role in cognitive functioning.

As already mentioned, studying this aspect is extremally important due to the increasing number of cancer cases around the world. Identifying risk and protective factors, could help to prevent cognitive deficits and promote a better quality of life and healthy aging. CR could have an important role on the development of these changes, even if not detected.

CR is dependent on the cognitive stimulation throughout the lifespan and, even later in life, it is also possible to continue to recruit more efficient neural networks (Stern, 2017). This would mean that CR could be manipulated during chemotherapy treatments through

cognitive interventions in order to help patients maintaining their CR level, slowing age-related decline, prolonging a healthy aging and consequently promoting a better quality of life.

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# APÊNDICES

## INFORMAÇÃO SOBRE O ESTUDO E CONSENTIMENTO INFORMADO

Determinação de fatores preditivos de melhor adaptação ao Cancro da Mama:  
BOUNCE estudo clínico piloto multicêntrico - Estudo de Cognição

(CHAMP\_\_/\_\_\_\_)”

Cara participante,

O estudo previamente descrito de sigla BOUNCE (H2020-SC1-2016-2017) vai conduzir também um sub-estudo opcional para avaliação da sua **função cognitiva** no caso de receber tratamento de quimioterapia ou tratamento hormonal.

Para além da resposta aos questionários referidos do estudo BOUNCE terá um encontro em presença física com uma investigadora para a realização de testes neuropsicológicos, cujo objectivo é avaliar a função psicológica cognição, isto é, a forma como o cérebro percebe, aprende, memoriza e executa a informação. Os testes neuropsicológicos testam assim a nossa capacidade de atenção, memória, associação, raciocínio e linguagem.

O tempo que terá que dispor para esta avaliação será de 90 minutos, em 3 momentos diferentes: 1) antes do início de qualquer tratamento de quimioterapia ou hormonoterapia; 2) após 6 meses da primeira avaliação; 3) após 1 ano da primeira avaliação.

No caso de participar no estudo da cognição, poderá também participar no sub-estudo de reserva cognitiva, definida como a capacidade cognitiva adquirida ao longo da vida. Esta, é assim uma medida, da capacidade que o cérebro tem, em lidar com uma alteração cerebral. Pretende-se neste estudo testar a capacidade de um questionário chamado CRIq (*Cognitive Reserve Index Questionnaire*), para a medição da reserva cognitiva.

Este é um estudo voluntário, que consistirá numa entrevista com uma neuropsicóloga, com duração máxima de 30 minutos.

### CONTACTOS PARA MAIS INFORMAÇÕES

Os investigadores principais pelo estudo são a Prof. Dr. Albino Oliveira Maia, Dr.<sup>a</sup> Fátima Cardoso e a Dr.<sup>a</sup> Berta Sousa.

Poderá contactar para o telefone ou via email caso necessite de mais informações sobre este estudo antes de decidir participar e/ou durante o seu curso se tiver alguma dúvida:

- Berta Sousa, ([berta.sousa@fundacaochampalimaud.pt](mailto:berta.sousa@fundacaochampalimaud.pt)), Tel: 210480048
- Contacto da unidade de investigação: Susan Valerio e Diana Frasilho: ([beatriz.costa@research.fchampalimaud.org](mailto:beatriz.costa@research.fchampalimaud.org)[diana.frasquilho@research.fchampalimaud.org](mailto:diana.frasquilho@research.fchampalimaud.org)), Tel: 210480048

## CONSENTIMENTO INFORMADO

Li este consentimento informado e confirmo que me foi dada oportunidade para discutir cada aspecto do *Estudo de cognição* com os responsáveis do estudo, que estes se mostraram disponíveis para me fornecer qualquer informação adicional necessária. Compreendo que a minha participação é voluntária. Fui suficientemente informada sobre os objetivos e métodos de investigação e estou capaz de decidir de forma livre e voluntária a minha participação neste estudo. Compreendo que posso decidir livremente e descontinuar a minha participação no estudo a qualquer momento. Recebi uma cópia do consentimento informado, assinada e datada.

Autorizo a utilização de amostras de material biológico (sangue e plasma), para o projectos de investigação que tentam entender os mecanismos pelos quais a cognição poderá estar afectada no decurso de tratamentos oncológicos e seguimento da doença.

Sim\_\_\_ Não\_\_\_\_\_

NOME E APELIDO DO PARTICIPANTE (em letras maiúsculas)

\_\_\_\_\_

ASSINATURA DO PARTICIPANTE:

\_\_\_\_\_

Data: \_\_\_\_\_

NOME E APELIDO DO INVESTIGADOR (em letras maiúsculas)

\_\_\_\_\_

ASSINATURA DO INVESTIGADOR

\_\_\_\_\_

Data: \_\_\_\_\_



Prof. Doutor José Manuel Cardoso da Costa (Presidente)  
Prof. Doutor Adelino Cardoso  
Prof. Doutor André Valente  
Prof. Doutor António Jacinto  
Prof. Doutor António Parreira  
Profª. Doutora Isabel Palmeirim  
Profª. Doutora Isabel Pavão Martins  
Prof. Doutor José Cunha Vaz  
Profª. Doutora Leonor Parreira  
Prof. Doutor Mário Miguel Rosa  
Dra. Paula Martinho da Silva

## Fundação Champalimaud

Lisboa, 02 de Fevereiro de 2021

### **Aprovado – Approved**

**Projeto: BOUNCE – Dra. Berta Sousa, Dra. Fátima Cardoso e Prof. Albino Oliveira-Maia.** "Predicting Effective Adaptation to Breast Cancer to Help Women to BOUNCE Back: a multicentre clinical pilot study."

Após análise dos documentos que servem de base à emenda ao projeto, a Comissão de Ética aprovou a mesma, sem objeções éticas, de acordo com os pareceres do Prof. Dr. Mário Miguel Rosa e da Dra. Paula Martinho da Silva.

O Presidente da Comissão de Ética,  
*The President of the Ethics Committee,*

Prof. Dr. José Manuel M. Cardoso da Costa, J.D.