NEUROCOGNITIVE FUNCTION DEFICITS AND THE ASSOCIATED BRAIN NETWORKS IN PATIENTS WITH GYNECOLOGICAL CANCER

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Neurocognitive Function Deficits and the Associated Brain Networks in Patients with Gynecological Cancer

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CERTIFICATE OF ORIGNIALITY

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ABSTRACT

Objectives: The objectives of this study were (1) to explore Chinese gynecological cancer patients' perceived neurocognitive complaints and relevant supportive care needs after primary cancer treatment; (2) to assess neurocognitive functioning, structural and functional brain networks in Chinese gynecological cancer patients pre- and post-chemotherapy; (3) to examine the possible neural mechanism of neurocognitive function deficits in gynecological cancer patients.

Methods: This study was divided into two parts (mixed qualitative and quantitative study components) and three study stages. The first stage of this study used a qualitative approach to explore neuropsychological issues among Chinese gynecological cancer patients. Based on the first stage findings, the study's second stage adopted a longitudinal approach to detect neurocognitive function deficits of gynecological cancer patients, and functional brain network changes in Chinese gynecological cancer patients at pre- and post-chemotherapy, while additionally including age-matched healthy subjects as the control group. In order to explore the possible neurobiological basis of CRCI, the final study stage used a multimodal magnetic resonance imaging approach to assess changes in brain networks, and neurochemical properties of patients pre- and post-chemotherapy.

Results: A total of 31 gynecological cancer patients were recruited in the qualitative study stage. Of that total, 20 women (64.5%) reported cognitive complaints after cancer treatment. The most common neurocognitive complaint was loss of concentration (n=17, 85.0%). Perceived contributing factors to these neurocognitive complaints included chemotherapy (n=15, 75.0%), and aging (n=8, 40.0%). These cognitive problems most commonly impacted daily living (n=20, 100%). The findings of first study stage indicated that cognitive complaints and neuropsychological problems have greatly impacted these women's daily lives, social functioning and quality of life. Hence, the second study stage focused on the detection of neuropsychological problems in gynecological cancer patients. This study stage recruited 40 subjects, with 20 subjects in each group (gynecological cancer patients versus healthy

controls). Results of the second study stage found that 35% of patients had mild neurocognitive function deficits at the time of cancer diagnosis, and neuropsychological measures were significantly associated with functional brain networks. During the post-chemotherapy assessment, there were significant differences in the mean scores of neurocognitive tests (including digit span tests, verbal memory, and psychomotor speed tests) (all Ps < 0 .05). Longitudinal graph analysis revealed statistically significant differences in the patient group, with significant decreases in both local efficiency ($P < 0.01$) and global efficiency ($P = 0.04$). Lower raw TMT-A scores were significantly associated with lower local efficiency ($r = 0.37$, $P = 0.03$). Lower verbal memory scores were statistically significant and associated with lower global efficiency ($r = 0.54$, $P = 0.02$) in the patient group, but not in the healthy control group. Using magnetic resonance spectroscopy in the final study stage, there was a significant decrease of relative concentration in NAA (N-acetylaspartate) in the patient group, in comparison with healthy controls. Diffusion tensor imaging data indicated that the global and local connectome properties in the patient group were lower than in the healthy controls. Hence, on a microstructural level, the possible underlying mechanism of CRCI may be attributed to an increase in demyelination and a reduction of the neuronal viability of white matter in the hippocampus.

Conclusions: This study demonstrated there is a growing body of research on neurocognitive complaints in women with gynecological cancer. The qualitative part of this study improved understanding of neurocognitive complaints, which could subsequently facilitate the development of relevant therapeutic interventions for the prevention of neurocognitive function deficits in this study population. The quantitative part of this study found that the risk of functional brain networks and neurocognitive function changes following chemotherapy could potentially guide patients in making appropriate treatment decisions, and help healthcare professionals prioritize patients for early intervention. By using a multimodal imaging approach, the quantitative study also provides novel insights into the neurobiological basis of neurocognitive function deficits in the human brain that have been induced by cancer and/or its treatment.

PUBLICATIONS ARISING FROM THE THESIS

- **Zeng YC,** Cheng ASK, Song T, Sheng XJ, Wang SJ, Qiu YW, Xie JH & Chan CCH. (2018). Changes in functional brain networks and neurocognitive functions in Chinese gynecological cancer patients after chemotherapy: a prospective longitudinal study. *Brain Imaging and Behavior*, (1st revision under review).

- **Zeng YC**, Cheng ASK, Song T, Sheng XJ, Wang SJ, Xie JH & Chan CCH. (2018). Effects of acupuncture on cancer-related cognitive impairment in Chinese gynecological cancer patients: A pilot cohort study. *Integrative Cancer Therapies*, 17(3):737-746.

- **Zeng YC**, Cheng ASK, Song T, Sheng XJ, Zhang Y, Liu XY & Chan CCH. (2017). Cognitive complaints and brain structural networks in Chinese gynaecological cancer survivors compared with age-matched controls: A cross-sectional study. *BMC Cancer*, 17: 796.

- **Zeng YC**, Cheng ASK, Liu XY & Chan CCH. (2017). Cognitive complaints and supportive care needs in Chinese cervical cancer survivors: a qualitative study. *BMJ Open*, 7(6): e014078.

- **Zeng YC**, Cheng ASK, & Chan CCH. (2016). Meta-analysis of the effects of neuropsychological interventions on cognitive function in non-central nervous system cancer survivors. *Integrative Cancer Therapies*, 15(4): 424-434.

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- **Zeng YC**, Cheng ASK, Liu XY & Chan CCH. The annual meeting of Chinese Psychosocial Oncology Academic Committee, organized by Chinese Psychosocial Oncology Society. On June 17-19 2016, Changsha, China. (Poster presentation)

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LIST OF ABBREVIATIONS

AD: Axial Diffusivity

AVLT: Auditory Verbal Learning Test

Cho: Choline

COWA: Controlled Oral Word Association

Cr: Creatine

CRCI: Cancer-Related Cognitive Impairment

DTI: Diffusion Tensor Imaging

EPI: Echo-Planar Imaging

FA: Fractional Anisotropy

FACT-Cog: Functional Assessment of Cancer Therapy-Cognitive Function

GRETNA: Graph Theoretical Network Analysis

HADS: Hospital Anxiety and Depression Scale

MD: Mean Diffusivity

MRI: Magnetic Resonance Imaging

MRS: Magnetic Resonance Spectroscopy

NAA: N-acetylaspartate

PANDA: Pipeline Toolbox for Analyzing Brain Diffusion Images

RD: Radial Diffusivity

RS-fMRI: Resting State-Functional Magnetic Resonance Imaging

TMT: Trail Making Test

CHAPTER 1

Introduction

1.1 Gynecological Cancer and Neurocognitive Problems

Gynecological cancers, as a group of cervical, uterus, ovary, vaginal and vulvar cancers, are the third most common cancers in Chinese women, followed by breast and lung cancer (Chen et al. 2018). Due to medical technology advancements and the possibility of curative treatment, such as surgery, radiotherapy, chemotherapy and targeted therapies (Lange et al. 2014), the five-year relative survival rate of cancer survivors was 67%, and for gynecologic cancer patients that figure ranges from 46% to 82% (Siegel et al. 2018). As more gynecological cancer patients live longer after curative treatment, long-term or late effects of cancer and its treatment are more commonly seen in cancer survivors (Treanor et al. 2014). One such long-term and late effect is neurocognitive function deficits, which have emerged as a significant problem affecting gynecological cancer survivors (Craig et al. 2014; Faubion et al. 2015).

Cognitive impairment often refers to chemotherapy-related cognitive dysfunction, colloquially named chemo brain or chemo fog (Wefel and Schagen 2012; Hines et al. 2014). Recent studies have indicated that cancer itself may also contribute to cognitive dysfunction, so that cancer-related cognitive impairment is also described as a neurocognitive function deficit (Janelsins et al. 2014; Wefel et al. 2015). The prevalence of cognitive problems can be detected in approximately 40% of cancer patients prior to any cancer treatment, with up to 75% of patients reporting some form of cognitive impairment during cancer treatment. Cognitive problems remain present in up to 60% of patients many years following treatment completion (Wefel et al. 2015; Vannorsdall 2017). Although very few studies explore the prevalence and impact of neurocognitive function deficits among gynecological cancer survivors, one study found that 69% of ovarian cancer survivors reported neurocognitive function deficits (Stavraka et al. 2012). Domains of neurocognitive function deficits may affect memory, concentration, information processing speed and executive function (Joly et

al. 2015). Neurocognitive function deficits have the potential to significantly impact social and occupational functioning, interfering with the ability to carry out normal activities of daily living, leading to lower quality of life in cancer survivors (Correa and Hess 2012; Craig et al. 2014; Wefel et al. 2015).

Neurocognitive function deficits may be related to a number of psychological factors that are seldom investigated in the context of gynecological cancer (Cheung et al. 2012; Ganz et al. 2013). Psychological distress has been found to be negatively associated with neuropsychological performance in cancer patients (Amidi et al. 2015; Ganz et al. 2013). Research has also found that perceived cancer-related fatigue and anxiety results in neurocognitive function deficits in cancer patients (Ganz et al. 2013; Menning et al. 2015). Furthermore, treatment-related mood changes, such as depression, have also significantly influenced many cancer patients' cognitive functioning (Ganz et al. 2013; Janelsins et al. 2017).

1.2 Neuroimaging Studies in Neurocognitive Function Deficits

Advanced neuroimaging studies in cancer patients provide a better understanding of neurocognitive dysfunctions after cancer treatment (Deprez et al. 2018). There is accumulating evidence to support that CRCI is a pathophysiologic process (Gehring et al. 2012; Craig et al. 2014; Dietrich et al. 2015). Previous neuroimaging studies have indicated that changes in brain structure and function are correlated with neurocognitive functioning in gynecological cancer patients (Correa et al. 2017; Zeng et al. 2017). While multiple neuroimaging studies have demonstrated structural and functional brain differences between cancer patients and healthy controls (Vannorsdall 2017), abnormalities in brain function usually appear before alterations in brain structure and clinical performance (Mayeux 2010).

Therefore, detecting alterations in functional brain networks might provide an earlier biomarker for neurocognitive function deficit diagnosis (Cheng et al. 2017).

Functional magnetic resonance imaging (fMRI) studies have shown that quantitative neuroimaging techniques, in combination with neurocognitive assessment, can be useful in advancing our understanding of treatment-induced neurocognitive dysfunctions in cancer patients (Correa et al. 2017; Kesler et al. 2017a,b). Resting-state functional MRI (rs-fMRI) is a noninvasive neuroimaging technique that measures spontaneous brain activity (Fox and Raichle 2007). Rs-fMRI does not require participants to engage in any cognitive activity, therefore providing unique advantages for clinical research studies (Kelly et al. 2012; Shen et al. 2015). Rs-fMRI studies show consistent evidence that resting state brain networks are correlated with cognitive function in cancer patients (Bruno et al. 2012; Kesler et al. 2013; Miao et al. 2016). Bruno et al. (2012) reported that cancer treatment has negative effects on the functional brain networks of cancer patients. Other studies have also confirmed the role of functional disconnection of brain default mode networks in neurocognitive function deficits (Kesler et al. 2013; Miao et al. 2016). Hence, utilizing a network analysis of rs-fMRI data, and linked neurocognitive changes with functional brain networks in cancer patients, would be promising to address the issue of interest in the present study.

Structural imaging modalities have also been utilized to assess cognitive functioning in gynecological cancer survivors (Craig et al. 2014). Overall, the decrease in gray matter volume, reduced white matter integrity, as well as altered brain activation, were observed several months to years following cancer treatment, and were generally associated with cognitive impairment (Janelsins et al. 2014; Dietrich et al. 2015; Joly et al. 2015). Although structural imaging studies documented reductions in brain volume related to cognitive impairment in cancer survivors (Gehring et al. 2012; Nelson and Suls 2013), these studies could not determine whether these changes represented dehydration, edema, or neural

degeneration (McDonald et al. 2010; Nelson and Suls 2013). In recent years, diffusion tensor imaging (DTI) has been able to characterize water diffusion and microstructure in biological tissues, especially for decreased white matter integrity and diffusivity (Deprez et al. 2011; de Ruiter et al. 2012; Nelson and Suls 2013). Using magnetic resonance DTI could also identify degradation of neural structures, and determine whether axonal death and/or deterioration of the myelin sheath are involved (Nelson and Suls 2013). However, the DTI could not provide information about the underlying mechanism of neural degeneration, or quantify these changes varying with different types of cancer and their treatment (Nelson and Suls 2013). More recent research has also reported that chemotherapy has negative effects on the structural brain networks of cancer patients (Amidi et al. 2017).

Magnetic resonance spectroscopy (MRS) is an imaging technique that can provide further insight into certain pathophysiologic mechanisms, whether it is white matter changes representing inflammation or axonal death, by detecting changes in brain metabolites, specifically Nacetylaspartate (NAA) (de Ruiter et al. 2012; Kelser et al. 2013; Nelson and Suls 2013; Wefel et al. 2015). Using MRS scanning, one study found that reductions in NAA are consistent with axonal degeneration (de Ruiter et al. 2012). While multimodal neuroimaging research offers significant insight regarding the neural mechanisms underlying neurocognitive function deficits, neuroimaging is not currently part of the clinical standard of care for cancer (Wefel et al. 2015). In addition, the ultimate goal of obtaining imaging biomarkers that closely reflect specific pathological features (e.g. neural degeneration leading to cognitive decline) has not yet been achieved (De Stefano and Giorgio 2015).

The majority of neuroimaging studies on the neurocognitive functioning of patients treated with chemotherapy for non-central nervous system cancers have been conducted on breast cancer patients (Cheng et al. 2017; Kesler et al. 2017b). Limited neuroimaging studies have

been conducted on patients with gynecological cancer (Hess et al. 2010; Hess et al. 2015; Correa et al. 2017; Zeng et al. 2017). Given the poor understanding of the impacts of cancer on neurocognitive function and brain networks in gynecological cancer patients, it is important to explore the neurocognitive changes and brain network alterations in this population. Therefore, there is a need for empirical studies to determine the onset of neural degeneration and identify potential imaging biomarkers for cancer patients at risk for neurocognitive function deficits; and then, there is a need to design prevention strategies.

1.3 Study Objectives

The objectives of this study were to explore the neurocognitive function deficits of gynecological cancer patients pre- and post-chemotherapy, and to examine the possible neural mechanism of neurocognitive function deficits in this study population. Neurocognitive function deficits in this study are defined as the experience of symptoms related to memory loss, decreased ability to concentrate, decline in executive functioning (planning, sustained attention, and problem solving), and difficulty in multitasking (Vannorsdall 2017). The specific aims of study Stage 1 were to explore Chinese gynecological cancer patients' perceived cognitive complaints and relevant supportive care needs after primary cancer treatment. The specific aims of study Stage 2 were to assess neurocognitive functioning and functional brain networks in Chinese gynecological cancer patients pre- and post-chemotherapy. The specific aims of study Stage 3 were to examine the possible underlying neurobiological mechanisms of neurocognitive function deficits in gynecological cancer patients.

1.4 Thesis Outline

This thesis consists of seven chapters. Chapter 1 presents the general study background and objectives. Chapter 2 is a literature review of neuropsychological interventions for gynecological cancer survivors. Due to limited interventions conducted for this study population, this thesis expanded the literature search into all non-central nervous system cancer survivors. Although this literature review indicates that cognitive rehabilitation and cognitive training may be effective in reducing neurocognitive function deficits in cancer survivors, the underlying mechanism of neurocognitive function deficits remains unclear, and there is a lack of a specific theoretical framework for investigating neurocognitive function deficits among gynecological cancer survivors. Thus, a qualitative research study has been conducted to establish a theoretical framework specific to this study population. The prospective longitudinal quantitative study undertook the detection of the possible early predictors of neurocognitive function deficits in gynecological cancer patients, and a multimodal MRI study followed to explore the underlying neural mechanisms of neurocognitive function deficits in Chinese gynecological cancer patients. Accordingly, Chapter 3 of this thesis reports the methods of these three study stages. Chapter 4 reports the findings or results of these three study stages, Chapter 5 reports the discussion and limitations of these three study stages, Chapter 6 presents the general implications of the study findings, and concludes this PhD thesis.

CHAPTER 2

Literature Review

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2.1 Introduction

Due to medical technology advances, coupled with earlier detection of cancer, survival rates for cancer patients have improved significantly. The five-year relative survival rate from all cancer sites is 68% (Siegel et al. 2015). Globally, 32.6 million people are cancer survivors (Torre et al. 2015). As cancer survival rates increase, neurocognitive function deficits have emerged as a significant problem affecting survivors (Alvarez et al. 2013; Denlinger et al. 2014). The prevalence of neurocognitive function deficits for cancer survivors was up to 75% both during and after treatment (Wefel and Schagen 2012; Vannorsdall 2017), particularly affecting attention, memory, executive function, and information processing speed (Janelsins et al. 2014; Treanor et al. 2014; King and Green 2015).

Increasing research evidence shows that neurocognitive function deficits were associated with having cancer, as well as with cancer treatment (Cimprich et al. 2010; Schuurs and Green 2013). There is an accumulating body of evidence suggesting that cancer patients could suffer cognitive impairment, even before systematic treatment begins (Schuurs and Green 2013; Mandelblatt et al. 2014). In addition, there are accumulating published studies showing that cancer treatments, particularly chemotherapy, could influence the cognitive function of cancer survivors upwards of months, to even years (Schuurs and Green 2013; Wefel et al. 2010). These cognitive impairments could exert a significant impact on social and occupational functioning, interfering with the ability to carry out normal daily activities, all of which in turn contributes to lower quality of life for cancer survivors (Craig et al. 2014; Kesler et al. 2013; Wefel et al. 2015).

There are limited pharmacological treatment approaches for the management of cognitive impairment, and it is noted that pharmacological treatments often have side effects (King and Green 2015; Gehring et al. 2012). Cognitive rehabilitation support and

neuropsychological modulation strategies are an increasingly common approach to supporting cancer survivors (Alvarez et al. 2013; Hofmann et al. 2012). One review by Gehring and colleagues (2012) comprehensively examined a range of pharmacological and non-pharmacological interventions for cancer-related cognitive deficits. Hines et al. (2014) conducted a systematic review focusing on the effectiveness of psychosocial interventions for chemotherapy-related cognitive dysfunction. However, both articles only reviewed relevant intervention studies published during or prior to 2011. According to King and Green (2015), many studies related to psychological interventions for cognitive dysfunction among adult cancer patients following treatment were published after 2012. Therefore, this chapter aimed to quantitatively evaluate the most recent studies on the effects of neuropsychological interventions on gynecological cancer survivors' cognitive function, and to identify implications for future research. Due to very limited studies in this target study population, this chapter expanded to review the effects of neuropsychological interventions on cognitive functions of patients with non-central nervous system tumors.

2.2 Methods

Data sources and searches

Three databases (PubMed, PsycInfo, and CAJ Full-text Database) were searched from January 2010 to September 2015, including articles published in both English and Chinese. The search terms included a combination of neuropsycholog*, cognit*, neurocognit*, neurobehavior*, intervention*, rehabilitation, trial, cancer, and cancer survivors. Searches were limited to adult human studies.

Study and participant types

Studies were eligible for inclusion if they were controlled clinical trials including randomized controlled trials and clinical trials without randomization, which addressed the effects of neuropsychological interventions on the cognitive function of individuals with cancer. Inclusion criteria comprised (1) patients diagnosed with primary cancer during adulthood-onset (aged 18 years or older), because patient-reported cognitive function measures for childhood-cancer survivors differ from adult measures (Gehring et al. 2008); and (2) with a non-brain or non-central nervous system (CNS) tumor, as a brain or CNS tumor can directly impact the brain, and thus the cognitive processes, of cancer survivors (Gehring et al. 2010). Exclusion criteria included patients diagnosed with primary cancer during childhood-onset (aged 18 years or younger), and with a brain or CNS tumor, as there were existing reviews focused on brain tumors or other CNS tumor (Gehring et al. 2010; Gross-King et al. 2010).

Types of interventions and outcome measures

Studies were included if they used any type of neuropsychological interventions aimed at the improvement of cognitive function in cancer survivors. The primary outcome was cognitive function by subjective and/or objective cognition outcome measures. Secondary outcomes included any adverse effects as a result of neuropsychological interventions.

Data extraction and assessment of bias risk

For each study, data was independently extracted from the original paper by one of the main researchers, and then verified by the second researcher. Any disagreements on data extraction were resolved by discussion among the research team members. The Cochrane Risk of Bias Assessment Tool was used to evaluate the risk of bias of the included trials. This assessment tool consists of seven domains: random sequence generation, allocation

concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases (Higgins and Green 2011). Each domain was carefully assessed as to whether it had low, high or unclear risk of bias in accordance with the judgment criteria.

Data synthesis and analysis

Data were synthesized and analyzed using the Cochrane Collaboration's Review Manager (RevMan 5.3) (The Cochrane Collaboration 2014). The heterogeneity of included trials was assessed using Chi-square and I^2 statistics, and a Chi-square of P-value greater than 0.1 or an I^2 value of less than 50% was considered to be indicative of statistical homogeneity (Higgins and Green 2011). The random-effects model was used to combine statistically heterogeneous clinical trials, whereas the fixed effects model was used to combine statistically homogeneous trials (Higgins and Green 2011). For the effects of intervention on cognitive function, weighted mean difference (WMD) was calculated when cognitive function outcomes were measured using the same scale, and the standardized mean difference (SMD) was used when different scales were used to measure cognitive functions among different trials, with corresponding 95% confidence intervals (CI) (Higgins and Green 2011). Data pooling in this meta-analysis was performed for the effects of neuropsychological interventions by subjective and objective outcome measures.

2.3 Results

Description of included trials

The flow diagram of the literature search process is given in Figure 2.1. A total of 10 trials (Alvarez et al. 2013; King and Green 2015; Schuurs and Green 2013; Kesler et al. 2013;

Cherrier et al. 2013; Ercoli et al. 2015; Ferguson et al. 2012; Goedendorp et al. 2014; McDougall et al. 2011; Von Ah et al. 2012) were included in this meta-analysis.

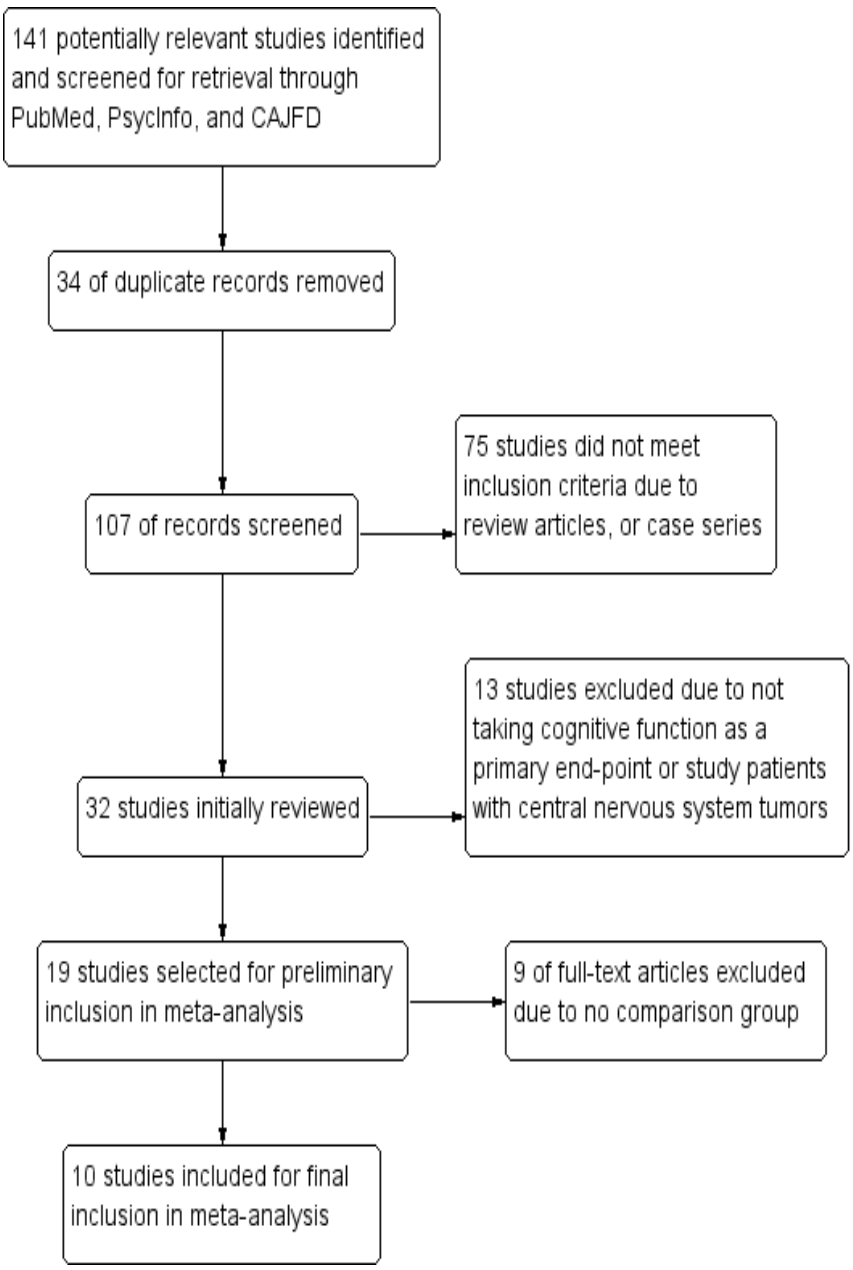

Figure 2.1 Study flow diagram of literature search

Table 2.1 summarizes the characteristics of these trials. Each trial was evaluated in terms of its risk of bias, and the overall bias risk is shown in Figure 2.2. Of these 10 studies, seven studies (King and Green 2015; Kesler et al. 2013; Cherrier et al. 2013; Ercoli et al. 2015; Ferguson et al. 2012; Goedendorp et al. 2014; Von Ah et al. 2012) were randomized trials. Three studies (Alvarez et al. 2013; Schuurs and Green 2013; McDougall et al. 2011) were case-control designs, leading to a high risk of bias for random sequence generation and allocation concealment.

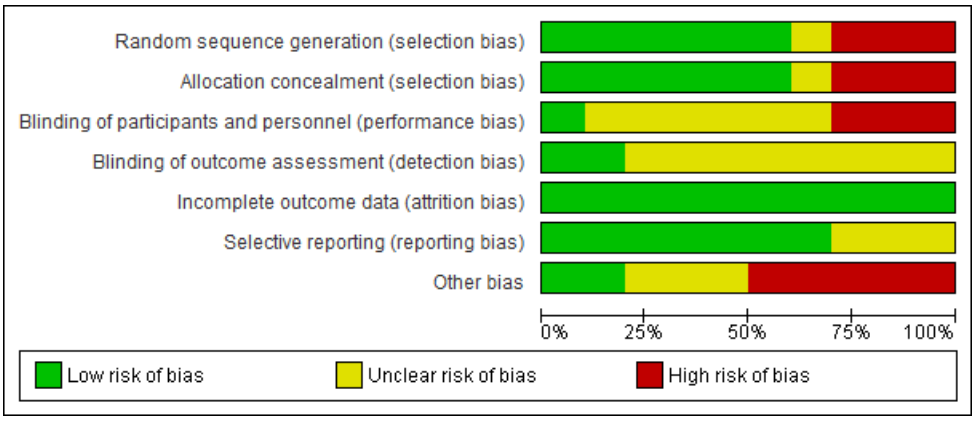

Figure 2.2 Overall risk of bias assessment using the Cochrane tool

Measurements of neurocognitive function deficits

From Table 2.1, there are subjective cognitive measures and objective neurocognitive tests. The most common subjective cognitive measures include FACT-Cog (Functional Assessment of Cancer Therapy-Cognitive Function) and MASQ (Multiple Ability Self-report Questionnaire). Common objective measures include brain imaging via qEEG and formal neurocognitive tests, such as verbal learning tests by RBANS (Repeatable Battery for Neuropsychological Status), RAVLT (Rey Auditory Verbal Learning Test), CVLT (California Verbal Learning Test), or HVLT-R (Hopkins Verbal Learning Test-Revised), Trial Making Test, Digit Symbol, and Digit Span. These neurocognitive tests were applied to measure participants' attention, verbal and visual memory, executive function and

information processing speed. In terms of interventions, one study (Alvarez et al. 2013) used a neuro-modulation intervention by EEG neuro-feedback for breast cancer survivors. Three studies (Kesler et al. 2013; McDougall et al. 2011; Von Ah et al. 2012) made use of cognitive training interventions. Six studies (King and Green 2015; Kesler et al. 2013; Cherrier et al. 2013; Ercoli et al. 2015; Ferguson et al. 2012; Goedendorp et al. 2014) used cognitive rehabilitation interventions, mainly delivering interventions in a group format. Intervention duration ranged from four weeks to six months (Table 2.1).

Table 2.1 Characteristics of 10 included studies in literature review

Authors (Year)	Design	Study Sample	Study Interventions	Outcome Measures for Cognition	Main Findings and Conclusion
Alvarez et al (2013)	CCT	23 female breast cancer survivors, aged 40 years or older, and with 6-60 months posttreatment	10-week (20 sessions) whole brain EEG neurofeedback training regimen vs normative sample	Subjective measure: FACT-Cog	Study revealed strongly significant improvements on 4 domains of FACT-Cog (P <0 .01)
Cherrier et al (2013)	RCT	28 female and male non-CNS cancer survivors, with a mean age of 60.5 years and with a median of 3 years posttreatment	7-week cognitive rehabilitation intervention vs waitlist control	Subjective measure: FACT-Cog Objective measure: RAVLT for verbal memory; Stroop Trial for executive function; Digit Symbol and Digit Span for attention	The treatment group demonstrated improvements in symptoms of PCI, PCA, and overall impact of quality of life related to cognitive symptoms (P < 0.01). This group also improved on objective measures of attention (P <0 .05)
Ercoli et al (2015)	RCT	48 female breast cancer survivors with a mean age of 54.5 years and	5-week group-based interventions included psychoeducation and	Subjective measure: PAOFI; Objective measure:	The cognitive rehabilitation group improved significantly on PAOFI total and memory score (both P =0 .01), and on

		with 18 months to 5 years posttreatment	cognitive exercises vs waitlist control	RAVLT for verbal memory	RAVLT total trials (*P* = .02) and delayed recall scores (P <0 .01). On qEEG, this group also showed a decreased in delta "slow wave" power and alpha power (both P <0 .05)
Ferguson et al (2012)	RCT	40 female breast cancer survivors, with a mean age of 50 years and after chemotherapy	8-week CBT intervention focused on memory and attention adaptation training vs waitlist control	Subjective measure: MASQ; Objective measure: CVLT for verbal memory; Digit Symbol for attention; Trail Making Number-Letter trial for executive function	The intervention group made significant improvements on verbal memory, but no statistical significance on self-reported cognitive complaints
Goedendorp et al (2014)	RCT	98 female and male non-CNS cancer survivors, with a mean age of 44.6 years old, and with at least 1 year posttreatment	6-month CBT intervention focused on memory and attention adaptation training vs waitlist control	Subjective measure: CIS-Concentration; Objective measure: Digit Symbol for attention; Reaction Time Task for speed of information processing	The CBT group reported significantly less cognitive disability. CBT also was associates with a clinically relevant reduction in concentration problems, but no significant differences in objective cognitive tests
Kesler et al (2013)	RCT	41 female breast cancer survivors, with a mean age of 55 years and experiencing long-term cognitive deficits	12-week online, home-based cognitive training program vs waitlist control	Subjective measure: BRIEF; Objective measure: HVLT-R for verbal memory; WCST for language; Digit Span for attention	Cognitive training led to significant improvements in cognitive flexibility, verbal fluency and processing speed, and self-rating executive function skills

King and Green (2015)	RCT	29 female and male non-CNS cancer survivors, with a mean age of 50.4 years and completed major treatment at least 6 months	4-week cognitive rehabilitation program for adults recovering from cancer vs waitlist control vs normative sample	Subjective measure: FACT-Cog; Objective measure: RBANS for immediate and delayed memory; TMT for attention and executive function	Participating in the intervention was associated with significantly faster performance on one objective cognitive task that measures processing speed and visual scanning. The intervention group also reported improvement on subjective measures of cognitive impairment and cognitive self-efficacy
McDougall et al (2011)	CCT	22 female and male non-CNS older cancer survivors, with a mean age of 73.86 years and experienced treatment-induced memory impairments	Memory intervention vs health training intervention over a 2-year period	Subjective measure: MSEQ and MIA; Objective measure: HVLT-R for verbal memory; VMT-R for visual memory	The memory intervention group tended to improve more than the health training group in daily verbal memory performance scores, memory self-efficacy, strategy use and memory complaints
Schuurs and Green (2013)	CCT	22 female and male non-CNS cancer survivors, with a mean age of 58.2 years and immediately completed cancer treatment	4-week group-based cognitive rehabilitation treatment vs no intervention cancer survivors vs normal adults	Subjective measure: FACT-Cog and MASQ; Objective measure: RBANS for immediate and delayed memory; TMT for attention and executive function	The intervention was effective in improving overall cognitive function, visuospatial performance, immediate memory and delayed memory
Von Ah et al (2012)	RCT	82 female breast cancer survivors, with a mean age of 56.5 years old, and at post–cancer	8-week group-based memory training vs waitlist control	Subjective measure: FACT-Cog; Objective measure: RAVLT for verbal memory;	Memory training intervention improved memory performance at 2-month follow-up ($P < 0.05$); speed of processing training improved processing

	treatment for at least 1 year	UFOV for objective speed of process	speed at postintervention and 2-month follow-up (both P <0 .05). Both interventions were associated with improvements in perceived cognitive functioning, symptom distress and quality of life

Abbreviations: BRIEF, Behavioral Rating Inventory of Executive Function; BVMT-R, Brief Visuospatial Memory Test-Revised; CBT, Cognitive–Behavioral Therapy; CCT, Controlled Clinical Trial; CIS, Checklist Individual Strength; CNS, Central Nervous System; CVLT, California Verbal Learning Test; EEG, Electroencephalography; FACT-Cog, Functional Assessment of Cancer Therapy–Cognitive Function; HVLT-R, Hopkins Verbal Learning Test-Revised; MASQ, Multiple Ability Self-report Questionnaire; MSEQ, Memory Self-Efficacy Questionnaire; MIA, Meta-memory in Adulthood; PAOFI, Patient's Assessment of Own Functioning Inventory; PCA, Perceived Cognitive Abilities; PCI, Perceived Cognitive Impairment; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for Neuropsychological Status; RCT, Randomized Controlled Trial; TMT, Trail Making Test; UFOV, Useful Field of View; VMT-R, Visuospatial Memory Test–Revised.

Effects of neuropsychological interventions on subjective cognitive function

Three trials (Cherrier et al. 2013; King and Green 2015; Schuurs and Green 2013) with a total of 86 subjects measured improved FACT-Cog subscales of perceived cognitive impairment (PCI), perceived cognitive abilities (PCA), and impact of perceived cognitive impairments on quality of life (IPCIQL). Figure 2.3 shows the WMD for the overall effect of cognitive rehabilitation (CR) interventions was -0.19 (95 % CI -2.98, 2.61). The WMDs for the three subscales of PCI, PCA, and IPCIQL were -0.76 (95 % CI -18.90, 17.38), 0.28 (95 % CI -4.29, 4.85), and -1.50 (95 % CI -4.59, 1.60), respectively. Although the improvement of subjective cognitive function was in favor of CR interventions, there is no statistically significant difference (Z score = 0.13, P = 0.90).

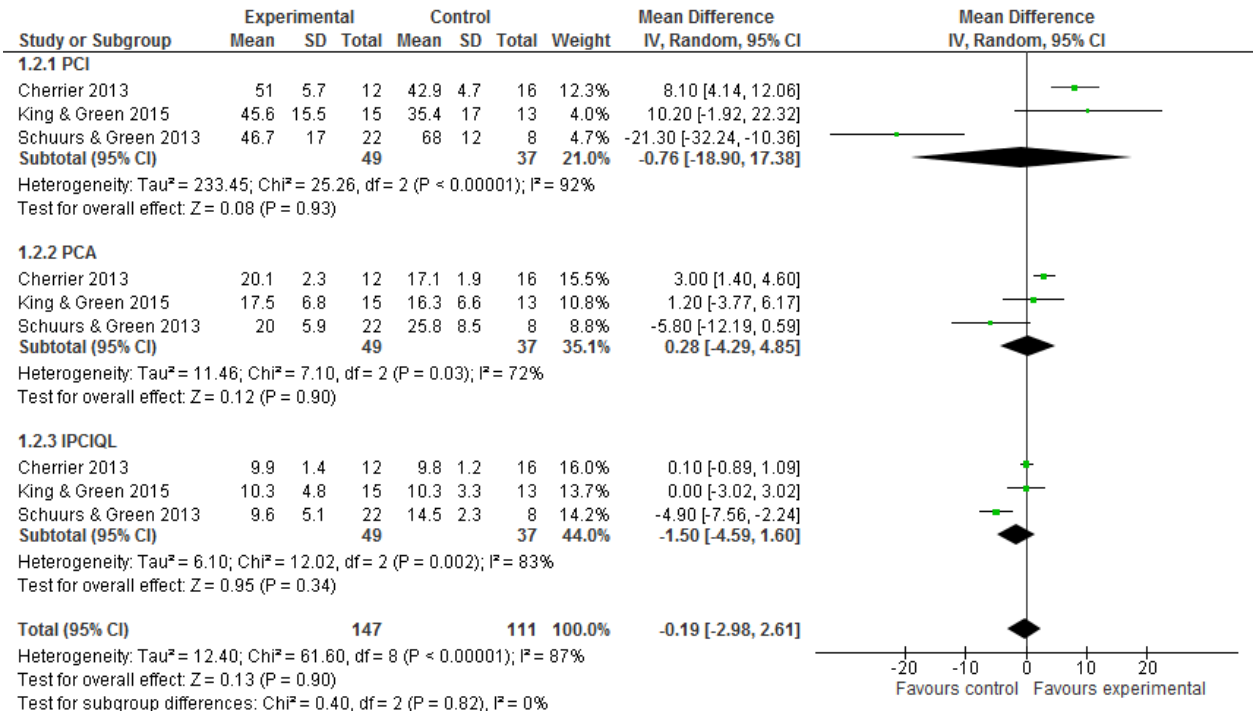

Figure 2.3 Subjective cognitive function (FACT-Cog) at post-intervention

Figure 2.4 shows that the SMD for the effect of cognitive training (CT) interventions was 0.52 (95 % CI 0.06, 0.98).

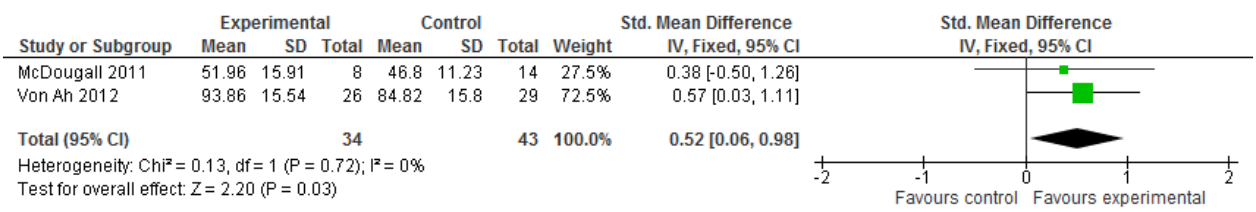

Figure2.4 Subjective cognitive function at post-intervention

By follow-up assessment of the effect of CT interventions for the subjective cognitive function, Figure 2.5 also shows its positive effects and the SMD was 0.54 (95% CI: 0.08-1.00; Z score = 2.29, P = 0.02), indicating that CT interventions had positive effects on improving the subjective cognitive function of cancer survivors in the follow-up evaluation.

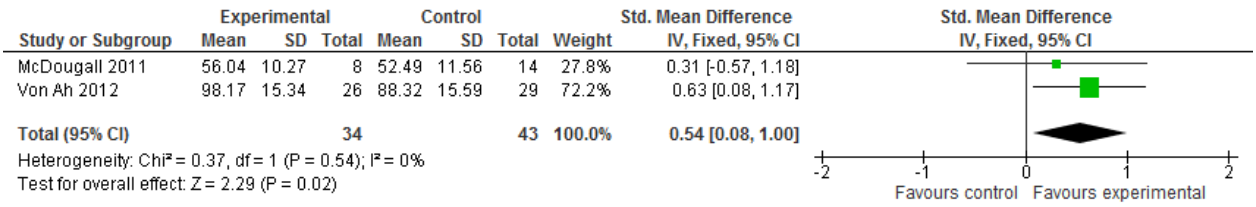

Figure 2.5 Subjective cognitive function at follow-up (≤ 6 months**)**

Effects of neuropsychological interventions on objective cognitive function

One trial (Alvarez et al. 2013) used brain imaging assessment via qEEG, and reported that the intervention group showed positive effects in terms of cognitive function improvement: a decrease in alpha power and delta 'slow wave' power (both P values < 0.05). By formal neurocognitive tests, Figure 2.6 shows the improvement of neuropsychological status in favor of intervention (WMD = 5.66, 95 % CI 2.97, 8.35) and with statistical significance (Z score = 4.12, P < 0.0001).

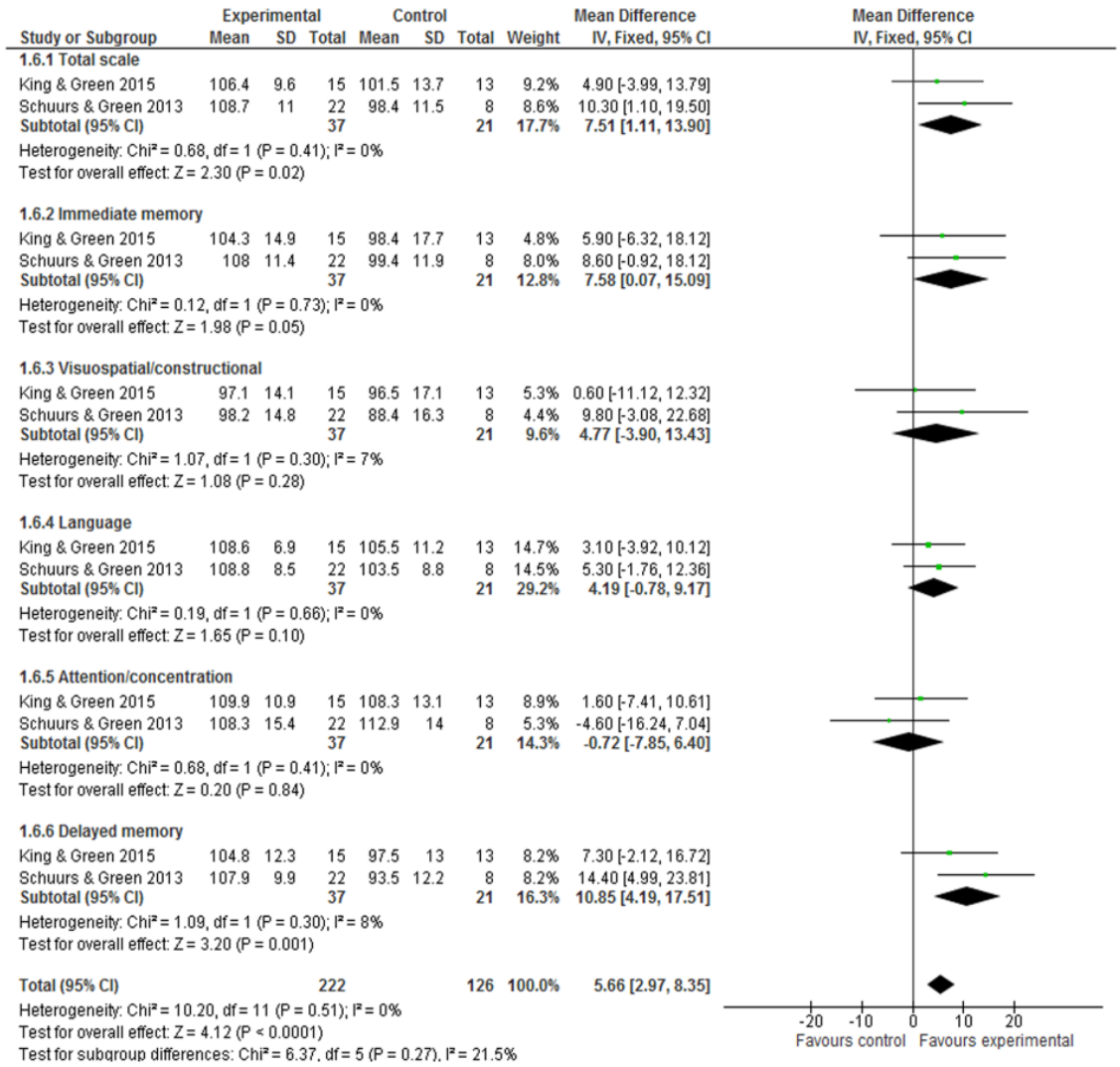

Figure 2.6 Repeatable Battery for Neuropsychological Status (RBANS) Test at post-intervention

Within the RBANS test, there were five subscales, but only two subscales - immediate memory and delayed memory - with statistical significance: the WMDs were 7.58 (95 % CI 0.07, 15.09), and 10.85 (95 % CI 4.19, 17.51). For the verbal learning tests by RAVLT, CVLT, or HVLT-R, Figure 2.7 indicates that the intervention group experienced an improvement in verbal learning function, with the SMD at 0.50 (95 % CI 0.19, 0.81).

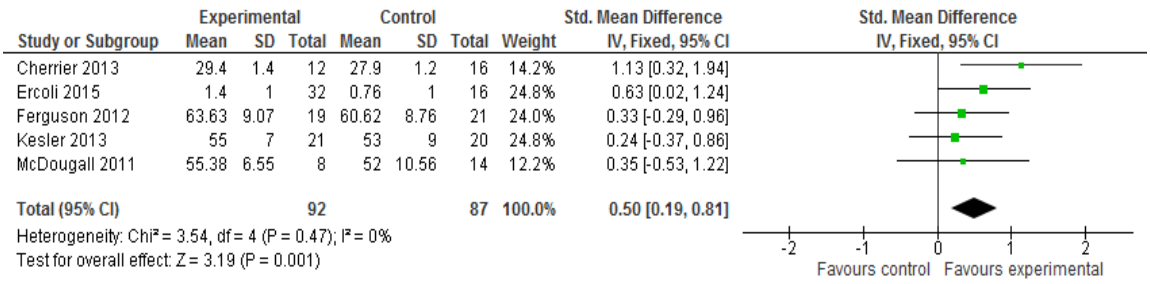

Figure 2.7 Verbal Learning Test (VLT) at post-intervention

Within a six-month follow-up, Figure 2.8 shows that the intervention had statistically significant effects on improved verbal learning function among cancer survivors. The SMD was 0.58 (95% CI: 0.19, 0.98; Z score = 2.88, P = 0.004).

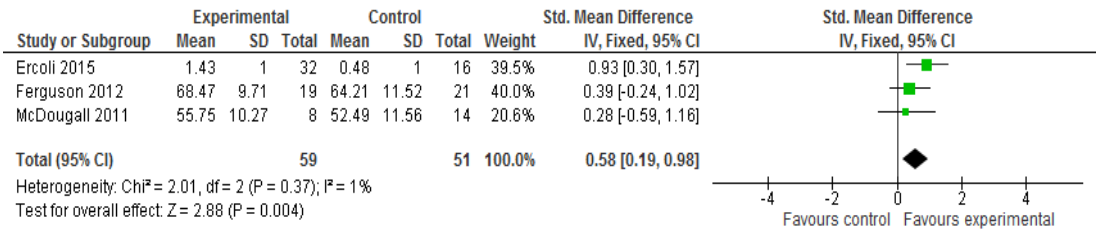

Figure 2.8 Verbal Learning Test (VLT) at follow-up (≤6 months)

For cognitive performance, as measured by Digit Symbol, Digit Span, and TMT, none of these cognitive tests have statistical significance. While CR interventions showed trends in the direction of improving attention, processing speed and working memory by Digit Symbol at post-intervention and follow-up within six months (Figures 2.9-2.10), the intervention effect sizes' CI were crossed zero (both WMDs = 0.90, 95%CI = -0.42 to 2.23; -0.79 to 2.59, respectively).

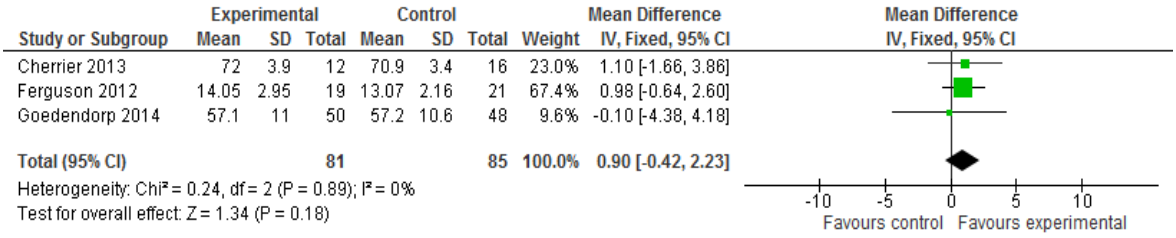

Figure 2.9 Digit Symbol Test at post-intervention

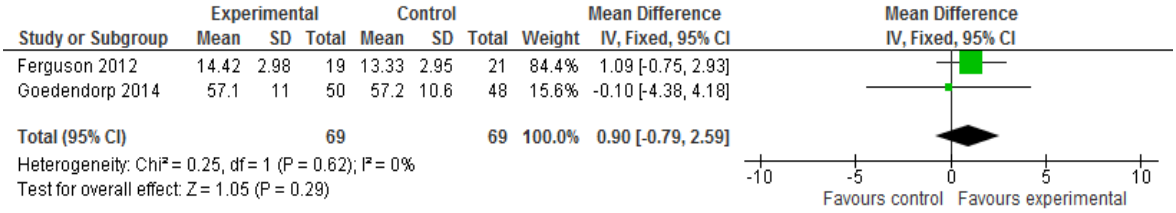

Figure 2.10 Digit Symbol Test at follow-up (≤6 months)

Cognitive performance, measured by Digit Span and TMT - including functions of attention, spatial organization, executive function and mental flexibility - was also in favor of intervention, but found no statistical significance (Figures 2.11-2.12).

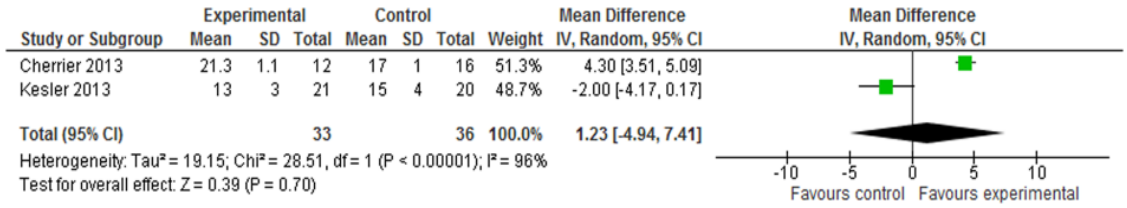

Figure 2.11 Digit Span Test at post-intervention

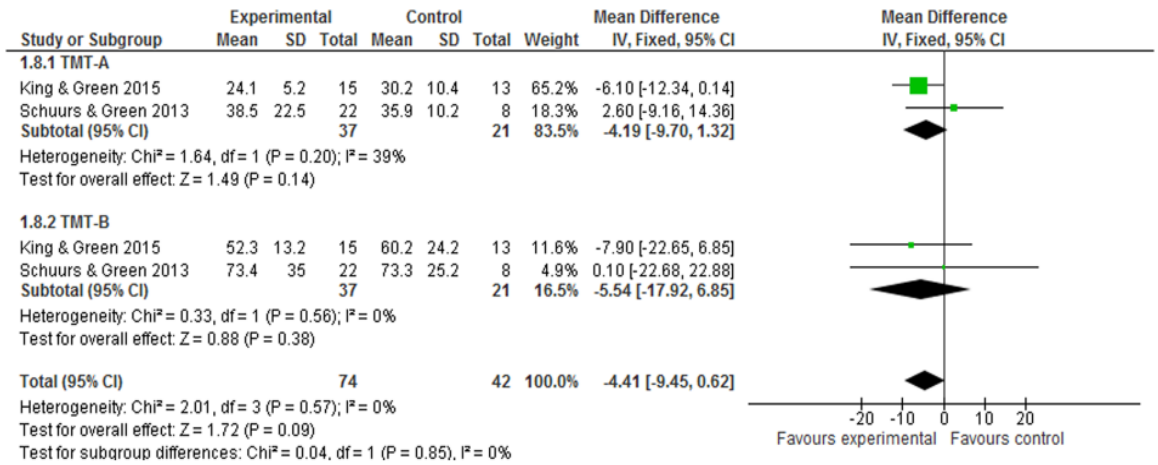

Figure 2.12 Trial Making Tests (TMT) at post-intervention

Of 10 included trials (Alvarez et al. 2013; Cherrier et al. 2013; Ercoli et al. 2015; Ferguson et al. 2012; Goedendorp et al. 2014; Kesler et al. 2013; King and Green 2015; McDougall et al. 2011; Schuurs and Green 2013; Von Ah et al. 2012), no study reported adverse effects related to neuropsychological interventions.

2.4 Discussion

Based on the most recent research literature, most common neuropsychological interventions could alleviate cognitive impairment in cancer survivors, including cognitive rehabilitation interventions by behavioral therapy approaches, mainly in a group format, and with cognitive brain training delivered mainly in an individual format. Findings from this literature review indicated that cognitive training interventions have positive effects on improving subjective and objective cognitive function in cancer survivors, although the effect sizes have been modest (SMDs ranging from 0.50 to 0.58). For example, CT interventions by an online and home-based program significantly improved multiple executive function skills, as reported by objective and self-report measures (Kesler et al. 2013). CR interventions have positive effects in formal neurocognitive tests, such as the domains of immediate and delayed memory by RBANS, and several verbal learning tests. In Ferguson et al. (2012)'s study, interventions by cognitive behavioral treatment were effective at improving memory and attention problems. Cognitive neuromodulation strategies offer new and noninvasive approaches for ameliorating cognitive dysfunction (Ercoli et al. 2015). One study, which used neurofeedback, found positive effects in self-reported cognitive measures and objective cognitive functions in breast cancer survivors (Alvarez et al. 2013).

Most trials included in this meta-analysis only assessed the immediate effects at post-intervention or short-term follow-up (six months or less), as long-term follow-up assessment can monitor the sustainability of intervention effects. Hence, future research should be conducted in a longer-term follow-up to establish whether neuropsychological interventions have long-term effects on the improvement of cognitive function in cancer survivors. More than half of the trials included in this review focused on a study population of breast cancer survivors, and the remaining trials, with mixed types of cancer survivors, also included a study sample of breast cancer survivors. While breast cancer is the most common type of cancer globally, with a relatively good five-year survival rate, many other cancer patients may experience similar survivorship issues, as the five-year relative survival rate for all cancer populations is now up to 68% (Siegel et al. 2015).

In addition, studies of other cancer populations could help researchers understand whether different types of cancers have specific risk factors and different underlying mechanisms leading to neurocognitive function deficits (Janelsins et al. 2014). In terms of outcomes, most trials included in this review used a combination of self-reported cognitive measures and formal neurocognitive tests. Self-reported measures may ask about cancer survivors' cognitive problems over a period of time, but neurocognitive tests can only detect their cognitive function at a certain point of time (Janelsins et al. 2014). Hence, future research should also utilize subjective and objective cognitive function measures, in order to better capture neurocognitive function deficits in cancer survivors. Furthermore, this review found that various neuropsychological tests have been used, which may contribute to error variance and type II error. A task force has recommended that a core set of neuropsychological tests be used across studies to facilitate interpretation of study findings (Wefel et al. 2011).

While the process of meta-analysis could obtain a weighted average effect size across a number of different trials (Jim et al. 2012), it is important to note that an important result

found in one study could be washed out by the null results of other studies (Hodgson et al. 2013). Ideally, the methodological limitations of meta-analysis could be resolved by a presentation of Integrative Data Analysis (IDA), which is also expected to increase statistical power and generalizability of results by combining raw data (Joly et al. 2015). Similar to a meta-analysis, raw data from multiple samples (e.g. different types of cancer survivors) could be combined into a single data analysis, despite the fact that all cognitive outcomes may not be measured using the same instruments (Joly et al. 2015). Hence, the IDA method analyzes the combined original data, and may overcome the limitations of the synthesis of summary statistics drawn from multiple studies, by calculating secondary data as meta-analysis. Another limitation of this meta-analysis was the conclusion drawn in a number of trials with small sample sizes. Findings of this meta-analysis should be confirmed in future randomized trials with larger sample sizes.

This meta-analysis found that neuropsychological interventions had positive effects, improving cognitive function in cancer survivors. Further research should be conducted to explore relevant risk factors for identifying patients at increased risk for neurocognitive function deficits, and to explore the possible underlying mechanisms of neurocognitive function deficits in cancer survivors by neuroimaging studies (Wefel and Schagen 2012; Craig et al. 2014; Wefel et al. 2015). Although breast cancer survivors have received relatively more attention in published literature, many other types of cancer survivors experience similar survivorship issues (Wefel and Schagen 2012). Thus, further research should be conducted on different types of cancer survivors to identify disease-specific risk factors in cognitive impairment. Moreover, the trials in this meta-analysis show moderate to high risk of bias. Future trial design should be randomized and the outcome assessors blinded, in order to minimize potential methodological bias.

From Hines and colleagues' review (Hines et al. 2014), patients treated on psychosocial interventions for cancer related cognitive dysfunction was limited, as current therapies only indicated short-term effects (less than 6 months) on their symptoms. This review of most recent intervention studies also indicated that the neuropsychological interventions did not show any long-term effects on cognitive function outcomes. Gehring and colleagues' review (Gehring et al. 2008), which included pharmacological and non-pharmacological interventions, found that "of the pharmacological agents studied and reviewed, off-label modafinil has the strongest evidence base for beneficial effects on cognitive function in patients with cancer." This review also indicated that neuropsychological interventions may improve aspects of objective cognitive function and subjective cognitive function. However, this review concluded that overall subjective cognitive effects are larger than objective cognitive effects. In contrast, this meta-analysis found effect size by objective neurocognitive tests (up to 5.66) is larger than subjective cognitive measures (0.52 to 0.54).

2.5 Conclusion

Findings from this meta-analysis indicate that neuropsychological interventions can improve cognitive function in cancer survivors, and support the need for future research. However, since the conclusion from this meta-analysis was drawn based on trials with small sample sizes, future research should be conducted on a larger sample.

2.6 Summary

This chapter presents a literature review of neuropsychological interventions for CRCI in gynecological cancer patients. Due to limited intervention conducting for this study population, this thesis expanded literature search into all non-central nervous system cancer survivors. While this review found that cognitive rehabilitation and cognitive training may be effective in reducing cognitive impairment for cancer survivors, the underlying mechanism of cognitive impairment is still unclear and there is a lack of specific theoretical framework for investigating cognitive impairment issues among gynecological cancer patients. Therefore, a qualitative research study conducted to establish a theoretical framework specific for this study population, and the prospective multimodal MRI study undertook to detect the possible early predictors of neurocognitive function deficits among gynecological cancer patients. The next chapter presents the methods of three study stages.

CHAPTER 3

Study Methods

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3.1 Methods of Study Stage 1

Design

Study Stage 1 utilized a qualitative research design. A semi-structured interview was used to probe cervical cancer patients' perceived cognitive complaints and supportive care needs.

Study framework

This study stage was guided by the conceptual model of chemotherapy-related changes in cognitive function proposed by Myers (2009). This model consists of three key components: antecedents (cancer diagnosis and cancer treatment), mediators (physiologic, psychosocial and situational factors), and consequences (quality of life and functional ability) (Myers 2009). While this model is described as chemotherapy-related cognitive impairment, recent evidence indicates that cancer itself is also related to cognitive impairment (Wefel et al. 2015). As suggested by Myers, when researchers learn more about the physiological and psychological aspects of cognitive impairment, this model may require refining (Myers 2009).

Study sample

All study participants were recruited from the Gynecological Oncology Unit at a cancer hospital. This study obtained ethical approval from the hospital's ethics committee. A purposive sample was drawn-up to recruit eligible informants. Inclusion criteria were: women who were at least 18 years old, with a primary diagnosis of cervical cancer, and who had completed their primary cancer treatment of surgery, radiation therapy or chemotherapy. Exclusion criteria included potential psychiatric disorders, previous cancer history, or traumatic brain injury.

Study procedure and qualitative interviews

After obtaining ethical approval, the participants were recruited from the hospital's gynecological inpatient department. The third author assessed participant eligibility. The eligible women were invited to the hospital's meeting room to individually complete the semi-structured interview. They were asked to participate in a semi-structured interview, and complete a socio-demographic sheet. This sheet was used to collect information on demographic and clinical characteristics, including age, education level, marital status, tumor stage, type of cancer treatment received, and time since completion of primary cancer treatment.

Qualitative interviews were guided by a narrative epistemology in order to encourage participants to provide narrative accounts of their perceived experience (Benzein et al. 2001). Researcher characteristics: The third author, who conducted the interview, is a nursing professor who holds a Master of Nursing degree. All researchers in this study have been conducting clinical research for more than five years, and all have received qualitative research training. The interviewer was an experienced female research nurse, and the data collection method was by written narrative, so that the interviewer's beliefs, biases and preconceptions would have no influence on the direction of the interviews. No non-participants were present for the interview, and the interviewer remained in the meeting room to take field notes, in order to capture any emerging thoughts to guide data analysis.

The interviews were conducted face-to-face in the in-patient ward's meeting room. All interviews utilized an interview guide comprised of the following open-ended questions: 1) Compared to before your cancer diagnosis, tell us about the overall change in your cognitive abilities? For example, your perceptions of understanding what people say to you; thinking of the right word when responding to others; and feeling confident about completing a task

or taking on new tasks. 2) What do you think the common contributing factors to any cognitive changes might be? 3) How do these perceived cognitive changes impact your daily life or your ability to work? 4) How do you deal with these changes? In other words, what types of coping strategies do you use as a result of any cognitive change you might be experiencing? 5) What types of supportive care services do you need from healthcare providers, to help you cope with any cognitive complaints? Each interview lasted 30 to 45 minutes, and was recorded by a digital recorder and transcribed verbatim. Data saturation was achieved much earlier than the final sample size of 31 patients, as data collection and analysis were performed simultaneously in an iterative process (Sandelowski 2000).

Data analysis

Qualitative interview data were transcribed to produce a verbatim transcript. During the entire data analysis process, the researcher consciously separated herself from personal biases, in order to be open to the information shared by study participants. NVivo 11.0 qualitative software (http://www.qsrinternational.com/nvivo-product/nvivo11-for-windows) was applied to organize and code the verbatim transcript. Qualitative content analysis was used to prepare, organize, and report the data (Elo and Kyngas 2008). A three-step content analysis process was followed: "1) The verbatim transcript was organized into meaning units (such as words, phrases, sentences or paragraphs that conveyed similar content deemed important in understanding patients' experiences). 2) The meaning units were coded and categorized. 3) The abstraction process was guided by Myers's conceptual model and continued until primary themes were identified (Elo and Kyngas 2008).

Two research members conducted content analysis independently. In case of any disagreement with the interpretation of clusters or categories, a third research member was involved in the discussion process, in order to establish a consensus. To ensure that the study

findings were accurately reflecting informants' actual perceived experience of cognitive changes, three research participants were invited to check the final verbatim transcript for the purpose of collecting participant feedback and validation. The consolidated criteria for reporting qualitative studies (COREQ) checklist was applied to guide this study and ensure study rigor (Tong et al. 2007).

3.2 Methods of Study Stage 2

Design

This prospective and longitudinal study assessed all eligible subjects using subjective and objective cognitive measures, structural and functional brain networks at pre- and post-chemotherapy treatment.

Study sample

Subjects were Chinese females aged 18 to 65 years; with a primary diagnosis of Stage I-III gynecological cancer (cervical, ovarian, or uterine cancer); and who were ready for adjuvant chemotherapy after surgical treatment. Inclusion criteria for healthy controls were women who were chosen based on age (within one year older or younger than the patients), and the same menopausal status as the patient group. Exclusion criteria for patients were women with a previous history of cancer (not a primary diagnosis of cancer), and/or who were in a terminal stage of cancer. Exclusion criteria for both patients and healthy controls included brain tumors; potential psychiatric disorders, such as depression and anxiety; a history of any neurological condition; traumatic brain injury; intellectual disability; and the use of psychotropic medication. All patients were recruited in the Unit of Gynecological Oncology at a general teaching hospital. All age-matched healthy controls were recruited from staff

members at this hospital. This study obtained ethical approval from the ethics committees at both The Hong Kong Polytechnic University and The Third Affiliated Hospital of Guangzhou Medical University. All research participants joined this study voluntarily and provided written informed consent.

Measures

Neurocognitive function assessment

As suggested by Joly et al. (2015), the most common domains of cognitive impairment in cancer survivors include learning and memory, information processing speed, and executive function. The International Cognition and Cancer Task Force (ICCTF) recommends the following measures (at minimum) be included in assessing cognitive function in cancer patients: the Hopkins Verbal Learning Test - revised (HVLT-R), the Trail Making Test (TMT), and the Controlled Oral Word Association Test (COWA) (Wefel et al. 2011). This study administered the Chinese version of the Auditory Verbal Learning Test - revised version (AVLT-R) to measure the domains of learning and memory (Guo 2016); the TMT-A, to measure information processing speed; the TMT-B, to measure executive function; and the COWA to assess verbal fluency and language comprehension in Chinese gynecological cancer patients (Strauss et al. 2006). According to Zeng et al. (2017), attention and working memory were the most common neurocognitive dysfunctions in Chinese gynecological cancer patients. This study also included the WAIS-III Digit Span test for measuring attention and working memory (Wechsler 2003).

Subjective cognitive measures

Self-reported cognitive functioning was assessed using the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) scale, a self-report questionnaire that measures PCI; impact on quality of life; comments from others; and perceived cognitive ability (Wagner et al. 2009). The FACT-Cog consists of 37 items and is designed to assess cognitive complaints in cancer patients (Wagner et al. 2009). This study used the FACT-Cog to assess subjective cognitive function in women with gynecological cancer.

Psychological measures and general information sheet

Depression and anxiety were evaluated using the Chinese version of the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1994). The HADS is a 14-item self-assessment scale to assess patients' anxiety and depression levels. Each item is scored from 0 to 3. The anxiety and depression sub-scores are both on scales of 0 to 21. Higher total scores indicate higher levels of anxiety and depression (Zigmond and Snaith 1994). The Chinese version of HADS has been reported to have acceptable internal consistency and validity (Lu et al. 2004; Nian 2012), and is found to be a reliable tool for assessing psychological disturbances in cancer survivors (Zigmond and Snaith 1994). The Brief Fatigue Inventory (BFI) has been validated as a short and comprehensive instrument to assess the severity of fatigue and fatigue-related impairment in cancer survivors (Dimeo et al. 2008; Mendoza et al. 1999). It consists of 10 items and allows a basic assessment of the dimensions of activity, ability to walk, mood, work, interpersonal relationships, and enjoyment of life (Mendoza et al. 1999). Lower scores indicate less severity of fatigue (Mendoza et al. 1999). A general information sheet collected subjects' demographic and clinical characteristics in terms of age, education level, employment, and marital status.

Patients' clinical information included cancer types, disease stage, and treatment received (e.g., Surgery, Radiation, Chemotherapy).

MRI data acquisition

According to the ICCTF's recommendations for neuroimaging studies in cancer and cognition, a minimal set of MRI sequences should include an rs-fMRI and a high-resolution T1-weighted anatomical MRI scan to assess functional brain networks (Deprez et al. 2018). Whole brain rs-fMRI data were collected on a Philips 3.0T scanner (Achieva; Philips, Best, The Netherlands), using an 8-channel SENSE head coil at The Third Affiliated Hospital of Guangzhou Medical University, China. Throughout the rs-fMRI data acquisition, patients were instructed to close their eyes and relax, but to remain in a maximally alert state. A T2-weighted gradient-echo EPI sequence was used to obtain the rs-fMRI scan. A total of 240 whole brain EPI volumes were acquired using the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, in-plane imaging resolution = 3 × 3 × 3 mm, in-plane field of view (FOV) = 256 × 256mm, slice thickness = 4 mm, axial slices = 33. The rs-fMRI scan time was 8 min 6 s. T1-weighted imaging was achieved for morphometric (GM volume, cortical thickness and surface area) analysis using three-dimensional fast spoiled-gradient recalled acquisition in steady state (3D-FSPGR) in 164 coronal slices with the following parameters: acquisition matrix = 256 × 256; TE = 3.8 ms; TR = 8.2 ms; flip angle = 7°; FOV = 256 mm × 256 mm; slice thickness = 1 mm; voxel resolution =1×1×1 mm. The 3D-T1 scanning time was 5 min 58 s.

MRI data preprocessing and network analyses

The rs-fMRI images were preprocessed using GRETNA: a graph theoretical network analysis toolbox for imaging connectomes (Wang et al. 2015). During the preprocessing process, the first 10 volumes for signal were removed to reach a steady state, leaving 230 functional volumes for each subject. The remaining functional volumes were corrected for

acquisition time delay between slices (slice timing) and head motion between volumes (realignment). Other steps in preprocessing these functional data consisted of spatial normalizing by DARTEL (warping individual functional images to the standard MNI space by applying the transformation matrix that can be derived from registering the final template file), spatially smoothing with a Gaussian kernel (full width at half-maximum of 4mm), regressing out covariates (white matter, cerebral spinal fluid, global signals, and head-motion profiles are removed to avoid noise signals by multiple regression analysis), temporally linear detrending, temporal band-pass filtering (0.01-0.1 Hz), and scrubbing to reduce the effects of head motion on rs-fMRI data. The networks were constructed based on a voxel or region of interest approach. The Automated Anatomical Labeling (AAL) atlas was used to parcellate the brain into 90 regions (cerebellum excluded). Functional brain networks were constructed by thresholding the correlation matrices with a density of 5%. All network analyses were performed using GRETNA (Wang et al. 2015). The values were mapped onto the cortical surface using BrainNet Viewer (Xia et al. 2013). Data preprocessing and network analyses are shown in Figure 3.1.

Hub identification

There are various methods to identify functional hubs. Some research suggests that hub regions can be defined as degree, betweenness centrality, and/or clustering coefficient values exceeding 1 SD (Standard Deviation) above the mean network, thus indicating hub status (Sporns et al. 2007). Other research indicates that nodes with a high degree, exceeding 1.5 SD above the mean network, can be identified as functional hubs, mean that they exhibit high connectivity to the rest of the brain (Cao et al. 2017). This study defined functional hubs of research participants with node degree values exceeding 1.5 SD above the mean network.

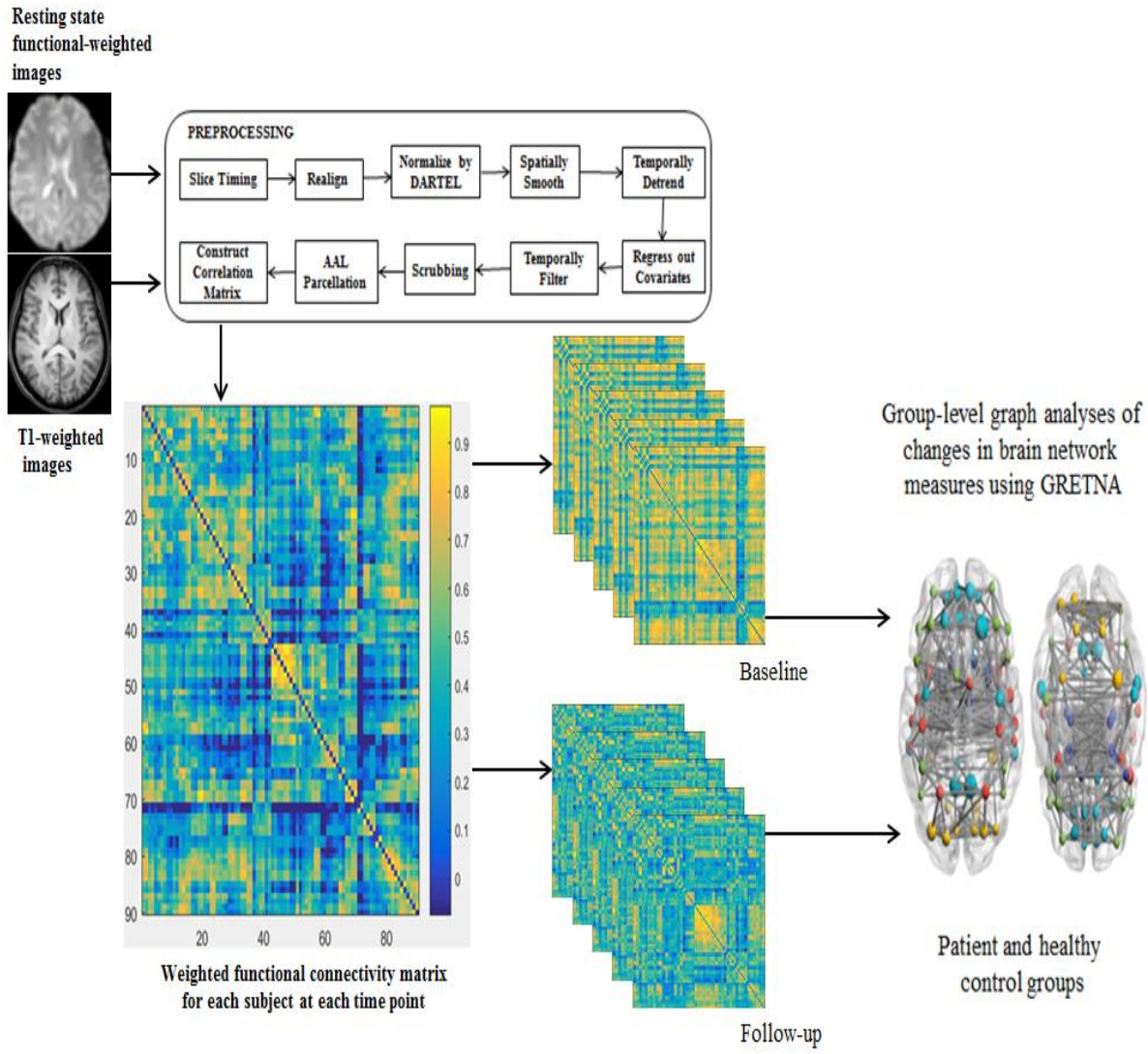

Figure 3.1 Illustration of functional brain network construction for longitudinal graph analysis

Statistical analysis

Descriptive statistics, correlation and comparison analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 23.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics are presented as mean, standard deviation (SD), and range. Cancer patients were rated as experiencing neurocognitive function deficits with a FACT-Cog score of 85 or less (Vardy et al. 2006; 2017). Correlations of neurocognitive function with

functional brain networks were made using Pearson correlation coefficients. Group differences were tested with t-tests for continuous variables, and chi-square tests for categorical variables. All statistical tests performed were two-sided, and a P value of less than 0.05 was considered statistically significant.

3.3 Methods of Study Stage 3

Design

This prospective multimodal MRI study was conducted to assess cancer patients' neuropsychological function, structural brain networks, and neurochemical properties pre- and post-chemotherapy.

Study sample

All subjects were recruited in the Unit of Gynecological Oncology at a general teaching hospital. Ethical approval was obtained from the ethics committees at both The Hong Kong Polytechnic University and The Third Affiliated Hospital of Guangzhou Medical University. Subjects were Chinese females aged 18 to 65 years; with a primary diagnosis of stage I-III gynecological cancer; and who were ready for adjuvant chemotherapy after surgical treatment. Exclusion criteria were women with a previous history of cancer (not a primary diagnosis of cancer), and/or who were in a terminal stage of cancer, and/or had a severe needle phobia. Inclusion criteria for healthy controls included women within one year of age and the same menopausal status as the patient group. Exclusion criteria for both the patient and healthy control groups included potential psychiatric disorders, such as depression and anxiety; a history of any neurological condition; traumatic brain injury; intellectual disability; and the use of psychotropic medication.

Neurocognitive function assessment

The neurocognitive assessment measures that were used were the same as the study's Stage 2, including the AVLT-R, TMT, COWA and WAIS-III Digit Span test.

MRI and MRS data acquisition

The MRI data were acquired using a Philips 3T Achieva MRI/MRS scanner with an 8-channel head coil. Neurocognition evaluation and MRI scans took place on the same day. DTI and MRS were used to investigate changes in subjects' brain structural connectivity, and changes in brain metabolites, respectively. DTI, high-resolution structural T1-weighted brain scans were obtained using single-shot echo-planar imaging (EPI) (acquisition matrix = 128 × 128; TE = Minimum; TR = 16,000 ms; field of view = 256 mm × 256 mm; slice thickness/gap = 2.0 mm/0 mm; scanning time = 6 min 56 s) with 32 distributed isotropic orientations for the diffusion-sensitizing gradients at a b-value of 1000 s/mm^2 and a b-value of 0. T1-weighted imaging was achieved for morphometric (GM volume, cortical thickness and surface area) analysis using three-dimensional fast spoiled-gradient recalled acquisition in steady state (3D-FSPGR) in 166 coronal slices (acquisition matrix = 128 × 128; TE = 3.9 ms; TR = 9.6 ms; field of view = 256 mm × 256 mm; slice thickness/gap = 2 mm/0 mm; scanning time approximately 7 min).

As the hippocampus is an important brain structure due to its well-known function in the maintenance of memory, especially on the left side of the brain (Menning et al. 2015), 1H-MRS data were located in the region of the left hippocampus. Single voxel proton MR spectroscopy was acquired in the left hippocampus to assess the neurochemical properties of white matter. The region of interest is 2.5 × 1 × 1 cm^3, and voxels contained the head, body, and tail of the hippocampus. Fully automated PRESS (point-resolved spectroscopy),

including global shimming (TR/TE=2000/35 ms, NSA=16) was acquired in the red box area of the left hippocampus (Figure 3.2).

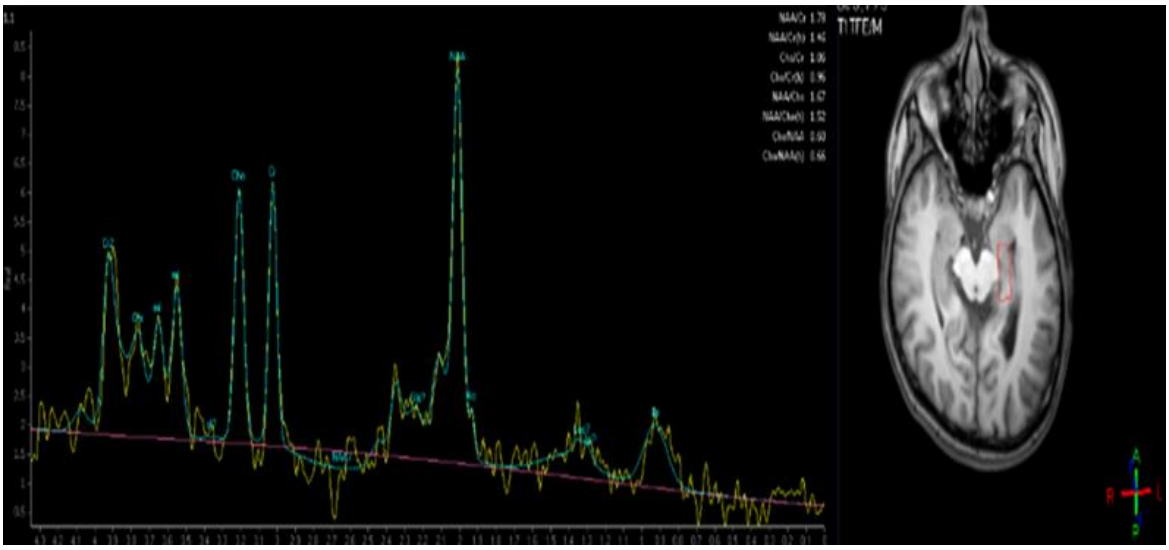

Figure 3.2 MRS data acquisition in the left hippocampus

MRI and MRS data processing and analyses

The DTI images were preprocessed using PANDA: a pipeline toolbox for analyzing brain diffusion images (https://www.nitrc.org/projects/panda/). Each individual's DTI data set was registered to the same individual's high-resolution structural image and then into the standard Montreal Neurological Institute (MNI) space using affine transformations. Fractional Anisotropy (FA) images were created from the pre-processed DTI data of all subjects. All FA images were then non-linearly aligned to a common space. The mean FA image was used to represent the center of all tracts common to the group. Then, all subjects' aligned FA data were projected onto the skeleton, and the resulting data were subjected to voxel wise cross-subject statistics. Whole brain tractography was then performed in the patient's native space for each subject at each time point using a deterministic streamlined

approach (Cui et al. 2013; Irfanoglu et al. 2012), in which fiber pathways were reconstructed by following the main diffusion tensor direction as indicated by the principal eigenvector, until an FA value of 0.20 or lower was reached, or until an angular turn of 45 degrees or more was made (Cui et al. 2013; Irfanoglu et al. 2012). The DTI data were used to construct the large-scale connectivity of the brain network and to assess network outcome measures using PANDA. The assessment of brain network measures was performed using the GRETNA (Wang et al. 2015). The following characteristic graph metrics were estimated to describe the topological organization of the whole brain structural networks: global topological properties consist of small-world measures and global network efficiency; local topological properties include local network efficiency, nodal clustering coefficient, and nodal shortest path length. MRS data were analyzed using MRS software integrated into the MR scanner. The experimentally measured spectra included N-acetylaspartate (NAA), creatine (Cr), and choline (Cho). Metabolites were expressed in relative concentrations. The ratios of NAA/Cr, NAA/Cho, Cho/Cr, and Cho/NAA were automatically determined by this integrated software.

Statistical analysis

Preliminary descriptive statistics and correlation analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 23.0 (SPSS Inc, Chicago, IL, USA). The threshold for statistical significance was set at $P < 0.05$. Descriptive statistics are presented as mean, standard deviation (SD), and range. Cancer patients were rated as experiencing neurocognitive function deficits "if two or more neurocognitive tests (AVLT, TMT, COWA and Digit Span test) had a Z-score at or below -1.5, and/or one test had a Z-score at or below -2.0 of the healthy control group (p.706)" (Wefel et al. 2011). Transformation of patient Z-scores was computed as patients' raw score minus the mean of the control group score and divided by SD. Correlations of neurocognitive outcomes with

structural brain networks and neurochemical properties were made using Pearson correlation coefficients.

3.4 Summary

This chapter presents study methods of all study stages. Study Stage 1 adopted the qualitative approach to explore the issues of perceived cognitive complaints and supportive care needs of Chinese gynecological cancer survivors. Open-ended questions by written narratives were adopted to obtain information on Chinese gynecological cancer survivors' perceptions of cognitive complaints. Stage 2 of this study used a prospective, longitudinal approach to assess Chinese gynecological cancer patients' neurocognitive functioning, and functional brain networks at pre- and post-chemotherapy, while additionally including age-matched healthy subjects as the control group. The final study stage was a multimodal MRI study that aimed to examine the possible neural mechanism of neurocognitive function deficits in gynecological cancer patients. This multimodal MRI study was used to assess structural brain networks, and neurochemical properties in this study population at pre-and post-chemotherapy. The next chapter presents empirical study findings and results.

CHAPTER 4

Study Results

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Zeng YC, Cheng ASK, Liu XY, & Chan CCH.

Cognitive complaints and supportive care needs in Chinese cervical cancer survivors: a qualitative study.

BMJ Open, 7(6): e014078.

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Cognitive complaints and brain structural networks in Chinese gynaecological cancer survivors compared with age-matched controls: A cross-sectional study.

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Submitted for publication to Brain Imaging and Behavior as

Zeng YC, Cheng ASK, Song T, Sheng XJ, Wang SJ, Qiu YW, Xie JH & Chan CCH. Changes in functional brain networks and neurocognitive functions in Chinese gynecological cancer patients after chemotherapy: a prospective longitudinal study.

This chapter presents a description of the study participants, analysis of qualitative and quantitative data, and interpretation of the study findings. As this study consists of three stages, this chapter reports the findings of these study stages accordingly.

4.1 Findings of Study Stage 1

A total of 50 patients with cervical cancer were approached, with 31 agreeing to participate in this written narrative interview. Those who did not join this study had no interest in participating in any type of research. Their characteristics in terms of age, cancer stage and treatment types were comparable to the patients who completed semi-structured interviews. Of the 31 participants, 20 women (64.5%) reported cognitive complaints after cancer treatment. The sociodemographic and clinical characteristics of women with cognitive complaints and those without perceived cognitive complaints are listed in the following table. From Table 4.1, the demographic/clinical characteristics of women with and without perceived cognitive complaints are compared.

Table 4.1 Demographic and clinical characteristics of participants with cognitive complaints and without cognitive complaints at study Stage 1

Variables	Mean (SD) / n (%)	
	With cognitive complaints (n=20)	Without cognitive complaints (n=11)
Age (years) (range)	46.40 (9.80) (19-57)	43.45 (12.08) (19-56)
Education levels		
Primary school or below	11 (55.0)	5 (45.5)
College	6 (30.0)	5 (45.5)
University or above	3 (15.0)	1 (9.0)
Employment status		
Employed but on medical leave	10 (50.0)	7 (63.6)
Unemployed or retired	10 (50.0)	4 (36.4)
Marital status		
Married	19 (95.0)	10 (90.9)
Divorced	1 (5.0)	1 (9.1)
Disease stage		
Stage IA	7 (35.0)	4 (36.4)
Stage IB-IIA	11 (55.0)	6 (54.5)
Stage IIB-IVA	2 (10.0)	1 (9.1)
Types of treatment		
Surgery	5 (25.0)	3 (27.3)
Surgery + chemotherapy*	5 (25.0)	4 (36.4)
Surgery + radiation therapy	2 (10.0)	0 (0.0)
Surgery+radiation+chemotherapy*	6 (30.0)	2 (18.2)
Radiation or chemotherapy*	2 (10.0)	2 (18.2)
Time since completion of primary treatment (months) (range)	1.70 (1.03) (1-5)	1.63 (1.20) (1-5)

*Chemotherapy regimens including Paclitaxel (TAXOL) with Carboplatin (CBP) or Cisplatin (DDP) or with both; CBP with Doxorubicin (ADM) or TAXOL with ADM; Bleomycin with Methotrexate (MTX) or MTX with DDP. All patients undertook a total of 4 cycles of chemotherapy.

Major categories that emerged from the data – which included cognitive complaints; perceived contributing factors; the impact of cognitive problems on women's daily lives, health outcomes and work capabilities; coping strategies; and patients' supportive care needs from health care providers - are shown in Table 4.2. The most common complaint was loss

of concentration (n=17, 85.0%), followed by memory problems (n=15, 75.0%). Other common cognitive complaints included difficulties in learning, language issues (finding the right words in everyday conversations), and a slowed rate of information processing.

Table 4.2 Major categories from the qualitative content analysis

Categories	n (%)	Illustrative quotes from participants
Cognitive complaints		
Lost concentration	17 (85.0)	*It's difficult to focus on a conversation or when reading newspapers or books. My biggest problem is lack of concentration*
Easily forgetting things or information from others	15 (75.0)	*My memory changed a lot after chemotherapy; when I meet my friend on the street, I can't even remember her name. Sometimes, nurses tell me about the illness, and I can't even remember what they have just told me*
Feeling it's hard to understand new things	7 (35.0)	*When I was reading books, I saw the words, but I could not make sense of the words, even when I read the same sentence several times.*
Difficulties in finding right word in general conversation	4 (20.0)	*When I speak with someone in general conversation, it's hard for me to find the right words*
Slowing down in working efficiency, compared with how they used to be	2 (10.0)	*I was used to being well organized in my work and daily life, but it's hard to get back all of those abilities, and my work has slowed down a lot*
Perceived causing factors		
Relating to chemotherapy	15 (75.0)	*Even during chemotherapy, I found that my memory changed a lot. Now I have completed the whole cycle of chemotherapy, and more and more memory impairment has appeared*
Side effects of cancer and its treatment	12 (60.0)	*I believe that a lot of physical examinations, such as CT at the time of diagnosis, the use of analgesics, and the surgery procedure are all related to my cognitive problems*
Aging	8 (40.0)	*Maybe due to my age, my memory is worse and I've started forgetting things quickly*

Psychosocial issues	3 (15.0)	*Having to deal with too many sources of stress, such as the financial issues related to medical treatment*
Relating to immune function	2 (10.0)	*After I developed this disease and had a series of cancer treatments, my immune function was destroyed, so my memory problems are partly due to this*
Coping strategies		
By writing memos	15 (75.0)	*Writing down important things, use of diaries or phone reminders to organize daily tasks*
Self-adjustment and relaxation techniques	14 (70.0)	*Asking myself to focus on one task at a time. When disturbed by other things or people, I'll adjust myself and refocus on what I was doing. I read, or listen to music for focus*
Doing nothing	6 (30.0)	*Now I can do nothing for this problem (cognitive impairment), as this may be due to my age; with older age, cognitive decline appears naturally. Other patients believe these cognitive problems are reversible and may get better gradually*
Environment organization	2 (10.0)	*To keep important personal belongs such as keys, eyeglasses, and mobile phone in a fixed place*
TCM such as acupuncture	1 (5.0)	*Doctors told me there were no effective drug therapies for this problem, so I tried acupuncture*
Supportive care needs from healthcare providers		
Providing information on common symptoms of cognitive impairment and effective therapies	11 (55.0)	*It's great for doctors and nurses to tell me about common signs or symptoms of cognitive impairment, and to provide intervention therapies to treat these problems*
Providing counselling services to family members	8 (40.0)	*It's hard for me to remember so much information. Healthcare providers should provide educational information and more counselling services to my family members*
Need information about possible rehabilitation service	7 (35.0)	*After hospital discharge, where should I seek further rehabilitation service for cognitive problems? Or can I gradually recover from these problems?*
Participating in peer support networks	2 (10.0)	*At the time of diagnosis and during cancer treatment, I was so worried. I need to connect*

		with women who have gone through a similar experience, in order to share coping strategies
Impacts on		
Daily life	20 (100)	*Sometimes, when people speak with me, I immediately forget what they were saying, or when I'm doing things and people interrupt me, I'll forget what I wanted to do*
Quality of life	9 (45.0)	*This disease and its treatment have severely impacted all aspects of my life, and have left me feeling overwhelmed. Now I have a poor memory, slowed thinking process, and a large financial burden as a result of the medical costs, causing tension in my family relationship*
Psychological health	5 (25.0)	*Sometimes my brain becomes a blank, and it seems my memory is not coming back, so I feel really scared*
Work capability	3 (15.0)	*I have to quit my job, due to my body image now. During and after chemotherapy I lost a lot of hair, and I can't work for very long, I can only work for a short period of time, then I have to rest*
Physical health conditions	2 (10.0)	*Cognitive function changes were not obvious, but my health condition was a lot worse; before the cancer diagnosis, my health was OK. But now my sleep is not good, my immune system is much weaker, and due to the loss of physical energy I can't work too long and need to take a break after working for just a short time*

Abbreviation: TCM, traditional Chinese medicine

The participants identified several factors they believed were contributing to their cognitive complaints, including chemotherapy (n=15, 75.0%), side effects of cancer and other treatment, such as surgery or radiation therapy (n=12, 60.0%), and aging (n=8, 40.0%). These cognitive complaints had negative impacts on daily life, sleep and rest (n=20, 100%). Two participants indicated their cognitive function had seen negligible change, but their physical health had deteriorated significantly after the diagnosis of cervical cancer. While

10 women were on medical leave at the time of data collection, two women indicated they were planning to leave their jobs due to loss of concentration and slowed information processing capacity.

As shown in Table 4.2, the most commonly used coping strategies were memo writing (n=15, 75.0%), and self-adjustment (n=14, 70.0%). Other coping strategies included "doing nothing" and organization of their environment. In addition, one woman sought out acupuncture as an alternative therapy, after her physician told her there was no effective medication for cognitive impairment thus far. Chinese cervical cancer survivors describe a variety of supportive care requirements, such as patient and family education on the common signs and symptoms of cognitive impairment, along with effective treatment therapies (n=11, 55.0%), counselling for family members (n=8, 40.0%), and information on further rehabilitation services (n=7, 35.0%). Two women expressed the need for peer support, and suggested that healthcare providers could organize a peer support group for patients starting from the diagnosis stage onward. Several patients indicated that their healthcare providers had never mentioned the potential for cognitive impairment, and only addressed this when patients asked about cognitive problems that appeared during cancer treatment.

Based on the conceptual model of chemotherapy-related changes in cognitive function proposed by Myers (2009), and in combination with a synthesis of these qualitative findings, a new cognition model among cervical cancer survivors is illustrated in Figure 4.1. Cognitive complaints are multifactorial in nature, with contributing factors that include demographic characteristics, biological factors, psychological distress, disease stages and cancer therapies.

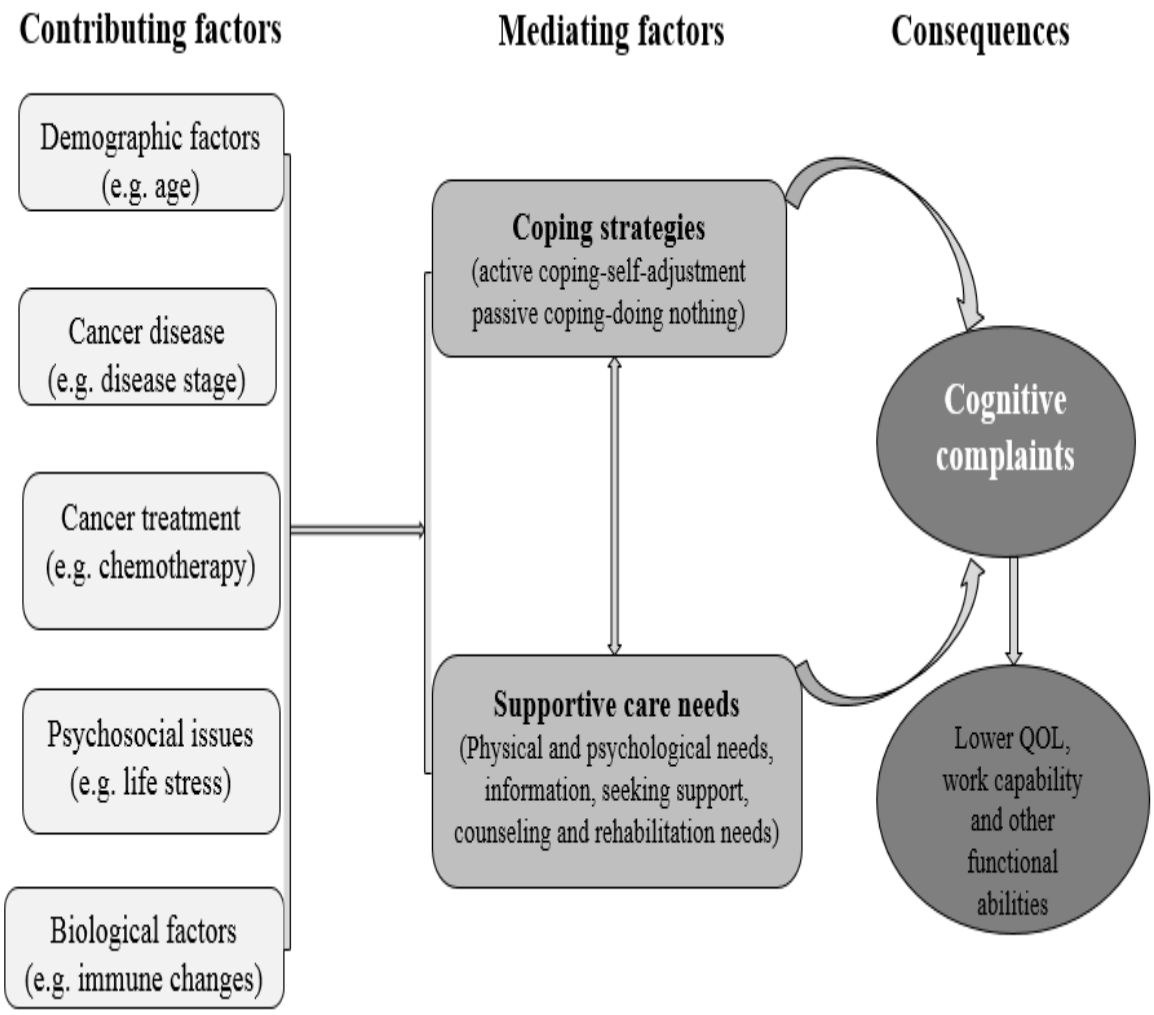

Figure 4.1 A preliminary cognitive impairment model among gynecological cancer patients

4.2 Results of Study Stage 2

Research participant characteristics

Of 37 eligible patients, a total of 20 patients agreed to join this study and completed the baseline rs-fMRI and neurocognitive assessment. Four patients refused to attend the MRI scans and neurocognitive assessment post-chemotherapy. There were 20 healthy control subjects who were matched in terms of age, marital and menopausal status. The demographic and clinical characteristics of the research participants are summarized in Table 4.3.

Table 4.3 Demographic and clinical characteristics of subjects at study Stage 2

Variables	**Mean (SD) / n (%)**	
	Cancer patients (n=20)	**Healthy controls** (n=20)
Age (years) Mean (SD)	47.15 (9.80) (28-60)	48.60 (6.80) (29-59)
Highest education		
Primary school or below	14 (70.0)	19 (95.0)
High school	4 (20.0)	1 (5.0)
University and above	2 (10.0)	
Employment status		
Employed	1 (5.0)	20 (100)
Unemployed	19 (95.0)	
Marital status		
Never married	2 (10.0)	1 (5.0)
Married	18 (90.0)	18 (90.0)
Divorced	0 (0.0)	1 (5.0)
Menopausal status		
Pre-menopausal	11 (55.0)	12 (60.0)
Peri-menopausal	8 (40.0)	7 (35.0)

Post-menopausal	1 (5.0)	1 (5.0)
Cancer type		
Cervical cancer	8 (40.0)	
Ovarian cancer	5 (25.0)	
Uterine cancer	7 (35.0)	
Disease stage		
Stage I-IIa	7 (35.0)	
Stage IIb-IIIa	8 (40.0)	
Stage IIIb	5 (25.0)	
Treatment type		
Surgery + Chemotherapy*	14 (70.0)	
Surgery + Chemotherapy* + Radiation	6 (30.0)	

*Chemotherapy regimens including Paclitaxel (TAXOL) with Carboplatin (CBP) or Cisplatin (DDP) or with both; CBP with Doxorubicin (ADM) or TAXOL with ADM; Bleomycin with Methotrexate (MTX) or MTX with DDP. All patients undertook a total of 4 cycles of chemotherapy.

Neurocognitive function of cancer patients compared to healthy controls

As illustrated in Table 4.4, with the exception of psychomotor speed, there was no significant difference pre-chemotherapy in the neurocognitive test mean scores between patients and healthy controls (Ps > 0.05).

Table 4.4 Mean scores of neurocognitive tests at pre-chemotherapy

Variables	Mean (SD)		*P*
	Cancer patients (n=20)	Healthy controls (n=20)	
Attention and working memory			
Digit span forward	6.75 (2.53)	7.30 (1.92)	0.44
Digit span backward	2.45 (1.43)	3.15 (2.30)	0.25
Verbal memory			
AVLT immediate recall	5.32 (1.72)	4.63 (1.41)	0.43
AVLT delayed recall	4.95 (2.58)	4.45 (2.32)	0.52
AVLT recognition	10.35 (1.72)	10.40 (1.46)	0.92
Psychomotor speed			
TMT-A	57.65 (21.65)	44.95 (16.01)	0.04
Executive function			
TMT-B	71.05 (26.94)	57.80 (21.30)	0.09
Language			
COWA	33.65 (8.89)	31.55 (6.48)	0.31

Abbreviation: AVLT, Auditory Verbal Learning Test; COWA, Controlled Oral Word Association Test; TMT, Trail Making Test.

As shown in Table 4.5, there were significant differences in neurocognitive test scores (including Digit Span tests, immediate and delayed recall of AVLT, and TMT-A) (all Ps < 0.05). Comparing the neurocognitive functions with healthy controls, patients at post-chemotherapy showed significantly deteriorated cognitive function in verbal and working memory ($P < 0.05$).

Table 4.5 Mean scores of neurocognitive tests at post-chemotherapy

Variables	Mean (SD)		*P*
	Cancer patients (n=16)	Healthy controls (n=16)	
Attention and working memory			
Digit span forward	6.75 (2.55)	7.53 (2.03)	0.02
Digit span backward	2.40 (1.69)	4.26 (2.23)	<0.01
Verbal memory			
AVLT immediate recall	5.10 (1.88)	9.15 (3.71)	<0.01
AVLT delayed recall	5.01 (2.92)	7.35 (2.34)	0.01
AVLT recognition	9.55 (3.21)	10.40 (1.75)	0.31
Psychomotor speed			
TMT-A	54.20 (19.02)	38.83 (25.53)	0.04
Executive function			
TMT-B	73.35 (29.40)	56.72 (33.95)	0.11
Language			
COWA	15.55 (5.96)	25.65 (22.18)	0.36

Abbreviation: AVLT, Auditory Verbal Learning Test; COWA, Controlled Oral Word Association Test; TMT, Trail Making Test.

Subjective cognitive functioning and psychological outcome measures

According to Vardy et al. (2006, 2017), subjects were categorized as having subjective cognitive deficits with a FACT-Cog score of 85 or less. Of 20 cancer patients, seven reported subjective cognitive deficits, pre-chemotherapy. There were significant differences in the total FACT-Cog scores and the subscales of perceived cognitive impairment and perceived cognitive ability between patients and healthy controls (Ps < 0.001) (Table 4.6).

Table 4.6 Mean scores of subjective cognitive measures at pre-chemotherapy

Measures	Mean (SD)		*P*
	Patient group (n=20)	Healthy controls (n=20)	
FACT-Cog	91.09 (17.43)	101.12 (19.24)	<0.01
Perceived cognitive impairment	54.21 (10.09)	64.13 (11.08)	<0.01
Comments from others	14.21 (2.43)	14.78 (3.31)	0.76
Perceived cognitive ability	16.11 (5.89)	20.21 (9.13)	<0.01
Impact on QOL	10.34 (4.75)	11.21 (3.13)	0.53

Abbreviation: FACT-Cog, Functional Assessment of Cancer Therapy-Cognition; QOL, Quality of Life.

At post-chemotherapy, 11 out of 20 patients (55%) had total FACT-Cog scores of 85 or less. With the exception of the subscale scores of comments from others, there were statistically significant differences in the subscales of perceived neurocognitive function deficits, perceived cognitive ability and impact on QOL (all P values < 0.01) (Table 4.7).

Table 4.7 Mean scores of subjective cognitive measures at post-chemotherapy

Measures	Mean (SD)		***P***
	Patient group (n=20)	Healthy controls (n=20)	
FACT-Cog	81.60 (11.21)	107.51 (17.43)	<0.01
Perceived cognitive impairment	46.09 (9.74)	61.45 (14.21)	<0.01
Comments from others	11.79 (3.18)	14.01 (4.22)	0.08
Perceived cognitive ability	12.73 (6.74)	19.79 (10.24)	<0.01
Impact on QOL	7.89 (3.98)	11.42 (4.47)	<0.01

Abbreviation: FACT-Cog, Functional Assessment of Cancer Therapy-Cognition; QOL, Quality of Life.

While there were no statistically significant differences between patients and healthy controls in terms of anxiety, depression, and fatigue levels at pre-chemotherapy, there were greater anxiety and fatigue levels in the patient group ($P = 0.01$, and $P < 0.01$, respectively) at post-chemotherapy (Table 4.8).

Table 4.8 Mean scores of psychological measures in each group at post-chemotherapy

Measures	Mean (SD)		***P***
	Patient group (n=20)	Healthy controls (n=20)	
HADS			
Anxiety	6.21 (4.34)	4.15 (3.67)	0.01
Depression	5.47 (4.13)	3.97 (3.18)	0.05
BFI-total	34.33 (22.26)	19.08 (17.41)	<0.01

Abbreviation: BFI, Brief Fatigue Inventory; HADS, Hospital Anxiety and Depression Scale.

Correlations of subjective cognitive deficits with psychological measures

While there were no statistically significant correlations between FACT-Cog total scores with BFI-total score (P> 0.05), there were significant correlations between FACT-Cog scores with mean scores of anxiety and depression (P < 0.01, and P = 0.02, respectively) (Table 4.9).

Table 4.9 Correlations of FACT-Cog total score with psychological outcome measures in the patient group at post-chemotherapy

Pearson correlation coefficients & P values	**FACT-total**	**HADS-Anxiety**	**HADS-Depression**	**BFI-total**
FACT-Cog total	1			
HADS-Anxiety	-0.51	1		
	<0.01			
HADS-Depression	-0.43	0.70	1	
	0.02	<0.01		
BFI-total	-0.22	0.28	0.19	1
	0.25	0.12	0.31	

Abbreviation: BFI, Brief Fatigue Inventory; FACT-Cog, Functional Assessment of Cancer Therapy-Cognition; HADS, Hospial Anxiety and Depression Scale.

Correlations of functional brain networks with subjective cognitive deficits

Lower small-worldness index was associated with more subjective cognitive deficits (r = 0.48, P = 0.02). For the local topological properties, there were no statistically significant differences including nodal efficiency, nodal clustering coefficient, and global efficiency (all P values > 0.05). Shorter characteristic path length, which indicates more efficient network organization, was significantly associated with fewer subjective cognitive deficits (r = -0.37, P = 0.04).

Brain functional global metrics and associations with neurocognitive outcomes

All participants in the patient group and healthy controls demonstrated a small-world organization as indicated by small-worldness greater than 1. There were significant differences in small-worldness pre- and post-chemotherapy between patients and healthy controls (P= 0.04, and P= 0.02, respectively) (Table 4.10). There were significantly increasing of characteristic path length at T2 between patients and healthy controls (P=0.01). Results from the longitudinal graph analysis revealed a reducing trend of local and global efficiency in the patient group (Table 4.10).

Table 4.10 Changes in brain global network measures between pre- and post-chemotherapy

	Pre-chemotherapy		*P*	Post-chemotherapy		*P*
	Patients (n=20)	**Healthy Controls** (n=20)		**Patients** (n=16)	**Healthy Controls** (n=16)	
Small-worldness	1.63 (0.46)	1.89 (0.66)	0.04	1.55 (0.34)	1.84 (0.51)	0.02
Characteristic path length	0.98 (0.37)	1.12 (0.19)	0.28	1.32 (0.42)	0.96 (0.15)	0.01
Local efficiency	0.34 (0.03)	0.22 (0.09)	0.26	0.59 (0.38)	0.27 (0.05)	<0.01
Global efficiency	0.21 (0.05)	0.24 (0.01)	0.64	0.17 (0.03)	0.25 (0.01)	0.45

Lower raw TMT-A scores were significantly associated with lower local efficiency (r = 0.37, P = 0.03), and lower verbal memory scores were statistically significant and associated with lower global efficiency (r = 0.54, P = 0.02) in the patient group, but not in the healthy control group.

Characteristics of hub brain regions relating to neurocognitive function deficits

Brain regions of research participants were evaluated for network hub status based on nodal degree values exceeding 1.5 SD above the mean network (Cao et al. 2017). Hub characteristics of brain regions are shown in Figures 4.2 and 4.3. As seen in Figure 4.2, functional hub brain regions for cancer patients are mainly located in temporal regions, while parietal regions are the functional hubs in healthy controls.

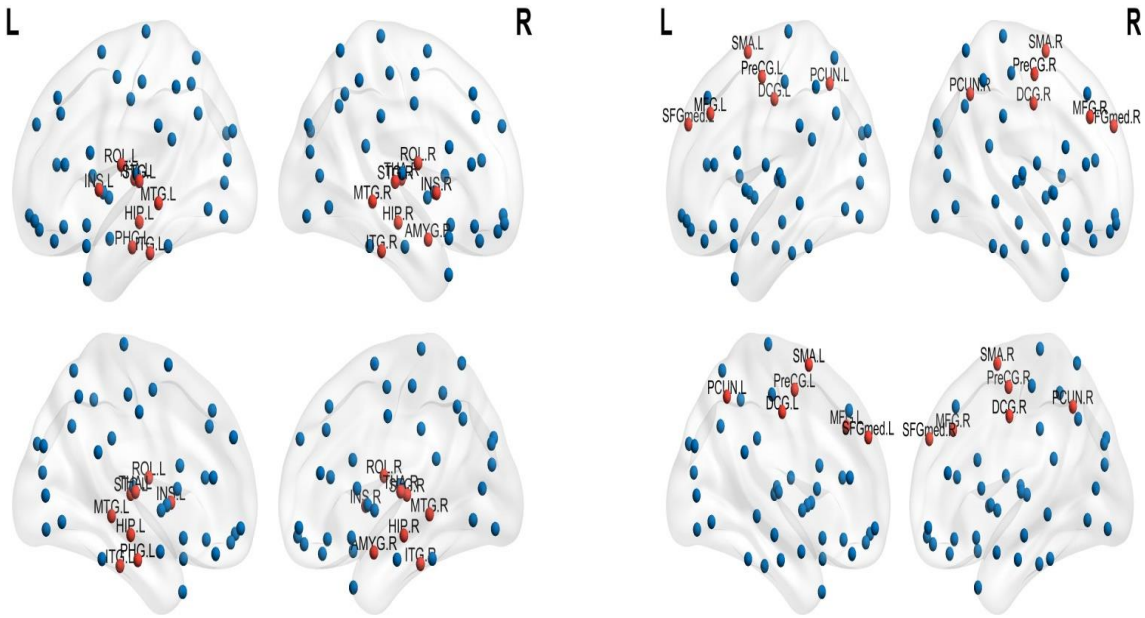

Figure 4.2 Hub brain regions (in red) of patients (left figure**) versus healthy controls (**right figure**)**

L, left; R, right.

AMYG, Amygdala; DCG, median cingulate and paracingulate gyri; HIP, Hippocampus; INS, insula; ITG, inferior temporal gyrus; MFG, middle frontal gyrus ; MTG, middle temporal gyrus; PreCG, precental gyrus; PCUN, precuncus; PHG, parahippocampal; ROL, rolandic operculum; SFGmed, superior frontal medial gyrus; SMA, supplementary motor area; STG, superior temporal gyrus; THA, thalamus.

Within the patient group, left hippocampus, left parahippocampal gyrus, left and right insula; middle temporal gyrus, and superior temporal gyrus are functional hubs for patients with neurocognitive function deficits (Figure 4.3).

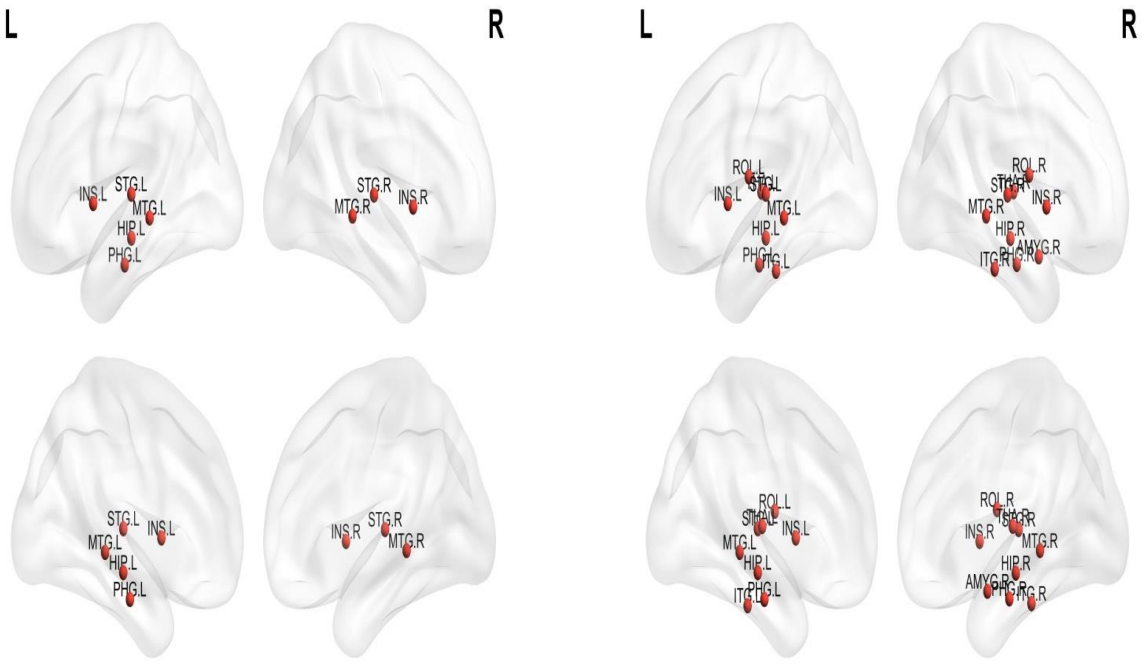

Figure 4.3 Hub brain regions of patients with neurocognitive function deficits (left figure**) versus patients without neurocognitive function deficits (**right figure**)**

L, left; R, right.

AMYG, Amygdala; HIP, Hippocampus; INS, insula; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; PHG, parahippocampal; ROL, rolandic operculum; STG, superior temporal gyrus; THA, thalamus.

4.3 Results of Study Stage 3

Results

Research participant characteristics

Of the 288 participants, 158 patients with gynecological cancer had completed primary cancer treatment, and 130 non-cancer controls were balanced in terms of age and marital status (Table 4.11). Nearly half of patient participants (n = 81, 51.3%) were in the early stages of cancer, more than 60 per cent of patients (n = 98, 62.0%) had a diagnosis of cervical cancer, and more than half of patients were receiving chemotherapy or a combination of chemotherapy and other cancer treatment. All research subjects' demographic and clinical characteristics are shown in Table 4.11.

Table 4.11 Demographic and clinical characteristics of participant groups at study Stage 3

Variables	Mean (SD) / n (%)		*P*
	Patient group (n=158)	**Healthy controls** (n=130)	
Age (years)	45.86 (10.56)	44.55 (9.72)	0.157
Education levels			<0.001
Primary school or below	103 (65.2)	65 (50.0)	
High school	34 (21.5)	15 (11.5)	
College or above	21 (13.3)	50 (38.5)	
Employment status			<0.001
Employed but on medical leave	32 (20.3)	100 (76.9)	
Unemployed or retired	126 (79.7)	30 (23.1)	
Marital status			0.895
Single	9 (5.7)	8 (6.2)	
Married	142 (89.9)	117 (90.0)	
Divorced	6 (3.8)	5 (3.8)	
Widowed	1 (0.6)	0 (0.0)	
Disease stage			
Stage I-IIa	81 (51.3)		
Stage IIb-IIIa	57 (36.1)		
Stage IIIb	20 (12.6)		
Disease diagnosis			
Cervical cancer	98 (62.0)		
Ovarian cancer	28 (17.7)		
Uterine cancer	14 (8.9)		
Other (e.g. GTN)	18 (11.4)		
Types of treatment			
Surgery	37 (23.4)		
Chemotherapy*	14 (8.9)		
Surgery + chemotherapy*	71 (44.9)		
Surgery+radiation+chemotherapy*	21 (13.3)		
Radiation + chemotherapy*	15 (9.5)		

Abbreviation: GTN, Gestational Trophoblastic Neoplasia. *Chemotherapy regimens including Paclitaxel (TAXOL) with Carboplatin (CBP) or Cisplatin (DDP) or with both; CBP with Doxorubicin (ADM) or TAXOL with ADM; Bleomycin with Methotrexate (MTX) or MTX with DDP. All patients undertook a total of 4 cycles of chemotherapy.

Neurocognitive function of cancer patients compared to healthy controls

From Table 4.12, mean neurocognitive test scores in the patient group were lower than in healthy controls at T1 (pre-chemotherapy), especially in the domain of attention and working memory scores (both P values < 0.05). Of 158 patients, 31 patients reported neurocognitive function deficits at the time of diagnosis, according to the criteria of two or more neurocognitive tests (AVLT, TMT, COWA and Digit Span test) had a Z-score at or below -1.5, and/or one test had a Z-score at or below -2.0 of the healthy control group (Wefel et al. 2011).

Table 4.12 Mean scores of neurocognitive tests at T1

Variables	**Mean (SD)**		***P***
	Patient group (n=158)	**Healthy controls** (n=130)	
Attention and working memory			
Digit span forward	6.76 (2.01)	7.99 (3.87)	0.03
Digit span backward	2.16 (1.24)	3.98 (1.89)	0.01
Verbal memory			
AVLT immediate recall	16.65 (6.45)	17.18 (5.43)	0.19
AVLT delayed recall	5.86 (1.73)	6.13 (3.64)	0.41
AVLT recognition	10.63 (1.97)	11.08 (2.96)	0.21
Psychomotor speed			
TMT-A	54.13 (26.25)	55.26 (22.65)	0.07
Executive function			
TMT-B	74.29 (32.12)	74.47 (35.72)	0.83
Language			
COWA	31.98 (8.11)	32.08 (8.79)	0.92

Abbreviation: AVLT, Auditory Verbal Learning Test; COWA, Controlled Oral Word Association; TMT, Trail Making Test.

At T2 (post-chemotherapy), there were a total of 46 patients who reported neurocognitive function deficits. The mean scores of working verbal memory were lower than in the healthy controls (all P values < 0.01) (Table 4.13).

Table 4.13 Mean scores of neurocognitive tests at T2

Variables	**Mean (SD)**		***P***
	Patient group (n=31)	**Healthy controls** (n=31)	
Attention and working memory			
Digit span forward	6.04 (2.73)	7.96 (1.99)	0.01
Digit span backward	1.96 (1.27)	3.93 (2.20)	<0.01
Verbal memory			
AVLT immediate recall	11.60 (4.76)	16.74 (3.65)	<0.01
AVLT delayed recall	3.86 (2.38)	6.36 (2.18)	<0.01
AVLT recognition	9.87 (2.61)	10.81 (0.96)	0.18
Psychomotor speed			
TMT-A	54.11 (25.48)	55.10 (24.86)	0.09
Executive function			
TMT-B	73.33 (36.07)	74.11 (29.55)	0.27
Language			
COWA	32.06 (6.48)	32.93 (8.89)	0.13

Abbreviation: AVLT, Auditory Verbal Learning Test; COWA, Controlled Oral Word Association; TMT, Trail Making Test.

DTI data and correlations with the mean changes scores of neurocognitive test performance

Differences between the groups in terms of DTI parameters are shown in Table 4.14. Within the left hippocampus, FA values decreased in the patient group (P=0.02) from T1 (pre-chemotherapy) to T2 (post-chemotherapy). MD values increased in the patient group (P=0.03) from T1 (pre-chemotherapy) to T2 (post-chemotherapy).

Table 4.14 Changes in DTI parameters for white matter in left hippocampus between T1 and T2

DTI parameters	**Patient group** (n=31)		***P***	**Age-matched healthy controls** (n=31)		***P***
	T1	**T2**		**T1**	**T2**	
FA	0.474 (0.018)	0.419 (0.016)	0.02	0.579 (0.021)	0.572 (0.022)	0.72
MD ($\mu m/s^2$)	0.421 (0.021)	0.473 (0.017)	0.03	0.770 (0.019)	0.773 (0.022)	0.91
AD ($\mu m/s^2$)	0.716 (0.031)	0.736 (0.017)	0.13	0.771 (0.018)	0.767 (0.022)	0.86
RD ($\mu m/s^2$)	0.269 (0.035)	0.281 (0.042)	0.21	0.259 (0.021)	0.257 (0.022)	0.92

Abbreviation: FA, Fractional anisotropy; MD, Mean diffusivity; AD, Axial diffusivity; RD, Radial diffusivity

For correlations of DTI parameters with cognitive test performance, FA (fractional anisotropy) values in the intervention group had positive significant correlations with the mean change scores of AVLT-delayed performance (r=0.52, P=0.01), although other DTI parameters of MD (mean diffusivity), AD (axial diffusivity), and RD (radial diffusivity) had no statistically significant correlations with the mean change scores of neurocognitive test performance.

1H-MRS data and correlations with the mean change scores of neurocognitive test performance

Differences between the groups in metabolite ratios relative to NAA (NAA/Cr and NAA/Cho) were lower in the patient group than in the age-matched healthy control group at both time assessment points: T1 (pre-chemotherapy) and T2 (post-chemotherapy). The changes of NAA/Cr and NAA/Cho ratios were found to have significantly decreased in the patient group (both P values <0.05) (Table 4.15).

Table 4.15 Changes of 1H-MRS of parameters in the left hippocampus between T1 and T2

MRS parameters	**Patient group** (n=31)		***P***	**Age-matched healthy controls** (n=31)		***P***
	T1	**T2**		**T1**	**T2**	
NAA/Cr	1.39 (0.11)	1.25 (0.13)	0.03	1.46 (0.12)	1.49 (0.14)	0.79
NAA/Cho	1.34 (0.13)	1.16 (0.16)	0.01	1.47 (0.12)	1.45 (0.09)	0.83
Cho/Cr	0.98 (0.16)	0.94 (0.08)	0.87	1.04 (0.11)	1.07 (0.16)	0.89
Cho/NAA	0.75 (0.07)	0.76 (0.13)	0.93	0.74 (0.04)	0.70 (0.07)	0.82

Abbreviation: NAA, N-acetylaspartate; Cr, creatine; Cho, choline.

There were significant positive correlations of NAA/Cr with the mean changes of total digit span test scores (r=0.71, P<0.01) in the patient group.

Structural brain networks and correlations with subjective cognitive deficits

Differences between the groups in structural network metrics were lower in the patient group than in the age-matched healthy control group at both time assessment points: T1 (pre-chemotherapy) and T2 (post-chemotherapy) (Table 4.16).

Table 4.16 Changes of structural brain network measures in each group between T1 and T2

Structural network metrics	**Patient group** (n=31)		*P*	**Age-matched healthy controls** (n=31)		*P*
	T1	**T2**		**T1**	**T2**	
Graph metrics						
Small-worldness	1.298 (0.027)	1.103 (0.034)	0.02	1.341 (0.012)	1.339 (0.014)	0.87
Global efficiency	0.135 (0.009)	0.126 (0.012)	0.04	0.139 (0.011)	0.134 (0.009)	0.92
Local efficiency	0.187 (0.007)	0.178 (0.006)	0.57	0.201 (0.009)	0.207 (0.004)	0.94
Clustering coefficient	1.674 (0.201)	1.312 (0.398)	0.01	1.765 (0.201)	1.793 (0.019)	0.89
Characteristic path length	1.489 (0.063)	1.427 (0.152)	0.27	1.326 (0.013)	1.367 (0.103)	0.65

4.4 Summary

This chapter reported study findings of all study stages. Study Stage 1 added new insight into the growing body of research on cognitive complaints among Chinese gynecological cancer survivors. Findings of this study stage revealed that the prevalence of cognitive complaints among Chinese cancer survivors was high, with the most common complaints being loss of concentration and memory problems, which severely impacted daily living, quality of life, physical and psychological health, and work capabilities. It is necessary to raise healthcare providers' awareness in order to address women's cancer-related cognitive problems in practice. Study Stage 2 reported the first longitudinal evidence of functional brain network alteration and neurocognitive changes in Chinese gynecological cancer patients. It found that the risk of brain function and neurocognitive changes following chemotherapy can potentially guide patients in making appropriate decision-making on treatment, and help health care professionals prioritize patients for early intervention. Study Stage 3 indicated that patients with neurocognitive function deficits reported poorer neurocognitive performance than age-matched healthy controls. By using a multimodal MRI approach, gynecological cancer patients reported the lowest FA values, NAA/Cr, NAA/Cho and structural network metrics at the end of chemotherapy. Hence, this study stage also provided novel insights into the neurobiological basis of neurocognitive function deficits in the human brain that have been induced by cancer and/or its treatment.

CHAPTER 5

Discussion and Study Limitations

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5.1 Discussion

Study Stage 1: This is one of the first published studies exploring cognitive complaints among Chinese cervical cancer survivors, although there is accumulating evidence documenting cognitive impairment issues among cancer survivors, mainly dominated by breast cancer survivors (Von Ah 2015). The prevalence of cognitive complaints among Chinese cervical cancer survivors was 64.5%, which is consistent with previous research (Wefel et al. 2015). As this study was preliminary and adopted a small and non-random sample, epidemiological studies are needed to further quantify the prevalence, impact and extent of cognitive complaints in this study population (Cheung et al. 2012).

Concurring with previous research evidence, chemotherapy and the side effects of cancer are the most common factors associated with cognitive complaints (Craig et al. 2014; Janelsins et al. 2014). This study identified that cervical cancer survivors perceive aging as a likely contributing factor to cognitive impairment. Study participants considered "aging as a normal process of cognitive decline," and viewed cognitive impairment as a process that could not be changed. Consistent with previous studies (Hart et al. 2003; Myers 2009), study participants also reported that worry, fatigue and pain all seem to be related to cognitive impairment.

The patient experience of cancer-related cognitive impairment may be the commonality of the phenomenon across tumor types (Myers 2013), as this study did not find unique cognitive deficits in women with cervical cancer. However, this study did identify unique cultural issues for Chinese women seeking coping strategies for cognitive impairment. Some women did nothing to try to cope with their cognitive complaints. 'Doing nothing' as a common coping strategy for cognitive complaints could be related to the Chinese Taoist philosophy: "Accepting the fact that a situation cannot be changed, and telling oneself that

one should do little, as things will be all right at the end of the day" (Zeng 2008). Hence, a coping strategy of doing nothing and self-adjustment could help these survivors maintain a sense of calm when facing difficulties that cannot be changed.

As in previous studies (Craig et al. 2014; Janelsins et al. 2014; Wefel et al. 2015), this study's findings also revealed that cognitive complaints had a variety of consequences that impacted on daily living, quality of life, physical and psychological health, and work capabilities. While research into the relationship between cognitive functioning and work ability is still in its infancy (Munir et al. 2011), returning to work is a critical milestone for many survivors, since work plays a key role in psychological, economic, and social well-being (Becker et al. 2015). If cancer survivors were able to obtain individualized support and work-related adjustments from their employer, they would be more likely to continue working (Cheung et al. 2012). Hence, cognitive complaints in cancer survivors generate numerous supportive care requirements, not only in the workplace, but also from healthcare providers.

In order to manage cognitive problems, common supportive care needs that patients require from healthcare providers include the provision of information on the common signs of cognitive impairment, as well as management strategies, effective treatment therapies and possible rehabilitation services. Although many healthcare providers may gloss over the issue of patient cognitive complaints, believing they have no curative treatment to offer (Duijts et al. 2014), findings from a meta-analysis indicate that neuropsychological interventions (cognitive rehabilitation, cognitive training and neuromodulation strategies) can improve cognitive function in cancer survivors (Zeng et al. 2016a). In particular, a recent Cochrane review indicates that cognitive training may be effective at improving patients' cognitive function, as well as their quality of life (Treanor et al. 2016). Additionally, behavioral intervention strategies (increasing physical activity levels and fostering

supportive social relationships) could be helpful in improving cognitive function in cancer survivors (Henneghan 2016).

Through a synthesis of these study findings, a preliminary cognition model for cervical cancer survivors after cancer treatment was established, to provide a theoretical underpinning for the perception of cognitive complaints, contributing factors, mediating factors, and the consequences of cognitive impairment in this study population. This model may be able to inform and stimulate further intervention studies. Certainly, this preliminary cognition model may be continuously refined through further empirical research investigations. Overall, this model illustrates coping strategies at a personal level, through self-adjustment or by doing nothing. Additionally, supportive care services, such as education and counselling for family members, could mitigate the consequences of cognitive impairment. In addition, participants felt a great need for support, including peer support, from diagnosis onwards, as well as for information on available rehabilitation services and counselling, in order to modulate the degree of cognitive complaints. For gynecological cancer survivors, cognitive complaints cause negative effects in terms of daily living, QOL, work capability, and physical and psychological health.

Study Stage 2: This is the first study to include a healthy control group with similar demographic characteristics, and a longitudinal design with repeated rs-fMRI assessment with the application of a longitudinal graph theoretical approach to analyze functional brain networks in Chinese gynecological cancer patients. This study found that after chemotherapy treatment, gynecological cancer patients had lower neurocognitive test performance and changes in functional network measures compared to age-matched healthy controls, which was in line with previous research on cancer patients after chemotherapy

(Cheng et al. 2017). In specific, disrupted small-world properties were found in gynecological cancer patients. Functional networks with prominent small-world properties ensure higher information-processing efficiency for both locally specialized and globally integrated processing (Bullmore and Sporns 2009). Decreased small-worldness index among cancer patients may result in lower information processing speed, which was supported by the significant associations of lower local network efficiency with lower raw TMT-A scores.

While the findings of this study indicated that the functional brain networks of both cancer patients and healthy controls show common small-world properties (both groups' index values >1), the local efficiencies were significantly higher in cancer patients post-chemotherapy than in the healthy controls. As local efficiency is a measure of average local subgraphs in a network, increasing local efficiency in cancer patients may result in disrupted information processing among distant brain regions (Latora and Marchiori 2001), and lower network attack tolerance was associated with greater neurocognitive dysfunction in cancer patients (Kesler et al. 2017a). In addition, this study found significantly decreased global efficiency, and significantly positive correlations between decreased global efficiency and lower verbal memory scores in the patient group only. Study findings were consistent with previous research, which reported reduced functional brain network efficiency in response to a simulated neurodegeneration in breast cancer survivors receiving chemotherapy, compared with healthy controls (Kesler et al. 2017b).

This study found that functional hubs were mostly located in the temporal regions for patients, and in the frontal and parietal regions for healthy controls, reflecting the main functions associated with these brain regions (Bullmore and Sporns 2009). These study findings discriminated between the functional hub networks of patients and those of healthy controls, and also identified functional hubs for patients with neurocognitive function

deficits as well as for patients without neurocognitive function deficits. Functional hubs for patients with neurocognitive function deficits include the left and right insula, middle temporal gyrus, and superior temporal gyrus, left hippocampus and parahippocampal gyrus, which are essential for network resilience and regulation information flow (Vertes and Bullmore 2015), as functional hubs play key roles in forming bridges between different networks (van den Heuvel and Sporns 2013). Brain regions with a high node degree were identified as hubs, which would be the most vulnerable areas in local functional networks (Kesler et al. 2017b). Taken together, these findings suggest that all of these hub brain regions are key regions implicated in the pathophysiology of neurocognitive function deficits; the connectome properties of these regions may to some extent predict neurocognitive functioning (Kesler et al. 2017b). Therefore, this study's findings provide new insights into the mechanism of neurocognitive function deficits in cancer patients.

Evaluating the relative importance of brain neuroimaging features and their association with neurocognitive function was essential in understanding specific brain functional network patterns involved in neurocognitive function deficits (Kesler et al. 2017b). Rs-fMRI may be a particularly promising tool in identifying cancer patients at risk of long-term cancer-related brain injury (Kesler et al. 2017a; 2017b). In addition, connectome metrics derived from rs-fMRI show good test-retest reliability (Termenon et al. 2016). Furthermore, the rs-fMRI acquisition required approximately eight minutes, making this scan a practical possibility in busy clinical settings. Thus, utilizing rs-fMRI could be a promising tool to better understand the longitudinal changes of treatment-related neurocognitive outcomes and functional network connectome properties.

Compared with healthy controls, patients reported a higher prevalence of subjective cognitive impairment in this study. This study finding suggests that neurocognitive function deficits could possibly be associated with chemotherapy rather than depressive symptoms.

Previous research found that Chinese female cancer survivors reported higher levels of anxiety and depression, resulting in lower levels of work productivity (Zeng et al. 2016b). While there is a growing concern regarding possible neurocognitive function deficits following primary cancer treatment (Van Londen et al. 2014), appropriately assessing cognitive impairment in cancer survivors is an important aspect of neurocognitive function deficits (Van Dyk and Ganz 2017). Neurocognitive function deficits are usually subtle, and standard definitions of impairment on neuropsychological assessments may not formally identify these mild, but nonetheless functionally disruptive changes (Ganz et al. 2013). In contrast, self-report methods may be more sensitive to identify subtle changes, "because self-report measures tap a patient's self-knowledge of their previous ability, whereas neurocognitive testing usually approximates premorbid functioning by using test-based norms (Van Dyk and Ganz 2017). In particular, self-reported cognitive measures also require substantially fewer resources than do formal neurocognitive tests, due to the lack of practice effects and clinical adaptability (Janelsins et al. 2017; Van Dyk and Ganz 2017). While self-reported cognitive measures have several important strengths in research settings, future studies should utilize both subjective and objective neuropsychological assessments to quantify the prevalence, severity, and impact of CRCI in the Chinese gynecological cancer population, as few studies have been conducted to date on Chinese cancer survivors.

This study found that patients after chemotherapy reported the lowest level of small-worldness index and global and local network efficiency, compared with age-matched non-cancer controls. Research evidence shows that disrupted functional networks have been demonstrated to have detrimental effects on cognitive functioning (Bruno et al. 2012; Cheng et al. 2017; Kesler et al. 2015; 2016). Global and local network efficiency has been demonstrated to be important for cognitive functioning, as global efficiency plays a key role in how information may be efficiently exchanged across the entire brain network (Tuladhar

et al. 2016). In contract, local network efficiency measures the average of local subgraphs in a network and indicates how tolerant a network is to local failures (Latora and Marchiori 2001). Regarding the associations between functional network properties and subjective cognitive function deficits, this study found that higher values of small-worldness index and shorter characteristic path length were related to higher FACT-Cog total scores (i.e. better cognitive functioning). Study findings reveal that primary cancer treatment can result in a more random organization of brain network changes, which contributed to reducing functional brain specificity and segregation, with implications for cognitive functioning (Bruno et al. 2012; Cheng et al. 2017).

Study Stage 3: The final study stage aimed to examine the effects of chemotherapy on neurocognitive functioning, white matter integrity and neurochemical properties in the left hippocampus of gynecological cancer patients, and to explore the neurobiological mechanism of cognitive impairment in cancer patients on a microscopic level by using DTI and MRS. Based on the mean score of the neurocognitive tests, the working memory and immediate verbal memory scores in the patient group were statistically significantly lower than in the age-matched patient controls. When investigating the microstructural white matter in the brain, DTI data in this study indicated that the global and local connectome properties in the patient group with cognitive impairment were lower than in the patient control group at baseline. "Group differences in nodal degree and global network efficiency of the brain can help find specific neural circuits and may be at high risk for loss of response plasticity (p.333)" (Bruno et al. 2012).

Although one of the essential DTI parameters-FA had a statistically significant association with delayed verbal memory score, this study did not find any significant correlation

between global and local connectome properties, and neurocognitive test scores. Consistent with previous research, Bruno et al. also found that breast cancer patients displayed alterations in global and regional network characteristics, but these network alterations had no significant correlation with cognitive performance (Bruno et al. 2012). However, a cross-sectional study found that breast cancer survivors had reduced brain structural network efficiency, which was associated with a simulated neurodegeneration in these patients compared with healthy controls (Kesler et al. 2015). Another cross-sectional study also indicated that poorer network organization was found to be associated with greater cognitive impairment (Kesler et al. 2016). Furthermore, recent longitudinal research reported that decreased small-worldness and local efficiency was related to poorer overall cognitive performance across time in a group of male cancer patients (Amidi et al. 2017). This study failed to find either small-worldness or nodal degree associated with neurocognitive test scores, which may be due to the small sample size, as supporting the optimal level of cognitive processes depends on an effective network organization and integration across brain regions (Sporns 2011).

By using multimodal neuroimaging of MRS, this study investigated absolute and relative concentrations of NAA, Cr, and Cho in the left hippocampus. Although the absence of absolute of NAA, Cr and Cho abnormalities in the patient group may be due to the mild degree of cognitive impairment in these patients before chemotherapy, the findings of the present study indicated a statistically significant reduction of NAA/Cr in the left hippocampus. As NAA is localized almost exclusively in neurons, the reduction in relative NAA in the left hippocampus suggests that axonal degeneration contributed to the observed diffusion abnormalities (de Ruiter et al. 2012). In addition, this study found that the reduction of NAA/Cr was associated with lower mean digit span score (lower working

memory functioning). Previous research also found that neurochemical properties were associated with neurocognitive deficits (de Ruiter et al. 2012). Perhaps abnormalities in both the metabolic-level and network-level changes in the brain may appear before the alterations in clinical performance of a neurocognitive test (Mayeux 2010). Thus, detecting alterations in structural brain networks and brain metabolic properties might provide the possible neurobiological basis of neurocognitive function deficits in gynecological cancer patients, which could be used for the relevant development of prevention strategies.

This is the first multimodal MRI study to explore the underlying mechanism of neurocognitive function deficits in Chinese gynecological cancer patients, which may be related to white matter injury in the left hippocampus. Patients at both time assessment points had impairment of white matter integrity (reduced FA values and increased MD values), and DTI parameter changes in the patient group were higher than in the healthy control group. Previous research has indicated that changes in FA and MD values could be due to demyelination (de Ruiter et al. 2012). Preclinical research evidence specifically indicates that the possible mechanism of decreased white matter integrity may be attributed to incoherence of myelin basic protein fiber (Zhou et al. 2016). Thus, the findings of this multimodal MRI study suggest that chemotherapy may aggravate cognitive impairment by decreasing myelination.

Additional negative effects of chemotherapy on CRCI included a reduction in relative concentrations of NAA for patients from pre-chemotherapy to post-chemotherapy in the patient group. Previous research also indicated that the ratio of NAA/Cr was obtained by measuring the level of NAA and Cr to evaluate neuronal activity in the hippocampus (Tang et al. 2012). A review suggested that lower levels of NAA may reflect inefficient neuronal

viability (Yoon et al. 2013). Therefore, on a microstructural level, chemotherapy exacerbating neurocognitive function deficits may be attributed to its decreasing myelination and reducing neuronal viability of white matter in the hippocampus. Monitoring structural alterations of white matter connections and concentrations of NAA could be potential underlying neurobiological mechanisms of neurocognitive function deficits in patients with gynecological cancer.

5.2 Study Limitations

This first study stage has two limitations. First, this preliminary study only recruited participants at a single medical center, and the sample size could not be representative of this population in general. This study primarily offers significant insights into perceived cognitive complaints, contributing factors and consequences of neurocognitive function deficits in gynecological cancer survivors. Second, this study utilized a cross-sectional design and included participants who had completed primary cancer treatment within a short period of time.

The main limitation of this study Stage 2 is the small sample size, which may have reduced its power to detect functional differences between patients and healthy controls. This study found limited group differences achieving statistically significant differences in neurocognitive test performance, which may be partially due to limited power. Hence, in future research, there is a need to recruit larger sample sizes and use longer-term follow-up to replicate these results, and to investigate the potential reversibility of chemotherapy-induced neurocognitive function changes (Amidi et al. 2017). In addition, this study only chose the AAL atlas with 90 regions (ALL-90) as a brain Parcellation scheme to calculate functional connectome properties, while excluding other brain Parcellation schemes, such

as Harvard-Oxford Atlas, as well as randomly parceling the brain into 1024 ROIs. According to previous studies on neurocognitive function deficits in cancer patients (Amidi et al. 2017; Kesler et al. 2017a,b), the AAL-90 Parcellation is one of the most common brain Parcellation schemes.

The main limitation of study Stage 3 was that MRI and MRS data were only acquired in patients with neurocognitive function deficits. In addition, the intrinsic clinical differences between cancer patients (e.g. types of cancer, disease stage or comorbidities) resulted in different chemotherapy regimens assigned to each patient. Therefore, future studies using a larger sample size and including homogeneous cancer patients, preferably with identical chemotherapy regimens, should be conducted to replicate these study findings. DTI data only used the deterministic tractography, future research can use the probabilistic tractography for the precision of cross fiber tracking. MRS data only analyzed the relative concentrations of NAA, Cr, Cho, NAA/Cr, NAA/Cho, future research should analyze the absolute concentrations. The neuroimaging mechanism of white matter injury as proposed underlying mechanism of neurocognitive function deficits, the biological mechanism of neurocognitive function deficits cannot be directly translated from brain imaging measures. Hence, future animal studies can help define potential biological mechanism of neurocognitive function deficits.

5.3 Summary

This chapter provides a discussion of study findings and the limitations of these study stages. The study implications of these study findings and conclusion of this study will be presented in the next chapter.

CHAPTER 6

Study Implications and Conclusion

6.1 Neurocognitive Function in Gynecological Cancer Patients

Clinical staff should recognize that non-central nervous system (CNS) cancer, including gynecological cancer may also be involved in cognitive impairment that patients find distressing (Joly et al. 2015). In this study, gynecological cancer patients reported high levels (35%) of neurocognitive function deficits prior to cancer treatment, and the rate of cognitive impairment at post-chemotherapy was as high as 64.5% (Zeng et al. 2017). As this PhD study only assessed gynecological cancer patients' neurocognitive functioning immediately after chemotherapy, future research should evaluate patients' neurocognitive functioning at least one year after chemotherapy or longer, to provide insights into the changes occurring in neurocognitive functioning in this study population. In addition, estimates of the prevalence of neurocognitive functioning deficits are largely variable, due to the diagnosis of neurocognitive function deficits, either based on subjective cognitive scales such as FACT-Cog, or on objective neurocognitive test performance, such as the core set of tests recommended by the ICCTF (Wefel et al. 2011). Future CRCI research should consider the new diagnosis criteria of "mild neurocognitive disorder" by DSM-V (American Psychiatric Association 2013), since the impairment of neurocognitive functioning in cancer patients is subtle per se (Vannorsdall 2017). Hence, the term "mild neurocognitive disorder" may be applied to cancer patients.

6.2 Possible Neurobiological Mechanism of Neurocognitive Function Deficits

By a synthesis of findings of the prospective cohort in the Chapters 4 and 5, patients reported aggravating neurocognitive function deficits after chemotherapy, attributed to the injury of white matter. DTI and behavioral data have shown that FA values were significantly correlated with the mean change in verbal memory scores. Decreased FA values indicate

worse white matter integrity, which may result in reduced brain flexibility with less efficient brain networks. MRS measurements of NAA/Cr and/or NAA/Cho indicated axonal degeneration and demyelination as possible causes of white matter injury (Kaiser et al. 2014). After chemotherapy, patients reported a significant level of reduction in the relative ratios of NAA/Cr, which were significantly correlated with the mean change in digit span test sores. Hence, MRS provides additional biochemical information to support the assertion that chemotherapy may have effects in deteriorating white matter injury. Possible white matter injury as a mechanism of neurocognitive function deficits in gynecological cancer patients is illustrated in Figure 6.1.

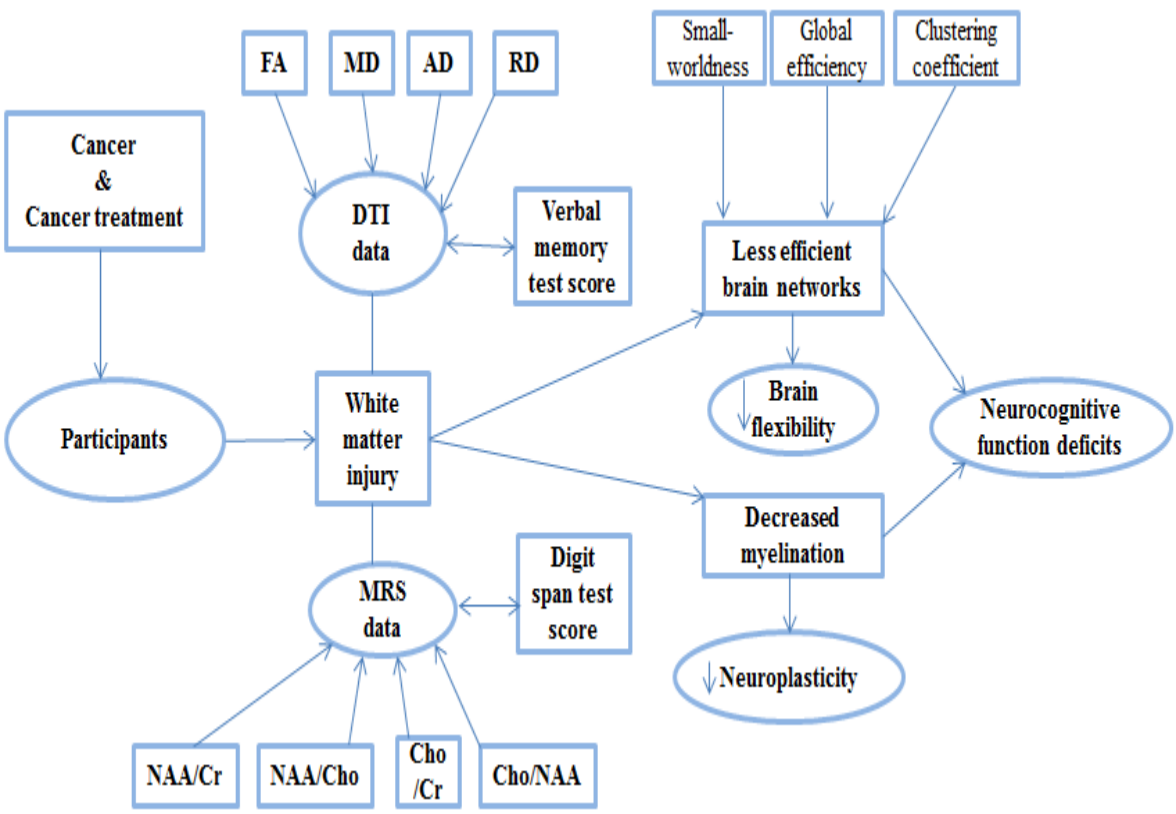


Figure 6.1 Putative mechanisms of neurocognitive function deficits in gynecological cancer patients

6.3 Cognitive Rehabilitation of Neurocognitive Function Deficits

Literature review of this thesis found three types of neuropsychological interventions that were used to manage mild neurocognitive function deficits in non-CNS cancer survivors. Cognitive training interventions demonstrated benefits in subjective and objective cognitive function, especially in the domain of executive function. Cognitive rehabilitation interventions produced significant effects in objective cognitive function, mainly in the domain of memory and verbal learning. While neuromodulation strategies indicated positive effects in the improvement of subjective and objective cognitive function, these intervention strategies are largely anecdotal, based on theorized causes, as the causes of neurocognitive function deficits in cancer survivors are still unknown (McHenry 2015). Because of this, it is difficult to determine which intervention strategies are better than others for patients experiencing neurocognitive function deficits. Thus, the key part of this PhD study is a prospective and longitudinal study that was conducted to explore the possible mechanism and cause of neurocognitive function deficits. Findings of this prospective cohort study could help healthcare professionals in designing better intervention strategies to ameliorate this distressing symptom in gynecological cancer patients.

6.4 Conclusion

In conclusion, the study demonstrated that there is a growing body of research on neurocognitive complaints in women with gynecological cancer, in particular, Chinese gynecological cancer patients. The qualitative study added new insight into the growing body of research on neurocognitive complaints of Chinese gynecological cancer survivors. Findings of this qualitative study revealed that the prevalence of neurocognitive complaints among Chinese cancer survivors was high, and the most common complaints were loss of

concentration and memory problems, which severely impacted daily living, quality of life, physical and psychological health, and work capabilities. These findings improved understanding of neurocognitive complaints, which could subsequently facilitate the development of relevant therapeutic interventions for the prevention of neurocognitive function deficits in this study population. It is also necessary to raise healthcare providers' awareness of women's cancer-related neurocognitive function deficits in practice. The quantitative part of this study reported the first longitudinal evidence of functional brain network alteration and neurocognitive function changes in Chinese gynecological cancer patients. This prospective cohort study found that information on the risk of neurocognitive function changes and brain networks following chemotherapy could potentially serve as a guide to patients in making appropriate treatment decisions, and help healthcare professionals prioritize patients for early intervention. By using a multimodal imaging approach, this multimodal MRI study also provided novel insights into the neurobiological basis of neurocognitive function deficits in the human brain that have been induced by cancer and/or its treatment.

APPENDICES

Appendix 1 Research Consent Form (English Version)

Project title: Neurocognitive function deficits and the associated brain networks in patients with gynecological cancer

Investigator(s): Dr Andy S.K. Cheng, Ms. Yingchun Zeng

Purpose of the Study: The purpose of this study was to explore the cognitive impairment of gynecological cancer patients pre- and post-chemotherapy and to examine the possible neural mechanisms of cognitive decline in this study population. The aims of study stage 1 were to explore Chinese gynecological cancer patients' perceived cognitive complaints and relevant supportive care needs after primary cancer treatment. The specific aims of study stage 2 were to assess cancer patients' neurocognitive functioning and functional brain networks in Chinese gynecological cancer patients pre- and post-chemotherapy. **Project Information:** This study includes a 2-hour cognitive assessment and 30-minute MRI brain scan. For the process of MRI scan, you just need to lie down in the scanner and take rest. During the scanning process, you will hear some noise from the scanner, so that we will ask you to wear the ear protector equipment.

Potential Risk: In the process of this study, there will be no danger on you. All information provided will be treated as strictly confidential. Participation is on voluntary basis and you are free to withdraw from the study at any time or any reason.

Consent

I, , have been explained the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name or photograph will not appear on any publications resulted from this study.

I can contact the investigator, Ms Zeng, at 27664340, or the project supervisor, Dr Cheng at 2766 5396 for any questions about this study. If I have complaints related to the investigator(s), I can contact Mr Mok, secretary of Departmental Research Committee, at 34003937. I know I will be given a signed copy of this consent form.

Signature (Subject)_____, Date_____

Signature (Researcher)_____, Date_____

Appendix 2 Research Consent Form (Chinese Version)

科研题目：妇科肿瘤病人的神经认识功能受损与相关脑网络的研究

科研人员：曾迎春 博士生，郑树基 博士导师

科研目的：此研究将分为两个阶段：第一个阶段访谈部分妇科肿瘤患者有关认知功能受损以及相关支持性照顾需求情况；第二阶段研究运用纵向研究评估化疗前后妇科肿瘤患者神经认知功能和脑功能网络的变化情况，通过主客观认知功能测试评估病人治疗前后的认知功能和 MRI 脑部扫描评估脑网络的变化情况。

科研资料：参与本研究需要完成一系列的认知测试、接受免费的 MRI 大脑扫描。MRI 大脑扫描也是无放射无创伤的检查方法。在整个扫描过程中，请您放松地躺好并保持静止，扫描过程中尽量避免讲话。整个 MRI 扫描过程可能会持续约 30 分钟。

潜在危险性：整个研究过程暂没有对您有任何危险。您有可能在 MRI 脑部扫描过程中，会听到噪音而可能引起不适但我们会给您做听力保护。所有提供的资料将视为绝对保密。参加者是自愿参加，并可以任何时间及无需提供任何理由下而放弃参与此研究。

同意书

本人_____已了解此次研究及明白我可以在任何时候、无任何原因放弃参与此次研究，而此举不会导致我受到任何惩罚或不公平对待。本人明白参加此研究课题的潜在好处和风险，而本人 的资料不会泄露给与此研究无关的人员，我的名字或相片不会出现在任何出版物上。本人若对此次研究有任何问题可联络此次研究课题负责人曾女士（27664340）及科研导师郑博士（27665396）。若本人对科研人员有任何投诉，亦可联络莫先生（科研委员会秘书），电话：34003937。本人亦明白会得到此份同意书的签署副本。

研究参与者签字_____ 日期_____

研究人员签字_____ 日期_____

Appendix 3 Research Information Sheet (English Version)

Project title: Neurocognitive function deficits and the associated brain networks in patients with gynecological cancer

Purpose of the Study: Up to 75% cancer patients experienced cognitive impairment after cancer treatment. The purpose of this study was to explore the cognitive impairment of gynecological cancer patients pre- and post-chemotherapy and to examine the possible prevention strategies for cognitive decline in this study population. The aims of study stage 1 were to explore Chinese gynecological cancer patients' perceived cognitive complaints and relevant supportive care needs after primary cancer treatment. The specific aims of study stage 2 were to assess cancer patients' neurocognitive functioning and functional brain networks in Chinese gynecological cancer patients pre- and post-chemotherapy, as well as acupuncture's possible underlying neurobiological mechanisms of mitigating cognitive impairment in gynecological cancer patients.

Project Information: Up to 75% cancer patients experienced acute cognitive impairment during chemotherapy. This study adopted the multimodal MRI to explore neurocognitive functions and its underlying neural mechanism of cognitive impairment among gynecological cancer patients. You can withdraw from this study at any time without giving reasons, and your withdrawal will not lead to any punishment or prejudice against you. Your personal information will not be disclosed to people who are not related to this study and your name or photograph will not appear on any publications resulted from this study.

Thank you very much for participating in this study.

Appendix 4 Research Information Sheet (Chinese Version)

科研内容说明书

研究题目：妇科肿瘤病人的神经认识功能受损与相关脑网络的研究

研究目的：化疗病人有高达 75%的不同程度的认知受损。此研究将分为两个阶段，第一个阶段访谈部分妇科肿瘤患者有关认知功能受损以及相关支持性照顾需求情况。第二阶段研究运用纵向研究评估化疗前后妇科肿瘤患者神经认知功能和脑功能网络的变化情况。通过神经认知功能测试和磁共振（MRI）脑部扫描等方法进行动态监测肿瘤患者治疗前后脑网络变化的情况。

检查过程描述：如果您同意参与研究，我们将询问您的过往病史，以确定您是否有资格参与。进入磁场区域前将对您仔细检查，以确保您的身体中没有任何金属物体，如动脉瘤夹、金属骨骼、关节钉、心脏起搏器或脊髓神经刺激器等，日常用品如信用卡、手表、珠宝、钱币和发夹被禁止进入磁共振扫描室。在整个扫描过程中，请您放松地躺好并保持静止，扫描过程中尽量避免讲话。整个 MRI 扫描过程可能持续约 30 分钟。

潜在风险：到目前为止，还未发现 MRI 检查会带来任何副作用。不过，如果在您的身体里有如上述的金属物体，磁体可能会对您造成伤害，您将被禁止参与 MRI 脑部扫描。在检查过程中，您可能会听到很大的噪音，这就是我们要求您戴上听力保护装置的原因。

研究的好处：您将免费获得认知功能的评估和脑部 MRI 免费的检查。

补偿和费用：参与该项研究包括 MRI 大脑扫描和认知功能评估不会向您收取任何费用，也不会向您的医疗保险公司或单位收取任何费用。

自愿参与或退出：参与本研究是自愿的，您可以自由地随时退出。您参加与否不会影响您当前或将来的医疗治疗。

信息保密：您提供给我们的信息是保密的，您的医疗信息及健康状况不会被泄露给任何人。该项研究可能会在科学会议和科学期刊上发表，但是在任何公开研究报告中都不会使用您的名字。

谢谢您参与此研究！

Appendix 5 Chinese Version of Data Collection Tool

本研究的主要目的是了解癌症化疗前后病人的认知功能状况，认知测试需时约2小时。您所提供的资料我们将会严格保密！

住院ID号：_____
姓名：_____
手机或微信号：_____

一、您的基本情况:请您在下列符合您情况的选项前的空格内打［√］或在横线上填写.

1.年龄:_____岁

2.文化程度: □ (1)初中及以下; □ (2)高中或中专; □ (3)大专;□ (4)本科;
□ (5)研究生及以上

3.就业状态: □ (1)在职; □ (2)不在职

4.婚姻状况: □ (1) 未婚; □ (2)已婚; □ (3)离异(在诊断前);
□ (4) 离异(在诊断后); □ (5)其它:_____ (请注明)

5.子女状况: □ (1)无; □ (2)有

6.您疾病的诊断名称:_____

7.初次诊断的日期:_____(年/月/日)

8. 疾病的分期: □ (1) 早期; □ (2) 中期; □ (3) 晚期

9. 治疗方式: □ (1) 单纯手术; □ (2) 单纯放疗; □ (3)手术加放疗;
□ (4)手术加化疗; □ (5)手术加放疗和化疗;
□ (6)其它:_____ (请注明)

10. 完成主要癌症治疗的时间:_____(年/月/日)

11.月经情况: □ (1)未绝经; □ (2)已绝经; □ (3)其它:_____(如围绝经期)

二、认知测试

2a. 听觉词语学习测验 （版权所有，不能展示测验词语具体内容）

我现在给你读12个词语，在我每次读完时请复述给我听。我将会读3次，请您即刻、5分钟后、20分钟后分别复述给我听，以及分类记忆和再认。

No.	项目	第一次	第二次	第三次		第四次		第五次	第六次		再认	
1					间隔其它测验5分钟		间隔其它测验20分钟		花朵类			
2												
3												
4												
5									职业类			
6												
7												
8												
9									服饰类			
10												
11												
12												
	正确数										正确再认数：	
	错误插入										错误再认数：	
	语义串联											

三、疲劳情况评估

在我们一生中大部分人都有感到疲倦或疲劳的时候，在过去一周内,您有没有感到异于平常的疲劳或劳累?： (0)没有 (1)有

	没有疲劳										极度疲劳
1.请圈选一个数字，最能形容<u>您现在疲劳的程度</u>（倦怠、疲惫或劳累）	0	1	2	3	4	5	6	7	8	9	10
2. 请圈选一个数字，最能形容您过去<u>24 小时内的平均疲劳</u>的程度	0	1	2	3	4	5	6	7	8	9	10
3. 请圈选一个数字，最能形容您过去<u>24 小时内的最严重疲劳</u>的程度	0	1	2	3	4	5	6	7	8	9	10
4. 请圈出一个数字最能说明您在过去 24 小时内，疲劳程度如何干扰到您的	没有干扰										完全干扰
“一般活动”	0	1	2	3	4	5	6	7	8	9	10
“情绪”	0	1	2	3	4	5	6	7	8	9	10
“行走能力”	0	1	2	3	4	5	6	7	8	9	10
“一般工作（包括在家以外的工作及日常家务）”	0	1	2	3	4	5	6	7	8	9	10
“与他人关系”	0	1	2	3	4	5	6	7	8	9	10
“享受生活”	0	1	2	3	4	5	6	7	8	9	10

四、您的认知功能情况：请在每行圈选或标出一个数字来表明适用于**<u>您过去7天情况</u>的回答。**

在过去 7 天	从来没有	每周约一次	每周两至三次	几乎每天	每天好几次
1.我曾在想东西时有困难	0	1	2	3	4
2.我在想东西时较慢	0	1	2	3	4
3.我曾在集中注意力方面有困难	0	1	2	3	4
4.我曾在对于寻找熟悉的地方有困难	0	1	2	3	4
5.我曾有困难记起把东西（如钥匙或钱包）放在何处	0	1	2	3	4
6.我曾在记住新信息（如电话号码）时有困难	0	1	2	3	4
7.当我和别人交谈时，我有困难记起某个物件的名字	0	1	2	3	4
8.我曾有困难寻找正确的词来表达自己	0	1	2	3	4
9.我曾用过错误的词汇来指某个物件	0	1	2	3	4
10.当我别人交谈时，我会有困难表达我想要说的话	0	1	2	3	4
11.我曾走进房间时忘了自己在房间里是要拿或做什么	0	1	2	3	4

	从来没有	每周约一次	每周两至三次	几乎每天	每天好几次
12.我需要更加努力地集中注意力，否则我会犯错	0	1	2	3	4
13.我会很快忘记刚被介绍给我认识的人的名字	0	1	2	3	4
14.我日常生活中的反应能力较慢	0	1	2	3	4
15.我需要比平常更加努力地专注我所做的事	0	1	2	3	4

16.我的思维比平常慢	0	1	2	3	4
17.我需要比平常更加努力来清楚地表达自己	0	1	2	3	4
18.为了不让自己忘记事情，我比平常更需要用到写好的字条	0	1	2	3	4

在过去 7 天其他人对你的评价

1.其他人曾说我似乎在**记住信息**方面有困难	0	1	2	3	4
2.其他人曾说我似乎在**把话说清楚**方面有困难	0	1	2	3	4
3.其他人曾说我似乎在**清楚思考**方面有困难	0	1	2	3	4
4.其他人曾说我看起来似乎很**困惑**	0	1	2	3	4

在过去 7 天对知觉认知能力的影响	一点也不	有一点	有些	相当	非常
1.我能够集中精神	0	1	2	3	4
2.当我与别人交谈时，我能够记起我想要用的词	0	1	2	3	4
3.我能够记起事情，如我把钥匙或钱包放在何处	0	1	2	3	4
4.我能够记得我要做的事，如吃药或买我需要的物品	0	1	2	3	4
5.我能够毫不费力地集中注意力和专注我正在做的事	0	1	2	3	4
6.我的头脑如往常一样敏锐	0	1	2	3	4
7.我的记忆力如往常一样好	0	1	2	3	4

在过去 7 天对生活质量的影响	一点也不	有一点	有些	相当	非常
1. 我曾为这些问题而感到苦恼	0	1	2	3	4
2. 这些问题曾干涉到我的工作能力	0	1	2	3	4
3. 这些问题曾干涉到我所享受事情的能力	0	1	2	3	4
4. 这些问题曾干涉到我的生活质量	0	1	2	3	4

五、**请您在下列选项前的空格内打[√]来表达您过去1周的情绪状况：**

在过去 7 天	0	1	2	3
1. 我感到紧张（或痛苦）	根本没有	有时候	大多时候	几乎所有时候
2. 我对以往感兴趣的事情还是有兴趣	肯定一样	不像以前那样多	只有一点	基本上没有
3. 我感到有点害怕好像预感到什么可怕的事情要发生	基本没有	有一点	有但不严重	非常肯定和十分严重
4. 我能够哈哈大笑，并看到事物好的一面	经常这样	有点不如以前	肯定不如以前	根本没有
5. 我的心中充满烦恼	偶然如此	有时	时常如此	大多数时间
6. 我感到愉快	大多数时间	有时	并不经常	根本没有
7. 我能够安闲而轻松地坐着	肯定	经常	并不经常	根本没有
8. 我对自己的仪容失去兴趣	我像以一样关心	可能不是非常关心	并不像我应该做的那样关心	肯定失去

9. 我有点坐立不安，好像感到非要活动不可	根本没有	并不很少	是有点	经常这样
10. 我对一切都是乐观地向前看	差不多这样	并不完全是这样	很少这样	几乎不这样
11. 我突然发现有恐慌感	根本没有	并非经常	非常肯定	确实很经常
12. 我好像感到情绪在渐渐低落	根本没有	有时	很经常	几乎所有时间
13. 我感到有点害怕，好像某个内脏器官变化了	根本没有	有时	很经常	非常经常
14. 我能享受喜欢的书，电台或电视节目	常常如此	有时	并非经常	很少

六、言语流畅性.(每项计时1分钟，调查员记录结果)

6a. 指导语:“现在，你有一分钟时间，请你尽量说出你能想到的动物的名称。”

评分 ：_____ |__|

_____

_____

_____

6b. 指导语:**“现在，你有一分钟时间，请你尽量说出你能想到的水果的名称。”**

评分 ：_____ |__|

_____

_____

_____

6c. 指导语:**“现在，你有一分钟时间，请你尽量说出你能想到的蔬菜的名称。”**

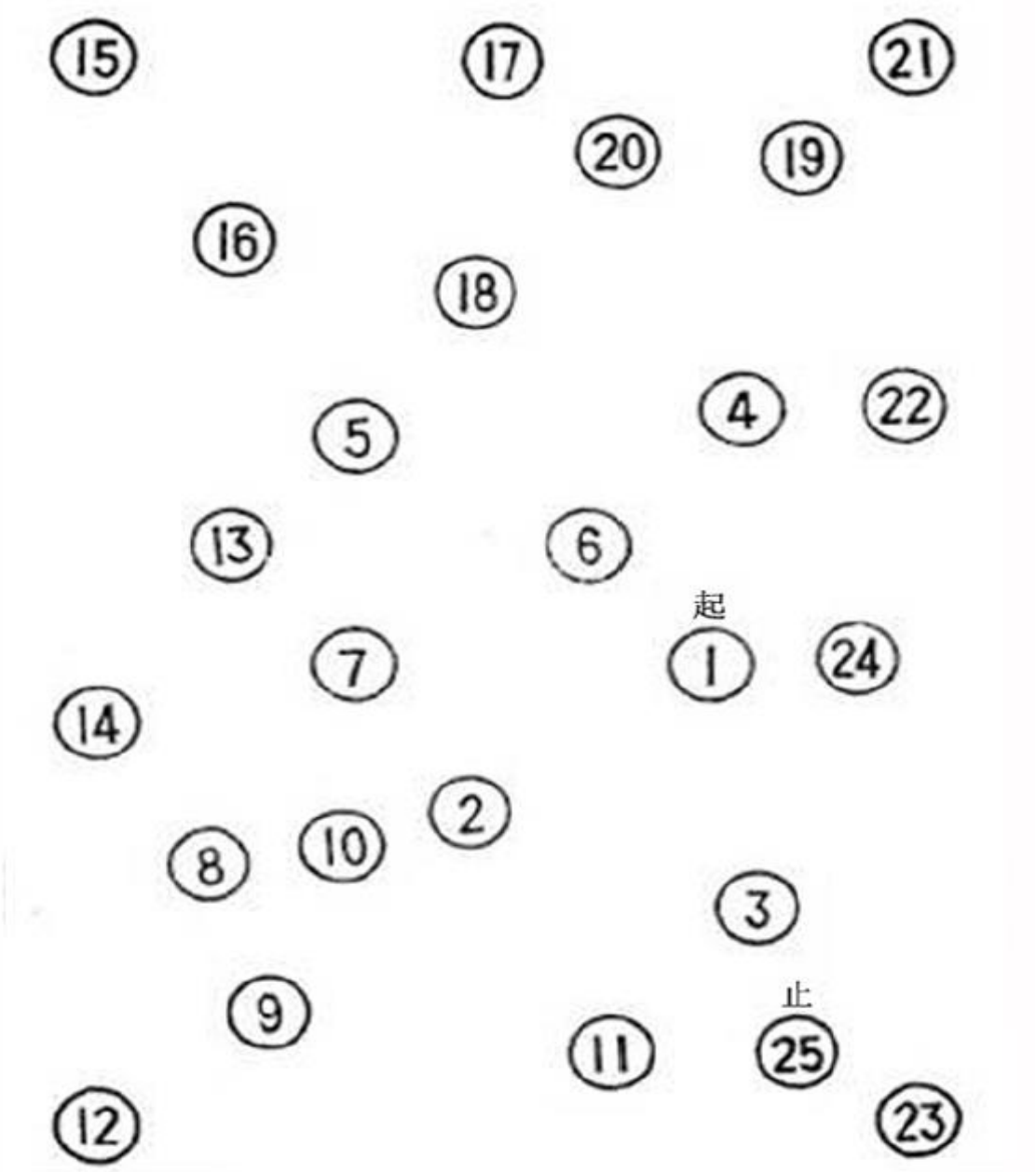
评分 ：_____ |__|

_____

七、连线实验

7a: TMT-A

指导语：在这张纸上会呈现1 到25 这些数字，它们没有规律散乱地分布，需要按照1、2、3 一直到25 的顺序把它们连接起来，不能跳隔数字，一个挨一个地连接，要求快速且准确。（确定被试明白要求，出示数字连线）起始1在这里，连接到25为止，开始。



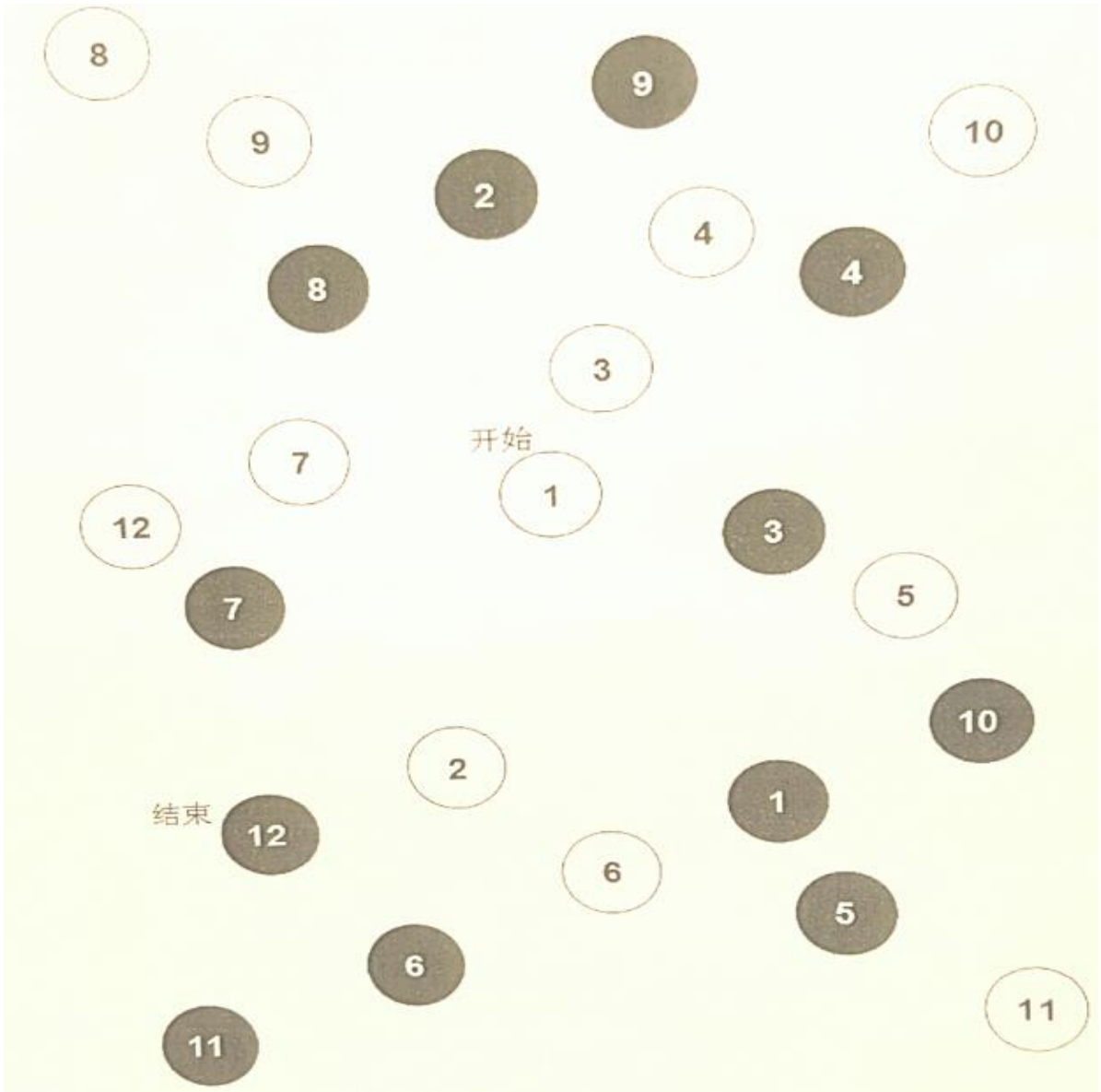
TMT-A 全部数字完成时间_____ （0-150）秒（如果超出150秒未完成，记录150）

提笔次数_____

提醒次数_____

7b. TMT-B

指导语：这里的数字包含白色的圆圈和黑色的圆圈中，现在要你把数字连起来，即从白色的圆圈1到黑色的圆圈1画一条直线，黑色圆圈1到白色圆圈2，再到黑色圆圈2，按顺序依次类推，直到结束。不能跳隔数字，一个挨一个地连接，要求快速且准确。（确定被试明白要求，出示数字连线）开始。



TMT-B 全部数字完成时间_____ （0-150）秒（如果超出150秒未完成，记录150）
提笔次数_____；提醒次数_____

八、数字广度测验（版权所有，不能展示测验具体内容）

Appendix 6 English Translation of Data Collection Tool

This tool consists of eight parts:

Part 1: Demographic Information Sheet

1. Age
2. Education level
3. Employment status
4. Marital status
5. Having child or not
6. Disease diagnosis
7. Primary diagnosis date
8. Disease stage
9. Treatment types
10. Primary treatment completed date
11. Menopause status

Part 2: Auditory Verbal and Learning Test (Copyright reserved)

Part 3: Brief Fatigue Inventory

Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: _____/_____/_____ Time: _____

Name _____ _____ _____

Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

F. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

Part 4: Functional Assessment of Cancer Therapy-Cog

FACT-Cognitive Function (Version 3)

Below is a list of statements that other people with your condition have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PERCEIVED COGNITIVE IMPAIRMENTS	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogA1	I have had trouble forming thoughts	0	1	2	3	4
CogA3	My thinking has been slow	0	1	2	3	4
CogC7	I have had trouble concentrating	0	1	2	3	4
CogM9	I have had trouble finding my way to a familiar place	0	1	2	3	4
CogM10	I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
CogM12	I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
CogV13	I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
CogV15	I have had trouble finding the right word(s) to express myself	0	1	2	3	4
CogV16	I have used the wrong word when I referred to an object	0	1	2	3	4
CogV17b	I have had trouble saying what I mean in conversations with others	0	1	2	3	4
CogF19	I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
CogF23	I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
CogF24	I have forgotten names of people soon after being introduced	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogF25	My reactions in everyday situations have been slow	0	1	2	3	4
CogC31	I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
CogC32	My thinking has been slower than usual	0	1	2	3	4
CogC33a	I have had to work harder than usual to express myself clearly	0	1	2	3	4
CogC33c	I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
CogMT1	I have trouble keeping track of what I am doing if I am interrupted	0	1	2	3	4
CogMT2	I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	COMMENTS FROM OTHERS	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogO1	Other people have told me I seemed to have trouble remembering information	0	1	2	3	4
CogO2	Other people have told me I seemed to have trouble speaking clearly	0	1	2	3	4
CogO3	Other people have told me I seemed to have trouble thinking clearly	0	1	2	3	4
CogO4	Other people have told me I seemed confused	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PERCEIVED COGNITIVE ABILITIES	Not at all	A little bit	Some-what	Quite a bit	Very much
Cog PC1	I have been able to concentrate	0	1	2	3	4
Cog PV1	I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
Cog PM1	I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
Cog PM2	I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
Cog PF1	I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
Cog PCH 1	My mind is as sharp as it has always been	0	1	2	3	4
Cog PCH 2	My memory is as good as it has always been	0	1	2	3	4
Cog PMT 1	I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
Cog PMT 2	I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	IMPACT ON QUALITY OF LIFE	Not at all	A little bit	Some-what	Quite a bit	Very much
CogQ35	I have been upset about these problems	0	1	2	3	4
CogQ37	These problems have interfered with my ability to work	0	1	2	3	4
CogQ38	These problems have interfered with my ability to do things I enjoy	0	1	2	3	4
CogQ41	These problems have interfered with the quality of my life	0	1	2	3	4

Part 5: HADS

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Part 6: Verbal Fluency Test

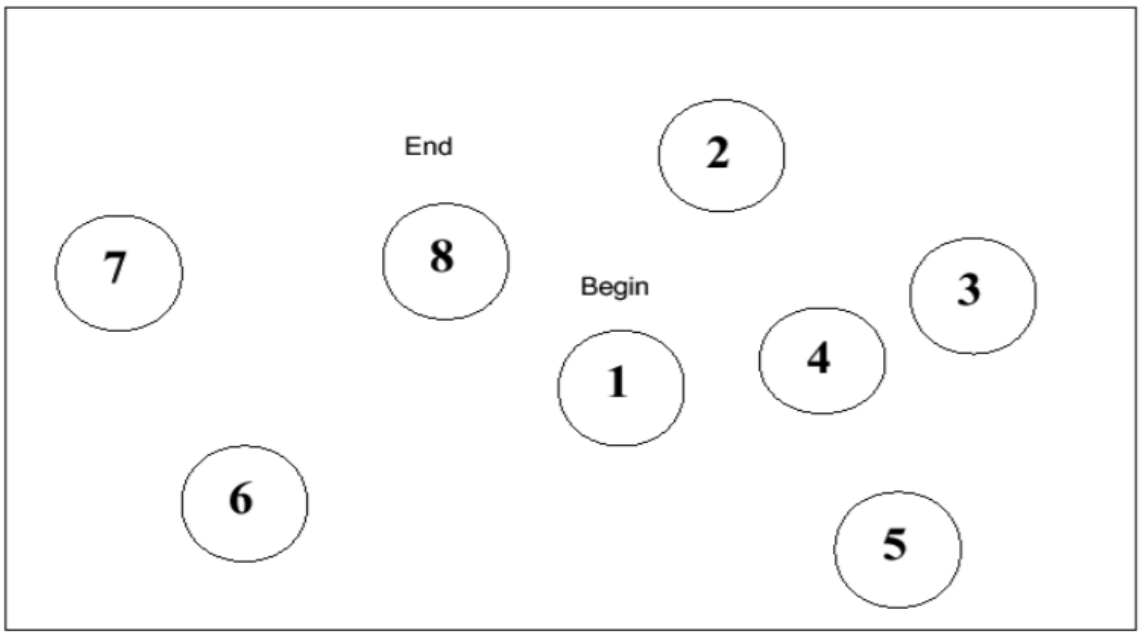
(1) Please you tell me animal's names as many as possible within one minute:

(2) Please you tell me fruit's names as many as possible within one minute:

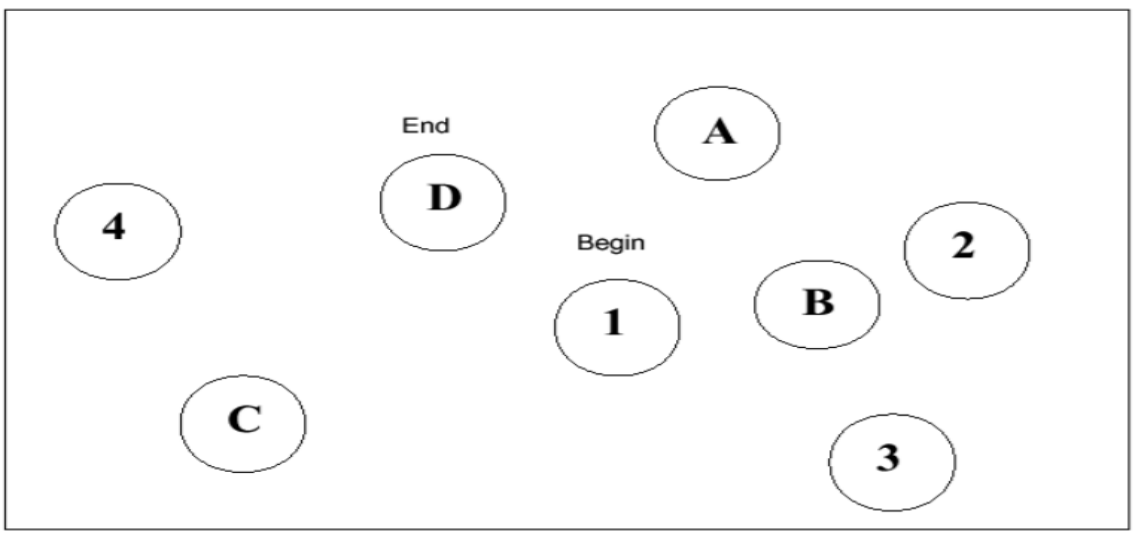
(3) Please you tell me vegetable's names as many as possible within one minute:

Part 7: Trial Making Test

Trail Making (Part A) – *SAMPLE*



Trail Making (Part B) – *SAMPLE*



Part 8: Digit Span Test (Copyright reserved)

(Assessment end, Thank You!)

CHAPTER 7

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