The Relationship between Subjective and Objective Cognitive Functioning, Depression and Anxiety in Primary Brain Tumor Patients, Postoperatively

Thesis, Bachelor Psychology and Health
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Abstract

A primary brain tumor (PBT) is a form of cancer that originates in the brain itself. Patients with PBT’s often experience cognitive deficits in executive functioning, memory and attention. Prior research had found that objective cognitive functioning (OCF) and cognitive complaints are either not related to each other, or this association shows only a small effect. It is not known how this relationship is in PBT patients. There is evidence that cognitive complaints are influenced by factors as depression, anxiety and fatigue. The present cross-sectional study investigated the relationship between OCF and subjective cognitive functioning (SCF) and the effect of depression and anxiety on OCF and SCF in 35 PBT patients, postoperatively.

Similar to prior research, a small effect between OCF and SCF was found. Also, PBT patients with depression or anxiety had more cognitive impairments, although only the difference between depression and no depression reached significance. Surprisingly, PBT patients with depression or anxiety reported less cognitive deficits than PBT patients without depression or anxiety. These results suggest that OCF and SCF are related in PBT patients and that depression and anxiety may be risk factors for OCF. Other variables such as coping mechanisms, quality of life and social support should be taken into account when examining SCF.

Keywords: Primary brain tumors, craniotomy, objective cognitive functioning, subjective cognitive functioning, depression, anxiety

Introduction

Brain Tumors

Brain tumors are diverse; there are over 120 different types (www.abta.org) and they can be divided in primary and secondary brain tumors. A brain tumor can be the result of cancer elsewhere in the body when a metastasis enters the brain; this type is a secondary brain tumor (www.abta.org; www.cancerresearchuk.org). Although real statistics for secondary brain tumors are scarce, it is estimated that they outnumber PBT’s (www.abta.org). PBT’s originate in the brain itself. PBT’s can arise from the cells that form the brain tissue, the nerves that enter and leave the brain or they can develop from the meninges. When a brain tumor develops from glia cells, it is called a glioma. Meningiomas arise from the meninges surrounding the brain. The
average age of patients suffering from a PBT is 40 years old (Kaleita et al., 2004; Satoer et al., 2014).

**Primary brain tumors**

Glioma is a common form of a PBT in the central nervous system (Jiang & Uhrbom, 2012). It is estimated that gliomas account for 30 - 45% of all PBT’s (Glioblastoma and malignant astrocytoma, 2012; www.cancerresearchuk.org). Gliomas are tumors that originate from supportive brain cells, which are called glia cells. They are responsible for the functioning and signaling speed of neurons and also keep the neurons in place (Satoer et al., 2014; American brain tumor association; Glioblastoma and malignant astrocytoma, 2012). Astrocytes, oligodendrocytes and ependymal cells are three sorts of glia cells that can all result in gliomas. They can also be mixed, in which case they are called an unspecified glioma (Louis et al., 2007; www.abta.org).

Meningiomas develop in the meninges. Meningiomas are less common than gliomas, but still account for 20-34% of all PBT’s. Meningiomas are usually slow in their growth and therefore benign. Meningiomas tend to grow towards the brain which causes pressure on the surrounding brain tissue (American brain tumor association; Meningioma, 2012).

Schwannomas and pituitary adenomas, next to gliomas and meningiomas, are mostly represented in this study and will therefore be explained briefly. Pituitary adenomas are slow-growing benign tumors that account for approximately 9-12% of brain tumors. Symptoms are the result of pressure on the surrounding areas, but also through the effect on hormones. A pituitary adenoma can either inhibit or stimulate the hormone (e.g. growth hormone, sex hormones and adrenal gland hormones) production (American brain tumor association; Pituitary tumors, 2012). Another slow-growing, and thus benign brain tumor is the schwannoma. Tumors of this kind arise from the nerve of hearing. Schwannomas can cause loss of hearing and dizziness. They represent about 8% of all PBT’s (www.abta.org).

Besides the division of brain tumors on basis of origin, there are differences in growing rate. The World Health Organization (WHO) has done research to obtain a standardized classification of brain tumors (Kleihues & Sobin, 2000; Louis et al., 2007). There are four WHO grades of growth. WHO graded I tumors, have low spreading potential. Besides, treatment is possible by surgical removal only. Grade II tumors have low spreading potential as well, but they
are more infiltrative and more likely to return after craniotomy (Louis et al., 2007). WHO graded tumors I & II (low grades) are the slowest to grow (Louis et al., 2007; Miebach et al., 2006; Satoer et al., 2014). Brain tumors with WHO graded I & II are benign tumors (www.cancerresearchuk.org; Miebach et al, 2006). Malignant tumors are WHO graded III & IV (high grades). These tumors grow relatively fast. They are more likely to return after treatment and to spread to other regions (Louis et al., 2007; Miebach et al., 2006; Satoer et al., 2014). Tumors graded III & IV generally receive adjuvant radiation and/or chemotherapy. A graded IV tumor is associated with rapid fatal outcomes pre and post operation (Louis et al., 2007).

**Symptoms in PBT patients**

Somatic symptoms are dependent on the location and size of the tumor. Armstrong et al. (2004) suggested that increased intracranial pressure is associated with perceived somatic deficits. Symptoms include headaches (38 - 74%), weakness (55%), drowsiness, nausea, vomiting and hemiparesis (Armstrong et al., 2004). PBT patients report significantly more fatigue than healthy control subjects and experience higher levels of depression and anxiety (Bunevicus, Tamasauskas, Deltuva, Tamasauskas & Bunevicius, 2013; Kaleita, et al., 2004; Rooney, Carson & Grant 2011; Talacchi et al., 2011). Gustafsson, Edvardsson and Ahlström (2006) found that of 39 low graded glioma (LGG) patients, more than 50% reported tiredness and sleep disturbances. Unexplained symptoms are reported by two-thirds of patients and one-third fulfills the criteria for a somatoform disorder (Mainio, Hakko, Niemelä, Koivukangas & Räsänen, 2009). The quality of life (QOL) of these patients is often, unsurprisingly, low (Gustafsson et al., 2006). Another common symptom is epilepsy. Of all PBT patients 71% experience epileptic seizures (Armstrong, Cohen, Eriksen & Hickey, 2004; Talacchi, Santini, Savazzi & Gerosa, 2011; Xu et al., 2013).

**Cognitive impairment in PBT patients**

Brain tumors give rise to several cognitive deficits as a result of cortical lesions and the pressure on the surrounding brain tissue (Taphoorn & Klein, 2004). Beside the tumor itself, the treatment is also thought to be related to cognitive deficits. (Heimans & Reijneveld, 2012; Lovely, 1998; Satoer, Vork, Visch-Brink, Smits, Dirven & Vincent, 2012; Taphoorn & klein, 2004). Cognitive deficits include memory impairment, such as: problems in retrieving
information and storing information in their long-term memory (Klein et al., 2001; Lovely, 1998). Patients can also experience verbal deficits (Lovely, 1998). Deficits in attention, concentration and executive functioning are higher functions that are often impaired in PBT patients (Satoer et al., 2014). These higher cognitive functions rely on basic functions such as motor and sensory skills as well as normal levels of consciousness, which can be distorted by a PBT (Taphoorn & Klein, 2004).

Taphoorn and Klein (2004) noted that it is not an easy task to determine whether cognitive deficits are a result of the tumor itself or its treatment. Higher cognitive functions can also be damaged or distorted by treatment. Heimans and Reijneveld (2012) discuss that besides a negative effect of treatment due to neural damage, a positive effect of treatment may also exist. Reducing pressure on the surrounding area of the tumor has an immediate positive effect in reducing risks of deterioration. A secondary effect is that the reduced pressure also promotes increased recovery of the brain by form of neuroplasticity.

**The influence of depression and anxiety on cognition**

Patients with PBT have higher levels of depression and anxiety than healthy controls (Buneveicus et al., 2013; Talacchi et al., 2011). Levels of depression and anxiety can predict health prognosis and even mortality, where high levels of depression are related to negative outcomes (Bunevicus et al., 2013; Rooney et al., 2011). Bunevicus et al. (2013), did a factor analysis of depression and anxiety scales in 205 brain tumor patients. The Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) were tested before and after the operation. Postsurgical assessment was tested right before hospital relief. Bunevicus and colleagues (2013) found that somatic, affective, cognitive and anhedonic factors explained 35%, 8%, 6%, and 6% of the total variance of the BDI. They also noted that somatic symptoms were unrelated to HADS measurements. Therefore you might say that the HADS is a better estimator for depression in PBT patients because they experience somatic deficits that are unrelated to depression.

Kaleita et al. (2004) found preoperatively, that 28% of their sample of 79 malignant PBT patients tested positive for major depression. Major depression was diagnosed with DSM-IV criteria. Although the majorly depressed PBT patients scored lower on cognitive tests than PBT patients without depression, these results did not reach significance. Rooney et al. (2011) did
find a connection between depression and OCF in their systematic review. Their systematic review regarded cerebral glioma patients. In five studies Rooney et al. (2011) found that depression was associated with cognitive impairment in patients with LGG before chemotherapy, in HGG in a follow-up, and in patients with LGG and HGG both pre- and postoperatively. These five studies used continuous scale scores to measure depression and made use of neuropsychological screening tests. Only one study didn’t show a connection between depression and objective cognitive functioning (OCF). This study used the Mini-Mental State Exam (MMSE) for neuropsychological screening. However, both Rooney et al. (2011) as Taphoorn and Klein (2004) stress in their reviews, MMSE is not the best choice for measuring neurocognitive functions in adults with brain tumors. The conclusion by Rooney et al. (2011) based on these previous studies, was that in the case of detailed neuropsychological testing, depression is associated with cognitive impairment in glioma patients.

Another related factor with depression that was found in this review was gender. In contrary to the healthy population where females have a higher risk for depression it is assumed that in glioma patients, males have a higher risk for developing depression. This can be assumed because prior research found no gender bias. While you would expect females to have a higher risk for depression considering their higher risk in the healthy population. Other associations, including age and marital status, were examined by many studies. Unlike you might expect, neither age nor marital status were associated with depression (Rooney et al., 2011).

Talacchi et al. (2011) examined 29 glioma patients (LGG and HGG) before and after operation. Patients were tested on neuropsychological domains like memory (e.g. Verbal Digit Span), language (e.g. Visual Object Naming test), executive functions (e.g. Word fluency, Trail Making Test A and B) and intelligence (e.g. Raven Colored Matrix). Patients were also assessed with the BDI and State and Trait of Anxiety Inventory (STAI) for measuring depression and anxiety. Before surgery, they found that 79.5% of the patients were impaired in one or more cognitive domains and after surgery this percentage was relatively the same, around 76%. Talacchi et al. (2011) found that 28% of the glioma patients were clinically depressed. Anxiousness was found amongst 14% of the 29 glioma patients. After the operation depression levels stayed the same, but anxiety rates higher than 8 dropped to 10%. Furthermore, they found that depression was significantly correlated with impaired functions of verbal memory pre and post operation. Anxiety levels were not significantly correlated with any neuropsychological test
scores. Note however, the group of tested patients is relatively small. The authors performed a multiple regression analysis to rule out any impact of depression and anxiety in cognitive functions. However, since a sample size of 50 is the required minimum, the correctness of this analysis can be discussed (Pallant, 2010) Therefore, this article can be seen as an interesting point for further research, but the results from Talacchi et al. (2011) should be addressed carefully.

**Subjective cognitive functioning in PBT patients**

Subjective cognitive functioning (SCF) is the self-assessment of a person’s OCF. Research on this topic in PBT patients is scarce. However, there is one recent study by van der Vossen, Schepers, Berkelbach van der Sprankel, Visser-Meily and Post (2014). They determined long-term cognitive complaints and symptoms of depression or anxiety in 136 cerebral meningioma patients. This research followed these patients post surgically and examined factors associated with SCF, depression and anxiety. In this study SCF was assessed with the Cognitive Failures Questionnaire (CFQ), anxiety and depression with the HADS. Their results showed that the scores on these questionnaires were all related to each other. Of these patients, 23% showed cognitive complaints, 29% was anxiousness and 23% experienced depressive symptoms. Factors related to cognitive complaints, depression and anxiety were: the country of birth and prior depression and/or burnout. Van der Vossen et al. (2014) stress that screening for these problems is important in order to help these patients.

Most research concerns other patient samples. Cockshell and Mathias (2012) for example, measured SCF with The Centre for Disease Control CFS Symptom Inventory in 50 chronic fatigue syndrome (CFS) patients and 50 controls. The found that CFS patients self-reported significantly more memory and attention problems in comparison with healthy controls. However, they did not find a significant correlation between SCF and objective cognitive functioning. What they did find was a significant correlation between depression and their objective cognitive functioning (e.g. memory and attention). Fatigue, sleep and anxiety were not related to SCF in this study.

Kinsinger, Lattie and Mohr (2010) studied possible factors (e.g. OCF, depression, fatigue and functional impairment) in relation to SCF and OCF in 127 Multiple Sclerosis (MS) patients. In this study SCF was measured with a subtest of the MS quality of life (QOL) inventory, the
Perceived Deficits Questionnaire. Objective cognitive functioning (e.g. verbal fluency, attention/concentration and verbal memory) and depression were screened over the telephone. Depression was screened using the Hamilton Rating Scale for Depression, and later tested by self-report with the use of the BDI. Fatigue was assessed by means of the Modified Fatigue Impact Scale. The Guy’s Neurological Disability Scale was used for assessment of functional impairment. After analyses they found no significant relation between OCF and SCF. Depression and fatigue were not associated with objectively measured neuropsychological functions. When patients scored lower on depression and fatigue however, they reported less cognitive problems. Kinsinger et al. (2013), suggest that treatment of depression and fatigue might positively influence the subjective cognitive functioning. Taphoorn and Klein (2004) stress in their review that emotional stress can cause impairments in attention, vigilance and motivation. Therefore these emotional factors should always be taken into account.

In the same year, Zlatar, Moore, Palmer, Thompson and Jeste (2014), examined whether SCF is suggestive of depression or OCF in a 1000 older adults without dementia. OCF was measured with the modified Telephone Interview for Cognitive Status (TICS-m), SCF was assessed with the Cognitive Failures Questionnaire (CFQ) and the 9-item Patient Health Questionnaire (PHQ-9) measured depression. The participants scored very low on depression, but the results still showed a medium to large effect between SCF and depression for each age group (e.g. decade). The relationship between SCF and OCF showed only a small effect. This suggests that intervention for depression can be useful in diminishing the cognitive complaints of people and perhaps in PBT patients.

Gehring et al. (2009) examined the short and long term effects of a cognitive rehabilitation program (CRP) in 140 low-grade and anaplastic glioma patients. These patients were randomly assigned in the intervention or the control group. The intervention group followed CRP twice a week during six weeks. In the CRP training, patients trained their cognition, but also the capacity to compensate. Neuropsychological (NP) tests and the CFQ were conducted when CRP ended and again after six months. The authors found a significant difference in cognitive impairments. The intervention group (n=70) showed less deficits in comparison to the control group (n=70). Interestingly, they also found a short-term effect in subjective cognitive complaints. The intervention group reported significantly less cognitive deficits immediately after the intervention. However, this effect was lost at the six month follow-
up while actual cognitive impairments diminished (Gehring et al., 2009). This research therefore suggests that patients benefit from CRP both subjectively and objectively on the short-term. However, patients need more than CRP to benefit emotionally from intervention on the long term. It could be that CRP makes the patients feel empowered, but this feeling diminishes because benefits regarding OCF take longer.

The authors Rath, Hradil, Litke and Diller (2011), note that an important factor of SCF in patients with acquired brain injury (ABI) is the attribution of problems. Problem orientation can be positive or negative. It is assumed that a negative attribution of problems may lead to feelings of being overwhelmed and maladaptive thoughts. Rath et al. (2011) argue, that when ABI patients replaced these emotions with adaptive thoughts they reported a higher life satisfaction. The authors stress that intervention for SCF with the use of problem attribution should be incorporated with normal neuropsychological rehabilitation. This would enhance the effect of rehabilitation because patients will learn to manage their own cognitive deficits and symptoms. This could also be helpful in PBT patients.

Another intervention that would benefit the emotional distress of PBT patients is self-efficacy. Wu et al. (2012) examined the relationship between self-efficacy, anxiety, depression, QOL and subjective cognitive impairment in 245 bone marrow transplant patients. SCF was measured using the Functional Assessment of Cancer Therapy (FACT), self-efficacy for symptom management with the use of TBI Self-Efficacy Questionnaire and depression and anxiety were assessed with the Brief Symptom Inventory (BSI). Results suggested that self-efficacy of emotions mediated depression and anxiety, but not SCF. This suggests that intervention on self-efficacy may directly positively influence depression and anxiety.

So far, prior research has shown that PBT patients are likely to be impaired in one or more cognitive domains (Klein et al., 2001; Satoer et al., 2014; Talacchi et al., 2011; Xu et al., 2013). Besides the presence of neuropsychological deficits, PBT patients also experience several emotional problems such as depression, anxiety and cognitive complaints. There does not seem to be a relationship between OCF and SCF in MS, CFS patients and cerebral glioma patients. However, research suggests that depression could negatively influence both (Bunevicus et al., 2013; Kaleita, et al., 2004; Rooney et al., 2011; Talacchi et al., 2011; van der Vossen et al., 2014). But what is this relationship in PBT patients, and does anxiety influences OCF and SCF
in the same way depression does? The aim of the present study is to examine the relationship between subjective cognitive functioning, objective cognitive functioning and depression and anxiety in PBT patients. Following this question, the following hypotheses will be tested:

- As previously described studies have shown, PBT patients score significantly lower on neurocognitive domains like executive functioning, memory and attention (Klein et al., 2001; Satoer et al., 2014; Talacchi et al., 2011 and Xu et al., 2013). Talacchi et al. (2011) noticed that post operation, 76% of glioma patients were impaired in one or more domain. Kaleita et al. (2004) and Talacchi et al. (2011) both found depression rates in 28% of their samples both pre and post operation. Furthermore, Talcchi et al. (2011) found that anxiety, preoperatively, was found in 14% of the patients and in 10% post operation. Thus, the first hypothesis is that PBT patients have neurocognitive impairments and experience depression and anxiety before and after the operation.

- The second hypothesis is that patients with depression or anxiety will score lower on neurocognitive tests than patients without depression or anxiety both pre and post operation. Because, Rooney et al. (2011) and Kaleita et al. (2004) saw in their results that depressed patients score lower on neurocognitive tests in opposite to non depressed patients. In this thesis the same is assumed for anxiety.

- Prior research has shown that OCF and SCF are barely associated to each other. This relationship shows a small to no effect (Cockshell & Mathias, 2012; Kinsinger et al., 2010; Zlatar et al., 2014). The fourth hypothesis is that there will only be a small effect between OCF and SCF post operation.

- The last hypothesis is that there will be a relationship between depression, anxiety and SCF. Prior research has shown that there is a positive relationship between depression and SCF (Cockshell & Mathias, 2012; Kinsinger et al., 2010; van der Vossen et al., 2014; Zlatar et al., 2014). However, Talacchi et al. (2011) found rates of anxiety in 14% of glioma patients. It will be interesting to see if anxiety will also influence symptom perception.
Method

Patients & procedures

Between November 2010 and September 2013, a number of 264 adult PBT patients were admitted in the St. Elisabeth hospital Tilburg, for craniotomy. All subjects in this study gave their written informed consent on forehand. The study was approved by the ethical committee. Figure 1 shows the flow of the participants through the trial. Exclusion criteria for this study were: (a) prior brain surgery, (b) ability to undergo neurocognitive tests, (c) co morbidity brain abnormalities (e.g. stroke, MS). This resulted in 216 PBT patients. One day before the operation the patients were tested on neurocognitive domains with use of the CNS Vital Signs (CNS VS), a computerized test battery. Also, patients were assessed on depression and anxiety using the HADS. Of the 216 included patients, 208 had a valid CNS VS score and of these 208 patients, 148 completed the HADS. Patients were tested again three months after the operation, on neurocognitive domains, depression and anxiety. However, postoperatively a subgroup of patients completed the CFQ, a questionnaire for cognitive complaints. Post operation, 141 PBT patients were assessed with the use of the CNS VS of which 138 proved valid results. Of the validly tested patients, 87 completed the HADS and of these patients 35 completed the complimentary CFQ. Extreme scores on the CNS VS were not excluded from the present study because there were no reasons to believe that this was the result of inadequate testing, rather than the reflection of cognitive impairments in patients.

Figure 1. Flow of Participants through the trial, Craniotomy, in- and Exclusion, Pre- and Postoperatively tested
Table 1 summarizes the characteristics of the pre and post operation tested patients. Preoperatively, there were three gender data missing and seventeen data were missing on education. The average age of the patients at the time of examination was 54 before the operation and 52 after the operation. The gender ratio pre and post operation resembled each other (T0 males 53.4%, T1 males 49.4%). In terms of education levels the observed median both pre- and postoperatively was 5, with a range from 2 to 7 where 1 = “not completed primary-education”, 2 = “primary-education”, 3 = “not completed secondary education”, 4 = “LBO, VMBO- practice”, 5 = “MBO, MULO, MAVO, VMBO- theoretic” 6 = “HAVO, VWO, HBO” and 7 = “university” (T0 28.4% completed higher education or more, T1 33.3% completed higher education or more). The majority of patients had a meningioma (T0 = 46.6%, T1 = 51.4%) glioma counts were 37.2% (T0) and 32.6% (T1). Other PBT’s accounted for 16.2% (T0) and 25.9% (T1).

<table>
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<tr>
<th>Table 1. Patient Characteristics</th>
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<tr>
<th>Male, n (%)</th>
<th>To pre operation n=148</th>
<th>T1 post operation n=87</th>
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<tbody>
<tr>
<td>Male, n (%)</td>
<td>76 (52.4)</td>
<td>43 (49.4)</td>
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<tr>
<td>Female, n (%)</td>
<td>69 (47.6)</td>
<td>44 (50.6)</td>
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<tr>
<td>Age, mean (SD)</td>
<td>54.1 (13.2)</td>
<td>52.4 (13.1)</td>
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<tr>
<td>Education, median (range)</td>
<td>5 (2-7)</td>
<td>5 (2-7)</td>
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<tr>
<td>Glioma, n (%)</td>
<td>55 (37.2)</td>
<td>26 (32.6)</td>
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<tr>
<td>Meningioma, n (%)</td>
<td>69 (46.6)</td>
<td>44 (51.4)</td>
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<tr>
<td>Other PBT, n (%)</td>
<td>24 (16.2)</td>
<td>17 (15.9)</td>
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Neurocognitive tests

To test neurocognitive functioning in the patients, the computerized CNS VS battery was used. Assessment consisted of seven overlapping domains. Therefore, one test measured various domains. Tested domains were: Memory (Verbal and Visual Memory), Processing Speed, Executive Functioning, Psychomotor Speed, Reaction Time, Complex Attention and Cognitive Flexibility. In Table 2 the neurocognitive domains and the tests used for measurement are summarized. The used tests were chosen to measure the speed and accuracy of these seven neurocognitive domains (www.cnsvs.com). The use of this battery takes approximately twenty-five minutes. Gualtieri and Johnson (2006) found in their study (N=1069) that the CNS VS is a reliable battery (test-retest, r = 0.65-0.88).
For all domains, standardized scores were automatically calculated by the CNS VS program. Severity of the tested patients was graded based on an age-matched normative comparison database. The raw scores are calculated per domain and converted into standardized z-scores with a mean of 100 and a standard deviation (SD) of 15. Standard scores > 110 are ranked as above average, 90 through 110 as average, 80 through 89 as low average, 70 through 79 as low and < 70 as very low (www.cnsvs.com). Figure 2 describes standard scores, percentile
scores and severity classification. Scores with more than 1.5 SD below average on the tested domain indicate impairment in this measured function. This includes scores up to 79 points. Different variables were used; continuous variables for every standardized domain scores, one dichotomous variable for “Not Impaired” and “Impaired” domain scores and one continuous variable that adds the number of domain impairments per patient: “Number Domains Impaired”.


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<tr>
<th>Clinical Domains</th>
<th>Domain Measurement Description</th>
<th>Tests</th>
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<tr>
<td>Verbal Memory</td>
<td>Ability to recognize, remember and retrieve words.</td>
<td>Verbal Memory (VBM)</td>
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<tr>
<td>Visual Memory</td>
<td>Ability to recognize, remember and retrieve geometric figures.</td>
<td>Visual Memory (VIM)</td>
</tr>
<tr>
<td>Processing Speed</td>
<td>Ability to recognize and process information.</td>
<td>Stroop Test (ST), Shifting Attention (SAT), Symbol Digit Coding (SDC)</td>
</tr>
<tr>
<td>Executive Functioning</td>
<td>Ability to recognize rules, categories and manage rapid decision making.</td>
<td>Stroop Test, Shifting Attention</td>
</tr>
<tr>
<td>Psychomotor Speed</td>
<td>Ability to perceive, attend, respond to visual-perceptual information, and performs motor speed and fine motor coordination.</td>
<td>Symbol Digit Coding, Finger Tapping (FTT)</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>How fast the subject can react (milliseconds) to a simple and increasingly complex direction test.</td>
<td>Stroop Test, Shifting Attention</td>
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<tr>
<td>Complex Attention</td>
<td>Ability to track and response to information over lengthy periods of time and/or perform mental tasks requiring vigilance quickly and accurately.</td>
<td>Stroop Test, Shifting Attention, Symbol Digit Coding, Continuous Performance (CPT)</td>
</tr>
<tr>
<td>Cognitive Flexibility</td>
<td>Ability to adapt to a rapidly changing and increasing complex set of directions and/or to manipulate the information.</td>
<td>Stroop Test, Shifting Attention</td>
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Psychological tests

Subjective cognitive functioning was measured by the CFQ. The CFQ is a self-report measurement that consists of 25 items. Measurement includes failures in: attention, perception, memory and action in the last month (Bruce, Ray & Carlson, 2007). Bridger, Johnsen & Brasher
(2013) noted that problems, measured with the CFQ, were associated with the likelihood of having an accident, making errors and psychological stress. Examples of questions in this questionnaire are: “How often do you forget the names of people?” “How often do you forget an appointment?” and “How often do you get angry and later regret this?” Scoring ranges from 0 (never) to 5 (very often). Higher scores mean a higher self-report on cognitive deficits (Bruce et al., 2007). Bridger et al. (2013) found in a two-year interval a test-retest reliability of 0.71 (N=535). In another study, Bruce et al. (2007) found an internal consistency of .90 (N=1040).

Depression and anxiety were measured using the HADS. Examples of HADS-depression sentences are: “I still enjoy the things I used to enjoy.” and “I have lost interest in my appearance.”. HADS-anxiety sentences are for example: “I can sit at ease and feel relaxed.” and “I get sudden feelings of panic.” (Luciano, Barrada, Aguado, Osma & García-Campayo, 2013). The standard cut-off scores for depression and anxiety ≥ 8 were used (Singer et al., 2009). Rooney et al. (2011) stress in their meta-analysis that the HADS is the best questionnaire for measuring depression in glioma patients. Namely, in comparison with another frequently used depression questionnaire, the BDI, the HADS reported less clinical depression. The authors concluded that the HADS didn’t overestimate depression outcomes in glioma patients (Rooney et al., 2011).

Luciano et al. (2013) researched the construct validity of the HADS and advised to combine the depression and anxiety scores because of the low reliability on separate domains. However, Bunevicius et al. (2013) found in their factor analysis that anxiety and depression measure different aspects and should therefore be separated. Because this thesis is specifically interested in the effect of depression and anxiety separately on SCF, depression and anxiety are considered as two different variables. Depression and Anxiety were used as continuous and dichotomous variables. When they were used as dichotomous variables; scores 0 through 8 were named: “No Depression” and “No Anxiety”. Scores higher than 8 were called: “Depression” and “Anxiety”.

**Analysis**

SPSS 21.0 was used for all statistical analyses (α = 0.05, two-sided). The sample was examined for missing data, outliers and normality.
- The first hypothesis that PBT patients have pre and post operation neurocognitive impairments and experience depressive symptoms and anxiety, was analyzed with descriptives. Percentages for the groups “Not Impaired” and “Impaired” were calculated pre- and postoperatively for all domains, same as percentages for depression and anxiety. Then, groups were tested on comparability. Dichotomous scores on the HADS were used in this analysis to measure differences in depression and anxiety. Pre and post operation, Independent Sample t-tests were performed on age and a Mann-Whitney U Test was used to test the difference in education. Pre operation, Chi-Squared tests were performed for the nominal variable gender. Post operation, the groups in gender were too small to be tested (female and depression = 2, male and anxiety = 2). Differences in glioma, meningioma and other PBT’s could not be tested pre- and postoperatively, because of the limited sample size.

- Independent Sample t-tests were performed pre and post operation to test for differences in the number of cognitive impairments between the groups: “No Depression”, “Depression” and “No Anxiety”, “Anxiety”. Additional Pearson Correlation analyses were done pre and post operation between standardized domain scores and the continuous HADS scores on depression and anxiety.

- The third hypothesis, as the following hypotheses, is only analyzed post operation because cognitive complaints, measured by the CFQ, were only assessed postoperatively. An Independent Sample t-test was performed between the groups “No Neurocognitive Impairments” and “≥ 1 Neurocognitive Impairments”, on CFQ total scores. Furthermore, Independent Sample t-tests were used to investigate differences in CFQ scores on the neurocognitive domains. For this analysis dichotomous scores on neurocognitive domains were used; “Impaired” or “Not Impaired”. Additionally, the relationship between SCF and OCF was analyzed with a Pearson Correlation between CFQ total scores and standard scores for each domain.

- To explore the relationship between depression and cognitive complaints the difference in CFQ total scores between the groups “No Depression” and “Depression” was explored first with an Independent Sample t-test. Second, the relationship between continuous scores on HADS-depression and CFQ total scores was explored with a Pearson Correlation analysis.
The same procedure was used to learn the relationship between anxiety and cognitive complaints. The difference in CFQ total scores between “No Anxiety” and “Anxiety” was explored with an Independent Sample t-test. After which a Pearson Correlation analysis was calculated between continuous scores on the HADS for anxiety and total scores on the CFQ for cognitive complaints.

Results

Patient characteristics

Before the operation, 74.3% PBT patients were impaired in one or more neurocognitive domains. PBT patients with depression accounted for 20.9% and PBT patients with anxiety accounted for 34.5% of all tested patients. After the operation, neurocognitive impairments dropped to 54.0%. Furthermore, depression rates dropped to 9.1% and anxiety dropped to 16.1%. Neurocognitive impairments, depression and anxiety rates pre and post operation are shown in Figure 3.

![Figure 3. Percentages of Impairments, Depression and Anxiety, Pre and Post Operation](image)

Statistical analysis showed that the dichotomous groups for depression and anxiety were comparable with respect to age and education, both before and after the operation (Table 3,
Gender differences in depression before operation were found to be significant ($\chi^2$ (1, $N = 145$) = 5.52, $p = .016$). Gender differences in anxiety were also significant ($\chi^2$ (1, $N = 145$) = 4.72, $p = .023$). Overall, females were more often found to be depressed or anxious than males.

Table 3. Differences on Patient Characteristics between Groups, T0 Pre Operation

<table>
<thead>
<tr>
<th></th>
<th>Total n=148</th>
<th>No Depression n=117</th>
<th>Depression n=31</th>
<th>No Anxiety n=97</th>
<th>Anxiety n=51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>76 (52.4)</td>
<td>66 (57.4)*</td>
<td>10 (20.7)*</td>
<td>56 (58.9)*</td>
<td>20 (40.0)*</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>69 (47.6)</td>
<td>49 (42.6)*</td>
<td>14 (66.7)*</td>
<td>39 (41.1)*</td>
<td>30 (60.0)*</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>54.1 (13.2)</td>
<td>53.0 (13.5)</td>
<td>58.0 (11.3)</td>
<td>53.2 (14.3)</td>
<td>55.8 (10.8)</td>
</tr>
<tr>
<td>Education, median (range)</td>
<td>5 (2-7)</td>
<td>5 (2-7)</td>
<td>5 (2-6)</td>
<td>5 (2-7)</td>
<td>5 (2-7)</td>
</tr>
<tr>
<td>Glioma, n (%)</td>
<td>55 (37.2)</td>
<td>49 (41.7)</td>
<td>6 (19.4)</td>
<td>39 (40.2)</td>
<td>16 (31.4)</td>
</tr>
<tr>
<td>Meningioma, n (%)</td>
<td>69 (46.6)</td>
<td>45 (38.5)</td>
<td>24 (77.4)</td>
<td>41 (42.3)</td>
<td>28 (54.9)</td>
</tr>
<tr>
<td>Other PBT, n (%)</td>
<td>24 (16.2)</td>
<td>23 (19.7)</td>
<td>1 (3.2)</td>
<td>17 (17.5)</td>
<td>7 (13.7)</td>
</tr>
</tbody>
</table>

* $p \leq .05$

Table 4. Differences on Patient Characteristics between Groups, T1 Post Operation

<table>
<thead>
<tr>
<th></th>
<th>Total n=87</th>
<th>No Depression n=79</th>
<th>Depression n=8</th>
<th>No Anxiety n=73</th>
<th>Anxiety n=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>43 (49.4)</td>
<td>39 (49.4)</td>
<td>5 (62.5)</td>
<td>39 (53.4)</td>
<td>5 (35.5)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>44 (50.6)</td>
<td>40 (50.6)</td>
<td>3 (37.5)</td>
<td>34 (46.6)</td>
<td>9 (64.3)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>52.4 (13.1)</td>
<td>51.8 (13.4)</td>
<td>58.1 (6.9)</td>
<td>52.3 (13.2)</td>
<td>53.0 (13.0)</td>
</tr>
<tr>
<td>Education, median (range)</td>
<td>5 (2-7)</td>
<td>5 (2-7)</td>
<td>5 (3-6)</td>
<td>5 (2-7)</td>
<td>5 (3-6)</td>
</tr>
<tr>
<td>Glioma, n (%)</td>
<td>26 (32.6)</td>
<td>25 (31.6)</td>
<td>1 (12.5)</td>
<td>24 (32.9)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Meningioma, n (%)</td>
<td>44 (51.4)</td>
<td>40 (50.6)</td>
<td>4 (50.0)</td>
<td>35 (47.9)</td>
<td>9 (64.3)</td>
</tr>
<tr>
<td>Other PBT, n (%)</td>
<td>17 (15.9)</td>
<td>14 (17.7)</td>
<td>3 (37.5)</td>
<td>14 (19.2)</td>
<td>3 (21.4)</td>
</tr>
</tbody>
</table>

The role of depression and anxiety on cognitive functioning

Analysis of data before the operation, showed that depressed patients ($M = 4.29$, SD = 2.61) had significantly more neurocognitive impairments than patients who were not depressed ($M = 2.20$, SD = 2.27); $t(146) = -4.42$, $p < .001$. Results of the analysis suggested that although PBT patients in the anxiety group had slightly more cognitive impairments than patients in the no anxiety group, this difference was not found significant.
Results of the additional Pearson Correlation analyses pre and post operation are summarized in Table 5. Results preoperatively, showed a significant relationship between depression and anxiety with a moderate effect size; \( r(146) = .54, R^2 = .29, p < .001 \). Other significant associations were found between depression and visual memory (\( r(146) = -.22, R^2 = .05, p = .007 \)), processing speed (\( r(146) = -.25, R^2 = .06, p = .003 \)), executive functioning (\( r(146) = -.31, R^2 = .10, p < .001 \)), psychomotor speed (\( r(146) = -.22, R^2 = .05, p = .007 \)), complex attention (\( r(146) = -.36, R^2 = .13, p < .001 \)) and cognitive flexibility (\( r(146) = -.33, R^2 = .11, p < .001 \)). However, significant correlations between depression and neurocognitive domains showed only a small effect, explaining no more than 13% of the total variance. Anxiety was preoperatively, significantly associated with complex attention (\( r(146) = -.20, R^2 = .04, p = .013 \)), but only with a small effect. Since all correlations between anxiety and cognitive domains and between depression and cognitive domains are negative, higher rates of anxiety and depression have a lower neurocognitive score.

Table 5. Results of Correlation Calculations, Pre Operation and Post Operation

<table>
<thead>
<tr>
<th>Measurements</th>
<th>T0 n = 148</th>
<th>1 r</th>
<th>1 R²</th>
<th>2 r</th>
<th>2 R²</th>
<th>T1 n = 87</th>
<th>1 r</th>
<th>1 R²</th>
<th>2 r</th>
<th>2 R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Depression</td>
<td></td>
<td>.54**</td>
<td>.29</td>
<td>.73**</td>
<td>.53</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Anxiety</td>
<td></td>
<td>-.09</td>
<td>.01</td>
<td>-.05</td>
<td>.00</td>
<td>-.24*</td>
<td>.06</td>
<td>-.20</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>3. Verbal Memory</td>
<td></td>
<td>-.22**</td>
<td>.05</td>
<td>-.12</td>
<td>.01</td>
<td>-.25*</td>
<td>.06</td>
<td>-.32**</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>4. Visual Memory</td>
<td></td>
<td>-.25**</td>
<td>.06</td>
<td>-.10</td>
<td>.01</td>
<td>-.16</td>
<td>.03</td>
<td>-.08</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>5. Processing Speed</td>
<td></td>
<td>-.31**</td>
<td>.10</td>
<td>-.12</td>
<td>.01</td>
<td>-.20</td>
<td>.04</td>
<td>-.22**</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>6. Executive Functioning</td>
<td></td>
<td>-.22**</td>
<td>.05</td>
<td>-.10</td>
<td>.01</td>
<td>-.20</td>
<td>.04</td>
<td>-.18</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>7. Psychomotor Speed</td>
<td></td>
<td>-.14</td>
<td>.02</td>
<td>.07</td>
<td>.00</td>
<td>-.14</td>
<td>.02</td>
<td>-.19</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>8. Reaction Time</td>
<td></td>
<td>-.36**</td>
<td>.13</td>
<td>-.20*</td>
<td>.04</td>
<td>-.30**</td>
<td>.09</td>
<td>-.34**</td>
<td>.12</td>
<td></td>
</tr>
<tr>
<td>9. Complex Attention</td>
<td></td>
<td>-.33**</td>
<td>.11</td>
<td>-.14</td>
<td>.02</td>
<td>-.21</td>
<td>.04</td>
<td>-.25*</td>
<td>.06</td>
<td></td>
</tr>
</tbody>
</table>

* p ≤ .05
** p ≤ .01

After the operation, no significant differences were found in the number of impairments between the groups no depression and depression or between the groups no anxiety and anxiety. However, PBT patients in the groups depression (M = 2.25) and anxiety (M = 2.50) scored
slightly higher in the number of impairments than PBT patients in the groups no depression (M = 1.53) and no anxiety (M = 1.42).

Postoperatively, the correlation between depression and anxiety were again found to be significant ($r(85)= .73$, $R^2 = .53$, $p<.001$). Depression was found to correlate significantly with Verbal Memory, Visual Memory and Complex Attention. However, the effect size was small. Anxiety was significantly, but with a small effect, correlated with Visual Memory, Executive Functioning, Complex Attention and Cognitive Flexibility.

**Subjective and objective cognitive functioning**

Analysis showed no significant difference between the groups “No Neurocognitive Impairments” (M = 92.7, SD = 14.51) and “≥ 1 Neurocognitive Impairments” (M = 94.5, SD = 21.35) in CFQ scores; $t(33) = -.249$, $p = .805$. For the different cognitive domains all results suggested that PBT patients who were not impaired, scored lower on the CFQ. The difference in complex attention between the groups impaired (M = 84.55, SD = 24.9) and not impaired (M = 98.25, SD = 14.75) on CFQ total scores were borderline significant; $t(33) = 2.043$, $p = .049$.

However, significant relationships were found between CFQ scores and Executive Functioning $r(33)=.39$, $R^2 = .15$, $p=.021$, Psychomotor Speed $r(33)=.38$, $R^2 = .14$, $p=.024$, Reaction Time $r(33)=.43$, $R^2 = .18$, $p=.010$, Complex Attention $r(33)=.46$, $R^2 = .21$, $p=.006$ and Cognitive Flexibility $r(33)=.38$, $R^2 = .14$, $p=.023$. What was striking, these neurocognitive domains named above are all significantly related to each other, ranging from $r(33) = .45$, $R^2 = .20$ to $r(33)= .99$, $R^2 = .98$. Correlations are summarized in Table 6.

**The relationship between emotional problems**

No significant differences were found while investigating the group differences between “No Depression”, “Depression” and between “No Anxiety”, “Anxiety” in CFQ scores. However, results suggest that the presence of depression or anxiety relates to less self-reported cognitive problems. Correlation analysis showed a significant relationship between CFQ and depression ($r(33)= -.54$, $R^2 = .29$, $p = .001$) and between CFQ and anxiety($r(33) = -.64$, $R^2 = .41$, $p < .001$). Results of the correlation analysis are found in Table 6.
Discussion

The aim of the present study was to examine the relationship between OCF, depression and anxiety, between SCF and OCF and between CFQ, depression and anxiety in PBT patients. Results suggested that the presence of depression was associated with more cognitive impairments both before and after craniotomy. As similar prior research has suggested, correlations with a small effect were found between SCF and OCF. Depression and anxiety were significantly correlated with SCF with a small effect for depression and a medium effect for anxiety. Although not significant, PBT patients with depression or anxiety reported less cognitive complaints.

Cognitive functions, depression and anxiety

Differences in opinion exist regarding cognitive deficits, post operation, as a result of the tumor or craniotomy (Heimans and Reijneveld, 2012; Taphoorn and Klein, 2004). The results of the present study suggest that a tumor is the best indication for cognitive impairments. The percentage of one or more cognitive impairments after the operation dropped from 74% to 54%. Therefore, it can be said that craniotomy has a favorable outcome on OCF. Furthermore, less patients had depressive symptoms or experienced anxiety after craniotomy. This suggests that the removal of the tumor will also benefit patients emotionally. However, it could be that a majority of PBT patients with depression were not tested postoperatively because of mortality (Bunevicus et al., 2013; Rooney et al., 2011).
Kaleita et al. (2004) and Talacchi et al. (2011) found that 28% of their patient sample were depressed. After operation Talacchi et al. (2011) found that depressed rates stayed the same. In the same study the authors found anxiety to be slightly related to treatment; anxiety was reported in 14% pre operation and 10% post operation. Postoperatively anxiety in 29% of patients was observed by van der Vossen et al. (2014). In the present study depression dropped from 21% to 9% and anxiety from 35% to 16%. Regarding the present results, depressed patients had more cognitive impairments preoperatively. This is in line with prior research where depression indicated lower cognitive scores (Kaleita et al., 20014; Rooney et al., 2001; Talacchi et al., 2011). The first hypothesis, that PBT patients have cognitive impairments and experience depression or anxiety, was confirmed. The second hypothesis was only half confirmed; depressed patients had more cognitive impairments, but no difference was found regarding anxiety. In the study of van der Vossen et al. (2014), anxiety did influence OCF significantly.

**Objective and subjective cognitive functioning**

Although previous studies (Cockshell & Mathias, 2012; Kinsinger et al., 2010) did not find a relationship between OCF and SCF, this study did find some relations. Subjective functioning related to executive functioning, psychomotor speed, reaction time, complex attention, cognitive flexibility and the number of cognitive impairment, but only with a small effect. A relationship with a small effect between OCF and SCF was also found by Zlatar et al. (2014). The present results suggest that patients without cognitive impairments scored lower on the CFQ than patients with one ore more cognitive impairments. PBT patients with an impairment in complex attention scored significantly lower on the CFQ than unimpaired PBT patients is this domain.

**Subjective cognitive functioning, depression and anxiety**

Further assessment showed that depression and anxiety were positively related. Furthermore, significant negative relationships were found between CFQ scores and Depression and CFQ scores and Anxiety. This suggests that higher levels of depression and anxiety indicate a lower score on self-reported deficits. Previous studies showed that the presence of depression showed a positive relation with self-reported deficits (Cockshell & Mathisas, 2012; Kinsinger et al., 2010). Further analysis with the Independent Sample t-test showed that there were no
significant differences between the groups “No Depression”, “Depression” and “No Anxiety”, “Anxiety” on CFQ scores.

**Study Limitations**

The first limitation of this study is that no CFQ scores preoperatively were available. Satoer et al. (2012) stressed that testing patients before and after treatment might help to learn the origin of cognitive deficits. While they made this statement regarding cognitive deficits, due to tumor or treatment, the same is to be said in this case. Therefore the assessment of the SCF would have been an asset to this research. If cognitive complaints would have been assessed before the operation, analysis would have been possible to discover the relationship between OCF and SCF post operation, same as the relationship between SCF, depression and anxiety. Furthermore, a path analysis could be attempted to predict SCF after the operation. This would be useful to know on which factor intervention should be focused to enhance the PBT patients emotional status. For further research, it is therefore advised that all variables are assessed pre and post craniotomy.

Another limitation is the limited sample size overall, resulting in a low power. Although a Multiple Regression Analysis would have been the correct analysis for answering this thesis’ question, the sample was too small and therefore the assumption of sample size was not covered. With CNS VS scores, depression and anxiety as independent variables and CFQ scores as dependent variable, a sample size with a minimum of \((N > 50 + 8m) 74\) is needed (Pallant, 2010). However, the sample size that included both CFQ scores and HADS scores counted 35.

Third, little information was known about the subjects. Information about fatigue, marital status, somatic symptoms, QOL, coping mechanisms and even personality could be useful predictors for the SCF in PBT patients. The profession was only available for a few patients. The level of activity, both mentally and physically should be assessed as well. Furthermore, the cross-sectional nature of this study is a limitation. Currently, no causality is investigated and we do not know how cognitive and subjective changes over time will relate to each other, and to depression and anxiety.

The biggest limitation in this study are the group differences post operation between depression, no depression and anxiety, no anxiety. These sample differences are extremely large. With only 8 patients in the depressing group and 14 patients in the anxiety group, results cannot
be generalized. Furthermore, it can be discussed if these results say anything at all for people in this population. Adequate analysis could not be performed and the groups could not be completely tested on comparability.

**Conclusions**

The results of this study suggest that depressed patients have more neurocognitive impairments than the non depressed PBT patients before the operation, but not after the operation. This could be a result of the small sample size for depressed patients, since results indicate that depressed patients had more impairments postoperatively as well. Furthermore, the study shows that there are some positive correlations with a small effect between OCF and SCF. This suggests that intervention of one, could positively influence the other, if only a little. This is in line with the results of Gehring et al. (2009). In contrast to what was found earlier, the presence of depression and anxiety were an indication of fewer cognitive complaints. Anxiety was not related to either OCF or SCF before or after operation. Although prior research concluded that intervention on depression could enhance SCF, the results of the present study suggest the opposite. Once again, this could be due to the small sample size of both the groups depression and anxiety, but also of the small group (35) of the PBT patients who completed the CFQ. More research is needed to see what would positively enhance the SCF of PBT patients.
References


