PSYCHOSOCIAL ADVANCES IN NEURO-ONCOLOGY

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PSYCHOSOCIAL ADVANCES IN NEURO-ONCOLOGY

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Neuro-oncology is a rapidly growing field concerned with scientific developments and clinical applications related to neuroscience, neuropsychology, cancer and oncology. Neuro-oncological disorders include cancers that directly affect the central nervous system (CNS), such as brain tumours and brain metastases, and non-CNS cancers with treatments that produce neurocognitive impairment.

To date, the biological mechanisms and neuropsychological effects of brain tumour and cancer have been the dominant focus in neuro-oncology literature. In terms of psychosocial aspects of care, people's understanding of their diagnosis and symptoms and how they cope with their illness has a major influence on their emotional well-being and quality of life.The development and evaluation of psychological and supportive care interventions for people with brain tumour is an area of emerging research and of high interest to health professionals working in the field.

This Research Topic aims to enhance understanding of the psychological and social consequences of brain tumour and other cancers impacting neurocognitive function. It also aims to showcase new developments in assessment and psychosocial intervention approaches.

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EDITORIAL
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Editorial: Psychosocial advances in neuro-oncology

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Keywords: neuro-oncology, brain neoplasms, psychosocial distress, neuropsychology, supportive care

Neuro-oncology is a complex field encompassing scientific and clinical developments in the diagnosis and management of cancers directly affecting the central nervous system (CNS). These include brain tumors and metastases, and non-CNS cancers and treatments that produce neurocognitive impairment. To date, the dominant focus of neuro-oncology literature has been on the biological mechanisms and neurocognitive effects of brain tumor and cancer. However, neurocognitive impairments and psychological disorders arise from an interaction between physiological, medical, and psychosocial factors (1). Therefore, to guide holistic models of care, a biopsychosocial perspective is needed (2).

Psychosocial aspects of care focus on how people perceive and react to their diagnosis and symptoms and the ways in which they cope with their illness within their social context. Subjective reports of symptoms are often more closely related to quality of life than objective indices, such as neuropsychological test performance (2). High rates of depression and anxiety have been consistently reported in neuro-oncology samples, with distress found to persist or even increase over time (3). Due to the increased emphasis on outpatient care, family members assume the primary role in supporting individuals to cope with symptoms and the everyday impact of their illness. Cancer can place strain on relationships and compromise the physical and mental health of family members, in turn impacting their ability to provide sustained support to the person with cancer (4).

This Research Topic aims to enhance understanding of the neurocognitive and psychosocial consequences of neuro-oncological disorders. It also aims to showcase advances in supportive care and highlight future research priorities for this population.

The neurocognitive consequences of cancer were the focus of three articles. A meta-analysis by Ono and co-authors found overall evidence that adjuvant chemotherapy for breast cancer is associated with subtle cognitive impairment. To strengthen the evidence base, they recommended that future prospective longitudinal research examine cognitive impairment levels before and after chemotherapy, with comparisons made to pre-diagnosis functioning. Robinson and co-authors posed the question of whether screening tools, such as the Montreal Cognitive Assessment (MoCA), are sufficiently sensitive to the cognitive effects of brain tumor. Their findings suggested that a brief but tailored assessment may have greater sensitivity to detect mild or focal effects. Dwan and colleagues examined whether rates of cognitive impairment after brain tumor vary according to source of reference used (i.e., norms, controls, and premorbid functioning). Reassuringly, comparisons showed that rates of impairment were largely consistent across sources. They advocated for a multifaceted neuropsychological test battery with a measure of estimated premorbid cognitive functioning to avoid over- or under-estimation of impairment.

Behavioral and social consequences of brain tumor were the topic of two articles led by Simpson and Ownsworth. Simpson and co-authors identified that rates of behavioral changes after brain tumor were variable based on both self-report (7–40%) and relative report (8–60%), and were higher for people with seizures and poorer functional status. Routine assessment and multi-level management of behavioral concerns was recommended. Qualitative research by Ownsworth and

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co-authors investigated family caregivers' experiences of support and relationship changes. Due to the many issues found to impact on caregiver perceptions, it was recommended that professionals explore caregivers' expectations and preferences for support throughout the illness.

Psychological well-being after brain tumor was the key theme of two articles. Trad and colleagues used the Distress Thermometer to screen for distress in different groups of patients and caregivers at initial diagnosis and tumor recurrence. The high rate of distress in the patient and caregiver groups at both time points underscores the key role of neuro-oncology care coordinators in providing access to psychosocial support throughout the care continuum. In their perspective article, Ownsworth and Nash emphasized the importance of assessing existential well-being or people's sense of meaning, purpose, and value in life, in addition to mood and distress levels. Different avenues of existential support were discussed for facilitating the meaning making process across the illness trajectory.

Supportive care interventions for the neuro-oncology population were a focus of five articles, including two intervention studies. Jones and co-authors piloted a telephone-based psychological support intervention for people with brain tumor. The results of their single-case research provided preliminary support for the feasibility and utility of tele-based therapy for enhancing mental health and quality of life. A larger controlled trial is needed to examine factors influencing the efficacy of tele-based therapy. King and Green evaluated the efficacy of group cognitive rehabilitation for cancer survivors in a randomized controlled trial. Their findings generally supported the efficacy of their group intervention, with gains most apparent for perceived cognitive impairment.

In a systematic review of interventions to improve information provision for brain tumor patients, Langbecker and Janda found that most studies reported high rates of satisfaction with information provision. However, few examined improvements in knowledge and the methodological quality was generally low. A scoping review of psychotherapy interventions by Kangas similarly highlighted the paucity of evidence-based interventions for managing anxiety and depressive symptoms for this population. Cormie and colleagues considered the potential for exercise interventions to counteract the broader consequences of cancer, including fatigue, cognitive impairment, depression, and anxiety. Their perspective article discusses the benefits of targeted exercise programs for patients with CNS cancers and the need for research that examines both safety and efficacy of interventions.

In the final article of this Research Topic, Chambers and colleagues present an overview of the challenges and strategies for integrating quality standards of psychosocial care into neuro-oncology. They call for the development of a comprehensive model of survivorship care for people affected by brain tumor and their families.

Overall, the development and evaluation of psychological and supportive care interventions for people with neuro-oncological illness is an area of emerging research and of high interest to health professionals working in the field. International quality standards stipulate the need for cancer care facilities to provide assessments of patient distress and appropriate interventions (5). This practical and evidence-based text provides a unique and timely resource on the psychosocial care needs of people with neuro-oncological conditions and emerging intervention approaches.

AUTHOR CONTRIBUTIONS

All editors contributed to the Editorial, including preparing and editing the draft and approved the final version.

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REVIEW ARTICLE
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A meta-analysis of cognitive impairment and decline associated with adjuvant chemotherapy in women with breast cancer

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A meta-analysis was performed to quantify the magnitude and nature of the association between adjuvant chemotherapy and performance on a range of cognitive domains among breast cancer patients. A total of 27 studies (14 cross-sectional, 8 both cross-sectional and prospective, and 5 prospective) were included in the analyses, involving 1562 breast cancer patients who had undergone adjuvant chemotherapy and 2799 controls that included breast cancer patients who did not receive adjuvant chemotherapy. A total of 737 effect sizes (Cohen's *d*) were calculated for cross-sectional and prospective longitudinal studies separately and classified into eight cognitive domains. The mean effect sizes varied across cross-sectional and prospective longitudinal studies (ranging from −1.12 to 0.62 and −0.29 to 1.12, respectively). Each cognitive domain produced small effect sizes for cross-sectional and prospective longitudinal studies (ranging from −0.25 to 0.41). Results from cross-sectional studies indicated a significant association between adjuvant chemotherapy and cognitive impairment that held across studies with varied methodological approaches. For prospective studies, results generally indicated that cognitive functioning improved over time after receiving adjuvant chemotherapy. Greater cognitive impairment was reported in cross-sectional studies comparing chemotherapy groups with healthy control groups. Results suggested that cognitive impairment is present among breast cancer patients irrespective of a history of chemotherapy. Prospective longitudinal research is warranted to examine the degree and persisting nature of cognitive impairment present both before and after chemotherapy, with comparisons made to participants' cognitive function prior to diagnosis. Accurate understanding of the effects of chemotherapy is essential to enable informed decisions regarding treatment and to improve quality of life among breast cancer patients.

Keywords: breast cancer, adjuvant chemotherapy, meta-analysis, cognitive functioning, moderators

INTRODUCTION

Breast cancer has been reported as the second most commonly diagnosed cancer (1). Adjuvant chemotherapy increases the survival rate in breast cancer patients and is currently administered to up to 60% of patients below the age of 60 years (2). Indeed, it was reported that the 5-year survival rates after breast cancer diagnosis were 89.2% during 2004–2010, and it was estimated that almost 2.9 million women were currently living with breast cancer in the United States in 2010 (1). Hence, quality of life has become an important issue for breast cancer survivors. Although its medical efficacy is undeniable, the negative effects of adjuvant chemotherapy on cognitive functioning have been reported by some breast cancer patients, even years after treatment in some cases (3–9). To support informed decision making, it is important to understand the magnitude and specific areas of cognitive impairment that breast cancer patients may experience after adjuvant chemotherapy.

An increasing number of studies have examined the effects of adjuvant chemotherapy for breast cancer on cognitive functioning (10–13). More specifically, levels of cognitive functioning between women with a history of chemotherapy and their comparison in cross-sectional studies (i.e., termed "cognitive impairment") and changes in levels of cognitive functioning pre- and post-chemotherapy in prospective longitudinal studies (i.e., termed "cognitive decline") have been investigated. A recent meta-analysis suggests that breast cancer patients exposed to adjuvant therapy perform worse than comparison groups (e.g., cancer patients who do not receive adjuvant therapy, non-cancer comparison group) or normative data (11). However, these studies have not found consistent evidence of impairment within a specific neurocognitive domain. For example, neuropsychological outcomes have varied according to characteristics of the breast cancer sample studied, such as stage of tumor, time since treatment or diagnosis, menopausal status, and the use of tamoxifen or other anti-estrogen

drugs, age, education level, and the amount of chemotherapy that patients received (10, 11, 14, 15). In addition, different control groups (e.g., pre-chemotherapy baseline, healthy control, or cancer control) have been used in these studies. Such inconsistencies make comparison between studies difficult since post-chemotherapy cognitive impairment may be observed only among a particular subgroup of breast cancer patients.

Furthermore, the definition of cognitive impairment/decline lacks consistency across studies. For example, it has been defined as a 1-SD decline (16), a 1.96 SDs decline (17), a 2 SDs (18) decline, or a 1.64 z-score decline (19) from pre- to post-chemotherapy. In cross-sectional studies, cognitive impairment has been typically defined as a score at least 2 SDs below the mean of a healthy control group on a test index (6, 20–23) or of the relevant published norm (24). Other studies categorized levels of impairment into mild (1 SD below on one test index) and moderate (2 SDs below on one test index) as compared to the relevant published norm (25). Cognitive impairment was also defined using the mean z-score of the relevant published test norm with various SDs, ranging from 1.4 SDs (26) to 2.0 SDs (27). The score at or below the fifth percentile of the control group was also used to define an overall impairment in some studies (5, 22). Consequently, evidence of post-chemotherapy cognitive impairment/decline among breast cancer patients may vary according to the definition employed in studies. Overall, it must be noted that there is no widely accepted statistical convention or cut-off in determining clinically significant declines or impairments in cognitive functioning. However, Zakzanis (28) proposed that a Cohen's d effect size greater than ± 3.0 is an appropriate marker of clinical significance in determining the sensitivity of neuropsychological tests.

Given the inconsistencies in the literature, the use of a single, universal unit (e.g., effect size) is ideal to synthesize findings and form a consensus on the negative effects of adjuvant chemotherapy on cognitive functioning among breast cancer patients. Indeed, four meta-analytic reviews have been conducted to date (10, 11, 14, 15). **Table 1** summarizes the cognitive domains examined by each review.

The first meta-analysis published by Falleti et al. examined the nature and severity of cognitive impairment associated with adjuvant chemotherapy using five cross-sectional studies and one prospective longitudinal study (10). Analysis of cross-sectional studies revealed that the chemotherapy group performed worse than controls in all six cognitive domains (see **Table 1**). Of these, significant cognitive impairment was observed in the domains of spatial ability ($d = -0.48$) and language ($d = -0.41$). The authors also reported statistically significant logarithmic relationships between larger effect sizes (i.e., more significant cognitive impairment) and shorter time since last chemotherapy, greater proportions of patients currently treated with tamoxifen, and younger patient age. Younger patients may have been treated with tamoxifen more often than older patients, although this was not examined. Regardless, the results suggest that specific subsets of breast cancer patients may be more vulnerable to the cognitive effects of chemotherapy. In contrast, analysis of a prospective longitudinal study showed a wide range of positive effect sizes (i.e., improvement) across cognitive domains ($d = 0.11$ in motor function to $d = 1.09$ in attention). It was concluded that the magnitude of impairment in each domain is moderated by particular variables (e.g., age, time since last chemotherapy and chemotherapy type) and influenced by study design (cross-sectional vs. prospective). However, only one prospective longitudinal study was included in this early meta-analysis.

The aim of the second meta-analysis, published in 2005 by Jansen et al. (13), was to examine the effects of post-chemotherapy cognitive impairment among cancer patients in eight cognitive domains (see **Table 1**). Sixteen studies were included in this

Table 1 | Meta-analytic studies and examined cognitive domains (k = number of comparisons within a meta-analysis, N = combined number of participants).

Cognitive domain	Authors (reference, K = Study N)				
	Falleti et al. [(10), $K = 6$]		Jansen et al. [(13), $K = 16$][a]	Stewart et al. [(15), $K = 7$]	Jim et al. [(11), $K = 17$]
	Cross-sectional	Prospective	Both cross-sectional and prospective		
Attention	$k = 36$, $N = 330$	$k = 3$	$N = 830$	$k = 14$, $N = 366$	$k = 21$
Executive function	$k = 31$, $N = 330$	$k = 5$	$N = 996$	Working memory: $k = 15$, $N = 266$	$k = 19$
Information processing speed	N/A		$N = 617$	$k = 23$, $N = 336$	$k = 11$
Motor speed/function	$k = 12$, $N = 275$	$k = 2$	$N = 816$	$k = 16$, $N = 325$	$k = 11$
Verbal ability/language	$k = 3$, $N = 70$		$N = 795$	$k = 12$, $N = 372$	$k = 15$
Visuospatial ability/skill	$k = 5$, $N = 153$	$k = 1$	$N = 782$	$k = 10$, $N = 344$	$k = 9$
Memory	$k = 35$, $N = 330$	$k = 4$	N/A	N/A	N/A
Verbal memory	N/A		$N = 902$	N/A	$k = 23$
Visual memory	N/A		$N = 591$	N/A	$k = 21$
Short-term memory	N/A		N/A	$k = 18$, $N = 328$	N/A
Long-term Memory	N/A		N/A	$k = 21$, $N = 364$	N/A

[a] *$K = 9$ focusing on breast cancer.*

analysis and, although not all, the majority of those studies ($k = 9$) focused on breast cancer patients. It also aimed to differentiate the effect sizes by type of control data: normative data, control group data, or chemotherapy patients' baseline data. Only visual memory showed significant impairment among chemotherapy patients across all comparison types. When the neuropsychological test scores of chemotherapy patients were compared with normative data, significant effect sizes ($d = -0.52$ to $d = -0.78$) were found in four cognitive domains (i.e., executive function, information processing speed, verbal memory, and visual memory). Conversely, a significant, but low level of impairment in language and verbal memory was identified when scores of chemotherapy patients were compared with those of healthy matched controls. However, no significant differences were identified on these domains when chemotherapy patients were compared with control patients treated with local therapy or with their own baseline scores. The analyses conducted only with breast cancer patients showed similar results (i.e., effect size, significance). Hence, the degree of impairment in each cognitive domain associated with chemotherapy varied, depending on control group characteristics. Nevertheless, the potential moderating role of control group type was not formally examined.

Stewart et al.'s (15) meta-analysis in 2006 examined seven studies (with one longitudinal), including the six examined by Falleti et al. (10). Of the eight cognitive domains evaluated (see **Table 1**), statistically significant small to medium weighted pooled effect sizes ($d = -0.24$ to -0.37) were found in all domains except simple attention and processing speed. The largest effect sizes were found in language ($d = -0.37$) and short-term memory ($d = -0.31$). However, the fail-safe numbers were smaller than recommended. It was concluded that cognitive impairment was subtle and/or only seen among a particular subgroup of women. The authors did not differentiate the effect sizes by type of control group or study design, and this may explain the relatively smaller grand mean effect sizes found in this review than those found in previous reviews. In addition, in this meta-analysis studies were manually removed from analyses for each cognitive domain to achieve homogeneity. Thus, the results may not be representative of the broader breast cancer population.

In the most recent meta-analytic review by Jim et al. in 2012 (11), cognitive functioning in the post-treatment period (i.e., at least 6 months post-therapy) among breast cancer patients was examined. It also examined demographic and clinical moderators of cognitive impairment in patients with breast cancer, including age, education, time since chemotherapy, and treatment with endocrine therapy. The authors included 17 studies, which varied in type of control group: patients' pre-chemotherapy baseline ($k = 4$); patients who received local therapy (i.e., radiation, surgery) or endocrine therapy ($k = 6$); patients without cancer ($k = 3$); two types of control group (pre-chemotherapy baseline and local or endocrine therapy only, $k = 2$); and all three types of control group ($k = 2$). Overall, chemotherapy patients performed worse in the domains of verbal ability ($g = -0.19$, $p < 0.01$) and visuospatial ability ($g = -0.27$, $p < 0.01$). As post-chemotherapy cognitive impairment in these domains depended on types of comparisons (i.e., type of control group), type of control group was reported as a likely moderating factor, although this was not formally tested. Thus, it remains unclear whether the type of control group significantly moderates the magnitude of post-chemotherapy cognitive impairment among breast cancer patients. In addition, no demographic or clinical factors were found to moderate observed cognitive impairment in verbal ability or visuospatial ability (all $p > 0.05$). This may be partly due to their inclusion criteria being at least 6 months post-treatment where any cognitive impairment experienced may have diminished with time. Alternatively, as significant moderators were reported by Falleti et al. (10), results may need to be analyzed separately by study design (cross-sectional vs. prospective longitudinal studies). In the current meta-analysis, moderating factors are examined for cross-sectional studies and prospective longitudinal studies separately.

While there is a general consensus in these meta-analytic reviews regarding the adverse effects of chemotherapy on cognitive functioning among breast cancer patients, their specific findings varied. For example, while some cognitive domains (e.g., language) have more consistently been identified as affected functions, the results have not been firmly conclusive. This may be due to the small number of studies included, and/or a strict inclusion criteria employed, that is, at least 6 months post-treatment in Jim et al. (11). In addition, it has been suggested that grand mean effect sizes may obscure the detection of subtle cognitive decline in a vulnerable subgroup (10, 27). Hence, identification of factors that moderate the magnitude of post-chemotherapy cognitive impairment is important. Indeed, as discussed above, Falleti et al. (10) reported moderators (e.g., time since treatment, younger age, current tamoxifen use), but these results were inconsistent with Jim et al.'s (11) results. Furthermore, although suggested (11, 14), the moderating role of type of controls has never been tested formally.

Some studies (3, 17, 29, 30) have reported that psychological factors such as fatigue, depression, and anxiety can have a negative impact on cognitive functioning in cancer patients. Previous studies that examined the role of chemotherapy in cognitive functioning typically either excluded breast cancer patients with past and/or current psychiatric disorders (5, 8, 17, 18, 20–24, 27, 31–36), found no significant group differences in emotional functioning (9, 12, 37), or statistically controlled for these factors (7, 26, 38). Indeed, the role of psychological factors in post-chemotherapy cognitive functioning was not examined in pervious meta-analyses. Consequently, the current meta-analysis did not include psychological factors as moderating factors.

The current meta-analytic review includes a broader selection of studies compared to previous reviews with two study aims. First, it aimed to identify the magnitude of cognitive impairment among breast cancer patients treated with adjuvant chemotherapy in eight cognitive domains: attention; executive function; long-term (delayed) memory; short-term memory; speed of processing; language; visuospatial; and motor function. The selection of domains was based on clinical practice and neuropsychological assessment literature (39–41). The categories of short- and long-term memories were deemed more appropriate than verbal and visual memories, given that the effect of chemotherapy is more global or diffuse in nature rather than localized in one hemisphere (42). Second, this review aimed to identify factors that moderate the magnitude of cognitive impairment among breast cancer patients treated with chemotherapy. As discussed

previously, the findings of moderating factors in previous meta-analyses have been mixed. However, this may be partly because cross-sectional studies and prospective longitudinal studies have different study focuses, i.e., cognitive impairment and cognitive decline, respectively. Indeed, study design (e.g., cross-sectional vs. prospective) has been suggested to moderate the results (10, 11). Thus, the moderating effects of time since treatment, type of control group, and patients' demographic characteristics (age and education level) were examined separately for cross-sectional studies and prospective longitudinal studies via meta-regression. Identification of moderators would advance knowledge of risk factors for experiencing cognitive impairment associated with chemotherapy among breast cancer patients.

METHOD

SEARCH STRATEGY

Three search strategies were employed to identify suitable published studies for inclusion in the meta-analysis. First, nine computerized databases were searched: PsychINFO, ProQuest Psychology, PsycARTICLES, PubMed/MEDLINE, CINAHL, Web of Science ISI, Scopus, Cambridge Scientific Abstracts, and Google Scholar. The keywords used to search the databases included: *breast cancer, breast neoplasms, chemotherapy, adjuvant chemotherapy, treatment effects, cognition, cognitive, cognitive functioning, neurocognitive, neuropsychological, neuropsychological tests, cancer treatment,* and *cognitive impairment*. Second, the reference lists of published studies collected, and previous meta-analyses and narrative reviews of the topic (10, 11, 14, 15) were scanned to locate further studies not found in the database searches. Third, manual searches of relevant journals were conducted to identify studies, including Clinical Breast Cancer, Journal of Clinical Oncology, Cancer, Journal of Neuro-Oncology, Neuropsychologia, Journal of Clinical and Experimental Neuropsychology, Psycho-Oncology, Neuro-Oncology, Neuro-Oncology Practice, and Acta Oncologia. The search was inclusive of studies published up to August 2014.

INCLUSION CRITERIA

To be included in the meta-analysis, studies had to satisfy the following criteria:

1. Studies report objective neuropsychological data regarding women with breast cancer who underwent adjuvant chemotherapy using either cross-sectional (i.e., comparison groups) or prospective (i.e., patients assessed before and after chemotherapy) designs;
2. For cross-sectional studies, the comparison group consisted of healthy individuals or breast cancer patients not receiving chemotherapy (e.g., local therapy only);
3. For prospective longitudinal studies, patients were assessed before the commencement of chemotherapy and at least one time point after the completion of chemotherapy;
4. At least one validated measure of neuropsychological functioning was used. Studies reporting data from screening measures only (e.g., Mini Mental Status Exam, High Sensitivity Cognitive Screen) were excluded;
5. The results were published in a peer-reviewed journal and in English;
6. Each study reported original group data – the data did not relate to individual case-studies, reviews, commentaries or meta-analyses; and
7. The results presented were sufficient to calculate effect sizes (i.e., means and SDs, *t*-values, *F*-values, *p*-values, or *r*-values).

Data extracted from studies included neuropsychological test data (i.e., mean scores, SDs, and sample size), study design characteristics (i.e., type of control group and timing of assessments), and participant characteristics (i.e., age, education, intelligence assessment, and time since chemotherapy). When sufficient information was not present to calculate effect sizes, an attempt was made to contact authors to obtain the required information. Nineteen authors were contacted to obtain additional information, and one author replied with sufficient data.

STUDY DESIGN AND CLASSIFICATION

As shown in **Figure 1**, a total of 27 studies were included in the meta-analysis, including 14 reporting cross-sectional data only, eight reporting both cross-sectional and prospective data, and five reporting prospective data only.

Effect sizes were calculated separately for cross-sectional and prospective designs. For studies reporting cross-sectional data, samples were grouped according to treatment type and dosage and comparison groups. Two studies (5, 26) included two groups of chemotherapy patients of standard-dose and high-dose chemotherapy, and one study (38) included two groups of chemotherapy patients, namely, those receiving chemotherapy alone and those receiving chemotherapy and tamoxifen. For these studies, two sets of effect sizes were calculated, one for each chemotherapy group contrasted against the comparison group. Four studies (33, 34, 38, 43) included cross-sectional data on cognitive functioning at multiple time points after the completion of chemotherapy [e.g., 5–6 months and 1 year follow-up for Collins et al. (33)] for chemotherapy and comparison groups. For these studies, a set of effect sizes was calculated at each time point, with time after completion of chemotherapy recorded for analyses of moderators. For cross-sectional studies included in the meta-analysis, a range of comparison groups were used to compare cognitive functioning of chemotherapy patients. Comparison groups included healthy controls (12 studies), breast cancer patients not receiving any treatment (one study), breast cancer patients receiving adjuvant endocrine/hormonal treatment only (four studies), and breast cancer patients receiving local therapy (i.e., surgery and/or radiation) only (11 studies). The type of comparison group (i.e., healthy vs. patient comparisons) was examined as a potential moderator of effect sizes using a meta-analytic regression random effects model (44, 45). Four cross-sectional studies (8, 32, 37, 43) included two comparison groups (i.e., healthy controls and patient controls) to contrast the cognitive functioning of patients receiving chemotherapy. For these studies, two sets of effect sizes were calculated, one for each control group contrasted against the chemotherapy group.

NEUROPSYCHOLOGICAL MEASURES

A total of 81 independent neuropsychological measures were used across the studies included in the meta-analysis. These

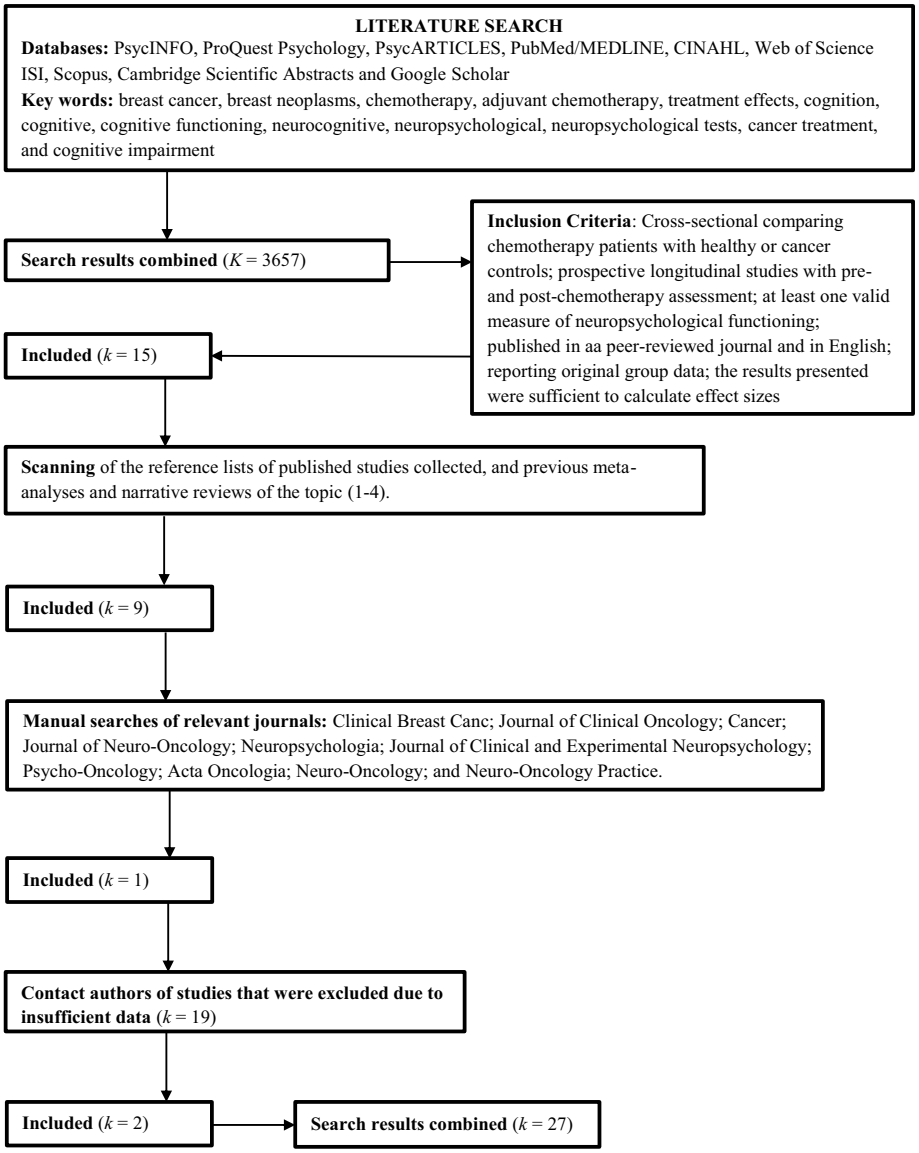

FIGURE 1 | Flow diagram: literature search and selection.

neuropsychological measures were categorized into eight separate cognitive domains according to the primary cognitive function each test is purported to assess based on clinical practice and neuropsychological assessment literature (39–41). **Table 2** displays the eight cognitive domains and the individual neuropsychological measures assigned to each category. Although a single neuropsychological measure may tap multiple cognitive functions, an effort was made to assign each individual measure to a single cognitive domain according to a primary domain of cognitive functioning as specified by major test compendiums. This approach was adopted to minimize over-inflation and violation of the independence of mean effect sizes in the meta-analysis. Tests of homogeneity of effect sizes were performed within each domain of cognitive functioning to assess whether the neuropsychological tests were measuring common parameters.

DATA COLLECTION AND EFFECT SIZE PROTOCOL

Twenty-seven studies met inclusion criteria for the meta-analysis. The following approach was adopted to calculate effect sizes:

1. Calculation of individual effect sizes (d) and corresponding variances for each neuropsychological test outcome in each study. For cross-sectional studies, this was the difference between chemotherapy and control group scores, and for prospective longitudinal studies, this was the difference between pre- and post-chemotherapy scores;
2. Calculation of weighted mean effect size for each study using fixed and random effects models;
3. Calculation of weighted mean effect sizes for each cognitive domain across studies using fixed and random effects models;

Table 2 | Cognitive domains assigned to the neuropsychological measures.

Cognitive domain	Neuropsychological measures[a]
Attention	Arithmetic (WAIS),[2,5,17,22,25,27] CNS-vital signs (flexibility, working memory),[6] continuous performance test (CPT),[1,2] D2 test (GZ-F),[11,18,19,23] digit span (forwards and backwards, WAIS and WMS),[2,5,6,10,11,14,15,17,18,19,21,22,23,24,25,26,27] digit symbol (WAIS),[1,4,5,6,7,9,10,11,12,15,18,22,23,25,26] paced auditory serial addition test (PASAT),[4,5,6,22] RBANS attention,[13] spatial span (WAIS and WMS),[5,10,14,15,22] test of everyday attention (TEA; auditory elevator[9], telephone search[24]), test battery for attentional performance (TAP; Alertness,[19] Go/No-Go[19]), trail making test A,[1,4,5,6,7,9,10,11,12,15,17,18,19,20,22,23,25,26,27] visual elevator,[24] visual span (WAIS),[19] and visual attention test[20]
Executive function	Consonant trigrams,[5,22] controlled oral word association,[6,17,26] D-KEFS Sorting Task,[24] IED Stage 5,[17,27] Regensburg word fluency test (RWT),[11,19] trail making test B,[1,4,5,6,7,10,11,12,15,17,18,19,20,22,23,25,26,27] stroop color-word,[4,7,8,12,13,14,16,18,20,21,23,24] verbal fluency,[1,4,5,6,7,10,11,12,15,16,18,19,20,22,23,24,25] and Wisconsin Card Sorting Test[5,17,22,27]
Long-term memory	15-Word learning test (delayed and recognition),[16] Benton facial recognition test,[17,27] Benton visual retention total errors,[17,27] brief visuospatial memory test (BVMT) revised (delayed),[6] California verbal learning test (delayed recall and recognition),[1,4,5,7,10,15,22] CNS-vital signs (visual and verbal, delayed),[6] family pictures (WMS; delayed and recognition),[2,5,22] logical memory (WMS; delayed and recognition),[1,4,5,11,14,21,22] Hopkins verbal learning test revised (delayed recall),[6,12,26] RBANS delayed memory,[13] Rey auditory verbal learning test (delayed recall and recognition),[3,5,14,17,18,19,21,22,23,24,27] Rey complex figure test (delayed recall and recognition),[3,4,12,14,17,19,20,21,23,27] visual verbal learning test (delayed and total),[8] and visual reproduction (WMS; delayed and recognition)[1,7,10,15,18,20,24]
Short-term memory	4WSTM,[3] 15-word learning test (immediate recall),[16] auditory consonant trigrams test,[6] Benton visual retention test revised,[6,17,27] BVMT revised (total),[6] California verbal learning test (immediate recall),[1,4,5,7,15,22] CNS-vital signs (visual and verbal, immediate),[6] Hopkins verbal learning test revised (total),[6,26] letter digit coding test,[8] letter digit substitution test,[16] letter-number sequencing (WAIS),[2,5,6,14,17,20,21,22,27] logical memory (WMS; immediate),[1,4,11,14] RBANS immediate memory,[8,13] Rey auditory verbal learning test (immediate recall),[3,5,14,17,19,20,21,22,23] Rey complex figure test (immediate recall),[3,12,14,18,21] and visual reproduction (WMS; immediate)[1,4,7,10,15,18,20,24]
Speed of processing	2 and 7 test,[15] Bourdon-Wiersma dot Cancelation test,[9] CNS-vital signs (processing speed, reaction time),[6] Fepsy (binary choice, visual reaction, and visual searching),[18,23] letter cancellation,[14,21] letter digit substitution test,[16] reaction time,[4,20] symbol digit modalities test,[24] symbol search (WAIS),[5,6,22] and test battery for attentional performance (TAP; simple reaction time)[4,19]
Language	Boston Naming Test[1,5,12,17,22,27], RBANS Language[8,13], Reading Subtest (WRAT-R)[1,17], Vocabulary (WAIS, WASI)[1,2,12,17], Similarities (WAIS-R, WASI)[2,17,25]
Visuospatial	Block design (WAIS, WASI),[1,2,4,5,12,17,22,25] design organization test,[16] matrix reasoning (WAIS, WASI),[2,17,24] novel image/novel location,[2] RBANS visual construction,[8,13] and Rey complex figure test (copy)[4,12,17,18,23,27]
Motor function	California computerized assessment package simple reaction time,[4] choice reaction time,[4] Fepsy finger tapping test,[1,7,10,18,20,23] and Perdue Grooved Peg Board[2,5,9,8,13,16,22,24,25]

[a] *Columns includes neuropsychological measures and studies that employed the measure where: 1, Ahles et al. (12); 2, Ayala-Feliciano et al. (31); 3, Bender et al. (38); 4, Castellon et al. (32); 5, Collins et al. (33); 6, Collins et al. (34); 7, de Ruiter et al. (20); 8, Debess et al. (37); 9, Deprez et al. (21); 10, Donovan et al. (24); 11, Hermelink et al. (25); 12, Hurria et al. (46); 13, Jansen et al. (35); 14, Jenkins et al. (43); 15, Jim et al. (36); 16, Koppelmans et al. (7); 17, Nguyen et al. (8); 18, Schagen et al. (22); 19, Scherwath et al. (26); 20, Schilder et al. (23); 21, Shilling et al. (19); 22, Stewart et al. (18); 23, van Dam et al. (5); 24, Vearncombe et al. (17); 25, Wefel et al. (27); 26, Wefel et al. (47); 27, Yamada et al. (9).*

4. Calculation of 95% confidence intervals (CIs) surrounding the two classes of weighted mean effect sizes (i.e., study and cognitive domain); and
5. Calculation of Q and I^2 statistics to assess heterogeneity of weighted mean effect sizes by cognitive domain and study weighted mean effect sizes.

Cohen's d (48) standardized mean difference effect sizes using pooled SDs and corrected for small sample bias (i.e., Hedge's g) were used to determine the magnitude of difference in performance of neuropsychological measures. Zakzanis (28) proposed that Cohen's d is the most appropriate measure for neuropsychological research primarily due to its ability to explicitly account for the variability observed between neuropsychological patients. Poorer cognitive functioning by chemotherapy groups was represented by negative effect sizes. Cohen (48) defines a small effect size as $d \geq 0.2$, a moderate effect as $d \geq 0.5$, and a large effect as $d \geq 0.8$. Zakzanis (28) proposed that a Cohen's d of >0.30 is an appropriate marker of clinical significance in neuropsychological functioning. All Cohen's d statistics are expressed in SD units.

Both fixed and random effect models for combined summary effect sizes were computed. For fixed effect models, it is

assumed that the true effect size is constant across all studies (e.g., cognitive impairment constant regardless of participant characteristics or cognitive domain), with variation being due to sampling error. For random effect models, it is assumed that the true effect size varies across studies due to known and unknown factors (e.g., participant characteristics, cognitive domain assessed).

Individual effect sizes were first calculated for every neuropsychological measure used by a study. For cross-sectional studies reporting means and SDs for neuropsychological test scores, d (Eq. 1) was calculated by subtracting the chemotherapy group mean score (X_1) from the comparison group mean score (X_2) and dividing the result by the pooled SD (S_{pooled}) (Eq. 2). N_1 is the number of participants in the chemotherapy group, N_2 is the number of participants in the comparison group, SD_1 is the SD of the mean score for the chemotherapy group, and SD_2 is the SD of the mean score for the control group:

$$d = \frac{(\overline{X_2} - \overline{X_1})}{S_{\text{pooled}}} \tag{1}$$

where

$$S_{\text{pooled}} = \sqrt{\frac{(N_1 - 1)\text{SD}_1^2 + (N_2 - 1)\text{SD}_2^2}{(N_1 - 1) + (N_2 - 1)}} \tag{2}$$

Similarly, for prospective longitudinal studies reporting means and SDs for neuropsychological scores, d was calculated using Eqs 1 and 2, subtracting the post-chemotherapy mean score (X_2) from the pre-chemotherapy mean score (X_1) and dividing the result by the pooled SD. N_1 is the number of participants pre-chemotherapy, N_2 is the number of participants post-chemotherapy, SD_1 is the SD of the mean score pre-chemotherapy, and SD_2 is the SD of the mean score post-chemotherapy.

All computed effect sizes were corrected for small sample bias (Hedges g) using the formula provided by Hedges (49) and displayed in Eq. 3. N is the total number of participants and d' is the unbiased standardized mean difference:

$$d' = d\left[1 - \frac{3}{4N - 9}\right] \tag{3}$$

The variance for each individual effect size (v_{d}) was calculated using Eq. 4, with N being the sample size for each group in cross-sectional studies and N being the sample size at each assessment point in prospective longitudinal studies:

$$v_{\text{d}} = \left[\frac{N_1 + N_2}{N_1 N_2} + \frac{(d')^2}{2(N_1 + N_2)}\right] \tag{4}$$

The inverse of the sampling variance (Eq. 5) was used to weight each effect size for the fixed effect model of analysis, while the inverse of the sampling variance plus a random effects variance constant (τ_θ) was used to weight each effect size for the random effect model of analysis (Eq. 6):

$$w_{\text{i}} = \frac{1}{v_{\text{i}}} \tag{5}$$

$$w_{\text{i}} = \frac{1}{v_{\text{i}} + \tau_\theta} \tag{6}$$

where

$$\tau_\theta = \frac{Q_{\text{T}} - (k - 1)}{\sum w_{\text{i}} - \left(\frac{\sum w_{\text{i}}^2}{\sum w_{\text{i}}}\right)} \tag{7}$$

After calculation of individual effect sizes, two classes of weighted mean effect sizes ($\overline{d}$)were calculated (steps 2 and 3 of the effect size protocol) for (1) studies and (2) cognitive domain. A mean effect size was calculated for each study by averaging all effect sizes and inverse variance weights within the study. Therefore, each study produced an average effect size and an average inverse variance weight. An average inverse variance weight was used for studies, as weights are a function of sample size and highly similar across effect sizes within a study. Weighted mean effect sizes for cognitive domain were calculated from the individual effect sizes using the formula provided by Hedges and Olkin (44). In Eq. 8, k is the number of effect sizes, $w_{\text{i}} = 1/v_i$ (inverse variance weight), and v_{i} is the variance of the individual effect size:

$$\overline{d} = \left[\frac{\sum_{\text{i}-1}^{\text{k}} w_{\text{i}} d_{\text{i}}}{\sum_{\text{i}-1}^{\text{k}} w_{\text{i}}}\right] \tag{8}$$

The variance of the weighted mean effect size was then calculated using Eq. 9, which was then used to calculate 95% CIs for weighted mean effect sizes to aid in the determination of statistical significance (Eq. 10):

$$v_{\overline{\text{d}}} = \left[\frac{1}{\sum_{\text{i}-1}^{\text{k}} w_{\text{i}}}\right] \tag{9}$$

$$95\%\ \text{CI} = \overline{d} \pm 1.96\sqrt{v_{\overline{\text{d}}}} \tag{10}$$

Tests of the homogeneity of the two classes of weighted mean effect sizes were performed to determine whether the effect sizes were assessing common parameters. When the variation of effect sizes is greater than that would be expected from sampling error alone, the distribution of effect sizes is deemed to be heterogeneous and not representative of a common parameter (45). The Q-statistic was calculated as a homogeneity test (Eq. 11):

$$Q = \sum_{\text{i}=1}^{\text{k}} w_{\text{i}}(d_{\text{i}} - \overline{d})^2 \tag{11}$$

where k is the number of effect sizes, w_i is the inverse variance weight of each individual effect size, d_i is the individual effect size, and $\overline{d}$ is the weighted mean effect size. If the Q-statistic exceeds a critical value associated with a pre-determined alpha level (in the present study, $p < 0.05$) the sample of effect sizes is characterized as heterogeneous.

A number of variables were examined that may potentially moderate the association between chemotherapy and cognitive

impairment using meta-analytic regression, including time since last chemotherapy treatment, type of control group, intelligence, and patients' average age at chemotherapy treatment. Weighted mean study effect sizes were used for all moderator analyses, which were performed separately for cross-sectional and prospective longitudinal studies. All moderators were examined as between-study variables impacting on effect size magnitude and performed separately for cross-sectional and prospective longitudinal studies. Finally, Duval and Tweedie's (50) trim-and-fill method was used to explore publication bias.

RESULTS

PARTICIPANTS

The 27 included studies comprised a total of 1562 breast cancer patients who received chemotherapy and 2799 comparison individuals. The mean age of the chemotherapy and comparison sample was 53.24 years (SD = 8.05) and 55.28 years (SD = 9.37), respectively. For the 16 studies reporting education as a continuous outcome, the mean years of education for the chemotherapy and comparison sample was 14.16 (SD = 1.18) and 14.37 (SD = 1.46), respectively. Previous studies typically reported that participants' age and education level were matched between groups. For the 19 studies reporting data on intelligence, the mean IQ for the chemotherapy and comparison sample was 108.79 (SD = 4.46) and 108.13 (SD = 5.79), respectively. There was no significant difference in mean IQ scores between chemotherapy and comparison groups using a paired-samples t-test, $t(14) = 0.42$, $p > 0.05$.

MEAN STUDY EFFECT SIZES

A total of 737 individual effect sizes for neuropsychological measures were calculated across all studies, with these effect sizes used to calculate a weighted mean effect size for each study and cognitive domain. Calculated effect sizes for each neuropsychological measure are available on request.

CROSS-SECTIONAL STUDIES

Weighted mean effect sizes for cross-sectional studies using fixed and random effect models are shown in **Table 3**. Mean effect sizes ranged from −1.22 to 0.62 using the more conservative random effect model, with 11 comparisons from eight studies producing positive mean effect sizes (i.e., chemotherapy patients exhibited *better* overall cognitive functioning in contrast to comparison groups). Of these, six comparisons showed a significant positive effect size, and they compared cognitive functioning between breast cancer patients with and without chemotherapy (e.g., chemotherapy vs. local therapy).

Nevertheless, overall, in cross-sectional studies, patients treated with chemotherapy exhibited significantly worse cognitive functioning when contrasted with comparison groups, as shown in a small but significant grand weighted mean effect size of $d = -0.12$ (95% CIs from −0.14 to −0.11) using a fixed effects model, and $d = -0.14$ (95% CIs from −0.18 to −0.09) using a random effects model. However, tests of homogeneity were statistically significant for fixed effect ($Q_{Total} = 2519.48$, $p < 0.05$) and random effect ($Q_{Total} = 857.64$, $p < 0.05$) grand weighted mean effect size models, indicating that the sampled effect sizes were not derived from a single population.

PROSPECTIVE LONGITUDINAL STUDIES

Weighted mean effect sizes for prospective longitudinal studies using fixed and random effect models are displayed in **Table 4**. Mean effect sizes ranged from −0.29 to 1.12 using the more conservative random effect model, with only two comparisons producing negative effect sizes representing worse cognitive functioning at follow-up compared to baseline assessments (34, 35). For prospective longitudinal studies, chemotherapy patients exhibited improved cognitive functioning from baseline (prior to chemotherapy) to follow-up (after chemotherapy) assessments, as shown in a small but significant grand weighted mean effect size of $d = 0.11$ (95% CIs from 0.09 to 0.14) using a fixed effects model, and $d = 0.16$ (95% CIs from 0.09 to 0.22) using a random effects model. However, tests of homogeneity were statistically significant for fixed effect ($Q_{Total} = 1212.07$, $p < 0.05$) and random effect ($Q_{Total} = 615.63$, $p < 0.05$) grand weighted mean effect size models, indicating that the sample of effect sizes were not derived from a single population. It is likely that the direction (i.e., better or worse cognitive functioning) and magnitude of effect sizes was partly dependent on the length of follow-up time (e.g., short vs. long follow-up), which is examined in subsequent moderator analyses.

For both cross-sectional and prospective longitudinal studies, there was significant variation within and across studies in the magnitude of effect sizes produced. This may suggest that other factors were impacting on the nature and magnitude of effect sizes within and across studies (e.g., type of neuropsychological measure, time since chemotherapy), with this being the focus of the remaining analyses.

COGNITIVE DOMAIN

Effect sizes were grouped according to cognitive domain (i.e., attention, executive function, language, long-term memory, motor function, processing speed, short-term memory, and visuospatial function) for cross-sectional and prospective longitudinal studies using both fixed and random effect models (**Table 5**). There was variation in the magnitude of weighted mean effect sizes across cognitive domains, indicating that receiving chemotherapy was likely to be associated with specific rather than generalized cognitive effects.

For cross-sectional studies, weighted mean effect sizes ranged from −0.04 to −0.25 for cognitive domains using the more conservative random effects model. The largest effect sizes using the random effects model were found for the processing speed ($d = -0.25$) and executive function ($d = -0.19$) domains, indicating that when aggregating data across all studies, chemotherapy patients were more likely to experience impairments in these two domains relative to comparison groups. Weighted mean effect sizes for the cognitive domains of language, long-term memory and visuospatial function were not significantly different from zero using the random effects model, indicating that on average chemotherapy patients did not experience consistently marked impairments in these domains in contrast to comparison groups. Tests of homogeneity were statistically significant for fixed effect ($Q_{Total} = 80.98$, $p < 0.05$), but not for random effect ($Q_{Total} = 28.02$, $p > 0.05$) cognitive domain weighted mean effect size models. This provides some evidence that variation

Table 3 | Weighted mean effect sizes for cross-sectional studies.

Study: authors, reference, comparison group	*k*	Fixed effect model				Random effect model			
		Effect size (SE)	95% CI	*z*	*Q*	Effect size (SE)	95% CI	*z*	*Q*
Grand mean weighted effect size	509	−0.12 (0.01)*	−0.14 to −0.10	−13.40	2519.48*	−0.14 (0.02)*	−0.18 to −0.09	−6.38	857.54*
Ahles et al. (12), local therapy only	24	−0.16 (0.05)*	−0.25 to −0.07	−3.31	18.67	−0.16 (0.10)	−0.35 to 0.03	−1.69	4.79
Ayala-Feliciano et al. (31), healthy comparison	10	−1.12 (0.11)*	−1.34 to −0.90	−10.01	85.92*	−1.22 (0.17)*	−1.55 to −0.89	−7.29	39.97*
Bender et al. (38), chemotherapy only vs. patients without tamoxifen and chemotherapy, 1 week follow-up	7	0.56 (0.17)*	0.23 to 0.88	3.33	66.68*	0.62 (0.22)*	0.19 to 1.06	2.80	41.11*
Bender et al. (38), chemotherapy and tamoxifen vs. patients without tamoxifen and chemotherapy, 1 week follow-up	7	0.32 (0.17)	−0.02 to 0.65	1.87	47.28*	0.35 (0.22)	−0.09 to 0.79	1.57	29.17*
Bender et al. (38), chemotherapy only vs. patients without tamoxifen and chemotherapy, 1 year follow-up	7	−0.42 (0.24)	−0.89 to 0.06	−1.73	70.43	−0.58 (0.29)*	−1.14 to −0.01	−2.01	56.54*
Bender et al. (38), chemotherapy and tamoxifen vs. patients without tamoxifen and chemotherapy, 1 year follow-up	7	−0.63 (0.28)*	−1.18 to −0.08	−2.26	94.89*	−0.68 (0.32)*	−1.30 to −0.05	−2.13	75.95
Castellon et al. (32), local therapy only	20	−0.39 (0.07)*	−0.51 to −0.26	−5.95	19.08	−0.39 (0.11)*	−0.61 to −0.17	−3.53	6.62
Castellon et al. (32), healthy comparison	20	−0.23 (0.06)*	−0.35 to −0.11	−3.71	19.44	−0.23 (0.11)*	−0.45 to −0.02	−2.15	6.43
Collins et al. (33), hormonal therapy only, one month follow-up	22	0.11 (0.04)*	0.02 to 0.20	2.51	18.29	0.11 (0.10)	−0.08 to 0.30	1.15	3.84
Collins et al. (33), hormonal therapy only, one year follow-up	22	0.01 (0.04)	−0.07 to 0.10	0.33	23.15	0.02 (0.10)	−0.17 to 0.20	0.17	4.97
Collins et al. (34), healthy comparison	12	−0.33 (0.06)*	−0.44 to −0.21	−5.57	14.53	−0.33 (0.13)*	−0.58 to −0.08	−2.58	3.09
de Ruiter et al. (20), without chemotherapy	15	−0.21 (0.09)*	−0.38 to −0.04	−2.40	6.43	−0.21 (0.13)	−0.47 to 0.05	−1.56	2.70
Debess et al. (37), local therapy only	4	0.13 (0.12)	−0.10 to 0.35	1.10	4.51	0.13 (0.22)	−0.30 to 0.55	0.59	1.28
Debess et al. (37), healthy comparison	4	−0.09 (0.06)	−0.20 to 0.03	−1.42	2.92	−0.09 (0.19)	−0.46 to 0.29	−0.45	0.29
Deprez et al. (21), healthy comparison	4	−0.83 (0.17)*	−1.17 to −0.49	−4.77	0.52	−0.83 (0.25)*	−1.32 to −0.33	−3.29	0.25
Donovan et al. (24), local therapy only	11	0.08 (0.05)	−0.01 to 0.18	1.66	7.94	0.08 (0.13)	−0.17 to 0.33	0.64	1.17
Jenkins et al. (43), healthy comparison, four weeks follow-up	13	−0.13 (0.05)*	−0.22 to −0.03	−2.63	6.68	−0.13 (0.12)	−0.36 to 0.11	−1.06	1.08
Jenkins et al. (43), local therapy only, four weeks follow-up	13	0.11 (0.05)*	0.01 to 0.21	2.19	6.26	0.11 (0.12)	−0.13 to 0.35	0.91	1.08

(Continued)

Table 3 | Continued

Study: authors, reference, comparison group	*k*	Fixed effect model				Random effect model			
		Effect size (SE)	**95% CI**	***z***	***Q***	**Effect size (SE)**	**95% CI**	***z***	***Q***
Jenkins et al. (43), healthy comparison, one year follow-up	13	−0.13 (0.05)*	−0.22 to −0.03	−2.66	19.20	−0.13 (0.12)	−0.36 to 0.11	−1.06	3.17
Jenkins et al. (43), local therapy only, one year follow-up	13	0.15 (0.05)*	0.05 to 0.25	3.03	9.08	0.15 (0.12)	−0.08 to 0.39	1.27	1.58
Jim et al. (36), healthy comparison	13	−0.75 (0.05)*	−0.83 to −0.66	−16.45	1071.00*	−0.74 (0.12)*	−0.98 to −0.50	−6.15	326.39*
Koppelmans et al. (7), healthy comparison	15	−0.11 (0.02)*	−0.15 to −0.07	−5.62	20.22	−0.11 (0.10)	−0.31 to 0.10	−1.03	0.69
Nguyen et al. (8), local therapy only	21	0.23 (0.06)*	0.11 to 0.34	3.93	51.14*	0.24 (0.10)*	0.03 to 0.44	2.26	16.62
Nguyen et al. (8), healthy comparison	21	−0.18 (0.06)*	−0.29 to −0.07	−3.07	64.00*	−0.19 (0.10)	−0.39 to 0.02	−1.78	19.87
Schagen et al. (22), local therapy only	20	−0.28 (0.05)*	−0.38 to −0.18	−5.41	17.48	−0.28 (0.10)*	−0.48 to −0.08	−2.72	4.37
Scherwath et al. (26), high-dose chemotherapy vs. without chemotherapy	15	−0.03 (0.07)	−0.17 to 0.10	−0.47	12.37	−0.03 (0.12)	−0.28 to 0.21	−0.27	3.91
Scherwath et al. (26), standard-dose chemotherapy vs. without chemotherapy	15	−0.04 (0.07)	−0.18 to 0.09	−0.62	6.05	−0.04 (0.12)	−0.29 to 0.20	−0.35	1.93
Schilder et al. (23), healthy comparison	17	−0.27 (0.04)*	−0.36 to −019	−6.25	24.20	−0.27 (0.11)*	−0.48 to −0.07	−2.59	4.11
Shilling et al. (19), healthy comparison	8	−0.22 (0.07)*	−0.36 to −0.09	−3.20	12.57	−0.22 (0.15)	−0.52 to 0.08	−1.46	2.61
Stewart et al. (18), hormonal therapy	22	0.04 (0.04)	−0.04 to 0.11	0.90	18.91	0.04 (0.09)	−0.15 to 0.22	0.39	3.41
van Dam et al. (5), high-dose chemotherapy vs. without chemotherapy	18	−0.27 (0.06)*	−0.38 to −0.16	−4.80	47.20*	−0.27 (0.11)*	−0.49 to −0.06	−2.48	12.75
van Dam et al. (5), standard-dose chemotherapy vs. without chemotherapy	18	−0.16 (0.06)*	−0.27 to −0.06	−2.99	20.27	−0.17 (0.11)	−0.38 to 0.05	−1.52	5.24
Vearncombe et al. (17), without chemotherapy	13	0.13 (0.06)*	0.01 to 0.26	2.15	9.61	0.14 (0.13)	−0.11 to 0.38	1.07	2.38
Yamada et al. (9), healthy comparison	12	−0.39 (0.07)*	−0.54 to −0.25	−5.40	26.54*	−0.40 (0.13)*	−0.67 to −0.14	−2.98	7.85
				Q total (df = 509)	2519.48*			*Q* total (df = 509)	857.64*
				Q within (df = 475)	1943.48*			*Q* within (df = 475)	697.21*
				Q between (df = 33)	576.00*			*Q* between (df = 33)	160.43*

*$p < 0.05$.

Table 4 | Weighted mean effect sizes for prospective longitudinal studies.

Study: Authors, reference, timing of follow-up	*k*	Fixed effect model				Random effect model			
		Effect size (SE)	**95% CI**	***z***	***Q***	**Effect size (SE)**	**95% CI**	***z***	***Q***
Grand mean weighted effect size	228	0.11 (0.01)*	0.09 to 0.14	8.78	1212.07*	0.16 (0.03)*	0.09 to 0.22	5.03	615.63*
Bender et al. (38), 1 week follow-up	18	1.02 (0.10)*	0.82 to 1.22	10.01	141.21*	1.12 (0.14)*	0.83 to 1.40	7.73	77.50*
Bender et al. (38),1 year follow-up	16	0.55 (0.13)*	0.30 to 0.79	4.36	266.88*	0.70 (0.16)*	0.38 to 1.03	4.30	181.48*
Collins et al. (33),1 year follow-up	23	0.21 (0.04)*	0.13 to 0.29	5.08	13.69*	0.21 (0.09)*	0.03 to 0.39	2.24	2.64
Collins et al. (33),1 month follow-up	23	0.10 (0.04)*	0.02 to 0.18	2.36	12.07	0.10 (0.09)	−0.09 to 0.28	1.03	2.31
Collins et al. (34), During chemotherapy	13	−0.22 (0.06)*	−0.34 to −0.10	−3.58	191.60*	−0.26 (0.13)*	−0.51 to −0.00	−1.98	182.66*
Debess et al. (37), 4 weeks follow-up	5	0.20 (0.07)*	0.06 to 0.34	2.75	2.94	0.20 (0.19)	−0.18 to 0.58	1.03	0.42
Hermelink et al. (25), between last second and last chemotherapy	12	0.20 (0.04)*	0.12 to 0.28	5.05	19.90	0.20 (0.12)	−0.04 to 0.45	1.67	2.15
Hurria et al. (16),6 months follow-up	13	0.05 (0.08)	−0.10 to.0.20	0.68	8.71	0.05 (0.14)	−0.21 to 0.32	0.40	2.79
Jansen et al. (35),6 months follow-up	7	−0.08 (0.07)	−0.22 to 0.05	−1.19	254.66*	−0.29 (0.17)	−0.62 to 0.04	−1.71	64.30*
Jenkins et al. (43),18 months follow-up	14	0.08 (0.04)	−0.00 to 0.16	1.95	19.79	0.08 (0.11)	−0.14 to 0.31	0.70	2.54
Jenkins et al. (43),4 weeks follow-up	14	0.03 (0.04)	−0.05 to 0.11	0.80	11.65	0.03 (0.11)	−0.19 to 0.26	0.29	1.49
Shilling et al. (19),6 months follow-up	9	0.05 (0.07)	−0.08 to 0.18	0.73	15.89	0.05 (0.15)	−0.24 to 0.34	0.33	3.19
Stewart et al. (18),2 months follow-up	23	0.12 (0.04)*	0.04 to 0.19	3.03	13.50	0.12 (0.09)	−0.06 to 0.30	1.28	2.37
Vearncombe et al. (17), 4 weeks follow-up	14	0.06 (0.03)*	0.00 to 0.13	1.98	66.04*	0.06 (0.11)	−0.16 to 0.28	0.57	5.67
Wefel et al. (27), 3 weeks follow-up	10	0.18 (0.11)	−0.03 to 0.38	1.67	2.47	0.18 (0.17)	−0.15 to 0.50	1.07	1.01
Wefel et al. (27), 1 year follow-up	10	0.26 (0.11)*	0.04 to 0.48	2.33	3.20	0.26 (0.17)	−0.07 to 0.59	1.55	1.41
Wefel et al. (27), 1 year follow-up	6	0.22 (0.10)*	0.02 to 0.42	2.16	15.66*	0.22 (0.19)	−0.16 to 0.60	1.14	4.33
				Q total (df = 228)	1212.07*			*Q* total (df = 228)	615.63*
				Q within (df = 211)	1059.84*			*Q* within (df = 211)	538.24*
				Q between (df = 16)	152.22*			*Q* between (df = 16)	77.39*

*$p < 0.05$.

Table 5 | Weighted mean effect sizes for cognitive domain.

Cognitive domain	*k*	Fixed effect model				Random effect model			
		Effect size (SE)	**95% CI**	***z***	***Q***	**Effect size (SE)**	**95% CI**	***z***	***Q***
Cross-sectional studies									
Attention	107	−0.13 (0.02)*	−0.18 to −0.09	−6.22	313.21*	−0.16 (0.05)*	−0.25 to −0.07	−3.49	74.93
Executive function	83	−0.16 (0.02)*	−0.21 to −0.12	−7.45	324.25*	−0.19 (0.05)*	−0.30 to −0.09	−3.72	62.57
Language	17	−0.04 (0.06)	−0.16 to 0.08	−0.60	42.25*	−0.08 (0.12)	−0.31 to 0.16	−0.64	14.68
Long-term memory	121	−0.08 (0.02)*	−0.12 to −0.04	−4.10	766.84*	−0.04 (0.04)	−0.13 to 0.05	−0.88	296.99*
Motor function	34	−0.11 (0.03)*	−0.17 to −0.05	−3.45	147.77*	−0.16 (0.08)*	−0.32 to −0.00	−1.98	55.54*
Processing speed	32	−0.23 (0.03)*	−0.29 to −0.16	−7.10	116.46*	−0.25 (0.08)*	−0.41 to −0.09	−3.04	19.41
Short-term memory	93	−0.11 (0.02)*	−0.15 to −0.07	−5.64	701.65*	−0.15 (0.05)*	−0.25 to −0.05	−3.04	296.20*
Visuospatial function	22	−0.02 (0.05)	−0.11 to 0.07	−0.48	80.98*	−0.06 (0.10)	−0.26 to 0.14	−0.55	28.02
				Q total (df = 509)	2519.48*			*Q* total (df = 509)	857.64*
				Q within (df = 501)	2493.41*			*Q* within (df = 501)	848.35*
				Q between (df = 7)	26.08*			*Q* between (df = 7)	9.29
Prospective longitudinal studies									
Attention	52	0.12* (0.02)	0.07 to 0.17	4.88	60.53	0.12 (0.06)	−0.00 to 0.24	1.93	11.98
Executive function	37	0.08* (0.03)	0.02 to 0.13	2.56	58.83*	0.08 (0.07)	−0.06 to 0.28	1.11	10.17
Language	8	0.31* (0.08)	0.16 to 0.47	3.91	15.69*	0.26 (0.17)	−0.07 to 0.59	1.57	2.92
Long-term memory	55	0.22* (0.03)	0.17 to 0.28	8.29	333.63*	0.41* (0.06)	0.28 to 0.54	6.38	162.97*
Motor function	9	−0.10 (0.07)	−0.23 to 0.04	−1.44	33.68*	−0.00 (0.16)	−0.37 to 0.24	−0.41	6.38
Processing speed	7	0.14* (0.07)	0.01 to 0.28	2.12	7.19	0.12 (0.17)	−0.21 to 0.45	0.73	1.37
Short-term memory	51	0.06* (0.03)	0.01 to 0.12	2.22	482.73*	0.08 (0.07)	−0.05 to 0.22	1.24	340.84*
Visuospatial function	9	−0.18* (0.07)	−0.31 to −0.04	−2.53	164.60*	−0.29 (0.16)	−0.60 to 0.18	−1.85	50.41*
				Q total (df = 228)	1212.07*			*Q* total (df = 228)	615.63*
				Q within (df = 220)	1156.89*			*Q* within (df = 220)	587.04*
				Q Between (df = 7)	55.18*			Q between (df = 7)	28.59*

*$p < 0.05$.

in effect sizes was reduced when taking cognitive domain into consideration for cross-sectional studies.

For prospective longitudinal studies, weighted mean effect sizes ranged from −0.29 to 0.41 for cognitive domains using the more conservative random effects model. Long-term memory was the only cognitive domain to produce a significant mean effect size ($d = 0.41$), indicating that chemotherapy patients typically exhibited improvements in long-term memory when re-assessed after baseline and after chemotherapy treatment had been completed. Tests of homogeneity were statistically significant for fixed effect ($Q_{\text{Total}} = 1212.07$, $p < 0.05$), and random effect ($Q_{\text{Total}} = 615.63$, $p < 0.05$) cognitive domain weighted mean effect size models. This indicated that variation in effect sizes remained even after taking cognitive domain into consideration for prospective longitudinal studies.

Figure 2 displays forest plots of weighted mean effect sizes for cognitive domains for cross-sectional and prospective longitudinal studies, where the mean effect size is represented by the marker, and the upper and lower 95% CIs for the estimate are represented by the horizontal lines connected to the marker. As shown in **Figure 2**, cross-sectional studies found a negative weighted mean effect size for all cognitive domains with a significant negative effect in five domains. On the other hand, prospective longitudinal studies found positive weighted mean effect sizes for most (6/8) cognitive domains with only one domain showing a significant positive mean effect size.

MODERATORS

Meta-analytic regression was performed separately for cross-sectional and prospective longitudinal studies reporting data for the potential moderators of time since last chemotherapy treatment, average age when receiving chemotherapy, and comparison group type (healthy vs. patient controls) for cross-sectional studies only. For these analyses, mean study effect sizes were the dependent variable, and the inverse variance of mean effect sizes was used as the weighting variable. Displayed in **Table 6** is a summary of the meta-analytic regression analyses for moderators using a random effects model.

For cross-sectional studies, the Q_{model} was significant ($Q_{\text{model}} = 24.63$, $\text{df} = 4$, $p < 0.001$; $Q_{Residual} = 89.49$, $\text{df} = 15$, $p < 0.001$), indicating that the moderator variables together accounted for a significant level of variability in effect sizes. The variables of comparison group and average years of education were significant moderators of mean study effect sizes. These results indicated that poorer performance on neuropsychological tests by chemotherapy patients (i.e., negative effect sizes) was associated with studies using healthy comparison groups (vs. patient comparisons), and chemotherapy patients with fewer years of education.

For prospective longitudinal studies, the Q_{model} was not significant ($Q_{\text{model}} = 6.76$, $\text{df} = 3$, $p > 0.05$; $Q_{Residual} = 83.96$, $\text{df} = 8$, $p < 0.001$), indicating that the moderator variables together did not account for a significant level of variability in effect sizes.

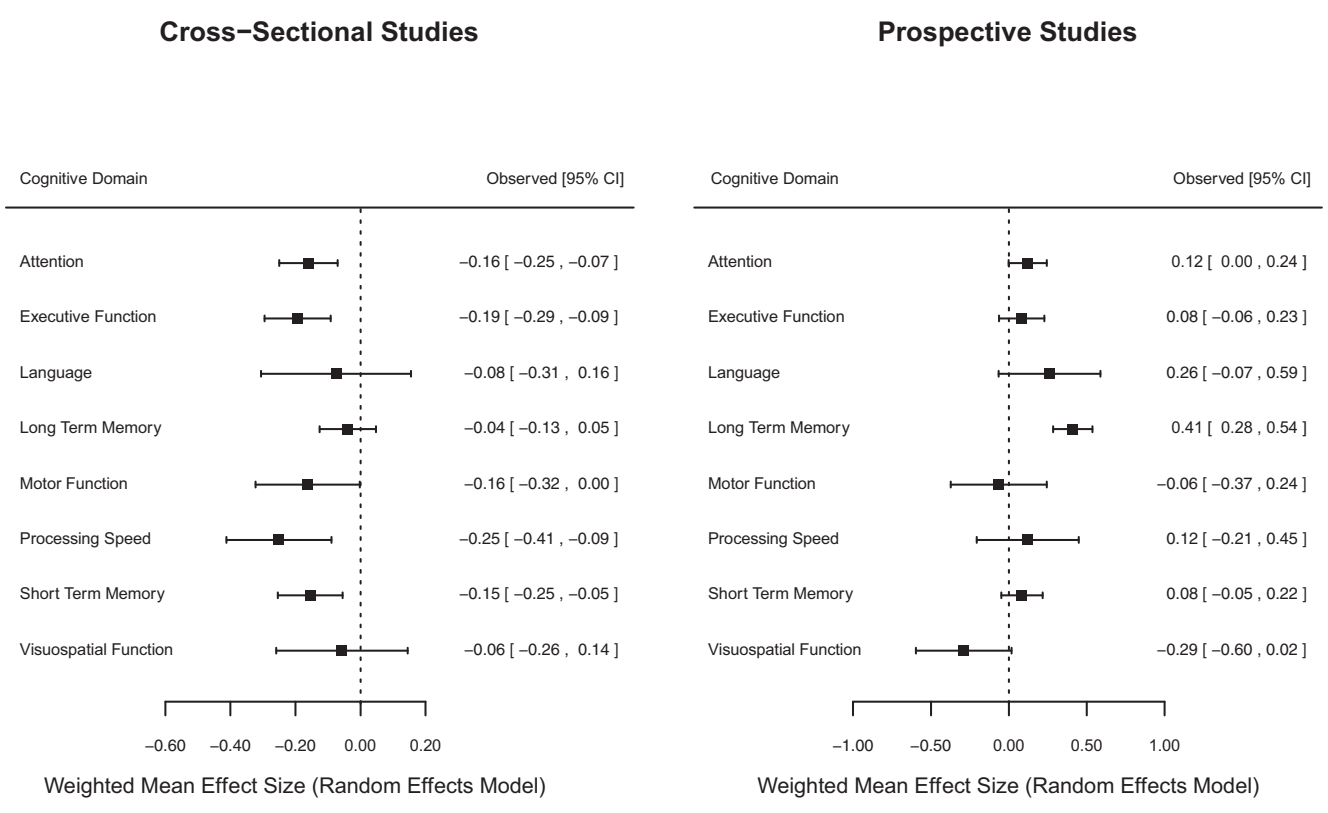

FIGURE 2 | Forest plot of cognitive domain weighted mean effect sizes for cross-sectional and prospective longitudinal studies.

Table 6 | Meta-analytic regression results for moderator variables.

Variable	*B*	SE	*z*	95% CI
Cross-sectional studies				
Intercept	0.75	0.90	0.83	−1.03 to 2.51
Comparison group	−0.52***	0.13	−4.02	−0.78 to −0.27
Age at treatment	0.02	0.01	1.82	−0.00 to 0.04
Time since final chemotherapy treatment	−0.00	0.00	−1.07	−0.00 to 0.00
Average years of education	−0.12*	0.05	−2.19	−0.22 to −0.01
$R^2 = 0.60$				
$Q_{Model} = 24.63$*** (df = 4)				
$Q_{Residual} = 89.49$*** (df = 15)				
Prospective longitudinal studies				
Intercept	1.25	1.05	1.19	−0.81 to 3.30
Age at treatment	−0.03**	0.01	−2.58	−0.06 to −0.01
Average years of education	0.04	0.07	0.59	−0.09 to 0.17
Time since final chemotherapy treatment	−0.00	0.00	−0.13	−0.00 to 0.00
$R^2 = 0.26$				
$Q_{Model} = 6.76$ (df = 3)				
$Q_{Residual} = 83.96$*** (df = 8)				

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

However, the variable of age at treatment emerged as a significant moderator, indicating that older age at chemotherapy treatment was associated with poorer performance on neuropsychological measures at follow-up.

For cross-sectional studies, effect sizes were calculated for IQ differences between chemotherapy and comparison groups for studies reporting such data, with negative effect sizes representing poorer intellectual functioning in chemotherapy groups. Study effect sizes (fixed effect model) ranged from -0.73 to 0.69, with the average weighted effect size for group differences in IQ being d = -0.02 (95% CIs from -0.10 to 0.07) across studies, indicating no significant difference between chemotherapy and comparison groups in IQ. Using meta-analytic regression (fixed effect model), mean IQ effect sizes were not significantly associated with mean study effect sizes for neuropsychological measures ($Q_{Model} = 1.47$, df = 1, $p > 0.05$; $Q_{Residual} = 491.16$, df = 23, $p < 0.001$).

There were only six prospective longitudinal studies reporting data on IQ. Given this small sample size, no analyses were conducted to examine the association between IQ and effect size magnitude for prospective longitudinal studies.

PUBLICATION BIAS

The trim-and-fill method (50) was used to assess publication bias separately for cross-sectional and prospective longitudinal studies using random effect model estimates. Inspection of the observed funnel plots of mean study effect sizes and the standard error of effect sizes in **Figure 3** indicated symmetry around the overall weighted mean effect size suggestive of no significant publication bias for both cross-sectional and prospective longitudinal studies. Trim-and-fill analyses confirmed that no additional studies were required to adjust for an asymmetrical distribution of effect sizes for cross-sectional and prospective longitudinal studies.

DISCUSSION

In the current meta-analysis, 27 studies ($N = 4361$ participants) were reviewed and 737 effect sizes were generated to address two study aims: to examine the magnitude of cognitive impairment in eight cognitive domains and to identify factors moderating the magnitude of post-chemotherapy cognitive impairment among breast cancer patients. The findings generally indicated that the magnitude of cognitive impairment among chemotherapy groups varied within and across studies. Regardless, the grand mean weighted effect size suggests that subtle cognitive impairment was associated with adjuvant chemotherapy among breast cancer patients. This is consistent with previous meta-analyses (10, 11, 14, 15). The small but significant grand mean effect size may be due, partly, to varying levels of impairment across different cognitive domains and moderating factors not being taken into account. The mean effect sizes are discussed separately for each study design (cross-sectional vs. prospective).

STUDY MEAN EFFECT SIZES BY STUDY DESIGN

Cross-sectional studies

Overall, breast cancer patients with a history of chemotherapy performed slightly, but significantly worse than their comparison groups. Nevertheless, 6 out of 34 comparisons from cross-sectional studies indicated that breast cancer patients previously treated with chemotherapy performed significantly better than individuals in the control group. However, these results were all based on comparisons of cognitive functioning between breast cancer patients with and without chemotherapy. Thus, these comparisons suggest that, generally, breast cancer patients previously treated with chemotherapy exhibit cognitive impairment as compared to their counterparts, but their impairment may not be worse than some breast cancer patients without chemotherapy.

Prospective longitudinal studies

In contrast, the grand mean effect size from the prospective longitudinal studies suggested that cognitive functioning among breast cancer patients treated with chemotherapy is slightly, but statistically significantly better after chemotherapy. However, this may not necessarily suggest that chemotherapy improves cognitive functioning or refutes the negative effects of chemotherapy on cognitive function. There are two other explanations, which are related to time since treatment and methodological limitations.

First, the results may be due to the timing of post-treatment assessment. It has been suggested that cognitive impairment associated with chemotherapy among breast cancer patients improves over time (10, 27, 43, 47). Follow-up assessment in these prospective longitudinal studies was conducted between 1–3 (33, 37, 38, 43) and/or 6–18 months (33, 35, 38, 43, 46) after last chemotherapy. Cognitive impairment at longer term follow-up may not be as marked as during or just after treatment. For example,

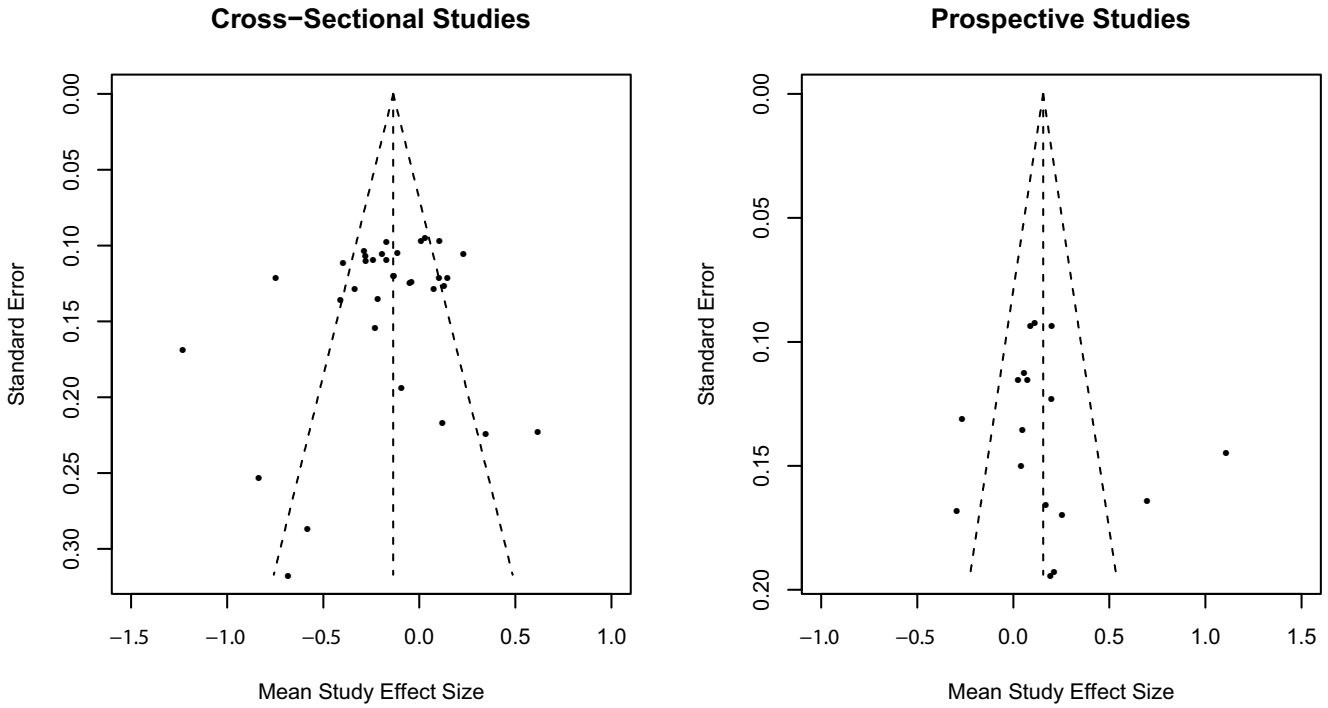

FIGURE 3 | Trim-and-fill analysis observed funnel plots for publication bias in mean study effect size.

breast cancer patients may have recovered from short-term cognitive impairment associated with chemotherapy and/or developed compensatory cognitive strategies after experiencing a series of chemotherapy doses. Given this possibility, time since treatment was examined as a moderating factor and is discussed later. However, some breast cancer patients treated with chemotherapy show long-term cognitive impairment (7), and a previous meta-analysis (11) did not find time since treatment to be a moderating factor. In addition, this does not explain why breast cancer patients' cognitive functioning is better than (rather than equal to) pre-chemotherapy levels. Thus, other explanations need to be explored.

An alternative explanation relates to methodological issues inherent in prospective longitudinal studies. The first methodological issue that may have affected the results is potential practice effects on patients' performance at follow-up. However, most prospective longitudinal studies included a method for managing practice effects. For example, a control group was employed to correct for practice effects (17, 25, 34) and/or alternative forms of tests were used at follow-up (27, 35, 38). Other studies employed a statistical correction for practice effects (18, 19, 27, 43). Regardless, practice effects were reported in studies that had employed alternative forms of tests at follow-up (35, 38). Indeed, only one study (34) reported significant post-chemotherapy cognitive decline among breast cancer patients. Furthermore, improved post-chemotherapy cognitive functioning was reported even when a control group was included (17, 25). These studies found improved post-chemotherapy cognitive functioning, even after quantifying and adjusting for practice effects based on improved performance in controls. Thus, practice effects may not fully explain improved post-chemotherapy cognitive function in patients.

The second methodological issue that may explain improved post-chemotherapy cognitive function relates to the timing of baseline assessment. More specifically, in all prospective longitudinal studies, patients' baseline cognitive functioning was measured prior to chemotherapy, but either after diagnosis with and without some treatment (19, 25, 27, 35, 46, 47) or even after surgery (17, 18, 33, 34, 37, 38, 43). Consequently, the patients were aware of the presence of breast cancer, and some underwent a surgery or treatment, waiting for the commencement of chemotherapy. All but three studies in the current meta-analysis (19, 25, 47) either excluded breast cancer patients with psychiatric disorders, reported no significant group differences in psychological factors (fatigue, depression, and anxiety); or controlled for such factors. However, it is possible that emotional factors associated with a diagnosis of breast cancer (i.e., acute stress, depression) could negatively influence cognitive functioning for some individuals. Therefore, baseline data used in those studies may not be the same as patients' pre-diagnosis baseline cognitive functioning. For instance, if chemotherapy patients' post-diagnosis (i.e., pre-chemotherapy) performance was significantly worse than their pre-diagnosis baseline, their post-chemotherapy performance is likely to be better than their pre-chemotherapy performance. Then, even if their post-chemotherapy performance was much better than their post-diagnosis/pre-chemotherapy baseline, this may still be significantly worse than pre-diagnosis performance. Indeed, some studies have noted impaired performance in women with breast cancer prior to chemotherapy, in support of this

explanation (25, 51). Therefore, the difference between pre- and post-chemotherapy cognitive performance in those studies may represent only a partial trajectory of post-chemotherapy cognitive functioning among breast cancer patients. This may in part explain improved post-chemotherapy cognitive function among breast cancer patients.

COGNITIVE IMPAIRMENT BY COGNITIVE DOMAINS

Cross-sectional studies

It was found that breast cancer patients previously treated with chemotherapy performed significantly worse than (healthy or cancer) controls in the domains of attention, executive function, motor function, processing speed, and short-term memory. The level of cognitive function among chemotherapy patients in the domains of language, long-term memory, and visuospatial function was not significantly different from their counterparts. Of the previous meta-analyses, only Falleti et al. (10) analyzed effect sizes for cognitive domains by study design, and they found significant cognitive impairment in the domains of attention, executive function, motor function, verbal ability, visuospatial ability, and memory. Therefore, the current results are partially consistent with Falleti et al. (10). The inconsistency may be partly due to an increased number of comparisons included in the current meta-analysis. It should be noted that the level of heterogeneity of cross-sectional studies was non-significant using a random effect model when studies were analyzed by cognitive domains. This supports the validity of the current results and suggests that the magnitude of post-chemotherapy cognitive impairment among breast cancer patients varies, depending on the cognitive domain.

Prospective longitudinal studies

In contrast, no post-chemotherapy cognitive decline was found among breast cancer patients in prospective longitudinal studies. Instead, breast cancer patients showed significantly improved long-term memory after chemotherapy. Although Falleti et al. (10) found post-chemotherapy cognitive improvement among breast cancer patients, they included only one study. Thus, there is no previous review to allow comparison with the current results. In addition, as discussed previously, issues regarding the varied timing of post-chemotherapy assessment, practice effects, and post-diagnosis baseline need to be considered in the interpretation of results from prospective longitudinal studies.

The cognitive domains (except visuospatial function) that showed less impairment in cross-sectional studies were also those more likely to show greater improvement in prospective longitudinal studies. For example, long-term memory was found to be least impaired in cross-sectional studies and was found to be the domain most likely to improve in prospective longitudinal studies. Although hypothetical, long-term memory may be the cognitive domain that is less likely to be affected by chemotherapy and/or is more likely to improve faster than other domains. Alternatively, it is possible that measures of long-term memory may be more susceptible to practice effects.

Language and visuospatial function have previously been reported as the most impaired cognitive domains among breast cancer patients treated with chemotherapy (10, 11, 14, 15). However, the magnitude of post-chemotherapy cognitive impairment and cognitive decline in language and visuospatial function among breast cancer patients was non-significant in this review. The discrepancy in findings between previous meta-analyses and this analysis may be due to an increased number of comparisons included in this study. More specifically, the results in previous meta-analyses were derived from a small number of comparisons ($k = 3$–15 for language and $k = 5$-10 for visuospatial function). Whereas in the present meta-analysis a larger number of comparisons was included, the domains were examined separately for cross-sectional studies ($k = 17$ for language and $k = 22$ for visuospatial function) and for prospective longitudinal studies ($k = 8$ for language and $k = 9$ for visuospatial function). Based on the large number of comparisons and separate analyses by study design, these domains were found to be non-significant. It should be noted that the CIs of the grand mean effect sizes for language and visuospatial function varied widely, and the non-significant results may be due to variability across studies in the results on these domains.

EFFECTS OF MODERATORS

Cross-sectional studies

Among cross-sectional studies, type of control group was found to significantly moderate the magnitude of cognitive impairment. More specifically, level of cognitive functioning among breast cancer patients with a history of chemotherapy was significantly worse than healthy controls, but not significantly worse than breast cancer patients without chemotherapy. In addition, level of education was found to significantly moderate the magnitude of post-chemotherapy cognitive impairment. That is, chemotherapy patients with lower levels of education tend to show greater cognitive impairment than those with higher levels of education. However, time since treatment and age at treatment were not significant moderators. These results contrast with those of Falleti et al. (10) but are partially consistent with Jim et al. (11) who found non-significant moderating effects of time since treatment and age. The meta-analysis by Falleti et al. (10) was based on only six cross-sectional studies and did not include type of control group as a moderator, which was found to be the most significant factor in the current review. These differences may explain the inconsistent findings. The main findings arising from the cross-sectional studies are that significantly greater cognitive impairment is observed among breast cancer patients previously treated with chemotherapy when compared to healthy controls, and that lower education level may be a risk factor for cognitive impairment. However, it is further noteworthy that levels of cognitive impairment are similar among breast cancer patients, irrespective of a history of chemotherapy.

Prospective longitudinal studies

Conversely, in prospective longitudinal studies older age was associated with increased levels of cognitive decline among breast cancer patients previously treated with chemotherapy. Falleti et al. (10) found the opposite results, with younger breast cancer patients exhibiting greater cognitive impairment after chemotherapy. However, their results were based on cross-sectional studies only and thus cannot be directly compared to the present findings. The current review suggests that cognitive decline associated with

chemotherapy for breast cancer may interact with age, whereby older patients may have a higher risk of developing and/or experiencing persisting cognitive decline after chemotherapy. The negative effects of older age on cognitive function are well documented (52), including cognitive decline in the domains of processing speed, attention and executive function. Thus, it is possible that chemotherapy exacerbates the effects of old age on cognitive function for breast cancer patients.

STRENGTHS AND LIMITATIONS OF CURRENT REVIEW

The current meta-analysis extended upon previous reviews to improve understanding of the effects of chemotherapy on cognitive functioning among breast cancer patients. The results were based on good search strategy and a larger number of studies that employed validated neuropsychological measures. Indeed, the results of the publication bias analysis supported the validity of the findings. In addition, study design (e.g., cross-sectional vs. prospective) has been suggested to moderate the results (10, 11). To address this issue, the grand mean effect sizes and meta-regression analyses of moderators were conducted for cross-sectional studies and prospective longitudinal studies.

Regardless of these strengths, some limitations need to be acknowledged, many of which are inherent in meta-analyses. First, as suggested in *Q* statistics, the effect sizes varied significantly across studies, and studies were heterogeneous with respect to many factors, such as the measures used, participants' characteristics, cancer stages, type and dosage of chemotherapy and hormone therapy, time since therapy, and control type. Therefore, whether these factors moderate the results is yet to be examined. In addition, although the type of control group was found to significantly moderate the magnitude of post-chemotherapy cognitive impairment, other potential moderators, such as type and dosage of chemotherapy and the current use of tamoxifen, were not included in this review.

FUTURE DIRECTIONS

As discussed above, it is important to examine other factors that potentially moderate the magnitude of post-chemotherapy cognitive impairment/declining, especially over the long-term. First, it is still uncertain whether the use of tamoxifen itself, or the interaction between tamoxifen and chemotherapy, leads to the development of and/or persistence of cognitive impairment among breast cancer patients. This question is not new, yet the findings of previous meta-analyses have been mixed (10, 11). Second, it also remains unclear whether or not level of cognitive performance at pre-chemotherapy (but post-diagnosis) is the same as that at pre-diagnosis. To answer these research questions, a prospective longitudinal study needs to be conducted, in which cognitive functioning is compared between four groups: healthy controls; breast cancer patients with chemotherapy only (and no hormone therapy); patients with chemotherapy and hormone therapy; and patients with hormone therapy only. Cognitive functioning should be measured prior to diagnosis (e.g., at regular screening examinations), as well as just before, during, and after chemotherapy. This type of study would also answer another research question that emerged from this review – whether or not the effects of chemotherapy on cognitive functioning are worse than those of other treatments. However, this type of study may not be easily conducted, and conducting a cross-sectional study with an improved study design would still be helpful. For example, comparing cognitive functioning between the following groups may identify the moderating factors: a matched healthy control group, a matched cancer control group (diagnosed, but not treated), and treated breast cancer groups (surgery only, chemotherapy only, chemotherapy and hormonal therapy, and hormonal therapy only).

No consistent association between psychological factors (i.e., depression, anxiety, or fatigue) and performance on objective measures of cognitive functioning has been found (7, 8). Some studies have even reported that depression and fatigue were significantly related to subjective, but not objective cognitive complaints (5, 36). However, the lack of association between psychological factors and post-chemotherapy cognitive impairment among breast cancer patients may be due partly to the issue of ecological validity of the objective measures (42). In addition, breast cancer patients with depression have typically been excluded from studies (5, 8, 17, 18, 20–24, 27, 31–36), or these factors were statistically controlled for (7, 26, 38). It is also possible that depressed breast cancer patients are less likely to participate in research. Hence, the relationship between mental health issues and post-chemotherapy cognitive impairment remains unclear, and this needs to be examined in future research.

Finally, it may be important to measure additional cognitive domains. For example, further subdivision of some cognitive domains may help identifying specific cognitive functions that are vulnerable to the process (diagnosis, treatment, and recovery) of breast cancer and, this would consequently help clinicians providing patients with focused intervention. More specifically, executive function may be subdivided into working memory, inhibition, and shifting, while attention may be subdivided into attention span, selective attention, and focused attention. Furthermore, an investigation of cognitive domains that have not included in previous studies would also be beneficial. For instance, impairments in prospective memory, or the ability to remember what to do in future, would have significant clinical implications.

CONCLUSION

The effects of chemotherapy on cognitive functioning among breast cancer patients were found to be subtle, but relatively global with five of eight domains being impaired. These findings indicate that some cognitive domains are more (e.g., processing speed) or less (e.g., long-term memory) susceptible to chemotherapy than others. Further, particular cognitive domains (e.g., long-term memory) may show greater improvement over time than others albeit these domains may be susceptible to practice effects. Because individuals' levels of cognitive performance at pre-chemotherapy assessment may not be the same as their pre-diagnosis performance, it remains unclear whether, and to what degree post-chemotherapy cognitive decline in breast cancer patients improves or persists. A significant level of cognitive impairment was observed in breast cancer patients previously treated with chemotherapy, as compared to healthy controls. However, level of cognitive impairment in chemotherapy patients did not significantly differ from breast cancer patients without

chemotherapy. Hence, cognitive impairment may be common among breast cancer patients irrespective of their treatment regimens. Furthermore, patient characteristics (age and educational level) and the processes of cancer diagnosis and treatment may moderate the magnitude of cognitive impairment. This is the first review that examined and found the moderating effect of the type of control groups in cross-sectional studies. Future prospective longitudinal research is warranted to examine the degree and persisting nature of cognitive impairment present after chemotherapy, with comparisons made to participants' cognitive function *prior to diagnosis*. Accurate understanding of the effects of chemotherapy is essential to enable informed decisions regarding treatment and to improve quality of life among breast cancer patients.

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Cognitive screening in brain tumors: short but sensitive enough?

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Cognitive deficits in brain tumors are generally thought to be relatively mild and non-specific, although recent evidence challenges this notion. One possibility is that cognitive screening tools are being used to assess cognitive functions but their sensitivity to detect cognitive impairment may be limited. For improved sensitivity to recognize mild and/or focal cognitive deficits in brain tumors, neuropsychological evaluation tailored to detect specific impairments has been thought crucial. This study investigates the sensitivity of a cognitive screening tool, the Montreal Cognitive Assessment (MoCA), compared to a brief but tailored cognitive assessment (CA) for identifying cognitive deficits in an unselected primary brain tumor sample (i.e., low/high-grade gliomas, meningiomas). Performance is compared on broad measures of impairment: (a) number of patients impaired on the global screening measure or in any cognitive domain; and (b) number of cognitive domains impaired and specific analyses of MoCA-Intact and MoCA-Impaired patients on specific cognitive tests. The MoCA-Impaired group obtained lower naming and word fluency scores than the MoCA-Intact group, but otherwise performed comparably on cognitive tests. Overall, based on our results from patients with brain tumor, the MoCA has extremely poor sensitivity for detecting cognitive impairments and a brief but tailored CA is necessary. These findings will be discussed in relation to broader issues for clinical management and planning, as well as specific considerations for neuropsychological assessment of brain tumor patients.

Keywords: neurocognitive deficits, brain tumor, cognitive screening, neuropsychology, brief cognitive assessment, MoCA

INTRODUCTION

Cognitive function is an independent prognostic factor in the survival of glioma patients (1, 2). For brain tumors, cognitive assessment (CA) can inform clinicians of areas to target for neurorehabilitation (3), monitor progress to facilitate decision making about further intervention (4), and if there has been a decline in cognitive function, address the question of whether the tumor has recurred or progressed (3). In addition, a CA is able to address the question of whether subtle alterations in cognitive function are significant or not, particularly when monitoring slow-growing low-grade gliomas (4). Assessment of cognitive status can be undertaken with a brief cognitive screen or by a longer formal neuropsychological evaluation. Cognitive screening is typically used in acute states, at bedside, hence the focus of our study is to identify whether a brief CA can be tolerated and completed in a relatively acute state (post-surgery but <3 months) and, if so, whether this yields better results in terms of detecting cognitive deficits.

Cognitive screening tools are popular but their sensitivity to cognitive impairment in general, and specifically for brain tumor patients, has been questioned (4). One reason may be that brain tumor-associated cognitive deficits have been thought to be relatively mild and non-specific (5), although this has recently been challenged (6). It is unsurprising that severity and specificity of cognitive deficits in brain tumor patients has been debated as prevalence rates vary from 29 to 91%. This variability may depend on several factors including time of assessment (pre- or post-surgery), tumor grade, treatments (radiation, chemotherapy), and lesion location (7). However, the main reason for this variability may be the method used to assess cognitive functions. For example, in one study, few patients with low-grade gliomas showed cognitive deterioration when screened with the mini-mental state examination (MMSE) (8), irrespective of radiation treatment (9). By contrast, Tucha and colleagues (10) investigated cognitive function with neuropsychological tests and reported that 91% of patients with frontal or temporal tumors were impaired in at least one cognitive domain. In this study, we aimed to investigate the most effective and efficient method of detection of cognitive impairments in the acute period following tumor resection by directly comparing a cognitive screening tool with a brief but domain-specific CA.

Cognitive screening tools have the advantage of brevity and simplicity of administration. The main question, however, is whether these tools are sensitive to detect abnormalities. In the last decade, the Montreal Cognitive Assessment (MoCA) (11) screening tool has been increasingly favored over the MMSE as it has been shown to have greater sensitivity for detecting cognitive dysfunction. This has been shown in patients with brain tumors (12) and brain metastases (13), as well as in other neurological conditions including stroke (14), sub-arachnoid hemorrhages (SAHs) (15), and silent cerebral infarcts (16). Bernstein et al. investigated the psychometric properties of the MoCA in three diverse brain

pathologies and concluded that it was reliable in detecting cognitive dysfunction as well as having the benefit of not fatiguing the patient (17). However, regardless of which cognitive screening tool has the greatest sensitivity, the original purpose of these tools was to detect global or generalized decline rather than domain-specific cognitive deficits. Indeed, the need for domain-specific cognitive tests for the brain tumor population was recently highlighted by a study of glioma patients (6). In this study, a range of specific visuospatial deficits were identified in right parieto-temporal gliomas that were not present in patients with prefrontal tumors Thus, it remains uncertain whether cognitive screening tools are sensitive to identify mild and/or focal deficits in brain tumors (4, 12).

Neuropsychological evaluations are held to be the "gold standard" for assessment of cognitive functions in focal neurological disorders like stroke (15, 18). However, evaluations differ in test composition and can range from long and comprehensive, with a fixed test battery, to brief and flexible, with tests chosen to assess specific cognitive domains (19). One advantage of neuropsychological evaluation is the freedom to include tests that tap specific cognitive functions, depending on tumor location and presenting symptoms (4). On the other hand, the main criticism is the length of assessment that can range from brief (1–2 h) to lengthy (8 h). Length is a particular issue in brain tumor patients as physical and mental fatigue has specifically been identified as a concern (12, 20). In fact, Olsen and colleagues (12) found a selection bias in which patients were willing to complete a 4-h neuropsychological assessment. In particular, they identified that those who completed both the 4-h assessment and cognitive screening tests, tended to be younger with a higher level of education, they obtained a higher MoCA score and were on lower doses of medications. Thus, Olsen and colleagues, like Papagno et al. (4), concluded that a brief and well-tolerated CA is desirable, when diagnostic accuracy can be maintained.

Neuropsychological evaluation has been compared to cognitive screening tools. As noted above, Olsen and colleagues (12) compared neuropsychological assessment to both the MMSE and the MoCA. The MoCA showed greater sensitivity to cognitive dysfunction than the MMSE; however, the main conclusion was that inclusion of a 4-h neuropsychological assessment was a significant deterrent for participation. The MMSE and MoCA, compared to neuropsychological assessment and return to work status, have been investigated in patients following aneurysmal SAH (15). In their study, 42% of patients were impaired on the MoCA, compared to none on the MMSE, and the MoCA correlated with domain-specific cognitive tests while the MMSE showed no association with specific tests. In addition, two MoCA items were associated with return to work. The MoCA was concluded to be more sensitive than the MMSE in SAH; however, it was not clear that the MoCA had sufficient sensitivity when compared to the neuropsychological assessment (15). Recently, a large retrospective study of acute stroke has unequivocally demonstrated that the MoCA underestimated cognitive impairment, compared to a brief 1–2 h neuropsychological assessment (18).

The current study compared the MoCA cognitive screening tool with a brief 1–1.5 h neuropsychological evaluation in primary brain tumors. The neuropsychological evaluation comprised a CA and mood and behavioral assessments as this is thought important to fully characterize level of function and inform care plans (7). The aim was to ascertain whether the MoCA is sufficiently sensitive to detect cognitive impairment at an acute, post-resection time point or whether a brief but domain-specific CA is necessary.

MATERIALS AND METHODS

PATIENTS

Thirty-six patients with primary brain tumors (low- or high-grade gliomas, meningiomas) were recruited by the Brain Tumor Nurse Practitioner (VB) from BrizBrain and Spine, The Wesley Hospital, Brisbane, QLD, Australia. Ethical approval for the study was granted by the UnitingCare and The University of Queensland Human Research Ethics Committees. Informed and written consent was obtained from all patients. Inclusion criteria were (1) confirmation of brain tumor ascertained by MRI and (2) all patients underwent surgical resection prior to the investigation of cognitive functions. The cognitive screening tool was administered before the CA, which was completed in one testing session. The third (3) inclusion criterion was that the cognitive screening tool and CA were completed within the same week to minimize effects due to timing of cognitive screening or assessment. Thus, due to the latter, only 23 patients aged 18–69 years old were included. The mean time between surgical resection and neuropsychological evaluation was 2.1 months (SD = 3.1; see **Table 1** for patient characteristics). We note that 2.1 months is sufficient time to allow for findings to be useful for neurorehabilitation (if available), planning for management of deficits for the patient and family/carers, and to address any questions related to returning to community roles at home or work.

COGNITIVE SCREENING

The MoCA (11) was used as the screening tool. Although it was developed as a brief measure of global cognitive function, it contains items that measure these cognitive domains: visuospatial/executive function; naming; memory; language; abstraction; and attention. Specifically, the MoCA is scored out of 30 points comprising these items: brief trail making, cube copy, and clock drawing (visuospatial/executive domain = 5 pts); animals to name (naming domain = 3 pts); five words to recall (memory domain = 5 pts); three brief attention tasks (attention domain = 6 pts); sentence repetition and word fluency (language domain = 3 pts); similarities (abstraction domain = 2 pts); time/place questions (orientation domain = 6 pts). A normal score is 26 or above.

NEUROPSYCHOLOGICAL EVALUATION

Cognitive assessment

A brief but tailored CA was administered that was completed in 1–1.5 h, depending on individual patient's level of fatigue and ability. The CA was devised based on neuropsychological assessment principles and assessment of standard cognitive domains, detailed in Cipolotti and Warrington (21). The cognitive tests were specifically chosen based on Robinson's recent lesion studies of brain tumor and stroke patients with focal frontal and non-frontal lesions [e.g., Ref. (22, 23)]. A similar approach was adopted by Papagno and colleagues (4) in their recent study of low-grade gliomas. Thus, estimated pre-morbid level of intelligence was ascertained in a

Table 1 | MoCA, demographic, and behavioral scores (mean ± SD): all patients and MoCA sub-groups (MoCA-Intact and MoCA-Impaired).

	All ($N = 23$)	MoCA-Intact ($N = 16$)	MoCA-Impaired ($N = 7$)
MoCA score (/30)	26.52 ± 2.11	27.63 ± 1.15	24.00 ± 1.53***
Age ($M \pm SD$)	48.39 ± 14.61	46.94 ± 15.81	51.71 ± 11.79
Gender (M:F)	16:7	12:4	4:3
Education	13.90 ± 2.98	14.33 ± 2.94	12.83 ± 3.06
Pre-morbid estimated intelligence (NART IQ)	104.13 ± 10.35	103.56 ± 10.24	105.43 ± 11.30
Chronicity (months post-surgery)	2.07 ± 3.11	2.54 ± 3.48	0.67 ± 0.41
Tumor type (WHO grade)			
Meningioma	4	3	1
Oligodendroglioma (II)	5	4	1
Astrocytoma (II)	4	2	2
Oligodendroglioma (III)	1	1	0
Astrocytoma (III)	1	1	0
Glioblastoma multiforme (IV)	8	5	3
Tumor location (L/R)	12/11	8/8	4/3
Frontal (L/R)	7/3	4/2	3/1
Temporal (L/R)	2/3	1/2	1/1
Parietal (L/R)	0/2	0/2	0/0
>1 lobe (L/R)	2/3	2/2	0/1
HADS anxiety (/21)	5.94 ± 3.86	5.83 ± 4.17	6.20 ± 3.43
HADS depression (/21)	3.88 ± 2.62	3.08 ± 2.43	5.80 ± 2.17*
Apathy Evaluation Scale (/72)	49.20 ± 15.41	50.86 ± 16.17	45.33 ± 14.05

*NART, National Adult Reading Test; L, left; R, right; HADS, Hospital Anxiety and Depression Scale. ***$p < 0.001$, *$p < 0.05$, MoCA-Intact compared to MoCA-Impaired patients.*

standard manner by administering the National Adult Reading Test (NART) (24). To ascertain current level of cognitive function, the CA comprised standard published neuropsychological tests that focused on the following domain-specific areas of cognition: (1) *Abstract reasoning*: non-verbal – Raven's advanced progressive matrices (25), verbal – Proverb Interpretation Test (26, 27); (2) *attention* – Digit Span subtest from the Wechsler Adult Intelligence Scale-III (28), Elevator Counting with Distraction from the Test of Everyday Attention (29); (3) *verbal and visual memory* – Recognition Memory Tests, Words, and Topography (30, 31); (4) *visual perception* – Incomplete Letters Test from the Visual Object and Space Perception Battery (32); (5) *language* – Graded Naming Test (33), Word Comprehension – Synonyms Test (34); and (6) *executive functions* – phonemic word fluency (35), Hayling Sentence Completion Test (36).

Mood and behavior assessment

As part of the neuropsychological evaluation, level of self-reported anxiety, depression, and apathy were assessed using the Hospital Anxiety and Depression Scale (HADS) (37) and the Apathy Evaluation Scale (AES) (38). A score on the HADS of 7 or below is in the normal range with a score at or above 11 indicating significant levels of anxiety or depression. The AES results in scores between 18 and 72, with higher scores indicating increased apathy and a score of 41 suggested as the cut-off.

Analyses

The MoCA and domain-specific cognitive tests were administered and scored in the standard and published manner. Patients were classified as cognitively intact on the MoCA if they obtained a score of ≥26 or impaired if they scored <26 (11). For each individual cognitive test, patients were classified as cognitively impaired if they scored <5th percentile (i.e., 5% cut-off), with an intact performance ≥5% cut-off [for similar methodology, see Ref. (18, 39)]. For the Proverb Interpretation Test of verbal abstraction, an impaired performance was a score of <5/8 [for scoring details, see Ref. (24)].

Performance was analyzed in several ways. First, we calculated a broad measure of impairment for both the MoCA and the CA. For the MoCA, the number of patients impaired is reported. For the CA, we calculated the number of patients impaired on any test and also the number of cognitive domains each patient was impaired in (i.e., 0–6 cognitive domains). Second, based on the method adopted by Chan and colleagues for stroke patients (18), we conducted two specific analyses: (1) MoCA-Intact patients were investigated for impairment in each cognitive domain assessed by the CA; and (2) Patients who scored the maximum points in each of the MoCA-specified cognitive domains, irrespective of the overall MoCA score, were analyzed in terms of discrepancy between this and performance on the domain relevant CA test. We also analyzed whether the MoCA-Impaired patients were impaired in at least one cognitive domain.

RESULTS

For the first broad measure, we found that 30.4% (7/23) of our patients were impaired on the MoCA as they scored <26. A summary of the MoCA, demographic, and mood and behavior scores for the whole group, and the MoCA-Intact and MoCA-Impaired sub-groups, are contained in **Table 1**. As expected, the MoCA score for the impaired group was significantly lower than the intact group, $t(21) = 6.31$, $p < 0.001$. Apart from slightly higher self-reported symptoms of depression by the MoCA-Impaired group compared to the MoCA-Intact group, $t(15) = 2.16$, $p < 0.05$, the two groups were well matched for age, gender, education, pre-morbid intelligence, and chronicity (time since surgery; all $p > 0.05$). Similarly, there was no difference between these two groups in self-reported anxiety or apathy. With regard to symptoms of depression, we note that the mean of both groups is in the "normal" range and not indicative of clinical or sub-clinical depression. If we examine individual scores, one patient in each group (MoCA-Intact and -Impaired) was in the abnormal range. For anxiety, abnormal scores were obtained by three patients in each group (MoCA-Intact and -Impaired). Finally, both groups reported mildly elevated levels of apathy with a number of patients in both groups above the suggested cut-off (11 in the MoCA-Intact and 4 in the MoCA-Impaired group), which may reflect the acute post-resection stage of assessment.

Table 2 | Domain-specific Cognitive Test Scores (mean ± SD): all participants, MoCA sub-groups (MoCA-Intact and MoCA-Impaired), and comparison statistic between MoCA sub-groups.

Cognitive domain/test	All ($N = 23$)	MoCA-Intact ($N = 16$)	MoCA-Impaired ($N = 7$)	p Value
Abstract reasoning				
Advanced progressive matrices (/12)	7.09 ± 2.15	7.31 ± 2.27	6.57 ± 1.90	$p = 0.460$
Proverb Interpretation Test (/8)	4.47 ± 1.28	4.67 ± 1.16	4.00 ± 1.58	$p = 0.344$
Memory				
RMT words (/50)	45.91 ± 4.51	46.19 ± 4.52	45.29 ± 4.79	$p = 0.670$
RMT topography (/30)	22.57 ± 6.33	23.40 ± 6.24	20.50 ± 6.63	$p = 0.356$
Attention				
Digit span total	17.00 ± 5.14	17.00 ± 4.45	17.00 ± 6.99	$p = 1.00$
Elevator counting + distraction (/10)	5.88 ± 3.38	6.20 ± 3.33	5.33 ± 3.72	$p = 0.095$
Language				
Graded Naming Test (/30)	18.22 ± 3.46	19.31 ± 2.82	15.71 ± 3.68*	**$p = 0.018$**
Synonyms (/50)	39.85 ± 3.66	40.36 ± 3.75	38.67 ± 3.45	$p = 0.358$
Visual perception				
Incomplete letters (/20)	19.50 ± 0.67	19.56 ± 0.73	19.33 ± 0.52	$p = 0.490$
Executive function				
Phonemic word fluency (FAS)	34.25 ± 13.23	38.36 ± 11.91	24.67 ± 11.78*	**$p = 0.030$**
Hayling Test Overall Scaled Score (1–10, 6 = Average)	3.52 ± 2.47	3.63 ± 2.36	3.29 ± 2.87	$p = 0.769$

*Bold represents a significant finding. *$p < 0.05$.*

For the CA broad measure, 69.6% (16/23) of the patients were impaired on at least one domain-specific cognitive test. The means and SDs for the whole group, and the MoCA-Intact and MoCA-Impaired sub-groups, are reported in **Table 2**. Overall, there was no difference between sub-groups in performance on 9 of the 11 cognitive tests (i.e., $p > 0.05$), which supports specific patterns of cognitive deficits rather than a generally lower performance of the MoCA-Impaired patients. By contrast, the MoCA-Impaired group performed significantly poorer on the Graded Naming Test of language, $t(21) = 2.567$, $p < 0.05$, and the phonemic word fluency test that is sensitive to executive dysfunction, $t(21) = 2.363$, $p < 0.05$. The number of cognitive domains each patient was impaired in was as follows: 4/16 impaired in one domain; 4/16 impaired in two domains; 6/16 impaired in three domains; and 2/16 impaired in four domains. Thus, 75.0% of the impaired patients were impaired on tests in *at least* two cognitive domains.

For the specific measures based on Chan et al. (18), first we investigated the 16 MoCA-Intact patients for impairment in each cognitive domain assessed by the CA. Of these patients, 56.3% were impaired in at least one of the six cognitive domains. The percentage of MoCA-Intact patients impaired on domain-specific cognitive tests is shown in **Figure 1**. The main cognitive domains impaired for MoCA-Intact patients were abilities related to higher level executive functions, including abstract reasoning, followed by attention and memory. By contrast, language was only impaired in <10% and no patient was impaired on the test of visual perception.

For the second specific measure, we examined patients who scored the maximum points in each of the MoCA-specified cognitive domains, irrespective of the overall MoCA score. Based on Chan et al. (18), we analyzed the discrepancy between this and performance on the domain relevant CA test. The number of patients who scored full marks on each MoCA-specified domain, were impaired on the relevant CA test and the negative predictive values are reported in **Table 3**.

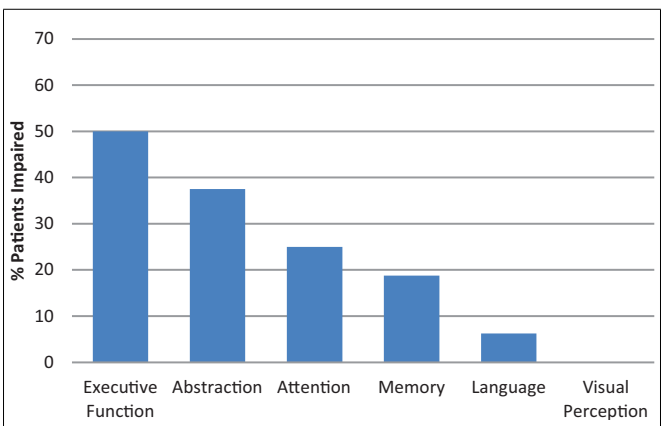

FIGURE 1 | Cognitive assessment: MoCA-Intact participants impaired in domain-specific cognitive tests.

For the MoCA-Impaired patients, 100% were impaired in at least one cognitive domain on the CA. Thus, when a patient obtains an impaired score on the MoCA this fully predicts significant impairment in at least one domain on CA. By contrast, the implications for cognitive function is less certain when a "normal" MoCA score is obtained as the MoCA showed very poor negative predictive value (0.44). Further, sensitivity for detecting cognitive impairment is extremely poor (0.44) in our primary brain tumor sample.

Table 3 | Cognitive assessment performance and negative predictive value for MoCA-specified domains.

MoCA-specified domain	No. patients scoring full marks on MoCA	No. patients (%) impaired on CA	Negative predictive value (NPV)
Visuospatial/executive	13	5 (38%)	0.62
Naming	21	3 (14%)	0.86
Memory	4	1 (25%)	0.75
Attention	13	4 (31%)	0.69
Language	7	3 (43%)	0.57
Abstraction	22	9 (41%)	0.59

DISCUSSION

In our unselected primary brain tumor sample, only 30.4% were impaired on the MoCA cognitive screening tool. By contrast, for the CA, 69.6% of patients were impaired on at least one domain-specific cognitive test and, of these, 75% were impaired in at least two cognitive domains. If we examine the MoCA-Intact patients, more than half (56.3%) were impaired in at least one of the six cognitive domains. Specifically, 50% of the MoCA-Intact patients were impaired on tests of executive function, including abstraction, and a quarter of these patients were impaired in the domains of attention and memory. The level of sensitivity of 0.44 for the MoCA in our patients was far lower than for other neurological disorders. For example, the sensitivity of the MoCA in an acute stroke population was 0.82 (18) and, notably, assessments were completed at comparable times post-stroke or tumor resection. However, we note that the MoCA has been found useful in patients with brain metastases (13) and it is reported to be adequate for the detection of mild cognitive impairment in neurodegenerative disorders such as Alzheimer's and Parkinson's disease [e.g., Ref. (40)]. Nevertheless, the sensitivity of 0.44 of the MoCA for our primary brain tumor population is *extremely poor*.

In light of this low detection rate of cognitive abnormalities, it is noteworthy that the mean MoCA score of 26.5 for our tumor patients is relatively high and indicative of mild global cognitive impairment. This was also the case for our mood and behavioral measures of anxiety, depression, and apathy. More specifically, the "MoCA-Intact" group obtained a score almost identical to the normal controls reported by Nasreddine et al. (11) while the mean score of 24 for the "MoCA-Impaired" group falls toward the top of the "mild cognitive impairment" group. The overall "mild" level of impairment on the MoCA in our sample differs from the lower MoCA mean score of 22 in patients with brain metastases (13). In fact, Olsen et al. suggested that the MoCA score may be helpful in this population as patients with low MoCA scores may be less likely to benefit from palliative whole-brain radiotherapy while patients with high MoCA scores may tolerate more intensive interventions (13). Thus, for prognostic and treatment purposes in brain metastases, the MoCA may be useful. However, our results at a global level support the notion that primary brain tumor-associated cognitive deficits are indeed mild and/or focal and are hard to detect using global screening tools like the MoCA.

For the 69.6% of patients impaired in at least one cognitive domain on the CA, executive functions and abstract reasoning were the most common domains impaired by far. In fact, 87.5% of patients were impaired in these two domains and the remaining two patients presented with a selective nominal aphasia. This is followed by attention (43.8% impaired) and memory (37.5% impaired). These cognitive domains being the most often impaired is consistent with the findings of Tucha et al. (10) for frontal and temporal tumor patients. Interestingly, of the two executive function tests, phonemic word fluency and the Hayling Test, 52.2% of *all* patients were impaired on just one test, the Hayling Test, which suggests that test choice is critical. With regard to memory, the MoCA does not assess visual memory and 21.7% of our patients were impaired on our specific visual memory test. By contrast, the intact performance of all our patients on our test of visual perception does not reflect the finding of Shallice and colleagues (6) of visuospatial deficits in right posterior tumor patients. There are two possibilities for the apparent disparity. One, our specific test of visual perception is not sensitive to mild deficits. Two, our seven patients with right posterior tumors are remarkably intact. Upon examination of individual patients, one right temporal MoCA-Impaired and three right posterior MoCA-Intact patients lost points on the MoCA-specified visuospatial items. In addition, one of the MoCA-Intact patients presented with a highly selective apperceptive amusia in the context of an otherwise intact cognitive profile (41). This latter case, in addition to the two patients with a selective nominal aphasia, highlight the potential for any cognitive deficit to be specific and focal in brain tumor patients, thus, necessitating freedom in test choice based on symptoms and/or tumor location.

Notably, patients who performed well on MoCA-specified domains were not always intact on the specific cognitive test, similar to Chan et al.'s findings in acute stroke patients. This is particularly so for the abstraction and executive/visuospatial MoCA-specified domains that are assessed by one item each, both clearly insensitive to our patients' deficits. By contrast, the two MoCA-specified domains that most closely resembled the CA impairments were language and memory. In terms of language, only 30.4% of patients scored full marks on the MoCA-specified items that comprised a sentence repetition item (>10 words in length) and a phonemic word fluency task. Of these two items, phonemic word fluency was one of two standard cognitive tests that MoCA-Impaired patients performed significantly poorer than MoCA-Intact patients and it can be classed a test of executive function. If we examine naming ability, almost all patients obtained full marks for the MoCA naming items, although 17.4% of all patients were impaired on the standard Graded Naming Test. Very few patients obtained full marks on the MoCA-specified memory items although, as noted above, a main limitation of the MoCA is that visual memory is not assessed.

The inclusion of all types of brain tumors in our study could be argued to limit our findings. This is unlikely for two reasons. First, in our study, patients with both meningiomas and gliomas (high/low-grade) were in the MoCA-impaired group (see **Table 1**). Secondly, in a recent study specifically investigating the effect of etiology on cognitive performance in patients with focal frontal lesion, once age and pre-morbid intelligence were accounted for,

there were no significant differences between patients of different etiologies (stroke, meningioma, high/low-grade gliomas (42). One caveat, however, is the practical implications of treatments for different brain tumor types. For example, the timing of a brief CA in patients with higher grade gliomas who proceed to receive initial radiation or chemotherapy at 2–6 weeks post-resection, followed by a gap with no treatment and then adjuvant chemotherapy (43), needs to be considered in specific contexts. If a neuropsychologist is attached to an acute neurosurgical ward, then assessment prior to treatment can be included in routine planned care. If this is unavailable, then an optimal time would be in the gap between treatments, which would be approximately 8–10 weeks post-resection. Findings from a brief CA at either of these time points will be useful in further management, informing specific cognitive strategies/interventions and for the patient to understand changes in thinking related to their tumor.

In summary, the MoCA has extremely poor sensitivity to cognitive impairment in our primary brain tumor sample, which means that if a "normal" MoCA score is obtained, a CA is necessary. Even if a patient is impaired on the MoCA, the severity may be underestimated and some areas of cognition are not assessed. In fact, only one MoCA-specified domain showed even remotely similar detection levels as a brief CA. A full discussion of other brief cognitive screening tools (e.g., ACE-III; CogMed) is beyond the scope of this preliminary study although we can speculate that similar issues would be revealed. Thus, despite the limitations of our small sample size, we strongly demonstrate that a brief and tailored CA lasting only 1–1.5 h is necessary and possible for the detection of cognitive impairments in primary brain tumor patients in the acute phase post-surgery. This is not only important for prognosis and monitoring, but it is crucial for neurorehabilitation and interventions (1, 2, 4). Moreover, mental deterioration, or fear of this, was rated as one of the highest concerns of patients and carers, contributing to quality of life (20). Our study suggests that the critical cognitive domains to assess are executive functions (initiation, suppression, abstraction), attention, memory (verbal and visual), and language (naming and verbal fluency). Finally, we highly recommend adopting the neuropsychological principle of tailoring an assessment based on lesion location and presenting symptoms.

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Neuropsychological assessment of individuals with brain tumor: comparison of approaches used in the classification of impairment

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Approaches to classifying neuropsychological impairment after brain tumor vary according to testing level (individual tests, domains, or global index) and source of reference (i.e., norms, controls, and pre-morbid functioning). This study aimed to compare rates of impairment according to different classification approaches. Participants were 44 individuals (57% female) with a primary brain tumor diagnosis (mean age = 45.6 years) and 44 matched control participants (59% female, mean age = 44.5 years). All participants completed a test battery that assesses pre-morbid IQ (Wechsler adult reading test), attention/processing speed (digit span, trail making test A), memory (Hopkins verbal learning test-revised, Rey–Osterrieth complex figure-recall), and executive function (trail making test B, Rey–Osterrieth complex figure copy, controlled oral word association test). Results indicated that across the different sources of reference, 86–93% of participants were classified as impaired at a test-specific level, 61–73% were classified as impaired at a domain-specific level, and 32–50% were classified as impaired at a global level. Rates of impairment did not significantly differ according to source of reference ($p > 0.05$); however, at the individual participant level, classification based on estimated pre-morbid IQ was often inconsistent with classification based on the norms or controls. Participants with brain tumor performed significantly poorer than matched controls on tests of neuropsychological functioning, including executive function ($p = 0.001$) and memory ($p < 0.001$), but not attention/processing speed ($p > 0.05$). These results highlight the need to examine individuals' performance across a multi-faceted neuropsychological test battery to avoid over- or under-estimation of impairment.

Keywords: cancer, oncology, neoplasm, brain tumor, neuropsychological impairment, assessment

INTRODUCTION

Brain tumor is rare (6.4/100,000 worldwide), but has one of the lowest survival rates of all cancers (1). Tumors of the central nervous system are classified according to the cells or tissue in which the tumor grows, as well as the grade or malignancy (2). Malignant brain tumors (Grades III–IV) are cancerous, grow rapidly, and are associated with poorer prognosis for survival. Low grade gliomas (Grades I–II) are histologically benign, but may recur or progress, particularly if complete removal is not feasible (2–4). Other benign tumors (e.g., meningiomas) rarely recur but can seriously affect neurological functioning (5). The site of tumor growth is typically related to neuropsychological deficits (e.g., left hemisphere tumors commonly affect language). However, due to compression and displacement effects more widespread damage and global neuropsychological impairment can occur (5).

The severity and nature of neuropsychological impairment is a key factor influencing quality of life in people with brain tumor (6). Obtaining accurate information about a person's neuropsychological status is central to planning their rehabilitation and supportive care (5, 6). Moreover, neuropsychological functioning has been found to be related to prognosis and tumor recurrence and may be more sensitive in predicting early tumor recurrence than imaging techniques (7–9). Accordingly, research in the brain tumor field has focused on the nature of neuropsychological impairment, relationships between neuropsychological status, tumor type, location, and size, and the impact of impairments on everyday functioning (7–11).

There is a considerable variability in the rates of neuropsychological impairment reported in brain tumor studies. For example, rates of neuropsychological impairment have been found to vary from 12.5 to 91% (10–16). A key reason for such variability appears to be the different methods for assessing and interpreting performance on neuropsychological tests. Three broad approaches to analysis or classifying impairment are evident across studies (10–16): test-specific analysis classifies impairment on the basis of an individual test (e.g., a particular memory test); domain-specific analysis determines impairment based on a composite of test scores that relate to a particular neuropsychological domain (e.g., attention/processing speed); and a global index of neuropsychological impairment involves calculating a composite

across different domains of cognitive ability (e.g., summing and averaging standardized scores across tests of several cognitive domains).

To date, few studies have compared rates of neuropsychological impairment according to the level of impairment (i.e., test-specific, domain-specific, and global indices). Tucha et al. (11) reported that rates of neuropsychological impairment were 91, 60–78, and 17% for test-specific, domain-specific, and global indices, respectively. Other researchers have compared impairment rates across two different levels of classification. For example, Talacchi et al. (10) found that 79% of a glioma sample was impaired on at least one neuropsychological test (i.e., test-specific level), whereas relatively fewer (i.e., 38%) were impaired at a domain-specific level. Lageman et al. (12) examined impairment rates at a test-specific level only, and reported that 59% of participants were impaired based on their conservative criteria (i.e., >2 SD below the norms).

Besides the issue of different levels for classifying impairment, a further potential concern in the brain tumor literature relates to the common approach of categorizing a person as impaired based solely on cut-off scores derived from normative data (11). Accurate interpretation of a person's neuropsychological functioning in the context of neurological disorder is reliant on an understanding of his or her level of pre-morbid intellectual functioning. This helps to avoid an overestimation or underestimation of any deficits evident on testing (17). For example, individuals who were previously functioning in the superior intellectual range may not demonstrate neuropsychological impairment relative to the norms (17). However, they may still experience significant deficits relative to their own pre-morbid functioning. Although it is common in clinical practice to measure estimated pre-morbid IQ to assist interpretation of neuropsychological test results after brain tumor, a comparison between rates of impairment based on normative data and impairment relative to pre-morbid functioning (i.e., relative to self) has yet to be conducted.

There is also a paucity of studies utilizing a matched control group to investigate the nature of neuropsychological impairments experienced after a brain tumor. Although normative data are available for the majority of neuropsychological tests, these data are often dated and demographic characteristics are often not well matched to participants with brain tumor (11). Studies employing a matched control sample typically report that participants with brain tumor display significantly poorer global neuropsychological functioning than controls (14, 15). For example, Bosma et al. (14) reported significant differences between the brain tumor and control samples on the domains of psychomotor function, working memory, processing speed, and attention. A comparison of rates of neuropsychological impairment according to source of reference is needed to determine whether different approaches yield comparable findings.

THE PRESENT STUDY

The main aim of the present study was to determine within the same sample whether rates of neuropsychological impairment vary according to source of reference (i.e., test norms, controls, and estimated pre-morbid IQ). Rates of impairment were examined according to three different levels of analysis (test-specific, domain-specific, and global functioning). Given that few brain tumor studies have employed a control sample, a further aim was to compare the neuropsychological functioning of participants with brain tumor and a control sample matched on age, gender, education, and estimated IQ. It was hypothesized that participants with brain tumor would demonstrate significantly poorer attention/processing speed, memory, and executive functioning than matched controls.

MATERIALS AND METHODS

PARTICIPANTS

Brain tumor sample

Forty-four participants were recruited from the community as part of a broader study on psychosocial outcomes of brain tumor. For the present study, only participants with primary brain tumor (benign or malignant) were included and those with a secondary tumor or metastases or recurrent multiple tumor diagnoses were excluded. Participants were required to be at least 1 month post diagnosis prior to undertaking the assessment, aged 18–75 years, and demonstrate adequate receptive and expressive English language skills.

Participants were recruited from a variety of sources including a brain tumor support service, cancer counseling services, neurosurgery clinics, and a brain injury outreach service. Participants included 19 males (43%) and 25 females (57%) with an age range of 21–71 years ($M = 45.57$, SD = 11.72) and time since diagnosis between 1.5 months and 22 years ($M = 4.26$, SD = 5.05). Education level for the brain tumor sample ranged from 7 to 19 years ($M = 12.84$, SD = 2.77) and estimated pre-morbid IQ (Wechsler test of adult reading) varied between 88 and 119 ($M = 103.27$, SD = 7.97). Medical reports indicated the following tumor types: glioblastoma multiforme ($n = 9$), oligodendroglioma ($n = 9$), astrocytoma ($n = 7$), meningioma ($n = 6$), unspecified type of glioma ($n = 6$), colloid cyst ($n = 3$), craniopharyngioma ($n = 3$), and ganglioglioma ($n = 1$). Sixteen participants had tumors located in the right hemisphere, 15 in the left hemisphere, and 13 participants had medial or bilateral tumors. **Table 1** presents the demographic and clinical characteristics of the participants with brain tumor. The majority of the sample had received surgery as their primary treatment (84%), with 20% also receiving radiotherapy and/or chemotherapy. Participants with benign tumors in the third ventricle, insula, or brain stem regions had typically not received surgery at the time of the study.

Control sample

Control participants were recruited through either a university research participant pool or the first author's social network. Participants were included in the study if they were aged 18–75 years, spoke English fluently, and had no history of a neurological event or other medical condition, which may impact on cognitive functioning. Recruitment particularly focused on adults across the age bands of 20–35, 36–55, and 56–71 years to ensure a similar age profile to the brain tumor sample. As shown in **Table 1**, the matched control sample included 44 participants (41% male) aged 26–71 years ($M = 44.45$, SD = 12.96), with an education level of 9–20 years ($M = 12.61$, SD = 2.36), and estimated IQ range of 90–116 ($M = 105.16$, SD = 6.67). The two samples did not

Table 1 | Demographic, clinical variables, and comparison of brain tumor and matched control participants.

Variables	BT participants ($n = 44$) *N* (%), *M* (SD), range	Control participants ($n = 44$) *N* (%), *M* (SD), range	Statistical difference
Age (years)	45.57 (11.72) 21–71	44.45 (12.96), 26–71	$t = 0.42$, $p = 0.67$
20–35	11 (25.0%)	12 (27.3%)	
36–55	24 (54.5%)	21 (47.7%)	
56–75	9 (20.5%)	11 (25%)	
Gender			
Male	19 (43.2%)	18 (40.9%)	$\chi^2 = 0.047$, $p = 0.83$
Female	25 (56.8%)	26 (59.1%)	
Education (years)	12.84 (2.77), 7–19	12.61 (2.56), 9–20	$t = 0.41$, $p = 0.68$
7–10 years	11 (25.0%)	8 (18.2%)	
11–12 years	14 (31.8%)	18 (40.9%)	
>12 years	19 (43.2%)	18 (40.9%)	
Estimated IQ	103.27 (7.97)	105.16 (6.67)	$t = -1.20$, $p = 0.23$
Range	88–119	90–116	
>110	7 (15.9%)	11 (25%)	
90–110	34 (77.3%)	33 (75%)	
<90	3 (6.8%)	0	
Time since diagnosis	4.26 (5.05), 0.13–22		
0–5 years	31 (70.5%)		
6–10 years	7 (15.9%)		
>10 years	6 (13.6%)		
Histology			
Malignant	19 (43.2%)		
Benign or low grade	25 (56.8%)		
Hemisphere			
Left	15 (34.1%)		
Right	16 (36.4%)		
Bilateral/other	13 (29.5%)		
Location			
Frontal	24 (54.5%)		
Temporal	3 (6.8%)		
Parieto-occipital	2 (4.5%)		
Brain stem/ventricle	5 (11.4%)		
Other	10 (22.7%)		

statistically differ on age, gender, education, or estimated IQ (see **Table 1**).

MEASURES

Neuropsychological functioning was assessed on verbal and non-verbal measures in the domains of attention/processing speed, memory, and executive function. Eight scores on five tests were converted to age-adjusted standardized scores (i.e., *z*-scores) based on normative data. Scores were summed and averaged to derive composite scores within each domain and a global index of neuropsychological impairment [see Ref. (7) for use of the same approach].

Attention/processing speed

Digit span. The digit span subtest of the Wechsler adult intelligence scale-third edition [WAIS-III (18)] has been found to be a reliable and valid measure of auditory attention and short-term memory (19, 20). Digit span forward consists of 16 trials, commencing with 2 digits and ending with 9 digits, with a maximum possible score of 16. Digit span backward measures working memory or mental manipulation (19, 20). Digit span backward consists of 14 trials starting with 2 digits and ending with 8 digits, with a maximum score of 14. The digit span total raw score was converted to an age-adjusted *z*-score based on the WAIS-III norms (18).

Trail making test A. The trail making test [TMT, Partington and Leiter, 1949, as cited in Ref. (20)] is a reliable and valid measure of visual and focused attention/processing speed (20). TMT part A (TMT-A) requires participants to connect circles numbered from 1 to 25 in order as quickly as possible. The test is timed and scoring is based on time taken (seconds) to complete the test, including any error correction time. The raw score was converted to an age-adjusted *z*-score based on normative data (20).

Memory

Hopkins verbal learning test-revised. The Hopkins verbal learning test-revised (HVLT-R) is a standardized measure of learning rate and immediate and delayed verbal recall (21, 22). The HVLT-R consists of a list of 12 words (four words from three semantic categories), which is read out aloud three times with the participant required to immediately recall as many words as possible after each list. Approximately 20 min later, participants are asked to recall the list read earlier. The HVLT-R total recall is scored by adding together the total number of words recalled in the first three trials; delayed recall is scored by the number of words remembered in the fourth trial. The raw scores for total words recalled and delayed recall were converted to age-adjusted *z*-scores based on the norms (21).

Rey–Osterrieth complex figure (recall). The Rey–Osterrieth complex figure (RCF) consists of a complex geometric design that participants are initially asked to copy as accurately as possible (20). The visual memory component of the RCF involves participants redrawing the figure from memory at an allocated time after the copy trial. In this study, participants were asked to redraw the figure approximately 30 min after copying the figure, thus assessing delayed memory. The raw score out of 36, based on scoring guidelines by Osterrieth [1944, as cited by Strauss et al. (20)], was converted to an age-adjusted *z*-score.

Executive functions

Rey–Osterrieth complex figure (copy). The copy trial of the RCF is considered a valid measure of planning and organization, based on the accuracy in which the geometric figure is copied. The same scoring system used for RCF recall was used for RCF copy (20).

Trail making test B. Trail making test part B (TMT-B) is considered to be a measure of mental flexibility, which requires

participants to alternate between connecting numbers and letters in numerical and alphabetical order. Similar to TMT-A, the TMT-B score is based on time taken to complete the test, including any error correction time (20). However, the use of TMT-B minus TMT-A (B–A in seconds) has been recommended as a more sensitive measure of executive control, and thus an age-adjusted *z*-score was calculated for this index in the present study using normative data (20).

Controlled oral word association test. The controlled oral word association test (COWAT) is a standardized measure of verbal fluency, word retrieval, and self-regulation (20). Participants are told a letter of the alphabet and instructed to generate as many words as possible beginning with that letter according to the rules (i.e., to avoid proper nouns, word derivatives, and repetitions). Participants have 1 min for each of the three letters administered (F, A, and S). The total number of correct words across the three trials was converted to an age-adjusted *z*-score using normative data (20).

Estimated pre-morbid IQ

Estimated pre-morbid IQ was measured using the Wechsler test of adult reading [WTAR; (23)]. The WTAR is a reliable and valid measure of pre-morbid IQ following brain injury (24). This word pronunciation test consists of 50 English language words that become progressively more difficult to pronounce. As per the manual instructions, one point was scored for each correctly pronounced word, and the total raw score was converted to a predicted IQ score based on age-adjusted norms (23).

PROCEDURE

Following ethical clearance from a university human ethics review committee and informed consent procedures, participants with brain tumor and control participants were individually administered the battery of neuropsychological tests in the following standardized order: WTAR, RCF (copy), HVLT-R (learning trials and immediate recall), COWAT, TMT-A, TMT-B, digit span, HVLT-R (delayed recall), and RCF (recall). Testing was conducted in the participants' own homes in a quiet place with no distractions.

STATISTICAL ANALYSIS

Data screening was conducted using SPSS 21 to examine accuracy of data entry, missing values, outliers, and normality. For each source of reference, the proportion of participants with brain tumor classified as impaired at the test-specific, domain-specific (attention/processing speed, memory, and executive function), and global level were calculated as follows.

Test norms

As commonly recommended in the literature (20, 25), an age-adjusted *z*-score of ≤ -1 was used to indicate impairment (note: this was used to denote at least mild impairment). Participants with an age-adjusted *z*-score of ≤ -1 on at least one of the eight neuropsychological tests were classified as "impaired" at the test-specific level, while those with scores of > -1 on all tests were classified as "not impaired." Participants with an age-adjusted *z*-score composite of ≤ -1 on at least one of the three domains (attention/processing speed, memory, and executive function) were classified as "impaired" at the domain-specific level and those with scores of > -1 on each domain were classified as "not impaired." Participants with an average age-adjusted *z*-score of ≤ -1 on the eight neuropsychological test scores [i.e., global impairment index = $(8 \times z\text{-scores})/8$], were classified as "impaired" at the global level, and those with a global impairment index of > -1 were classified as "not impaired."

Matched controls

To classify impairment relative to matched controls, the following three age bands were established: 21–35 years ($n = 12$), 36–55 years ($n = 21$), and 56–71 years ($n = 11$). Participants with brain tumor were classified as impaired or not impaired using the data for their age band (i.e., impaired = score ≤ 1 SD below the mean). The raw score and age-adjusted *z*-score means on each test for the brain tumor and matched control samples are presented in **Table 2**.

Estimated pre-morbid IQ (relative to self)

A number of steps were used to classify impairment relative to self. Participants' estimated pre-morbid IQ on the WTAR was initially converted to a standardized score adjusted for age (i.e., *z*-score). One *z*-score was then subtracted from this standardized score to provide an individualized cut-off point at which a participant would be considered impaired (20). For example, one participant with brain tumor had a standardized IQ score of 0.82 relative to the WTAR norms. Subtracting one *z*-score from 0.82 yielded a cut-off score of −0.18. This participant was classified as impaired if scores on the neuropsychological test, composite, and global indices were ≤ -0.18.

Two-proportion *Z*-tests were conducted to compare rates of participants classified as impaired according to source of reference. Due to the dichotomous nature of the data, the weighted crosstabs procedure was used in SPSS to produce a Pearson Chi Squared statistic. A square root of this statistic was calculated to yield the two-proportion *z*-statistic [see Ref. (26)].

Between-group analyses were conducted to compare the neuropsychological functioning of participants with brain tumor and matched controls. A MANCOVA was conducted to examine group differences on the combination of the three neuropsychological domains (i.e., neuropsychological composite), controlling for relevant covariates. Univariate analyses with a Bonferroni correction were used to examine group differences for the domains of attention/processing speed, memory, and executive function.

RESULTS

COMPARISON OF IMPAIRMENT RATES ACCORDING TO SOURCE OF REFERENCE

A comparison of impairment rates according to source of reference identified the same pattern of results across the test-specific, domain-specific, and global levels. Specifically, as presented in **Table 3**, for each source of reference a higher proportion of participants were classified as impaired at a test-specific level than at a domain-specific level, and at a domain-specific level than at a global composite level. Further, the results of two-proportion *z*-tests indicated no significant differences in rates of impairment according to source of reference ($p > 0.05$). Overall, participants were most likely to be classified as impaired at the test-specific level when relative to self was used as the source of reference. This

Table 2 | Raw score and age-adjusted normative *Z*-score means for the brain tumor and control groups.

Domain	Test	Brain tumor group				Control group			
		Raw scores		Age-adjusted *z*-scores		Raw scores		Age-adjusted *z*-scores	
		M	SD	*M*	SD	*M*	SD	*M*	SD
Attention/processing speed	DS	16.64	4.32	0.06	0.96	17.45	3.99	0.21	0.96
	TMT-A	36.03	12.98	−0.42	1.30	28.11	8.74	0.35	0.78
Memory	HVLT-T	23.00	5.36	−1.35	1.41	26.39	3.98	−0.54	1.03
	HVLT-D	7.30	3.32	−1.65	1.94	9.73	1.85	−0.27	1.08
	RCF-R	16.85	7.08	0.06	1.10	22.75	4.70	0.88	0.71
Executive functions	RCF-C	31.74	3.64	−0.08	1.21	34.70	1.25	0.93	0.41
	COWAT	32.25	12.78	−0.73	1.22	46.93	10.89	0.64	0.98
	TMT-B-A	51.46	53.80	−1.38	4.07	37.95	17.98	−0.39	1.21

COWAT, controlled oral word association test; DS, digit span; HVLT, Hopkins verbal learning test (T = Total, D = Delayed); RCF, Rey complex figure (C = Copy, R = Recall); TMT, trail making test (TMT-A = Trails A, TMT-B-A = Trails B minus Trails A).

Table 3 | Two-proportion *Z*-tests on rates of brain tumor participants classified as impaired according to source of reference.

Source of reference	% Impaired on at least one test	% Impaired on at least one domain	% Impaired on global composite
Norms	86.40[a]	61.40[d]	31.80[g]
Matched controls	90.90[b]	72.70[e]	50.00[h]
Self (estimated pr-emorbid IQ)	93.20[c]	70.50[f]	40.90[i]
Two-proportion *z*-statistic	[ab]$z = 0.67$, $p = 0.50$ *ns*	[de]$z = 1.06$, $p = 0.26$ *ns*	[gh]$z = 1.73$, $p = 0.08$ *ns*
	[ac]$z = 1.06$, $p = 0.29$ *ns*	[df]$z = 0.90$, $p = 0.37$ *ns*	[gi]$z = 0.89$, $p = 0.38$ *ns*
	[bc]$z = 0.39$, $p = 0.69$ *ns*	[ef]$z = 0.24$, $p = 0.81$ *ns*	[hi]$z = 0.86$, $p = 0.39$ *ns*

finding indicates that most participants (i.e., 93%) performed ≥1 *z*-score below their estimated pre-morbid on at least one test. However, similar findings were evident at the test-specific level for the norms (86%) and matched controls (91%). Although group-level rates of impairment did not differ substantially according to the source of reference, it was also relevant to determine whether the same individuals were classified as impaired or not impaired for these three sources of reference.

As a supplementary analysis, an inspection of individual participant data identified that 89% were classified the same (i.e., impaired or not impaired) at the test-specific level, 73% were classified the same at the domain-specific level, and 64% were classified the same at the global level. Notably, inconsistencies were most common between the classification based on relative to self and those based on the norms and matched controls.

NEUROPSYCHOLOGICAL FUNCTIONING OF PARTICIPANTS WITH BRAIN TUMOR AND CONTROLS

As shown in **Table 4**, a one-way between-groups MANCOVA revealed a significant effect of the covariate of estimated IQ on the neuropsychological composite ($p < 0.05$), whereas education was not significant ($p = 0.14$ ns). A significant difference was found between the brain tumor and control groups on the neuropsychological composite, Pillai's trace = 0.20, $F\ (3, 82) = 6.72$, $p < 0.001$, $\eta^2 = 0.20$. Consequently, univariate main effects were examined using analysis of covariance (ANCOVA). Due to violation of the assumption of homogeneity for the memory domain and the multiple comparisons, alpha level was adjusted to $p < 0.016$ for the attention/processing speed and executive function domains, and $p < 0.008$ for the memory domain to interpret the main effects (27). The results of the ANCOVAs revealed significant group differences for executive function ($p = 0.001$) and memory ($p < 0.001$), as presented in **Table 4**. No significant group difference was found for attention/processing speed ($p = 0.018$ ns). Matched controls performed significantly better on the domains of memory and executive function than the participants with brain tumor.

DISCUSSION

People with brain tumor commonly receive neuropsychological assessments to monitor their cognitive and behavioral functioning and to assist in determining the impact of the tumor and its treatment on everyday functioning (5). The accuracy of this assessment is crucial given that opinions formed on the basis of these assessments influence people's perceptions of their illness and can influence the type of support and rehabilitation provided. This study primarily aimed to determine whether rates of neuropsychological impairment after brain tumor vary according to the source of reference. Overall, rates of neuropsychological impairment did not significantly differ between classifications based on normative data, matched controls, or estimated pre-morbid IQ. Participants with brain tumor demonstrated poorer overall

Table 4 | A comparison of neuropsychological functioning between the control and brain tumor groups.

Variables	Control group ($n = 44$)		Brain tumor group ($n = 44$)		F	p value	η^2
Neuropsychological functioning (*z*-scores)							
MANCOVA results	Pillai's trace = 0.20				6.72	<0.001	0.20
Estimated IQ	Pillai's trace = 0.14				4.55	0.005	0.14
Education	Pillai's trace = 0.05				1.35	0.26	0.05
ANCOVA results	*M*	SD	*M*	SD			
Attention/processing speed	0.28	0.67	−0.18	0.95	5.79	0.018	0.07
Memory	−0.13	0.71	−1.02	0.1.20	17.47	<0.001	0.17
Executive function	0.39	0.60	−0.73	1.78	13.02	0.001	0.13

neuropsychological functioning than matched controls, which was mainly due to impairments in memory and executive function rather than attention/processing speed.

COMPARISON OF IMPAIRMENT RATE ACCORDING TO SOURCE OF REFERENCE

The main novel finding of this study is that, reassuringly, rates of impairment did not substantially differ according to the source of reference at any of the testing levels (i.e., test-specific, domain-specific, or global). Further, most individuals were classified consistently (i.e., impaired or not impaired) using approaches based on the norms, matched controls, and estimated pre-morbid IQ. Although the difference was not significant, classification of impairment based on the control group was slightly higher than impairment based on the norms. This may have occurred because the control group performed relatively well on several of the neuropsychological tests (i.e., RCF-C, RCF-R, and COWAT).

Examination of individual participant data indicated inconsistent classification results for approximately one third of the sample. In particular, 27 and 36% of individuals were classified inconsistently across the sources of reference at the domain-specific and global levels, respectively. In most cases, the inconsistency occurred because classification of impairment based on pre-morbid IQ (i.e., relative to self) differed from classification of impairment based on the norms or matched controls. Such results indicated two potential classification errors; namely, participants with an estimated pre-morbid IQ in the low average range (i.e., WTAR predicted IQ < 90) being incorrectly classified as "impaired," and participants with an estimated pre-morbid IQ in the high average range (i.e., WTAR predicted IQ ≥ 110) being incorrectly classified as "not impaired." Therefore, for a small but not insignificant subgroup of participants, classification of impairment based on the norms or matched controls may have yielded misleading results. This supports the need to interpret individuals' neuropsychological test results in the context of their estimated pre-morbid IQ.

Consistent with previous research by Tucha et al. (11), rates of impairment were highest at the test-specific level (i.e., 86–93%) for each source of reference. This result is likely to reflect normal individual variability in cognitive performance, which is evident for people without a neurological disorder (28). Thus, most people with brain tumor in this study were classified as impaired on at least one test. They were less frequently classified as impaired at the domain-specific (61–73%) or global (32–50%) levels because these reflect performance averages. Such findings suggest that the use of a single test to infer the presence or absence of impairment is likely to be misleading. This is especially the case for the brain tumor population given that tumor location, size, and treatment effects could lead to diverse presentations of neuropsychological deficits (5, 10, 12). Furthermore, global indices of impairment that are based on a composite of different tests may fail to reveal selective neuropsychological deficits as well as preserved abilities and strengths. Previous research (11, 12) indicates that results from both a range of individual tests and a global neuropsychological index may be useful in distinguishing between focal and mass effects caused by brain tumor. In particular, selective impairment on testing is more likely to indicate focal effects and more generalized impairment across a range of tests (i.e., global impairment) may indicate mass effects (11).

Overall, the present findings support the need to examine individuals' neuropsychological functioning across a multi-faceted test battery and to also interpret findings in the context of their estimated pre-morbid IQ to avoid either overestimation or underestimation of impairment. Interpretation based on a combination of individual tests, domains, and a global index is optimal to provide a comprehensive profile of functioning for the treatment team and individuals and their families. Such an approach can also assist to identify preserved abilities or strengths that may assist individuals to compensate for their neuropsychological deficits, guide rehabilitation planning, and support the development of realistic goals for home and community functioning (15).

Bearing in mind the advantages of conducting a comprehensive neuropsychological assessment, a pragmatic issue surrounding testing in both research and clinical contexts is that of specificity versus brevity (12, 29, 30). Fatigue and psychological distress are common for people with brain tumor and therefore a lengthy test battery not only places burden on the individual but can also compromise the validity of test results. Therefore, a balance between specificity and brevity is important for neuropsychological testing to yield valid and meaningful information (12). Screening batteries that assess multiple neuropsychological domains but also provide a global index of functioning based on the same norms, such as the repeatable battery for the assessment of neuropsychological status (RBANS) (31), may have utility when a brief assessment (i.e., 25–30 min) is warranted. Research by Lageman et al. (12) supported the utility of the RBANS for assessing impairments in attention, language, visuospatial construction, and immediate and delayed

memory after brain tumor. However, the RBANS does not measure executive functioning, which is essential given that research has demonstrated that this domain is the most commonly impaired after brain tumor (10, 11).

The response assessment in neuro-oncology [RANO; (29)] working group and the international cognition and cancer task force [ICCTF; (30)] proposed a core set of cognitive tests, which include three of the tests administered in the present study. This 25–30 min core battery is commonly used to detect neurotoxicity of brain tumor treatment and includes the HVLT (learning and memory), trail making test (processing speed and executive function), and COWAT (verbal fluency) (29). All three tests have good psychometric properties and demonstrated sensitivity to cognitive dysfunction experienced by the neuro-oncology population (29). The test battery employed in the present study took approximately 40–45 min to administer, and included an estimate of pre-morbid IQ and verbal and non-verbal measures of attention/processing speed, memory, and executive function. Although more stringent criteria are typically used to define cognitive impairment in neurotoxicity trials (30), the cut-off of ≤ -1 z-score was used in the present study to reflect at least mild impairment (i.e., $<$16th‰) (20). The selection of both the test battery and criteria for impairment needs to be guided by the particular question/s posed in research (e.g., is there evidence of neurotoxicity?) or clinical practice (e.g., would this person benefit from a referral for cognitive rehabilitation?). Although the current battery was considered to have good utility for screening purposes, a more comprehensive test battery is likely to be required in various referral contexts, for example, to determine vocational capacity.

NEUROPSYCHOLOGICAL FUNCTIONING OF PARTICIPANTS WITH BRAIN TUMOR AND CONTROLS

Consistent with previous research (14, 15), participants with brain tumor performed significantly poorer overall on tests of neuropsychological functioning than matched controls. Their performance was significantly impaired on the executive function and memory domains, but not on the attention/processing speed domain. Talacchi et al. (10), and Tucha et al. (11), also reported higher levels of impairment on tests of executive function and memory as compared to other domains; however, a control group was not employed in these studies. However, unlike the findings of Bosma et al. (14), participants in the present study did not perform significantly poorer than controls on tests of attention/processing speed. Aside from different tumor characteristics, a likely reason for the inconsistent findings between studies relates to the selection of tests to assess neuropsychological functioning. This reflects a broader issue in the neuropsychological literature whereby researchers commonly employ different tests to assess the same abilities, thus making comparisons between studies difficult (29, 30).

In the present study, the attention/processing speed domain was comprised of scores on digit span forward (auditory spanning), digit span backward (auditory spanning, working memory), and TMT-A (visuo-motor scanning, focused attention, processing speed) (19). A supplementary examination of between-group differences on these tests revealed no significant differences on digit span forwards or digit span backwards; however, participants with brain tumor performed significantly poorer than controls on TMT-A. A possible explanation for this finding is that functions that rely on more localized neural networks (e.g., auditory spanning and working memory) are less likely to show deficits than functions that rely on more widely distributed networks (visuo-motor scanning) (19, 32). This finding supports previous research indicating that attention/processing speed is not a unitary construct and that dissociable components have a different neuroanatomical basis (19). However, this explanation is only speculative as precise neuro-imaging data were not available to enable an investigation of the relationship between tumor location and test performance in the present study.

LIMITATIONS

A further key limitation of this study relates to the convenience sampling approach employed whereby participants had diverse tumor characteristics and were assessed at varying time periods after their diagnosis and treatment. In clinical practice, individuals with brain tumor may receive a neuropsychological assessment prior to their primary treatment, soon after this treatment, or at a more long-term phase of their illness (e.g., following tumor recurrence). Therefore, the varied characteristics of the present sample mirror many clinical settings. Nonetheless, further research examining the extent to which classification approaches influence the rate of neuropsychological impairment in a larger and more homogenous brain tumor sample at the same stage of illness is needed.

In particular, it would be beneficial to examine the relative risk (with confidence intervals) of being classified as impaired or not impaired according to different approaches to classification. Furthermore, the present study focused on the presence or absence of neuropsychological impairment, rather that the severity or degree of impairment. Focus on the latter is also important given that severity of neuropsychological impairment has been found to be associated with quality of life after brain tumor in some studies (6). As a further study limitation, the -1 SD cut-off adopted as the criterion for impairment increased the chances of people with high IQ being misclassified as "impaired" because they were more likely to have scores fall 1 SD below their estimated IQ. In future research, the number of individual tests on which a person is impaired may provide a more meaningful index of global impairment rather than using a composite based on the average z-score of the tests. This could be compared with estimates of the expected number of impaired scores in the healthy population using Monte Carlo simulations with comparisons based on differing cut-off scores (e.g., -1, -1.5, -2 SD).

CONCLUSION

Overall, a key novel finding of the present study was that rates of neuropsychological impairment after brain tumor were generally comparable when classifications were based on the norms, controls, and estimated pre-morbid IQ. Although using different sources of reference may not produce major variations in group-level rates of impairment, interpretation of test results based on the test norms and a person's estimated pre-morbid functioning is likely to be most accurate. The selection of tests in an assessment battery and criteria for impairment needs to be

guided by the specific questions posed in the research and clinical context. Nevertheless, ongoing efforts to improve consistency in the approaches to administering and interpreting neuropsychological tests are expected to contribute to optimal management and support for people with brain tumor.

AUTHOR CONTRIBUTIONS

All authors made a substantial contribution to the conception and design of the study, participant recruitment, data collection, and/or data analysis phases. Each author was involved in drafting the work or critically revising it for important intellectual content and gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Frequency, clinical correlates, and ratings of behavioral changes in primary brain tumor patients: a preliminary investigation

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Purpose: Few studies have addressed the specific behavioral changes associated with primary brain tumor (PBT). This paper will report on the frequency and demographic/clinical correlates of such behaviors, and the reliability of rating such behaviors among people with PBT, family informants, and clinicians. The association of behavioral changes and patient functional status will also be discussed.

Methods: A total of 57 patients with 37 family informants were recruited from two large Australian metropolitan hospitals. Each completed three neuro-behavioral self-report measures; the Emotional and Social Dysfunction Questionnaire, the Frontal Systems Behavior Scale, and the Overt Behavior Scale. Patients also completed a depression symptom measure. Functional status was defined by clinician-rated Karnofsky performance status.

Results: Patients were on average 52 years old, a median of 4 months (range 1–82) post-diagnosis, with high grade (39%), low grade (22%), or benign tumors (39%). Patients reported frequency rates of 7–40% across various behavioral domains including anger, inappropriate behavior, apathy, inertia, and executive impairment. The presence of epileptic seizures was associated with significantly higher levels of behavioral changes. Notably, behavior did not correlate with tumor grade or treatment modality. There was moderate agreement between patients and relatives on the presence or absence of behavioral changes, and substantial agreement between relative and clinician ratings. Depressed patients did not generally report more changes than non-depressed patients. Increases in the relative and clinician-rated behavior scores were significantly correlated with decreasing functional status in the patient.

Conclusion: Behavioral changes were a common sequela of both benign and malignant PBT. Larger scale studies are required to confirm these results. The results suggest the importance of including behavior in brain cancer psychosocial assessments and the need to develop interventions to treat these patients and reduce the burden of care on families.

Keywords: brain tumor, behavioral change, challenging behaviors, executive dysfunction, awareness, functional status

INTRODUCTION

There are a range of well-known neurological, cognitive, and psychological effects that can manifest in adults with primary brain tumor (PBT). These occur as a result of direct tumor infiltration, associated treatment-related effects, and also dealing with, as in the case high-grade glioma, the psychological impact of a disease with such a poor prognosis. Neurologic symptoms (1, 2), impairments of cognition (3–5), and changes in mood (6–8) have been documented across high, low, and benign tumor grades. However, the frequency and correlates of behavioral changes that adults with PBT may experience have received limited attention. In contrast, a diverse range of behavioral changes have been documented across other neurologic diseases and injuries including stroke, Alzheimer's disease, and traumatic brain injury (9–11), as well as among children with PBTs (12).

Neurologically-mediated behavioral changes can span dysregulated behavior, executive elements of cognitive function and diminished motivation/initiation (e.g., apathy) (10, 13). Various regions of the frontal lobes play a major but not exclusive role in these behavioral/cognitive processes. Behaviors such as social

disinhibition, physical and verbal aggression, limited insight, and loss of social judgment may be associated with lesions to the orbitofrontal and ventromedial prefrontal cortex (10, 13–15). Behaviors including apathy, adynamia, and perseveration can be associated with damage to the medial prefrontal cortex and its connections (10, 13, 16). Finally, lesions in the anterior cingulate and dorsolateral prefrontal circuit may be associated with disorders in the executive components of cognitive functioning, which also have a role in overseeing or monitoring behavior (10, 13, 15, 17). In addition to the local effects of neoplasms in the prefrontal cortex, the remote effects of tumors located in other cortical and subcortical regions of the brain may also affect behavioral/cognitive functioning (18).

To date, the data on behavioral changes associated with PBT is fragmented and limited. Research focusing on malignant tumor patients specifically has described neuropsychiatric symptoms including agitation, irritability, apathy, and hallucinations (5, 19). Single-case reports (20) and first-hand accounts of relatives documented in qualitative studies (21–23) have also been published, reporting aggression, personality change, and erratic emotional behavior among patients with low- and high-grade malignant tumors. A handful of group studies have reported rates of behavior change between 16% (24) and 62% (25) among patients with oligodendrogliomas (24), primary and metastatic brain tumors (25), and survivors of acromegaly (25). However, these results need to be viewed with some caution due to retrospective study designs (24, 25); a lack of standardized criteria used to define behavior (24, 25), or the use of psychopathology and personality measures not validated for a population with neurological impairment (26).

In the first study to prospectively document behavioral changes employing a standardized measure validated for use in a neurologically impaired population, rates of apathy (46%), disinhibition (58%), and executive dysfunction (62%) were reported by 26 patients with frontal low-grade tumors (27). One other study that employed a standardized neuro-behavioral measure did not report frequency data (28). There therefore remains a need to further systematically and prospectively document behavioral changes among PBT patients across all tumor grades, employing standardized measures validated for neurologic populations.

In addition to understanding how widespread such problems may be among the PBT population, the causes of behavioral changes require investigation. Proposed mechanisms that have been advanced to account for the presence of cognitive impairments among people with PBT have included the tumor itself (all grades), the site of the tumor, tumor progression, tumor-related neurological complications, the presence of epilepsy, and side-effects from cancer treatments (3, 5). It is not known whether the same types of mechanisms are also associated with changed behavior after PBT.

Seeking to quantify changes to behavior after PBT poses both methodological and clinical challenges. Since behavior occurs within a dynamic social context, it is difficult to assess by objective measures in a standardized setting (i.e., the test room) in the same way as cognitive abilities are evaluated (3). Furthermore, clinicians are rarely able to directly observe all the behaviors of concern. Consequently, clinicians typically gather information about behavior through patient self-report using interviews or validated neuro-behavioral measures (29). However, the presence of memory impairments or a lack of insight may limit the reliability of patient self-report. This problem can be offset by gathering additional information from family members (30). Relatives and carers are often able to contribute valuable complementary information to provide a more complete clinical picture of a patient, and may do so via proxy ratings on standardized measures. Therefore, an examination of the level of concordance between clinical assessment and both patient self-report and proxy (relative) ratings of behavioral change after PBT may help to inform the development of valid assessment approaches (27).

Finally, the possible association between changed behavior and functional status needs testing. Poorer performance on cognitive measures has been associated with lower levels of functional status (4) and a similar pattern may be present with behavioral change. Therefore, this study aimed to (i) investigate the frequency of behavioral changes after PBT across tumor grades; (ii) examine the demographic and clinical correlates of such behaviors; (iii) investigate the concordance of clinical assessment with patient and proxy reports of behavioral changes; and (iv) examine the association of behavioral changes with functional status.

MATERIALS AND METHODS

SETTING/PARTICIPANTS

Ethical approval to undertake the study was provided by the relevant New South Wales Area Health Service Human Research Ethics Committees. Over a 12-month period (from October 2007), all active cases of the neuro-oncology service at Liverpool Hospital and the neurosurgical service at Royal North Shore Hospital in Sydney, NSW, Australia, were reviewed to prospectively recruit patients who met the study criteria. Informed consent was obtained from all participants, with capacity to consent determined by treating clinicians.

Patients were considered for inclusion at any stage along the continuum of care (from recently confirmed diagnosis to palliative care) and irrespective of treatment modality received. Inclusion criteria for patients were (i) histologically confirmed PBT of any grade or histology; (ii) aged $\geq$18 years at time of diagnosis; and (iii) cognitively able to complete the measures. Recruited patients were invited to nominate a relative who might also participate. Family members needed to be first degree relatives who were also $\geq$18 years old at the time of the study. Exclusion criteria for patients and relatives were an inability to speak English and/or the presence of severe psychiatric or substance abuse issues, as defined by the treating healthcare team.

MEASURES

Three paper-and-pencil neuro-behavioral rating measures were employed (see **Table 1**). The measures were selected on the following basis: (i) the validation samples for the three measures had included people with PBT; (ii) self-rating and proxy report versions were available, and (iii) all had good psychometric properties. One measure [the overt behavior scale (OBS) (31)] could also be clinician-administered. Higher scores indicated higher levels of the target problem on all three measures. "Caseness" on each of the measures refers to behaviors that are clinically significant (i.e., require further assessment or intervention). More details about

Table 1 | Description of three neuro-behavioral measure subscales (patient versions), sample reliability coefficients ($n = 54$), and subscale content descriptors.

Measure	Subscale	Cronbach α
Frontal Systems Behavioral Rating Scale[a]	**Disinhibition** (15 items) Impulsive, childish, breaks rules, silly	0.71
	Apathy (14 items) Neglect personal appearance, does nothing, lost interest in activities	0.72
	Executive dysfunction (17 items) Disorganized, forgetful, does not learn from mistakes	0.81
Emotional and Social Dysfunction Questionnaire[b]	**Anger** (7 items) Easily annoyed, irritable	0.89
	Emotional dyscontrol (8 items) Excess or wrong emotional displays	0.92
	Helplessness (9 items) Scared or worried, without hope	0.90
	Inertia (3 items) Requiring prompts, lack of interest in activities	0.71
	Fatigue (4 items) Tired, requires more sleep	0.70
	Indifference (8 items) Lacks sensitivity, does not care	0.77
	Inappropriate (6 items) Causes embarrassment, over excitable	0.60
	Euphoria (6 items) Disregard for wellbeing, relationship difficulties, denies problems	0.65
Overt Behavior Scale[c]	**Verbal aggression** (4 levels) Shouts at others, makes threats	–
	Physical aggression (combined 3 subscales with 4 levels) Aggression versus objects, Aggression versus self, Aggression versus others	–
	Inappropriate sexual behavior (6 levels) Lewd talk, inappropriate touch, coercive sexual behavior	–
	Perseveration (3 levels) Repetitious questioning, picks at skin until injured	–
	Wandering/absconding (6 levels) Wander into others rooms, gets lost, escapes secure area	–
	Inappropriate social behavior (5 levels) Socially awkward, nuisance, oppositional, danger to self/others	–
	Adynamia (1 level) Needs prompting daily or multiple times daily	–

[a] *FrSBe patient and proxy versions employ same subscales and items.*

[b] *ESDQ – patient version subscales displayed in table. Six of the eight relative subscales have same titles as patient version, but some items are different: anger = 8 items, emotional dyscontrol = 6 items, helplessness = 8 items, indifference = 7 items, inappropriate = 6 items, fatigue = 4 items. Relative version has two scales that are not part of the patient self-report version: maladaptive = 9 items, insight = 4 items.*

[c] *Overt Behavior Scale-patient, proxy and clinician versions use same levels.*

the measures and descriptors of the subscale content are displayed in **Table 1**.

Emotional and Social Dysfunction Questionnaire

The Emotional and Social Dysfunction Questionnaire (ESDQ) (32) is a measure of emotional and social dysfunction developed among neurosurgical patients with central nervous system disorders. Items are grouped into eight subscales (see **Table 1**), each producing a subscale score. Respondents rate all items on a 10-cm visual analog scale (anchors "no problem" and "big problems"). Scale scores for the self-report and relative informant versions have been shown to discriminate between a central nervous system group and a control group of non-central nervous system neurosurgical patients/relative informants (24). Caseness on the ESDQ for each subscale represents scores 2 SD above the control group mean (32).

Frontal Systems Behavior Scale

The Frontal Systems Behavior Scale (FrSBe) (33) is a 46-item behavior rating instrument that measures impairments across behavioral and cognitive domains of executive impairment. Items are grouped into three subscales (apathy, disinhibition, and executive dysfunction). Respondents rate the items on two response sets (before the injury/illness; after the injury/illness) using a 5 point Likert-type scale (1 = almost never, to 5 = almost always) and the three raw subscale scores can be converted into standardized T-scores ($M = 50$, SD = 10). The patient and proxy versions of the FrSBe use the same items. FrSBe caseness represents scores 1.5 SD or more (i.e., T-score of 65 or greater) above results derived from a normative sample (33).

The Overt Behavior Scale

The OBS (31) is an instrument that measures nine categories of challenging behaviors among brain-injured populations (see **Table 1**). Within each category, all behavioral levels are scored as simply present (1) or absent (0) (severity score). An accompanying scale weights the levels to reflect the variation in clinical severity among behaviors (e.g., on the inappropriate sexual behavior scale, sexual assault is more serious than lewd comments), producing the clinically weighted severity score (range 0–77). The OBS can be completed by clinicians and relatives (using the same levels) and also has a patient self-report version. The OBS global caseness represents the presence of the most severe behaviors in each of the nine categories.

A data protocol was devised to collect information on demographic, clinical, and psychosocial variables (see **Table 2**). A clinician-rated Karnofsky performance status (KPS) (34) was also collected. The KPS is a classification scale widely used in the neuro-oncology field. Clinicians rate patients into an ascending series of categories ranging from full functionality (KPS score = 100) through to death (KPS score = 0).

DATA COLLECTION

Patients with PBT who met the study criteria were mailed an information letter and were followed up with a phone call to ascertain if they wished to participate. After providing informed consent, patients completed the measures in a face-to-face interview conducted by the study research staff at the hospital's outpatient

Table 2 | Sociodemographic and clinical characteristics ($n = 54$).

Variable	*n* (%) or *Mdn* (range)
Age (years)	53 (19–91)[a]
Months post-diagnosis	4 (1–81)
Sex	
Male	24 (44)
Female	30 (56)
Years of education	12 (6–16)
Histological diagnosis	
Astrocytoma Grade 1–2	6 (11.1)
Astrocytoma Grade 3	4 (7.4)
Glioblastoma grade 4	16 (29.6)
Oligodendroglioma/oligoastrocytoma Grade 2–3	4 (7.4)
Meningioma	15 (27.8)
Other[b]	9 (16.7)
Tumor grade/type	
High-grade glioma	21 (38.9)
Low-grade glioma	12 (22.2)
Benign PBT	21 (38.9)
Tumor site	
Frontal/temporal	29 (53.7)
Other	25 (46.3)
Tumor lateralization	
Left-side	24 (44.4)
Right-side	22 (40.8)
Both	8 (14.8)
Treatment stage[c]	
Post-surgery	3 (5.6)
Active treatment (RT, chemotherapy)	15 (27.8)
Post-treatment	35 (64.8)
Palliative	1 (1.9)
Neurosurgical intervention	
Biopsy	12 (22.2)
Resection (sub or gross total)	42 (77.8)
Radiation therapy	
Yes	32 (59.3)
No	22 (40.7)
Chemotherapy	
Temozolomide	16 (29.6)
Other	1 (1.9)
None	37 (68.5)
Radiation (RT) dose	
5040–6000 cGy	30 (55.6)
<5040 cGy	2 (3.5)
None	22 (40.7)
Epileptic seizures	
Yes	25 (46.3)
No	29 (53.7)
Corticosteroids (current use)	
Yes	10 (18.5)
No	36 (66.7)
Unknown	8 (14.8)
Karnofsky performance status	80 (50–100)
100–90	19 (35.2)
80	23 (42.6)
70–50	12 (22.2)

[a] For analysis of age and time post-diagnosis variables, group divided by median split ≥53 versus <53 years, and ≥4 versus <4 months, respectively.

[b] Other: craniopharyngioma n = 2, epidermoid tumor n = 1, ependymoma Grade 2 n = 2, medulloblastoma n = 1, pituitary adenoma n = 2, schwannoma n = 1.

[c] Post-treatment = disease monitoring phase with no active tumor treatment regimen, Palliative = no further active treatment indicated other than supportive care.

clinics or at the respondent's home. Patients and relative informants independently completed the measures during the same appointment. The patients tolerated the test battery, which took between 30 and 60 min to administer. Only one patient was discontinued due to an inability to comprehend items on the measures. No patient discontinued the battery due to fatigue or cognitive overload. Some respondents completed the measures by hand, others through oral administration. Interviewing clinicians rated the respondent on the OBS and KPS. Patient's clinical information for the data protocol was extracted from hospital medical files, which included reports from neuroimaging investigations, clinical history taking, and clinical examination (see **Table 2** for range of variables).

DATA ANALYSIS

Data were entered into SPSS version 17.0. Descriptive statistics were generated for all variables. Inspection for normality found that only two variables (ESDQ subscale scores) from the measures had non-normal distributions using the criterion specified by Tabachnick and Fidell (35). Following Andrewes et al. (32), a square root transformation was performed on the two subscale scores (ESDQ patient version: emotional dyscontrol, hopelessness). The subscales then met the criterion for normality, enabling the use of parametric statistics for subsequent analyses.

To report on the frequency rates (*Aim i*), dichotomous variables recording caseness (yes versus no) were generated for the ESDQ, FrSBe, and OBS variables (see **Table 3**). To examine the relationship between demographic or clinical variables and the 12 behavioral variables (OBS clinical weighted score, the 3 FrSBe, and 8 ESDQ self-rated subscale scores) (see **Table 3**), a series of *t*-tests and three-factor analyses of variance were conducted (*Aim ii*). Independent variables comprised sex, age, treatment timing (time post-diagnosis, treatment phase), tumor grade, tumor site and lateralization, tumor stage, treatment modality (neurosurgical intervention, radiation therapy, radiation dose, and chemotherapy), epileptic seizures, and use of corticosteroids (see **Table 2**). The significance level was adjusted using a Bonferroni correction ($0.05/12$, $\alpha = 0.004$) in order to control for Type 1 error due to multiple comparisons.

To examine the reliability of the behavioral reports (*Aim iii*), two approaches were taken. Internal consistency for the patient reports on the FrSBe and ESDQ subscales was tested

Table 3 | Mean scores and frequency of behavioral changes ($n = 54$).

Variables	Patients ($n = 54$)	
	***M* (SD)**	***n* (%) caseness**
FrSBe[a]		
Apathy	59.2 (14.3)	19 (35.2)
Disinhibition	52.5 (11.6)	9 (16.7)
Executive impairments	60.8 (15.1)	22 (40.7)
ESDQ		
Anger	2.5 (2.0)	11 (20.4)
Emotional dyscontrol	1.5 (1.9)	4 (7.4)
Helplessness	1.9 (1.9)	4 (7.4)
Inertia	2.3 (2.1)	18 (33.3)
Fatigue	3.1 (2.2)	11 (20.4)
Indifference	1.6 (1.3)	5 (9.3)
Inappropriate behavior	1.2 (1.0)	12 (22.2)
Euphoria	1.5 (1.2)	4 (7.4)
OBS: category severity score		
Verbal aggression	–	15 (27.8)
Physical aggression	–	9 (16.7)
Inappropriate sexual behavior	–	0 (0.0)
Perseveration	–	8 (14.8)
Wandering/absconding	–	2 (3.7)
Inappropriate social behavior	–	3 (5.6)
Initiation problems	–	14 (25.9)
Global caseness	–	17 (45.9)
Clinical weighted severity	1.9 (3.1)	–

[a]*T-scores.*

FrSBe, frontal systems behavior scale; ESDQ, emotional and social dysfunction questionnaire; OBS, overt behavior scale.

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using Cronbach's α (36). The coefficients were interpreted following the recommendations by Streiner (37) (<0.8 = excellent; 0.7–0.8 = adequate; 0.6–0.7 = questionable; >0.6 poor). Second, comparison of agreement between clinicians, family, and patient self-report was possible for the subset of patients ($n = 37$) with participating family members. Kappa (κ) statistics were calculated to ascertain the level of agreement between clinician ratings and both patient self-report and proxy (family) ratings, based on responses to a specifically created OBS global "caseness" variable (any behavioral change present versus absent). Following Landis and Koch (38), a κ statistic of 0.21–0.40 was interpreted as representing *fair* agreement, 0.41–0.60 *moderate* agreement, and 0.61–0.80 *substantial* agreement. Using the same OBS global caseness variable, frequencies of false positives and false negatives in identifying behavioral changes were calculated (clinician assessment versus patient self-report). Analyses (*t*-tests) were also carried out to test for any between-group differences (patients versus carers) in the patient versus carer ratings on the FrSBe, ESDQ, and OBS clinical weighted severity variable scores. Finally, Pearson product-moment correlation was employed to examine the association between behavior variable scores and the KPS (*Aim iv*).

RESULTS

SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS

A total of 154 patients with PBT from Liverpool and Royal North Shore hospital were reviewed, with 85 patients meeting the inclusion criteria. Exclusion reasons were too unwell/cognitively impaired ($n = 41$), non-English speaking ($n = 5$), presence of severe psychiatric problems ($n = 4$), and not contactable ($n = 21$). A total of 57 out of the 85 (a 67% response rate) agreed to take part and completed the study protocol. Three patients from the 57 were identified as outliers for time post-diagnosis (>10 years post-diagnosis) by means of the visual inspection of a histogram and were therefore excluded, leaving a final sample of 54 participants. The demographic and clinical variables for the sample are reported in **Table 2**.

From the sample of 54 patients, 45 family members were identified. No family member could be identified for seven participants, and two were from non-English speaking families. The sample were a mean age of 48.1 years (SD = 16.2), predominantly female ($n = 25$, 68%), with an average of 12.0 years (SD = 3.2) education. Most family respondents were the spouses of the patient with PBT ($n = 26$, 70.3%), with smaller numbers of adult children ($n = 5$, 13.5%), parents ($n = 4$, 10.8%), and siblings ($n = 2$, 5.4%) participating. Eight family members declined to take part in the study (39).

FREQUENCY OF BEHAVIORAL DISTURBANCE

Rates of patient ($n = 54$) self-reported behavior that reached "caseness" levels varied from a high of 40% (executive impairment) to 7% (emotional dyscontrol, helplessness, euphoria) (see **Table 3**). Clinically significant levels of apathy, inertia, anger, and inappropriate behavior were reported at rates between 20 and 35%.

Family members ($n = 37$) rated behaviors that met the caseness criteria ranging from 60% (apathy) to 8% (Euphoria) (see **Table 4**). Clinically significant behavioral changes were also observed for disinhibition, executive impairment, anger, indifference, fatigue, and initiation problems, with rates ranging from 22 to 36%. Patients ($n = 37$) and families ($n = 37$) also provided pre-diagnosis ratings on the three FrSBe subscales. Comparing the pre-diagnosis and current scores (paired *t*-tests), significant increases in apathy (pre-diagnosis mean 49.5 ± 14.0, $p = 0.001$) and executive impairment (pre-diagnosis $M = 51.9$, SD = 13.6, $p = 0.001$) were reported by patients but not disinhibition (pre-diagnosis $M = 51.9$, SD = 13.6, $p = 0.10$). Families also reported significant increases in apathy (pre-diagnosis $M = 56.7$, SD = 18.0, $p = 0.001$) and executive impairment (pre-diagnosis $M = 51.9$, SD = 13.6, $p = 0.001$) with a trend for disinhibition at $p < 0.01$ (pre-diagnosis $M = 52.4$, SD = 15.6, $p = 0.08$). The behavioral changes reported by patients and family members were indicative of disorders of activation and executive dysfunction (10, 13).

DEMOGRAPHIC AND CLINICAL CORRELATES OF BEHAVIORAL CHANGES ($N = 54$)

Only one clinical variable, epileptic seizures, demonstrated a pattern of association with the behavioral variables. With Bonferroni correction, patients experiencing epileptic seizures reported significantly higher levels of Inertia (on ESDQ, $p = 0.002$) and challenging behaviors (clinical weighted OBS score, $p = 0.003$).

Table 4 | Mean scores and frequency of behavioral changes ($n = 37$).

Variables	Patients ($n = 37$)		Carers ($n = 37$)[b]		Clinicians ($n = 37$)	
	M (SD)	*n* (%) caseness	*M* (SD)	*n* (%) caseness	*M* (SD)	*n* (%) caseness
FrSBe[a]						
Apathy	61.2 (13.6)	15 (40.5)	69.4 (18.5)	22 (59.5)	–	–
Disinhibition	52.3 (10.9)	7 (18.9)	55.6 (16.4)	10 (27.0)	–	–
Executive impairments	63.1 (13.0)	19 (51.4)	61.8 (17.2)	13 (35.1)	–	–
ESDQ						
Anger	2.8 (2.1)	10 (27.0)	2.8 (2.0)	11 (30.6)	–	–
Emotional dyscontrol	1.6 (1.9)	3 (8.1)	1.4 (2.1)	6 (16.7)	–	–
Helplessness	2.1 (1.9)	3 (8.1)	2.0 (2.1)	6 (16.7)	–	–
Fatigue	3.3 (2.3)	6 (16.2)	3.3 (2.3)	9 (25.0)	–	–
Indifference	1.8 (1.3)	5 (13.5)	1.9 (2.2)	13 (36.1)	–	–
Inappropriate behavior	1.3 (1.0)	10 (27.0)	0.9 (1.2)	3 (8.3)	–	–
OBS: category severity score						
Verbal aggression	–	10 (27.0)	–	10 (27.0)	–	3 (8.1)
Physical aggression	–	6 (16.2)	–	7 (18.9)	–	3 (8.1)
Inappropriate sexual behavior	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)
Perseveration	–	5 (13.5)	–	6 (16.2)	–	9 (24.3)
Wandering/absconding	–	1 (2.7)	–	2 (5.4)	–	0 (0.0)
Inappropriate social behavior	–	2 (5.4)	–	4 (10.8)	–	8 (21.6)
Initiation problems	–	8 (21.6)	–	8 (21.6)	–	9 (24.3)
Global caseness	–	17 (45.9)	–	20 (54.1)	–	15 (40.5)
Clinical weighted severity	1.8 (3.4)	–	1.9 (2.7)	–	1.4 (2.1)	–

[a] *T-scores.*

[b] *Carers n = 36, missing data = 1.*

FrSBe, frontal systems behavior scale; ESDQ, emotional and social dysfunction questionnaire; OBS, overt behavior scale.

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In addition, several other subscale scores were higher in the seizure group at the $p = 0.05$ (FrSBe: apathy, disinhibition, and executive dysfunction; ESDQ: anger, helplessness, and fatigue). No similar pattern of significant association with behavioral change was observed among the other demographic and clinical variables.

The distribution of patients reporting epileptic seizures (yes versus no) across tumor grade (high, low, benign) was then examined. The overall chi-square statistic was significant ($\chi^2 = 6.6$, $p = 0.036$), with the raw data indicating that significantly higher numbers of patients reported seizures among the low-grade tumors. Apart from epileptic seizures, patients with a frontal/temporal tumor were more likely to report a higher score on the ESDQ indifference subscale. This was the only other significant association. There were no differences related to age, time post-diagnosis, sex, education, tumor grade, tumor lateralization, or treatment (phase, neurosurgery, radiation, chemotherapy, or current use of corticosteroids).

RELIABILITY IN RATING BEHAVIORAL CHANGES

The internal consistency coefficients were found to range from adequate to excellent (Cronbach's $\alpha > 0.7$) for all ESDQ and FrSBe self-report subscales, with the exception of inappropriate behavior and euphoria (see **Table 1**). These results indicated that patients with PBT were able to respond consistently to the questionnaire items, rather than in an inconsistent or random way. Kappa values for the level of clinician-patient agreement on the presence versus absence of behavioral change was significant ($\kappa = 0.45$, $p < 0.006$) but represented moderate agreement only. The agreement between clinician and relative ratings was stronger ($\kappa = 0.63$, $p < 0.000$), representing a substantial level of agreement. In 10.8% (4/37) of cases, clinicians identified the presence of a behavioral change, which was not identified by the patient. In 16.2% (6/37) of cases, patients reported the presence of a behavioral change not classified as present by the clinician. Finally, there were no significant between-group differences among carers versus patients ($n = 37$) comparing the median scores on the FrSBE, ESDQ, or OBS-clinically weighted severity scores (*t*-tests).

FUNCTIONAL STATUS AS A CORRELATE OF BEHAVIORAL CHANGE

Pearson product-moment correlations were employed to examine the relationship among patient, relative and clinician behavioral ratings ($n = 37$), and the KPS. Significant negative correlations were present between the KPS and relative ratings ($p = 0.01$) for the FrSBe apathy $r = -0.48$, FrSBe executive dysfunction $r = -0.47$, and the ESDQ fatigue $r = -0.46$ scores. Three variables were also correlated to the KPS at $p = 0.05$ level (ESDQ helplessness $r = -0.38$, inappropriate $r = -0.37$, insight $r = -0.39$). The

clinician-rated score on the OBS also showed a strong negative correlation with the KPS (OBS clinical weighted score $r = -0.55$, $p = 0.01$). No significant correlations were found between patient self-reported behavior and the KPS.

DISCUSSION

This study has systematically documented the frequency of behavioral changes after PBT, drawing upon patient self-report, family, and clinician perspectives. Rates of behavioral changes were widespread in the current study, with 7–60% present at clinically significant levels based on patient and family informant reports. Notably, the behavioral changes were observed across high-grade glioma, low-grade glioma, and benign brain tumors. If this finding is supported by further larger scale studies, it will have implications for psychosocial care, because a wide range of families will need support to manage such changes (39).

Although the presence of dysregulated behaviors after PBT have been documented in case studies and qualitative reports, to the best of our knowledge this is only the second study to have systematically and prospectively investigated this issue. At the global level, the rates of disinhibition in the current sample were lower than those reported by Gregg and colleagues (27), and this may reflect differences in the tumor profiles between the two samples (i.e., in Gregg's study, half the sample were recruited on the basis of having focal frontal tumors). Looking at more specific types of dysregulated behavior, elevated levels of irritability or anger have been reported (8), and anger including the more severe presentation of verbal and physical aggression were found at levels around 30%, as rated both by patients and family carers.

Disorders of activation such as apathy have been investigated more frequently in previous studies and the current report reinforces such findings (3–5, 27). The rates in this study were in a similar range to those reported by Gregg and colleagues (ranging between 40 and 60%) (27). The next step will be to test the extent to which disorders of activation or dysregulation are independent of, or can be accounted for, by the presence of depression, also commonly observed after PBT.

The current study also documented the prevalence of executive cognitive impairments, but once again at rates lower than those reported by Gregg et al. (27). The findings from a behavioral rating scale such as the FrSBe assists in providing more comprehensive data about such impairments in everyday life, supplementing data from objective neuropsychological tests. The behavioral rating scales address concerns about the ecological validity of standardized cognitive tests in predicting "real world" performance due to the lack of novelty and unpredictability in the structured test environment, for which people need to draw upon their executive cognitive systems (40). Overall, the frequency of behavioral change is a further reminder of the vulnerability of all regions of the prefrontal cortex and their connections to the effects of PBT. There is evidently a complex interplay between the direct effects of the tumor location and infiltration (4), compounded by the potential effects of surgical resection, radiotherapy (41), and/or chemotherapy. In addition, concomitant medications including anti-convulsants (42, 43), may contribute to the pathophysiological alterations that can manifest as behavioral changes across all tumor grades.

Patient self-report showed a moderate agreement with clinician assessment of the presence of behavior changes. This provides support to previous findings that many people with PBT still have sufficient intact cognitive reserves to reliably report on their own behavior to some degree (44). In contrast, Gregg et al. (27) found that patients with frontal tumors reported significantly higher levels of disinhibition than patients with non-frontal tumors. In the current study, despite the level of patient–clinician agreement, there was stronger, substantial agreement between proxy (family) reports and clinician ratings. These findings are consistent with other studies, which have investigated levels of agreement in identification of symptoms among patients with other neurologic conditions (e.g., dementia), treating clinicians, and family members (30). Finally, the current study did not find significant differences in reporting of behavioral/executive impairments between carers and patients on the FrSBe, similar to the earlier study by Gregg et al. (27).

The strong correlation between the presence of epileptic seizures and behavioral change has not been previously documented after PBT, but has been found among children in the general population with seizures [e.g., Ref. (45)]. Epileptic seizures have been identified as a risk factor for a mix of cognitive and behavioral impairments in adults with PBT and the current results may reflect similar underlying mechanisms (3, 5, 27, 46). The significant number of seizures in the low-grade glioma group in the current study is consistent with the broader literature, which has reported high rates of epilepsy among patients with low-grade tumors (43, 47–49). Some anti-epileptic medications, particularly Levetiracetam, can be a confounding variable; however, as behavioral disturbances are a known side effect. Only two patients in the current sample were on Levetiracetam at the time of the study recruitment, and thus the effect of such a medication could not account for the elevated levels of behavioral change reported across the sample.

The nature of the association between behavioral changes and the KPS remains to be elucidated. The behaviors may be an expression of frustration arising from the experience of living with lower functional status. Equally possible, the presence of disruptive and challenging behaviors may lead to decreasing social and occupational engagement, which is then reflected in the declining functional rating. Alternatively, lowered functional status and increased behavior change may both be accounted for by another variable, such as the worsening of the tumor.

The study has a number of limitations. A total of 41 patients were too unwell or cognitively impaired to participate in the study. Therefore, the current frequency rates may be conservative, as few patients experiencing progressive or recurrent disease in the palliative phase of management participated in the study, particularly in the high-grade subgroup. This remains an ongoing methodological challenge when studying this patient cohort, as this group may well include a significant number of patients with behavioral changes. Furthermore, it is likely that different mechanisms contribute to the presence of behavioral change across the different tumor grades (e.g., epilepsy as a causal factor among the low-grade tumor group) but a more detailed analysis of the possible causes within different tumor grades was beyond the scope of this study. Finally, the reason why eight family carers declined to participate

in the study are not known, and therefore the impact this may have had on the carer ratings is difficult to assess.

Larger scale studies within each tumor grade are required to confirm these initial findings. These results require replication in a longitudinal study in a broader population. This will help clarify whether behavioral changes fluctuate and resolve during the recovery phase after treatment, or are part of the longer-term effects of the tumor and/or treatments. The correlation between behavioral changes and cognitive functioning also needs exploration, as well as the impact of behavioral changes on health-related quality of life. Clinically, the study findings highlight the importance of including questions to patients and family members about behavioral changes in clinician assessments and reviews. The subsequent challenge is to develop both appropriate screening measures and subsequent interventions to effectively manage such issues when they arise and to reduce the burden of care on families (6, 39).

AUTHOR CONTRIBUTIONS

All authors contributed to the study concept, design and implementation, and to the content and development of this manuscript.

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Support after brain tumor means different things: family caregivers' experiences of support and relationship changes

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Shorter hospital stays and greater emphasis on outpatient care means that family members have the primary responsibility for supporting a person with brain tumor to manage the physical, cognitive, behavioral, and emotional effects of the illness and its treatment. Given the integral role of family caregivers, it is essential to understand their experience of the impact of brain tumor and their own support needs. Accordingly, this qualitative study aimed to investigate family caregivers' experiences of support and relationship changes in the context of brain tumor. In-depth interviews were conducted with 11 family caregivers (8 spouse/partner, 3 parents) of people with malignant or benign tumor. A thematic analysis of interview transcripts identified two major themes, namely, "Meanings of Support" and "Relationship Impacts." The Meanings of Support theme was characterized by intertwined and distinct support needs, varied expectations of support and factors influencing support expectations. The Relationship Impacts theme depicted mixed experiences of strengthened, maintained, and strained relations with the person with brain tumor. Overall, the findings highlight that there is considerable variability in caregivers' experiences and expectations of support and the impact of brain tumor on relationships. The implications of these findings for the provision of caregiver support are discussed.

Keywords: family caregivers, brain tumor, support, relationships, qualitative research

INTRODUCTION

Family caregivers of people with brain tumor experience high levels of stress related to unique care demands associated with both cancer and brain injury. Stressors include their loved one's uncertain prognosis, protracted treatment, and reduced lifespan, as well as neurocognitive deficits and personality changes commonly arising from the tumor or its treatment (1). Due to the trend for shorter hospital stays and increased emphasis on outpatient care, family members assume the primary role in supporting individuals to cope with their symptoms and the day-to-day impact of the illness. Although the majority of primary caregivers are spouses, parents, and children can also function within a support role, thus reinforcing the notion that brain tumor is a family disease (2). There is a paucity of research examining caregivers' experiences in the context of brain tumor, particularly studies focusing on their own support needs and the impact of brain tumor on relationships.

A diagnosis of a brain tumor is usually traumatic and can occur after the sudden onset of neurological symptoms such as a seizure, or following a prolonged period of more gradual and perplexing changes in a person's functioning (3). Caregivers often find themselves in a rapidly changing situation with a short time frame between the diagnosis, start of treatment, and their commencement of caregiver responsibilities (4). Most feel under-prepared and overwhelmed by the demands of caregiving, which may vary from minimal assistance with activities of daily living (ADLs) to the complete care and supervision of someone with severe disability (5, 6). Caregiver tasks include supporting the person with basic and instrumental ADLs, monitoring his/her health status and administering medication, organizing and attending appointments, decision making, and providing emotional and social support (7, 8). Caregivers also usually assume greater responsibilities for childcare, running the household, earning an income, and managing finances (3, 9).

The increased responsibilities placed on family members can lead to significant strain on their relationship with the person with brain tumor and, in some cases, relationship breakdown (9). Carlson (10) reported that females with brain tumor were nearly 10 times more likely to become divorced or separated during the course of their illness compared to males with brain tumor. Other negative consequences of caregiving include physical and psychological health problems and economic and social burden (9, 11, 12). Caregivers often perceive their role as physically exhausting and experience health problems such as insomnia and headaches (3, 7). They also commonly develop mental health problems, with 20–30% endorsing clinical levels of depression (13, 14), 40–60% reporting clinical levels of anxiety (13, 14), and 35% found to experience significantly higher levels of stress than the general population (15). In a study by Petruzzi and colleagues (16), caregivers were

found to report poorer quality of life than individuals with brain tumor.

The considerable uncertainty associated with the illness represents a major source of stress for caregivers. In a series of in-depth interviews conducted over a 6-month period, Wideheim et al. (17) identified that caregivers of people with malignant brain tumor experienced fear concerning their loved ones' prognosis for survival and treatment outcome and had a low sense of security in their everyday lives. Planning ahead was difficult and caregivers often wanted to be near their loved one in case their condition deteriorated. Edvardsson and Ahlstrom (7) similarly found that caregivers experienced a sense of uncertainty, shock, despair, and apprehension about the future as the tumor progressed. Caregivers referred to the "emotional rollercoaster" experienced when a setback (e.g., seizures) occurred, which reminded them of the life threatening nature of brain tumor.

The neurological and functional effects of the illness (e.g., behavioral and personality changes) can restrict the social participation of people with brain tumor and their caregivers and contribute to a sense of isolation (11, 17, 18). In particular, Edvardsson and Ahlstrom (7) identified that caregivers often felt "invisible and neglected" by friends, family and doctors. Loss of friends and diminished social ties contributed to caregivers' grief regarding the long-term prospects of caring for an individual with extensive care needs without the benefit of social support (11). Consistent with this notion, research has identified that social support can buffer the impact of functional impairments. Specifically, caregivers supporting an individual with more severe functional impairment had better psychological wellbeing when they were highly satisfied with their social support (19).

Research has found that caregivers especially value support from family and friends during the early phases of diagnosis and treatment (11, 19, 20). Interestingly, Hricik et al. (21) found that as the disease progressed, caregivers often sought more support from people going through a similar situation because they were able to relate to their situation and provide information on how to cope. Brain tumor support groups and online support networks can provide a helpful forum for caregivers to troubleshoot difficult situations and express their frustration. Support groups can also serve as a valuable source of information and help caregivers to maintain their morale (3, 11). However, it can be difficult for caregivers to access support for their own needs because the focus of support is generally on the person with brain tumor (7).

Caregivers of people with brain tumor perceive a range of unmet support needs, including a lack of practical support, such as help managing financial issues and government agencies, access to information about brain tumor and caregiving (5, 22) and existential and emotional support around end of life issues (5, 9, 11, 12, 23, 24). Cornwell and colleagues (23) found that caregivers were often unsure about support available to them, and expressed that they would have accessed services, such as support groups, if they had been made aware of them by hospital staff. Janda and colleagues (11) identified some parallels in the support needs of people with brain tumor and their caregivers. Although many of the unmet practical, informational, and emotional support needs were similar, their study did not specifically investigate caregivers' support needs as distinct from the needs of the person with brain tumor. Furthermore, the influence of support on caregivers' ability to adjust to their changing roles in the family was not explored.

Changes in relationship dynamics and family roles have been highlighted in numerous brain tumor studies (3, 9, 25, 26). In particular, caregivers have described their experience of grieving the loss of the person still living and a loss of intimacy and relationship breakdown (1, 9). McConigley et al. (4) referred to the process of "renegotiating relationships," which was required to adapt to changes, such as the person with brain tumor no longer being able to contribute intellectually or financially to the relationship due to cognitive difficulties. Spousal caregivers often perceived a loss of equality in their relationship whereby they no longer had an equal partnership (4, 27). In the study by Edvardsson and Ahlstrom (7), some caregivers described feeling like a single parent, despite being one of two parents. They also perceived a change from a being romantic partner to assuming the role of parent due to helping the individual with personal care tasks such as dressing and hygiene. Such role changes were distressing for some caregivers, whereas others viewed these in more positive light, expressing their satisfaction with supporting their loved one with these tasks (7). Salander (28) found that personality changes were the hardest to adjust to. In particular, spousal caregivers were more likely to report relationship strain when their spouse displayed personality changes (e.g., "demanding" and "dominating"), which contributed to caregivers distancing themselves from the person.

Notwithstanding the detrimental physical, psychological, and social effects, caregivers have also been found to report positive outcomes associated with their role. Consistent with findings in the broader cancer literature (8, 29), providing care to a person with brain tumor can have many positive psychological consequences, including increased strength and resilience, greater appreciation of life and development of closer relationships (7, 27, 30, 31). For example, some caregivers of people with primary malignant brain tumor felt they had formed a stronger bond with their loved one because the illness created more opportunities to spend time together (27). In their interviews of bereaved caregivers, Sherwood et al. (3) identified that many caregivers felt "grateful" and "privileged" to have provided care to the person with brain tumor and perceived a strengthening of their relationship. In reflecting on the past, caregivers identified both difficult and satisfying aspects of their role. Although it is evident that caregiving can be associated with negative and positive consequences for relationships, the influence of support on relationship changes is unclear.

Overall, there is little understanding of caregivers' perceptions of their support needs and how these may differ to those of the person with brain tumor. Given the findings that lack of social support contributes to psychological distress and lower perceptions of coping (19, 23), greater understanding of caregivers' perception of their own support needs is essential to provide holistic psychosocial support. Further, although changes in family roles and responsibilities after brain tumor have been well researched, the issues contributing to relationship changes and the influence of support has received little attention.

Qualitative research methods are particularly well suited to understanding complex social situations or contexts in which the perceptions of the people directly involved provide a rich source of data (32). The aims of this qualitative study were, first, to

investigate how caregivers perceive their support needs, and second, to identify relationship changes in the context of brain tumor. The two main research questions were as follows:

1. How do caregivers perceive their support needs in the context of brain tumor? In addressing this question, emphasis was placed on their perceptions of (a) the support needs of the person with brain tumor; and (b) the caregiver's own support needs.
2. How does brain tumor impact on the relationship between the caregiver and person with brain tumor? Additionally, the influence of social support on relationship changes was explored.

MATERIALS AND METHODS

DESIGN

The study methodology was informed by guidelines for conducting and assessing qualitative research, as summarized in **Table 1** (33–35). A phenomenological approach was considered most consistent with the nature of the aims and research questions. Phenomenology is concerned with understanding "the meaning, structure, and essence of the lived experience of this phenomenon, for this person or group of people" [(36), p. 104]. Interviews are the most common means of data collection and data analysis techniques are designed to facilitate the interpretation of meaning (37). Questionnaire data were also used in the current study to provide information about caregivers' psychological functioning and their sources of and satisfaction with social support.

Table 1 | Guidelines and considerations for conducting and appraising qualitative research [see Ref. (33–35)].

Guidelines	Specific considerations
Relevance of research	Research question is relevant Aim is sufficiently focused and clearly stated
Appropriate method and design	Qualitative research method chosen is the best approach for the research question/aims Researchers acknowledge their personal background and experiences relevant to the phenomenon under investigation (i.e., reflexivity)
Data collection and sampling	Strategy for data collection is clearly stated and appropriate to the research question Theoretical: based on preconceived or emergent theory Purposive: diversity of opinion Volunteer: feasibility, hard to reach groups Justification for the approach is given Recruitment is conducted using appropriate methods Characteristics of the sample and setting are stated clearly and in sufficient detail
Data analysis	The type of analysis is appropriate for the study Principles and procedures for data analysis are fully described How categories and frameworks were identified is clearly stated Trustworthiness/rigor of the data and interpretation is established (e.g., triangulation)
Findings	Quotes are used appropriately and effectively to support findings Findings are relevant to the aims
Discussion	Findings are compared with appropriate theoretical and empirical references The design is scrutinized Limitations are considered Clear consequences of the study are proposed
Ethical issues	Approval from an appropriate ethics committee received Informed consent was sought and granted Participants anonymity and confidentiality ensured
Clarity	Well-written and accessible

PARTICIPANTS

Caregiver participants ($n = 25$) were part of a broader study, which examined how individuals with brain tumor make sense of and adjust to their illness (38). In this broader study, individuals with brain tumor ($n = 30$) were recruited from a brain tumor support group or a neurosurgical practice and interviewed regarding their experiences of adjustment with a family caregiver present. After a pilot interview, a semi-structured interview was developed to explore caregivers' experiences of support throughout the illness.

A subgroup of caregivers from the broader sample ($n = 25$) was selected to participate in this research. Purposive sampling was used to identify 12 caregivers with diverse characteristics likely to impact on perceptions of support, including tumor type, gender, age, and relationship to the person with brain tumor. The aim of purposive sampling is not to generalize findings to the larger population, but to select information rich-cases for study that provide an in-depth understanding of a topic (36). The primary sampling criterion was that participants were caring for an adult with a benign or malignant tumor, followed by selection on the basis of caregiver gender, age (<50, 50–60, >60 years) and relationship to the individual with brain tumor (married/*de facto* or parent). Although 12 caregivers were identified, 1 audio file was corrupted and therefore the data for participant 12 (the mother of 28-year-old woman with malignant brain tumor) could not be included in the study, resulting in a final sample of 11 caregivers. The demographic characteristics and pseudonyms of the caregiver participants are shown in **Table 2**.

The 11 caregivers included 6 males and 5 females who were aged 33–79 years ($M = 57.91$, SD = 12.62). Six were married to the person with brain tumor, two were *de facto* partners and three were parents (mother = 2, father = 1). Six participants were caregivers of a person with a benign or low grade brain tumor and five were caregivers of someone with a malignant tumor. Caregivers' level of education ranged from 9 to 18 years ($M = 12.80$, SD = 3.04). Two caregivers were working full-time, three were employed on a part-time/casual basis, one was a volunteer, one was unemployed, three were retired, and one caregiver did not provide this information.

Caregivers were supporting an individual with brain tumor who was between 9 months and 22 years post diagnosis ($M = 5.88$, SD = 6.30). All had undergone treatment involving surgery and either radiation, chemotherapy or both. The majority of

Table 2 | Caregiver demographic characteristics and tumor type (note: the pseudonym and participant number are used to indicate caregivers' gender, age, and relationship status to the person with brain tumor and the tumor type).

Caregiver characteristics		Tumor type			
		Grades I–II		Grades III–IV	
Relationship status		Married/*De facto*	Parent	Married/*De facto*	Parent
Caregiver gender	**Age**				
Male	<50	James (PT 4)			
	50–60	Sam (PT 9)		Barry (PT 1)	
	>60	Jim (PT 10)	William (PT 8)	Michael (PT 7)	
Female	<50			Wendy (PT 6)	PT 12
	50–60	Susan (PT 11)	Laura (PT 5)	Joanne (PT 2)	
	>60				Shelley (PT 3)

individuals had one type of tumor; however, one person had three different tumors diagnosed at different time points (Wendy). Tumor types included Grade I or Grade II tumors (low grade astrocytoma = 2, meningioma = 3, colloid cyst = 1, unknown benign subtype = 1); and Grade III or Grade IV tumors (oligodendroglioma = 2, glioblastoma multiforme = 2, anaplastic astrocytoma = 1, unknown malignant subtype = 1).

MEASURES

Caregivers completed the depression, anxiety and stress scales [DASS-42; (39)], caregiver strain index [CSI; (40)], and brief social support questionnaire [BSSQ; (19)] to provide descriptive information regarding their emotional wellbeing, level of demands experienced in their caregiving role and social support.

The DASS-42 is a 42 item questionnaire designed to assess symptoms of depression, anxiety, and stress. Each scale includes 14 questions and participants rate their responses from 0 "*did not apply to me at all*" to 3 "*applied to me very much*" with higher scores indicating increased levels of depression, anxiety, and stress-related symptoms.

The CSI is a 13 item measure of the degree of strain caregivers experience in their role. The yes/no items refer to physical, emotional, and financial strain, family, social, and work adjustments and demands on the caregiver's time. A total score is calculated by summing the number of yes responses, with a score of 7 or higher indicating clinically elevated strain.

The BSSQ is a modified brief version of the social support questionnaire [SSQ; (41)]. Caregivers were asked to list up to nine people or services that have provided them with support since their loved one's diagnosis. For each source of support, caregivers rated their level of satisfaction on a 6-point Likert scale ranging from 1 "*very dissatisfied*" to 6 "*very satisfied.*" These scores were averaged to derive a mean satisfaction with social support score, whereby higher scores reflected greater satisfaction with support.

DATA COLLECTION

In-depth semi-structured interviews were conducted in caregivers' homes, with the exception of one caregiver (Laura) who elected to complete the interview over the telephone. Time was spent building rapport prior to the interview. The format and topics were designed to support caregivers to reflect back on the time when their family member was diagnosed with a brain tumor and to facilitate open dialog regarding their experiences of support, the impact on their relationship, and what they have learnt from their experience. Although the latter topic was not directly related to a research aim or question, it was considered as a positive topic on which to conclude the interview. Throughout the interview prompts were used to facilitate further discussion and topics of relevance to caregivers were explored in a responsive and flexible manner. The interview guide, questions, and example prompts were as follows.

Introduction to interview

Can I get you to think back to the time when (name of person with brain tumor) found out about the brain tumor. I would like to know about the different types of support received during that time.

1. Support
   - What were the different types of support received by (name of the person with brain tumor) following diagnosis? (Example prompts: during treatment, when leaving hospital, after hospital)
   - What type of support, if any, did you receive? (Example prompts: particular people at the hospital, medical, and nursing professionals, people in your own social network)
   - BSSQ: for each source of support identified, caregivers were asked to rate their satisfaction with the support received on a scale of 1 (extremely dissatisfied) to 6 (extremely satisfied).
2. Impact on relationships
   - What impact, if any, has the brain tumor had on your relationship with (name of the person with brain tumor)?
3. Lessons learned from experiences and insights to share with others in a similar situation
   - If you met someone today who just found out their relative has a brain tumor, would there be any advice you would give them, and if so, what would that be?

The two interviewers were females with an Honors degree in psychology, who were enrolled in a Masters or PhD in Clinical Psychology. Both received specific training in qualitative interviewing techniques (36). All interviews were audio-taped and the

average recorded duration was 51 min (range = 27–88 min). Two caregivers, Shelley and Barry, chose to complete their interviews with their family member with brain tumor present.

PROCEDURE

The study was approved by a university human ethics committee prior to recruitment. All research procedures were conducted in accordance with the National Statement on Ethical Conduct in Human Research. People with brain tumor were initially approached by the coordinator of a brain tumor support service at the Cancer Council Queensland or the neuro-oncology nurse practitioner at a private neurosurgery clinic to discuss the study. If the person with brain tumor agreed to participate in the research, his or her caregiver was also approached. Researchers met with caregivers in their own homes (note: Laura was an exception as she preferred a telephone interview) and gained written informed consent. Caregivers participated in the interview first and then completed the questionnaires. The audio-recordings were transcribed verbatim prior to coding and thematic analysis. Sources of support identified by caregivers throughout the interview and comments regarding the benefits or effectiveness of support sources were tabulated using a frequency table during the transcription process. Throughout the transcription and analysis, a reflexive journal was kept by the researcher (Elizabeth Goadby) to record personal feelings and opinions to monitor any potential source of bias or influence on the findings (36).

DATA ANALYSIS

Descriptive statistics and frequency data were examined using IBM SPSS statistic software version 20. The qualitative analysis involved thematic analysis of the transcribed interviews based on the open, axial, and selective coding approach (42), as outlined in the following section. Although this analytic process is most commonly employed in grounded theory research, it is suitable for use in phenomenological studies as it facilitates in-depth understanding of subjective experience (43).

Open and axial coding

During these initial stages of coding, three caregiver transcripts were read through and a preliminary coding framework was developed. This framework highlighted a number of initial codes and categories relating to caregivers' experiences of support and the impact of brain tumor on their relationship with the person with brain tumor. Using this preliminary coding framework, one transcript was coded separately by two authors (Tamara Ownsworth and Elizabeth Goadby). Consensus coding was conducted on the 39 paragraphs of the transcript, which yielded an agreement level of 74%. Through this initial process a number of changes were made to the coding framework and consensus coding was then completed on three additional transcripts (184 passages), which yielded an agreement level of 90%. In the instances where there were differences in coding, these were discussed to reach consensus on an appropriate category. The remaining eight transcripts were then read through and experiences that were consistent with this framework were identified. This process also highlighted new experiences not captured by the coding framework, and thus it was altered to incorporate different experiences through collaborative discussion between the researchers.

Selective coding

As the final stage of the coding process, selective coding involves in-depth reflection and discussion of the coding framework by the research team, to draw a higher level of abstraction and meaning from the data (42). The categories identified during the open and axial coding stages were examined and overarching themes around support and relationships were developed, along with a number of subthemes that were considered to best represent the experiences of the caregiver sample.

Strategies to enhance rigor

A number of strategies were utilized to enhance the rigor or trustworthiness of the findings and minimize the potential for researcher bias. These included keeping a reflexive journal, accounting for the "positionality" or background and preconceptions of the researcher (i.e., reflexivity) and consensus coding (36). A reflexive journal was kept by the researcher throughout the data transcription and analysis process to record personal feelings and opinions that emerged as the research proceeded, in order to monitor the influence of these experiences on the interpretation of the results. As described previously, consensus coding was utilized throughout each stage of data analysis. During the open and axial stages of coding, this process involved transcripts being independently coded and then discussed by two researchers. During the selective coding phase, in-depth and collaborative discussion occurred between members of the research team to facilitate scrutiny and clarity of the emerging themes (36).

The consensus coding process also helped to ensure that the researchers' past experiences and preconceptions did not unduly influence the interpretation of the data. For example, in addition to her professional experience as a psychologist, the researcher primarily involved in the data analysis had personal experiences of caring for a relative with breast cancer and another relative with brain tumor. Her experiences as a caregiver were acknowledged and considered in the process of formulating the themes and subthemes to limit the potential for researcher bias (33–35).

RESULTS

CAREGIVER WELLBEING AND PERCEPTIONS OF SUPPORT

Caregivers were administered with the DASS and the CSI to provide information regarding their emotional wellbeing and the level of demands experienced in their caring role. Two caregivers (James and Laura) did not return the questionnaires despite multiple follow ups. According to the DASS, one caregiver (Susan) was experiencing a moderate level of anxiety (score = 10) and another caregiver (Wendy) was experiencing a moderate to severe level of stress (score = 25). Other caregivers were experiencing levels of depression, anxiety, and stress in the normal range on the DASS. The CSI indicated that most caregivers were experiencing non-clinical levels of strain ($M = 3.55$, SD = 2.29, range: 0–8). One caregiver, Joanne, reported a clinically elevated level of caregiver strain (score = 8/13).

Scores on the BSSQ indicated that although the number of sources of social support varied (range: 1–9/9), caregivers were typically satisfied with the support they received ($M = 4.55$, SD = 1.50). **Table 3** provides the frequency data regarding the number of caregivers who identified different sources of support

Table 3 | Sources of support and caregiver comments on the nature of support (*N* = 9).

Source	*N*	Comments (no. of people providing comment)
Brain tumor support group	8	Sharing experiences with others (4) Provided information (3) Could not attend due to work conflicts (2)
International brain tumor website	4	Provided useful information (4)
Brain injury outreach service	1	Supportive (1)
Cancer support association	3	Provided information (2) Was unsure if helpline could help (1)
Hospital (generally)	2	Friendly staff (1) We never got a follow up call at home (1)
Oncologist	1	Nice manner of interacting (1)
Doctor (specialty not specified)	3	Lovely, explained it all (1) Knew who you were (1) Medical support, not emotional support (1)
Nursing staff	4	They knew our situation (1) Nice, but busy (1) Medical support rather than psychological (2) No follow up post discharge (1)
Social worker	4	Gave information about other services (1) Too busy to see us (1) No information about available services (2)
General practitioner	6	Emotional support (2) Provided reassurance (1) Provided information (3)
Neurosurgeon	6	Kind, caring, supportive (3) Provided information (1) No reassurance provided (2) Blunt, lacking in empathy, defensive (2)
Acupuncturist	1	Easy to talk to, supportive manner (1)
Psychologist	1	Supportive (1)
Government agency	2	Provided financial assistance (1) Friendly (1)
Health insurance	3	Helped to alleviate financial pressure (1) Provided financial assistance (2)
Cancer community (i.e., online, face-to-face contact)	3	Shared similar experiences (1) Shared information (2)
Family (children, partner, siblings, parents)	9	Emotional support (3) Practical support (e.g., making meals) (3) No emotional support (1) Infrequent support (1)
Friends	9	Supportive (3) Provided practical support (2) Did not know how to be supportive (2)
Neighbors	3	Supportive (1) Available for a chat (1) Provided practical support (1)
A person with brain tumor	1	Supportive (1)
Church	3	Supportive (2) No support offered (1)
Work colleagues	5	Supportive (2) Allowed time off (1) Financial support (1)

(Continued)

as well as their comments regarding the effectiveness or nature of support. Caregivers identified both informal (e.g., family and friends) and formal support from professionals in their health care team and community services.

RESULTS OF OPEN, AXIAL, AND SELECTIVE CODING

The open and axial coding stages of the thematic analysis aimed to generate categories representing caregivers' perceptions of support and the impact of the brain tumor on their relationship. Examples of key words and phrases highlighted during the open coding process included

- Friend: "We had a friend who was a good support for a little bit there"
- Knowledge: "The support that I was looking for was knowledge"
- Stronger: "It is made our relationship a lot stronger over time."

During the axial coding process, key words and phrases with common meanings were grouped together to generate subcategories. For example, lending money, doing housework, and making meals were grouped together under the sub-category "Practical Support." Practical support was grouped together with emotional support and information under the main category, "Types of Support." A summary of the coding framework derived from the open and axial coding stages is presented in **Table 4**.

Following in-depth reflection and discussion of the categories and subcategories by the research team, two overarching themes around support and relationships were identified. The first major theme was "Meanings of Support" and the second one was "Relationship Impacts." The following section presents the major themes and subthemes related to support and relationships. Quotes from transcripts are used to illustrate caregivers' experiences, and questionnaire data are drawn on when relevant to consider caregivers' perceptions in the context of their levels of strain, emotional distress, and support.

Meanings of support

The first major theme that emerged from the data related to the different meanings of support for caregivers. It was not merely the presence or absence of support that appeared to influence caregivers' perceptions, but rather the extent to which support met their expectations. The Meaning of Support theme was characterized by three subthemes, namely, intertwined and distinct support needs, varied expectations of support and factors influencing support expectations.

Table 4 | Summary of categories, subcategories, and example key words or phrases.

Main category	Sub category	Example key words or phrases
Source of support	Health professionals	Nurse
		General practitioner
		Neurosurgeon
		Oncologist
		Social worker
		Psychologist
	Services	Brain tumor support group
		Cancer support association
		Health insurance provider
		Government (e.g., disability support)
		Brain injury outreach service
	Informal network	Family
		Friends
		Neighbors
		Work colleagues
		Cancer community
Type of support	Emotional	Someone to talk to
		Keeping in touch
		Being there when it mattered
		Sharing experiences
	Practical	Financial support
		Housework
		Made meals for us, childcare
	Information	Brain tumors
		Treatment
		Supporting someone with a tumor
Nature of support	Time frame	Not daily, but there when we needed it
		No support when we left hospital
		Only contacted every couple of months
	Manner of interacting	Warm, kind
		Gave hope
		Blunt
		Not empathetic
		Gave no reassurance
Factors impacting on support	Support being offered	Distance
		Short time between diagnosis and treatment
		People not knowing what to say
	Support being sought	Short time between diagnosis and treatment
		Shock after diagnosis
		We thought he would be ok
		Lack of knowledge about services
		Time constraints/work conflicts
		No services in our area
Impact on relationships	Changes in relationship	Made us closer
		Abuse and criticism all day
		Close before and still close now
	Changes in roles	Full-time parent
		Main breadwinner
		Increased household responsibilities
		Change in employment

Intertwined and distinct caregiver support needs. When caregivers were specifically asked about their own support needs, some expressed that their support needs were closely intertwined with the needs of the person with brain tumor. For these caregivers, there was no distinction made between support perceived for themselves and that of the individual with brain tumor. For example, when Michael was asked if friends were supportive of him and his wife he replied: "*Yes, which are basically the same thing*." These caregivers often used phrases like "*when we were diagnosed*" or "*when we went through treatment*," highlighting their shared experiences of both the brain tumor and support.

Other caregivers reported feeling supported if their loved one was supported. Laura (mother): *The oncologist wasn't personally supportive of me, I didn't expect that, but by the fact that I knew she was so wonderful for my daughter that supported me.* When discussing support groups, which typically focused on the individual with brain tumor, some caregivers reported feeling supported if their loved one was receiving support and benefiting from this. Similarly, when asked to reflect on support he would have liked, James (partner) expressed: *Not really for myself – more for Lucy . . . for other people to support her.* These caregivers did not appear to expect support for themselves because their focus was on their family member. Although some caregivers acknowledged the general lack of support for caregivers, they were often unsure if they would have access this support had it been available. Sam (husband): *No one really worries about you (the caregiver); they worry about the person with the brain tumor. I'm not sure I needed it either.*

While most caregivers did not refer to seeking support specifically for themselves, one caregiver, Wendy (wife) identified her own need for psychological support. Distinct from other caregivers she reported significant changes in her husband's personality: *I've actually started to admit to myself he's not the person he used to be . . . you've lost that person you've married and you've got to deal with that.* Wendy reported moderate to severe levels of stress on the DASS and was seeking counseling to cope with her feelings of grief regarding changes in her husband.

One area in which caregivers often perceived their own distinct support needs was information. In particular, they wanted easy to understand information on what to expect when caring for someone with a brain tumor, including different types of brain tumor, treatment, and side effects. Barry (partner): *I wasn't really seeking support, most of the support that I was looking for was knowledge.* Caregivers perceived that access to information would have helped them to adjust to their caregiver role. William (father): *Even if we had been aware of the support group and all the information available . . . that could have made our lives so much easier.*

Varied expectations of support. Caregivers held different expectations of support with respect to the time frame over which it was provided, the type or nature of support and the extent to which support should be offered to, or sought by the caregiver. In terms of the time frame, some caregivers had expected that support from family, friends, or professionals would continue throughout treatment and post-treatment. When asked about support following her daughter's discharge from hospital, Joanne noted: *We never had any call back from them (hospital) . . . or a call at*

home to see if we got there, nothing. Another caregiver reported ongoing support from family and professionals, but felt that the support was too infrequent. James (partner): *There were family members . . . and they kept in touch, but that was only every couple of months.* Other caregivers perceived that ongoing support even on a less frequent basis was supportive. Michael (husband): *Well, (Hospital) you know there was support there all the time . . .. Even now when we go in we still meet some of them.* Professionals were viewed as supportive when support was available as needed. For example, in discussing their GP, Sam (husband) noted: *He wasn't a daily source of support, but when we had to go and talk to him he was excellent.*

Caregivers' expectations of the type of support also varied. Most caregivers received a range of practical supports including financial assistance, house-keeping, childcare, and workplace flexibility. However, their perceptions of emotional support appeared to impact the most on their overall sense of feeling supported. For example, when reflecting on support from friends and family, Shelley (mother) expressed: *It's the emotional support I think people need more than anything.* For Shelley, despite receiving support from multiple sources including friends, family, and professionals (BSSQ = 9/9 sources), a lack of emotional support from these sources appeared to influence her perception: *I don't think we got very much support at all from anywhere.* Caregivers who received minimal or no emotional support typically reported low satisfaction with support, even if they received practical assistance. For example, James (partner) noted: *My parents have been there . . . but they've been more financial support when we really needed it, not emotional.*

Caregivers also perceived that emotional support from healthcare professionals was very important, particularly in their manner of interaction. When discussing his wife's neurosurgeon Sam expressed: *His manner's been very encouraging and very supportive and I would classify him as being a source of support.* Doctors with a kind and caring manner were perceived as providing emotional support even when giving bad news. Laura (mother): *She (neurosurgeon) had to give us some bad news some of the time . . . and you couldn't ask for a better manner in her delivery of that bad news, or her support in what we were going through.* These two caregivers also described negative experiences with other medical professionals who were perceived as cold and clinical or offering little hope or reassurance. Sam (husband): *There was no hello, we walked into the room and he (neurosurgeon) looked up from his desk and said you've got a very large brain tumor and it is an eight hour operation.* Laura (mother): *(We asked) do you think she will live? and he very tersely told us well, you want to be grateful that we're not dead now . . . from our point of view all we really wanted was a little bit of reassurance.*

Caregivers differed in their views on whether support should be offered to, or sought by them, which in turn influenced their support seeking behaviors. Some caregivers were very proactive in seeking the support they needed. Wendy (wife) lived in a remote community away from support and services and noted: *That's something I had to strike out and find on my own.* These caregivers often used the Internet to access information about brain tumors and treatment and to share their own experiences with the online cancer community. Jim (husband), who utilized multiples website to search for information, noted: *I've taken to tumors like a hook to a fish. I just had to – I was hungry for information.*

Other caregivers had expected professionals and services to extend offers of support. When reflecting on support from the hospital Shelley (mother) expressed: *Nobody ever rang up and said oh your daughter's got a brain tumor, how can I help you? You know I'm from the hospital what can I do?* Similarly, Joanne (wife) thought that services would contact her to provide information and support: *I mean no one has sent us a letter or gave us a phone call and said as soon as you had a cancer you want to come to this seminar.* For some caregivers, additional stressors had impacted their ability to seek support for themselves. For example, Shelley (mother) was also the caregiver of her husband who had terminal cancer.

Factors influencing expectations of support. Factors that appeared to influence caregivers' expectations of support included the time frame between diagnosis and treatment, geographical distance, work commitments, lack of awareness about support available, and expectations about their family member's prognosis.

Most caregivers recalled the shock they experienced in learning about the brain tumor. There was often a very short time frame between diagnosis and treatment. Barry (partner): *They looked at the CAT scan . . . and got her straight back in for an MRI and then it was within a week that the operation happened.* Caregivers advised that in the early stages following diagnosis they did not expect to receive nor seek support as they were more focused on treatment for their family member. Sam (husband): *That was a time I guess of great shock in terms of support no, you're basically just dealing with the issue.* As an exception, Michael sought support from his church community and friends and family shortly after his wife's diagnosis. He and his wife had previously experienced major health issues and were able to quickly mobilize the support that had helped them to cope in the past.

Several caregivers advised that they would have liked to receive more information about brain tumor once the initial shock had subsided. Sam (husband): *I guess we just wish that someone would have said to us right at the beginning here's a very good guide, because when you have a brain tumor situation, oh you're lost.* Susan (wife) noted: *I think that's the time when some sort of support would be very helpful perhaps to a lot of families.* The range of support services available, and what to expect as a caregiver, were identified as important types of information helpful for caregivers to receive soon after diagnosis. Wendy (wife): *I think that's one of the biggest problems with the services, it's hard when you don't know where to even begin . . . I did not know where to go really and I suppose that was half the problem of not getting help.* Some misconceptions about support services also posed a barrier to accessing support. For example, Susan perceived that people with benign tumor were unable to access support from a cancer support service. Other caregivers suggested the need for better publicity and marketing around services so people are more aware of the support they can access.

Practical issues such as time and distance and expectations about prognosis impacted caregivers' expectations of support. In particular, caregivers' work commitments reduced the amount of time they could spend looking for information on brain tumors or seeking options for support for themselves. James (partner): *I*

could have done with something myself but I was pretty busy working. Those living a long distance away from family or friends had less expectation of support from their informal support network, and hence the person with brain tumor and caregiver had become more reliant on support from each other. Expectations of positive outcomes after treatment were perceived to impact support seeking for two caregivers. They were advised that their family members would regain their former functioning. Susan (wife) noted: *We did not know we needed any . . . all the indications were everything was going to be fine . . . and when everything is going to be fine you don't need any help.*

In summary, the Meanings of Support theme highlighted variations in caregivers' perceptions of their own support needs in relation to those of the person with brain tumor. However, there was a general consensus on the need for caregiver-specific information. Caregivers had different expectations regarding the timing and type of support received, which was influenced by various factors (e.g., work commitments, their family member's prognosis).

Relationship impacts

From the caregivers' perspective, the brain tumor was associated with three main relationship outcomes, namely, the experience of strengthened, maintained, or strained relations. Issues that appeared to influence these outcomes were mood and personality changes of the person with brain tumor, changes in caregiver roles and responsibilities and the quality of the relationship before the diagnosis. Social support was perceived to influence relationship outcomes to varying degrees.

Strengthened. Two caregivers noted that their relationship was strengthened by the experience of brain tumor. Susan noted that she and her husband now share more as a couple; *I think it has made us closer . . . I'm a lot more tuned into him than I was before.* She advised that there were no major changes in her husband's personality and only minor changes in her household responsibilities, which they had coped with by re-structuring their home environment. She felt that the limited support from friends, family, and professionals had drawn them closer together: *We pulled together for the family because we've always lived away from our families.*

A second caregiver, Barry advised that he had been through his own health issues and his partner had cared for him. Their mutual experiences as caregivers had brought them closer as a couple: *I think things like that have happened with Sarah and me; we've grown very close together as soul mates.* Similar to Susan's experience with her husband, there were no major changes to Sarah's personality or abilities. Barry had also made small modifications to their home environment to make things easier for his partner; however, he did not perceive any major changes to his role or responsibilities within the household. Barry advised that his work was very supportive, allowing him to take days off and have remote access.

Maintained. Two parent caregivers (Laura and Shelley) reported no change in their relationship with their adult children. Both noted that they were close to their daughters before the tumor and continued to be close after diagnosis and treatment. Laura (mother): *We did then and still have a close relationship.* Neither caregiver reported changes in their daughter's mood or personality, although both caregivers reported minor changes in their responsibilities, such as driving their daughters to appointments or spending more time looking after their grandchildren. These caregivers differed in their perceived support needs; Shelley, who also cared for her husband with terminal cancer, reported a need for more emotional support as a caregiver, whereas Laura felt emotionally support by her husband.

Strained. The remaining caregivers perceived that the brain tumor had placed varying levels of strain on their relationship with their family member. These caregivers often reported changes in their loved one's mood and personality, such as irritability and frustration. Sam (husband): *That was hard to take, to cop the abuse and criticism all day long.* In one instance, the personality of the person with brain tumor was perceived to have dramatically changed. Wendy (wife): *I've had to grieve for the man I married even though I've still got him . . .. It's hard because some days John is really almost like the old John and you could sort of, do you say something to him or not? Yeah that's hard.*

Changes in roles and responsibilities, such as taking on more household chores and childcare, also contributed to relationship strain. James reflected on the changes in his life following his partner's treatment: *I did not really have too much to do with kids. I was riding dirt bikes and having a good time out there and sort of being single, to looking after Lucy and having bubs and the whole tumor ordeal.* Many caregivers described taking on more of the decision making regarding finances as they become the main or sole breadwinner. For caregivers who took on additional roles and responsibilities, lack of support appeared to contribute to their experience of relationship strain. For example, Wendy reported few sources of support (3/9) and low satisfaction with the support received (score: 2/6).

For other caregivers, the quality of the relationship prior to the brain tumor and other pre-existing stressors impacted on their current relationship. For example, Sam discussed the loss of the family business and his wife's earlier diagnosis of breast cancer as issues contributing to relationship strain prior to the brain tumor diagnosis. *I was finding I was getting a lot of abuse and this was months before the diagnosis.*

Overall, while most caregivers perceived that their family member's brain tumor placed strain on their relationship, some perceived no change or a strengthening of their bond. Mood and personality changes, role demands and responsibilities, and the quality of the relationship prior to diagnosis appeared to influence relationship outcomes. Social support was not found to have a consistent influence on relationship functioning. In particular, a lack of support was perceived to bring one couple closer together, have minimal impact on some relationships, and place strain on others.

DISCUSSION

This study aimed to understand how caregivers perceive their own support needs and the impact of brain tumor on relationship functioning. The two main themes highlighted the different meaning of the concept of support and diverse ways in which brain tumor affects relationships. Caregivers' perceptions of support were influenced by their expectations of the timing and type of support received. More generally, their sense of being supported was dependent upon their subjective understanding of

what constitutes support (e.g., practical vs. emotional, short-term vs. long-term, frequent vs. infrequent).

Overall, caregivers tended to view their support needs as indistinguishable from, or secondary to those of the person with brain tumor. For some caregivers, no distinction was made between support for themselves and support for the person with brain tumor; hence, they typically felt supported if their loved one was receiving support. Other caregivers had not considered their own support needs because they viewed these as secondary to their family members' treatment and support needs. Wasner et al. (31) also found that caregivers often prioritized the support needs of the individual with brain tumor over their own. The intertwined vs. distinct support needs subtheme represents a novel finding in the context of brain tumor.

Caregivers in the present study nevertheless expressed a desire to receive more information about brain tumor, treatment effects, what to expect in caring for someone with a brain tumor and options for support. Other research has found that access to information can reduce caregivers' anxiety and frustration (20, 23, 44). For example, Cornwell et al. (23) reported that during the early stages of the illness (i.e., 2 weeks post discharge) caregivers were often not receptive to information offered to them because they felt overloaded with information and unable to process it, due to their worries about the person with brain tumor. In contrast, Schubart et al. (9) found that information seeking by caregivers was highest immediately following the diagnosis of brain tumor, and helped families to cope with changes in their loved one and the challenges of their role. These mixed findings concerning caregivers' preferences for information soon after diagnosis may be related to the type of information and the way in which it is delivered.

Emotional support was also recognized as an important component of support. For some caregivers the provision of practical support alone (e.g., financial assistance) did not contribute to a sense of being supported if emotional support was perceived to be lacking. Other studies have similarly highlighted the importance of emotional support from caregivers' informal support network, which can include support groups or meeting other people in a similar situation (3, 11, 44). Caregivers also stressed the importance of emotional support from health care professionals, as conveyed by a kind and reassuring manner of interaction. In research by Wideheim et al. (17), caregivers described encounters with health care professionals as positive when they patiently listened to and answered their questions. Conversely, health professionals who failed to provide reassurance or focused solely on physical care as opposed to emotional support were perceived as unsupportive (20).

Caregivers' expectation of the timeframe over which support would be provided varied. For example, some caregivers perceived that formal and informal support was most important during the early stages of the brain tumor, whilst other caregivers expressed the desire for ongoing or long-term support. A similar issue found in previous research is that that while family and friends may initially offer practical and emotional support, this dwindles over time (3, 45). Such findings are concerning when considering that the stressors experienced by caregivers are often long-term and their support needs may potentially increase due to tumor recurrence and functional decline (17). Overall, the findings highlight the importance of seeking to understand individual caregiver's expectations and preferences for support at different times throughout the illness.

The main issues found to impact on caregivers' access to support in the present study were lack of awareness of available supports, time and work commitments, and expectations around support seeking. Although there is limited previous research on support seeking behaviors in caregivers of people with brain tumor, Arber et al. (5) found that caregivers who perceived a lack of support often developed their own strategies for accessing information to reduce the uncertainty and stress related to brain tumor. However, Schmer et al. (27) found that caregivers were less likely to seek or access support options (e.g., attend support groups) when they had high care demands placed upon them. Given the findings of previous research (19) that social support can buffer the effects of caring for someone with severe disability, there is a need for more accessible and flexible avenues of support for caregivers of people with brain tumor.

The experience of brain tumor was found to impact on relationships in different ways, including strengthened, maintained, and strained relations between the caregiver and person with brain tumor. The experience of major personality change, or the sense that the person is no longer who they were prior to the illness, and cognitive difficulties appeared to contribute to relationship strain. Other research suggests that the excessive strain placed on caregivers can contribute to a relationship breakdown (4, 9, 17). It is noteworthy that all caregivers in the present study were currently supporting the person with brain tumor, and therefore issues precipitating relationship breakdown could not be explored.

The complex cognitive and behavioral changes that distinguish brain tumor from other cancers have been documented in previous studies (1, 3, 28). In particular, behavioral problems have been found to contribute to caregivers distancing themselves from their loved one (28), and are associated with lower levels of caregiver mastery and greater depressive symptoms (46). The link between behavioral problems and relationship strain highlights the need for behavioral support interventions for this population. Encouragingly, Whiting and colleagues (47) have developed a multi-tiered intervention approach for managing cognitive and behavioral deficits after brain tumor. A single case study was used to evaluate a behavioral therapy and skills training intervention for reducing problem behaviors (e.g., excessive talking, lack of turn taking) displayed by the person with brain tumor. A second intervention focused on educating and training family members ($n = 7$) in a half-day workshop on managing challenging behavior. The third intervention for health professionals ($n = 43$) involved a one day workshop on psychoeducation and skills training for managing clients' challenging behaviors. Each intervention was found to be effective in terms of decreasing target behaviors, increasing knowledge and use of strategies. These findings highlight the potential value of multi-level behavioral support interventions, although controlled trials are needed to determine their efficacy.

Despite the more common experience of relationship strain, other caregivers in the present study reported an ongoing closeness or strengthening of their bond with their family member. These caregivers did not report changes to the person's personality or a major shift in their responsibilities. Rather, becoming caregivers

for their spouse was perceived to have brought them closer as they shared more as a couple. Salander and Spetz (26) similarly found that couples with more open communication about the tumor developed a joint platform for coping. Conversely, when the individual with brain tumor would not share their experiences with their spouse and there was no shared understanding of the situation they were more likely drift apart. These observations suggest that couples therapy interventions may be beneficial for this population in addition to caregiver education and skills training (48). For example, Leboeuf (49) described a family centered approach used by a clinical nurse specialist to enhance communication and coping strategies of a couple in the context of malignant brain tumor.

The quality of the relationship prior to the brain tumor also appeared to influence relationship functioning in this study. Although this is a novel finding for brain tumor, previous cancer research found that caregivers who perceived a close relationship prior to diagnosis felt less burdened by caregiving and reported fewer depressive symptoms (50). Similarly, greater relationship satisfaction prior to the onset of dementia has been found to be associated with less burden and reactivity to cognitive and behavioral problems (51). Overall, the present findings suggest that a more cohesive relationship prior to the illness onset contributes to better dyadic adjustment. Couples with a pre-existing close bond may be able to draw upon their mutual knowledge of coping skills (e.g., communication and problem-solving) and commitment to support each other.

CLINICAL IMPLICATIONS

The finding that caregivers' sense of being supported is subjectively construed highlights the importance of professionals seeking to understand their expectations of the timing and nature of support. Although a support needs assessment can be conducted by any health professional involved in the person's care, some researchers have suggested that a designated staff member be allocated to provide tailored information and support throughout the illness (11). The integral support role of brain tumor care coordinators is being increasingly recognized (52); however, lack of funding is a key barrier to increasing the number of coordinator positions within the community. Pilot research suggests that a brain tumor specific question prompt list may help to reduce the unmet information needs of individuals with brain tumor (53), and this resource could potentially be extended to caregivers' support needs.

As preferences concerning the timing and type of information received vary it would be beneficial to develop modular information kits that can be personalized to caregivers' needs at different time points (e.g., shortly after diagnosis, before and after treatment, or following discharge). These modules could provide information about different types of brain tumor, treatment, side effects, care following discharge, long-term caregiver responsibilities, and support options. In the present study, online international forums and websites were perceived as valuable sources of support in addition to support services within people's local area. Caregivers identified that living in remote areas or having work commitments posed barriers to accessing support services in person (e.g., attending support groups). Tele-health services offer considerable scope to overcome these barriers. In addition to video-conferencing with health professionals, web-cameras or teleconferencing may encourage caregivers to attend support groups remotely (54). Further, information seminars can be made available using audio-recordings and podcasts.

LIMITATIONS

Although this study provides important insights into caregivers' experiences of support and relationship, some limitations need to be considered. First, convenience sampling was used to recruit caregivers within a broader study focusing on the adjustment of individuals with brain tumor. While a purposive sampling strategy was used to select caregivers with diverse characteristics likely to influence perceptions of support, none of the caregivers had experienced a relationship breakdown with the person with brain tumor whereby they were no longer in a support role. Further, a larger sample size would have enabled exploration into the influence of caregiver gender on experience of support and the impact on relationships.

A prospective longitudinal study that monitors dyadic adjustment over time would enhance understanding of issues contributing to relationship strain and protective factors. A second related issue is that the interviews required caregivers to reflect back on their experiences of diagnosis and treatment which, for some, was over 20 years ago. It is possible that this approach affected caregivers' recall of experiences relevant to their support and relationship functioning. As a third limitation, member checks were not used to enable caregivers to check their transcript after the interview or to more broadly verify that the key findings reflect their experiences (36). Finally, the present study was only concerned with caregivers' perceptions of support and relationship outcomes. In future research it would be valuable to incorporate the perspectives of individuals with brain tumor on their caregivers' support needs.

CONCLUSION

This study identified variations in caregivers' experiences of support and the effects of brain tumor on relationship functioning. The major finding concerning meanings of support underscores the value of seeking to understand what constitutes support for caregivers. Although caregivers varied in their expectations of the timing and type of support, most perceived the need for greater access to information and valued emotional support from professionals and their informal support network. Caregivers who perceived major changes in their family member, and had greater role adjustments typically experienced relationship strain. Overall, the findings highlight the importance of flexible and accessible support options and need for future research to evaluate caregiver support interventions.

AUTHOR CONTRIBUTIONS

All authors made a substantial contribution to the conception and design of the study, participant recruitment, data collection, and/or data analysis phases. Each author was involved in drafting the work or critically revising it for important intellectual content and gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Screening for psychological distress in adult primary brain tumor patients and caregivers: considerations for cancer care coordination

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Introduction: This study aimed to assess psychological distress (PD) as scored by the Distress Thermometer (DT) in adult primary brain tumor patients and caregivers (CGs) in a clinic setting and ascertain if any high-risk subgroups for PD exist.

Material and methods: From May 2012 to August 2013, $n = 96$ patients and $n = 32$ CG underwent DT screening at diagnosis, and a differing cohort of $n = 12$ patients and $n = 14$ CGs at first recurrence. Groups were described by diagnosis (high grade, low grade, and benign) and English versus non English speaking. Those with DT score ≥ 4 met caseness criteria for referral to psycho-oncology services. One-way ANOVA tests were conducted to test for between-group differences where appropriate.

Results: At diagnosis and first recurrence, 37.5 and 75.0% (respectively) of patients had DT scores above the cutoff for distress. At diagnosis, 78.1% of CGs met caseness criteria for distress. All CGs at recurrence met distress criterion. Patients with high-grade glioma had significantly higher scores than those with a benign tumor. For patients at diagnosis, non English speaking participants did not report significantly higher DT scores than English speaking participants.

Discussion: Psychological distress is particularly elevated in CGs and in patients with high-grade glioma at diagnosis. Effective PD screening, triage, and referral by skilled care coordinators are vital to enable timely needs assessment, psychological support, and effective intervention.

Keywords: primary brain tumor, screening, psychological distress, neuro-oncology, care coordination

Introduction

Patients with primary brain tumors (PBT) experience a myriad of complex physical, emotional, cognitive needs (1, 2), which can have adverse psychological effects on both the patient and their caregivers. In particular, patients diagnosed with high-grade glioma (HGG) have a poor prognosis and limited life expectancy and as such often experience rapid decline in physical and cognitive functioning (3). They can often exhibit a dynamic constellation of needs throughout the care trajectory, from initial diagnosis to tumor recurrence through to the palliative phase (4, 5), with profound changes not only in physical functioning but also in psychological distress (6), mood, cognition, and behavior.

Due to the high emotional sequelae of having a PBT (7), it is important that patients are routinely screened for psychological distress and have effective and timely interventions instituted. The National Comprehensive Cancer Network (NCCN) Distress Thermometer (DT) is one of the most familiar and widely adopted psychological distress screening tools utilized in oncology populations (8, 9). Several studies have described DT screening in malignant and benign PBT cohorts, with the majority undertaking assessments relatively soon after initial diagnosis. Keir et al. (10) assessed a convenience sample of malignant PBT patients with time interval from tumor diagnosis to testing varying from 10 days to 22 years, with a median time of 1.8 years. Using a cutoff score of DT $\geq$4, 52% of their cohort were classified as suffering from elevated psychological distress. Similarly, Kvale et al. (11) applied the DT in a sample of 50 glioblastoma patients, with 22% of patients seen within the first 4 months after diagnosis. They reported a mean distress score of 2.15 (SD = 2.66), with caseness criteria using a DT score of $\geq$4 met by 28%.

Only a few studies have published serial or longitudinal DT data in PBT populations; however, assessment was acquired at pre-defined chronological time points such as baseline, and six monthly (12), or after a short interval such as pre- and post-radiotherapy (13). These time points did not specifically reflect the actual treatment phase or disease status such as at tumor recurrence (14) or the terminal phase when distress is known to be elevated (4, 15). Keir et al. (6) categorized 83 glioblastoma patients into those who had been diagnosed either less than or greater than 18 months. They reported that 59% of long-term survivors (LTS) met the DT $\geq$4 cutoff score for distress (M = 4.61, SD = 3.12) compared with 49% of those diagnosed <18 months.

It is widely acknowledged that the impact and burden on caregivers of brain tumor patients is significant (3, 16–19). Caregivers can experience a range of unmet supportive care needs and remain at risk of physical, emotional, and financial stressors themselves (2, 20–22). Despite this, there is currently only sparse literature documenting both patient and caregiver psychological distress levels.

It is notable that even in subgroups of PBT survivors with more favorable outcomes such as pituitary tumors (23) or low-grade glioma (LGG) (24), a spectrum of concerns including neurocognitive and behavioral issues (25) and elevated psychological distress has been detected (13). PBT patients and caregivers are faced with a new reality of living over months to even years with the sequelae of brain tumor, due to the tumor and/or the effects of therapy (26). Furthermore, it is likely that the existing language barriers, the knowledge and ability to navigate through a complex healthcare system, cultural insensitivities, and a lack of patient-centered care (27, 28) affecting Culturally and Linguistically Diverse (CALD) cancer groups (29), are likely to be heightened in those patients and caregivers faced with the diagnosis of PBT (30).

The complexity and scope of needs experienced by brain tumor patients and their caregivers requires a coordinated response from healthcare services and providers. In Australia, a cancer care coordinator is a position focused specifically on improving the patient journey. The care coordination role is designed to incorporate the critical functions of assessment and evaluation of clinical and supportive care needs and liaising with multidisciplinary teams (MDTs) to achieve timely and high quality care (31, 32).

This study aimed to assess the psychological distress of PBT patients and caregivers, as measured by the DT, in a clinic setting. The second aim was to ascertain if any high risk subgroups for psychological distress exist, for example, caregivers and those of non English speaking background (NESB).

Materials and Methods

Patient Population

The study population comprised PBT patients who were either newly diagnosed or who were experiencing first tumor recurrence. Likewise, as a separate group, caregivers of PBT patients with either malignant or benign tumors were assessed and underwent DT screening from the period of May 2012 to August 2013. PBT categories included HGG, LGG, and benign brain tumors (BBTs), the most common of which included meningioma and pituitary tumors.

Neuro-Oncology Care Coordinator Role in South-West Sydney

The NOCC in South Western Sydney Local Health District (LHD), serving a population of almost one million people, is a one full-time equivalent position that encompassed the care of all primary malignant and benign brain and spinal tumor patients diagnosed across three main teaching hospitals in the LHD. New cases and referrals were identified at MDT meetings held every 2 weeks where all new and recurrent PBT cases were discussed with a consensus management plan recommended.

Psychological Distress Screening

Study Procedures

Ethical approval to undertake the study was provided by South Western Sydney Area Health Service Human Research Ethics Committee. The NOCC conducted a screening assessment with each participant using the DT tool for psychological distress screening. DT screening was performed around the time of initial PBT diagnosis or at the time of first tumor recurrence. Likewise, DT screening was undertaken in caregivers of PBT patients either at initial diagnosis or first recurrence. DT screening for non English speaking patients was administered in the presence of a hospital-based interpreter where available or alternatively an English speaking caregiver. The majority of DT screening assessments were performed with the NOCC face-to-face in an oncology outpatient

setting, or alternatively by phone, especially if patients were too unwell to attend clinic or had other logistical challenges.

Study Measures

The DT, a measure (8, 9, 33) validated in a variety of multisite cancer populations, was used to screen for psychological distress in the study cohort. Participants rated their level of distress in the past week on a scale of 1–10, with 0 = no distress, 5 = moderate distress, and 10 = extreme distress. Patients were then asked to indicate areas of problems listed under the following five main categories: physical, family, emotional, spiritual/religious, and practical. Patients and/or caregivers were subsequently referred onto relevant psycho-oncology services for further evaluation and intervention according to the problems identified.

The DT has traditionally been designed for and utilized in cancer patients only (33). However, it is widely acknowledged that there are multiple identified supportive care needs that exist in PBT caregivers (1, 3, 34). In addition, Zwahlen et al. reported a validation study supporting the use of the DT in screening the caregivers of cancer patients (35). Hence, where feasible in the current study, caregivers were also asked to complete the DT.

Patients and/or caregivers with a DT score ≥4 were referred by the NOCC to relevant psycho-oncology, Allied Health or community services, in keeping with documented and accepted clinical practice guidelines for psychological distress management in oncology (9).

Selected patient demographic data including age and country of origin, English speaking versus non English speaking background, as well as clinical data including the PBT diagnosis, nature/timing of relevant treatments, and date of first (but not subsequent) tumor recurrence were collected.

It is widely acknowledged that there are many differing definitions for CALD groups. Although the Australian Bureau of Statistics (36) utilizes the category of "people who were born overseas," for the purposes of the current study and also for the subsequent analysis, patients and caregivers were grouped into English speaking versus non English speaking groups rather than by country or regions of birth.

Data Management and Statistical Analyses

The oncology electronic medical record, Mosaiq®, was used as a platform to collect and extract relevant clinical information concerning all DT scores from patients and caregivers. Once extracted from Mosaiq®, descriptive statistics were generated for all variables.

Results have been ordered according to four independent participant groups: patients at diagnosis, patients at recurrence, caregivers at diagnosis, and caregivers at recurrence. Descriptive and frequency data were generated for DT scores. Next, for patients at diagnosis, an independent samples *t*-test tested for differences on DT scores between English speaking and non English speaking background participants. Then, a one-way ANOVA was conducted to test for statistical differences among the three tumor diagnosis groups (HGG versus BBT versus LGG). Scheffe *post hoc* comparisons were then conducted with an adjusted Bonferroni alpha of $p < 0.016$ (0.05/3). Due to insufficient sample size, similar tests were not conducted for any of the other three participant groups. Finally, scores on the DT were divided into two groups (<4 and ≥4) to identify caseness. Caseness can be defined in this context as any participant with psychological distress levels that were clinically significant, i.e., that require further assessment and/or intervention by psycho-oncology services. Participants with DT scores ≥4 were classified as meeting caseness criteria (8).

Results

Sample

In total, 190 DT scores were collected. Of these, 25 patients and 11 caregivers had completed the DT at more than one time point. In these cases, only the first instance of DT completion was retained for analysis. Data from a total of 154 DT scores remained. DT scores were collected from a varied neuro-oncology cohort that comprised HGG, LGG, and BBT patients, as categorized by the international WHO 2007 classification of brain tumors (37). All patients had a confirmed histopathological diagnosis. LGG patients were those with grade I or II glioma in contrast to those with BBT who were predominantly patients with meningioma and pituitary tumors.

Of the total number of DT assessments, 30.5% (47/154) were performed in NESB participants. **Table 1** provides a summary of DT scores for PBT patients and caregivers, both at diagnosis

TABLE 1 | Summary of distress thermometer scores for primary brain tumor patients and caregivers, both at diagnosis and first tumor recurrence, according to tumor subgroups and English speaking background.

	Patient		Caregiver	
	Diagnosis (*n* = 96)	Recurrence (*n* = 12)	Diagnosis (*n* = 32)	Recurrence (*n* = 14)
Total				
Mean, SD	3.15 ± 2.20	5.42 ± 3.09	5.34 ± 1.89	7.64 ± 1.50
Range	0–8	1–10	2–8	5–10
HGG				
n, %	39 (40.6)	8 (66.7)	22 (68.8)	11 (78.6)
Mean, SD	4.03 ± 2.36	5.13 ± 2.98	5.86 ± 1.81	7.64 ± 1.29
Range	0–8	1–9	3–8	5–9
LGG				
n, %	8 (8.3)	1 (8.3)	4 (12.5)	1 (7.1)
Mean, SD	2.25 ± 1.28	2.00	4.25 ± 1.71	8.00
Range	0–4	–	2–6	–
BBT				
n, %	49 (51.0)	3 (25.0)	6 (18.8)	2 (14.3)
Mean, SD	2.59 ± 1.97	7.33 ± 3.06	4.17 ± 1.72	7.50 ± 3.54
Range	0–8	4–10	2–7	5–10
ESB				
n, %	69 (71.9)	9 (75.0)	19 (59.4)	10 (71.4)
Mean, SD	3.03 ± 2.26	5.11 ± 2.67	5.53 ± 1.87	7.40 ± 1.43
Range	0–8	1–9	2–8	5–9
NESB				
n, %	27 (28.1)	3 (25.0)	13 (40.6)	4 (28.6)
Mean, SD	3.44 ± 2.06	6.33 ± 4.73	5.08 ± 1.98	8.25 ± 1.71
Range	0–7	1–10	3–8	6–10

HGG, high-grade glioma; LGG, low-grade glioma; BBT, benign brain tumor; ESB, English speaking background; NESB, non English speaking background.

and first tumor recurrence, and according to tumor subtypes and English speaking background.

Patients

A total of 96 DT scores were collected from patients at diagnosis, comprising 40.6% (39/96) with a diagnosis of HGG, 8.3% (8/96) with LGG, and 51.0 (49/96) with BBT. The highest mean DT scores were those with HGG tumors, followed by BBT and then LGG. For patients at diagnosis, 28.1% (27/96) were from NESB participants. DT scores were similar among NESB participants and those from an English speaking background (**Table 1**). Of all patients at the time of diagnosis, 37.5% (36/96) met criteria for caseness using the DT.

An independent samples *t*-test found no significant differences on DT scores between those from an English speaking and non English speaking background. A one-way ANOVA found statistically significant differences on DT scores among the three tumor groups, $F(2, 93) = 5.882$, $p < 0.05$. Scheffe *post hoc* tests showed that scores on the DT for the HGG diagnosis group were significantly higher than those with a diagnosis of BBT ($p < 0.016$). No other significant differences were found.

Twelve patients at recurrence completed the DT. Of these, 66% (8/12) had a diagnosis of HGG, 8.3% (1/12) had LGG, and 25.0% (3/12) had BBT. Those with a diagnosis of BBT had the highest scores on the DT. Similar to patients at diagnosis, 25.0% (3/12) of patients at recurrence were from an NESB; however, scores on the DT were slightly elevated in comparison with those from an English speaking background. The majority of patients at recurrence met caseness criteria using the DT (75.0%, 9/12).

Caregivers

A total of 32 caregivers at diagnosis completed the DT. These comprised 68.8% (22/32) supporting someone with HGG, 12.5% (4/32) with LGG, and 18.8% (6/32) with BBT. The highest DT scores were for those with a diagnosis of HGG. There was a high rate of caregivers at diagnosis from an NESB (40.6%, 13/32), and they had slightly higher DT scores than those from an English speaking background (**Table 1**). A large proportion of caregivers at the time of diagnosis met the caseness criteria for the DT (78.1%, 25/32).

Finally, DT scores were collected from 14 caregivers at recurrence. These were composed of 78.6% (11/14) supporting someone with HGG, 7.1% (1/14) LGG, and 14.3% (2/14) BBT. Scores on the DT were high among all tumor gradings for caregivers at recurrence, although the small group numbers did not allow for further comparison. Just under 30% of caregivers at recurrence were from an NESB (28.6%, 4/14) with similar mean scores on the DT (**Table 1**). All caregivers completing the DT at first recurrence had scores which met caseness criteria (100%, 14/14).

Discussion

Primary brain tumor patients have complex supportive care needs, and caregiver burden is high (2, 3, 21). At initial diagnosis, the poor prognosis associated with HGG, coupled with physical, neurocognitive, and behavioral sequelae associated with the disease and its associated therapies, can contribute to elevated psychological distress. Furthermore, due to the almost certain pattern of recurrence in HGG over time leading to high mortality rates, psychological distress levels can potentially increase throughout the disease journey.

In the current study, 37.5% of all newly diagnosed patients in the current population met caseness criteria for psychological distress using the DT. This is comparable to other published literature where, using the same cutoff value, caseness ranged from 28% in newly diagnosed patients with glioblastoma with mean distress score of 2.15 (SD = 2.66) (11) to 52% in another PBT cohort at diagnosis (10). Similarly, Goebel et al. (38) assessed 159 patients with varied types of malignant and benign PBT, the majority of whom were diagnosed within the last 3 months. Using a higher DT cutoff of ≥6, 48.4% of patients were experiencing distress with 6.9 sources of cancer-related distress. DT scores were significantly associated with depression and anxiety as well as the reported number of concerns.

The findings of the current study confirm that levels of psychological distress as measured by the DT are high in patients with PBT. In patients overall, the DT score a mean of 3.15 (SD, 2.20) at initial diagnosis and a mean of 6.49 (SD, 2.61) at first tumor recurrence. In comparison, distress was higher in caregivers overall, with mean DT score at diagnosis of 5.34 (SD, 1.89) and 8.2 (SD, 1.47) in caregivers assessed at first recurrence.

The results presented here also highlight that psychological distress was particularly elevated in patients with HGG compared with low grade and benign tumor groups overall. Such a finding is intuitive, given the propensity for relatively rapid tumor recurrence and progressive functional decline, and is supported by other studies with similar conclusions (10, 11). Given the cross-sectional design of the current study and the small numbers of patient–caregivers dyads who were assessed with the DT at both diagnosis and again at first recurrence, it is not possible to make any conclusions about the longitudinal patterns of psychological distress.

There are a number of published studies that have attempted to describe the longitudinal patterns of psychological distress and/or mood disorder. Rooney et al. (12) sampled newly diagnosed glioma patients at three time points: T1 ($n = 154$ patients) shortly after starting chemo/radiotherapy, T2 ($n = 103$ patients) 3 months later, and T3 ($n = 83$ patients) 6 months later. Significant distress was present in 36.4% at T1, 35.9% at T2, and 33.7% at T3. Longitudinally, subjects with high distress at T1 (median DT score = 8) remained highly distressed at follow-up (T2 median = 8, T3 median = 7). Younger age, functional impairment, and concurrent major depressive disorder were independently associated with high distress with emotional difficulties among the most common causes of distress at all three time points. In a study by Keir et al. (6), 83 glioblastoma patients were arbitrarily divided into those who had survived less than or greater than 18 months. Of the LTS, 59% met DT ≥4 cutoff for distress compared with 49% of those diagnosed <18 months ago. This study concluded that regardless of LTS status, distress continued to be a part of the disease trajectory for many glioblastoma patients. This study also concluded that understanding the sources of distress in PBT patients would aid clinical teams in better developing targeted interventions to help address and reduce psychological distress (6).

The longitudinal time course of psychological distress and its relationship to other mood-related symptoms remains to be clarified. Kangas et al. (13) studied the effects of radiotherapy on the psychological [i.e., posttraumatic stress symptoms (PTSS)] and cognitive functioning of adults with PBT, who were assessed at two time points – pre-radiotherapy (T1) and 3.5 months post-radiotherapy (T2). Minimal differences in functioning were found between patients according to BT type (benign $n = 45$ versus malignant $n = 25$). Seventeen percent of the cohort reported clinically elevated PTSS at T1, which reduced to 13% at T2. Younger age (<65 years), reduced quality of life (QoL), and elevated anger symptoms at T1 predicted PTSS at T2, while having a benign BT, low PTSS, and depressive symptoms at T1 were predictive of improved QoL at T2. Lamperti et al. (14) analyzed 81 patients with recurrent central nervous system tumors and found that rather surprisingly the emotional well-being mean score was significantly higher in the recurrence sample than in patients with brain tumors at first diagnosis. Anxiety did not seem to be influenced by a relapse diagnosis; instead, depression was higher and differed significantly from normative data. Their data suggested that some patients retained highly preserved coping strategies for managing emotional distress despite intact judgment and disease awareness.

To our knowledge, the present study has reported DT findings in one of the largest cohorts of non English speaking neuro-oncology populations. Despite this, the current study did not find significant differences in DT scores between non English speaking and English speaking groups. It is appreciated that cultural diversity is a much more holistic concept than spoken language alone. Kayser et al. (39) undertook a systematic review of 148 psycho-oncology studies and reported that screening measures of distress had comparable reliability, sensitivity, and specificity for Caucasian, Latino, and Asian samples, but it was unclear if equivalent psychometrics could be found among minority ethnic groups (e.g., African American) and immigrants within countries. Donovan et al. (40) reported on 18 non English translations of the DT and found that although cutoff scores varied by language, country, clinical setting, and sample characteristics, a DT score of 4 maximized sensitivity and specificity. Ongoing research by McGrane et al. (41) in CALD populations has addressed the utility of a culturally competent multilingual unmet needs survey in cancer patients.

Findings from the current study substantiate existing studies reporting that PBT caregivers experience significantly elevated psychological distress (1, 16, 22, 42–44). In the current study, of the 32 caregivers screened at the time of initial PBT diagnosis, 78% met caseness criteria with DT ≥4. Furthermore, 100% (all 14 caregivers) met distress criterion at the time of first tumor recurrence.

Petruzzi et al. (45) assessed patients with the Hospital Anxiety and Depression Scale (HADS), Functional Assessment of Cancer Therapy – Brain (FACT-Br) and caregivers with HADS, Caregiver Reaction Assessment Scale (CRA), and the 36-Item Short-Form Health Survey (SF-36). They reported that most caregivers experienced more depressive and anxiety symptoms compared with patients. In addition, the clinical and psychological features of patients did not correlate with psychological patterns of their own caregivers. In another study by Brown et al. (46) addressing the serial QoL measurements of 197 PBT patients and their caregivers, there was better agreement between patient and caregiver scores when the QOL scores were higher. Such studies underscore the complex interrelationship between the emotional state of the PBT patient and their caregiver over time.

It is therefore relevant to consider potential reasons why caregivers might experience higher levels of psychological distress than patients at the time of diagnosis and at recurrence. Although clinical disclosure of tumor recurrence would always ideally occur in the presence of both the patient and their caregiver/s, it is possible that due to altered recall, insight, or changes in memory and other cognitive processes, the patient is not able to retain all the information and management plans disclosed. In practical terms, it is also not uncommon for caregivers to intentionally seek out additional prognostic information from the treating healthcare team in another confidential forum. Caregivers sometimes prefer to shield the patient from exchanges where poor prognostic news is relayed. Another possible contributing factor to distress is that caregivers may be faced with the additional decisions regarding palliative care options, increasing symptom (physical, cognitive) burden and financial stress.

Implications of Study Findings

The results presented here have a number of implications for clinical care of adults with PBT. Firstly, given the elevated levels of psychological distress in this cohort of patients and caregivers, it is imperative that they undergo systematic and routine psychological distress screening. Distress screening is considered a fundamental component of a holistic model for psychological services, which should contribute to the development of a treatment plan and appropriate and timely referrals and thus effective interventions (47).

Due to the projected trajectory of tumor recurrence in HGG patients, such screening, triage, and referral systems need to incorporate repeat screening over time for patients and caregivers at relevant points in the illness trajectory (i.e., diagnosis, recurrence, and the terminal phase). A population of PBT patients and their caregivers would be a potentially ideal group in which to adopt a tiered approach to psychological interventions, as outlined by Hutchison et al. (48), whereby the level of distress and expressed need is matched to an appropriate level of care. Such levels of care range from 1 (universal) for those with minimal or mild distress to supportive (2) and (3) extended care (mild to moderate distress), then increasing to (4) specialized and (5) acute care for those affected by moderate to severe psychological distress.

This then leads to the discussion of the workforce that could provide such care for this particular group of patients and caregivers. In Australia and New Zealand, the majority of cancer care coordinators come from a specialist nurse or allied health professional background (49). Given the rarity of primary malignant brain tumors, with just over 1,700 new projected cases of brain cancer diagnosed in 2014 in Australia, and an incidence of 7.2 per 100,000 (50), a neuro-oncology-specific care coordinator is understandably a very uncommon role and recurrent funding remains an ongoing challenge. The title and the constituents of the role varies considerably, as described in

Europe (51–53), North America (26), and other regions such as Israel (54). Some of the roles focus on cancer treatments (such as chemotherapy management) versus a more holistic model of supportive care throughout the entire care trajectory.

A neuro-oncology-specific care coordinator is well positioned to facilitate symptom and needs assessment, psychological support and referrals or intervention throughout the care continuum, and particularly so at predictable time points along the care journey where patients and caregivers are likely to experience higher distress levels. Due to the complexity, this role necessitates an experienced health practitioner familiar with the symptomatology, needs, and journey of a brain tumor patient. It is important that patient and caregiver needs are anticipated, proactively screened for and detected early, to ensure that timely intervention can occur. Furthermore, as many Australian cancer services will not routinely collect nor screen cases such as benign brain tumor patients (as their data are not typically collected by cancer registries), a neuro-oncology service should ideally have mechanisms to support this specific subgroup of PBT patients and their caregivers with a longer survivorship trajectory.

As most cancer services will not have the benefit of a dedicated, neuro-oncology-specific care coordinator, alternate models of service delivery will rely more fully on psycho-oncology staff and/or a programmatic system-wide approach for distress screening (55) and overall coordination of care by all members of the healthcare team. Given the rarity of PBT overall, there have been efforts to expand the knowledge and skillset and educate and train healthcare professionals regarding brain tumors as exemplified by the Australian initiative which included a specific online module about brain cancer (56). Tailored information provision and education is a vital component of the care coordination role (57, 58). In the setting of uncommon tumors, although there are now adequate English language resources covering most aspects of cancer care, there remains a paucity of translated high quality material in non English languages. The costs of translating existing resources remain another practical barrier.

There were several limitations of the current study. Firstly, DT data beyond the first tumor recurrence were not captured, and thus it is possible that patients and/or caregivers could have experienced even higher psychological distress levels during the terminal phase of care. Secondly, not all NESB participants and not all caregivers were able to be assessed – hence, it is unclear to what extent the caregiver sample and NESB sample were representative of the broader population. It is also acknowledged that the caregiver group was relatively small and thus results should ideally be verified in a larger sample. In addition, a notable proportion of benign PBT caregivers were not accessible for assessment due to the fact that benign PBT patients often attended clinical consultations alone.

Finally, it was not possible to compare the level of psychological distress and caseness between the four subgroups due to the differing composition of these groups. Rather, the current study was largely descriptive in summarizing DT data for four different groups in a clinical setting.

Finally, future research directions could include an investigation of the impact of screening for psychological distress at various time points upon the workflow of a cancer care coordinator. It would also be interesting to compare distress levels in patients and caregivers during phases in which there is evidence of disease stability, to better understand the support that is needed.

Conclusion

This study demonstrates the prevalence of elevated psychological distress in a neuro-oncology population of patients at diagnosis and at first recurrence and also in caregivers. The groups exhibiting the highest distress levels included patients with HGG, patients with disease recurrence, and caregivers. It is thus imperative that both patients and caregivers have access to timely, systematic care coordination and needs assessment as well as a skilled and knowledgeable healthcare team who can provide effective intervention and support across the care trajectory.

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Existential well-being and meaning making in the context of primary brain tumor: conceptualization and implications for intervention

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When faced with a significant threat to life, people tend to reflect more intensely upon existential issues, such as the meaning and purpose of one's life. Brain tumor poses a serious threat to a person's life, functioning, and personhood. Although recognized as an important dimension of quality of life, existential well-being is not well understood and reflects an overlooked area of support for people with brain tumor. This perspective article reviews the historical underpinnings of the concept of existential well-being and integrates this discussion with theoretical perspectives and research on meaning making and psychological adjustment to primary brain tumor. We then provide an overview of psychosocial support interventions for people with brain tumor and describe the findings of a recently published psychotherapy trial targeting existential well-being. Overall, this article highlights the importance of assessing the existential support needs of people with primary brain tumor and their family members, and providing different avenues of support to facilitate the meaning-making process across the illness trajectory.

Keywords: brain tumor, existential well-being, meaning making, psychosocial support, end-of-life

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Introduction

The threat to life associated with brain tumor frequently propels people to consider their own mortality and the meaning and purpose of life (1–3). Spiritual well-being broadly refers to one's sense of inner peace, connectedness to others, and reverence for life, and encapsulates both religious well-being and existential well-being (2, 4, 5). Spirituality may or may not entail formal religious practices, but relates more generally to people's propensity to seek meaning in their lives, grow, and transcend beyond the self (4). Existential well-being refers to a person's present state of subjective well-being across existential domains, such as meaning, purpose, and satisfaction in life, and feelings of comfort regarding death and suffering (6). People's confrontation or comfortability with such issues signifies their relative levels of existential well-being or distress (7).

Historical Underpinnings and Conceptualizations of Existential Well-Being

Existential well-being is rooted in the work of existential philosophers such as Kierkegaard and Nietzsche dating back to the nineteenth century (8, 9). *Existentialism* refers to overarching human concepts of personal freedom, suffering and death, and the pursuit of meaning and purpose (9). Existential perspectives focus on the structure of a person's experience and understanding of self

at the level of "being." The only reality of our existence is what we are conscious of and relate to ourselves in the moment (10). Heidegger (8) and Yalom (9) proposed that threat to life often propels individuals from an inauthentic *business as usual* state where one is unaware of the authorship of one's life, to a more authentic *mindfulness of being* state where existential themes are considered with greater intensity. Facing mortality may lead to a disequilibrium that provides opportunity for fundamental reconsideration of life values and the meaning of one's existence (9, 11).

Society's attitudes toward existential issues underwent great change during the twentieth century (9). Previous generations saw death as a natural part of life, or a cyclic event where generations followed generations and deceased ancestors would greet you after death. Today, many people experience a slower death with terminal symptoms and relatively few people have seen a dead person (12). Death and dying have been transferred from the home to a health care setting where there is usually greater emphasis on physical aspects of quality of life than psychosocial or existential aspects (12–14). Further, a decline in religious beliefs, including the concept of life after death, has not been replaced by philosophical alternatives. Therefore, many believe that death implies annihilation where one ceases to exist, contributing to existential distress (9, 12). Societal changes have meant that existential issues are scantly addressed or discussed in daily life. Consequently, people may not contemplate the meaning of life or death until their own life or a significant other's life is threatened (14). Death anxiety is common and typically relates to people's concerns about leaving loved ones, fear of premortal (e.g., pain and suffering) or postmortal (what occurs after death) possibilities, and fear of annihilation (9). Experiencing a threat to one's life can also propel people to question "have I lived the life I wanted to live?" and motivate them to embrace living (14).

The twenty-first century has seen a greater focus on existential well-being in the context of chronic illness, including conceptualization, measurement, and support needs (2–6, 15–22). Nevertheless, the concepts of spirituality and existential well-being have been referred to as ambiguous and difficult to study (5, 18). Some researchers view spirituality and existential well-being as core dimensions of health-related quality of life that are related to but distinct from physical, emotional, and social well-being domains (6, 18, 22). For example, Brady and colleagues (22) found that spirituality was uniquely associated with quality of life after controlling for physical, social/family, and emotional domains. Others have examined spirituality and existential beliefs as predictors of quality of life and emotional well-being (19, 20). Specifically, existential well-being has been described as an internal coping resource whereby people draw upon their beliefs to cope with stressful situations and improve their emotional well-being (5, 15). Despite different conceptualizations, a consistent finding in the cancer literature is that people with higher levels of existential well-being report lower emotional distress and better quality of life (15, 19, 21, 22).

According to Clarke and colleagues (23), distress in the context of medical illness refers to a range of affective, somatic, dissociative, and grief-related symptoms. They developed an empirically derived taxonomy of common distress syndromes in patients with diverse medical conditions. Differentiated by levels of demoralization, grief, and anhedonia, six main classes were identified, as follows: low distress, uncomplicated grief, moderate distress, anhedonic depression, demoralized grief, and demoralization. The classes with the highest levels of distress (i.e., anxiety and depression) were demoralization and demoralized grief. Demoralization was indicated by a sense of helplessness, hopelessness, and inability to cope, whereas people with demoralized grief additionally recognized a loss of some kind and showed grief-like reactions. Anhedonic depression was characterized by loss of interest and inability to experience pleasure. Importantly, their study indicated that depression with loss of interest and pleasure can occur in the absence of high levels of demoralization or grief (23), Clarke et al. (24) replicated these findings in a severe illness sample including people with metastatic cancers.

Several researchers have assessed both mood symptoms and spirituality and existential concerns in the context of cancer and brain tumor [e.g., Ref. (7, 18, 19, 22)]. Tools assessing spirituality and existential well-being typically include statements regarding feelings and beliefs (7, 18, 22). For example, the Functional Assessment of Chronic Illness Therapy-Spiritual well-being (FACIT-Sp) includes statements such as "I feel peaceful" and "I have a reason for living" [(18), p. 79]. Similarly, the existential well-being subscale of the McGill Quality of Life [MQoL (6)] asks people to rate their feelings and beliefs about life's purpose and meaning and the future (e.g., not afraid – terrified). Scores on these instruments signify people's relative levels of existential distress or well-being.

The experience of illness has been found to strengthen some people's spiritual beliefs or faith (1, 25). Alternatively, for others, the illness may challenge their beliefs about themselves, other people, and the world, and stimulate a search for meaning (25, 26). Existential well-being can be enhanced by *sense making*, or exploring how the event fits with one's worldviews, and *meaning making* or determining the significance of the event for one's life (27).

Meaning Making and Existential Well-Being After Brain Tumor

Primary brain tumor is a unique illness with the combined effects of cancer and brain damage. Therefore, brain tumor poses a threat to a person's life, functioning, and sense of self (12). People may mourn the loss of changes in their abilities, lifestyle, and years ahead of spending time with one's family and achieving goals. The impact of brain tumor on existential well-being has mainly been investigated using qualitative methodology [e.g., Ref. (1, 3, 12, 13, 28)]. These particular studies suggest that existential distress is common at different phases of the illness. Adelbratt and Strang (12) found that the possibility of death and an uncertain prognosis propelled some participants to question the meaning and purpose of life. Within these qualitative studies participants expressed fear about separation from family members, a loss of autonomy, and/or anxiety about the unknown. For example, *"I am afraid of vanishing away, and I think of that several times a week"* [(12), p. 503]; *"You sort of look forward and you wonder what's there"* [(1), p. 131–132].

Another theme emerging from some qualitative studies is the oscillation between hope and despair in the adjustment to brain tumor (12, 13). The struggle with death and dying was implicit

from contradictory statements. For example, in the study by Adelbratt and Strang (12), some participants denied being scared by death, but later disclosed that they were afraid of dying and that it was always on their mind. This oscillation was also described by Carvers et al. (13), who found that existential fears were frequently expressed alongside efforts to find meaning in the journey toward death; a state of flux also identified in the broader cancer literature (29, 30).

Existential issues and uncertainty about the future also represent major sources of stress for family members. In qualitative research, some caregivers reported fear and despair concerning their loved ones' prognosis, and low sense of security in their own lives (31, 32). Some caregivers also expressed that it was difficult to plan ahead due to worry about tumor progression, functional decline, and other set-backs such as seizures (31). In quantitative research, caregivers have been found to endorse high levels of depression (30%) and anxiety [40–60%; (33, 34)], and in one study they reported poorer quality of life than individuals with brain tumor (35).

A literature search conducted on spirituality or existential well-being and primary brain tumor using PubMed and PsycINFO identified two quantitative studies [one full article (7) and one conference abstract (36)]. Pelletier et al. (7) found that up to 50% of their brain tumor sample reported existential distress or death anxiety on the MQoL existential subscale (6). Greater existential distress was associated with poorer quality of life, fatigue, and depressive symptoms. Similarly, Randazzo et al. (36) found a significant positive association between spiritual well-being on the FACIT-Sp12 and health-related quality of life. In our own research (37), we found that levels of existential well-being on the MQoL did not differ according to tumor type, time since diagnosis, or neuropsychological status. However, older age, higher optimism, and lower perceptions of threat and increased perceptions of controllability were associated with greater existential well-being. The relationship between optimism and existential well-being was mediated by perceived controllability, suggesting that optimism is related to better existential well-being through perceptions of controllability. Further, global cognitive status moderated the relationship between optimism and existential well-being, whereby people with high optimism and poor global cognitive function had lower existential well-being than those with high optimism and good global cognitive functioning (37). Higher optimism may promote greater existential well-being by influencing illness appraisals (e.g., increasing focus on aspects that are controllable); however, for people with high optimism, global cognitive impairment may reduce their capacity to maintain a sense of purpose, meaning, and control in life.

The implications of existential fears and concerns for people with brain tumor and their caregivers are vast. Neglect of existential issues is proposed to contribute to despair, loneliness, and anxiety for those with a terminal illness, and may lead to people distancing themselves from loved ones and being distracted from enjoying the pleasures of life (28, 38, 39). Experienced alongside the physical, cognitive, and behavioral effects of brain tumor, existential distress amplifies the negative consequences of a life threatening illness (12, 28).

In contrast, examining the meaning and purpose of one's life can enhance people's psychological adjustment to brain tumor (1, 3, 12, 13). Adopting a "sense of coherence" framework, Strang and Strang (3) explored how people make sense of, cope with, and find meaning in their illness. Some participants generated their own theories and explanations for their illness to increase comprehensibility, and drew upon personal and social resources to increase their sense of control and manageability. Other participants expressed that they had strengthened their relationships and redefined life values and roles to find meaning (3). Other qualitative studies have reported similar themes in terms of enhanced relationships, redirecting the focus to living in the "here and now," and an increased sense of meaning and purpose in life (1, 12, 13). For example, a patient with glioma stated: *"I am looking here and I'm thinking, what are we pushing for all the time? Sometimes you should actually just sit back and enjoy what you've got and relax"* [(13), p. 378]. These accounts reinforce existential theorists' proposition that facing mortality provides an opportunity for reconsideration of life values (9, 10, 14).

Despite the evidence linking existential well-being with lower depression and better quality of life in the brain tumor (7, 36) and broader cancer (15, 19, 21, 22) literature, the supportive care of people with brain tumor often does not reflect this focus. Strang and Strang (28) found that while patients and their caregivers identified existential support as core to holistic care, existential issues were poorly understood by nurses. Nurses reported that patients' existential concerns were difficult to manage due to time restrictions, their own anxiety, and a lack of knowledge of existential support and related communication skills (3). Similarly, Carvers et al. (13) found that general practitioners' lack of resources, competency, and communication skills were perceived by patients as barriers to meeting their existential support needs. Communication guidelines for medical practitioners highlight the importance of calming peoples' fears, discussing the scientific aspects, addressing prognosis issues, forming a partnership with the patient and family, and focusing on their concerns (40). Although these guidelines underscore useful principles for communication, there is a need for support interventions focusing on existential well-being.

Existential Support Interventions in the Cancer and Brain Tumor Literature

Reviews in the broader psycho-oncology literature have identified various interventions addressing spiritual or existential support needs (41, 42). Henoch and Danielson (41) identified 18 intervention studies for people with cancer, which included hypnosis, individual and group psychotherapy, retreats, psychoeducation, physician counseling, and nurse training. Most of these interventions were multi-faceted with psychoeducation, coping skills, symptom management, and existential support components. A review of 16 positive psychology interventions in breast cancer (42) identified five main approaches, namely, mindfulness-based therapy, expression of positive emotions, spiritual interventions, hope therapy, and meaning-making therapy. Overall, these interventions were found to improve quality of life and different

aspects of psychological well-being (e.g., self-esteem, hope, sense of coherence), although methodological quality was variable (41, 42). Examples of controlled interventions focusing primarily on existential issues include cognitive-existential group psychotherapy (43) and meaning-centered group psychotherapy (44). A 20-week group cognitive-existential intervention for women with early-stage breast cancer was associated with significantly reduced anxiety and greater satisfaction with therapy relative to a relaxation only control group (43). The 8-week meaning-centered intervention for people with advanced cancer was associated with significantly greater gains in spiritual well-being and sense of meaning compared to supportive group psychotherapy (44).

A systematic review of supportive care interventions for brain tumor (45) identified mainly case-level descriptions of programs or services providing existential support, such as nurse-led telephone support (46, 47), brain tumor support groups (48), and multi-disciplinary palliative care services (49, 50). Neuro-oncology nursing practitioners have specialized training and expertise in coordinating care throughout the illness trajectory. A vital part of their role entails providing existential support to facilitate adjustment to diagnosis, treatment, and end-of-life issues (51). Our previous research (1) suggested that many people appreciate the opportunity to discuss existential fears and concerns early in the illness rather than support only being offered toward the end of life. This is particularly important given that functional decline associated with a progressive neurological condition can greatly compromise people's cognitive and communication skills (52).

In contrast to the broader psycho-oncology literature, the main focus of controlled supportive care interventions for brain tumor has been on rehabilitation of physical and cognitive impairments (53). These studies generally support the benefits of rehabilitation for improving cognitive and functional status (53–55); however, gains in mental health and quality of life were not evident after rehabilitation. Furthermore, existential and spiritual dimensions of well-being were not typically focused on or assessed.

The Making Sense of Brain Tumor Program

To address a major gap in the brain tumor intervention literature, Ownsworth and colleagues (56) developed the "Making Sense of Brain Tumor" (MSoBT) program and evaluated its efficacy in a randomized controlled trial. Conducted in people's own homes, the 10-session psychotherapy program was guided by the sense of coherence framework (3) and goal-directed. A key focus of the program was on meaning making or supporting people to understand the personal significance of the illness in their own life situation [see Ref. (56)].

Of the 50 people who commenced the program, 44 completed all 10 sessions. After controlling for pre-treatment differences, the MSoBT intervention group reported significantly lower levels of depression, and higher levels of existential well-being (MQOL), functional well-being, and global quality of life at post-assessment than the waitlist group. Significantly lower levels of depression and stress, and higher existential well-being and quality of life were also reported at 6-months follow-up relative to pre-intervention. Importantly, program outcomes did not vary according to tumor type or global neuropsychological status. Having a family member involved in the program was associated with lower levels of depression and better social/family well-being at post-intervention (56). Further, improvement in existential well-being was related to higher levels of therapeutic alliance. These findings highlight that the social context in which people search for meaning and cope in their illness is essential to consider.

Summary and Future Research Directions

Research indicates that people with brain tumor often experience existential fears and concerns. Unlike the broader cancer literature (41, 42), there are few evidence-based approaches for enhancing existential well-being for this population. The findings of the MSoBT trial (56) indicated that a home-based psychotherapy intervention was effective for improving mood, existential well-being, and quality of life. Providing in-home therapy enabled people with significant physical and cognitive symptoms, and lack of transport, to participate. However, the feasibility and utility of remote access intervention modes (e.g., tele-health) needs to be evaluated. Research by Ownsworth et al. (57) indicated that family caregivers may have both distinct and interrelated support needs. Hence, development of family-system interventions that combine individual, couple, and family-based sessions remain a priority for this population. Furthermore, peer-support interventions may have psychological and social benefits for the neuro-oncology population, such as reducing social isolation, and enhancing morale for the future (48).

Working with people with a terminal illness who experience progressive functional decline can be very challenging, as the topic of death and dying can be an area of disquiet for many health professionals (28). Although professional guidelines for effective communication have been developed (40), further resources and training programs focusing specifically on existential support would be beneficial to enhance the skills and self-efficacy of neuro-oncology practitioners. As highlighted by Strang and Strang (3), most people with brain tumor have spiritual and existential beliefs that support them to find meaning in their illness. Having the opportunity to express one's fears and values about life and death in a safe and supportive context can make a profound difference to a person's sense of inner peace and hope for the future.

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Feasibility and utility of telephone-based psychological support for people with brain tumor: a single-case experimental study

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Rates of psychological distress are high following diagnosis and treatment of brain tumor. There can be multiple barriers to accessing psychological support, including physical and cognitive impairments and geographical limitations. Tele-based support could provide an effective and more flexible option for delivering psychological interventions. The present study aimed to investigate the feasibility and utility of a telephone-based psychotherapy intervention for people with brain tumor. A single-case multiple-baseline design was employed with a 4–7-week baseline phase, 10-week treatment phase, and 5-week maintenance phase including a booster session. Four participants with a benign or malignant brain tumor (three males and one female; aged 34–49 years), received 10 sessions of tele-based therapy and a booster session at 4 weeks post-treatment. Levels of depression, anxiety, and illness cognitions were monitored on a weekly basis throughout each phase whilst measures of quality of life, stress, and self-concept were administered at the start and end of each phase. Weekly measures were analyzed using a combination of both visual analysis and Tau-*U* statistics. Of the four participants, two of them demonstrated significant gains in mental health (depression and/or anxiety) and a significant decrease in their levels of helplessness ($p < 0.05$). The other two participants did not show gains in mental health or change in illness cognitions. All participants reported improvement in quality of life post-treatment. The results of the study provide preliminary support concerning the feasibility and utility of tele-based therapy for some people with brain tumor. Further research examining factors influencing the outcomes of tele-based psychological support is needed.

Keywords: neuro-oncology, brain tumor, psychological distress, psychotherapy, telephone-based support, counseling

INTRODUCTION

Levels of psychological distress following brain tumor diagnosis are high, with 41–47% of people found to experience depression or anxiety beyond the primary treatment phase (1). There are numerous practical barriers to people accessing face-to-face (FTF) psychological support, including cognitive and physical difficulties, costs, and geographical distance. Despite this, there is very limited research on the feasibility and efficacy of flexible delivery modes of psychological intervention (e.g., telephone, internet).

Depression has been found to be consistently related to poor quality of life for people with brain tumor (2–6). Some symptoms of depression are likely to arise directly from the biological effects of the tumor and its treatment (e.g., weight loss, sleep disturbance, concentration difficulties). Other symptoms may develop in reaction to the threat to life and stressors associated with functional impairments and activity restrictions (7). In particular, people with brain tumor experience a prominent sense of threat and uncertainty about the future (8). For example, people with low-grade glioma may live with relatively mild neurological symptoms for many years and be able to perform normal occupational activities until the disease progresses and their functional state declines. Conversely, people with a Grade IV glioma may not be able to resume occupational roles and they often face a much shorter life expectancy with rapid functional decline.

Adelbratt and Strang (9) identified a common theme of "death anxiety," which referred to the preoccupation with threat to life experienced by the person with brain tumor and their next of kin. Symptoms and gradual loss of functions were seen as metaphors of dying and death (9). These illness appraisals can impact both physical and psychological health (10). Higher levels of psychological distress are generally associated with perceptions of high threat or helplessness and low levels of controllability or self-efficacy regarding coping (11). For example, people with higher perceptions of threat and lower perceptions of controllability 2 weeks after stroke had poorer psychological adjustment at 6 months post-stroke (12).

With the combined effects of brain injury and cancer, brain tumor poses some unique stressors. Cancer is often considered uncontrollable and highly threatening, with limited potential for benefit (10, 13, 14). Most people experience tumor re-growth or progression and functional decline. The physical, cognitive, and behavioral impairments associated with the tumor and its treatment lead to increased dependence on others, relationship strain, and inability to resume valued activities (e.g., driving and work). Experiencing a sense of threat and low controllability

in combination with severe functional impairments can have a devastating impact on quality of life.

Antonovsky's (15) sense of coherence (SOC) model has been applied to understand how people strive to maintain well-being in the context of adversity. The SOC model proposes that three components, namely, comprehensibility (understanding of what is happening), manageability (perceived ability to access resources to cope), and meaningfulness (capacity to find meaning within the situation) influence people's psychological and physical well-being. In support of this model, stronger SOC has been found to be protective against the development of depression and anxiety in people with cancer and their partners (16). Further, there is evidence to suggest that SOC can be enhanced through intervention (17, 18).

Closely related to the concept of SOC, Salander et al. (19) found that people with malignant glioma varied in their "time of everyday life," or level of engagement in activities that were similar to those prior to their diagnosis, and "time of disease" or extent to which they were occupied with the disease and its treatment. One-third of working age patients described a loss of life continuity, only experiencing "time of disease"; these patients reported an absence of everyday living. The remaining two-thirds of individuals were found to have spent a period focusing on "time of life" before they progressed to "time of disease." "Time of life" included work, hobbies, and activities of daily living which serve to maintain a sense of connection to everyday life, and foster hope, not of a cure, but of a remaining life not dominated by disease and death.

Overall, this research highlights that interventions focusing on making sense of, finding meaning, and participation in meaningful "time of life" activities have the potential to enhance psychological adjustment and quality of life after brain tumor. Despite the well-recognized need for psychological support for people with brain tumor and their families, there is limited published research on the efficacy of interventions (4, 8, 20–22). Controlled trials of psychological interventions for people with cancer have typically excluded people with brain tumor or those with cognitive dysfunction (23–25), thus limiting the capacity to generalize findings from the general cancer literature.

A review of counseling and rehabilitation interventions for adults with brain tumor identified 13 studies, which included 6 case studies or case series (see **Table 1**), 4 RCTs, and 3 pre-post group studies with no control group (see **Table 2**). Overall, there was evidence of gains in psychological well-being from case studies. However, although the controlled trials of cognitive rehabilitation demonstrated some gains in cognitive functioning and strategy use (21, 26, 27), such gains did not extend to psychological well-being or quality of life. This suggests that rehabilitation focusing on cognitive impairments may not be sufficient to improve broader psychosocial well-being. Promisingly, a recent study protocol (28) described a study underway that is investigating the efficacy of internet-based guided self-help for people with glioma with mild to moderate depression.

The first RCT of a psychotherapy intervention for people with brain tumor was conducted by Ownsworth and colleagues (37). The 10-session Making Sense of Brain Tumor (MSoBT) intervention ($n = 50$) was home-based, goal-directed, and guided by principles of the SOC model. Although the focus of support was mainly on the person with brain tumor, involvement of family members was strongly encouraged and 60% of programs involved a family member who attended 1–10 sessions. An evaluation of post-intervention outcomes identified that participants with brain tumor experienced significantly lower levels of depression and higher levels of existential well-being and global quality of life relative to wait list controls. At the 6-month follow-up, participants were found to have significantly better psychological well-being than prior to the intervention (37).

Despite the promising psychological outcomes of the FTF MSoBT intervention, the program was both time and cost intensive. The authors identified that to maximize participant engagement, practitioners often drove over an hour to provide an

Table 1 | Summary of case studies evaluating psychological interventions for people with brain tumor.

Reference	Intervention	Tumor characteristics	*n*	Intervention outcomes
Rao and Bieliauskas (29)	Psychological (16 couple sessions) and cognitive retraining (16 sessions)	Grade II–III	1	Improvements in neuropsychological functioning and behavior (e.g., social interactions, leisure, driving skills), and efficiency on work tasks
Sherer et al. (30)	Cognitive and vocational rehabilitation in clinic and community setting	High grade	13	Gains in independence for six participants (six remained the same, one declined) and productivity for eight participants (four remained the same, one declined) which was maintained at 8-month follow-up
Kowal et al. (31)	Emotion-focused couples therapy (12 sessions)	Low grade	1	Description of positive psychological outcomes
Tepper (32)	Psychosocial support	High grade	4	Description of positive psychological outcomes
Duval et al. (33)	Cognitive and ecological rehabilitation (26 sessions), information meetings (two sessions)	Grade II	1	Improvement in working memory at 3-month follow-up with generalization to everyday life
Whiting et al. (34)	2-h session of psychoeducation, communication, and relaxation skills training	Grade II	1	Decrease in target behavior and increase in knowledge of strategy use

Table 2 | Summary of group studies evaluating psychological interventions for people with brain tumor.

Reference	Intervention	Design and sample characteristics	*n*	Intervention outcomes
Locke et al. (21)	12 sessions of cognitive rehabilitation (CR) and problem-solving therapy vs. standard medical care	RCT; mixed grades	19	Positive feedback from people with brain tumor and caregivers on the program; 88% used compensation strategies and 88% found the intervention helpful. No significant differences on quality of life (QOL), functional capacity, mood, or fatigue between control and intervention group at 3-month follow-up
Gehring et al. (26)	CR (retraining and compensation, six sessions); 3-month telephone-based booster	RCT with waiting list; Grade II and III	140	Significant effects at post-treatment for subjective cognitive function and perceived burden; not maintained at 6-month follow-up. At 6-month follow-up, significant gains on tests of attention and verbal memory and improvements with mental fatigue
Hassler et al. (35)	10 sessions of group cognitive training (attention, verbal, and memory skills) over 12 weeks	Pilot study with no control group; Grade III and IV	11	Significant improvement in verbal memory at post-intervention
Zucchella et al. (27)	16 sessions of CR for 4 weeks	RCT; mixed grade	58	Significant improvement in cognitive functioning at post-intervention
Khan et al. (36)	Individualized social support program: interview plus peer support or community education/counseling	Prospective longitudinal pre-post design; mixed grade	43	Significant improvements in psychological functioning, physical QOL, coping strategies, functional, and cognitive independence at 6-week follow-up. Gains in anxiety, stress, and QOL were not maintained at 6-month follow-up, although broader psychosocial gains were maintained long-term
Ownsworth et al. (37)	10 sessions of home-based psychotherapy	RCT with wait list; mixed grade	50	Significantly reduced depression and improvements in existential well-being and QOL at post-intervention and 6-month follow-up

intervention for the person with brain tumor and his or her family members (37). Such travel time may not be feasible for service delivery within the community. Furthermore, due to travel time, the program was restricted to people living within a major metropolitan area. To reduce such barriers to accessing psychotherapy, tele-health may be an option for service provision.

Telephone-based and internet interventions are increasingly being utilized to reduce barriers to accessing psychotherapy. A meta-analysis by Andersson and Cuijpers (38) for internet and other computerized psychological treatments for depression found a moderate to large average effect size ($d = 0.41$) across 12 studies. The authors noted that the studies that provided some form of direct therapist support to participants (e.g., email, telephone contact, or additional FTF contact) yielded larger effect sizes ($d = 0.61$). Hammond and colleagues (39) compared the clinical and cost-effectiveness of FTF and over-the-telephone (OTT) low-intensity CBT interventions for mild to moderate anxiety and depression ($n = 4{,}106$). They found that outcomes of the OTT and FTF interventions were comparable, with the exception of those with more severe illness, where FTF was found to be more effective. The service costs of OTT were found to be approximately one-third lower than FTF sessions (39). The researchers proposed that OTT interventions are a convenient and effective mode of delivery for those requiring low-intensity interventions (39).

From a practical perspective, tele-based therapy may result in lower attrition and greater access to psychological therapy for people restricted by mobility or geography. In a meta-analysis of FTF therapies between 2000 and 2010, Swift and Greenberg (40) reported mean attrition rates of 19.7%. In contrast, Mohr and colleagues (41) found that the mean attrition rate across 12 RCTs of tele-based psychotherapy for depression was only 7.6%. Tele-based psychotherapy has been shown to be effective for improving emotional adjustment for people with multiple sclerosis (42), HIV-AIDS (43), depression (44), and traumatic brain injury (45). Such findings support the potential utility of telephone-based psychotherapy for people with a brain injury.

Whilst tele-based therapy may increase the opportunity for people with brain tumor to access psychotherapy, neuropsychological impairments such as language difficulties, memory problems, distractibility, and difficulties with sustained attention may pose a barrier to engagement and efficacy for treating mood problems. Psychotherapy relies upon on verbal communication, including understanding of spoken and written information. Tele-based therapy does not allow for the use of visual aids and techniques (such as diagrams or handouts) to support understanding of concepts. Instead, there is reliance on auditory communication in terms of both verbal and non-verbal responses (e.g., sighs, crying, and laughing), which may affect the therapeutic alliance (46). Telephone-based therapy also has the increased potential for interruptions and distractions, particularly when conducted in the person's home. In addition, family members may have more difficulty engaging in the therapeutic process. Therefore, an evaluation of the feasibility and utility of telephone-based therapy for people with brain tumor is clearly warranted.

Accordingly, the broad aim of the present study was to evaluate the feasibility and utility of a telephone-based psychotherapy intervention for people with brain tumor. The present study seeks to extend on the previous FTF MSoBT intervention for people with brain tumor (37). An additional booster session was included 2 weeks after the 10-session program to support maintenance and generalization of gains (47). In relation to utility, it was hypothesized that telephone-based psychotherapy would result in a significant decrease in levels of depression, anxiety, and hopelessness between the baseline and treatment phase (as measured weekly), which would be maintained at 5 weeks follow-up. Additionally, it was hypothesized that there would be a significant increase in levels of acceptance and perceived benefit between the baseline and treatment phase (as measured weekly), and that these gains would be maintained at 5 weeks follow-up. Broader gains in quality of life and self-concept were also assessed.

MATERIALS AND METHODS

DESIGN

A single-case experimental design (SCED) with multiple baselines across participants (see **Figure 1**) was used to examine the impact of a telephone-based therapeutic intervention on psychological well-being. Single-case methodology is beneficial when evaluating a new treatment in conditions that are rare, in which it is difficult to obtain large samples with homogenous characteristics. The design entails repeated measurements of functioning over time to evaluate the impact of treatment relative to the baseline period (48).

Multiple-baseline designs reduce the likelihood of extraneous, potentially confounding factors influencing the results (49, 50). Beeson and Robey (51) recommended a minimum baseline of three data points to control for threats to validity. Utilizing repeated observation prior to the commencement of the intervention allows for analysis of trends in the data both within and between phases. In the present study, there was a minimum of four baseline data points (random allocation P1) and a maximum of seven baseline data points (random allocation P4), prior to the 10 treatment sessions. Participants were randomly allocated to baseline length (four, five, six, or seven) using a pre-determined randomized computer sequence with concealed allocation of numbers placed in sealed opaque envelopes (50).

PARTICIPANTS

In the earlier MSoBT program [see Ref. (37)], individuals with primary brain tumor were recruited through major hospitals, neurosurgery clinics, and community services supporting people with cancer and brain injury. When the FTF MSoBT program ceased recruitment, participants inquiring about the initial program after July 2012 were referred to the telephone-based program. Adults with a primary brain tumor were eligible to participate in the study, irrespective of their tumor type and status. Participants were eligible from across Queensland. Participants undertaking current psychological interventions related to the effects of their brain tumor were not eligible to participate. Very severe cognitive deficits or receptive and/or expressive language deficits were considered likely to preclude telephone-based assessment or therapy. A telephone-based cognitive assessment tool was used to screen for cognitive and language deficits to determine eligibility. Additional eligibility criteria included ongoing access to a telephone, availability for weekly telephone assessment and therapy over a 20–24-week period (inclusive of baseline, treatment, and maintenance phases), and no significant hearing deficits that would preclude the use of a telephone.

A sample of four participants was considered an appropriate number for a SCED with the length of baseline varying from 4 to 7 weeks. The demographic and medical characteristics of the four participants (Mark, John, Robyn, and Samuel) are summarized in **Table 3**. More details of the health, cognitive, and psychological status of each participant is provided in the Section "Results."

MEASURES

Cognitive screening

In the initial telephone session, participants completed the brief test of adult cognition by telephone [BTACT; (52)] to screen for very severe cognitive deficits that were considered likely to affect people's capacity to engage in the intervention program. The BTACT is a brief (20 min) test of auditory attention, processing speed, memory, verbal fluency, and reasoning. In this study, five of the seven subtests were completed as follows: Word List Recall, Digits Backward, Category Fluency, Backwards Counting, and Short-Delay Recall. The BTACT has sound psychometric properties and has been validated in the general population ($n = 4268$).

Results on the BTACT indicated that Samuel performed in the "below average" range relative to age norms on measures of immediate and delayed memory, verbal fluency, and processing speed. Robyn's scores indicated "below average" performance on a delayed verbal memory task and Mark's scores indicated "below average" performance on a verbal fluency task. John's performance was in the "average" range for all five domains. Although Samuel demonstrated age-related impairments on four cognitive tasks (i.e., >1 to <2 SD below the norms), he was considered to have

Phase	A						B			C					
P1				x	x	x	x + T1	…	x + T10	x	x	x	x + T11	x	x
P2			x	x	x	x	x + T1	…	x + T10	x	x	x	x + T11	x	x
P3		x	x	x	x	x	x + T1	…	x + T10	x	x	x	x + T11	x	x
P4	x	x	x	x	x	x	x + T1	…	x + T10	x	x	x	x + T11	x	x

FIGURE 1 | Multiple baselines across participants design [A, baseline; B, treatment; and C, maintenance and booster (T11) session].

Table 3 | Summary of participants' demographic and health characteristics.

Characteristics	Mark[a] (P1)	John[a] (P2)	Robyn[a] (P3)	Samuel[a] (P4)
Age (years)	43	34	49	40
Gender	Male	Male	Female	Male
Highest level of education	Post-secondary school diploma	Secondary (high school)	Undergraduate degree	Undergraduate degree
Current employment	Part-time	Part-time	Full-time	Full-time
Current relationship status	Divorced, no children	Married, three children	Divorced, two children	Single, no children
Time since diagnosis	13 years	2.5 years	3 months	16 years
Brain tumor type	Cystic astrocytoma	Anaplastic astrocytoma	Pituitary tumor	Oligoastrocytoma
Tumor malignancy	Grade I	Grade III	Grade I	Grade II
Brain tumor location	Hypothalamus/optic pathway	Left temporal lobe	Pituitary gland	Left temporal lobe
Treatment/s	Surgery Radiotherapy	Surgery Radiotherapy chemotherapy Anti-convulsants	Surgery Hormone replacement therapy	Surgery Radiotherapy chemotherapy Anti-convulsants
Geographical location	Regional	Regional	Metropolitan	Metropolitan
Ability to drive	Yes	Yes	No	No

[a] *Pseudonym used to protect participant's identity.*

adequate cognitive functioning to undertake a telephone-based therapy program.

Psychological outcomes

At the start and end of each phase, participants completed the full set of self-report measures, including the 21 item Depression, Anxiety, and Stress Scale [DASS-21; (53)], Generalized Anxiety Disorder Scale [GAD-7; (54)], FACT-Brain (55), Illness Cognition Questionnaire [ICQ; (10)], and Continuity and Discontinuity of Self Scale [CDSS; (56)]. The brief set of outcome measures for session-by-session assessment included the depression scale of the DASS-21, GAD-7, and ICQ. The Session Rating Scale [SRS; (57)] was completed after every therapy session (from session two onward) to assess therapeutic alliance.

Mood state. The seven-item depression subscale of the DASS-21 was designed to assess symptoms of depression and has been validated for use with people with brain tumor (7). The clinical cut-offs are: normal, ≤9; mild, 10–13; moderate, 14–20; severe, 21–27; and extremely severe, ≥28. The GAD-7 is a measure of symptoms of generalized anxiety disorder which has been validated in primary care settings (54) and the general population (58). The clinical cut-offs for the scale are: normal, <5; mild, 5–9; moderate, 10–14; and severe, ≥15.

Illness cognitions. The ICQ is an 18-item measure of illness cognitions for people with chronic disease (10). It was modified in this study so that items applied to brain tumor (i.e., the word "illness" was replaced with "tumor"). The subscales measure helplessness (e.g., "*Because of my tumor, I miss the things I like to do most*"), acceptance (e.g., "*I can handle problems related to my tumor*"), and perceived benefits (e.g., "*Dealing with my tumor has made me a stronger person*"). Higher scores indicate increased levels of helplessness, acceptance, or perceived benefits.

Quality of life. The FACT-G (33 items) is comprised of four subscales that assess physical, social/family, emotional, and functional well-being aspects of health-related quality of life (55). An additional subscale developed by Weitzner and colleagues (59) assesses brain-related concerns. Higher scores indicate increased quality of life, with scores ≥0.5 SD below the norms ($M = 80.1$, SD = 18.1) indicating low quality of life (55).

Self-concept. The CDSS (24 items) assesses discontinuity of self (e.g., "*I sometimes give up on something because it is too much trouble*"), continuity of self (e.g., "*I have control of my life*"), and continuity with others (e.g., "*I feel accepted by others*"). Higher scores indicate greater levels of discontinuity of self (range = 1–36) or continuity of self (range = 1–15) and continuity with others (range = 0–21). Originally developed for the stroke population, the CDSS was considered suitable for use with people with brain tumor based on research indicating that sense of self and life continuity can often be disrupted (19).

Therapeutic alliance. The SRS, Version Three (57) was converted to an 11-point scale (e.g., 0,"I did not feel heard, understood, and respected" to 10,"I felt heard, understood, and respected") to assess: (1) quality of the relational bond, (2) agreement between the individual and therapist regarding the goals, and (3) agreement on the method and approach used.

PROCEDURE

Ethical clearance was obtained from the Griffith University Human Research Ethics Committee (PSY/37/10/HREC) as part of the larger MSoBT project. During the initial screening process, demographic and medical information was obtained from participants (e.g., tumor type, time since diagnosis, age, gender, and employment status). Participants were provided with details about the

study OTT and through written information posted to them. Participants returned a signed consent form prior to commencing the study.

Participants were randomly allocated to one of the four baselines lengths. Numbers (4–7) corresponding to the length of baseline were placed in sealed opaque envelopes and then randomly ordered. The envelopes were opened in consecutive order as each participant entered the study. Prior to commencing the initial assessment, participants were posted a booklet of the outcome measures for ease of administration. The booklet also contained a copy of the consent form, SRS, and plastic sleeves for participants to store any notes they made. The booklet was divided into sections for ease of use.

After allocation, the researcher conducted the initial assessment session, which included the BTACT and full set of outcome measures. Participants were assessed on a weekly basis on a brief set of outcome measures ("brief") for the duration of their allocated baseline (see **Figure 2**). Prior to the commencement of therapy, participants were re-administered the full set of outcome measures, with the exception of the BTACT. During therapy, participants completed the brief set of outcome measures at the start of the telephone call, just prior to therapy. Participants subsequently completed 10 sessions of individual telephone-based therapy with an additional booster session 4 weeks after their completion of the 10 sessions.

The SRS was completed after each telephone-based therapy session from session two onward, including the booster session. The full set of outcome measures was re-administered after the completion of the 10 telephone-based therapy sessions and again at the end of the maintenance phase, 6 weeks later, as seen in **Figure 2**.

THERAPEUTIC INTERVENTION

Consistent with the FTF program, 1 h telephone therapy sessions comprised of both core (sessions 1, 2, and 10) and individualized components, with the latter tailored to each participant's specific therapy goals and life circumstances. During the initial session, participants described their experience of symptom onset, diagnosis, treatment, and the impact of the tumor and its treatment on daily living (i.e., "telling my story"). Session two explored personal values and associated goals and priorities. From the information gained and rapport built during sessions one and two, three to five therapy goals were collaboratively set. Goals most typically related to understanding the effects of the brain tumor, learning strategies to manage negative emotions and cognitive difficulties, improving relationships, and increasing social participation and healthy lifestyle behaviors.

The tenth session summarized the main content of prior therapy sessions and involved reflecting on gains and progress. A plan for maintaining skills and managing set-backs was also a focus of the session. The booster session also focused on maintenance of strategy use and skills generalization and discussed issues associated with termination of therapy.

Individual treatment modules included: psychoeducation on the brain and brain tumor, cognitive rehabilitation and associated strategies (e.g., memory and organization), cognitive-behavior therapy, psychoeducation on emotional and behavioral changes (e.g., symptoms of anxiety, depression, and panic attacks), mindfulness techniques (e.g., mindful eating, present focused awareness), pleasant activity scheduling, relaxation techniques (e.g., progressive muscle relaxation, abdominal breathing), couple and family support (communication, problem-solving), and existential and end-of-life discussions (i.e., family care plan).

DATA ANALYSIS

The analysis of the weekly repeated measures was conducted via a combination of visual inspection, and a Tau-*U* tool [singlecaseresearch.org; (60, 61)]. Steps to data analysis for the weekly measures included: checking relevant assumptions for SCED, analysis of baseline stability, and case-level analysis, including evaluation of treatment effects within phase. Data on broader subjective well-being measures was not subject to statistical analysis due to insufficient data points.

The Tau-*U* is a statistical approach derived from the Kendall Rank Correlation and Mann–Whitney-*U* tests, providing a combined index of non-overlapping data between two conditions (phases) and examination of trends both within and across phases. This type of analysis has been recommended for simple AB designs with particular strengths in controlling for baseline trend and variability, ceiling and floor effects, and has sensitivity to phase change when data have been collected over a short period of time, irrespective of baseline length (60). The Tau-*U* allows for analysis of baseline stability (A) and controls for trend. The analysis provides

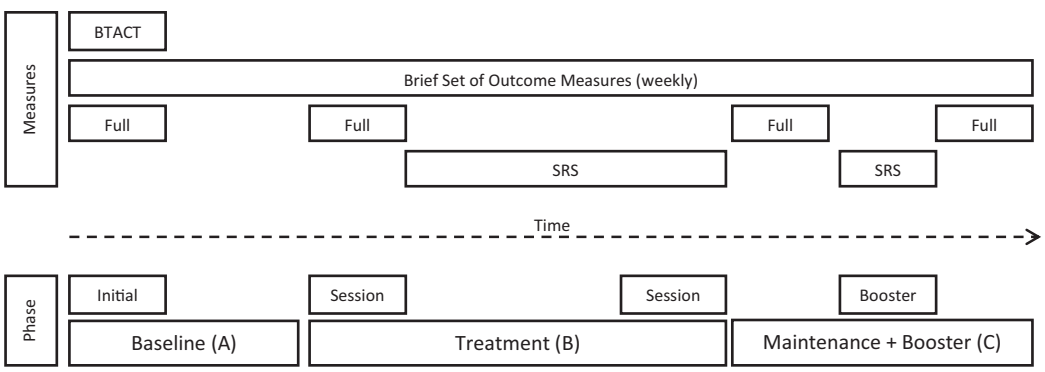

FIGURE 2 | Phases of the intervention program and assessment time points (SRS, Session Rating Scale).

a more accurate evaluation of non-overlap or "dominance" of one phase over another (AB) than mean or median differences. The Tau-*U* has been found to have good statistical power for short data series and is robust to outliers or extreme scores (60). Tau-*U* is also relatively resistant to the effects of autocorrelation or serially correlated residuals, as demonstrated through field testing of 382 published data series, comparing the results before and after cleansing for autocorrelation (60).

Visual analysis allows for inspection as to whether there has been an observable change on the dependent variable by an intervention (62, 63). This method was used in conjunction with Tau-*U*, clinical cut-offs, and normative data.

RESULTS

ANALYSIS OF BASELINE STABILITY

Three participants consistently scored within the clinical range for depression during the baseline phase, albeit there was some variability. As shown in **Figure 3**, Mark and Robyn's scores varied between "moderate" and "severe" levels whilst John and Samuel's scores ranged from "normal" to "severe." There was also variability in anxiety scores for all four participants (see **Figure 4**). Mark's scores ranged between the "normal" and "mild" range. John and Samuel's scores varied between "mild" and "severe" levels of anxiety, whilst Robyn's scores were in the "moderate" to "severe" range during the baseline phase. Three participants had scores consistently within the clinical range for anxiety during the baseline phase. Visual inspection of the ICQ data in **Figure 5** indicated most variability on the helplessness scale for Mark and on the acceptance scale for John and Samuel. Robyn's scores on the three ICQ scales appeared relatively stable.

CASE DESCRIPTIONS AND EVALUATION OF TREATMENT EFFECTS

Mark

Mark had been diagnosed with a Grade I cystic astrocytoma near the hypothalamus 13 years ago. He was diagnosed after undergoing a routine pre-employment medical assessment overseas, which identified visual difficulties. He was told that he did not have long to live and was advised against further medical treatment. After further research into treatment, Mark underwent radiotherapy, which reduced the size of the tumor, and he subsequently had a partial resection. Since diagnosis, Mark reported a change in his personality and anger outbursts. His marriage broke down during the earlier years after his diagnosis and he has since had difficulty making friends and forming relationships. He reported some strained relationships with his family and a major loss when his mother died. He also reported ongoing difficulties with balance and strength (impacting on recreational activities) and a skin condition that affects his self-esteem and confidence. Mark was referred to the program by a family member who was concerned about how he was coping.

An analysis of the baseline phase identified no significant trend in DASS depression levels (Tau-$U = 0.5$, $p = 0.308$). A comparison of between phase variability (AB) indicated no significant difference between the baseline and treatment phases (Tau-$U = -0.1$, $p = 0.777$). Mark's scores were consistently in the clinical range for depression ("mild" to "moderate") with a notable increase between baseline assessments two and three (see **Figure 3**). During treatment, depressive symptoms were reduced between sessions two and three, with a subsequent increase in symptoms from sessions four to seven (i.e., "extremely severe" range). After session eight, his depression levels reduced to the "mild" range, until the end of treatment. During the maintenance phase, Mark's depression scores varied between the "normal" and "moderate" ranges.

There was no significant trend in Mark's GAD-7 anxiety levels in the baseline phase (Tau-$U = 0.5$, $p = 0.308$). Phase comparison (AB) indicated no significant difference between baseline and treatment phases (Tau-$U = 0.625$, $p = 0.077$). During the baseline, treatment, and maintenance phases, Mark's anxiety levels ranged between "normal" and "mild" levels (see **Figure 4**).

On the ICQ, there was no significant trend in Mark's baseline phase for levels of helplessness (Tau-$U = 0$, $p = 1$), acceptance (Tau-$U = 0.333$, $p = 0.497$), or perceived benefit (Tau-$U = -0.167$, $p = 0.734$). Phase comparison for helplessness identified no significant difference between baseline and treatment phases (Tau-$U = -0.325$, $p = 0.358$). Yet, over the course of treatment and maintenance phases, a gradual reduction in helplessness was observed (see **Figure 5**). Phase comparisons for levels of acceptance and perceived benefit were found to be significant between the baseline and treatment phases (Tau-$U = -0.85$, $p = 0.016$; Tau-$U = -0.9$, $p = 0.011$). Contrary to the hypothesis, Mark's level of acceptance and perception of benefits associated with his brain tumor declined during the treatment phase.

On the measures of broader subjective well-being, Mark's scores on the FACT-G improved during the baseline period (as shown in **Table 4**). This improvement mainly occurred on the social/family and functional well-being subscales. His initial baseline FACT-G score suggested low quality of life relative to the norms, which improved to within the "average" range for the normal population. On completion of the program, Mark's scores remained in the normal range. There was a small improvement in self-concept (i.e., increase in continuity with others and decreased discontinuity of self).

Mark reported high levels of therapeutic alliance on the SRS. For all sessions, Mark consistently rated the alliance (relationship, goals and topics, approach or method, and overall) at the maximum score (10).

Overall, visual and statistical analysis of Mark's psychological functioning indicated limited therapeutic benefits in terms of reducing his levels of depression and anxiety. Minor improvement in helplessness was found, although this coincided with decreased acceptance and perceived benefits. Minor improvements in social and functional well-being and self-concept were also reported.

JOHN

John was diagnosed with a Grade III anaplastic astrocytoma after a grand-mal seizure 2 years prior to the program. He reported that the seizure and diagnosis of brain tumor was unexpected and sudden, with no history of illness or need for medical attention. John underwent immediate debulking surgery, with subsequent rounds of chemotherapy and radiotherapy. He reported very little recollection of these events. Following treatment, John reported infrequent seizures and ongoing concerns about his limited memory

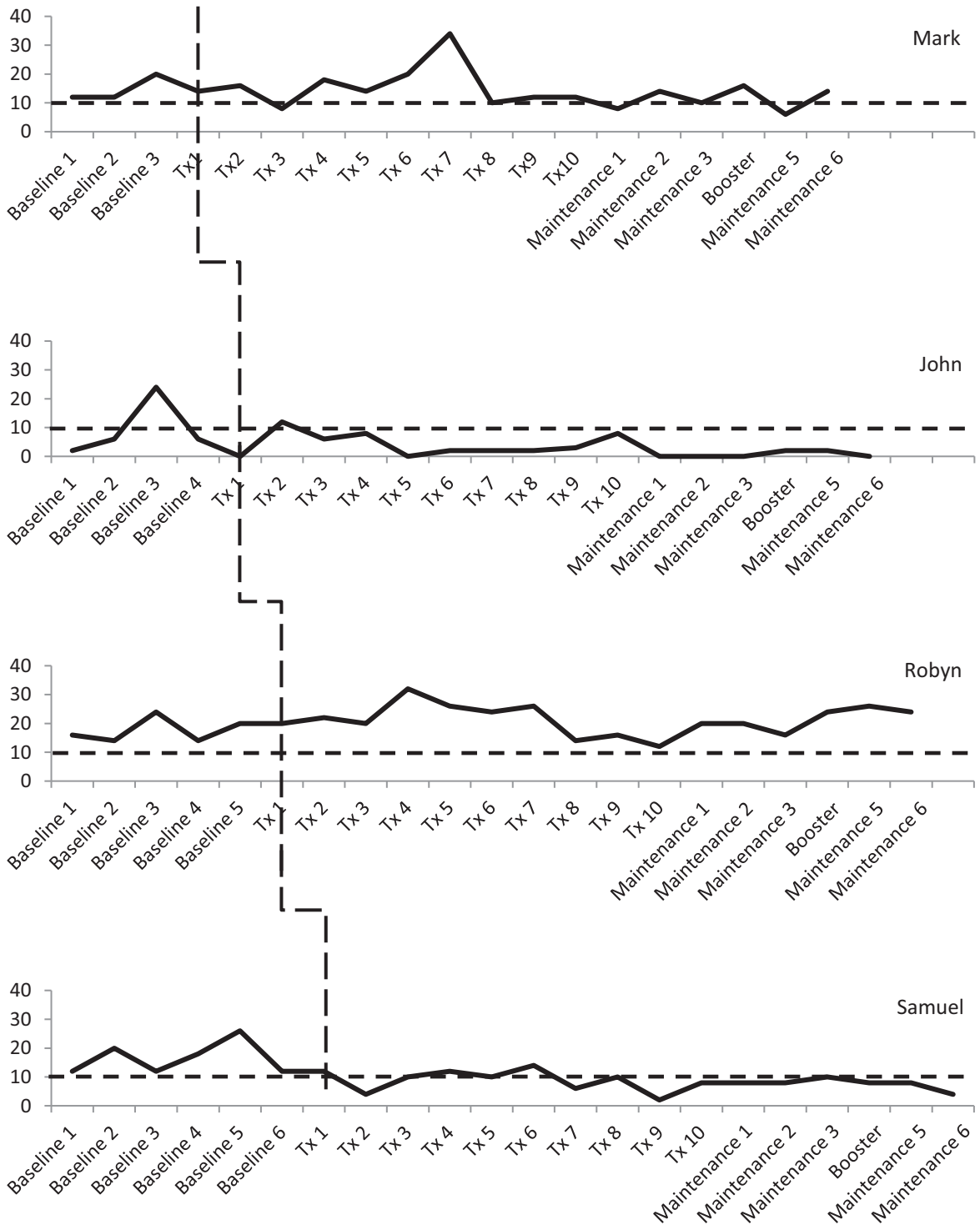

FIGURE 3 | Depression (DASS-21) levels across the three phases, with clinical cut-off for "mild" range (as indicated by broken line).

of the diagnosis and events since the diagnosis. His main concern was that his brain tumor would preclude him from taking part in everyday activities and that those around him would treat him differently. John was also distressed about being a burden on his family and felt guilty that he needed rest breaks during the day. He also expressed grief that he would be unable to see his children grow old and achieve milestones (e.g., school graduations, birthdays, and weddings).

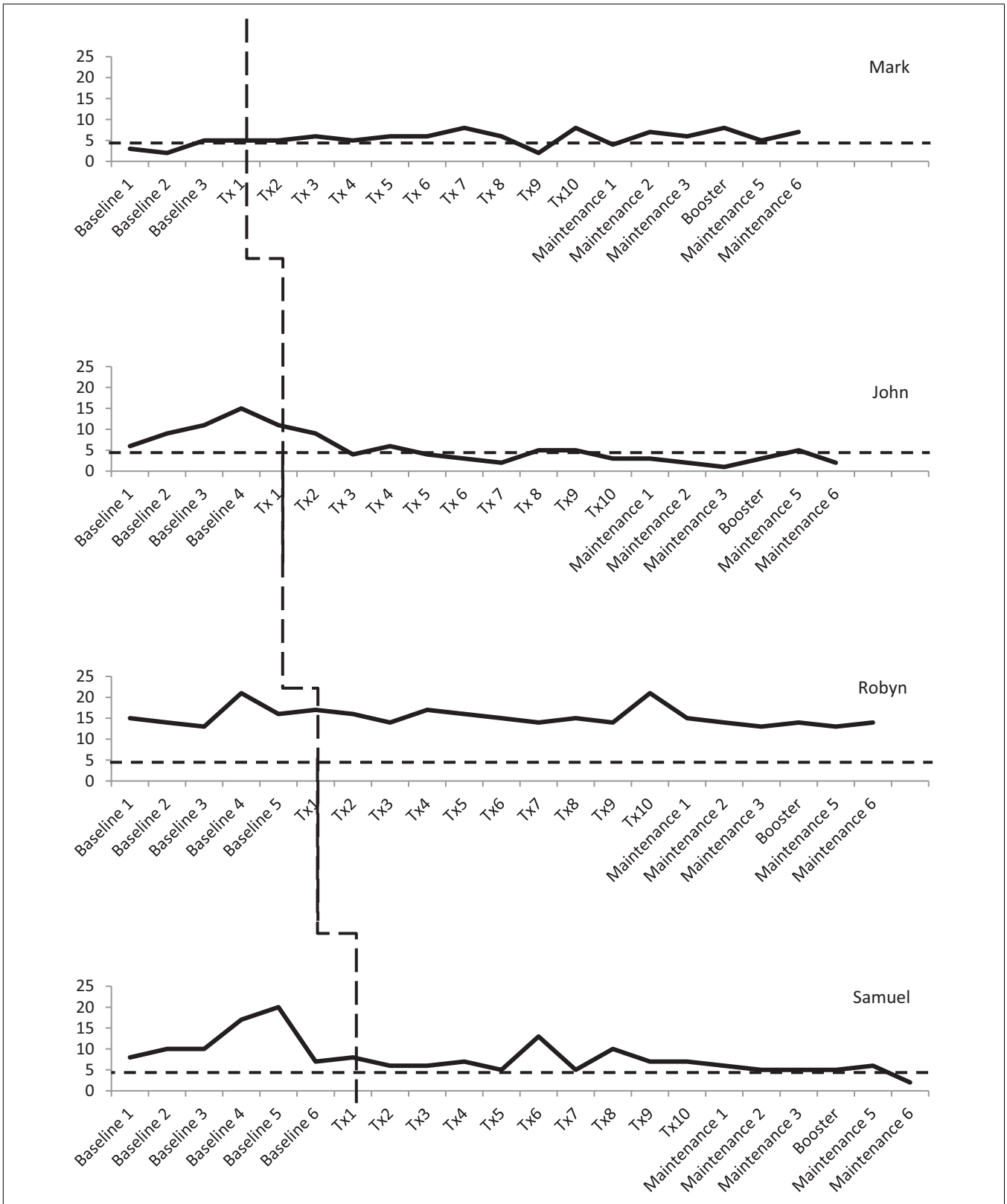

FIGURE 4 | Anxiety (GAD-7) levels across the three phases, with clinical cut-off for "mild" range (broken lines).

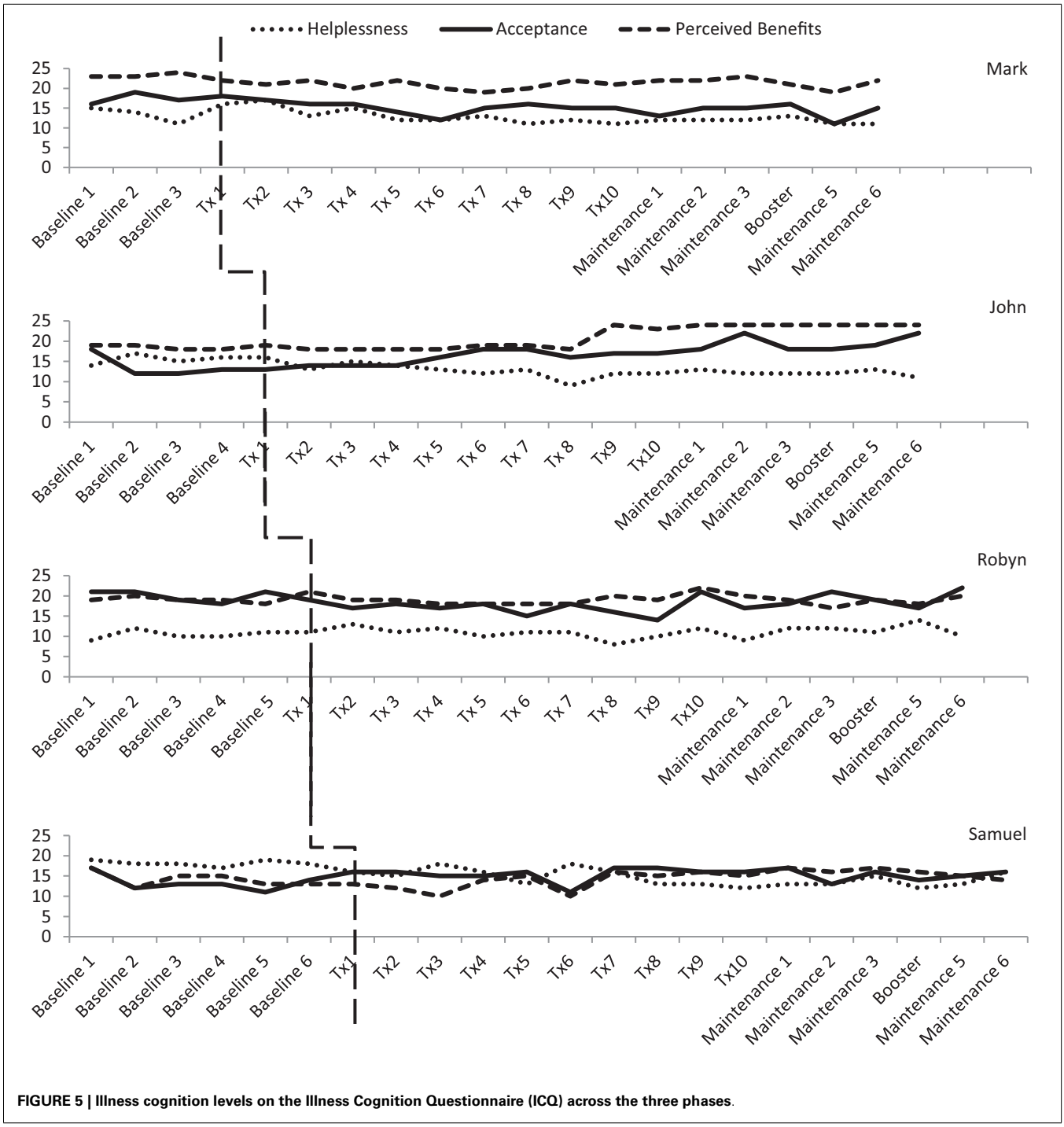

FIGURE 5 | Illness cognition levels on the Illness Cognition Questionnaire (ICQ) across the three phases.

There was no significant trend in John's DASS depression scores in the baseline phase (Tau-$U = -0.1$, $p = 0.807$). A comparison of between phase variability (AB) indicated no significant difference between the baseline and treatment phases (Tau-$U = -0.1$, $p = 0.760$). Visual inspection of the treatment phase identified that after the initial treatment session of "telling my story," depression scores were in the "mild" range with scores reducing to the "normal" range for the remainder of the treatment phase and the maintenance phase.

No significant trend in GAD-7 anxiety levels was found in the baseline phase (Tau-$U = 0.7$, $p = 0.086$). Phase comparison indicated a significant reduction in anxiety between the baseline phase and treatment phase (Tau-$U = -0.92$, $p = 0.005$). Baseline scores ranged between "mild" and "severe" whilst scores in the treatment phase were in the "normal" to "mild" range. During the maintenance phase, John's level of anxiety was in the "normal" range with the exception of maintenance session five, for which his score was in the "mild" range.

Table 4 | Broader subjective well-being scores for Mark across phases.

Measure	Initial baseline (A)	Final baseline (A)	End of treatment (B)	End of maintenance (C)
FACT-Brain				
Physical	24	25	24	23
Social/family	11	15	17.5	14
Emotional	18	18	17	21
Functional	13	16	14	16
G	66	74	72.5	72
Brain	33	34	34	35
CDSS				
Discontinuity self	34	33	33	31
Continuity self	13	11	15	12
Continuity others	19	18	20	21

Table 5 | Broader subjective well-being scores for John across phases.

Measure	Initial baseline (A)	Final baseline (A)	End of treatment (B)	End of maintenance (C)
FACT-Brain				
Physical	17	14	16	23
Social/family	20	20	21	25
Emotional	16	15	17	23
Functional	20	17	18	27
G	73	66	72	98
Brain	37	36	49	34
CDSS				
Discontinuity self	28	28	28	23
Continuity self	11	5	13	15
Continuity others	18	21	21	21

On the ICQ, there was no significant trend in the baseline phase for John's levels of helplessness (Tau-$U = 0.3$, $p = 0.462$), acceptance (Tau-$U = 0.0$, $p = 1$), or perceived benefit (Tau-$U = -0.2$, $p = 0.624$). Phase comparison indicated a significant difference in illness cognitions between the baseline and treatment phases, which reflected a decrease in level of helplessness (Tau-$U = -0.92$, $p = 0.005$) and an increase in acceptance (Tau-$U = 0.66$, $p = 0.043$). Phase comparisons for perceived benefits indicated no significant difference between baseline and treatment phases (Tau-$U = 0.08$, $p = 0.807$).

Between the initial baseline assessment and final baseline assessment, John's scores declined on the FACT-G (see **Table 5**), indicating low quality of life relative to the norms. However, on completion of the program, John's scores had markedly increased from 72 to 98. At the end of treatment and maintenance phases, John reported minor improvements in self-concept (i.e., increased continuity of self, increased continuity with others, and decreased discontinuity of self).

John reported high levels of therapeutic alliance on the SRS throughout treatment [relationship ($M = 8.8$, SD $= 0.91$), goals and topics ($M = 9$, SD $= 0.66$), approach or method ($M = 9$, SD $= 0.66$), and overall ($M = 9.2$, SD $= 0.78$)].

In summary, visual and statistical analysis of John's psychological functioning indicated a significant reduction in levels of anxiety and helplessness and increased levels of acceptance. There were no significant changes in John's levels of depression or perceived benefits. Improvements in self-concept and quality of life were also observed.

ROBYN

Robyn reported a gradual onset of symptoms, including visual difficulties, facial numbness, right-sided numbness, lower limb edema, abnormal menstruation, emotional blunting, and significant weight gain. After 12 months of symptoms, Robyn was diagnosed with a benign (Grade I) pituitary tumor near the optic nerve. She had key-hole surgery 3 days after her initial neurosurgical consultation. On entry to the program 3 months post-diagnosis, Robyn reported difficulty coping with returning to full-time employment and part-time study. She reported concerns that her illness was invisible to others (i.e., family, friends, and colleagues) as there was no physical injury or sign of surgery. She also found it difficult to cope with heightened emotionality as prior to the surgery she had experienced emotional blunting. She reported being unhappy in her job, having a limited support system, and strained relationships with family members.

No significant trend was found in DASS-21 depression scores across the baseline phase (Tau-$U = 0.2$, $p = 0.573$). A comparison of between phase variability (AB) indicated no significant difference between the baseline and treatment phases (Tau-$U = 0.333$, $p = 0.278$). Robyn's scores were consistently in the clinical range for depression, with scores mainly between the "moderate" and "severe" range, although there was a notable increase to an "extremely severe" level of symptoms after the third treatment session.

There was no significant trend in GAD-7 anxiety scores in the baseline phase (Tau-$U = 0.333$, $p = 0.348$). Phase comparison indicated no significant difference between the baseline and treatment phases (Tau-$U = -0.033$, $p = 0.914$). Visual inspection identified scores consistently between the "moderate" and "severe" range across all phases.

On the ICQ, there was no significant trend in the baseline phase for Robyn's levels of helplessness (Tau-$U = 0.333$, $p = 0.348$), acceptance (Tau-$U = 0.333$, $p = 348$), or perceived benefit (Tau-$U = 0$, $p = 1$). Phase comparison for helplessness and perceived benefits indicated no significant difference between the baseline and treatment phases (Tau-$U = 0.118$, $p = 0.704$; Tau-$U = -0.183$, $p = 0.551$). Phase comparison for acceptance revealed a significant decrease in Robyn's level of acceptance between baseline and treatment phases (Tau-$U = -0.8$, $p = 0.009$).

Between the initial baseline assessment and final baseline assessment, Robyn's scores declined on the FACT-G (see **Table 6**), this decline occurred across all subscales, suggesting low quality of life relative to the norms. However, on completion of the program, Robyn's scores had increased, with further improvements at the end of the maintenance period, reflecting improved quality of life. Between the initial and final baseline assessments, Robyn's scores showed slight decline in self-concept (i.e., continuity with

Table 6 | Broader subjective well-being scores for Robyn across phases.

Measure	Initial baseline (A)	Final baseline (A)	End of treatment (B)	End of maintenance (C)
FACT-Brain				
Physical	15	12	17	20
Social/family	18	15	17	17
Emotional	15	14	9	14
Functional	15	17	19	20
G	63	58	62	71
Brain	52	60	60	63
CDSS				
Discontinuity self	24	32	26	27
Continuity self	13	12	13	13
Continuity others	18	16	17	21

Table 7 | Broader subjective well-being scores for Samuel across phases.

Measure	Initial baseline (A)	Final baseline (A)	End of treatment (B)	End of maintenance (C)
FACT-Brain				
Physical	23	18	21	27
Social/family	21	21	21	19
Emotional	15	12	16	15
Functional	20	20	22	21
G	79	71	80	82
Brain	39	33	36	26
CDSS				
Discontinuity self	28	26	24	26
Continuity self	12	13	13	14
Continuity others	19	16	21	21

others, discontinuity of self). At the end of the maintenance phase, Robyn's scores reflected improvements in self-concept (i.e., increased continuity with others and a return to initial baseline levels of discontinuity of self).

Robyn reported high levels of therapeutic alliance on the SRS. With the exception of session seven (relationship score of 7), Robyn rated the alliance at a score of 8 or higher [relationship ($M = 8.8$, SD $= 0.63$), goals and topics ($M = 8.9$, SD $= 0.31$), approach or method ($M = 9$, SD $= 0$), and overall ($M = 8.8$, SD $= 0.42$)].

Overall, visual and statistical analysis of Robyn's self-reported functioning indicated limited therapeutic benefits in terms of her levels of anxiety, depression, helplessness, and perception of benefits. Her level of acceptance of her illness actually declined across the program. Despite this, Robyn's quality of life and self-concept increased throughout the intervention.

SAMUEL

At the time of the intervention, Samuel was a single male working full-time as a shift-worker. He was in his twenties when he suffered his first grand-mal seizure, having had no previous history of seizures or major health concerns. He was diagnosed with a low-grade (II) oligoastrocytoma in the left temporal lobe and underwent surgical debulking, chemotherapy, radiation therapy, and ongoing use of anti-convulsants. He continued to have absence seizures at least twice per week. Samuel reported frequent panic attacks (more than one per week) and concerns about his memory and level of independence. He had been advised that the rate of tumor progression was unpredictable but was likely to recur (possibly at a higher grade), which contributed to his anxiety. In addition, because of the loss of his driver's license, Samuel felt he was becoming a burden on his family and friends. Samuel reported strong family and social relationships and stable employment with a supportive employer.

There was no significant trend in DASS-21 depression scores during the baseline phase (Tau-$U = -0.048$, $p = 0.881$). A comparison of between phase variability (AB) indicated a significant reduction in level of depression between the baseline and treatment phases (Tau-$U = -0.829$, $p = 0.005$). During the baseline phase, Samuel's scores were all in the clinical range ("mild" to "severe"). There was a noticeable reduction in depressive symptoms after the initial treatment session ("telling my story"). Throughout the treatment and maintenance phases, his depression scores fluctuated between the "normal" and "mild" range.

No significant trend was found in the GAD-7 anxiety scores during the baseline phase (Tau-$U = 0.048$, $p = 0.881$). Phase comparison indicated a significant reduction in anxiety between the baseline and treatment phases (Tau-$U = -0.7$, $p = 0.002$). Samuel's baseline scores were mainly in the "mild" to "moderate" range, although there was a notable reduction in the week prior to the treatment commencing. His scores fluctuated between the "normal" and "moderate" range during the treatment phase. During the maintenance phase, his levels of anxiety were in the "normal" to "mild" range.

On the ICQ, there was no significant trend found in the baseline phase for Samuel's level of helplessness (Tau-$U = -0.429$, $p = 0.177$), acceptance (Tau-$U = 0.095$, $p = 0.764$), or perception of benefit (Tau-$U = -0.333$, $p = 0.293$). Phase comparison for helplessness indicated a significant decrease in levels of helplessness between the baseline and treatment phases (Tau-$U = -0.771$, $p = 0.008$). There was no significant difference between baseline and treatment phases for acceptance and perceived benefits (Tau-$U = 0.486$, $p = 0.097$; Tau-$U = 0.086$, $p = 0.770$).

Samuel's FACT-G scores declined between the initial and final baseline assessments (see **Table 7**). His final baseline FACT-G score indicated low quality of life relative to the norms. On completion of the program, Samuel's FACT-G scores had increased to within the range of 80–82, thus suggesting improvement in quality of life. Samuel's scores indicated slight improvements in self-concept (i.e., increased continuity of self, continuity with others, and decreased discontinuity of self).

Samuel reported high levels of therapeutic alliance on the SRS. With the exception of session six (where relationship and approach or method were rated at a score of 7), Samuel rated the alliance at 8 or higher [relationship ($M = 9$, SD $= 0.94$), goals and topics

($M = 9$, SD = 0.67), approach or method ($M = 8.9$, SD = 0.88), and overall ($M = 8.9$, SD = 0.57)].

In summary, visual and statistical analysis of Samuel's psychological functioning indicated a clear reduction in his levels of anxiety, depression, and helplessness. Samuel's levels of acceptance remained stable across the program while his perception of benefits was variable. There were minor improvements in his self-concept and quality of life.

DISCUSSION

The present study aimed to assess the feasibility and utility of a telephone-based psychological intervention for individuals with brain tumor. The evaluation of a telephone-based program was considered an important extension of the FTF MSoBT program (37) to provide a potentially more cost-effective option for the delivery of psychological support services, particularly for people living outside a major metropolitan area.

As the first study to evaluate a telephone-based psychological intervention for people with brain tumor, the SCED methodology provided a rigorous analysis of both within phase (i.e., baseline) and across phase variability on measures of psychological functioning. All four participants completed the intervention, which supports the feasibility of tele-based therapy for this population. Overall, two of the four participants demonstrated significant gains in mental health and more positive cognitive appraisals (John and Samuel). The other two participants (Mark and Robyn) did not demonstrate the hypothesized gains in mental health or cognitive appraisals. Despite these mixed findings, all participants reported some degree of improvement in quality of life and high levels of therapeutic alliance.

The mixed findings in the current research are consistent with those of previous support interventions that measured changes in psychological functioning. For example, Locke and colleagues (21) found that although participants increased their use of compensatory strategies, no significant differences in mood were found at post-intervention. However, unexpectedly, both Mark and Robyn reported an increase in mood symptoms over the course of treatment and lower levels of acceptance of the brain tumor. It is possible that discussion of recent and past stressors (e.g., marriage breakdown) heightened their awareness of the implications of their illness.

It is noteworthy that both Mark and Robyn had tumors located in the hypothalamic and pituitary areas. Mark identified difficulties with anger outbursts and emotion regulation and Robyn reported a major change in her emotional experiences prior to diagnosis (emotional blunting) and after diagnosis (mood swings and heightened emotions). Numerous studies have identified that dysregulation of the hypothalamic–pituitary adrenal axis contributes to mood disorders and difficulties down-regulating heightened emotional response to negative stimuli (64, 65). As a result, Mark and Robyn's ability to apply the emotion regulation strategies (e.g., cognitive reappraisal) taught during the program in everyday situations may have been compromised by the nature of their brain injury.

Additionally, both Robyn and Mark identified cognitive difficulties that may have reduced the efficacy of telephone-based support. Mark displayed impaired verbal fluency which may have impeded his ability to express himself OTT, without the benefit of non-verbal cues. Robyn's delayed verbal memory impairment may have affected her retention of the content of therapy sessions. Indeed, she identified in the latter part of the program that she is a visual learner and would have preferred FTF contact with the therapist. Further, Robyn and Mark both perceived a lack of understanding and support from friends, family, and colleagues. Therefore, despite a relatively favorable prognosis (i.e., Mark's long-term survival with no re-growth or progression; complete removal of Robyn's benign tumor), they both reported significant levels of emotional distress. This is consistent with previous research indicating that tumor characteristics are not consistently related to quality of life or psychological adjustment (3).

Further to this, impression management and insight were not measured throughout the program. Hence, it is possible that Mark was initially reluctant to fully disclose the extent of his distress during the baseline phase, and became more open about his mood symptoms and illness appraisals during the treatment phase. The use of self-report methods relies on the assumption that a participant will describe their symptoms and behaviors openly and accurately (66, 67).

In contrast to Mark and Robyn, both John and Samuel identified strong support systems through their family and social networks. Their stress associated with family and friends related to concerns around the loss of their independence and being a burden on the people they cared about. They also identified supportive workplaces where their roles were adapted to accommodate their difficulties, thus increasing their sense of life continuity (19). Psychotherapy techniques assisted with strengthening the roles identified as important to their sense of identity, despite their less favorable prognoses and ongoing health and functional difficulties. The tele-based therapy program provided a confidential space to discuss their hopes, fears, and concerns, without burdening or upsetting friends and family members.

CLINICAL IMPLICATIONS

Overall, results of this study provide some preliminary support for the feasibility and utility of telephone-based psychological support for people with brain tumor. Tele-based therapy may increase the opportunity to provide interventions to people otherwise unable to access brain tumor specific support. In the current study, a participant living over 4 h away from a major metropolitan area was able to be involved and he experienced significant gains in his psychological functioning. The tele-based intervention avoided the need for travel for all participants and the therapist, thus reducing common barriers to attending regular psychotherapy sessions, including transport, cost, and health-related barriers. As such, tele-based therapy may provide a cost and time-effective intervention option for individuals unable to access traditional (FTF) psychological support (39).

Despite the lack of FTF interaction, high levels of therapeutic alliance were reported by all four participants, suggesting that a strong rapport and alliance can be established OTT. As previously noted, therapeutic alliance is a strong predictor of outcome and thus the ability to establish good alliance on the telephone supports the viability of this therapy mode (41).

Participant feedback on intervention provided further important information about feasibility and utility of tele-therapy. As previously noted, Robyn stated that her first choice would have been for FTF contact due to her preference for visual processing of information. In particular, she found it disconcerting to only hear the therapist's voice. Robyn regularly sent the therapist photos or art work via traditional mail (e.g., of a work function, of the table she sat at during therapy) in an effort to communicate using visual means. Robyn's preference for FTF contact is consistent with research findings that 27.8% of participants had a preference for FTF contact, although this was not associated with treatment adherence (41).

In contrast, Mark and Samuel expressed surprise that rapport was so easily established without FTF interaction. Samuel also discussed the benefits of being able to undertake sessions from his own home, rather than having to travel which was difficult and upsetting for him due to the loss of his driver's license. John expressed gratitude at being able to access psychotherapy, despite living outside a major metropolitan area. Like Samuel, he appreciated attending sessions from his own home to avoid fatigue. Overall, participants' feedback indicated the importance of exploring people's preferences for mode of delivery to enhance their experience of treatment, especially in the context of cognitive deficits.

Undertaking psychotherapy via telephone poses a number of unique challenges. To provide educational handouts, the practitioner needs to send material via traditional mail or email, prior to or after a session. The relevance of such materials is not always known in advance. There is a strong reliance on verbal cues (e.g., tone of voice) and feedback from the client regarding their understanding of the information and skills being trained. As such, there is the potential for increased preparation time for the therapist either prior to or after therapy sessions. This is particularly the case for clients with cognitive difficulties who often benefit from session summaries and visual aids (e.g., drawing a diagram to explain concepts) to process and retain new information (11). Further research is needed to explore the feasibility and utility of other tele-health or internet-based interventions (e.g., Skype and video-conferencing).

METHODOLOGICAL CONSIDERATIONS

The current SCED utilized a multiple-baseline design, examining stability of psychological functioning prior to treatment (51). Multiple baselines across participants and weekly observations over an extended period helped to assess for potential extraneous and confounding factors (49, 50). The combined use of statistical and visual analyses also increased the methodological rigor of the study, as recommended by recent methodological guidelines (50).

Despite these strengths, it is important to acknowledge potential limitations to generalizability. In particular, convenience sampling was used to recruit the four participants who were all proactive in help-seeking. Such characteristics may have enhanced their continued participation in the program and responsiveness to the intervention. As such, larger scale research (such as an RCT) should attempt to broaden intake processes to increase the representativeness of participants. Further, while each questionnaire administered has been validated in a brain injury, cancer, or community population, the measurement of change was based on self-report alone, with no collateral information obtained (48). As such, there is the potential for socially desirable responses, especially on measures of rapport and therapeutic alliance. Future research should attempt to measure outcomes independent from therapy, by use of a blind assessor or technology (i.e., online questionnaires), to reduce this potential (50). In addition, future research should attempt to obtain collateral information from a significant other or more objective indicators of psychological change (e.g., behavioral indices).

As the focus of the current research was on feasibility and utility, only a 5-week maintenance period was used. An extended period of follow-up (i.e., 3- or 6-month follow-up) is needed to assess more long-term benefits of telephone-based support interventions. Finally, future research may also benefit from assessing participants' preference for intervention style (e.g., FTF or telephone-based). Whilst treatment adherence has not been found to be linked to preference (41), the outcomes of the intervention may have been influenced by the preference for FTF therapy. More generally, the circumstances in which tele-based psychotherapy is most effective for people with brain tumor need to be better understood.

SUMMARY

Overall, this study provides some preliminary support concerning the feasibility, practical benefits, and utility of tele-based psychological interventions for people with brain tumor. As the current study utilized four single-case studies, the ability for the findings to be generalized to the broader brain tumor population is limited. Nonetheless, the in-depth description of each participant and their intervention outcomes may enable clinicians to determine the relevance of the findings for their own setting. The results of this pilot study may guide future research on accessible and effective psychotherapy interventions for people with brain tumor.

AUTHOR CONTRIBUTIONS

All authors made a substantial contribution to the conception and design of the study, participant recruitment, data collection, and/or data analysis phases. Each author was involved in drafting the work or critically revising it for important intellectual content and gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Psychological intervention for improving cognitive function in cancer survivors: a literature review and randomized controlled trial

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Although the impact of cancer and associated treatments on cognitive functioning is becoming an increasingly recognized problem, there are few published studies that have investigated psychological interventions to address this issue. A waitlist randomized controlled trial methodology was used to assess the efficacy of a group cognitive rehabilitation intervention ("ReCog") that successfully targeted cancer-related cognitive decline in previously published pilot research. Participants were 29 cancer survivors who were randomly allocated to either the intervention group or a waitlist group who received the intervention at a later date, and 16 demographically matched community volunteers with no history of cancer (trial registration ACTRN12615000009516, available at http://www.ANZCTR.org.au/ACTRN12615000009516.aspx). The study was the first to include an adapted version of the Traumatic Brain Injury Self-Efficacy Scale to assess cognitive self-efficacy (CSE) in people who have experienced cancer. Results revealed participating in the intervention was associated with significantly faster performance on one objective cognitive task that measures processing speed and visual scanning. Significantly larger improvements for the intervention group were also found on measures of perceived cognitive impairments and CSE. There was some evidence to support the roles of CSE and illness perceptions as potential mechanisms of change for the intervention. Overall, the study provided additional evidence of feasibility and efficacy of group psychological intervention for targeting cancer-related cognitive decline.

Keywords: cancer, cognitive function, cognitive rehabilitation, group, randomized controlled trial, survivorship

INTRODUCTION

Research supports a relationship between cancer and associated treatment and subsequent cognitive impairment in some cancer survivors (1–3). Reported changes in areas like memory, attention, executive function, and processing speed have been linked to type of cancer and advancement of the disease (4), treatments (5), as well as other issues like increased stress and fatigue (6). As cognitive impairment has the potential to impact quality of life (QoL), relationships, and adjustment to occupational functioning after cancer (7), it is an important survivorship issue.

Although the impact of cancer and associated treatments on cognitive functioning is increasingly recognized, relatively few published studies have investigated psychological intervention programs to address this issue in survivors of adult-onset cancers. The theoretical basis for such interventions and results of previous studies will be discussed before describing new randomized controlled trial (RCT) findings.

BACKGROUND

CANCER AND COGNITION

Reviews assessing the impact of cancer treatments on cognition, in the absence of known primary or secondary tumors in the central nervous system (CNS), have indicated cognitive dysfunction frequencies ranging from 13 to 75% (8–10). A recent meta-analysis that examined 13 studies including a range of cancer types and cognitive domains found executive function to be most affected by chemotherapy and found evidence for impairment in language and memory (11). Seventeen studies met inclusion criteria for another meta-analysis and findings indicated significant cognitive deficits to be limited to verbal and visuospatial abilities (12). Despite variability in these domains, the meta-analyses have demonstrated a consistent relationship between cancer and cognitive impairment. Dysfunction following treatment is often considered an acute issue that should subside within months after treatment (13) and some research has indicated no long-term differences in cognitive function between people with and without a history of cancer (14). However, longitudinal research has also shown that cognitive complaints following treatment may endure for up to 10 years (15). Several studies have highlighted the impact of type of cancer and treatments including influence of treatment received (16–19). It is therefore suggested that a range of factors may contribute to the variability in prevalence of cognitive dysfunction after cancer.

Objective and subjective cognitive function

Cognitive dysfunction is measured using both objective and subjective forms of assessment. Objective measures often provide information about specific areas of cognition (e.g., working

memory) allowing for comparison of different domains. Prevalence rates of dysfunction are primarily based on objective measures, but subjective cognitive impairment is reportedly more prevalent in cancer survivors (9). Subjective measures assess self-perceptions of cognition including cognitive functioning in a person's daily life, and involve self-report assessments such as questionnaires (9). One large-scale study assessed 1933 breast cancer survivors, compared to 500 healthy controls, on a range of subjective measures of cognition and found statistically significant differences between groups (9% of survivors reported subjective cognition in a problematic range vs. 2.8% for controls) (20).

The association between objective and subjective cognitive impairment in people with cancer is inconsistent, with some studies finding a positive association but a higher number of studies finding no relation between these different forms of measurement (8, 9). An explanation for the discrepancy between objective and subjective measures of cognitive function is that subjective impairment is often more an indicator of psychological distress than a measurement of cognition (8, 21), and several studies have indicated a relationship between perceived cognition and psychological factors like mood and distress. It is therefore suggested that subjective and objective measures of cognition should be treated as separate assessments and that those who self-report cognitive concerns should also be screened for other psychological concerns (17).

Other proposed issues include the potential poor ability of objective measures to assess the subtle cognitive changes that may occur as a result of cancer treatment (22) and the need for a more comprehensive evaluation of mood so the influence of psychological factors can be accounted completely. In light of the variable evidence regarding cancer-related cognitive decline and complex relationships impacting cognition (e.g., objective and subjective function, psychosocial factors), it is helpful to consider conceptual models designed to assist with interpretation of the research findings.

Explanatory models

Models have been proposed in order to summarize the relationships among physiological and psychological factors associated with cancer and cognitive impairment (23–25). Hess and colleagues included 70 articles in a systematic review, and developed a conceptual model of pathways by which cancer treatments may lead to changes in cognitive functioning (24). Their model incorporates antecedents; mediating factors and associated toxicities; moderators; and consequences for treatment-related cognitive dysfunction. The model illustrates that multiple factors impact on subjective/objective cognitive function (grouped together), and consequently on QoL and functional ability. The model also accounts for moderating factors which have been shown to influence the relationship between cancer and cognition (24). When considering how specific cancer types (termed an "antecedent" in this model) may be associated with changes in cognitive function, one issue of note is that various adult-onset cancers have different rates of CNS metastases. The frequency of metastases may be underreported because specific investigations for such metastases may not occur unless symptoms of CNS dysfunction are evident. Another point of note is that the model lists varied toxicities that potentially link some cancer treatments to cognitive changes for some patients, including anemia, cytokines, hormonal status, and vascular injury, as well as direct neurotoxicity. Therefore, the evidence does not support one specific, universal mechanism for all cancer-related cognitive dysfunction.

A model by a different research group proposed predictors of both subjective and objective cognitive function in people with cancer (23). The model suggests cancer treatments, emotional health, and physical health to be predictors of objective cognitive impairment and that emotional health and objective impairment may predict subjective cognitive impairment. These authors noted that, in many instances, subjective measures of cognition are more strongly related to psychosocial factors such as coping, emotions, and personal interpretations of a situation (termed "appraisal"), than to objective cognitive function. Furthermore, their model suggests psychosocial elements including appraisal and coping can impact the level of emotional distress and consequently correlate with physical health. It is proposed that the model may inform interventions by incorporating assessment of individual vulnerabilities and current difficulties, assisting patient education regarding current and prospective cognitive function, and identifying potential areas for remediation (23).

Vearncombe and Pachana reviewed 22 studies to evaluate the impact of treatments, health, and psychological factors on cognition for women with breast cancer (26). They proposed that indirect factors, including psychological well-being, may influence cognitive performance and found a major gap in the literature in terms of study of the impact of these indirect factors on cognition after cancer treatment. Their research highlighted the potential contribution of psychological variables to cognitive performance for cancer survivors, including the potential to intervene with psychological approaches even when biological causes may contribute.

PSYCHOSOCIAL VARIABLES

Quality of life

A psychological variable that has been researched in terms of its relationship to cancer and cognitive function is QoL. QoL has been described as subjective perception of how well a person functions across areas of their life and is domain-specific encompassing the interactions of psychological, physical, social, and spiritual well-being (27). Areas of QoL impacted by cancer are commonly reported to include areas like physical, sexual, role, and social functioning (28). Meta-analyses in this area have even supported use of QoL as a prognostic indicator of survival in some people with cancer (29, 30).

A systematic review of 28 studies showed worse outcomes on QoL are reported significantly more frequently by women with breast cancer than community controls (31). QoL impacted by breast cancer was related to reduced physical functioning, premature menopause, and the impact of psychosocial outcomes as a result of diagnosis and treatment (e.g., depression). Another review examining the long-term impact of cancer on QoL indicated that survivors (at least 5 years post-treatment) reported good overall QoL but reported issues with specific areas of QoL like sexual functioning (32). Predictors of better QoL included fewer current medical issues, better social support, and higher

income; chemotherapy treatment was a predictor of worse scores on measures of QoL.

Although limited, there is some research into the impact of cancer-related cognitive decline on QoL. Research has shown perceived cognitive impairment after cancer treatment to be linked to reduced QoL, daily functioning, reduced work efficiency, and negative reactions from others (7). One study of health-related QoL in 76 people with cancer found individuals with higher subjective cognitive deficits reported worse health-related QoL (33). A qualitative study of men randomized to androgen-suppressing medication for prostate cancer found that decreased cognitive function was the most frequent change in behavior or symptoms that participants attributed to their medication (34). Overall, existing research indicates that there is a need for more research investigating the relationship between cognitive functioning and QoL in cancer survivors.

Psychological distress

Research supports that diagnosis of cancer and treatment may lead to increases in mental health issues including depression and anxiety (35–37). A meta-analysis of 58 studies that investigated psychological outcomes related to cancer diagnosis found varied results in terms of significantly less psychological problems when compared to a psychiatric population, but significantly higher levels of depression than a "normal" population (38). Among a sample of 1083 people with breast cancer, at least 40% had one psychological diagnosis, 38% exhibited moderate-high rates of anxiety, 22% reported moderate-high depression, 12% exhibited post-traumatic stress disorder, and 7.8% met diagnostic criteria for all three diagnoses (39). Increased rates of comorbid depression have also been correlated with the advancement of the disease (40).

It has been reported that psychological disorders like depression and anxiety may impact cognitive function in the general population and a range of clinical populations (41, 42). Depression has been particularly linked to deficits in attention and a large study that examined depression, anxiety, and cognitive function in an elderly population found a significant and almost linear relationship between depression and objective measures of impaired cognitive function (41). Some research has not found a correlation between psychological distress and objective cognitive function in people with cancer (13, 43, 44). However, a number of studies have shown a relationship between mental health and subjective cognitive impairment in this population (13, 18). These findings indicate that subjective complaints regarding cognitive impairment may be more revealing of emotional distress than objective cognitive impairment (18), and also suggest there may be other psychosocial variables that impact psychological well-being in this population.

Fatigue

Survivors of cancer often report persistent fatigue and it has been found to affect individuals irrespective of type of cancer or treatment received (45, 46). Cancer-related fatigue has been associated with QoL (47) and psychosocial well-being (35). A systematic review including 44 studies demonstrated consistently more fatigue in cancer groups than the general population with prevalence ranging between 39 and 90% (48). Research also suggests up to a third of people treated with radiation or chemotherapy continued to experience fatigue 5–10 years after treatment was completed (49, 50). Cancer-related fatigue may also be associated with financial burden as it can impair an individual's ability to work and perform activities of daily living (51).

The relationship between fatigue and cognitive functioning is well established in a range of clinical populations including multiple sclerosis (52) and chronic fatigue syndrome (53), but results have been mixed when investigating populations with cancer. One study found no differences between severely fatigued cancer survivors, non-severely fatigued cancer survivors, and the control group on objective neuropsychological assessments; but the severely fatigued group scored significantly worse on self-report assessments of cognitive functioning (54). These results suggested that cancer-related fatigue may be associated with subjective but not objective cognitive functioning. This is supported by other studies, which have failed to find a relationship between fatigue and objective cognitive dysfunction in cancer survivors (55, 56).

Benefit finding

Benefit finding refers to the potential for individuals who have experienced cancer or other potentially traumatic events to view aspects or outcomes of their experience as positive or beneficial (57). Positive experiences post-diagnosis for cancer as reported by some people may include increased sense of spirituality and purpose, improved relationships, and increased skills (58).

A meta-analysis of 87 studies investigating benefit finding in populations with cancer found the construct was related to measures of positive well-being and less depression but was not related to measures of anxiety or global distress (59). It was suggested from this research that benefit finding may be important to consider when researching survivorship issues as it appears to represent positive outcomes from illness as opposed to "a mere lack of distress" (59).

Cognitive self-efficacy

The relationship between confidence in ability to perform cognitive tasks and objective measures of cognitive performance is a robust finding in the literature (60, 61). Cognitive self-efficacy (CSE) refers to an individual's confidence and/or perceptions regarding the effectiveness of their cognitive functioning in expected situations (62). An individual with low CSE may avoid tasks they believe to exceed their abilities, for example, they may not feel that they can solve problems related to their cognitive complaints. In contrast, another person with high CSE may attempt more challenging tasks, viewing them as goals rather than threats (63).

Research suggests that among individuals with physical disease or disablement, functional disability is more strongly predicted by perceived self-efficacy than by the level of impairment or duration of illness (64, 65). Specific to cognitive dysfunction, studies have found CSE and cognitive complaints to be more closely related than CSE and cognitive capacity (66–68). Measures of self-efficacy have also been shown to predict cognitive performance independently of the individual's level of skill (69, 70).

Several studies have measured aspects of CSE across cognitive training programs (64, 71). Results have generally found that as

CSE increases, cognitive performance improves, and where self-efficacy has not increased, there have also not been substantial gains in objective performance (71). The theory that CSE may mediate the degree of improvement during cognitive training programs, such that an increase in CSE facilitates a more positive outcome, has also been suggested (64). Further research into the role of CSE in cognitive rehabilitation programs is therefore warranted as it "may have considerable heuristic and explanatory value for understanding the effective ingredients of interventions" (64) (p. 949).

Illness perceptions

Illness perception is a construct encompassing an individual's appraisals and beliefs about their illness (72). A self-regulation framework posits that an individual's perceptions of their illness lead to their choices of coping strategies for dealing with an illness (73). A meta-analytic review of 45 studies found people who perceive their illness as highly symptomatic use avoidance coping strategies in contrast to people who view their illness as curable/controllable and show more positive social functioning, improved mental health, and reduced distress and disease states (74).

Preliminary evidence from one psychological intervention study for cognitive impairment in cancer survivors showed a significant improvement for intervention participants on one subdomain of illness perceptions (75). This was "illness coherence" regarding cognitive problems, which refers to an individual's beliefs about how well they understand the health problem. It has been suggested that if successfully targeted by interventions, improvement in illness perceptions would likely be related to improvement in a range of illness and psychosocial outcomes (76). Thus, the illness perceptions construct shows promise as a mediator of outcomes in psychosocial intervention studies but there has been little research to test this in the context of cognitive concerns for cancer survivors.

INTERVENTIONS FOR CANCER-RELATED COGNITIVE DYSFUNCTION

Pharmacological interventions

A number of pharmacological agents have been trialed for their use in addressing cognitive impairment after cancer. Reviews have identified erythropoietin, methylphenidate, and modafinil as pharmacological agents that may reduce cognitive impairment following treatment (25, 77). Despite these promising results, there are studies which have not shown any improvement in cognitive performance with medications (78) and it is noted that pharmacological treatments often have side-effects (79). For example, the presence of erythropoietin receptors in many cancers may raise concerns about potential increased risk of tumor growth or recurrence with use of erythropoietin to address these issues. Therefore, consideration of non-pharmacological, psychosocial interventions is important.

Psychosocial interventions

Published research has only relatively recently reported psychological interventions for cognitive dysfunction following treatment for adult-onset non-CNS malignancies. Many of these studies were published after the current study began in 2012. Some studies have focused on cognitive training, such as computerized exercises designed to strengthen relevant cognitive processes. Other studies have taken a broader cognitive rehabilitation approach, which may include cognitive skills training but also incorporates program elements such as psychoeducation, compensatory strategy training, and between session homework tasks (80). Cognitive rehabilitation usually incorporates cognitive behavioral therapy (CBT) principles. Some studies have used individually delivered interventions, whereas others have taken place in a group format. Please see **Table 1** for information on psychological interventions addressing cancer-related cognitive impairment.

The studies described in **Table 1** show support for both group and individual psychosocial interventions for this clinical issue. In the limited research to date, no specific advantage has been shown for interventions with a broader cognitive rehabilitation approach compared to more focused cognitive training. Research has supported beneficial effects of psychological interventions for cancer-related cognitive impairment in studies of mixed tumor types (75, 81, 84, 87) as well as in studies limited to women treated for breast cancer (82, 83, 85, 86, 88, 89).

However, there are limitations in the research to date. Only one of the studies described in **Table 1** included a matched attention control condition, and did demonstrate additional beneficial intervention effects in comparison to the health information arm (84). However, this research context was not specific to cancer survivors (84), so it is unclear whether an attention control that more specifically focuses on the concerns of cancer survivors might have additional benefits. The one study that did not find any additional benefit of psychological interventions designed to improve cognitive performance in comparison to treatment as usual was conducted in conjunction with inpatient cancer rehabilitation received by all participants, so it could be that the overall rehabilitation program acted as an attention control (83).

Psychological intervention studies to date have had relatively small sample sizes, and in some instances the findings associated with the intervention have represented only a small proportion of the statistical comparisons within the studies. Measures have varied, so it is difficult to make direct comparisons between studies. The majority of studies either investigating or intervening for cognitive impairment in cancer survivors with no known CNS tumors have been limited to samples with female breast cancer survivors and people treated with chemotherapy, making generalization of results to males and other cancer types difficult. Nevertheless, cancer-related cognitive impairment has been found in both sexes, in association with a range of cancer types and treatments, and clinically significant responses to cognitive rehabilitation have been found following colorectal, prostate, and testicular cancer as well as breast cancer (75). Moderators and mediators of intervention effectiveness are yet to be identified.

OVERVIEW OF CURRENT STUDY

The present study aimed to test the efficacy and potential psychological mechanisms of a group intervention (ReCog) for cancer survivors targeting cognitive decline. Design elements intended to address gaps in the literature included incorporating a range of cancer types, using RCT design, and testing relevant psychological outcomes including potential explanatory variables.

Table 1 | Psychological intervention studies addressing cognitive impairment in cancer survivors.

Reference	Design	Participants	Intervention	Results
(81)	RCT (intervention vs. waitlist)	78 adults aged 65+ years with a history of chronic disease ($n = 11$ history of cancer)	Cognitive Behavioral Model of Everyday Memory (CBMEM): efficacy and awareness building, health promotion, strategy use, and relaxation. Group intervention, 8 sessions of 1.25 h each, over 4 weeks	Cancer survivors in intervention group improved in short-term memory on the Rivermead Behavioral Memory Test, memory self-efficacy, and metamemory. (Note: not planned as a cancer substudy)
(82)	Single-arm study	29 women at least 3 years post-chemotherapy for breast cancer	Memory and Attention Adaptation Training (MAAT): education, self-awareness training, self-regulation, compensatory strategies. Individual therapy, 4 sessions of 30–50 min each, once per month, plus up to 3 phone calls and participant workbook	Significant improvements in neuropsychological test performance, self-reported cognitive function, and QoL
(83)	Partially Randomized Controlled Trial (two interventions vs. treatment-as-usual)	96 women post-chemotherapy for stage I or II breast cancer, undergoing inpatient cancer rehabilitation	Neuropsychological Training Group: small group functional training and compensatory strategies for memory and attention in everyday situations. Computer intervention: individual therapist support for using software addressing memory/attention. Both groups attended 4 1-h sessions per week during their stay in hospital (3–5 weeks)	Improvements across most neuropsychological measures for all participant groups (i.e., no effects were specific to the interventions)
(84)	RCT (intervention vs. active control)	267 adults aged 65+ years; 22 cancer survivors: 14 intervention group, 8 control group	CBMEM (see above) compared to health information control condition	Cancer survivors in CBMEM declined less in visual memory performance over 14 months and improved more than control group on subjective memory measures. (Note: not planned as a cancer substudy)
(85)	RCT (two interventions vs. waitlist)	88 breast cancer survivors	Memory training: group memory exercises and skills practice. Processing speed: computerized training using increasingly difficult processing tasks. Both interventions used 10 1-h training sessions in small groups over 6–8 weeks	Both intervention groups improved neuropsychological test performance more than waitlist group, but processing speed training showed earlier benefits and generalized to memory performance whereas memory training not associated with changed processing speed. Both showed improvements in subjective cognition, QoL, and distress
(86)	RCT (intervention vs. waitlist)	40 women 18-months post-treatment for breast cancer	MAAT (see above)	Intervention group improved significantly more than waitlist participants on verbal memory (California Verbal Learning Test) and one QoL subscale (spiritual well-being)
(75)	Non-Randomized Controlled Trial (intervention vs. waitlist vs. community)	55 participants. 32 cancer survivors >4 months post-treatments; 23 community comparison	Responding to Cognitive Concerns (ReCog): education, compensatory and enhancement strategies for memory, attention, emotional adjustment, sleep, and fatigue. Group sessions lasting 2 h held weekly for 4 weeks, participant workbook/homework	Significantly greater improvement on overall cognitive function, immediate memory, visuospatial/constructional, and delayed memory measures for intervention group. Reduction in subjective cognitive impairment and distress for intervention group
(87)	RCT (intervention vs. waitlist)	28 adult cancer survivors >6 months post-treatment	Workshops addressing memory aids, memory skills, and mindfulness meditation. Group sessions lasting 1 h held weekly for 7 weeks	Intervention group improved significantly more than waitlist group on digit span and subjective cognition

(Continued)

Table 1 | Continued

Reference	Design	Participants	Intervention	Results
(88)	Single-arm study	27 women 1.5–5 years post-treatments for breast cancer. $n = 8$ for EEG substudy	Cognitive rehabilitation, targeting attention, executive and memory challenges. Group sessions lasting 2 h held weekly for 5 weeks, participant workbook/homework	Significant improvements on Symbol Digit, Stroop reaction time, Trails A time, and subjective cognition. Increase in EEG alpha power was associated with improved subjective cognition at 2-month follow-up
(89)	RCT (intervention vs. waitlist)	41 breast cancer survivors	Online, computerized training program targeting executive function. Individual, home-based sessions lasting 20–30 min conducted 4 times per week for 12 weeks	Adherence was high. Intervention group improved significantly more on Wisconsin Card Sort Test, letter fluency, and symbol search, as well as some aspects of subjective executive function

It was hypothesized that there would be significantly greater improvements on objective cognitive function for participants in an intervention group than for participants in waitlist and community groups (Hypothesis 1). Similarly, it was predicted that the intervention group would show significantly greater improvements than other participants in subjective cognitive function (Hypothesis 2); in psychosocial measures including QoL, fatigue, distress, and benefit finding (Hypothesis 3); and in potential psychological explanatory variables of CSE and illness perceptions (Hypothesis 4). It was predicted that improvements in CSE and illness perception would be significantly associated with greater improvements in objective and subjective cognitive function (Hypothesis 5).

MATERIALS AND METHODS

PARTICIPANTS

There were 16 intervention participants (aged 37–65, $M = 50.4$, SD = 8.8 years), 13 waitlist control participants (aged 40–72, $M = 51.8$, SD = 9.4), and 16 community comparison participants (aged 27–77 years, $M = 52.9$, SD = 4.3). Intervention and waitlist participants had experienced adult-onset cancer, excluding cancer affecting the CNS, and had completed major treatments for cancer at least 6 months prior. A further requirement was that these participants report subjective cognitive impairment on the EORTC Cognitive Functioning Subscale prior to the intervention (score of less than 100). Inclusion criteria for the community comparison group stipulated participants to be adults (over 18 years) who had never been diagnosed with cancer. RCT participants were recruited in 2012 and 2013 via Griffith University email and cancer support groups. Community comparison participants were recruited in 2009 and 2010 via contacts of the research assistants for a parallel psychometric study of 36 participants, from which 16 were selected to match the intervention participants for sex, age, and years of education. Statistical analyses revealed no significant differences among groups on demographic variables at baseline.

Cancer survivors were randomly allocated to intervention ($n = 16$) and waitlist control groups ($n = 14$). Randomization was conducted by a colleague unconnected to the research project who used a random number table to generate the allocation sequence and prepared numbered opaque envelopes that were opened at the end of the initial assessment session. One participant who was randomly allocated to the waitlist group was excluded from analyses due to a pre-existing neurological condition.

MEASURES

Primary outcomes: cognitive measures

The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) (90) is a 30-min battery that assesses objective cognitive function. Good validity and reliability of the RBANS have been reported (91, 92), with strong internal consistency in clinical populations, e.g., total score Cronbach's alpha of 0.84 in people with traumatic brain injury (92).

The Trail Making Test (TMT) assesses attention, spatial organization, visual scanning, executive function, speed of processing, and mental flexibility (93). The TMT has exhibited good validity and reliability and is particularly sensitive to neurological impairment (93, 94).

The Functional Assessment of Cancer Therapy – Cognitive Scale Version 3 (FACT-Cog 3) (95) was designed for people with cancer and is used to measure areas of subjective cognitive function including perceived impairment, perceived ability, comments from other people regarding cognition, and QoL. Research has found high internal consistency for subscale scores on Version 2 of the scale, which has similar items and subscales to Version 3 (96).

The Brief Assessment of Prospective Memory (BAPM) (97) was used to assess subjective prospective memory. There are two subscales comprising the BAPM: the basic activities of daily living (BADL, e.g., forgetting to lock the door when leaving home) and instrumental activities of daily living (IADL, e.g., leaving the iron on). The BAPM has shown Cronbach's alpha of 0.74–0.76 for subscales (97).

Secondary outcomes: psychosocial measures

The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30) (98) is designed to assess aspects of QoL relevant to cancer. Recent research demonstrates high internal reliability with Cronbach's alpha above 0.80 for the functional scales (99), and reliability and consistency across cultures (100).

The Kessler Psychological Distress Scale (K10) (101) is designed to measure psychological distress including depression and anxiety. Research has indicated high levels of internal consistency, concurrent validity, and discriminant validity for the K10 (101).

The Benefit Finding Scale (102) assesses perceptions of positive contributions to life due to cancer diagnosis and treatment. Cronbach's alpha of 0.90 or higher has been reported (103).

The current study adapted the Traumatic Brain Injury Self-Efficacy Scale (104) to assess CSE. Items ask participants to rate confidence that they can manage their symptoms related to their TBI or cognitive disorder. This wording was adapted slightly so that it referred to "symptoms related to your cancer-related cognitive difficulties." The original scale was piloted with 21 military veterans experiencing mild cognitive disorder and with a history of TBI (104). Reliability of the adapted scale was assessed to be good for the current sample (Cronbach's alpha = 0.91–0.95).

The Brief Illness Perception Questionnaire (B-IPQ) (72) was designed to assess cognitive and emotional representations of illness. Cancer survivor participants completed this measure in relation to "your cognitive difficulties" and community participants were asked to respond by imagining what they thought it would be like to experience "cognitive difficulties, such as a problem with your attention or memory." Questions address issues like personal concern about cognitive difficulties, beliefs about benefit of treatment, and control over their difficulties. Previous research showed good test–retest reliability over 3- and 6-week time periods ($r = 0.42$–0.75) and good concurrent validity (72).

A participant satisfaction survey was completed by participants in the intervention group after the final group session (75).

INTERVENTION

The current study implemented an intervention that was previously developed and evaluated in an initial feasibility study (75). The intervention was titled "Responding to Cognitive Concerns (ReCog): a four session cognitive rehabilitation program for adults recovering from cancer." The program comprised four topics: (1) aging, health, cancer, and cognitive function; (2) memory; (3) attention; and (4) fatigue, emotions, and cognition. The program is manualized for clinicians (105) and participants (106). The intervention included four 2-h sessions held weekly across 4 weeks and participants were required to complete homework between sessions. Each session included psychoeducation, group discussion, and skill development and application (75). The three intervention groups of three to eight participants were co-facilitated by two psychologists, offered at no cost, conducted at university campuses, and also offered to all waitlist control participants once they had completed assessments. Waitlist participants were able to seek any medical or health services they required during the study, with no restrictions apart from not being eligible to undertake the ReCog intervention until they had completed data collection.

PROCEDURE

The study was approved by the Griffith University Human Research Ethics Committee (PSY/16/12/HREC) and met the required regulatory standards for research with human participants. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000009516). Data were collected at Griffith University in South-East Queensland, Australia. Baseline assessments took place within 2 weeks before the intervention commenced. At Time 1, participants completed objective measures of cognitive function followed by questionnaires, and group assignment was then revealed. At Time 2 and Time 3 assessments (within 2 weeks of intervention completion and at 3 months post-intervention), all participants were asked to complete the assessment battery.

Time 1 assessments were conducted by the first author, and Time 2 and 3 assessments were conducted by independent psychologists who were blind to the participant's group membership. Participants in the community comparison group completed the same assessment battery as participants in the other two groups (excluding three of the questionnaires), across Times 1 and 2 only.

STATISTICAL ANALYSES

Subscales and total scores for questionnaires were calculated using pro-rating methods suggested in the EORTC-QLQ-C30 scoring manual (107). The algorithms computed for each measure calculated the mean of all completed items where there was a minimum of 50% response and then substituted this value for the missing items.

Analysis of data from the RCT participants was conducted using 2 (Group) × 3 (Time) mixed factorial analyses of variance (ANOVA). Analysis of all three groups was conducted using 3 (Group) × 2 (Time) ANOVA. Simple effects analysis was used to follow up significant interactions. Planned contrasts comparing the intervention group to the waitlist group and to the community comparison group were used to follow up any effects of group. Effect sizes were calculated following guidelines for pre-test–post-test control group designs, using the Cohen's *d* approach (108).

A sample size of 40 RCT participants was planned, based on *a priori* power analysis showing that this would yield more than 80% power for detecting Group × Time interactions for primary outcome measures, at $\alpha = 0.05$ and with effect size estimated as Cohen's $d = 0.5$–1.0 from previous research. Personnel and financial resources allowed 30 participants to be recruited for the RCT during the time available for the study, which was computed to provide adequate power based on previous estimates of effect. Intention-to-treat (ITT) analysis was conducted in the case of two participants who missed two assessments (109). There was no difference to the pattern of results when these two cases were included or excluded, and so these cases were excluded from relevant longitudinal analyses to provide "completer" analyses.

Clinical significance and reliable change scores were calculated with the clinical cut-off score being 1 SD below the Time 1 mean of the community comparison group. For measures where there was no data for this group (e.g., CSE), the Time 1 mean and SD for the waitlist group was used. The Reliable Change Index (RCI) was calculated using a formula, which includes a correction for practice effects as a result of test–retest designs (110). On the basis of clinical significance and reliable change scores, individuals were classified into change categories (recovered, improved, unchanged, deteriorated, or false positive) and the frequencies of the change categories were compared between groups using Fisher's Exact Test.

To investigate potential mechanisms of change, change scores between Time 1 and Time 2 were calculated for CSE and illness perceptions. To be candidate mechanisms of effect, these variables would need to be associated with receiving the intervention and to show changes that preceded change on outcome measures (111). Therefore, the change scores for CSE and illness perceptions were investigated for correlations with group assignment (intervention or waitlist) and with objective and subjective cognitive changes between Time 1 and Time 3.

RESULTS

DATA SCREENING AND PRELIMINARY ANALYSES

One intervention participant withdrew after Time 1 assessment and one waitlist participant did not complete Time 2 questionnaires or any Time 3 assessment. Missing data for specific questionnaires at single time points reduced the sample size slightly for analyses of Benefit Finding (by three intervention participants and two waitlist participants), K10 (one intervention and one waitlist participant), and FACT-Cog 3 (one waitlist and one community participant). There were no other missing data.

Several variables were skewed. Because transformations to correct skewness did not change the pattern of results, the untransformed data were retained for analyses. Inclusion or exclusion of outliers did not change results, and therefore outliers were retained for analyses. No corrections were needed for heterogeneity of variance (112).

Across the intervention group programs, 10 of the 15 participants attended all four group sessions (67%), and 5 participants attended three group sessions (33%). Five waitlist participants attended the intervention offered after completing their third assessment (39%).

PARTICIPANT CHARACTERISTICS

Participant demographic and medical data at Time 1 are shown in **Table 2**. There were no statistically significant differences among the groups in any of the demographic or medical variables. The two cancer groups also did not differ significantly from each other at Time 1 on any of the cognitive or psychosocial measures.

COGNITIVE RESULTS

Objective cognitive function

Descriptive statistics and RCT effect sizes for objective and subjective cognitive measures are shown in **Table 3**. At Time 1, only one cognitive measure, the RBANS Visuospatial/Constructional measure, showed a significant difference among the groups, F (2, 41) = 4.45, $p = 0.018$. This effect occurred because the intervention group scored significantly worse than the community group, $p = 0.031$, and the waitlist group showed a trend toward worse performance than the community group, $p = 0.063$.

For ANOVAs comparing the two cancer groups across three time points, there were no main effects of group on objective cognitive function. There was a main effect of time on all objective cognitive measures except for TMT B, indicating significant improvements over time. For TMT B, the time effect approached significance, F (2, 50) = 2.95, $p = 0.062$, $\eta_p^2 = 0.11$. There was a significant Group × Time interaction for TMT A,

Table 2 | Participant characteristics.

Variable	Intervention ($n = 16$)		Waitlist ($n = 13$)		Community ($n = 16$)	
	M (SD)	Range	*M* (SD)	Range	*M* (SD)	Range
Age (years)	50.4 (8.8)	37–65	51.8 (9.4)	40–72	52.9 (17.0)	27–77
Education (years)	15.8 (4.0)	11–26	13.8 (3.5)	9–20	13.9 (3.8)	10–20
Time since cancer diagnosis (months)	46.1 (22.8)	15–87	69.2 (56.5)	14–189	–	–
Time since finished cancer treatment (months)	37.1 (24.6)	6–84	46.5 (46.1)	6–137	–	–
	%		%		%	
Living with partner	68.8		84.6		75.0	
Female	93.8		100.0		93.8	
Born in Australia	62.5		76.9		56.3	
Neurological history	0.0		6.3		0.0	
Cancer type						
Breast	75.0		76.9		–	
Hematological	6.3		15.4		–	
Colorectal	6.3		7.7		–	
Prostate	6.3		–		–	
Ovarian	6.3		–		–	
Previous treatment						
Chemotherapy	81.3		100.0		–	
Radiotherapy	81.3		84.6		–	
Surgery	87.5		84.6		–	
Other	81.3		69.2		–	
Hormone treatment (current)	68.8		69.2		–	

Table 3 | Effect sizes, means (and standard deviations) for cognitive measures.

Measure	$d_{Int-Wait}$	Time 1			Time 2			Time 3	
	T2/T3	Intervention ($n = 15$)	Waitlist ($n = 13$)	Community ($n = 16$)	Intervention ($n = 15$)	Waitlist ($n = 13$)	Community ($n = 16$)	Intervention ($n = 15$)	Waitlist ($n = 12$)
Neuropsychological battery (RBANS)									
Total scale	0.19/ 0.32	97.2 (10.2)	94.5 (13.2)	98.3 (12.8)	106.4 (9.6)***	101.5 (13.7)**	94.6 (13.9)	110.5 (10.4)***	104.0 (10.0)***
Immediate memory	0.40/−0.04	97.7 (11.6)	97.2 (14.4)	100.5 (16.6)	104.3 (14.9)	98.4 (17.7)	99.3 (18.5)	112.3 (17.1)**	112.2 (10.2)**
Visuospatial/constructional	0.11/ 0.79	88.3 (12.8)	89.3 (14.3)	101.9 (15.1)	97.1 (14.1)*	96.5 (17.1)†	91.4 (18.3)**	98.5 (12.3)	88.5 (12.6)
Language	−0.16/ 0.13	102.5 (15.1)	97.3 (7.2)	94.8 (14.0)	108.6 (6.9)†	105.5 (11.2)*	102.3 (11.6)*	107.2 (10.1)	100.4 (8.1)
Attention/concentration	−0.25/−0.18	106.6 (13.7)	101.0 (17.9)	98.9 (15.3)	109.9 (10.9)	108.3 (13.1)*	101.1 (17.1)	112.8 (8.9)†	110.2 (16.3)**
Delayed memory	0.49/ 0.06	96.9 (8.8)	96.3 (17.3)	98.9 (11.1)	104.8 (12.3)**	97.5 (13.0)	101.5 (14.8)	106.5 (7.8)***	105.1 (12.9)**
Trail making test (TMT)									
TMT A	0.40/ **0.58**	32.9 (7.4)	34.7 (12.9)	30.5 (8.8)	24.1 (5.2)**	30.2 (10.4)	26.5 (7.7)	23.2 (5.1)***	31.2 (9.4)
TMT B	−0.06/ 0.14	54.9 (11.7)	63.9 (24.1)	67.5 (22.1)	52.3 (13.2)	60.2 (24.2)	63.3 (20.6)	48.7 (14.8)	60.3 (24.9)
Self report (FACT-Cog 3)									
Perceived cognitive impairments	**0.67**/ 0.31	33.7 (15.5)	34.4 (16.1)	75.4 (5.3)	45.6 (15.5)***	35.4 (17.0)	73.4 (8.5)	50.2 (15.2)***	46.0 (17.0)*
Comments from others	0.26/−0.20	12.7 (1.8)	12.0 (3.8)	15.4 (0.9)	14.5 (1.9)**	13.1 (2.2)†	15.8 (0.6)	13.9 (12.1)	13.8 (3.4)†
Perceived cognitive ability	0.65/ 0.68	13.5 (6.1)	16.2 (6.4)	32.1 (3.9)	17.5 (6.8)**	16.3 (6.6)	30.8 (6.8)	18.6 (8.1)*	16.9 (8.7)
Impact on QoL	0.13/ 0.22	8.8 (3.6)	9.3 (3.2)	15.6 (0.9)	10.3 (4.8)*	10.3 (3.3)	15.2 (1.8)	12.3 (4.6)***	12.0 (2.3)**
Self report (BAPM)									
Instrumental activities	−0.15/ 0.56	19.5 (4.5)	22.2 (8.5)		18.8 (7.2)	20.5 (9.6)		17.9 (7.9)	16.8 (6.4)†
Basic activities	0.13/ 0.06	11.9 (4.1)	12.2 (4.3)	–	12.4 (9.5)	13.3 (7.9)	–	10.7 (4.2)	10.8 (3.4)

*†p < 0.10, *p < 0.05, **p < 0.01, ***p < 0.001 for within-group comparison to Time 1.*

Higher scores indicate better performance for RBANS and FACT-Cog 3. Lower scores indicate better performance for Trail Making and BAPM. $d_{Int-Wait}$ = effect size for Intervention improvement corrected for Waitlist improvement. Effect sizes associated with statistically significant interactions for RCT participants (p < 0.05) are shown in bold text; effect sizes associated with interaction trends (p < 0.10) are underlined.

$F\ (2, 50) = 5.88$, $p = 0.005$, $\eta_p^2 = 0.19$. The interaction occurred because the two groups did not differ significantly in TMT A completion times at Time 1, $F\ (1, 25) = 0.08$, $p = 0.785$, $\eta_p^2 = 0.00$ whereas the intervention group was significantly faster than the control group at both Time 2, $F\ (1, 25) = 4.77$, $p = 0.038$, $\eta_p^2 = 0.16$, and Time 3, $F\ (1, 25) = 7.98$, $p = 0.009$, $\eta_p^2 = 0.24$. No other objective cognitive measure showed a Group × Time interaction when analyzed for the two cancer groups only.

For ANOVAs that included cancer and community groups from Time 1 to Time 2, there were no main effects of group on objective cognitive function. There was a main effect of time on several variables, in each case indicating significant improvements over time. These time effects occurred for the RBANS Total score, $F\ (1, 41) = 14.55$, $p < 0.001$, $\eta_p^2 = 0.26$, RBANS Language Index, $F\ (1, 41) = 10.97$, $p = 0.002$, $\eta_p^2 = 0.21$, and TMT A, $F\ (1, 41) = 11.50$, $p = 0.002$, $\eta_p^2 = 0.22$. RBANS Total also showed a Group × Time interaction, $F\ (2, 41) = 5.34$, $p = 0.009$, $\eta_p^2 = 0.21$. The interaction occurred because there were significant improvements on RBANS Total from Time 1 to Time 2 for intervention, $F\ (1, 41) = 16.10$, $p < 0.001$, $\eta_p^2 = 0.28$, and waitlist, $F\ (1, 41) = 7.90$, $p = 0.008$, $\eta_p^2 = 0.16$, but not community participants, $F\ (1, 41) = 0.11$, $p = 0.737$, $\eta_p^2 = 0.00$. A Group × Time interaction for the Visuospatial/Constructional index, $F\ (2, 41) = 9.88$, $p < 0.001$, $\eta_p^2 = 0.33$ occurred because the cancer groups scored significantly worse than the community group at Time 1 (as noted above), but there was no difference among the groups at Time 2, $F\ (2, 41) = 0.54$, $p = 0.585$, $\eta_p^2 = 0.03$. Delayed Memory showed a trend toward a Group × Time interaction, $F\ (2, 41) = 3.02$, $p = 0.060$, $\eta_p^2 = 0.13$. Simple effects testing showed that Delayed Memory improved significantly from Time 1 to Time 2 for the intervention group, $F\ (1, 41) = 9.01$, $p = 0.005$, $\eta_p^2 = 0.18$, but not for waitlist, $p = 0.687$, or community participants, $p = 0.771$. No other objective cognitive measure showed a Group × Time interaction when analyzed across all three participant groups.

Clinical significance and reliable change scores were calculated for changes from Time 1 to Time 2 and Time 1 to Time 3, respectively, in order to more fully understand changes over time for individuals in each of the groups. Fisher's Exact Test showed significant differences among the groups in the frequency of reliable change categories for the RBANS visuospatial/constructional scale at Time 2 ($p = 0.030$) and TMT A at Time 3 ($p = 0.002$). The difference in category frequencies for Visuospatial/Constructional scores at Time 3 approached statistical significance ($p = 0.072$). Visuospatial/Constructional scores showed reliable improvement or recovery at Time 2 for 27, 13, and 6% of intervention, waitlist, and community participants, respectively, with an unexpected reliable deterioration for 31% of community participants compared with 0% of cancer survivor participants. By Time 3, 47% of intervention and 8% of waitlist participants were classified as recovered on the Visuospatial/Constructional score. For TMT A, 0% of intervention participants, 13% of waitlist participants and 6% of community participants showed reliable improvement or recovery at Time 2. By Time 3, 46% of intervention and 0% of waitlist participants showed recovery on TMT A.

Subjective cognitive function

Descriptive statistics and RCT effect sizes are shown in **Table 3**. Both cancer groups reported significantly worse subjective cognitive function than the community group at Time 1, on all four FACT-Cog 3 subscales (all ps < 0.001).

For ANOVAs comparing the two cancer groups across three time points, there were no main effects of group on subjective cognitive function. There was a main effect of time on all FACT-Cog 3 measures, indicating significant improvements over time in these subjective cognitive functions. For BAPM-instrumental activities, a time effect approached significance, $F\ (2, 50) = 3.14$, $p = 0.083$, $\eta_p^2 = 0.10$. There was a trend toward a Group × Time interaction for FACT-Cog perceived cognitive impairments, $F\ (2, 50) = 3.14$, $p = 0.052$, $\eta_p^2 = 0.11$. This trend was associated with significantly reduced perceived impairments for the intervention group at Time 2, $p = 0.002$, and Time 3, $p < 0.001$, in comparison with the waitlist group showing no change at Time 2, $p = 0.999$, but significant improvement at Time 3, $p = 0.013$. There were no statistically significant effects for the measures of subjective prospective memory (BAPM), which were assessed in cancer survivor groups only.

For ANOVAs that included cancer and community groups from Time 1 to Time 2, there were main effects of group on all FACT-Cog 3 subscales, indicating worse subjective cognitive function reported by the cancer survivor groups than the community comparison group. There were main effects of time for perceived cognitive impairments, $p = 0.025$, and comments from others, $p = 0.001$, and trends toward time effects for perceived cognitive ability, $p = 0.070$, and impact on QoL, $p = 0.083$. In each case, the time effects indicated better subjective cognitive function over time. There was a Group × Time interaction for Perceived Cognitive Impairments, $F\ (2, 40) = 7.72$, $p = 0.001$, $\eta_p^2 = 0.28$. The interaction occurred because the intervention group reported significant improvement on Perceived Cognitive Impairment at Time 2, $F\ (1, 40) = 20.39$, $p < 0.001$, $\eta_p^2 = 0.34$, whereas the other groups did not change significantly (waitlist $p = 0.736$, community $p = 0.448$). Impact on QoL showed a trend toward a Group × Time interaction, $F\ (2, 40) = 2.47$, $p = 0.097$, $\eta_p^2 = 0.11$. Simple effects testing showed that Impact on QoL improved significantly from Time 1 to Time 2 for the intervention group, $F\ (1, 40) = 5.25$, $p = 0.027$, $\eta_p^2 = 0.12$, but not for waitlist, $p = 0.170$, or community participants, $p = 0.484$. No other subjective cognitive measure showed a Group × Time interaction when analyzed across all three participant groups.

Changes for individuals according to clinical significance and reliable change criteria showed a significant difference among groups in categories of change from Time 1 to Time 2 in perceived cognitive impairments, $p = 0.002$. There was clinically significant improvement or recovery on perceived cognitive impairments by Time 2 for 60, 17, and 0% of intervention, waitlist, and community participants respectively. By Time 3, perceived cognitive impairments showed clinically significant improvement or recovery for 73% of intervention and 50% of waitlist participants. A difference among groups also occurred in change categories for comments from others for Time 1 to Time 2, $p = 0.047$. There was clinically significant improvement or recovery on this measure for 27% of intervention, 18% of waitlist, and 0% of community participants

at Time 2. At Time 3, clinically significant improvement or recovery in comments from others was seen in 13% of intervention and 27% of waitlist participants, respectively. There were trends toward differences in change categories for the BAPM-instrumental measure at Time 2, $p = 0.075$, and Time 3, $p = 0.075$. These effects for the instrumental measure were associated with reliable change in waitlist participants only and were the same at both time points: one waitlist participant recovered (8 cf. 0% for intervention group) and two other waitlist participants who were classified as "false positive" (17 cf. 0% for intervention group).

PSYCHOSOCIAL RESULTS

Descriptive statistics and RCT effect sizes are shown in **Table 4**. There were significant group effects at Time 1 for distress ($p < 0.001$), QoL ($p < 0.001$ to $p = 0.021$), and fatigue ($p = 0.005$). For distress, emotional function, cognitive function, and social function, both cancer groups reported significantly worse function at Time 1 than the community group. For physical function, role function, global QoL, and fatigue, the intervention group reported significantly worse Time 1 function than the community group and the waitlist group did not differ significantly from the other two groups.

For ANOVAs comparing the two cancer groups across three time points, there were no main effects of group on psychosocial measures. Seven of the 11 psychosocial measures showed time main effects, indicating statistically significant improvements over time in physical function, emotional function, subjective cognitive function, social function, global QoL, CSE, and illness perceptions. The time main effect approached significance for fatigue, $F\ (2, 50) = 3.16$, $p = 0.051$, $\eta_p^2 = 0.11$, and K10 distress, $F\ (2, 46) = 2.90$, $p = 0.065$, $\eta_p^2 = 0.11$. There was no effect of time for either role function or benefit finding. There was a trend toward a Group ×Time interaction for social function, $F\ (2, 50) = 2.52$, $p = 0.091$, $\eta_p^2 = 0.09$. This trend was associated with statistically significant improvement in social function over time for the intervention group, $F\ (2, 24) = 10.87$, $p < 0.001$, $\eta_p^2 = 0.48$, but not the waitlist group, $F\ (2, 24) = 1.92$, $p = 0.168$, $\eta_p^2 = 0.14$. There were no other interactions for the two cancer survivor groups on the psychosocial measures.

For ANOVAs that included cancer and community groups from Time 1 to Time 2, there were main effects of group on all psychosocial measures except for illness perceptions. These main effects indicated worse QoL and more distress for cancer survivors than for the community group. There were also main effects of time, indicating significant improvement on physical function, role function, emotional function, global QoL, fatigue, distress, and illness perceptions. Social function showed a trend toward a time effect, $F\ (1, 40) = 3.69$, $p = 0.062$, $\eta_p^2 = 0.08$, leaving subjective cognitive function as the only psychosocial measure that did not have a time main effect across the three groups. There was a Group × Time interaction for social function, $F\ (2, 40) = 4.54$, $p = 0.017$, $\eta_p^2 = 0.19$. The interaction occurred because the intervention group improved significantly in social function, $F\ (1, 40) = 12.74$, $p = 0.001$, $\eta_p^2 = 0.24$, but there was no change for the waitlist, $F\ (1, 40) = 0.06$, $p = 0.804$, $\eta_p^2 = 0.00$, or community groups, $F\ (1, 40) = 0.19$, $p = 0.668$, $\eta_p^2 = 0.01$.

Table 4 | Effect sizes, means (and standard deviations) for psychosocial measures.

Measure	$d_{Int\text{-}Wait}$	Time 1			Time 2			Time 3	
	T2/T3	Intervention ($n = 15$)	Waitlist ($n = 12$)	Community ($n = 16$)	Intervention ($n = 15$)	Waitlist ($n = 12$)	Community ($n = 16$)	Intervention ($n = 15$)	Waitlist ($n = 12$)
QoL (QLQ–C30)									
Physical	−0.06/0.13	80.9 (24.9)	81.1 (18.4)	97.9 (4.0)	84.4 (17.6)	86.1 (10.4)*	98.3 (14.8)	88.9 (14.2)	86.1 (16.4)
Role	0.40/0.28	72.2 (27.2)	79.2 (23.7)	93.8 (14.8)	85.6 (29.5)*	81.9 (19.4)	96.9 (9.1)	81.1 (32.0)	80.6 (15.6)
Emotional	0.00/−0.13	56.7 (28.2)	59.7 (15.8)	87.5 (12.9)	69.4 (27.6)*	69.4 (19.2)	88.4 (12.1)	70.6 (29.7)*	73.6 (13.2)*
Cognitive	0.37/0.17	55.6 (18.6)	59.7 (19.4)	96.9 (6.7)	65.6 (21.3)*	62.5 (19.0)	96.9 (6.7)	70.0 (28.9)†	70.8 (14.4)
Social	0.63/0.64	53.3 (24.6)	68.1 (26.1)	99.0 (4.2)	71.1 (28.5)**	69.4 (24.5)	96.9 (9.1)	81.1 (28.1)***	79.2 (17.6)
Global QoL	0.32/0.39	61.7 (23.1)	68.1 (15.6)	82.8 (15.1)	71.7 (22.0)*	71.5 (14.8)	85.4 (13.8)	73.9 (20.4)*	72.2 (13.9)
Fatigue	0.08/0.53	51.1 (27.1)	45.8 (19.0)	22.9 (20.1)	42.2 (23.5)†	38.9 (17.9)	14.6 (14.8)†	42.2 (28.1)	50.0 (26.6)
Distress (K10)	0.38/0.10	21.2 (7.0)	20.8 (5.2)	12.6 (2.6)	17.9 (7.4)**	19.8 (4.5)	12.2 (2.1)	18.4 (10.4)	19.3 (3.1)
Benefit finding	0.48/0.06	58.1 (13.8)	65.6 (12.2)	–	64.7 (9.4)†	64.7 (10.0)	–	60.8 (16.7)	67.4 (11.0)
CSE	0.13/**0.18**	39.1 (12.3)	43.6 (8.5)	–	42.3 (12.6)	43.8 (8.2)	–	47.0 (9.7)***	46.0 (5.7)
Illness perceptions (BIPQ)	0.36/0.45	45.9 (10.3)	43.1 (11.4)	49.3 (12.4)	37.4 (13.2)*	38.5 (9.5)	40.0 (9.0)**	35.6 (18.0)***	37.7 (11.3)

†$p < 0.10$, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ for within-group comparison to Time 1.

Higher scores indicate better QoL for all QLQ–C30 measures except fatigue; more benefit finding; and better CSE. Lower scores indicate less QLQ–C30 fatigue, less distress on K10 and more functional illness perceptions. $d_{Int\text{-}Wait}$ *= effect size for Intervention improvement corrected for Waitlist improvement. Effect sizes associated with statistically significant interactions for RCT participants ($p < 0.05$) are shown in bold text; effect sizes associated with interaction trends ($p < 0.10$) are underlined.*

There was a trend toward a Group × Time interaction for distress, F (2, 39) = 2.46, p = 0.099, η_p^2 = 0.11. This trend was associated with a significant reduction in distress from Time 1 to Time 2 for the intervention group, F (1, 39) = 10.69, p = 0.002, η_p^2 = 0.22, but no change for the waitlist, F (1, 39) = 0.68, p = 0.414, η_p^2 = 0.02, or community groups, F (1, 39) = 0.15, p = 0.698, η_p^2 = 0.00. There was no indication of interaction effects on other psychosocial measures when analyzed across all three participant groups.

Changes for individuals according to clinical significance and reliable change criteria showed a trend toward a difference among groups in categories of change from Time 1 to Time 3 in K10 distress, p = 0.059. From Time 1 to Time 2, one waitlist participant showed reliable improvement in distress (8%) compared to 0% of intervention and community participants. From Time 1 to Time 3, there was clinically reliable recovery (five participants) or improvement (two participants) in distress for intervention participants (50% of intervention participants), compared to zero waitlist participants recovered and three improved (25%). However, there was also clinically reliable worsening of distress by Time 3 for two intervention participants (14%) and one waitlist participant (8%). No other psychosocial measures approached statistical significance for differences among participant groups in categories of change for individuals.

ASSOCIATIONS BETWEEN COGNITIVE MEASURES AND POTENTIAL PSYCHOSOCIAL MECHANISMS

In order to investigate the relationships between cognitive functioning and potential mechanisms of change, a number of correlations were calculated within the cancer survivor groups. Change scores from Time 1 to Time 2 were calculated for illness perceptions and CSE. These two sets of change scores were then investigated for correlations with group (intervention or waitlist) and with Time 1 to Time 3 change scores for objective and subjective cognitive measures (see **Table 5**).

As **Table 5** shows, there was a statistically significant correlation between improved CSE at Time 2 and improved FACT-Cog Impact on QoL between Time 1 and Time 3. There was a similar trend for CSE and FACT-Cog Perceived cognitive abilities, as well as trends toward correlations between improved illness perceptions and later improvements in FACT-Cog comments from others and perceived cognitive abilities. Correlations between the CSE and illness perceptions change scores with group assignment were not statistically significant, but were in the predicted directions (as were 17 of the 20 correlations in **Table 5**). The correlation between CSE change and illness perceptions change was not statistically significant, r (26) = –0.23, p = 0.269.

Table 5 | Correlations between change in psychosocial predictors at Time 2 and change in cognitive measures at Time 3.

Variable	CSE T2–T1 *r (p)*	BIPQ T2–T1 *r (p)*
Group[a]	0.19 (0.349)	−0.29 (0.156)
Objective change scores Time 3 – Time 1		
RBANS (Total)	0.22 (0.279)	−0.06 (0.777)
TMT A	0.17 (0.411)	0.24 (0.248)
TMT B	−0.14 (0.480)	−0.10 (0.627)
Subjective change scores Time 3 – Time 1		
FACT-Cog 3		
Perceived cognitive impairments	0.30 (0.129)	−0.21 (0.301)
Comments from others	−0.11 (0.605)	−0.35 (0.086)
Perceived cognitive abilities	0.36 (0.068)	−0.36 (0.068)
Impact on QoL	0.45 (0.020)	−0.27 (0.188)
BAPM		
IADL	−0.01 (0.981)	0.02 (0.937)
BADL	−0.06 (0.785)	0.20 (0.321)

[a]*Waitlist = 0, Intervention = 1.*

Higher scores indicate better performance for RBANS, FACT-Cog 3, and CSE. Lower scores indicate better performance for TMT, BAPM, and Illness Perceptions.

Outcome measures that showed significantly larger effect sizes for intervention than waitlist participants were TMT A, perceived cognitive impairments from FACT-Cog 3, and CSE. Additional noteworthy trends indicating possible effects of the intervention occurred for perceived cognitive ability from FACT-Cog 3, social functioning, and fatigue. There were some indications of improved CSE and illness perceptions being associated with later improvements in subjective cognitive functioning.

OBJECTIVE COGNITIVE FUNCTION

There was partial support for Hypothesis 1, which predicted that participating in the intervention may lead to improvements in objective cognition. Intervention participants improved significantly more than waitlist participants in the time taken to complete TMT A. These results were consistent with the previous study assessing ReCog (75), and another study assessing the MAAT program (82), which also found significantly greater improvement for the intervention group on this measure as well as continued improvement from Time 2 to Time 3. These findings suggest ReCog to be beneficial for cognitive processes required in TMT part A, such as processing speed, visual scanning, and numeric sequencing. The current findings, in combination with results of previous research, also suggest that participants may continue to improve on some measures over a longer rather than shorter follow-up period after the intervention. This may be due to the practice-based nature of strategies included in ReCog and therefore further development of skills measured by these assessments over time. These findings are relevant in the context of literature indicating attention and concentration, processing speed, and executive functioning to be domains particularly vulnerable to problems following cancer treatment (113). For all other objective cognitive measures, there were main effects of time (or

DISCUSSION

The current study used an RCT design to investigate the impact of a group intervention program targeting cancer-related cognitive dysfunction. Participants were cancer survivors who were randomly allocated to the intervention or waitlist, as well as a sample of people from the general public who participated as an additional non-randomized control group. The design incorporated evaluation of two potential psychological mechanisms of change, illness perceptions, and CSE.

near-significant trends) for RCT participants, showing improvement over time for cancer survivors but no Group × Time interactions in ANOVA. Two previous RCTs have also found objective benefits for a cognitive rehabilitation intervention compared to waitlist to be limited to a single measure in the battery (86, 87).

Cancer survivors and community participants had equivalent objective cognitive performance at baseline except for the RBANS visuospatial/constructional index, which was significantly worse for cancer survivors. This finding was congruent with previous research indicating that visuospatial and verbal domains may be areas mostly affected by cancer and cancer treatments (12). Analyses of the community and cancer survivor data showed statistically significant interactions for RBANS total and visuospatial/constructional indices and a trend toward an interaction for delayed memory. These interactions were associated with bigger improvements for cancer survivors than for community participants, but with no difference in improvements between intervention and waitlist participants. The RBANS findings contrasted with a previous study of the same intervention, which found significant improvement on the RBANS total score for those who completed ReCog with a larger between-groups effect size when compared to the cancer comparison group than found in the current study ($d = 1.00$ vs. 0.19) (75). Research has suggested that effect sizes reported in pilot studies often differ from consequent RCT studies implementing the same interventions (114).

It is possible that both the intervention and waitlist groups showed improvement on RBANS measures due to practice effects or increased effort at re-testing. For the community group, although they may have also been motivated to participate due to awareness they were assisting with cancer survivorship research, they may not have been as motivated as the other two groups to do well or to improve their performance. Another interpretation of these findings could be that cancer survivors were less able to demonstrate their cognitive abilities at initial assessment and thus showed more benefit from repeat assessments than community participants, but the lack of objective cognitive baseline differences between cancer survivors and community participants on all but one measure makes this interpretation less likely. A further possibility is that participating in the assessments (with or without the intervention, and in the absence of feedback) helped give cancer survivors a sense that their cognitive performance was not as bad as they had initially thought, improving CSE, which may have helped them to improve their performance. This interpretation is consistent with improvements over time for both intervention and waitlist participants on subjective cognition and other psychosocial measures.

Looking at changes for individuals in relation to reliable change and clinical significance criteria, there were significant differences between groups in categories of change, with more intervention than waitlist participants showing "recovery" at Time 3 (TMT A 46 vs. 0% recovered; visuospatial/constructional index 47 vs. 8% recovered). These results were promising and indicated greater clinical improvement for participants who completed ReCog. Unexpectedly, 31% of community participants showed reliable "deterioration" on the visuospatial/constructional index at Time 2 (as also reflected in a significant simple effect of time within the community group), which suggests that results on this measure should be interpreted with caution.

SUBJECTIVE COGNITIVE FUNCTION AND OTHER PSYCHOSOCIAL MEASURES

There was partial support for Hypothesis 2 regarding intervention effects on subjective cognition. Intervention participants improved significantly more than waitlist participants on FACT-Cog perceived cognitive impairments from Time 1 to 2, but both groups showed similar improvements from Time 1 to Time 3. By Time 3, 73% of intervention and 50% of waitlist participants showed clinically significant improvement or recovery on perceived cognitive impairments. Perceived cognitive ability showed a trend toward greater improvements for intervention than waitlist participants. Other FACT-Cog subscales tended to improve over time for both RCT groups. Again the improvements in the waitlist group may indicate improved awareness, and an improvement in perceptions, of cognitive functioning as a result of the testing sessions. The variable length of time since participants had completed cancer treatments (see **Table 2**) argues against improvement in the waitlist group being attributed solely to ongoing recovery. Measures of prospective memory showed no statistically significant effects, which differed from another intervention study in this area that demonstrated improvement on this construct (104), but a different measure was used in the current study.

Hypothesis 3, which proposed intervention effects on psychosocial variables, was partially supported in relation to the intervention group demonstrating trends toward greater improvement in social functioning and fatigue, as shown by effect size comparisons in **Table 4**. The social function trend replicated a finding from the previous study of ReCog, but in both studies the interpretation of this finding is tempered by the consideration that the intervention group tended to report poorer social function at baseline (75). The social support element of group therapy and inclusion of broad elements in ReCog including self-care issues such as fatigue management mean that these effects could plausibly be associated with the intervention.

In contrast to objective measures, all four subjective cognitive measures showed worse performance of the cancer survivors than community participants at baseline. Cancer survivors also reported significantly worse QoL, fatigue, and distress than community participants at baseline. These results were consistent with previous literature suggesting an impact of cancer and cancer-related treatments on these psychosocial areas of functioning, as well as the finding that discrepancies between cancer survivors and community participants are often greater on subjective than objective measures of cognitive function (9). Although many of the subjective cognitive and psychosocial measures improved over time for the cancer survivors in the study, they continued to report worse average functioning than demographically matched community participants on most self-report measures, as can be seen from descriptive statistics in **Tables 3** and **4**. It would be of interest to find out whether a longer intervention, individual treatment, or more focus on broader issues would result in a higher proportion of cancer survivors finishing an intervention or follow-up period in the same range on subjective cognition and psychosocial measures as people who have not experienced cancer.

POTENTIAL MECHANISMS

There was partial support for Hypotheses 4 (regarding intervention effects on illness perceptions and CSE) and 5 (regarding changes in illness perceptions and CSE predicting other intervention effects). CSE showed a significantly greater effect size for the intervention than waitlist group, and simple effects of time within group showed that both illness perceptions and CSE improved significantly in the intervention but not the waitlist group. If an intervention such as ReCog can deliver benefits by activating or strengthening participants' beliefs that they are capable of improving cognitive performance by means they can control (such as use of skills practice or compensatory strategies), this would be expected to be reflected in improvements on variables such as illness perceptions and CSE and there was some evidence for this in the findings. However, neither variable could be directly compared with community data at baseline, because the measures were linked to perceptions of existing cognitive problems. To provide some basis of comparison, community participants reported illness perceptions in relation to a hypothetical scenario: what they thought it would be like if they experienced cognitive difficulties. Cancer survivors, in contrast, reported illness perceptions in relation to the cognitive problems that they actually experienced (as an inclusion criterion for the study). The illness perceptions that cancer survivors reported were no worse than what community participants imagined these problems would be like.

The occurrence of several statistically significant or near-significant correlations between earlier change scores for CSE or illness perceptions and later change scores for subjective cognitive FACT-Cog-3 subscales gave some support for these variables as potential mediators of intervention effect. The importance of mindset to self-reported cognitive problems in cancer survivors has previously been demonstrated via effects such as priming (115). However, these correlations could also indicate the reverse direction of causality or a third, common cause of change in both sets of variables. Larger studies are needed for more rigorous investigation of potential mediators of effect.

STRENGTHS AND LIMITATIONS

The study had a number of strengths. Groups were well matched and included a non-cancer group for further understanding of change over time as well as providing data for computing reliable change and clinical significance. Retention of participants was high across all groups. Assessors were unaware of group allocation for RCT participants serving to minimize observer bias. The study used a previously reported, manualized intervention and included assessment of potential mechanisms of intervention effect. The study was also the first to include an adapted version of the Traumatic Brain Injury Self-Efficacy Scale to assess CSE in cancer survivors.

A limitation of the current study is that the community group did not complete all of the measures administered to the treatment and waitlist group, and community participants did not complete a third assessment point. These issues occurred due to the community data being collected prior to the final selection of RCT measures, and this has limited comparison of certain measures and follow-up effects to the cancer groups only. The sample size in the current study was also relatively small, which is similar to most previous studies in this area, and impacts the power of analyses to detect smaller effects that may nevertheless be of clinical significance. The risk of Type 1 error was adjusted within analyses of each variable (e.g., use of simple effects analysis with a pooled error term and Bonferroni correction) but not between variables. For studies of this kind with larger sample sizes, it may also be beneficial to consider stratification by types of cancer and/or treatment during the randomization stage since these factors may influence the results. Results for the visuospatial/constructional index should be interpreted with caution, because the community participants unexpectedly performed significantly worse on this index at retest, suggesting variability in performance on this index may have been affected by factors other than practice and intervention effects. One possibility is that community participants may have felt less motivated to perform at their best at retest, but an RBANS "effort index" comprised of tests independent of the visuospatial/constructional scale (116) did not detect diminished effort among community participants with significantly worse visuospatial/constructional performance at retest. The need for subjective scoring of one of the subtests in the measure also does not fully account for the decrease, because it was also seen in performance on an objectively scored subtest in the same index. Another consideration in future studies could be to assess the use of hormonal replacement therapy in community participants, since this may impact outcomes. A final limitation of the current study was the use of a waitlist rather than an active control group, which increases the possibility of other factors contributing to the results and limits the ability to attribute changes to the intervention. The use of an active control group, and providing participants who are not immediately engaged in an intervention with some form of activity in the meantime, may control for issues associated with potential expectation of benefit, time of testing, and attention. This methodological improvement would provide a stronger research design and allow interpretation of effects as being more clearly attributable to the intervention.

FUTURE DIRECTIONS

Overall, these findings have provided further insight into the utility of a psychological intervention for people experiencing cognitive dysfunction following treatment for cancer. There was evidence to support improvements in areas of subjective and objective cognitive function, as well as areas of psychosocial functioning, for those who completed the ReCog program. As the study was limited by small sample size, it is difficult to generalize the results to the broader population of people who experience cancer-related cognitive dysfunction. However, the improvements observed in the intervention group warrant further investigation of interventions such as ReCog. Formal assessment of economic costs and benefits would be helpful; the main costs associated with the intervention are staff time and other resources required are few, although the use of more costly or extensive assessments would increase the resource requirements.

All intervention studies reported in this paper have found some degree of improvement in objective and/or subjective cognitive performance for post-treatment cancer survivors who are retested over time. However, improvements also frequently occur in participants who are waitlisted or who take part in interventions that are

not specifically targeted toward cognitive rehabilitation. It will be important for future research to more clearly define active ingredients of interventions and to consider alternative approaches of assisting cancer survivors with this issue. Careful selection of comparison conditions and studies with larger number of participants will be important in this endeavor.

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Systematic review of interventions to improve the provision of information for adults with primary brain tumors and their caregivers

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Background: Adults with primary brain tumors and their caregivers have significant information needs. This review assessed the effect of interventions to improve information provision for adult primary brain tumor patients and/or their caregivers.

Methods: We included randomized or non-randomized trials testing educational interventions that had outcomes of information provision, knowledge, understanding, recall, or satisfaction with the intervention, for adults diagnosed with primary brain tumors and/or their family or caregivers. PubMed, MEDLINE, EMBASE, and Cochrane Reviews databases were searched for studies published between 1980 and June 2014.

Results: Two randomized controlled, 1 non-randomized controlled, and 10 single group pre–post trials enrolled more than 411 participants. Five group, four practice/process change, and four individual interventions assessed satisfaction (12 studies), knowledge (4 studies), and information provision (2 studies). Nine studies reported high rates of satisfaction. Three studies showed statistically significant improvements over time in knowledge and two showed greater information was provided to intervention than control group participants, although statistical testing was not performed.

Discussion: The trials assessed intermediate outcomes such as satisfaction, and only 4/13 reported on knowledge improvements. Few trials had a randomized controlled design and risk of bias was either evident or could not be assessed in most domains.

Keywords: neuro-oncology, brain tumor, information, doctor–patient communication, caregivers

INTRODUCTION

The provision of appropriate and timely information, tailored to the medical condition, needs, and preferences, is essential to allow patients and their families to cope with the diagnosis, access supportive resources, and reduce uncertainty and distress (1, 2). Information provision is essential for participation in decision-making and to enable patients to give informed consent for treatment (3–5). It also may improve compliance with treatment (6). Both during and after active treatment, information can aid patients and their families to monitor symptoms and undertake self-care. Information can also assist family members to develop skills to undertake caring tasks (7–9).

A range of strategies have been developed to facilitate information provision in the cancer setting more widely. Traditional approaches include written information, videos, CD or, more recently, websites and apps (10, 11). Strategies may also aim to improve communication between patients and healthcare professionals by means of treatment summary letters, provision of audio-tapes of consultations to patients, and communication skills training for doctors. Overall, these have been developed and evaluated widely for patients with cancer. Promising findings have specifically been shown with the use of such strategies for those with high needs, including patients requiring treatment for lung cancer or palliative care, with promising findings (12, 13).

Specifically for patients with brain tumors, studies suggest that they are not satisfied with the information that they have been provided. Patients want to receive more information, and wish the information to be more detailed (14–22). Further information is particularly required in two areas: (1) fatigue, insomnia, and psychological disturbance (17, 23); and (2) changes in physical function and body image (24). Caregivers require information on how to provide care (25), and how to manage physical, cognitive, and personality changes in the patient and cope with changes in family roles (26). The reasons why these needs are not well met are not clear; however, certain factors are apparent. In terms of patient characteristics, distress resulting from the diagnosis may impair some patients' abilities to process information, particularly as the brain is commonly understood to define the "self" (27). Cognitive and physical changes resulting from a brain tumor or its treatment may also impair information seeking or comprehension for some patients (28). Cognitive impairment is the most common deficiency in primary brain tumor patients, particularly affecting executive function, visuoconstructive abilities, attention, and verbal memory (29). Memory

loss, information processing, and attention are commonly affected by radiotherapy and chemotherapy (30). Deficits may also arise due to the tumor itself, raised intracranial pressure, or as the result of surgery (31). Cognitive impairment has been shown to affect patients' awareness of their prognosis and ability to process information (32). Considering factors relating to healthcare professionals, the information provided may be insufficient due to clinicians' views of what patients need. For example, some healthcare professionals may hold back "unnecessary" information in an attempt to "protect" patients from distress, particularly with regard to issues such as preparing wills, advanced health directives, or the immediacy of palliative care required (33). Materials used to convey information also have limitations, as they often require higher levels of literacy than is common in the population (34).

Patient, healthcare professional, and interactive issues are also likely to impact how well interventions aiming to improve information provision will reach patients with brain tumors and improve their satisfaction with care. Although some (but by no means all) informational interventions have been well studied in general cancer populations, the cognitive impairments experienced by brain tumor patients and the resulting concerns of this group are unique, and it cannot be assumed that interventions will be equally effective when applied to these patients and their caregivers. This review thus aimed to examine whether patient-, caregiver-, or healthcare professional-directed interventions improve information provision, satisfaction with the intervention, or other commonly assessed outcomes (35) such as knowledge, understanding, or recall for adults diagnosed with primary brain tumors and/or their family or caregivers.

MATERIALS AND METHODS

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Randomized and non-randomized trials including single arm studies were eligible for inclusion. To be included, studies needed to test one or more interventions, which tested an educational component (i.e., involving knowledge transfer, using any format or materials) and which reported one or more of the outcomes: information provision, knowledge, understanding, recall, or satisfaction with the intervention. There were no language restrictions. Case reports, personal narratives, editorials, commentaries, and reviews were excluded.

As this review was concerned with outcomes for adults diagnosed with primary brain tumors and/or their informal caregivers, studies with both adults and children need to report outcomes for adults (18+ years) and children (<18 years) separately, or at least 75% of the sample needed to be aged 18+ years. Similarly, at least 75% of patients needed to be diagnosed with primary (malignant or benign) brain tumors, or outcomes needed to be reported for primary brain tumor patients separately. Studies involving caregivers were eligible either in conjunction with or separately to studies involving patients. Caregiver studies were eligible only for informal or family caregivers (i.e., not paid caregivers or healthcare professionals), although studies involving interventions targeting healthcare professionals were eligible where the aim of the intervention was to ultimately improve information provision to primary brain tumor patients or caregivers.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

Searches of PubMed, MEDLINE, EMBASE, CINAHL (via EBSCOhost), and PsychINFO (via EBSCOhost) were conducted for the years 1980–2014, to identify reports of relevant studies. Search terms used medical subject headings (MeSH) and keywords relating to brain tumors, patient education, doctor–patient communication, and information provision (see **Box 1** for an illustration). We also reviewed the reference lists of included studies and relevant reviews for further references to relevant trials.

DATA COLLECTION AND ANALYSIS

Articles identified from all sources were downloaded into a reference management software package and duplicates were removed. One author pre-screened all results (titles and abstracts) for possible inclusion based on the inclusion criteria. The full text of selected articles was then obtained and assessed against the inclusion criteria. Data were extracted by one author using a template, collecting study design, population, intervention characteristics, and outcomes. Where data were missing or unclear, or to obtain additional data, we attempted to contact lead study authors, to obtain the data needed for analyses. Where necessary, titles, abstracts, and full text were translated into English to allow assessment and data collection.

Both authors independently assessed risk of bias in individual studies in seven domains (random allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias), taken

Box 1 | Search terms used for MEDLINE.

Search	Query content
S1	Brain neoplasms (MeSH)
S2	Neuro-oncology OR neuro-oncology (title/abstract)
S3	Glioma OR glioblastoma OR astrocytoma OR meningioma OR schwannoma OR oligodendroglioma OR medulloblastoma OR ependymoma (title/abstract)
S4	Brain tumor OR brain tumor OR brain cancer OR brain neoplasm (title/abstract)
S5	1 OR 2 OR 3 OR 4
S6	Patient Education as Topic (MeSH)
S7	Professional Patient Relations (MeSH)
S8	Information Dissemination (MeSH)
S9	Consumer Health Information (MeSH)
S10	Pamphlets (MeSH)
S11	Audiovisual aids (MeSH)
S12	Information provision (title/abstract)
S13	6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
S14	5 AND 13
S15	Animals NOT humans (MeSH)
S16	14 NOT 15
S17	Limit date 1980–June 30 2014

from the Cochrane Handbook of Systematic Reviews (36). Non-randomized and single arm studies were assessed and reported as being at a high risk of bias on the random allocation sequence generation and allocation concealment items of the "Risk of bias" tool. Risk of bias ratings was compared and consensus reached.

We had planned to pool the data across studies statistically using meta-analysis but the heterogeneity in intervention types, outcomes, and study designs meant that the data were unsuitable for this. We have thus conducted a narrative synthesis of results, grouping the data based on the category that best explores the heterogeneity of studies, in this case nature of the intervention (group level, practice or process change, or individual level). Within each category, we narratively summarized the results.

RESULTS

SEARCH RESULTS

Eight hundred and thirty-nine original articles were identified, 48 of which were assessed at the full text level for eligibility. The screening and selection process is outlined in a PRISMA flow chart, see **Figure 1**.

INCLUDED STUDIES

A total of 16 articles reporting on 13 studies involving more than 210 patients, 87 caregivers and 104 healthcare professionals were selected for inclusion (**Tables 1** and **2**). Studies for which quantitative data were available are described in **Table 1**; **Table 2** reports on the studies for which no quantitative results were reported. Two studies were randomized controlled trials (37, 38), one was a non-randomized trial with control group (39), and the remainder was single arm trials (40–48). Studies were most commonly conducted in the US [6 studies (38, 41–44, 46)] and Australia [3 studies (39, 47)], with single studies conducted in Canada (40), Austria (45), the Netherlands (37), and the UK (48). Six studies involved patients only (37–39, 41, 42, 48), two targeted caregivers only (43, 47), two healthcare professionals only (44, 47), and two both patients and caregivers (45, 46). A single study reported patient and healthcare professional participants (40), although only the patient participants were eligible for and included in this review. Four studies did not specify the sample size (43, 48), or data collection was in progress at the time of reporting (37, 42). Median participant sample sizes were 32 (range 13–50) for patients, 39 (range 7–41) for caregivers, and 52 (range 43–61) for healthcare professionals. One study was published only as a protocol (37), and four studies only in conference abstracts (41–43, 46). An attempt was made to contact corresponding authors of all included studies in order to verify methods and to obtain missing data, and six authors responded to requests for additional information.

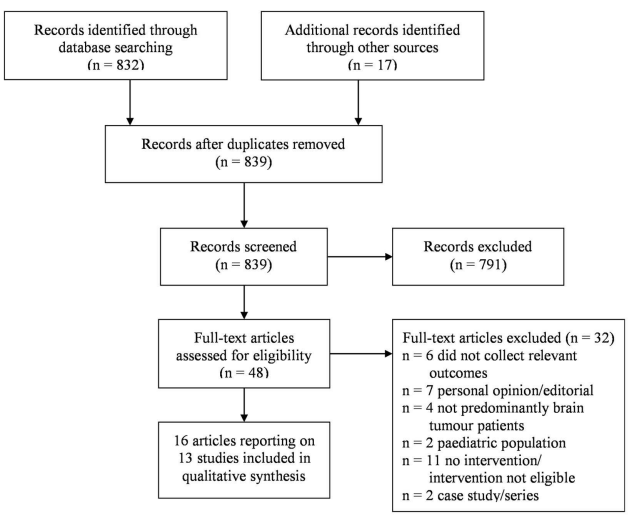

FIGURE 1 | Inclusion/exclusion process following article search.

Five interventions were delivered at the group level, four intervened to facilitate practice or process changes, and four were individual level interventions. At the group level, two workshops provided training in using compensatory strategies to manage challenging behaviors; one half-day duration workshop delivered by a multi-disciplinary group covering didactic sessions and clinician-facilitated discussions was for family members (47) and the other 6-h workshop, also led by a multi-disciplinary team and involving didactic presentations and small-group exercises, was for healthcare professionals (47). A further workshop of 8 h duration provided training for family members to develop practical care skills and provide information about brain tumors (43). Schratter-Sehn (45) and colleagues described a mixed patient/family member information and support group, which took place monthly with flexible attendance. Rabow and colleagues (44) developed and screened a 48 min documentary film for neurosurgeons, neuro-oncologists, and other clinicians to teach them about family caregiving for patients with brain tumors.

At the practice or process level, Lima and colleagues (42) described an evaluation currently in progress of a new survivorship care model involving nurse practitioner survivorship visits in coordination with neuro-oncologists. This intervention includes scheduled survivorship visits, a personalized education notebook, calendar, pedometer, and "walking challenge," electronic medical record-created "After Visit Summary" and written summaries sent to all treatment team members. Delaney and colleagues (40) described the integration of a pharmacist into the neuro-oncology team, with the pharmacist meeting with or telephoning patients three times during their course of chemotherapy, and returning patient-initiated calls during this time. Pharmacists provided standardized counseling regarding chemotherapy administration, managing side effects, dosing of supportive medications and drug interactions, and communication with pharmacists, and answered other medication-related questions. Green and colleagues described the use of a videoconferencing system to allow brain tumor patients to undergo follow-up neuro-oncology visits at a medical center closer to home, rather than having to attend a tertiary hospital further away. Following the taking of history and physical examination, clinical and laboratory data and neuro-images were shared by desktop by a neuro-oncologist located at the tertiary center. Finally within this category, Grimes and colleagues described the evaluation of changes to a number of processes within a hospital neurosciences service. Changes included documentation for staff relating to the patient admission process; training programs for staff relating to the communication of "bad

Table 1 | Characteristics of included studies reporting quantitative results.

Study (country)	*N*	Setting and participants	Intervention characteristics and comparison	Outcomes of interest and measures	Reported findings according to authors
RANDOMIZED CONTROLLED TRIALS					
El-Jawahri et al. (38, 51) (US)	50	Consecutive patients with malignant glioma, recruited via hospital oncology outpatient clinics	Video after verbal narrative, describing three levels of medical care in advanced cancer (life-prolonging care, basic medical care, comfort care). Six minute video shown on portable computer included visual images of the goals of care described verbally. Comparison: verbal narrative only	Knowledge (goals of care options assessed via questionnaire, yielding score 0–6). Patient satisfaction (perceived value of video, three items on 4-point Likert scale) assessed for intervention group only, immediately after intervention	Significantly higher mean increase in knowledge score for intervention (mean 1.9, 95% CI, 1.3–2.4) than control group (mean 0.9, 95% CI, 0.4–1.3), $p = 0.004$. Most intervention participants were "very comfortable" watching the video (82.6%), found it "very helpful" (78.3%), and would "definitely recommend it" (82.6%)
NON-RANDOMIZED TRIALS WITH CONTROL GROUP					
Langbecker et al. (39, 49, 50) (Australia)	20	Primary brain tumor patients diagnosed in previous 6 months and/or undergoing treatment, recruited via four hospitals	Brain tumor-specific question prompt list (booklet with list of questions patients may wish to ask) designed to facilitate patient-HCP communication with questions about: diagnosis; prognosis; symptoms and changes; treatment; support; after treatment finishes; the healthcare professional team. Control participants given standard brochure only	Quantity and quality of information received (assessed using EORTC QLQ-INFO25 questionnaire); satisfaction (acceptability of the intervention or standard brochure assessed using 17 questions, combined into summative index), collected 4–6 weeks after intervention	Higher median change in information received for intervention (2.7, range −24.0 to 18.6, $n = 9$) than control group (−2.0, range −36.0 to 9.3, $n = 8$), indicating greater information received. Median acceptability score higher for intervention (31, range 27–34) than control group (28, range 15–31), indicating greater acceptability
SINGLE ARM STUDIES					
Grimes (48)(UK)	NS	Patients with brain tumors using a neurosciences service at a hospital	(1) New package of patient admission process documentation covering issues to discuss with/communicate to patients at appropriate points during their stay; (2) procedures to reduce time waiting for biopsy result and for nurse to coordinate meeting to delivery results to patient; (3) communication training programs for staff; (4) information to familiarize patients with the hospital and covering types of diseases, treatments, and support services	Patients' views on clarity of explanation, collected via survey using visual analog scales following patients' receipt of their biopsy results. Collected prior to and 6 months after implementation of intervention	At baseline, 48% rated clarity of explanation; this was 73% after intervention (no data supplied to interpret result)

(Continued)

Table 1 | Continued

Study (country)	*N*	Setting and participants	Intervention characteristics and comparison	Outcomes of interest and measures	Reported findings according to authors
Delaney et al. (40) (Canada)	13	Consecutive newly diagnosed HGG patients undertaking chemoradiotherapy at a neuro-oncology outpatient clinic	Pharmacist integration into multi-disciplinary team. Initially took medication history and provided counseling re: chemotherapy administration; side effect management; dosing of supportive medications; drug interactions; communication with pharmacists; other medication-related questions. Called patient the next day and 5 days after treatment initiation to address medication-related questions and review treatment protocols; patient could also initiate contact	Patient satisfaction (perceptions of the pharmacist and benefit of their involvement in their healthcare team), collected at the end of the 3-month study	11/11 participants reported receiving useful information from pharmacist; 8/10 felt pharmacist's presence was helpful in their initial consultation; 7/10 said pharmacist's call on day 5 of treatment was useful; 8/10 said pharmacist answered additional drug-related questions to their satisfaction; 9/10 recommend pharmacist remains part of team
Green et al. (41) (US)	38	Patients with primary brain tumors living regionally from a Neuro-oncology Center	Use of a videoconferencing system for neuro-oncology follow-up visits, involving history-taking, physical examination, desktop sharing of clinical and laboratory data using an electronic medical record, sharing of neuro-images	Patient satisfaction (16 question online survey), timing unclear	Average level of satisfaction reported by patients was 9.8 (1–10 scale, SD not reported)
Rabow et al. (44) (US)	61	Neurosurgeons, neuro-oncologists, and other clinicians from a neurological surgery or integrated medicine department or attending national conferences	48 min documentary film entitled "The Caregivers" depicting stories of four family caregivers of adults with brain tumors and designed to improve neurosurgery training around supporting family caregivers. Screenings held for staff and at conferences	Satisfaction (perceived quality of the film, perceived importance; belief they learned something from the film, believe that the film was an effective way to teach about family caregivers, belief that the film should be seen by all clinicians caring for patients with brain tumors, collected on 10-point Likert scale) immediately after screening	Mean scores: 9.27 for quality; 9.03 for importance; 9.67 for learning something new; 8.98 for the film being an effective way to teach; 9.23 for the film should be seen by all clinicians (SDs not reported)

(Continued)

Table 1 | Continued

Study (country)	*N*	Setting and participants	Intervention characteristics and comparison	Outcomes of interest and measures	Reported findings according to authors
Schratter-Sehn et al. (45) (Austria)	104	Patients with high-grade glioma (glioblastoma, mixed glioma and astrocytoma) and their relatives recruited through neuro-oncology ward at hospital	Interdisciplinary group intervention led by a psychologist and physician, offered monthly, for participants to receive or exchange information. Flexible group therapy with 6–10 participants covering up to 2 therapy units (1.5 h). Aims: to be responsive to each participant's needs and develop coping strategies, based on principle of "care, encourage, inform, and guide"	Satisfaction (how much participants liked the intervention) assessed via questionnaire, timing unclear	92% of participants said the intervention provided a context in which they could openly talk about their anxieties, concerns and needs. 93% indicated their questions were answered through the intervention. Requirements and expectations were met for 82% of patients and 78% of relatives
Whiting et al. study 1 (47, 52) (Australia)	7	Family caregivers of adult primary brain tumor patients who had participated in previous descriptive study	Half-day didactic workshop delivered by multi-disciplinary team to train family members in compensatory strategy use to manage challenging behaviors (reasons for, types of and strategies for managing behavioral and cognitive changes). Caregivers and patients attended sessions together with clinician-facilitated discussion	Knowledge and use of compensatory strategies, measured via Strategy Use Measure (SUM-Family), a 9-item Likert-type scale; satisfaction (usefulness of each workshop section) assessed via questionnaire immediately after workshop	Median SUM-Family global scores significantly increased from before (3.29, IQR = 0.80) to after (3.86, IQR = 0.81) the intervention, $p < 0.05$. Average rating of the workshop was 4.73 (4 = good; 5 = very good)
Whiting et al. study 2 (47, 52) (Australia)	43	HCPs recruited via professional networks	6 h workshop delivered by multi-disciplinary team including didactic presentations and small-group exercises covering the journey of a brain tumor patient, description of challenging behaviors and prevalence following brain tumor; principles of behavior management; case study and group activity	Knowledge of compensatory strategies measured via Strategy Use Measure (SUM), a 16-item Likert-type scale developed for study); satisfaction (evaluation of all sections of workshop) assessed immediately after workshop	Average SUM rating scores significantly increased from before (3.17) to after (4.1) the intervention (SDs not provided, paired *t*-test $p < 0.001$). Satisfaction mean scores were ≥ 4 (4 = good; 5 = very good)

HCP, healthcare professional; CNS, central nervous system; NS, not specified; EORTC QLQ-INFO25, European Organisation for Research and Treatment of Cancer Information module; SD, standard deviation; IQR, interquartile range.

Table 2 | Characteristics of included studies not reporting quantitative results.

Study (country)	*N*	Setting and participants	Intervention characteristics and comparison	Outcomes of interest and measures	Reported findings according to authors
RANDOMIZED CONTROLLED TRIALS					
Boele et al. (37) (The Netherlands)	NS	Adult grade II, III or IV glioma patients with mild-moderate depressive symptoms and their informal caregivers, recruited through advertising and treating HCPs	Internet-based self-help course based on principles of problem solving, with information about specific diseases and treatment, and psychological impact on everyday life. Five modules (text and exercises), 2 h/week over 5 weeks. Feedback from personal coach. Wait list control and non-CNS malignancy control group	Satisfaction (usability, readability, usefulness of the course and coach's feedback assessed by questionnaire) immediately and 6 months after intervention	Data collection in progress
SINGLE ARM STUDIES					
Lima et al. (42) (US)	NS	Newly diagnosed primary brain tumor patients at a Comprehensive Cancer Center	Survivorship care delivery model involving nurse practitioner survivorship visits in coordination with primary neuro-oncologist. Aims: to identify and manage symptoms and distress; patient education; facilitation of communication among care providers; navigation of resources. Visits scheduled within 3 weeks of diagnosis and at specific points in the disease trajectory. Included personalized education notebook, calendar, pedometer, and "walking challenge," after visit summary and written summaries sent to all treatment team members	Satisfaction regarding initial survivorship visit and patient education notebook (collected by survey), timing unclear	Data collection in progress
Patterson and Lovely (43) (US)	NS	Family caregivers of brain tumor patients, implemented at medical centers	8-h workshop curriculum providing information on topics such as medical overview of brain tumors, symptom management at home, understanding cognitive changes, how to safely move a patient. Offered by oncology nurses and aims to develop practical care skills	Caregiver knowledge (measured by questionnaire), satisfaction (overall benefit of the workshop as perceived by participants), timing unclear	No results reported
Spezeski et al. (46) (US)	75	Callers to a neuro-oncology telephone service (35% patients, 52% family/friend of patient)	Neuro-oncology information telephone line providing information on topics such as brain tumor types and treatments, caregiving issues, symptom management, and referrals to support-related resources	Satisfaction (measurement tool unclear)	"Callers expressed satisfaction with their experience and found the information to be quite helpful" (p. 549). "Virtually all callers said they would recommend the hotline to others needing information about brain tumors" (p. 549)

HCP, healthcare professional; NS, not specified.

Table 3 | Risk of bias for included studies.

Study	Random sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Boele et al. (37)	Low	Low	High	Unclear[a]	Unclear[a]
El-Jawahri et al. (38, 51)	Low	Low	High	Low	Unclear
Langbecker et al. (39, 49, 50)	High	High	High	Low	Low
Grimes (48)	High	High	High	Unclear	Unclear
Delaney et al. (40)	High	High	High	Low	Unclear
Green et al. (41)	High	High	High	Unclear	Unclear
Lima et al. (42)	High	High	High	Unclear[a]	Unclear[a]
Patterson and Lovely (43)	High	High	High	Unclear	Unclear
Rabow et al. (44)	High	High	High	Low	Low
Schratter-Sehn et al. (45)	High	High	High	Unclear	Unclear
Spezeski et al. (46)	High	High	High	Unclear	Unclear
Whiting et al. study 1 (47, 52)	High	High	High	Unclear	Unclear
Whiting et al. study 2 (47, 52)	High	High	High	Low	Unclear

[a] *Unclear risk as data collection in progress.*

news" to patients; documentary information for patients and families covering types of disease, treatment, and support services; new systems for the management of scans and biopsy results; and a half hour preparation session for patients held at the beginning of each neuro-oncology clinic, during which patients were allocated to a single clinician based on their needs (rather than seeing each clinician as done previously).

At the individual level, a wide variety of interventions were evaluated. El-Jawahri and colleagues (38) tested a 6-min video designed to facilitate end-of-life discussions in a randomized controlled trial. The video depicted life-prolonging care [for example, including cardiopulmonary resuscitation (CPR), intubation and mechanical ventilation], basic care (including hospitalization, intravenous fluids, and antibiotics but excluding CPR, etc.) and comfort care (usually including medications to improve symptoms but not hospitalization). Boele and colleagues (37) described a self-administered internet-based intervention based on problem-solving therapy for glioma patients with mild to moderate depressive symptoms. The intervention consisted of five modules with text and exercises, with feedback provided by a personal coach. Spezeski and colleagues (46) described the evaluation of a neuro-oncology information hotline, which patients and caregivers could call as desired and which covered topics ranging from brain tumor types and treatments, caregiving issues, symptom management, and referrals to support-related resources. Langbecker and colleagues (39) tested a brain tumor-specific question prompt list, which is a structured list of questions for patients to ask of healthcare professionals if they wish and which may foster the provision of tailored, personally relevant information.

The most commonly reported outcome was satisfaction with the intervention, assessed in some form (e.g., found the intervention helpful or acceptable) by 12 of the 13 studies (37–47, 49–52). Four studies assessed knowledge by questionnaire (38, 43, 47) in terms of knowledge of different levels of medical care in the advanced stage of cancer (38), knowledge and use of compensatory strategies to manage behavioral and cognitive changes (47), or caregiver knowledge not further defined (43). Two studies assessed information provision (39, 48). No studies assessed recall or understanding, and only two studies assessed more distal outcomes such as quality of life (37, 39). Outcomes were most commonly assessed immediately after the intervention (37, 38, 44, 47), although the timing of assessment was not clear in six studies (41–43, 45, 46, 48).

RISK OF BIAS IN INCLUDED STUDIES

Both randomized controlled trials (37, 38) were rated as low risk for random sequence generation and allocation concealment (**Table 3**). As all other studies were non-randomized or single arm studies, risk was rated as high for these biases. Blinding of outcome assessment was rated only for the three studies with control groups, and was rated as high for all three (37, 38, 49) as well as all single arm studies due to the nature of the interventions. Five studies (38–40, 44, 47) were rated as low risk with regard to incomplete outcome data, with all other studies rated as unclear risk due to absence of a published protocol. Only two studies (39, 44) were rated as low risk for selective reporting, with corresponding authors confirming that all outcomes were reported.

EFFECTS OF INTERVENTIONS

The effects of interventions are reported only for the studies described in **Table 1**, for which quantitative results are available. Where appropriate, we have highlighted where studies assessed outcomes but did not report the results of these outcomes.

Outcome: information provision

One non-randomized study and one single arm study assessed information provision (39, 48). Grimes (48) compared the views of inpatients on the clarity of information provided to them before and after intervention implementation. Patient-reported

clarity of explanation increased from 48 to 73% after the intervention (no information was provided to explain how to interpret these percentages). Langbecker and colleagues (39) assessed the quality and quantity of information received by participants using the European Organisation for Research and Treatment of Cancer (EORTC) information module (QLQ-INFO25). In a non-randomized trial, the median change in information received between baseline and follow-up was higher for intervention group participants (a brain tumor-specific question prompt list) compared to brochure only controls. However, statistical testing of the significance of these group differences was not reported, and the sample size was small, with follow-up data collected for 17 of 20 participants only due to attrition. Overall, both studies showed that greater information was provided to participants who received the interventions compared to those who did not, although the high risk of bias for both studies for randomization, allocation concealment, and blinding of outcome assessment limits the confidence that can be had in these findings.

Outcome: knowledge

One randomized controlled trial (38) tested a video and three single arm pre-/post-test studies (43, 47) tested the effect of workshop-delivered interventions on participants' knowledge; however, no results were reported for one study, which evaluated the effect of a workshop for family members (43). Among the three studies for which results were available, the randomized controlled trial showed a statistically significantly greater mean increase in patients' knowledge of the different levels of medical care in the advanced stages of cancer for patients who received the video intervention compared to those who received the control condition (38). Compared to pre-workshop levels, Whiting and colleagues' (47) interventions led to statistically significantly increases in participant knowledge (for family members and for healthcare professionals) following the workshops.

Although these results are promising, study-specific instruments were used to assess knowledge for all three of these studies (38, 43, 47). Whiting et al. (47) reported that the instrument (the Strategy Use Measure) used to assess knowledge for healthcare professionals (and a modified version of this was also used to assess knowledge for family members) showed strong internal consistency and did not demonstrate ceiling or floor effects (47). While this psychometric information demonstrates reliability, the validity of the instrument and its sensitivity to change is unclear.

The contextual significance of these results is also unclear. Statistical significance may be shown with a large enough sample even if the clinical or contextual significance of the findings is unremarkable. However, the sample sizes of three studies were small, including 50 patients (38), 7 family members (47), and 43 healthcare professionals (47). The presence of statistically significant results with such small samples provide support for the significance of the results, but further research to validate the instruments and establish the significance of different levels of change is needed.

Risk of bias was not significantly different across the three studies for which data were available, so sub-analysis of the impact of risk of bias was not possible.

Outcome: satisfaction

Twelve studies (37–47) considered satisfaction with the intervention as an outcome, and nine studies reported (38–41, 44–47) data relating to this outcome, primarily described as the intervention's acceptability, perceived usefulness, value, or quality. Among the nine studies for which results were available, only one study reported comparative data for intervention and control groups; Langbecker et al. (39) reported that a greater proportion of participants who received a question prompt list compared to those who received a control brochure highly agreed that the brochure was helpful, assisted them to ask questions, and other satisfaction items. All other studies reported satisfaction in intervention group participants only. They found high rates of satisfaction, evidenced by mean satisfaction scores of at least 8 out of 10 (or equivalent), or at least 80% of participants selecting the highest rating on a Likert-type scale. This was true regardless of the nature of the intervention, whether it was delivered in a group or individual setting, or constituted a practice or process change, and regardless of the risk of bias of the studies involved.

DISCUSSION

Our findings suggest that if an intervention is provided to patients with brain tumors, their caregivers, or the healthcare professionals who treat these patients, satisfaction ratings improve. These findings are based largely on non-randomized pre–post single arm intervention studies, mostly with relatively small sample sizes. Although similar to reports from previous reviews in the wider cancer population, the analyses focusing on those affected by brain tumors reported here provide additional insight. First, the review provides evidence for the feasibility of conducting studies with this patient and caregiver population. This is important as some may doubt that the highly distressed and often cognitively impaired population may be willing to be included in such investigations. Based on this review's findings, those who agree to participate can be reassured that they will benefit at least subjectively. The reviewed studies also provide suggestions for optimizing data collection in the brain tumor patient population to reduce study burden, such as collecting data immediately after the intervention (38) or collecting data by interview rather than self-administered forms (39). Both of these strategies are recommended for palliative care research and may have value in this population (53).

However, the review also highlights a lack of stringent outcome measurements, which can be compared across studies or can be objectivized. This could include standardized tests of knowledge or improvements in treatment compliance, which often are target aims, but were seldomly formally assessed. Notable exceptions are the study by El-Jawahri et al. (38), who used a standardized knowledge score as outcome measure, and Langbecker et al. (39), who used an EORTC module to assess improvements in information. The most appropriate outcomes to measure in future studies must also be considered. Satisfaction with the intervention was the most commonly assessed outcome, but this concept lacks theoretical underpinning and may not be a good indicator of intervention quality (54). The use of global satisfaction ratings is particularly susceptible to the "halo effect" whereby raters overestimate performance with global impressions influencing responses to specific items. In interventions involving health professionals, patients may

also report on the clinicians' interpersonal skills rather than the clinicians' technical competence or the intervention's usefulness (55, 56). It is hoped that the emergence of standardized tools such as the EORTC QLQ-INFO25 will encourage the assessment of information provision and related constructs, thus providing greater understanding of whether interventions achieve real change and allowing comparison across studies of intervention effects. If satisfaction ratings are to be used, it is recommended that surveys emphasize that the ratings will be used to improve the intervention (rather than merely to evaluate it) and include more items assessing specific aspects of the intervention, rather than using a global rating. Both of these suggestions have been shown to reduce the impact of the halo effect (56).

The number of studies conducted with this population seemed to increase over time, with several conducted during the most recent decade. This is promising and may reflect a renewed interest in improving the treatment outcomes for patients with brain tumors, and also the encouragement provided through successfully conducted previous studies. Most studies, however, employed research designs that resulted in either high risk of bias or inability to assess risk of bias, lacking a published study protocol and a control group in most instances. Although the nature of the interventions mean that it would not be possible to blind participants to study outcomes, blinding of assessors would be feasible. Greater specification of analysis methods (for example, if intention-to-treat analysis was carried out) is also needed. Finally, none of the included studies investigated whether intervention efficacy was affected by patients' cognitive status, despite cognitive impairment being a common issue in this population (29, 31, 32). This should be considered in future studies.

STRENGTHS AND LIMITATIONS OF THIS REVIEW

To the best of our knowledge, this is the first systematic review of interventions to improve information provision for adult primary brain tumor patients and their caregivers. Strengths of this systematic review include the extensive search of the literature in multiple databases, the inclusion of publications written in languages other than English, and the assessment of risk of bias of included studies. However, due to the limited number of studies, heterogeneity in interventions and methods, and inadequate reporting of data for some studies, we were unable to statistically pool the study results to determine the relative benefit of different interventions. Further work is necessary to determine the most effective intervention components and most appropriate timing for intervention delivery, as well as the effect of interventions on more distal outcomes such as quality of life, treatment adherence, or survival.

CONCLUSION

This systematic review showed that interventions with an educational component improve information provision and knowledge for adults with brain tumors, their families, and caregivers. Furthermore, satisfaction with these interventions was high. Although these results are promising, future efficacy and effectiveness trials with rigorous study designs are needed, particularly to determine the most useful intervention components and to understand if certain subgroups of the population are differentially affected.

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REVIEW
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Psychotherapy interventions for managing anxiety and depressive symptoms in adult brain tumor patients: a scoping review

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Background: Adult brain tumor (BT) patients and longer-term survivors are susceptible to experiencing emotional problems, including anxiety and/or depression disorders, which may further compromise their quality-of-life (QOL) and general well-being. The objective of this paper is to review psychological approaches for managing anxiety and depressive symptoms in adult BT patients. A review of psychological interventions comprising mixed samples of oncology patients, and which included BT patients is also evaluated. The review concludes with an overview of a recently developed transdiagnostic psychotherapy program, which was specifically designed to treat anxiety and/or depressive symptoms in adult BT patients.

Methods: Electronic databases (PsycINFO, Medline, Embase, and Cochrane) were searched to identify published studies investigating psychological interventions for managing anxiety and depressive symptoms in adult BT patients. Only four randomized controlled trials (RCTs) were identified.

Results: Only one of the RCTs tested a psychosocial intervention, which was specifically developed for primary BT patients, and which was found to improve QOL including existential well-being as well as reducing depressive symptoms. A second study tested a combined cognitive rehabilitation and problem-solving intervention, although was not found to significantly improve mood or QOL. The remaining two studies tested multidisciplinary psychosocial interventions in heterogeneous samples of cancer patients (included BT patients) with advanced stage disease. Maintenance of QOL was found in both studies, although no secondary gains were found for improvements in mood.

Conclusion: There is a notable paucity of psychological interventions for adult BT patients across the illness trajectory. Further research is required to strengthen the evidence base for psychological interventions in managing anxiety and depressive symptoms, and enhancing the QOL of distressed adults diagnosed with a BT.

Keywords: brain tumor, psychological treatment, anxiety, depression, emotional well-being

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Introduction

Adult individuals diagnosed with a primary brain tumor (BT) represent a unique group of patients on the basis that both benign and malignant tumors are associated with disease and treatment

side-effects, and can be life-threatening. Depending on the site and size of the BT, these side-effects can lead to substantial neurocognitive, psychosocial, and behavioral problems (1–3). Importantly, a growing body of studies has found that BT survivors are prone to experiencing a high incidence of psychological problems following their diagnosis. Prevalence rates for depression and anxiety symptoms have been documented to be as high as 62% (1, 4). Given the potential life-threatening nature of this disease, several studies have further found that BT survivors may also be susceptible to clinically elevated acute and posttraumatic stress symptoms (PTSS) (5–7).

Research has further shown that if emotional symptoms are left untreated, they have an unremitting, chronic course hampering quality-of-life (QOL) and productivity [e.g., Ref. (8)]. Importantly, these findings accentuate the importance of providing psychological interventions for adult BT patients in order to manage acute psychological problems, as well as prevent chronic psychopathology and maintain QOL in longer-term survivors.

To date, no published study has evaluated the evidence base of psychosocial interventions suitable for distressed (notably, anxious and/or depressed) adult BT patients. This line of inquiry is important in order to guide clinicians and researchers working with this population. Accordingly, the primary objective of this scoping review is to evaluate published psychological-based clinical trials which were either: (a) specifically tailored for adults diagnosed with a primary BT, or (b) comprised heterogeneous oncology patients including BT patients, in order to assess the efficacy of psychological interventions in managing anxiety and depressive symptoms, as well as maintaining or improving the QOL in adult BT patients including longer-term survivors. Given the infancy of this field, this review will conclude with an overview of a recently developed transdiagnostic psychotherapy program, which was specifically designed to treat anxiety and/or depressive disorders in adult BT patients.

Methods

Scoping Review

Given this type of review is a relatively new methodological approach, to date, there is no universal definition, or consensus on a definitive methodological procedure on reporting guidelines (9). Whereas some authors have proposed that scoping reviews provide a "descriptive overview" of relevant material without critically evaluating and/or synthesizing evidence across different studies (10), more recently, other authors have indicated the importance of synthesizing and critically evaluating the evidence reviewed [e.g., Ref. (11, 12)]. Indeed, without critical evaluation of the methodology of identified studies, researchers and clinicians are unable to delineate relevant gaps in the field in order to guide further research, clinical practice, and policy guidelines (9, 11). To this end, although Arksey and O'Malley in 2005 (10) published the first methodological framework for scoping reviews, several authors have proposed revisions to this framework (11–13). In particular, Pham and colleagues (9) recommend that researchers utilize the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (14) as a further guide in reporting results for scoping reviews. Accordingly, for the purposes of the current scoping review, Arksey and O'Malley's (10) six-stage iterative framework was used in combination with relevant components of the PRISMA framework (14). However, as the 6th step (consulting with relevant stakeholders) is proposed to be optional in Arksey and O'Malley's framework, this final step was excluded for the purposes of the current review. Moreover, in selecting the research question (i.e., Step 1 of Arskey and O'Malley's framework), Levac and colleagues (13) further recommend to clearly define the question including target population and health outcomes in order to clarify the specific focus of the review. In line with these recommendations as outlined above, the specific aims of the current scoping review explicitly focused on evaluating psychological-based intervention studies for managing anxiety and/or depressive symptoms and/or improving QOL in adult BT survivors. Given this specific focus, the review outcomes are expected to identify relevant gaps in the literature concerning interventions for managing anxiety and depressive symptoms in adult BT patients, in order to guide clinical practice and relevant future research in this area.

Search Strategy

The following electronic databases were searched from their respective inceptions through to the 10 December, 2014: Cochrane, Embase, Ovid Medline, and PsycINFO. The searches were conducted using the following subject headings and/or keywords and combinations: (i) brain (or CNS) tumor/tumour, brain neoplasm, brain cancer, neurooncology, glioma, meningioma; and (ii) psychosocial intervention terms [including counseling/counselling, psychotherapy, psychoeducation, psychosocial intervention/psychosocial/psychological therapy/treatment, stress management, cognitive behavioral/(behavioural) therapy, cognitive therapy, CBT, behaviour/behavior therapy, relaxation]. The searches were restricted to abstracts and articles published in English. A further search was conducted to identify review articles based on psychosocial interventions for oncology populations (specifically comprising heterogeneous samples of oncology patients). The bibliographies of retrieved articles, narrative reviews, and commentary articles on BTs and psychosocial intervention reviews for cancer patients (comprising heterogeneous samples) were also manually searched for additional references. The abstracts of articles identified by electronic searches (1904 in total) as well as manual searches were screened for consideration of inclusion in this review.

Study Selection

All abstracts and/or titles of articles that were identified via electronic and manual searches were screened applying the following selection criteria: (i) published in a peer reviewed journal in full manuscript format; (ii) written in English language; (iii) included a psychosocial intervention (with details of key components provided), which was compared to a standard care, wait-list control, or other type of comparison condition, single design and/or case studies focusing on managing psychological distress were also considered; (iv) participants were a minimum of 18 years of age; (v) the study sample explicitly comprised of patients diagnosed with a primary BT, or for mixed oncology samples, a minimum of 10% of the sample was diagnosed with a BT; and (vi) a specific

quantitative measure of psychological well-being (including anxiety and/or depression/mood and/or a QOL scale) was included as a primary or secondary outcome measure, and the measure was administered at minimum pre- and post-intervention.

Data Extraction and Evaluation of Clinical Trials

Studies which met inclusion criteria were read in full, and the following data were extracted and summarized in table format: references, country of study, aim of study, study design, participant characteristics (including sample size, mean age, and BT composition), intervention details, assessment phases and measures, study outcomes, and limitations.

Results

A total of five published articles (15–19) met the inclusion criteria, although only four of the studies (15–18) were included in this review. The fifth study (19) was excluded, as it was based on the same dataset as one of the included studies (17), and did not report any new data. Although two further case studies were identified (20, 21), they were excluded as both studies did not include a measure of psychological well-being. These two excluded studies focused on testing psychological interventions for managing challenging behaviors in BT patients (20), and managing anger disturbances more broadly with brain injured adults including BT patients (21). In addition, a further recent non-randomized, controlled trial was identified (22), which was designed to evaluate the effectiveness of a multidisciplinary rehabilitation (MDR) program for adults diagnosed with a primary glioma in an Australian community cohort. However, this study was excluded as no details were provided pertaining to the psychological intervention(s) used. Notably, the authors reported that part of the MDR program comprised 30-min blocks of therapy sessions conducted 2–3 times per week for up to 8 weeks, which included psychology, social, occupational, and physiotherapy. However, no specific information was provided as to what these components comprised, and whether the psychological therapy approach was consistent across patients.

Table 1 summarizes the sample characteristics, intervention details, and outcomes of four randomized controlled trials (RCTs). Only two of the four identified studies were solely based on a primary BT sample. Specifically, based on a RCT design, Ownsworth et al. (15) tested the efficacy of a multimodal, home-based intervention [i.e., the "Making Sense of Brain Tumor" (MSoBT) program], which was designed to improve QOL, existential, and mental health well-being in adults with a primary BT. The manualized intervention was administered in individual and/or combined couple/family support sessions, over 10 weekly, 1-h sessions. At post-intervention, patients who received the MSoBT program were found to report significantly lower depressive symptoms, and an improvement in existential and functional well-being relative to patients randomized to a wait-list condition. At 6-months follow-up, the results for the two conditions were combined, and the findings indicated that participants experienced an improvement in existential well-being and overall QOL, as well as a significant decline in depressive symptoms, but not anxiety symptoms.

In the second study which focused solely on BT patients, Locke et al. (16) quasi-randomly allocated a very small dyadic sample ($n = 19$) of adults diagnosed with a primary BT and their carers, to a combined cognitive rehabilitation and problem-solving intervention or to the standard medical (control) condition. The design was quasi-RCT as the final three patient-dyads recruited were directly allocated to the intervention condition. The majority of participants (88%, $n = 7$ of 8) who received the intervention reported using the intervention strategies for a minimum, several times per week at the end of the 2-week trial period, while 50% continued to use these strategies several times per week at 3-months follow-up. Similarly, 88% of participants in the intervention condition reported finding the program "somewhat" or "very" helpful. However, no differences were found between the intervention and standard care/control conditions in terms of improvement in QOL, functional capacity, emotional distress, or fatigue at the completion of the trial period, or at the 3-months follow-up assessment. In particular, a high proportion of participants ($n = 16$) reported average to above average scores on the QOL measure at baseline, and at the two subsequent follow-up assessments. Comparably, over 77% of participants mood scores indicated good emotional adjustment at each of the three assessments (inclusive of the baseline period). Furthermore, the effects of the intervention on cognitive functioning could not be tested, as the majority of patients at the follow-up assessment were assessed via telephone, thus ruling out the administration of the neurocognitive test.

The other two randomized controlled studies were based on mixed samples of patients diagnosed with advanced cancer. In the first study, Rummans et al. (17) tested the efficacy of a structured multidisciplinary intervention in maintaining QOL in advanced cancer patients (including 12% of patients with BTs) scheduled to receive a minimum of 2 weeks radiation treatment. The group-based intervention comprised eight weekly, 90 min sessions conducted over 3 weeks, and which included weekly physical and relaxation exercises as well as cognitive-behavioral strategies and open group discussions. The primary endpoint was 4 weeks post-baseline assessment (i.e., 1 week post-intervention), although a 27-week (5-month) follow-up assessment was also conducted. The results revealed that at 1-week post-intervention, participants were found to maintain their QOL relative to patients randomized to the standard care condition, which reported a decline in QOL scores. However, by 5 months follow-up, no significant differences were evident between conditions. Specifically, both groups QOL scores were comparable to baseline functioning.

In a more recent study, Clark et al. (18) adapted Rumman et al.'s (17) program and tested the efficacy of this structured multidisciplinary intervention in maintaining QOL in a further sample of advanced cancer patients (including 22% with BTs), which were recommended to receive at least 1-week of radiation treatment. In this study, the intervention was reduced to six sessions, which included caregiver participation, as well as an additional 10 brief follow-up phone counseling sessions. The primary endpoint for this study was also at 4 weeks following the baseline assessment, although a 5-month follow-up was also included. At the 4-week assessment, participants in the intervention condition reported elevated QOL scores, particularly an improvement in physical

TABLE 1 | Study characteristics and outcomes.

Reference and country	Participant characteristics	Intervention design and details	Assessment phases and outcome measures	Results	Limitations
(A) STUDIES COMPRISING SOLELY OF PRIMARY BRAIN TUMOR PATIENTS					
Ownsworth et al. (15) Australia	• *N* = 50 adults (54% males) diagnosed with primary BT assessed at baseline (min. 18yrs old; range: 17–82) • 54% with benign or low grade BTs • Mean = 2.6 yrs since BT diagnosis (range: 6 weeks to 18 yrs) • *N* = 27 randomized to MSoBT [Ns per Ax: 27, 25, 21]; dropouts due to death (*n* = 2); declined FU assessment (*n* = 3); unable to contact (*n* = 1) • *N* = 23 randomized to wait-list control [Ns per Ax: 23, 21, 15]; dropouts due to death (*n* = 2); declined FU assessment (*n* = 2); unable to contact (*n* = 1); withdrew from study before intervention (*n* = 1) or FU assessment (*n* = 2)	• RCT with wait-list control • MSoBT: 10 × 1 hourly weekly sessions, comprising core components covered in sessions 1, 2, and 10, and module components covering goals, life situation, and cognitive capacity; Program included family members – MSoBT format: home based, manualized, individual and/or combined couple/family support sessions – Tx modules included psycho-education, neuropsychological feedback, cognitive rehabilitation, psychotherapy for anxiety, anger, and depression, couple and family support • Wait-list control – received MSoBT after T2 Ax	• Ax phases: T1 – baseline T2-Post-Tx T3-6 months FU • Measures: – Neuropsych battery to index global functioning – QOL: McGill Quality of Life Questionnaire (MQOL) [inc. existential subscale] – QOL for BT: Functional Assessment of Cancer Therapy – Brain subscale (FACT-BR) (T1 and T2 only) – Depression severity: Montgomery-Asberg Depression Rating Scale (MADRS) – Anxiety, stress, depressive symptoms: Depression Anxiety Stress Scale (DASS21)	• All analyses based on *N* = 50, as ITT analyses were used, although only *N* = 44 completed T3 • T1–T2 outcomes • MSoBT: sig. lower depressive symptoms on MADRS but not on DASS21 • MSoBT: sig. elevated existential wellbeing (MQOL) • MSoBT: sig. greater functional well-being and total QOL score on FACT-BR, but not for overall score on MQOL • T1–T3 outcomes: • Sig. lower depressive symptoms on MADRS and DASS21 • Sig. higher existential well-being scores and overall QOL (MQOL) • Sig. lower stress symptoms on DASS21, but not for anxiety symptoms • Secondary analyses at T3: • Benign BTs: sig. less depressive symptoms (MADRS) and stress (DASS21), but no sig change for existential well-being, anxiety, or overall QOL (MQOL) • Malignant BTs: sig. less depressive symptoms (MADRS) and sig. increase in existential well-being and QOL (MQOL). However, no sig. change on DASS21 scores	• No blinding of assessors or therapists, and no details of therapist fidelity checks reported • T3/6 mth FU analyses not based on RCT as data merged for both MSoBT and wait-list conditions. Also access to other services between T2 and T3 not monitored
Locke et al. (16) USA	• *N* = 19 patient-carer dyads (58% males) diagnosed with a primary BT scheduled to receive radiotherapy (min. 18 yrs old; range: 30–78) • 32% with benign or low grade BT • 53% also received neurosurgery and 63% received chemotherapy • *N* = 9 randomized to the combined intervention plus *N* = 3 directly allocated to the intervention (combined *N* = 12) [*N* = 8 completed study inclusive of 3-mth FU; dropouts due to carer not willing to accompany patient to intervention and fatigue] • *N* = 7 randomized to the standard medical care/control condition [*N* = 5 completed 3-mth FU; dropouts due to BT progression]	• RCT (quasi-design as final 3 dyads directly allocated to the intervention) with a standard medical care (control) condition • Combined Cognitive Rehabilitation (CR) and Problem-Solving (PS) intervention: Each component (CR & PS) comprised 6 × 50 min sessions each over a 2-week period, concurrent with radiotherapy • CR component based on Sohlberg and Mateer's techniques based on using a specific calendar format to compensate for cognitive symptoms • PS component was based on Nezu et al.'s techniques and focused on positive problem-solving skills to manage stress reactions • Standard medical care (control) condition – no details reported	• Ax phases: T1 = baseline T2 = post-Tx T3 = 3 mths FU • Primary measures: – Compensation Techniques Questionnaire – Mayo-Portland Adaptability Inventory-4 (MPAI-4) – functional capacity Ax – QOL for BT: Functional Assessment of Cancer Therapy – Brain subscale (FACT-BR) • Secondary measures: – The Repeatable Battery for the Assessment of Neuropsychological Status (R-Bans) – test multiple areas of cognitive functioning – One-item Linear Analog Self-Assessment (LASA) – assess overall QOL – The Caregiver QOL Index-Cancer – Profile of Moods State (POMS) – mood severity – The Brief Fatigue Inventory (BFI)	• No significant between or within group differences found on any primary or secondary measure	• Very small sample size, and low response rate from potential pool of *N* = 160 patients. 38% screened excluded as they had no cognitive deficit, while 16% declined the neuropsych. Ax • Patients not recruited on basis of baseline emotional and general well-being, hence results indicate potential ceiling effects as majority of sample were well adjusted emotionally at baseline • Due to very low number assessed in person at T3, cognitive Ax could not be conducted • No details reported of what the standard medical care condition received and whether access to additional services was assessed

(Continued)

TABLE 1 | Continued

Reference and country	Participant characteristics	Intervention design and details	Assessment phases and outcome measures	Results	Limitations
(B) STUDIES COMPRISING HETEROGENEOUS SAMPLES OF ONCOLOGY PATIENTS INCLUDING BRAIN TUMOR PATIENTS					
Rummans et al. (17) USA	• *N* = 112 adults [*N* = 55 intervention, *N* = 57 standard care] with advanced cancer, diagnosed within last 12 mths, with min. 6 mth survival, and prescribed radiation Tx (min. 2 weeks) • Mean age = 59.5 yrs (range: 31–85 yrs) • Complete data *N* = 103 (66 males; 12% BT patients) with *N* = 49 intervention (*N* = 6 BTs; 12.2%), and *N* = 54 standard care (*N* = 6 BTS, 11.1%)	• RCT with standard care • Primary Intervention: – Structured multidisciplinary program comprising 8 × 90 min sessions conducted over 3 weeks – Session structure inc. 20 min physical exercises; educational information; cognitive behavioral strategies for coping with cancer (inc. problem-solving, stress management, assertiveness, relapse prevention); open group discussion (inc. social and spiritual topics, interpersonal relations, grief), and concluded with 10–20 min guided relaxation exercises – Participants issued with workbook • Standard care: – Inc. regular medical consults and opportunities for receiving support from outside agencies, e.g., America Cancer Society	• Ax phases: T1 – baseline T2-Post-Tx/4 weeks later (primary study end-point) T3-8 weeks from T1 T4–27 weeks from T1 • Primary outcome measures: – Spitzer QOL Uniscale & Linear Analog Scales of Assessment of QOL (LASA) • Secondary outcome measures: – Symptom Distress Scale – Profile of Mood States (POMS) – Functional Assessment of Chronic Illness Therapy (FACIT) – Spiritual well-being scale	• *N* = 103 in final analyses; [*N* = 49 Intervention (*n* = 6 withdrew due to incomplete session attendance), *N* = 54 Standard care (*n* = 3 declined)] • T1 to T2: • Greater QOL scores for intervention condition (intervention condition increased scores by 3 points – vs. standard care condition decreased scores by 9 points at T2); hence intervention group maintained QOL by T2 • T1–T4 (5 mths FU): • No sig. group differences, both conditions continued to increase QOL scores • Secondary measures: • Only POMS – tension/anxiety and confusion/bewilderment subscales improved for the intervention condition at T2	• Program limited to participants receiving radiation Tx • At post-assessment, 92% (*N* = 45) of intervention grp still receiving radiation Tx at 4 weeks, and 87% (*N* = 47) of standard care grp still receiving radiation Tx • Cost of intervention was $2000 per patient for eight sessions • Standard care could access outside services
Clark et al. (18) USA	• *N* = 131 adults (inc. 22% BTs [*N* = 65 Intervention – inc. *n* = 11 BTs, *N* = 66 standard care – inc. *n* = 18 BTs] with advanced cancer, diagnosed within last 12 mths, with intermediate to poor prognosis and prescribed radiation Tx (min. 1 week) • Mean age = 59.3 yrs	• RCT with standard care • Primary intervention: – Structured multidisciplinary program comprising 6 × 90 min sessions followed by 10 brief structured phone counseling sessions – Session structure inc. 20 min physical exercises; education; cognitive-behavioral strategies; open discussion; support; and concluding with 15 min deep breathing and guided imagery relaxation – Content of program derived from previous Rumman [10] study with several modifications inc. caregiver participation (Sessions 1, 3, 4, and 6); and focus on substance use, mood, anxiety and sleep disorders – Sessions led by clinical psychologist or psychiatrist – Participants issued with 200 page manual • Standard care condition: – Received standard medical care services	• Ax phases: T1 – baseline T2-Post-Tx/4 weeks later (Primary study end-point) T3 – 27 weeks from T1 • Primary outcome measures: – QOL: Functional Assessment of Cancer Therapy (FACT-G) • Caregiver QOL: The Caregiver Quality of Life Index – Cancer Scale • Secondary outcome measures: – Mood: Profile of Mood States (POMS) – Functional Assessment of Chronic Illness Therapy (FACIT) – Spiritual well-being scale – Sleep: Pittsburgh Sleep Quality Index – Exercise behaviors	• T1–T2 • Complete data at primary endpoint (week 4 post-baseline) *N* = 117 [*N* = 54 intervention; *N* = 63 standard care]; drop-outs due to no baseline and/or T2 data (*n* = 10); death (*n* = 1), incomplete treatment sessions (fout attended) (*n* = 7) – Greater QOL scores for intervention condition (especially physical and functional wellbeing scores) (intervention condition maintained scores – vs. standard care condition decreased scores at T2) • T1–T3 (5 mths FU): (*N* = 110; *N* = 51 intervention, *N* = 59 Standard care) – No sig. group differences, both conditions continued to increase QOL scores (back to baseline/T1 levels) • Secondary measures: – All measures were not sig at both T2 and T3 • Caregiver QOL: No sig differences between conditions	• Program limited to participants receiving radiation Tx

Ax, assessment; BT, brain tumor; grp, group; inc., includes/including; FU, follow-up; min, minimum; mths, months; ITT, intent-to treat; N, number of participants; QOL, quality-of-life; RCT, randomized control trial; sig., significant; T1, assessment phase 1 (baseline); T2, assessment phase 2; T3, assessment phase 3; T4, assessment phase 4; Tx, treatment; yrs, years.

well-being, relative to participants in standard care who reported a decline in QOL scores. However, by 5-months follow-up, no significant differences were evident between conditions. Notably, both groups had returned to baseline functioning for QOL outcomes. Additionally, no significant group differences emerged at 4-week or 5-months follow-up for the secondary measures including emotional and spiritual well-being, as well as sleep functioning.

Discussion

For this scoping review, only four published RCT studies (15–18) [one of which was a quasi-RCT design; (16)] were identified, which included adult BT patients in evaluating the efficacy of psychosocial interventions designed to maintain and/or improve QOL including existential well-being. Three of the studies (15, 17, 18) comprised structured, manualized multimodal interventions, which included cognitive-behavioral strategies. The fourth study (16) comprised a quasi-randomized design given the final 3 patient dyads were directly allocated to the intervention condition, which comprised a combined cognitive rehabilitation and structured problem-solving therapy program.

In one of the only two published studies to date, which were specifically designed for adults diagnosed with primary BTs, Ownsworth et al. (15) found that the MSoBT program was found to improve QOL and existential well-being, and reduce depressive symptoms up to 6-months post-intervention. Given this is the only published RCT study, which was designed for BT patients, this reflects the notable paucity of psychosocial interventions specifically tailored for adult BT patients. Although the findings from this study are promising, there are several short-comings that need to be considered in informing future interventions in this field. First, only the initial, post-treatment results were based on the RCT design, as the 6-month follow-up outcomes included participants allocated to the wait-list condition. Second, the intervention was not found to improve anxiety symptoms. Furthermore, although depressive symptoms were found to improve post-intervention, this study was not specifically tailored to clinically distressed (i.e., anxious and/or depressed) BT patients. Hence, the effect of this intervention in managing anxiety and depressive disorders in distressed BT patients is unknown. Third, given the multimodal intervention, which also included neuropsychological feedback and cognitive rehabilitation, it is not clear which components contributed to specific treatment gains. Finally, the home-based, in-person therapy sessions raise feasibility issues for hospital and community settings, which may not have the resources to roster staff to weekly offsite home visits.

In the second study, which was specifically designed for patients with a primary BT (as well as their carers) (16), a combined cognitive rehabilitation and positive problem-solving intervention was found to be acceptable by patients newly diagnosed with BT undergoing radiation treatment, and who were assessed to have mild to moderate cognitive impairments. However, this combined intervention was not found to lead to significant improvements in terms of QOL, functional capacity, mood or fatigue compared to patients who received standard medical care. These null outcomes can most likely be attributed to the majority of patients having good emotional adjustment and general well-being at baseline (i.e., soon after their BT diagnosis), and which was maintained at 3-months follow-up. In addition, given the very small sample size ($N = 19$ dyads at baseline and $N = 13$ at the 3-month follow-up), Locke et al. acknowledge that their study was not adequately powered to detect statistical changes. Although the majority of patients who received the combined intervention reported finding this program "somewhat" to "very" helpful, the findings indicate that patients which are relatively well adjusted emotionally may not derive further benefits in terms of improvement of mood and QOL by receiving an intensive cognitive and psychological short-term intervention while undergoing radiation treatment. Indeed, Locke et al. recommend that for future research, targeting BT patients who report reduced QOL, elevated emotional distress, and/or poor functional performance may be fruitful to further test the feasibility of this type of intervention.

The other two RCTs (17, 18) included in this review comprised heterogeneous samples of adults diagnosed with advanced cancer (including BT patients), who were recommended to receive radiation treatment. Both RCTs were based on a comparable structured, multidisciplinary psychosocial intervention, which also included physical and relaxation exercises. Interestingly, both studies were found to facilitate maintenance of QOL within 4 weeks post-baseline (on average 1-week post-intervention). However, the intervention was not found to differ from standard care at 5-months follow-up. A potential explanation for this latter outcome is that participants in standard care were documented to have the opportunity to receive external support from agencies such as the American Cancer Society [e.g., Ref. (17)]. However, access to additional support services was not reported to be monitored in these trials. It cannot therefore be ruled out that the lack of group differences at 5-months follow-up may in part be due to patients in the standard care condition accessing external support. A further reason may also in part be due to the recovery period required to overcome the acute radiation treatment side-effects. In fact, at the 4-week assessment, more than 85% of the sample was still receiving radiation treatment in the Rummans et al. (17) study. Taken together, these findings suggest that this multidisciplinary program is useful in helping patients maintain their QOL during the course of their radiation treatment, although there does not seem to be any additive benefits at 5-months follow-up. This is further reflected in the non-significant results reported for the secondary outcome measures. Notably, the intervention was not found to lead to significant improvements in psychological distress, mood, and spiritual well-being. Moreover, given the heterogeneous sample composition, which comprised only a small proportion of patients diagnosed with BTs (between 12 and 22%), the findings from these two RCTs for patients with advanced BTs are considered preliminary.

Collectively, the findings from this review accentuate the paucity of studies that have been specifically designed for primary BT patients, and which have assessed the effects of psychological interventions in managing anxiety and/or depressive symptoms and/or improving QOL. Although a number of cognitive rehabilitation programs for BT patients have also included

measures of psychological distress and/or QOL [e.g., Ref. (23)], however, with the exception of Locke et al.'s combined cognitive and problem-solving intervention (16), no further published cognitive rehabilitation studies were identified that also included a psychological intervention. Moreover, as aforementioned, one controlled MDR program for adult BT patients was identified (22), and which did include access to psychological therapy. However, no details were reported pertaining to what the therapy entailed, and whether this was consistent across patients. Notwithstanding this lack of detail, interestingly, this program was not found to lead to significant improvements in anxiety, depressive, and QOL scores for participants who completed the MDR program. Comparable to Locke et al.'s findings (16), the null results from the MDR program may be due to patients not being clinically distressed at baseline, and hence, did not derive significant improvement in emotional well-being by having access to psychotherapy. Taken together, the findings from these two integrative cognitive and psychological intervention programs attest to the need to conjointly screen for both cognitive impairment and emotional distress to ascertain which patients may benefit most from multidisciplinary interventions which include a psychotherapy component.

Importantly, given the high rates of psychological problems experienced by BT patients [e.g., Ref. (1, 4)], it is surprising that no published study to date was identified which was specifically tailored to clinically distressed BT patients. Indeed, small to medium effects with mixed outcomes have emerged in the efficacy of psychosocial interventions in managing emotional disturbances in the broader (non-BT) oncology literature (24, 25). This may in part be due to floor effects if patients are not experiencing clinically elevated levels of distress at baseline. Indeed, in the most recent and largest meta-analytic review of the effects of psychosocial interventions to manage emotional distress and QOL in cancer patients, Faller et al. (24) found that only a very limited number of studies preselected participants according to baseline distress levels. Importantly, these studies showed the largest effect sizes. In the current review, although Ownsworth et al. (15) found a reduction in depressive symptoms, this was not comparably found for anxiety symptoms. Moreover, the clinical diagnostic status of patients at baseline was not reported.

Research has shown that depression and anxiety disorders share common latent structures, which have contributed to a recent increase in studies testing the concurrent treatment of anxiety and mood disorders in the general population using cognitive and behavioral based transdiagnostic therapies (26), including the integration of behavioral strategies with acceptance-based therapies [such as Acceptance and Commitment Therapy (ACT)] (27, 28). Considering that anxiety problems have been found to be associated with comorbid depressive symptoms in adults diagnosed with a primary BT [e.g., Ref. (4, 7)], ACT-based interventions may have particular relevance for distressed BT patients given the objective of this approach is to improve patients functionality and QOL in concordance with their values, while also factoring in their shortcomings (19–30). Hence, for adult BT patients, contingent on the extent of cognitive, sensory, and physical deficits sustained due to the tumor and/or treatment side-effects, patients can still re-learn how to maintain an adaptive QOL by engaging in value-based activities (e.g., enjoyment of participating in team-based social events) they can partake in, despite any impairment(s) they have sustained. Moreover, ACT aligns with transdiagnostic approaches as the treatment components are comparable for both managing anxiety and depressive disturbances.

An ACT-Based Transdiagnostic Intervention for BT Patients: A Pilot Case Study

Kangas et al. (31) developed a manualized ACT-based transdiagnostic intervention (which included patient handouts, worksheets, and a CD) with the aim of improving the emotional well-being and QOL of distressed adults with primary BTs. In line with ACT principles, the program comprised the following components which targeted: (1) education about common reactions to being diagnosed with a BT; (2) acceptance, defusion, and mindfulness based exercises to promote awareness and acceptance of internal physical sensations and cognitions; (3) learning to deal with the uncertainty of a BT diagnosis and prognosis by using acceptance and mindfulness strategies; (4) behavioral exercises to re-engage in avoided activities; and (5) re-evaluating life-goals concordant with one's values in at least three key domains – interpersonal, personal/self-care, and occupational, in order to engage or re-engage and commit to pursuing valued life goals. This program was designed to be conducted in-person over 6-weekly, 90 min sessions, including two additional "booster" sessions to consolidate skills learnt, scheduled at fortnightly intervals.

Kangas et al. (31) initially pilot tested the ACT intervention with a middle-aged male, "Luke" (aged 53 years), diagnosed with a meningioma 2.3 years prior and had completed his BT treatment (including a craniotomy and 20 sessions of fractionated stereotactic radiotherapy) 18 months prior to referral to the program. Luke completed a comprehensive assessment including a diagnostic clinical interview, self-report measures, and neuropsychological testing at four phases: baseline (T1), end of therapy (T2), 1-month (T3), and 3-months (T4), following completion of the 8-session program. At baseline, Luke met comorbid criteria for both Major Depressive Disorder and anxiety (including Generalized Anxiety Disorder and BT-related PTSD). His QOL scores on the Functional Assessment of Cancer Therapy – General and Brain subscale (FACT-G/BR) (32) were very low, >3 SDs below published norms. He also reported low acceptance and high experiential avoidance of negative cognitions and physiological bodily sensations since his BT diagnosis, as assessed by the Acceptance of Actions Questionnaire (AAQ) (33). This scale measures an individual's avoidance of negative perceived cognitions (including thoughts, beliefs, and perceptions) and physical sensations. His memory and cognitive skills were assessed to be in the average to above average range, although his problem-solving scores were slightly below average. By the end of therapy, Luke no longer met criteria for depression or anxiety. With a reduction in depressive symptoms [as measured by the Beck Depression Inventory – 2nd Edition; (34)], and a decline in experiential avoidance, Luke also increased his problem-solving skills and QOL. In particular, he engaged in substantially more social events and reintegrated with his social network. These effects were maintained at 3-months

follow-up. These case report findings demonstrate that this ACT-based intervention has potential, promising utility in treating both anxiety and depression disturbances in distressed adults diagnosed and treated for a primary BT. However, the efficacy of this program needs to be tested in future research using a large scale controlled trial design, particularly as there is a dearth of studies that have been specifically tailored for distressed adult BT survivors.

It is acknowledged that this scoping review was limited to published studies in the English language. Also, the abstracts and extracted data were not independently evaluated by a second reviewer. Notwithstanding these limitations, a more integrative scoping review method was used to keep the study aim specifically focused on identifying psychological interventions for adult BT patients which anxiety, depression, and/or QOL indices were included as outcome measures in evaluating the effects of the intervention. Moreover, in accord with recent recommendations for scoping reviews (9), the methodology of identified studies was critically evaluated in line with relevant components of the PRISMA (14) framework in order to clearly delineate gaps in this field and guide future research trials.

Conclusion

In conclusion, the findings from this scoping review demonstrate that there is a notable paucity of published controlled trials which have tested the efficacy of any type of psychological based intervention in managing the emotional wellbeing (notably, anxiety and/or depressive symptoms) and QOL of adults diagnosed with a primary BT across the illness trajectory. To date, the outcome from Ownsworth et al.'s (15) RCT study accentuates the potential utility in using a multimodal approach including cognitive and behavioral strategies to enhance the QOL and existential wellbeing of BT survivors. In order to strengthen the evidence base in this field, future research is pressingly warranted to further test the efficacy of psychological interventions in managing emotional disturbances and maintaining and/or improving the QOL, particularly in clinically distressed BT patients and longer-term survivors.

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The potential role of exercise in neuro-oncology

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Patients with brain and other central nervous system cancers experience debilitating physical, cognitive, and emotional effects, which significantly compromise quality of life. Few efficacious pharmacological strategies or supportive care interventions exist to ameliorate these sequelae and patients report high levels of unmet needs in these areas. There is strong theoretical rationale to suggest exercise may be an effective intervention to aid in the management of neuro-oncological disorders. Clinical research has established the efficacy of appropriate exercise in counteracting physical impairments such as fatigue and functional decline, cognitive impairment, as well as psychological effects including depression and anxiety. While there is promise for exercise to enhance physical and psychosocial wellbeing of patients diagnosed with neurologic malignancies, these patients have unique needs and research is urgently required to explore optimal exercise prescription specific to these patients to maximize safety and efficacy. This perspective article is a discussion of potential rehabilitative effects of targeted exercise programs for patients with brain and other central nervous system cancers and highlights future research directions.

Keywords: exercise, physical activity, brain tumor, brain metastases, cancer

INTRODUCTION

Malignant brain tumors and other central nervous system cancers (referred to as brain cancer hereafter) represent a highly challenging and devastating group of cancers. While the incidence of brain cancer is relatively low, mortality is high with the most recently reported 5-year survival rates at ~19–35% in Australia, United Kingdom, and America (1–3). Median survival varies with tumor pathology, grade, and demographic factors with older patients who have higher grade cancer and poor performance status faced with the worst prognosis of only limited months of survival (4). Not only does brain cancer have one of the lowest survival rates but it is also one of the leading sites contributing to burden of disease caused by cancer (1). Brain cancer patients experience debilitating physical, cognitive, and emotional effects, which significantly compromise quality of life (QOL) both for patients and their families (5, 6). The profound effect on physical and mental function leads to a premature loss of independence and significant economic burden both at the individual and societal level (7–9). This concern is accentuated by the fact that brain cancer is not just a disease of the elderly but occurs across all age groups, commonly affecting patients at the peak of their work and child-rearing responsibilities (average age of diagnosis is 57 years; ~65% of diagnoses occur at 45–84 years) (10). This paper focuses on the adult rather than pediatric setting.

At diagnosis, patients with brain cancer frequently experience neurological deficits including impaired balance, motor skills, and vision as well as headaches, seizures, and cognitive declines including memory and/or speech loss (11). In addition to tumor symptoms, treatment itself is associated with a range of toxicities. Treatment modalities include surgery, radiation, chemotherapy, and corticosteroids, alone and in combination (12). Some of the most troublesome adverse effects associated with these treatments include fatigue, myopathy, impairments in physical functioning, insomnia, additional cognitive decline, mood disturbance, and psychological distress (6, 13–20). Frequently used anticonvulsant medications may further accentuate fatigue and somnolence experienced by patients (21). As a consequence, patients are often unable to continue working and cannot legally drive. These issues combine to significantly compromise QOL (5). Currently, there are few established pharmacological strategies, which may ameliorate the debilitating effects associated with brain cancer and its treatment. Thus, not only do patients experience high symptom burden but also the symptoms are difficult to treat and based on the dearth of established management therapies may not be addressed. This is highlighted by the level of unmet supportive care needs among patients and their caregivers (22–24). Clearly, there is a pressing need to discover viable management options to counteract the incapacitating effects of brain cancer and address the unique needs of these patients. In this article, we discuss the potential of exercise as one such option.

EXERCISE TO COUNTERACT PHYSICAL EFFECTS OF BRAIN CANCER

Brain cancer patients experience considerable physical impairments that compromise QOL and independence. The average level of fatigue experienced by these patients is ~40–50% more severe

than normative levels for cancer patients, equating to approximately five times the clinically meaningful difference (25–29). Markedly reduced strength and fitness capabilities compared to age- and sex-matched norms have also been reported (26). Specifically, maximal muscular strength was observed to be 57 ± 28% of predicted values and cardiorespiratory fitness reported to be 41 ± 10% of predicted values among clinically stable patients following surgery (26). Functional capacity as assessed by the 6-min walk test has also been reported to be compromised in brain cancer patients, corresponding to 56 ± 13% of age- and sex-matched normative values (25). Notably, these data were collected in relatively well patients with good performance status (i.e., ≥70% Karnofsky performance status) and as such the degree of impairment for more debilitated patients is expected to be further compromised. Unfavorable changes in body composition are also apparent with a loss of lean mass and gains in fat mass evident following surgery (26). Additionally, while fatigue and somnolence are evident, insomnia is also commonly experienced by patients with brain cancer at higher rates than the general population (30).

To date, there have been no clinical trials evaluating the efficacy of exercise in counteracting the physical impairments experienced by brain cancer patients. However, clinical research has established the beneficial effect of exercise in ameliorating many of these impairments in other cancer populations. Specifically, appropriate exercise prescription has been shown to reduce cancer-related fatigue (31), enhance strength, fitness, and common functional movements (e.g., ambulation, chair rise, and stair climb ability) (32–35), promote favorable changes in body composition (i.e., increased lean mass and reduced fat mass) (33–35), and improve sleep quality (36). While these data were not specifically obtained from brain cancer patients, they provide strong theoretical rationale for the potential beneficial effect of exercise in these patients.

As of November 2014, there were no clinical trials registered in Australia, USA, or Europe, exploring the possible role of exercise in managing the side effects of brain cancer in adults. However, two small exercise intervention trials enrolling children with brain cancer have been recently launched in USA (NCT01944761, NCT02000986). Our team has been conducting pilot work to determine the feasibility and safety of exercise in adult grade III/IV glioma patients with initial observations suggesting that well-designed and appropriately supervised exercise may help to counteract many of the adverse physical side effects. To date, eight well-functioning (Eastern Cooperative Oncology Group performance status of 0–1) patients with high grade glioma have completed an exercise program involving three supervised exercise sessions weekly for the duration of chemoradiotherapy (~7 weeks) and are continuing with an additional 7 weeks of the exercise program after completing radiation therapy. Participants tolerated the exercise program well with no adverse events occurring during the exercise sessions and only one patient withdrawing due to time constraints. Despite intensive concurrent treatment, attendance was high at 87% and the average perceived exertion was in line with the target for people with cancer (13.4 ± 1.0 on the Borg 6–20 rating of perceived exertion scale; target = 12–16). Initial observations include 20 ± 16% improvement in muscle strength, 9 ± 10% improvement in cardiorespiratory fitness, and enhanced functional ability with improvements of 12 ± 7% in ambulation, 7 ± 11% in chair rise ability, and 12 ± 17% in dynamic balance. While only a short intervention period, favorable body composition changes were also observed with a 1.0 ± 2.4% average increase in lean muscle mass and varying results for changes in fat mass depending on whether or not patients were receiving dexamethasone (loss of 6 ± 6 vs. gain of 12 ± 12% fat mass in patients not receiving and receiving dexamethasone, respectively). Future research is needed to expand on this very early pilot work by exploring the efficacy of appropriately prescribed and supervised exercise for brain cancer patients in randomized controlled trials. Early results convey that dexamethasone use may be a relevant stratification factor and may require consideration in exercise prescription given the sequela of weight gain and proximal myopathy (37). It will also be important to investigate the potential role of exercise in patients with poorer performance status given the high demand for improving existing deficits and preventing further declines in physical functioning.

EXERCISE TO COUNTERACT COGNITIVE EFFECTS OF BRAIN CANCER

Few patients avoid experiencing impairments in cognitive function associated with brain cancer (38–40). While the etiology and degree of impairment varies, declines commonly occur in memory, attention, executive function, verbal fluency, and visuospatial perception (39, 40). Such deficiencies significantly compromise QOL through adversely impacting daily activities and interpersonal relationships (41, 42). Impact on the carer and other family members' QOL is considerable especially given the subsequent reductions in independence (39–42). While pharmacological and cognitive rehabilitation interventions have been proposed and show promising evidence, the management of cognitive effects caused by brain cancer and its treatment remains a major challenge (22, 43–45).

The potential role of exercise in attenuating such cognitive impairments has not been evaluated in brain cancer patients. However, a robust body of literature involving animal models as well as various patient models of healthy aging and other diseases associated with impaired cognition (e.g., Alzheimer's disease, stroke) has established the efficacy of exercise as a potent therapy for maintaining and improving cognitive function (46–50). Exercise has a neuroprotective effect, reducing the risk of cognitive decline during aging as well as the incidence of dementia and Alzheimer's disease (46–50). The vast majority of longitudinal research also indicates exercise is an effective intervention for improving cognitive function in cognitively healthy adults (46–50). Importantly, exercise has been observed to be particularly beneficial in reversing deficits among patients with cognitive impairments, resulting in improved cognitive function across a variety of domains (46–50). Findings from one of the first investigations specific to cancer suggest that exercise may also help counteract cognitive impairments caused by chemotherapy agents (based on an animal model of colorectal cancer) (51). A considerable body of literature including neuroimaging, human, and animal studies outside the cancer setting has elucidated the main mechanisms believed to be responsible for the preventative and restorative effects of exercise on cognition (52–55). Specifically, exercise mechanistically drives improvements in brain function

and structure through stimulating neurogenesis and neural plasticity, up-regulating growth factors including brain-derived neurotropic factor, reducing levels of endogenous corticosteroids and pro-inflammatory cytokines, reducing oxidative stress, preserving brain volume, improving vascularization and increasing blood flow throughout the central nervous system, and increasing levels of hormones beneficial to neural structure and function (52–55). Despite clear differences in the pathophysiology of cognitive declines experienced by brain cancer patients, this establishes exercise as a promising intervention to counteract the cognitive effects experienced by patients.

Currently, there are a handful of registered trials evaluating the potential of exercise to prevent or rehabilitate cognitive impairments in cancer patients. The only investigation specifically involving people with brain cancer was recently opened in USA (NCT02153957) and will determine whether exercise improves cognitive problems in children treated with radiation at least 2 years prior to enrollment in the study. There are also two trials being conducted in adults with breast cancer; one led by our team exploring whether exercising during treatment prevents chemotherapy-induced cognitive impairment (ACTRN12614000051640) and the other ongoing in Canada investigating if exercise can improve cognitive dysfunction following the completion of chemotherapy (NCT01296893). While the results of these trials are pending, it is clear that specific research is required to evaluate the effects of exercise on cognitive function in patients with brain cancer. Based on evidence from other populations, future research should assess objective outcome measures of cognitive function including formal neurocognitive function testing, imaging studies, and self-report performance indicators from both patients and their carers. It would be beneficial to examine if exercise can delay onset and/or worsening of cognitive impairments as well as alleviate established deficiencies.

EXERCISE TO COUNTERACT EMOTIONAL EFFECTS OF BRAIN CANCER

The diagnosis and treatment of brain cancer is undoubtedly a distressing experience, which has significant impact on psychosocial wellbeing (6, 20). There is a high prevalence of moderate to severe depression and anxiety among this patient group (20). In fact, the prevalence and severity of depression, anxiety, and overall emotional distress in people with brain cancer are consistently among the highest experienced for any cancer site (56). Beyond these well-defined disorders, patients experience a range of additional emotional challenges including existential issues, loss of self-identity, fear of and guilt about burden imposed on carers, stress, worry, uncertainty, loneliness, and a sense of waiting for cancer progression/death (57–60). The emotional effects of brain cancer extend to carers who also experience considerable declines in psychosocial wellbeing (61). Not surprisingly, the resulting negative impact on QOL is indeed significant (6, 62). Clearly, the psychosocial morbidity caused by brain cancer is profound and leads to a complex suite of supportive care needs for both patients and care-givers (63).

While there is a paucity of research investigating the potential of exercise in counteracting the emotional issues associated with brain cancer, there is clear evidence to suggest a potential therapeutic benefit. Most notably, exercise is recognized as a treatment option for the management of clinical depression by major psychological societies internationally (64, 65). These recommendations are informed by a series of meta-analyses establishing a significant positive effect of exercise in reducing depressive symptoms in adults without cancer (66–70). The efficacy of exercise in managing the psychological distress experienced by cancer patients has also been reported, with meta-analyses confirming the beneficial impact of exercise extends to people with cancer (71–73). A relatively small but statistically significant reduction in psychological symptoms has been observed although larger effects were reported for exercise programs that were supervised, clinic based, and involved a greater volume of exercise (71). Notably, the majority of participants were within the normal range on depression scales, raising the potential of more pronounced effects in distressed patients. The impact of exercise on other components of psychosocial wellbeing is rarely evaluated in existing literature but qualitative research provides evidence of considerable benefit across a range of psychosocial elements (74).

An interrelated group of biopsychosocial factors are theorized to be driving these exercise-induced improvements. Physiologically, exercise elicits favorable adaptations in endorphins, monoamine neurotransmitters (e.g., serotonin, dopamine and norepinephrine), neurotropic growth factors, inflammatory cytokines, and corticosteroids (47, 75–77). Additionally, specific exercise produces acute surges in testosterone in men and women, a powerful anabolic hormone with considerable non-genomic effects on the nervous system including reduced depression and anxiety (78–80). Furthermore, superior functional status is associated with lower depressive symptomology in brain cancer patients (81, 82), suggesting that exercise may also alleviate psychological distress by preserving physical capabilities and functional independence. There is a range of psychosocial factors that may also contribute including improved self-efficacy, social support provided by instructors, and peers involved with the exercise program and the potential of exercise to act as a distraction from negative thoughts (74, 83). Moreover, exercise is an intervention that patients have control of and it is possible that involvement in a structured exercise program may represent an opportunity to empower patients in dealing with the emotional impact of brain cancer (74).

Future research investigating the efficacy of exercise in counteracting the psychosocial morbidity associated with brain cancer is warranted for both patients and their carers. The potential complementary effect of exercise, psychological, and pharmacological interventions in counteracting these emotional problems poses an exciting avenue for novel research and superior clinical practice.

EXERCISE AND SURVIVAL

Higher performance status is a well-established prognostic factor in brain cancer, which is associated with better survival outcomes (4, 84). Given this relationship, it would seem intuitive that greater levels of exercise may also confer a protective effect against brain cancer progression and epidemiological evidence has suggested such an effect (85). Specifically, patients with brain cancer who achieved a greater volume of weekly aerobic exercise had a significantly reduced risk of mortality compared to those

who exercise less (hazard ratio 0.64; 95% confidence intervals 0.46–0.91; $p < 0.001$) (85). This effect was independent of a range of prognostic factors including age, sex, grade, number of prior progressions, and performance status (85). The mechanisms driving this protective effect are unclear, but may involve a range of physiological adaptations that modulate tumor progression (86) and/or an enhanced ability to tolerate greater dosages of adjuvant treatment (87). However, it is possible that patients with superior exercise behavior have lower symptomology and as such these observations may reflect reverse causality rather than a physiological effect (85). While future research is required to elucidate the mechanisms, these data add to a growing body of literature reporting that exercise reduces the risk of cancer mortality in other patient groups (88–91). Additionally, it has been recently reported that increased aerobic exercise levels are associated with a reduced risk of fatal brain cancer (multivariate adjusted hazard ratio 0.58; 95% confidence intervals 0.35–0.95; $p = 0.030$), raising the hypothesis that exercise may also protect against the development of brain cancer (92).

IMPLICATIONS FOR PRACTICE

Exercise shows promise as a supportive care intervention to counteract the adverse impact of brain cancer. Despite their poor prognosis, a relatively high proportion of brain cancer patients participate in exercise throughout (59%) and after (69%) anticancer treatments (93). Furthermore, 60 and 76% of brain cancer patients are open to receiving information about exercise, and 66 and 91% of patients believe they may be able to participate in an exercise program during and after treatment respectively (94). In the absence of any brain cancer specific data, health professionals should rely on the current guidelines for all cancer patients when providing exercise advice to this group (95, 96). These guidelines recommend patients avoid inactivity even when undergoing difficult treatments and aim to participate in regular aerobic (e.g., walking, cycling) and resistance (i.e., lifting weights) exercise. To realize significant health benefits, patients should perform at least 150 min of moderate intensity aerobic exercise and two to three moderate intensity resistance exercise sessions weekly (95, 96). Decades of exercise science research have demonstrated that the quality of the exercise program, especially in terms of the mode, intensity, and volume of exercise, moderates the type and magnitude of adaptations in a dose-response fashion. Given this coupled with the complexity of physiological and psychological impairments common to people with brain cancer, sophisticated exercise prescription and monitoring are required. As such, referral to a clinical exercise physiologist is strongly recommended to ensure an appropriate exercise prescription that maximizes safety and patient benefits.

CONCLUSION

There is strong theoretical rationale to suggest that exercise may be an effective intervention to aid in the management of brain cancer symptoms and treatment side effects. Clinical research has established the efficacy of appropriate exercise in counteracting physical impairments such as fatigue and functional decline, cognitive impairment, as well as psychological effects including depression and anxiety, within other cancer patients and chronic disease populations. This is supported by promising early evidence and clinical observations in brain cancer patients, but more research is required to explore optimal exercise prescription specific to the unique needs of these patients in order to maximize safety and efficacy. The potential rehabilitative effect of targeted exercise interventions in neuro-oncology is exciting, especially given that exercise represents a relatively inexpensive and highly accessible intervention that has very few adverse side-effects when appropriately prescribed and supervised.

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Integrating psychosocial care into neuro-oncology: challenges and strategies

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Approximately 256,000 cases of malignant brain and nervous system cancer were diagnosed worldwide during 2012 and 189,000 deaths, with this burden falling more heavily in the developed world. Problematically, research describing the psychosocial needs of people with brain tumors and their carers and the development and evaluation of intervention models has lagged behind that of more common cancers. This may relate, at least in part, to poor survival outcomes and high morbidity associated with this illness, and stigma about this disease. The evidence base for the benefits of psychosocial care in oncology has supported the production of clinical practice guidelines across the globe over the past decade, with a recent mandate to integrate the psychosocial domain and measurement of distress into routine care. Clinical care guidelines for people with brain tumors have emerged, with a building focus on psychosocial and survivorship care. However, researchers will need to work intensively with health care providers to ensure future practice is evidence-based and able to be implemented across both acute and community settings and likely within existing resources.

Keywords: neuro-oncology, psychosocial care, brain tumours, survivorship, distress

THE HEALTH BURDEN OF BRAIN TUMORS

It was estimated that there were approximately 256,000 cases of malignant brain and nervous system cancer (ICD-10 codes C70-C72) diagnosed worldwide during 2012 (age standardized rate of 3.4/100,000) and 189,000 deaths (2.5/100,000) (1). The incidence rate of cancers of the brain and nervous system was almost double in more developed countries compared to less developed countries (5.1/100,000 and 3.0/100,000, respectively) and was higher for males (3.9/100,000) than females (3.0/100,000). Five-year prevalence was 343,000 in total. This disease carries a heavy psychosocial burden (2, 3), and often occurs at the age of middle adult life with 41% of brain tumor patients globally aged younger than 50 years (median age range of 55–59 years) (1). The middle adult life stage is a time of potential generativity (4), such that the loss of function and loss of life from an individual, family, community and economic perspective is substantial.

Patients with brain tumor suffer from a high rate of psychiatric and psychological disorders that are quite specific and distinct from other areas of psycho-oncology. In fact, unlike systemic effects of other tumors and treatment, brain tumors have a direct effect on brain functioning affecting cognition, mood, and personality, with profound changes in mood and cognition and impairments in several dimensions of functioning (5) and quality of life (6–8). A series of data have been collected regarding the effects of primary brain tumors on individual psychological functioning and psychosocial dimensions. The most significant and common disorders regard cognitive dysfunction, affecting about 70% of the patients. Disorders of memory, attention, and concentration have been described, with a tendency to worsen as the lesion increases or invades CNS areas. Acute confusional states (i.e., delirium) are also common neurocognitive complications of brain tumors. Clinically, some dysfunctions and symptoms are described in terms of "specific" syndromes, such as frontal lobe syndromes (caused by tumors in the frontal lobe) with several manifestations, including agitation, behavioral disruption and emotional lability (e.g., orbitofrontal disinhibited syndrome), psychomotor slowness and apathy (e.g., mesial frontal apathetic syndrome), and disorders of the executive functions, perseveration, and psychomotor slowing (e.g., dorsolateral prefrontal dysexecutive syndrome); temporal lobe syndrome, with impairment of verbal and non-verbal memory and seizures (9). A further major challenge of these disorders, and in neuro-oncology in general, is represented by a frequently undetected and under-recognized possible effect of psychiatric disorders, mainly cognitive impairment, in reducing patients' mental capacity with problems in providing informed consent (10, 11).

Further syndromes related to brain tumors that have to be taken into account regard mood disorders, including depression and mania (25–30%), anxiety disorders (15–70%), changes

in personality traits (sometimes subtle in the beginning phase, sometimes abrupt and dramatic), and psychotic disorders (12). Significant neuropsychiatric disorders may be the consequence of intervention, including surgery, radiotherapy, and, especially, drugs (e.g., psychotic syndromes and behavioral disorders secondary to corticosteroids) (13). Evaluation of patients' symptoms, by conducting a careful neuropsychological and psychiatric assessment, is mandatory in clinical settings in order to provide the most proper psychopharmacological (e.g., antidepressants, anticonvulsants, antipsychotics) and psychotherapeutic intervention. With regard to the latter, the need for specific educational, supportive, and psychosocially oriented intervention for the patients' families has also been repeatedly underlined (14–16). However, a recent review concluded that the research to date on the complex needs of brain tumor patients and how to best help them is limited in scope, with little attention to how to provide supportive care (17). This gap also extends to survivorship care and planning.

CANCER SURVIVORSHIP, STIGMA, AND SOCIAL REPRESENTATIONS OF ILLNESS

The National Cancer Institute defines cancer survivorship as focusing on the health and life of a person with cancer from diagnosis and treatment until end of life, including the physical, psychosocial, and economic issues of cancer through the balance of his or her life. Within this definition, the experience of family members, friends, and caregivers are also considered relevant (18). The language applied within this discourse is intended to be empowering, signaling a shift from cancer "victim" terminology to a survivor framework. However, not all people who have had cancer perceive themselves to be a cancer survivor (19), and some suggest that this label marginalizes those who have a poor prognosis or high cancer-related morbidities (20, 21).

Stigma is when a person is seen by society as tainted, damaged, or less valuable as a result of an attribute or characteristic (22). Stigmatizing marks can be linked to appearance (e.g., physical appearance or overt behavioral differences) or group membership (e.g., race or religion), and is relationship and context specific (23). In health, stigma is reported to be higher for illnesses that are linked to modifiable lifestyle factors (e.g., smoking, drug or alcohol abuse, sexual activity), disfigurement or outward signs of illness, or a painful death (24). For example, cervical cancer has been reported as stigmatizing on the basis of its relationship with human papilloma virus and from this inferred sexual activity (25). People with lung cancer report feeling stigmatized based on the connection between smoking and lung cancer, as well as the high morbidity and mortality of the disease (24). The changes in facial appearance that may accompany head and neck cancer have been linked to stigma in this patient group (26) and patients with Parkinson's disease who have facial masking are more negatively judged that those with normal expressivity (27). Finally, epilepsy is reported as being globally one of the most stigmatizing health conditions, linked to perceptions of it as being unpredictable, unattractive and violent, and representative of mental illness (28, 29).

Hence, although it is suggested that stigma about cancer in general has declined over the past four decades (30), some patient groups still experience stigma. People with brain tumors may experience stigma as a result of the cognitive, behavioral, and physical changes that may result from the tumor or treatment, as well as fears about a cancer that for some may have a poor outcome. Brain tumor patients therefore may experience social stigma as a result of their cognitive and neurological symptoms, and this may deepen these patients' sense of social isolation and discrimination (31). Within this, the perception of a brain tumor as "mind-body" illness may be stigmatizing for both the patient and their family. In some cultures, this effect is worsened by lay beliefs about the causes of illness. For example, in a qualitative study in Bangalore, people with glioblastoma reported that their illness was a punishment from God for previous sins, or Karma, or a result of black magic (32). Palese et al. proposed that patients with frontal lobe neoplasms may be more at risk of stigma and having their problems underestimated by nurses than those with other cerebral neoplasms (33). However, findings were mixed with a tendency for nurses to overestimate problems more common. It is perhaps surprising, however, how little research has been undertaken about health-related stigma in brain tumor patients and how this affects their lives and their access to and utilization of health care services.

In this regard, stigma is connected to poorer outcomes in life across the domains of health, education, and access to social resources and in the case of people with stigmatized health conditions contributes to higher subjective distress about their illness (34). It is well accepted that there is a stigma around mental illness in Western culture (35, 36), and it has been further suggested that this stigma is also a barrier to cancer patients seeking and obtaining help for the distress associated with cancer (37). This means that patients who have a stigmatizing cancer may be doubly disadvantaged: more distress and less help. In addition, a broader health sector outcome of stigma [that has been well discussed in lung cancer (38)] is that stigmatized conditions may be underfunded for research and services. Consistent with this, in 2004 in the House of Commons John Brecow, the Chair of the brain tumor All Party Parliamentary Group made the point that "the issue of brain tumors is under-debated, under-reported, and underfunded. In this Parliament, the issue has attracted minimal – dare I say it, derisory – attention." In this context, quality frameworks for health service delivery can play a crucial role in evening the playing field.

GUIDELINES AND QUALITY STANDARDS FOR PSYCHOSOCIAL CARE

Psycho-oncology and psychosocial oncology are, relative to biomedical treatments for cancer, a recent development in modern cancer care. Surgical treatment was the forerunner of cancer treatment, an approach that became more widely possible in the nineteenth century with the development of anesthesia and the first successful brain tumor surgical removal reported in 1879 (39). At the beginning of the twentieth century radiation therapy emerged as a cancer treatment (40), followed in 1940s by chemotherapy (41). By contrast, although the psychosocial care of people with cancer arguably does not hinge on technological advancement, the emergence of this field followed decades later, perhaps best heralded by the formation in 1984 of the International Psycho-Oncology Society (IPOS). IPOS led the mission to improve the care of cancer patients and their families globally by promoting the science of psycho-social and behavioral oncology (42) and the

publication in 1989 of the first textbook in the field (43). A more recent milestone was the introduction of quality standards for psychosocial care by IPOS in 2010 (44). Parallel to these developments was the emergence of the cancer survivorship movement, with the formation in 1986 of the National Coalition for Cancer Survivorship (NCCS). The NCCS promoted itself as an advocacy collective for cancer survivors followed a decade later by the National Cancer Institute Office of Cancer Survivorship with the mission to promote cancer survivorship programs and research.

Over the past decade, a number of countries have developed generic clinical practice guidelines for the psychosocial care of adults with cancer. In Australia, these were first developed for women with breast cancer, and then later revised in 2003 to cover all adults with cancer (45). Similar work followed after in Canada, United Kingdom, and European Union (46–48). However, while clinical practice guidelines provide an evidence-based reference point to guide care, they are limited by the *a priori* review scope and are of less direct application in a field where evidence is scant. This means that the depth of direction and advice to addressing the specific and specialized needs of brain tumor patients and their families in such guidelines is limited. As well, the development and dissemination of guidelines do not necessarily change practice (49). Further actions to improve practice in psychosocial care included the Institutes of Medicine 2007 report "Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs" with the major recommendation that "quality cancer care today must integrate the psychosocial domain into routine cancer treatment" (50). In 2010, IPOS published a new international quality standard supporting the integration of psychosocial care and proposing a distress screening and management be included in routine care by placing it as one of the six Vital Signs (44). These standards have now been widely endorsed internationally.

A number of medically focused guidelines specific to brain tumors have been developed in Australia, United Kingdom, and North America (34, 51–55). While broadly speaking these tend to focus on the medical management of diagnosis and treatment, the Australian Clinical Practice Guidelines for the Management of Adult Gliomas: astrocytomas and oligodendrogliomas addresses the cognitive and personality changes that can occur in these patients and provides recommendations for identification and management of psychological disorders, cognitive problems and personality, and other changes related to the tumor or its treatment (52). This includes advice about the need for early identification of psychological distress and referral for psychosocial treatment for those with or at risk of significant distress. Neuro-rehabilitation within a multi-disciplinary care model is also advised. This approach of psychological assessment and support as an integral part of the management of patients with brain tumor is also advised elsewhere with referral to neuropsychology and neuropsychiatry services advised for patients who require specialist intervention for cognitive, emotional, or behavioral problems (54). Nursing clinical practice guidelines developed by the American Brain Tumor Association and the American Association of Neuroscience Nurses also specifically address nursing assessment for a range of problems including fatigue, distress, and body image with referral for rehabilitation (51). Notably, these guidelines also discuss survivorship issues including the need for support for caregivers. Finally, the National Comprehensive Cancer Network survivorship guidelines do note that that cognitive impairment is prominent in survivors of primary central nervous system cancers or people with brain metastases; however, acknowledge that there is limited evidence to date to guide management of this condition, especially for cancers other than breast (53).

Despite these encouraging developments there are barriers to the implementation of psychosocial and survivorship care in oncology settings, which include the continued dominance of biomedical care models; gaps in knowledge about research translation; diminishing health budgets in the face of escalating costs; and individual and community attitudes to illness and help seeking (44, 56, 57). In brief, while quality standards and guidelines provide guidance for key characteristics of good oncology care, operationalizing these in the clinical or community setting presents its own challenges. Care models that are practically translatable are needed.

STEPPED CARE MODELS

One approach to this problem has been to develop care frameworks that show how services articulate across levels of distress and that focus on delivering the most in-depth (and expensive) services to those who need them most. A tiered approach tailors services to need through screening, triage and referral to different levels of intervention appropriate to each patient (58). At the most basic level, psychosocial care would include cancer-related information and brief support from a health care professional in the treatment team; cancer-related telephone helpline and other information focused interventions. Those with higher levels of distress that require more specific psychological interventions, including people with pre-existing vulnerabilities or complex problems (e.g., neurocognitive deficits) are referred to more intensive, specialized, or multidisciplinary approaches. Transition to more specialized and in-depth levels of care is guided by standardized distress screening, as per the best practice internationally, and interview assessment by the treating health professional. A stepped care approach differs in that a decision analytic approach is applied with systematic identification of high need patients followed by an integrated treatment program where care is stepped up progressively until the problem is resolved (59). These approaches have not yet to our knowledge been applied to people with brain tumors; however, the articulation of a tiered or stepped care model for this patient group that incorporates specific needs of brain tumor patients seems warranted.

All such models are predicated on applying screening for distress to guide referral to the appropriate level of care, or stepping up of care as needed. The distress thermometer is an ultra-brief screening measure that has been widely validated globally across cultures and tumor sites and found to be a reliable first-line screening tool for detecting psychological distress in cancer patients (60, 61). This measure includes a problem checklist and a single item asking the patient how much distress they have been experiencing in the past week including the current day on a scale of 0, no distress to 10, extreme distress (62, 63). Although the most commonly recommended cut-off for this scale is >4, in the case of people with intracranial tumors a cut-off of >6 has been reported as having optimal sensitivity for detecting distress (64). A key

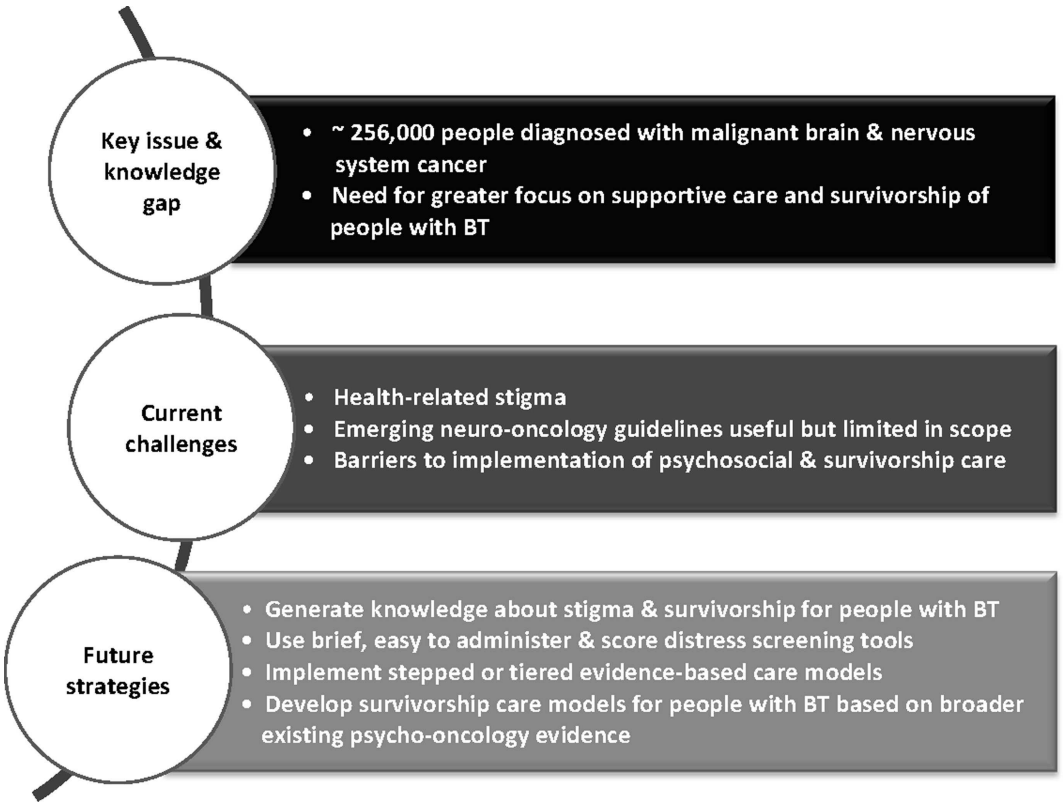

FIGURE 1 | Overview of challenges and strategies for integrating psychosocial care into neuro-oncology.

advantage of the distress thermometer is that it is short and easy to administer and score thus making it ideal for translation into acute settings. Other researchers have found the two item Patient Health Questionnaire-2 (65) to have acceptable psychometric properties for detecting moderate to severe psychological distress in brain tumor patients (66). In contrast, Rooney et al. (67) have recommended longer scales and in particular the Hospital Anxiety and Depression Scale (68) and Patient Health Questionnaire-9 (69) for detecting major depressive disorder in well-functioning glioma patients as a preceding step to more in-depth clinical assessment (67). The important question of how screening for neurological and cognitive impairment can be undertaken in these patients alongside distress screening, particularly in settings where specialist staff may not be easily accessed, is a key future question for both researchers and health care providers.

CONCLUSION

There is a need for a comprehensive model of survivorship care for people affected by brain tumor and their families and this should be a priority for neuro-oncology (**Figure 1**). Given the more advanced stage of development of such care in other cancers, there is a platform of existing knowledge upon which neuro-oncology practitioners may build. This includes screening for distress with referral as needed into stepped and evidenced-based care models. However, although clinical care guidelines specifically for people with brain tumors are emerging, there is a scarcity of intervention research in the field. There is a clear need for a strategic focus on knowledge generation around survivorship for this patient group.

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