Cancer-related cognitive impairment: Neuropsychological function, neurogenesis biomarkers, and a nonpharmacological intervention

Research Proposal
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Table of Contents

Abstract

Cancer and its treatment are often accompanied by a decline in mental acuity. Whilst specific mechanistic pathways are still contended, the current understanding holds cancer-related cognitive impairment as a complex condition, implicating several factors such as individual lifestyle, cognitive ability, psychosocial wellbeing, age, genetics, tumour biology, treatment type, neurotoxicity, inflammation, and medical history. The proposed research will investigate cancer-related cognitive impairment in people living with cancer, through biomarkers pertaining to neurogenesis, alongside psychocognitive, demographic, and medical history variables. The research will also conduct a randomised control trial assessing the efficacy and feasibility of a nonpharmacological intervention. To account for the complex nature of cancer-related cognitive impairment, machine learning approaches will be used.

Keywords: cancer; cancer-related cognitive impairment; chemobrain; neurodegeneration; machine learning; cognitive training

Research Questions and Objectives

This research aims to adopt an interdisciplinary approach to investigate, through machine learning, the relationships between impaired cognitive functioning, psychosocial factors, medical history, and blood neurogenesis biomarkers in people with cancer, and then apply a novel cognitive training intervention informed by recent meta-analytic evidence (Cheng et al., 2022). These findings will also be evaluated with regard to their translatability to daily oncology care. The overall research uses a sequential design, incorporating both longitudinal and cross-sectional elements, and is split into two stages. Refer to Appendix A for a simple study design flowchart. Stage I will address research questions i, ii, and iii; Stage II will address research questions iv and v.

i. Which of the assessed neurogenesis, psychocognitive, demographic, and medical history factors are associated with cancer-related cognitive impairment presence and severity in people with cancer?
ii. How much predictive utility do the machine learning models have in risk stratification of cancer-related cognitive impairment?
iii. Which of the biological, psychocognitive, demographic, and medical history factors should oncology care providers assess to identify patients at risk of cancer-related cognitive impairment?
iv. How does the intervention group respond to the cognitive training task compared to the control group?
v. If beneficial, how can this intervention be implemented into oncology care?

Uncommon Abbreviations

Aβ: Amyloid beta
AD: Alzheimer's disease
APOE: apolipoprotein E
BBB: blood-brain barrier
BDNF: brain-derived neurotrophic factor
CNS: central nervous system
CRCI: cancer-related cognitive impairment
MCI: mild cognitive impairment

Literature Review of Cancer-Related Cognitive Impairment

In 2021, an estimated 150000 people were diagnosed with cancer in Australia (Australian Institute of Health and Welfare, 2021). Aside from the primary physiological effects, cancer is a debilitating health condition associated with negative outcomes for patients, such as depression, anxiety, chronic pain, social and relational issues, occupational challenges, and worse quality of life (Carreira et al., 2018). Depending on type, stage, tumour subtype, and hormonal status, cancer is primarily treated with surgery, chemotherapy radiotherapy, endocrine therapy, antibody therapy, and/or immunotherapy (Waks & Winer, 2019). The Australian Institute of Health and Welfare (2021) reported the five-year survival for individuals with cancer, relative to noncancer controls from the general Australian population, has increased over the last few decades, from 51% (1988-1992), to 70% (2013-2017). With an increasing sophistication of detection and treatment, which reduce cancer mortality rates, understanding and mitigating the sequelae of cancer and interventions has become tantamount (Gutmann, 2019). Cancer-related cognitive impairment is one sequela associated with worsened mental health, quality of life, and employment outcomes for cancer patients and survivors, which can last up to years after cancer remission (Mayo et al., 2021).

Introduction

Cancer related cognitive impairment (CRCI) is the mental decline that is often experienced by individuals with non-central nervous system (CNS) cancer and/or ancillary treatment (Gutmann, 2019). It is important to make this distinction, as CNS cancers would typically implicate and compromise neural networks, and, transitively, cognition. Hereafter, all references to cancer in this paper will only mean non-CNS cancers, unless otherwise explicated. CRCI has also been observed alongside various cancers, such as breast, colorectal, testicular, head, neck, and haematological (Mayo et al., 2021). Most, if not all, CRCI research varying in point(s) of assessment converges on the fact that affective and cognitive impairments are more prevalent in cancer patients than healthy controls (Santos & Pyter, 2018). Whilst the precise mechanistic workings remain unknown, it is suggested that a myriad of biological, psychosocial, and individual factors contribute to CRCI. CRCI is common, with longitudinal studies estimating the effects are experienced by 30% to 40% of individuals before treatment, and 50% to 75% during and after treatment (Mayo et al., 2021; Oppegaard et al., 2021). CRCI is also referred to as “chemofog” or “chemobrain” – misnomers stemming from early observations of the phenomenon occurring in response to chemotherapy (Gutmann, 2019). Further investigation dispelled the notion that CRCI is limited to chemotherapy; importantly, a review of murine literature by Seigers and Fardell (2011) indicated that the existence of a non-CNS tumour alone (i.e., pre-treatment) is sufficient to impair functioning of the hippocampus, a region involved in learning and memory (Anand & Dhikav, 2012; Wefel et al., 2015). Despite this, CRCI occurs more often during treatment periods; the failure to manage such an adverse side effect, may dissuade patients from pursuing, and adhering to, lifesaving interventions (Chao et al., 2021). Whilst acute cancer-related stressors and exposure to treatment agents reduce substantially after remission and treatment cession, longitudinal studies report CRCI persistence in a third of cancer survivors one-year post-treatment (Collins et al., 2014; Janelsins et al., 2014).

Cognitive Domains of Impairment

Impairments in short-term/working memory, executive function, and language have been consistently reported across several meta-analyses, before, during, and after treatment (Horowitz et al., 2019). However, these same meta-analyses drew conflicting conclusions for impairments in processing speed, visuospatial processing, and attention (Horowitz et al., 2019). Further investigations have also reported impairments in other domains, such as learning, motor functioning, and visuospatial skills, likely associated with the myriad of comorbidities discussed later (Bai & Yu, 2021; Chao et al., 2021). Severity of experienced symptoms can range from mild attentional issues to disruptive cognitive impairment; however, relative to other neurodegenerative disorders, CRCI severity is considered to be mild to moderate (Mayo et al., 2021). Patients experiencing CRCI may report difficulty with remembering things, multitasking, word retrieval, following conversation/instructions, completing complex tasks, and poor concentration (Bai & Yu, 2021; Horowitz et al., 2019). The only conclusion that can be drawn with certainty is that CRCI has a heterogenous presentation (Horowitz et al., 2019).

One theory suggests the body naturally prioritises lower order, “primitive/basal” processes that are more critical to immediate survival over higher order functions like short-term memory (Ebaid & Crewther, 2020). Whilst this model is functional, it is limited by its simplistic and discrete conceptualisation of cognitive domains and neurophysiology. An alternative theory suggests minor impairments in the lower order and more robust domains disperse out to have more noticeable impairments in higher order functioning (Ebaid & Crewther, 2020; Greenwood, 2000). For example, it has been proposed that cancer-related

attentional disruption may subsequently affect memory and executive function (Ahles et al., 2012; Janelsins et al., 2018; Root et al., 2015). Recently, there has been advocacy against categorising cognitive function assessments, on the basis that most current cognitive tests assess an amalgamation of executive functioning and other domains; this, alongside the complex intertwining of various modalities, renders parsing and demarcating cognitive domains somewhat arbitrary (Díaz-Mardomingo et al., 2017; Lambert et al., 2018).

The degree of cognitive impairment is reflected differently across subjective and objective measures, and are not well correlated (Horowitz et al., 2018). For example, in participants with breast cancer, 50% ≤ self-reported CRCI, whilst only 15-25% exhibited objectively measurable CRCI (Ahles et al., 2012; Lange et al., 2019). Whilst greater degrees of anxiety, distress, and depression are associated with more severe self-reported cognitive impairment, neither subjective cognitive impairment, nor affective functioning, are well correlated with objective measures of cognitive impairment (Chao et al., 2021; Wefel et al., 2015). Older age is associated with greater objective CRCI, whereas younger age is associated with greater self-reported CRCI (Chao et al., 2021). Despite their intrinsic biases, self-reported measures are recommended for inclusion alongside objective neuropsychological measures when assessing CRCI and intervention efficacy, as self-report is more sensitive to changes in cognition and appears to reflect daily functioning more realistically than their counterparts (Fernandes et al., 2019; Horowitz et al., 2018; Kesler et al., 2017). Higher premorbid cognitive reserve may be associated with the limitations of objective measures attempting to detect CRCI (Janelsins et al., 2018). Individuals with higher levels of intelligence, education, daily cognitive stimulation, and multilingualism prior to carcinogenesis, diagnosis, and treatment tend to have a greater cognitive reserve, allowing for greater resistance against neurophysiological damage (Song et al., 2022). Transitively, such individuals may demonstrate no apparent cognitive impairment on objective measures but may still report needing to exert greater effort to complete tasks they experienced less challenging prior to their cancer diagnosis (Janelsins et al., 2018). Numerous other risk and protective factors influencing cognitive reserve exist, but as they have a more direct link to CRCI, they are discussed later. As such, the proposed study shall assess cognitive reserve, and shall incorporate both subjective and objective measures of cognition.

Neurobiological Factors and Mechanisms

Contributing Factors

Several biological risk factors may be associated with CRCI in cancer (noninclusive of potential mechanistic pathways), including older age, obesity, post-menopausal status, cancer-related anaemia, pain sensitivity, blood pressure, and pre-existing medical conditions, such as diabetes (Bai & Yu, 2021; Cheung et al., 2013; Henneghan, 2016; Lange et al., 2019). Differences in CRCI may also exist across sex, race, and genetic variations (Bai & Yu, 2021). The cancer itself influences the severity of CRCI; namely, the tumour type, size, and stage (Mayo et al., 2021). Cancers that are associated with more severe cognitive impairment are generally invasive, greater in mass, and in the later stages (especially metastatic cancers; Mayo et al., 2021). One of the most frequently cited biological risk factors of CRCI is the presence of the epsilon 4 isoform of apolipoprotein E (*APOE-ε4*; Buskbjerg et al., 2019). Mapping onto chromosome 19 in humans, *APOE* is a polymorphic gene with three major allelic variants: ε2, ε3, and ε4. Cancer survivors carrying *APOE-ε4* in both chromatids of chromosome 19 (i.e., *APOE-ε4,4*) reported greater incidence of cognitive impairment than survivors with different genotypes (e.g., *APOE-ε2,3*; Mayo et al., 2021). Furthermore, cancer patients with the ε4 allele, in one or both chromatids, are less resistant to neurotoxicity associated with cancer treatment (Bai & Yu, 2021). Notably, *APOE-ε4* is also considered to be the strongest predictor for Alzheimer's disease amongst most ethnicities (Sadigh-Eteghad et al., 2012; Wisniewski & Drummond, 2020). Similarly, certain genetic polymorphisms of catechol-*O*-methyltransferase (*COMT*), DNA methyltransferase 1 (*DMTI1*), epidermal growth factor 2 (*ERBB2*), oestrogen receptor 1 and 2 (*ESR1* & *ESR2*), and progesterone gene (*PGR*) have been proposed as potential risk or protective factors (Buskbjerg et al., 2019; Fernandez et al., 2020; Lv et al., 2020; Ng et al., 2016). Given this, it is understood that premorbid pathophysiology can complicate, and even aggravate, CRCI presentation.

Link to Neurodegenerative Disorders

Neuroanatomical changes associated with (primarily treatment-related) CRCI have been observed in the frontal-subcortical profile, which is similar to Alzheimer's, Huntington's, and Parkinson's disease (Bonelli & Cummings, 2007, 2008; Zhao et al., 2015). Although mild cognitive impairment (MCI) is theoretically more similar to CRCI than early-stage Alzheimer's disease (AD), research on the latter is often given precedence when designing CRCI studies, assessments, and interventions (Tao et al., 2020). This is because what is shared between early-stage AD and CRCI is of greater clinical relevance: for example, certain biological mechanisms (e.g., *APOE-ε4*; inflammatory markers); psychological distress associated

with terminal diseases; changes in brain structure; risk factors; and even presentation (Henneghan et al., 2020; Tao et al., 2020). Kesler et al. (2017) reported that compared to healthy controls, chemotherapy-treated cancer survivors and chemotherapy-naïve cancer survivors were more likely to develop AD. Note that whilst these similarities and findings do not support, nor suggest, a causative association between early-stage AD and CRCI, they illuminate a potentially shared neural phenotype (Kesler et al., 2017). Furthermore, neurodegenerative disorders and CRCI were once proposed to be aggressive, accelerated forms of ageing, but have since been discredited as overly simplistic (Gonneaud et al., 2021; Leparulo et al., 2022). Recent murine and human CRCI and AD research has refined the theory. Gonneaud et al. (2021) reported that subjects genetically predisposed to AD showed preclinical signs of accelerated ageing as they approached the expected age of onset. CRCI and AD share certain mechanisms with ageing, such as cell senescence and proinflammatory markers (Hurria et al., 2016). Within the proposed study, this "transdiagnostic" approach illuminates potential avenues for CRCI research, already hewn by investigation of mechanistically similar encephalopathies with larger literature bodies (i.e., early-stage AD).

Treatment Related Factors

All cancer treatment, by nature, involves the ablation of tissue matter, whether that be through radiation, surgery, or chemotherapy. Whilst this destruction is targeted at cancerous cells, adjacent, noncancerous tissue is often collateral damage – the extent of which varies depending on the treatment (Waks & Winer, 2019). The treatments most commonly associated with CRCI are chemotherapy, radiation therapy, immunotherapy, targeted therapy, endocrine therapy, and stem cell transplantation (Henneghan, 2016; Mayo et al., 2021). Dosage, cycle, time since last administration, drug combination, emetogenicity of agents, and any treatment related complications may also contribute to CRCI presentation (Di Liso, 2021; Mayo et al., 2021; Oppegaard et al., 2021). To mitigate adverse interventional side effects, cancer patients undergoing treatment are often prescribed adjunct medications such as sedatives, anxiolytics, antidepressants, antiemetics, analgesics (particularly opioids), antioxidants, and corticosteroids; these medications have also been associated with poorer cognitive functioning, even without factoring in pharmacological interactions (Chao et al., 2021).

Possible Mechanistic Pathways

The neuroanatomical structures most affected in CRCI are global and local grey matter volume, brain neural networks, white matter integrity, particularly within frontal-subcortical and temporal regions (Amidi & Wu, 2019; Zhao et al., 2015). In rodents, pre-treatment impairment has been tentatively attributed to disrupted hippocampal neurogenesis caused by the tumour (Seigers & Fardell, 2011; Wefel et al., 2015). In humans, ancillary mechanisms have been proposed by the way of diagnosis-related stress factors; increased, chronic peripheral proinflammatory cytokines; and dysfunctional RNA/DNA repair systems (Hermelink et al., 2007; Mayo et al., 2021; Seigers & Fardell, 2011; Wefel et al., 2015). Note that the numerous theorised mechanistic pathways are in no way mutually exclusive; no individual theory can yet explain the extent of CRCI impact (Schagen et al., 2022). The proposed research will focus on impaired neurogenesis; the following sections summarise key proposed pathways in relation to neurogenesis.

Impaired Neurogenesis. In CRCI (and neurodegenerative diseases), neural apoptosis occurs at a faster rate than neurogenesis, reducing neuronal density, which in turn is associated with a reduction in cognitive capacity and resources (Sun et al., 2021). Neurogenesis and apoptosis, as well as neuroplasticity and neural differentiation, are significantly influenced by brain derived neurotrophic factor (BDNF), which is a neurotrophin primarily active in the hippocampus, cortex, and basal forebrain, as well as components of the peripheral nervous system (Yap et al., 2021). These regions are involved in learning, memory (especially long-term), and higher-order cognition (Yap et al., 2021). Lower BDNF plasma levels, and transitively slower neurogenesis, have been associated with greater perceived cognitive impairment in cancer patients (Ng et al., 2017); however, a certain BDNF polymorphism (Val66Met) has been suggested as protective factor against CRCI, indicating that cancer related changes in BDNF levels are mediated by BDNF gene expression (Tan et al., 2019). Interestingly, CRCI trajectory type (acute vs. persistent) was found to bifurcate the relationship between levels of BDNF and certain proinflammatory cytokines (Yap et al., 2021).

Inflammation. Chronic neuroinflammation has been posited as a likely mechanism underlying CRCI development and maintenance (Oppegaard et al., 2021). Inflammation also underlies two other posited mechanisms: oxidative damage and disrupted neurogenesis/apoptosis. Proinflammatory cytokines are naturally secreted by immune cells when damaged by injurious agents (e.g., carcinogenic cells, chemotherapeutic drugs) in order to stimulate inflammation as a biological defence. Adaptively, inflammation is acute (a few minutes to 2 weeks) and serves to i) limit the spread of the injurious agent by

creating a physical barrier around site of origin, ii) neutralise the injurious agent, and then iii) initiate healing of impacted site. Physiologically, as proinflammatory cytokines are relatively small, they can permeate the blood-brain barrier (BBB). Upon the onset of cancer-related chronic inflammation, proinflammatory cytokines become (further) dysregulated, and may induce neuroinflammation, which, in turn, dysregulates neurogenesis/apoptosis signalling pathways (Oppegaard et al., 2021; Schroyen et al., 2021).

Oxidative Stress and RNA/DNA Damage. Another proposed mechanism is the effect of oxidative stress and RNA/DNA damage on neural tissue brought on by proinflammatory cytokines and therapeutic agents permeating the BBB (Schagen et al., 2022). Oxidative stress is associated with a physiological imbalance resulting in dysregulation of reactive oxygen species (ROS) – a molecule integral for homeostatic, immune, and apoptotic cellular functions (Torre et al., 2021). RNA/DNA mutations can occur directly resultant of oxidative stress, or through cytostatic and therapeutic agent neurotoxicity (Bagnall-Moreau et al., 2019; Seigers & Fardell, 2011). These mutations, in turn, induces ROS dysregulation and oxidative stress (Seigers & Fardell, 2011). This cyclical process lends itself to neuronal senescence, inflammation, and dysfunction, including impaired neurogenesis and apoptosis, and is associated with CRCI, AD, and MCI (Hutterer & Oberndorfer, 2021; Schagen et al., 2022).

Amyloid Beta and Tau Protein. Dysfunctions in amyloid beta (Aβ) and tau protein expression have been regarded as the hallmark pathophysiology for neurodegeneration; however, such biomarkers are not exclusive to neurodegeneration, and have recently been broadened to be indicative of neurophysiological injury (Henneghan et al., 2021). Tangentially, Aβ and tau dysfunction have been associated with certain *APOE* polymorphisms (Baek et al., 2020; Wisniewski & Drummond, 2020). Overexpression of Aβ precursor proteins, and elevated levels of tau protein, are common amongst numerous cancers, and have been associated with the greater severity of tumours (Darlix et al., 2019; Jin et al., 2017; Pandey et al., 2016). Such abnormalities of Aβ and tau protein can result in stunted or mutated neuronal cells during neurogenesis and differentiation, as well as accelerated apoptosis of healthy neuronal cells. Furthermore, dysfunctional Aβ and tau has been associated with cognitive impairment in healthy adults (Baek et al., 2020; Sperling et al., 2019). Whilst the theoretical link is intuitive, empirical substantiation has been scarce until recently; Henneghan et al. (2020) using machine learning (random forest regression) reported the combination of Aβ, tau, and proinflammatory cytokine biomarkers accounted for 71% of variance in neuropsychological assessments. Other studies have reported similar associations between CRCI and Aβ and tau protein dysfunction, indicating that this is a likely mechanism (Koh et al., 2020; Liou et al., 2019).

This brief review of possible biological mechanisms is noncomprehensive; other possible contributing factors are dysregulation of cortisol, exosomes, astrocytes, oestrogen, progesterone, and microglia (Fernandez et al., 2020; Lv et al., 2020). Given the scope and constraints of the proposed PhD research, a large-scale study investigating all possible neurophysiological mechanistic pathways is unfeasible. As such, the proposed study will focus on key biomarkers implicated in neurogenesis. Although the diagnostic precision of neuroimaging and cerebral spinal fluid biomarkers is greater than that of blood biomarkers, assessment of the latter is less invasive for patients, more cost-effective, and more time efficient (Chen et al., 2021) – rendering any improvements in precision to be of diminishing returns for the scope of this PhD project. This study will therefore collect and measure blood-based biomarkers.

Psychosocial Factors and Mechanisms

A myriad of psychosocial factors can mitigate or contribute to the onset, severity, and maintenance of CRCI. Protective factors include higher premorbid intelligence quotient (i.e., cognitive reserve), higher education, balanced diet, active lifestyle, and being married (Hutterer & Oberndorfer, 2021; Mayo et al., 2021; Oppegaard et al., 2021; Zhou et al., 2021) Risk factors include insomnia/poor sleep, pre-existing psychological/psychiatric issues, chronic pain, sedentary lifestyles, being divorced/widowed, financial distress and social isolation (Brewster et al., 2017; Lange et al., 2019; Mayo et al., 2021; Zhou et al., 2021). Psychological symptoms commonly associated with CRCI include depression, anxiety, low mood, loss of motivation, distress, fatigue, and changes in behaviour/personality (Lambert et al., 2018; Mayo et al., 2021). Poor sleep, mood disturbances, and chronic pain can compromise cognition in healthy adults; with the alleviation of such symptoms, cognition also improves (Chao et al., 2021; Otte et al., 2015). The stress accompanying cancer diagnosis, treatment, and indeed the disease trajectory, has been likened to post-traumatic stress disorder symptomology (Lange et al., 2019); chronic periods of elevated stress can drain cognitive resources, as evidenced by associations between higher scores on psychological distress measures and lower scores on cognitive assessments in cancer patients (see Yang & Hendrix, 2018). Furthermore, this decline in mental acuity is often a source of distress and frustration for cancer patients, feeding back into

affective disturbances as a bidirectional relationship (Chao et al., 2021). It logically follows that mood disturbances associated with cancer, and CRCI, likely aggravate the cognitive impairment (Bai & Yu, 2021). Interestingly, cancer patients given psychoeducation on treatment specific cognitive impairments were more likely to report cognitive complaints after treatment (Schagen et al., 2012), indicating that CRCI has a diagnosis threat, also present in other encephalopathies (Carter-Allison et al., 2016; Farrer & Cook, 2021).

Living with cancer is reported to impact self-efficacy, as patients are often dependent on family/carers and healthcare professionals whilst receiving treatment (Maeir et al., 2022). Weaving in a transdiagnostic perspective, reduced self-efficacy has been well-documented as a premorbid factor of declining cognition in the elderly, as well as individuals with MCI and neurodegenerative disorders (Beaudoin, 2018; Tonga et al., 2020). Whilst still sparse, research indicates self-efficacy to have a role in CRCI (Bains et al., 2012; King & Green, 2015; Maeir et al., 2022). Existential factors associated with terminal illnesses influence patient quality of life, mood, optimism, personality, motivation, and even convalescence; such existential factors include purpose of life, death anxiety, feeling burdensome, demoralisation, and remorse around missed opportunities (Cohen et al., 2019; Kouhpas et al., 2020; Ownsworth & Nash, 2015; Philipp et al., 2021; Sharp et al., 2018). In particular, demoralisation has been associated with memory and concentration impairments in cancer and other terminal illnesses (Robinson et al., 2015); and death anxiety has been associated with perceived cognitive impairment in advanced cancer patients (Eggen et al., 2020). Existential factors have largely been studied in advanced stage cancer and have become a target for palliative care, and, despite the improved survivability of cancer, these existential factors may still be present in most, if not all, cancer patients; as such, exploration in wider cancer populations has been recommended to improve the lives of all cancer patients (Sharp et al., 2018).

The psychosocial factors reviewed, along with the cognitive impairments, have been associated with poorer life outcomes including worsened quality of life, reintegration into employment/education, and ability to perform daily activities such as reading and driving (Wefel et al., 2015; Williams et al., 2016). Furthermore, this amalgamation of cognitive, psychosocial, and affective dysfunctions can impede adherence to cancer treatment regimens and can even impede survivability – emphasising the need for CRCI research (Hshieh et al., 2018). After considering the numerous potential mechanistic pathways, varying risk/protective, subjective differences in experience, and the overall complexity of CRCI, it follows that CRCI may be largely heterogenous, both in aetiology and presentation, much like cancer itself. Such heterogeneity could partially account for conflicting findings in previous studies, which have largely endeavoured to statically define and operationalise CRCI. To address this limitation in past research, it may be useful to conceptualise CRCI as a broad cluster of cancer-related symptomologies and aetiologies eventuating in cognitive dysfunction, perceived or otherwise, instead of a unidimensional disorder.

Intervention and Treatment

The uncertainty around the precise underlying mechanisms, and the extent and nature of debilitation, associated with CRCI have impeded the development of potentially efficacious interventions, and standardisation thereof. Preliminary studies have trialled pharmacological interventions, such as psychostimulants and anti-inflammatories, and nonpharmacological interventions, such as physical exercise, psychotherapy, and cognitive-behavioural therapy (Bai & Yu, 2021; Chao et al., 2021). The conclusions drawn from these studies were largely conflicting, likely due to the heterogeneity of CRCI. However, clinical trials with similar biopsychopathologies (e.g., early-stage Alzheimer's disease) and recent CRCI meta-analyses/systematic reviews indicate that cognitive training may be a promising nonpharmacological intervention (e.g., Cheng et al., 2022; Fernandes et al., 2019; Kallio et al., 2017; Kang et al., 2019; Von Ah & Crouch, 2020; Zeng et al., 2020).

Cognitive Training

The rehabilitation process of cognitive training involves training cognitive functions; this achieved by having the patient routinely complete sufficiently challenging, but not overwhelming, paper or computer-based cognitive tasks (Fernandes et al., 2019). In CRCI patients, interventions comprised of distributed cognitive training sessions, for as few as 10 total hours, have been reported to elicit significant improvements in processing speed, memory, subjective cognitive performance, and even psychosocial/affective factors (Fernandes et al., 2019; Von Ah et al., 2012; Wefel et al., 2015). Reflecting the earlier discussed notion that cognitive domains are intertwined and demarcating them is somewhat arbitrary, trials assessing improvements in individual cognitive domains have found that a global battery of tasks is equally, if not more, effective, when compared to interventions targeting individual impaired domains (Zhang et al., 2019). That is, participants with single domain impairments show greater improvement and longer interventional

efficacy maintenance when engaging in multiple cognitive tasks across varying domains (i.e., a global battery), than with domain-specific interventions (Cheng et al., 2012; Hong et al., 2021; Zhang et al., 2019). In the context of CRCI and other MCI, overall training of major cognitive functions can also elicit neurocognitive and psychosocial improvements in domains not specifically targeted by the intervention (Cheng et al., 2022; Fernandes et al., 2019). The theorised biophysiological mechanism underlying cognitive training is the stimulation of neuroplasticity – a process intricately linked with neurogenesis, the mechanistic pathway of interest within the proposed study (Wei et al., 2022).

Computerised cognitive training has a growing evidence base indicating comparable efficacy to the original pen and paper based methods (Binarelli et al., 2021; Faria et al., 2019). An intervention modality that can be engaged with from home is beneficial for immunocompromised individuals with limited energy, as it obfuscates the additional toll associated with visiting clinics for practitioner-based interventions, such as psychotherapy. Given the multiple taxing health appointments associated with cancer treatment, ancillary healthcare is given second priority, often falling to the wayside during difficult weeks, effectively limiting adherence and efficacy; as such, minimising the burden on cancer patients is imperative. With the increasing reliance on telehealth, Binarelli et al., 2021 describes computerised modalities as practical and economical to implement, facilitating accessibility to patients who are geographically isolated, have financial/logistical difficulties, and/or have special needs. Furthermore, amidst COVID-19, researchers and practitioners have relied upon computerised methods to conduct investigations and deliver interventions (Thulesius, 2020). The benefits of such methods include automatised adjustment of task difficulty to match participant abilities; standardised administration; minimised errors/biases to which clinician administrations are susceptible; and reducing researcher/health professional workload and pressure (Binarelli et al., 2021; Thulesius, 2020).

A recent systemic review of cognitive training in CRCI noted a marked scarcity in blinded trials with control groups – gold standards when assessing therapeutic efficacy (Fernandes et al., 2019). Wefel et al. (2015) recommends ensuring sufficient differentiation between cognitive training tasks and neurocognitive outcome assessments, as to mitigate practice effects; similarly, computer tasks are recommended to maintain an adequate degree of transferability to day-to-day life tasks, so that the intervention efficacy can be preserved across daily functioning. Lastly, it has been well-documented that intervention adherence is optimised by simpler regimens, such as administration at regular intervals (Ingersoll & Cohen, 2008; Jimmy & Jose, 2011. Integrating recommendations from literature, the proposed research will assess cognitive training efficacy by conducting a blinded, randomised control trial with a control group; the intervention will be a computerised, global battery, with sufficient dissimilarity from the objective cognitive assessments, and adequate transferability to daily tasks.

Rationale and Significance

This brief review seeks to highlight key theorised pathways and the gaps in literature. Two lines of justification for the proposed research can be drawn: i) CRCI is associated with poorer life outcomes, and may even impede patient recovery, and ii) CRCI likely involves neurobiological and psychocognitive factors, indicating a need for an interdisciplinary approach in research and oncology care. As previously stated, the proposed mechanisms potentially associated with CRCI are not necessarily mutually exclusive. It is likely CRCI has multiple aetiologies varying in type and degree of contributing mechanisms. Whilst such proposed mechanisms of cognitive dysfunction have been somewhat explored individually, there is limited investigation into how these paradigms intersect, and, indeed, how to interpret the resultant integrated profiles. Few studies have integrated biophysiological and the neuropsychological findings, with many giving precedence to the role of therapeutic agents and objective neuropsychological assessments – with little regard for individual experience. As such, this study will endeavour to create a more holistic profile of CRCI, which will likely yield greater translational benefit to people living with cancer.

The proposed research will address gaps in the current literature, by using machine learning to disentangle the complex relationship of neurobiological, psychocognitive, demographic, and medical history factors, as well as how these factors may influence computerised cognitive interventional efficacy. Machine learning and non-parametric/non-linear statistical modelling have been advocated for in cancer and CRCI research, as they can better model complex relationships than standard regressions (Cheng et al., 2021; Henneghan et al., 2020). To the best of the researchers' knowledge, the proposed research will be the first study to use sophisticated machine learning to explore CRCI and neurogenesis. The current existing studies of this ilk, found using Boolean search techniques, were primarily focussed on proinflammatory cytokines, Aβ plaques, genetic polymorphisms, neuroanatomy, single nucleotide polymorphisms, or tumour histopathology (Chen, Lin, et al., 2020; Henneghan et al., 2018, 2019, 2020; Kesler et al., 2017, 2020;

Sharafeldin et al., 2020; Zhou et al., 2021). This study will focus on the neurogenesis pathway, coupled with the novel machine learning methodology proposed, as i) it is relatively unexplored; ii) cognitive training is theorised to function by improving neuroplasticity and neurogenesis; and iii) this approach will most effectively contribute to the fields of CRCI research, machine learning, and oncology care, within the constraints of a PhD project. This investigation will provide evidence to potentially inform screening criteria for patients at risk of CRCI, which can be assessed quickly and economically (i.e., blood tests, demographics, medical history) by oncology care providers. The second part of the proposed research will investigate the efficacy of cognitive training for CRCI, implemented through a computerised modality.

Hypotheses

1. It is hypothesised a combination of the assessed neurogenesis, biological, psychosocial, demographic, and/or medical history factors can significantly predict variance in impaired cognition within this study's sample, and that the pertinent machine learning model will have significant predictive utility in risk stratification of CRCI.
2. It is hypothesised the cognitive training group will show greater improvements in cognitive, psychosocial, and BDNF factors than the baseline and the control group post-intervention.
3. It is hypothesised this study will identify factors for oncology care providers to assess when screening for CRCI.

Methodology of Stage I

Research Design

Stage I will explore the relationships between neurobiological, psychocognitive, demographic, and medical history variables in cancer patients undergoing treatment and noncancer demographic-matched controls. A cross-sectional design will be used to collect in person data for the cognitive/psychosocial battery and by drawing peripheral blood for the biomarkers. All participants will complete all assessments. Participation in this stage is expected to take 90-120 minutes.

Participants and Recruitment

Inclusion criteria require participants to be aged over 18 years old, currently live in Perth and Peel regions of Western Australia (or be willing/able to attend Curtin University for appointment(s)), have been diagnosed with non-CNS cancer, be currently undergoing a form of cancer treatment (excludes palliative and treatment-naive patients), and have a working proficiency of the English language. Exclusion criteria preclude participation of individuals with premorbid clinical psychological/psychiatric issues; primary CNS and/or metastases; enrolment in other trials (some exceptions); and pregnancy (Henneghan et al., 2020; Lambert et al., 2018; Zhou et al., 2021). To provide a comparative baseline across assessments, 20-25% of our sample will consist of healthy controls that meet all other inclusion criteria but are cancer-naïve. Recruitment material will encourage cancer patients with AND without cognitive complaints to participate. These decisions were informed by past literature which recommend exposing the model/algorithm to the potential range of CRCI - from normal cognitive functioning to more severe levels of impairment - as to augment predictive utility (Chen, Zhang, et al., 2020; Henneghan et al., 2020; Wefel et al., 2015).

Exceptions to the enrolment in other trials exclusion criterion may be made if the other trial is researching variables the current study is not investigating; e.g., direct cancer treatment, cross-sectional surveys, diabetes blood tests. Eligibility of interested participants enrolled in another trial will be considered on case-by-case basis. The exclusion of participants with premorbid psychological / psychiatric / neurodegenerative conditions will allow researchers to ascertain with a relative degree of confidence that observed cognitive impairments are likely CRCIs. This exclusion criteria will be implemented in the screening phone call by directly asking the potential participant whether they have been diagnosed with the aforementioned. Premorbidities without overt diagnostic implication of cognition will not be grounds for participant exclusion; e.g., mild to moderate mood/affective disorders, ADHD, eating disorders. Premorbidities that directly compromise cognition and neuropsychological functioning will be considered grounds for study exclusion: e.g., dementia/Alzheimer's, frank intellectual disabilities, moderate-severe traumatic brain injuries. These decisions shall be made by the doctoral candidate based on past literature and on a case-by-case basis; should there be uncertainty regarding participant eligibility, the doctoral candidate shall consult with the other researchers.

Although the proposed analyses (detailed further on) are mostly non-parametric, a sufficiently large sample in Stage I is necessary to recruit eligible participants for Stage II, thereby ensuring adequate

statistical power to assess interventional efficacy. As such, Stage I aims to recruit 180 participants, which includes an additional 20% to pre-emptively mitigate potential attrition effects (150 x 1.2 = 180; Hopkin et al., 2015); of this 180, 35-45 participants will be healthy controls, and the remainder will be diagnosed with cancer. Data collection will cease if 250 participants are recruited, in order to preserve ethical integrity. Recruitment will involve convenience and snowball sampling through various cancer organisations (e.g., Cancer Council WA, Solaris Care, Breast Cancer WA), colleagues/networks, social media, flyers, newsletters, and possibly a press release through local radio channels.

Materials

Unless otherwise stated, the selected cognitive and psychosocial measures have been adequately validated for use with cancer patients and in samples demographically similar to the one proposed in this study (e.g., age, sex, ethnicity/country of residence); as such, the references and psychometrics provided in the descriptions (see Appendix B and C) have largely been drawn from studies using similar samples.

Cognitive Measures

The planned objective cognitive measures are the: Australian National Adult Reading Task (AUSNART); Hopkins Verbal Learning Task (HVLT); Paced Auditory Serial Addition Task (PASAT); Trail Making Task (TMT); Controlled Oral Word Association Task (COWAT); Stroop Task; and Star Cancellation Test (only if left neglect is suspected). Note that this battery includes the gold standard neuropsychological tests recommended by the International Cognition and Cancer Taskforce (ICCTF) for CRCI assessment (Wefel et al., 2011) The planned subjective cognitive assessment is the Functional Assessment of Cancer Therapy (FACT-Cog). See Appendix B for further detail.

Psychosocial Measures

The planned psychosocial measures are the: Patient Health Questionnaire-9 (PHQ-9); General Anxiety Disorder-7 (GAD-7); Pittsburgh Sleep Quality Index (PSQI); McGill Quality of Life Questionnaire – Expanded (MQOL-E); McGill Pain Questionnaire–Short Form (MPQ-SF); Death and Dying Distress Scale (DADDS); Demoralisation Scale-II (DS-II); and New General Self-Efficacy Scale (NGSE). These are self-report, involving respondents' subjective appraisal of their own lives. See Appendix C for further detail.

Demographics and Medical History

The planned demographic items will cover sex, age, ethnicity, employment status, marital status, highest education level, exercise habits, current height/weight, and personal contact information. The planned medical history items will cover premorbidities, comorbidities, current health conditions, and cancer histology/stage/receptor status. The planned treatment regimen items will include type of cancer treatment, therapeutic agent composition, neurotoxicity, BBB permeability, and adjunct medications. Much of this information will be obtained by participants requesting a full medical history from their general practitioner. This information will be obtained before/at the first assessment.

Blood Biomarkers

The types of blood biomarkers assessed will be plasma BDNF levels and *APOE* polymorphisms, collected with 3 x 10ml EDTA tubes. Immunoassays will be used to analyse these biomarkers; the researchers are currently in the process of liaising with suppliers and Curtin Health Innovation Research Institute (CHIRI), so specific assay brands/types are yet to be determined.

Procedure

Upon ethical approval, potential participants who have registered interest will first be contacted by phone call; this will serve as an information exchange and screening procedure. From here, eligible and interested participants will be sent an email with the information sheet and will be scheduled in for the first appointment. In both communications, participants will be clearly requested to obtain their current medical history from their treating practitioner, and provide this documentation to the researchers before/at the first appointment. Data collection will be conducted by the researcher in the CHIRI laboratories. To prevent administrator fatigue, the primary researcher will schedule no more than four participants a day.

Upon arrival to the testing facilities, participants will be greeted. Once identity is confirmed, informed consent will be obtained, followed by demographics and height/weight. Next, the neuropsychological battery will be administered in the following order: AUSNART, HVLT-R, PASAT, TMT, COWAT, Stroop Task; FACT-Cog, PHQ-9, GAD-7, PSQI, MQOL-E, MPQ-SF, DADDS, DS-II, and NGSE. If left neglect is suspected, the Star Cancellation Test will be administered as soon as possible. The verbal response questions will be audio recorded for validity and double-scoring. The cognitive measures and psychosocial measures will be separated by a scheduled break; other breaks will be taken as needed, where appropriate. Peripheral blood will be drawn at the end of the battery. Participation is expected to take

approximately 90-120 minutes. At the end of this, participants will be debriefed and given an opportunity to ask questions and make comments; the cancer patients will also be reminded to monitor their communications for information about Stage II.

Methodology of Stage II

Research Design

Stage II involves a double-blinded, randomised control trial (RCT) and a follow up assessment. Stage I data will provide a pre-intervention baseline to assess the efficacy of cognitive training. The proposed research has been designed to allow participants to progress through the stages of each study individually, thereby completing baseline assessments, the intervention, post-intervention assessments, and the follow up assessment following their own timeline. If time and resources allow, a three-month follow up will be conducted to assess maintenance effects of the cognitive training. This assessment will use the same variables and measures as Stage I and II.

Participants and Recruitment

Around 60-100 participants with cancer and evident cognitive impairment will be recruited from Stage I. Aligned with recommendations from past literature, inclusion criteria require participants that demonstrate CRCI, on objective, self-reported, or both measures, so intervention efficacy can be adequately assessed (Lambert et al., 2018; Von Ah et al., 2012). The Stage I participant information sheet for cancer patients explicates that involvement in the first stage may transpire to involvement in Stage II.

Participants invited to take part in Stage II will have cancer, access to and ability to use a phone/tablet/computer with internet for six weeks, and will demonstrate cognitive impairment, operationalised by scores meeting one or more of the following criteria (Vardy et al., 2007; Wefel et al., 2011): scores ≥ 1.5SD below the norm on two or more objective cognitive measures; scores ≥ 2SD below the norm on one or more objective cognitive measures; Global Deficit Score (GDS) ≥ 0.5 points. GDS = mean of deficit scores (which are converted from T scores). A GDS of 0.5 or greater indicates the mean of the objective cognitive measure scores is ≥ 1SD below the norm. Note that "norm" means demographic matched normative scores from neuropsychological compendium.

Should the SD cutoffs for objective cognitive impairment be deemed as overly restrictive during early data collection, then the eligibility criteria for Stage II will be broadened by 0.5SDs. That is, participants would be eligible if they met one of the following adjusted criteria: scores ≥ 1.0SD below the norm on two or more objective cognitive measures; or score of ≥ 1.5SD below the norm on one or more objective cognitive measures. This contingency has been partially guided by Sherman et al. (2023). If necessitated, subjective impairment will also be considered; evidence thereof will be identified through FACT-Cog Perceived Cognitive Impairment (18-item) subscale scores < 54 (Dyk et al., 2020).

Materials

A validated and extensively used computerised cognitive training programme (Cognifit) will be piloted for use in managing CRCI in this study (McCallum & Boletsis, 2013). Stage II post-intervention measures and laboratory equipment will mirror that of Stage I. An additional measure assessing acceptability of intervention will also be administered (Sekhon et al., 2022); the generic Theoretical Framework of Acceptability (TFA) has been adapted for cognitive training in CRCI by the doctoral candidate.

Procedure

Eligible participants will be allocated into either the intervention or control group, using computerised random allocation. If needed, randomisation may be subject to stratification of certain variables. Participants and the researcher will be blinded to group assignment to maximise research validity (Fernandes et al., 2019). The procedure for participants entails completing brain training tasks. The task difficulty will be tailored by the programme software to each individual participant, in order to be sufficiently challenging but not overwhelming. This is to facilitate yield of optimal cognitive benefit. The tailoring of the difficulty is done automatically by the programme throughout each training session. Cognitive training tasks may include (but are not limited to): puzzles, games, word problems. The cognitive training will be a global battery of tasks, with stimulated domains including (but not limited to) memory, attention, executive function, and processing speed. This intervention is self-administered with reminders. The doctoral candidate leading the study will provide information on use to participants. Each participant will follow their own timeline. The intervention will be delivered across six weeks, with a minimum of 4 daily administrations per week; each session will be a minimum of 20 minutes. The base requirement is that participants must complete a minimum of 120 minutes of training per week - i.e., 720 minutes / 12 hours of

training across the six weeks. To clarify, the additional requirements are that the weekly 120 minutes must be completed across four or more training sessions, and each session should be a minimum of 20 minutes. However, note that four sessions of 20 minutes do not actually meet the minimum weekly 120 minutes - they merely form the minimum training parameters. The actual duration of each session will depend on total weekly number of sessions. There is no maximum amount of training. Each participant will be asked to complete the training in their own home at whichever times best suit them, so long as the minimum 12 hours of training is achieved, in the required weekly increments. Additionally, a CogniFit General Cognitive Assessment (30 min) will be completed at the start and end of the six weeks; this is an in house tool is required for the programme to calibrate and evaluate the participants' training. Intervention adherence and fidelity will be assessed by the doctoral candidate. The daily reminders will help minimise attrition. Within a week of the intervention period ending (ideally), participants will attend the clinic once more to complete the neuropsychological battery and blood collection, mirroring that of Stage I. After this, participants will be debriefed to their allocation. Given the double-blind, the participants cannot be unblinded until data collection has been completed.

Proposed Data Analysis

Data collection will cease once 250 participants' data have been collected for Stage I. Neuropsychological, demographic/medical, and biomarker data will be digitised as soon as feasible. Data will also be analysed intermittently to identify and address potential issues. On R Studio, datasets will be screened for missing/anomalous data. Scores on psychocognitive scores will be reverse coded as needed, and potentially standardised to facilitate inter-scale comparisons. Descriptive statistics and correlations between all items and factors will be conducted and reported, with associations of clinical significance highlighted.

Several composite, "manifest" variables will be created, across distinct levels of magnification. This will first be attempted through theory driven confirmatory factor analysis; if interpretation of these results is difficult, then exploratory factor analyses will be conducted to extract factors specific to this study's data. Such an eventuality is more pertinent for psychocognitive variables, in which the distinction between domains and factors is a little more arbitrary; the use of extracted factors in lieu of theoretical ones is commonplace in CRCI research and is supported by meta-analyses and reviews (Cheung et al., 2013; Lambert et al., 2018; Yang & Hendrix, 2018). There are advantages and disadvantages of both types of factor analysis; the factor structure(s) for psychocognitive variables will be determined by range of criteria, before being used in the main analyses. Regardless of chosen factor structure, internal consistency will be analysed and reported through Cronbach's α values. The final set of factors account for the most amount of variance in cognitive measures, without compromising interpretability of results. For the gold standard tests recommended by the ICCTF, scores of each cognitive measure are generally compiled to create a Global Deficit Score (GDS), described as "an actuarial approach that applies weight to below-average scores in the battery" (Chao et al., 2021; Vardy et al., 2007). The GDS is more sensitive at detecting MCI and also mitigates type II error rate. The decision to use a GDS will be determined later by the data.

To disentangle the complex relationships within CRCI, meta-analyses advocate for sophisticated statistical modelling and machine learning (Santos & Pyter, 2018; Seigers & Fardell, 2011; Wefel et al., 2015). As such, the proposed research will conduct three different algorithms for the main analysis, and the model that most validly represents the data for each study will be selected. It is not uncommon to test models against each other in machine learning research; this method has also been adopted by CRCI studies (e.g., Zhou et al., 2021). The proposed models are random forest regression (RFR), support vector machine (SVM), and least absolute shrinkage and selection operator (LASSO) logistic regression. To provide comparative benchmarks, basic logistic/hierarchical regressions will be run with variables mirroring the ones evinced as significant by the machine learning counterparts. The predictive utility of the machine learning models will be assessed by comparing error rate when testing the validation sample, as well as percentage of variance accounted for in outcome variable. The training/validation split will be the conventional 80/20. Treatment efficacy will be assessed more simply with ANOVAs or similar. If the intervention task cannot be sufficiently differentiated from cognitive battery, researchers may statistically adjust assessment scores for practice effects: e.g., Reliable Change Index (Erlanger et al., 2002). The open-ended questions in the TFA assessing participant experience with the intervention (in the form of a brief semi-structured interview) will be subject to a content analysis.

Ethical Considerations

This research shall be conducted in accordance with the National Statement on Ethical Conduct in Human Research as delineated by the National Health and Medical Research Committee (NHMRC). Upon acceptance of candidature, the researchers shall apply for ethical approval from Curtin University. To mitigate risk of infectious disease transmission, basic hygiene and safety protocols will be followed when administering assessments in person (e.g., sanitising testing facility after each use; wearing personal protective equipment if needed). Whilst multiple meta-analyses of RCTs have reported that no adverse events occurred directly resultant of the neuropsychological interventions, including cognitive training (Cheng et al., 2022; Zeng et al., 2016, 2020), eliciting distress is always a possibility with psychological research. As such, relevant resources will be provided in debriefing material (e.g., contact details of Cancer Council, Lifeline, Solaris Care). The researchers have been, and will continue, consulting with a breast cancer survivor who has lived experience with CRCI, in order to: field test the questionnaire/assessment; identify and incorporate respectful/appropriate language; discern areas to minimise cognitive loads on participants; and, in general, endeavour to optimise the participation experience for participants with cancer. Although participation cannot be anonymised, researchers will preserve confidentiality where possible, and all information will be deidentified before writeup. Hardcopy data will be stored under lock and key in restricted access facilities. Electronic data will be stored on encrypted software, devices, and the Curtin Research Drive, accessible only to researchers, parties involved in data collection, and relevant persons if an audit trail is required. Furthermore, the primary researcher has been and will continue to maintain a reflexive journal, which shall include reflection upon ethical decisions, and will also provide documentation if an audit trail is necessitated.

Cognitive, psychosocial, and genetic testing may reveal important health information. In the PICF, participants will need to consent to their treating practitioner(s) to receive pertinent health information, regarding their APOE genotype, as well as results of cognitive and psychosocial measures. This section of the PICF will be highlighted and clarified verbally by the researcher as needed. Participants withholding consent thereof will be disincluded. Delivery of information to practitioner(s) will be thorough, comprehensive, and will use general practice friendly language, with the intention of minimising potential harm, stigma, misinformation, and misinterpretation. The difference between research and clinical testing will be stressed; namely, that the scope of research testing is not diagnostic, and that there may be a need for follow up clinical testing. Participants will NOT receive raw health information directly from researchers, unless in the case of an emergency. This protocol has been developed in accordance with the National Statement on Ethical Conduct in Human Research – particularly Section 3.3 (NHMRC, 2018).

To mitigate adverse effects of possible diagnosis threat, the intervention/placebo material will emphasise the need to continue cancer treatment and following oncology care provider advice. As the cognitive training is hypothesised to benefit the target population, control group participants may be offered the intervention (if it yields significant improvement), after their participation in Stage II, in order to maintain equity and justice. Although unlikely, contingencies for breaking the blind will be in place on the off chance the intervention yields significant, *life-altering* improvements, in which case withholding the intervention until the end of trials would be unethical. The occurrence of a health emergency necessitates the primary physician to be aware of all treatments the participant is receiving; certain, improbable situations may necessitate breaking the blind, and informing the participant and treating physician of the intervention. To ensure expedient transfer of information, each form of communication to the participant will have emergency numbers of the researchers to contact (NHMRC, 2016). Overall, the researchers will endeavour to minimise/eliminate any undue distress or strain for participants.

Facilities and Resources

This study will use CHIRI, School of Population Health, School of Medicine, and other Curtin facilities, rooms, laboratories, software, hardware, and infrastructure. Laboratory consumables are anticipated to be the largest expense. The PhD researcher's personal computer will be used for most data analysis. This PhD will be a hybrid thesis by publication. Five publications are planned (see Appendix D for descriptions and target journals). The final thesis will be a compilation of those papers.

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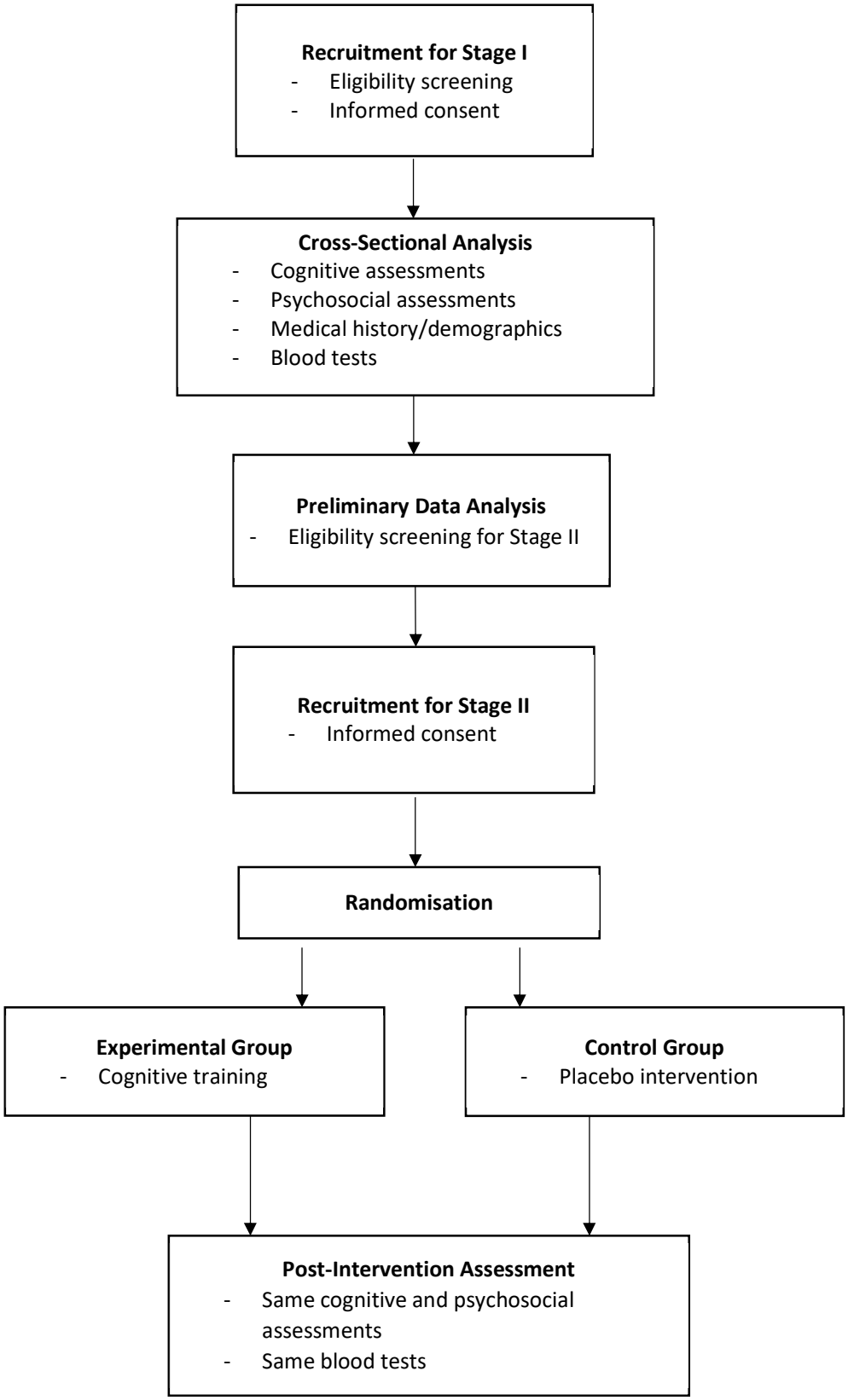
Appendix A: Simple Study Design Flowchart



Appendix B: Psychometrics of Proposed Cognitive Measures

Wide Range Assessment Test – Fourth Edition

Developed by Wilkinson and Robertson (2006), the Wide Range Assessment Test – Fourth Edition Word Reading Subtest (WRAT-4-WR), with reference to norms, is one of four subtests of the WRAT-4, and assesses the academic skill of baseline reading ability. The WRAT-4 has primarily been used to investigate learning, behavioural, and vocational difficulties; the WRAT-4-WR has been used as a measure of premorbid IQ, serving as a proxy measure of cognitive reserve, in individuals with mild-moderate cognitive impairment (e.g., Baker et al., 2017). As reading ability is a crystalised form of intelligence, research suggests it is relatively unaffected by mild to moderate cognitive decline, in healthy ageing, neurodegenerative disorders, and CRCI (Janelsins et al., 2018; Johnstone et al., 1996; Olsen et al., 2015). Respondents are given 75 written words, increasing in lexical complexity, and are asked to read them aloud. The test is terminated when 10 consecutive words are mispronounced. Administration will take 5-10 minutes. These raw scores are converted into a standardised score with a mean of 100, that can be referenced against normed scores. The WRAT-4-WR is psychometrically robust, indicated by adequate construct validity with years of formal education (r = .60) and quality of education (r = .37), and excellent internal consistency (Cronbach's α = .92-96; Casaletto et al., 2014; Sayegh et al., 2014).

Verbal Recognition Memory

Developed by Cambridge Cognition, the Verbal Recognition Memory test (VRM) assesses immediate and delayed recall, by measuring the ability to learn/remember new information, and then subsequently retrieve that information (Sharma, 2013). This is achieved through free recall and forced choice recognition. Respondents are shown a list of 12 words, one word at a time. Immediately after which, they are asked to recall as many of those words as possible. Then, respondents are asked to recognise the original words from a list of 24 words – comprising of both the 12 original and 12 distractors. For the next 20 minutes, other assessments are administered; following which, the respondents are asked to recognise the original words from another list of 24 words – comprising of 12 original and 12 *new* distractors. Performance is evaluated with regard to latency and accuracy. Administration takes 6-8 minutes in total. The VRM is psychometrically robust, with adequate validity indicated by moderate-strong correlations with traditional assessments (r = .46-.64), and sufficient test-retest reliability (intraclass correlation coefficient [ICC] = .49-76; Feenstra et al., 2018; Smith et al., 2013).

Delayed Match to Sample

Developed by Cambridge, the Delayed Match to Sample test (DMTS) assesses visual matching ability and recognition memory (Janelsins et al., 2018). Respondents are to correctly match a target pattern to one of four options. The delay period between being presented target pattern and being presented the four options varies (0, 4, & 12 second delays). Performance is evaluated with regard to latency and accuracy. Administration takes about 10 minutes (Sharma, 2013). The DMTS has robust psychometrics, with construct validity indicated by moderate-strong correlations with traditional tests of memory (r = .36-.74), and adequate test-retest reliability (ICC = .34-.56; Johan et al., 2012; Lowe & Rabbitt, 1998).

Rapid Visual Information Processing

Developed by Cambridge, the Rapid Visual Information Processing test (RVP) assesses visual sustained attention and processing speed (Janelsins et al., 2018). Respondents are asked to recognise a set of target number series of three numbers (e.g., 3, 5, 7), when presented with a series of 100 single digit numbers, one at a time; respondents are to click the screen when they believe the last number of a target sequence has been presented. Performance is evaluated with regard to latency and accuracy. Administration takes about 7 minutes (Sharma, 2013). The RVP has robust psychometrics, with construct validity indicated by moderate correlations with traditional tests of processing speed and attention (r = .35-.49) and adequate test-retest reliability (ICC = .52; Feenstra et al., 2018; Smith et al., 2013).

Tower of Hanoi

The Tower of Hanoi (TOH) assesses executive function and working memory (Humes et al., 1997). Respondents are presented with four different sized discs resting upon three equal length pegs. The aim is to duplicate a target configuration whilst adhering to the following rules: never place a larger disc upon a smaller disc; only one disc can be moved at a time; and all discs must be upon a peg or in hand (Humes et al., 1997). Performance is evaluated with regard to latency and accuracy. Administration takes about 10 minutes (Sharma, 2013). The TOH has robust psychometrics, with construct validity indicated by moderate correlations with other established tests of executive function and working memory (r = .37), and excellent internal consistency (Cronbach's α = .90; Humes et al., 1997; Welsh et al., 1999).

Functional Assessment of Cancer Therapy-Cognition

The Functional Assessment of Cancer Therapy-Cognition (FACT-Cog) assesses subjective cognitive impairment, specifically in cancer patients and survivors (Dyk et al., 2020). Respondents score 37 items (e.g., "My thinking has been slow") on a 5-point Likert type scale, with reference to how often each statement applied to them over the last seven days (*0 = Never; 1 = About once a week; 2 = Two to three times a week; 3 = Nearly every day; 4 = Several times a day*). The FACT-Cog has four subscales: perceived cognitive impairments (scores range: 0-72); comments from others (scores range: 0-16); perceived cognitive abilities (scores range: 0-28); and impact on quality of life (scores range 0-16). After reverse-coding necessary item scores, take the mean of items within each subscale to obtain subscale scores; then sum subscale scores to derive total scores. Lower scores indicate greater perceived impairment. It is recommended the perceived cognitive impairments subscale is used as the primary outcome measure, with the sensitivity cut off of scores below 60, as proposed by Dyk et al. (2020). Administration takes 10-15 minutes. The FACT-Cog is psychometrically robust, with crossvalidation through from interviews with cancer patients, and adequate internal consistency (Cronbach's α = .77-86; Dyk et al., 2020; Von Ah & Tallman, 2015).

Appendix C: Psychometrics of Proposed Psychosocial Measures

Patient Health Questionnaire-9

Developed by Kroenke et al. (2001), the Patient Health Questionnaire (PHQ-9) assesses depressive symptomology and has often been used in populations with terminal or life-changing illnesses (Hinz et al., 2016; Naser et., 2021) Respondents score nine items (e.g., "Loss of interest") on a 4-point Likert type scale, with reference to how much they were bothered by that symptom over the last two weeks (*0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day*). Item scores are summed, and total scores range from 0-27, with higher scores representing higher levels of depressive symptomology; scores ≥ 5, ≥ 10, ≥ 15, and ≥ 20 indicate mild, moderate, moderately severe, and severe depressive symptomology, respectively (Kroenke et al., 2001). The PHQ-9 was selected over other measures of the same/similar construct, as it has been the measure of choice when assessing outpatients in primary care settings (e.g., Naser et al., 2021). Completion takes three minutes. The PHQ-9 is psychometrically robust, indicated by convergent validity with the mental health scale of the Short Form Health Survey (.73), and excellent internal consistency (Cronbach's α = .89; Kim et al., 2022; Kroenke et al., 2001; Shunmugasundaram et al., 2020).

General Anxiety Disorder-7

Developed by Spitzer et al. (2006), the General Anxiety Disorder (GAD-7) is a measure intended for anxiety screening and is recommended for use in cancer outpatients in primary care settings, rather than hospitalised ones (Naser et al., 2021). It is also suitable when wishing to detect both lower levels of anxiety as well as clinical levels (Clover et al., 2020). Respondents rate seven items (e.g., "Trouble relaxing") on a 4-point Likert-type scale, with reference to how much they were bothered by that symptom over the last two weeks (*0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day*). Item scores are summed, and total scores range from 0-21, with higher scores indicating higher levels of anxiety symptomology; scores ≥ 5, ≥ 10, and ≥ 15 indicate mild, moderate, and severe anxiety symptomology, respectively (Spitzer et al., 2006). It is recommended to use cut-off point of 4 for optimal sensitivity, rather than initially proposed cut-off points (Clover et al., 2020). Completion takes two minutes. The GAD-7 is psychometrically robust, indicated by adequate convergent validity with the Beck Anxiety Inventory (r = 0.72), and excellent internal consistency (Cronbach's α = .92; Spitzer et al., 2006).

Pittsburgh Sleep Quality Index

Developed by Buysse et al. (1989), the Pittsburgh Sleep Quality Index (PSQI) assesses sleep quality and screens for sleep disorders. Respondents answer 19 items (e.g., "During the past month, how would you rate your sleep quality overall?"), with each item scored from 0-3 by the administrator (*0 = very good; 1 = fairly good; 2 = fairly bad; 3 = very bad*). Items map onto seven subscales: subjective quality of sleep; sleep latency; sleep duration; usual sleep efficiency; sleep disorders; use of sleeping pills; and daytime dysfunction. Mean subscale scores, ranging from 0-3, are summed; reflecting global sleep quality, total scores range from 0-21, with higher scores indicating lower quality of sleep and greater sleep disorder symptomology. Total scores ≥ 5 indicate significant sleep disturbances and can specify the impaired domain(s); to maintain diagnostic sensitivity for cancer patients, total scores ≥ 8 has been recommended as the new threshold, with total scores ≥ 10 indicating clinical insomnia (Akman et al., 2015; Otte et al., 2015; Palmer et al., 2020). Completion takes 5-10 minutes. The PSQI is psychometrically robust, indicated by adequate convergent validity with the Insomnia Severity Index (r = .80), and sufficient internal consistency (Cronbach's α = .70-83; Mollayeva et al., 2016).

McGill Pain Questionnaire–Short Form

Adapted from the original version developed by Melzack and Torgerson (1971), the McGill Pain Questionnaire–Short Form (MPQ-SF) assesses neurophysiological and psychological pain and has been recommended for clinical use (Harrington et al., 2018; Melzack, 1975; Ngamkham et al., 2012). The MPQ-SF has 17 items. The first 15 items are pain descriptors split into 11 sensory items (e.g., "Throbbing") and four affective items (e.g., "Sickening"), which are rated in terms of experienced severity on a 4-point Likert-type scale (*0 = none; 1 = mild; 2 = moderate; 3= severe*). The last two items assess overall pain intensity, by asking respondents to i) indicate the pain they currently feel out of six options (*0 = no pain; 1 = mild; 2 = discomforting; 3 = distressing; 4 = horrible; 5 = excruciating*), and ii) indicate the average pain felt on a visual analogue scale, with no increments save anchoring endpoints of "No Pain" and "Worst Possible Pain" (scored 0-10 by administrator). The item scores for descriptors are summed, with total scores ranging from 0-45 (sensory subscale: 0-33; affective subscale: 0-12), with higher scores indicating greater experienced pain. The last two items are usually not included in this total score (Melzack, 1987). Completion takes 2-5

minutes, compared to the original 5-10 minutes (Melzack, 1987). Factor structures have differed between studies, with recommendations converging on selecting and reporting the structure that best fits the individual study (Harrington et al., 2018; Ngamkham et al., 2012). The shortened measure was selected as it minimises cognitive load for respondents, without compromising on psychometric properties, as indicated through adequate concurrent validity with the original MPQ (r = .77–.88), and excellent internal consistency (Cronbach's α = .91; Harrington et al., 2018).

New General Self-Efficacy Scale

Developed Chen et al. (2001), the New General Self-Efficacy Scale (NGSE) assesses an individual's belief in their capability to successfully engage in and meet situational demands (Maeir et al., 2022; Whitehall et al., 2020). Respondents rate eight items (e.g., "Even when things are tough, I can perform quite well") in terms of agreement on a five-point Likert scale (*1 = strongly disagree; 2 = disagree; 3 = neither agree nor disagree; 4 = agree; 5 = strongly agree*). After summing item scores, total scores range from 8-40, with higher scores indicating greater self-efficacy. Completion takes 2-3 minutes. The NGSE is psychometrically robust, indicated by adequate content validity (98% agreement between experts), and excellent internal consistency (Cronbach's α = .86-.91; Maeir et al., 2022; Wagland et al., 2015).

McGill Quality of Life Questionnaire – Expanded

Adapted from the original version developed by Cohen et al. (1995), the McGill Quality of Life Questionnaire – Expanded (MQOL-E) assesses quality of life and subjective well-being in individuals with a terminal or life-threatening illness, throughout that illness trajectory (Cohen et al., 1996; 2019). The MQOL-E endeavours to measure eight domains of quality of life: four domains from the original MQOL (physical, psychological, existential, social); and four new domains (healthcare, cognitive functioning, [feeling like a] burden, environment). It is recommended to structure questionnaire with the original questions first, in case of attrition. This significantly improved the comprehensiveness of this measure by an increase of only six items to the original MQOL's 15 items, justifying the added (however marginal) cognitive burden (Cohen et al., 2019). With reference to the past two days, respondents are asked to rate 21 items (e.g., "Getting the information I needed from the health care team was:") on a numeric response scale from 0-10, with extreme descriptors as anchoring endpoints (e.g., *0 = Difficult; 10 = Very easy*). Completion is estimated to take 7-10 minutes. The MQOL-E is psychometrically robust. Convergent validity was demonstrated through moderate correlations (r = .65) with a global quality of life question, indicating both sufficient conceptual similarity *and* sufficient conceptual dissimilarity. The subscales with more than one item had sufficient internal consistency (Cronbach's α = .76-.87), barring the physical subscale (Cronbach's α = .66). Cohen et al. (2019) hypothesised that this slightly suboptimal internal consistency is likely due to the items reflecting diverse facets of physical health. Cohen et al. (2019) recommend using individual subscale scores, as they provide greater information than a total score. Furthermore, the factor structure may differ between populations, suggesting a need for exploratory factor analyses within the proposed research.

Death and Dying Distress Scale

Developed by Lo et al. (2011), the Death and Dying Distress Scale (DADDS) assesses death anxiety in cancer patients. The first version of the DADDS (14 items) was slightly modified with the addition of one item and has been subsequently validated (e.g., Krause et al., 2015). Respondents rate 15 items (e.g., "Running out of time.") on the level of distress that thought/concern elicited over the last two weeks, on a six-point Likert-type scale (*0 = I did not experience this thought or concern; 1 = I experienced very little distress; 2 = I experienced mild distress; 3 = I experienced moderate distress; 4 = I experienced great distress; 5 = I experienced extreme distress*). After item scores are summed, total scores range from 0-75, with higher scores indicating greater death anxiety. Scores ≥ 25 and ≥ 47 indicate moderate and severe death anxiety, respectively. Completion takes 5-10 minutes. The DADDS is psychometrically robust. Divergent validity was demonstrated through moderate-high negative correlations (r = -.68) with less preparation with end of life, and sufficient internal consistency was indicated by high Cronbach's alphas (α = . 93-95; Krause et al., 2015; Lo et al., 2011).

Demoralisation Scale-II

Adapted from the original version developed by Kissane et al. (2004), the Demoralisation Scale-II (DS-II) assesses morale levels and quality of coping in patients with advanced cancer (Robinson, Kissane, Brooker, Hempton et al., 2016; Robinson, Kissane, Brooker, Michael et al., 2016). The DS-II is eight items shorter than original 24 item measure, and consists of two 8-item factors: i) Meaning and Purpose; and ii) Distress and Coping Ability. Respondents rate 16 items (e.g., "I would rather not be alive") with regard to frequency a 3-point Likert-type scale (*0 = never; 1 = sometimes; 2 = often*). After summing item scores, subscale scores range from 0-16 and total scores range from 0-32, with higher scores indicating greater

demoralisation. Completion takes 5-10 minutes. The DS-II is psychometrically robust; convergent validity was indicated by moderate correlations with an established measure of psychological distress (Memorial Symptom Assessment Scale; $r = .65$). Whilst factor structure may differ across populations, the internal consistency of subscales has generally been reported as acceptable (Cronbach's $\alpha = .82\text{-}84$); the internal consistency of the total scale is excellent (Cronbach's $\alpha = .84\text{-}94$; Philipp et al., 2021; Robinson, Kissane, Brooker, Hempton et al., 2016; Robinson, Kissane, Brooker, Michael et al., 2016).

Appendix D: Proposed Publications and Target Journal Information

Proposed Publication	Target Journals	2021 Impact Factor (Quartile Range)
1. Cross section of biological, psychosocial, and demographic mechanisms with cognitive function	*Psycho-Oncology*	3.611 (Q1)
	Journal of Cancer Survivorship	4.428 (Q1)
2. CRCI and affective factors	*Psycho-Oncology*	3.611 (Q1)
	Supportive Care in Cancer	3.450 (Q2)
3. Intervention effects and longitudinal CRCI mechanisms in relation to cognitive function	*Journal of Cancer Survivorship*	4.428 (Q1)
	Translational Oncology	4.741 (Q2)
4. Machine learning to predict CRCI	*Journal of Cancer Survivorship*	4.428 (Q1)
	Cancers	6.319 (Q1)
5. Recommendations for practice for oncology health professionals and patients	*Patient Education and Counseling*	3.181 (Q2)
	Supportive Care in Cancer	3.450 (Q2)

Derived from: https://www.scimagojr.com/

Please note that these are merely descriptive journal article names and will not be used as the titles for the actual publications.