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Glioma and Caregivers

Caregivers' quality of life and psychological health in response to brain tumor patients'
deficits: A cross sectional design

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Abstract

Introduction: Patients with gliomas generally present cognitive, neuropsychiatric and functional deficits. Although previous research showed that their caregivers present a poor quality of life and a poor mental health, only few studies have tested in a comprehensive way which deficits/preserved abilities predominantly impact their caregivers. Furthermore, only few studies have focused on the social impact of gliomas, which may also deteriorate caregivers' quality of life. Therefore, this cross sectional study aims to investigate which patients' impairments are particularly deleterious for the caregivers and the moderating role of the histological characteristics of the gliomas.

Methods and analysis: In order to examine these research questions, this study intends to include 120 patients (60 patients with low grade glioma; 60 patients with a high grade glioma), their caregivers and 60 healthy controls. While patients will complete a full battery of cognitive, neuropsychiatric, functional and social tests, caregivers will complete questionnaires about their quality of life, depression, anxiety and burden. Their reports of depression and anxiety will be compared to the scores of healthy controls. Eventually, our aim will be to provide specific care support to reduce patients' deficits together with the improvement of caregivers' difficulties.

Ethics: The study has obtained the approval of the Ethical Local Committee.

Main strengths and limitations

- This study is the first to test the Sherwood et al.'s [5] model in a comprehensive way by experimentally investigating the functional, social, cognitive and neuropsychiatric deficits of the patients, and by examining their direct impacts on the caregivers' quality of life as well as their mental health (i.e., burden, anxiety, depression).

- In order to better understand the specificity of caregivers of gliomas further studies will compare caregivers of patients who suffer from gliomas and patients with another form of cancer.

1. Introduction

Caregivers are one of the main actors in patient's health. Indeed, 55% persons who are disabled rely at least partly on other people's informal care and support [1]. Caregiving can range from physical help in daily living (e.g., housekeeping, meal preparation), personal care (e.g., distribution of medication, assistance in bathing or dressing), financial help (e.g. managing finances), medical (e.g., communication between the patient and the medical teams) or emotional and social support (e.g. visiting, transportation) [2]. The caregiver could be a relative (e.g., child, spouse) or a friend designated as caregiver by themselves or referred to as such by the patient.

Previous findings clearly showed that independently of the patient's disease, caregivers often report distress, fatigue, and burden [3]. Nevertheless, the deleterious impact of being a caregiver may also differ based on the symptoms, treatments and prognosis of the disease. Caregivers of adult patients affected with glioma are a specific subset of caregivers because they are particularly exposed to mental and physical disorders [4–6]. For instance these caregivers are at risk for depression, stress and have significantly higher adjusted mortality [3,7]. This could be explained by the fact that they have to take care of patients with both *oncological* and *neurological* issues [8]. The interaction between these both conditions may particularly increase their difficulties due to several causes. First, compared to people who are carrying for individuals with other health disabilities, they have to take care of patients with reduced life expectancy. Moreover, caregivers have to cope with prolonged and diverse treatments as well as uncertain prognosis. Second, gliomas may impact the caregivers' needs, daily experience, and quality of life. Two recent reviews have indeed highlighted that the caregivers of patients affected with gliomas have special needs and experiences in terms of the management of uncertainty about the progression of the tumour, social support, and information supply [9]. Furthermore, caregivers report specific worries and difficulties regarding symptoms, treatments, change of role, responsibilities, financial impact, as well as the management of the prospect of the end of life. In terms of distress and quality of life deterioration, some studies reported that compared to caregivers of patients with others cancers (e.g. lung, breast, colorectal, prostate, pancreas), these carers report higher levels of strain and lower levels of mental well-being [6,10]. Finally, as primary brain cancer patients are significantly younger than other cancer patients, their caregivers are also younger [6], which may be linked to increased distress compared to older caregivers [10].

Furthermore, in addition to these serious characteristics of the disorder itself (i.e., poor prognosis, healthcare costs, or social support needs), the functional, cognitive and neuropsychiatric impairments presented by patients may directly impact caregivers' state [5]. According to Sherwood and al.'s [5] conceptual model, these impairments influence the

quality of life, psychological well-being, social isolation and burden for the caregivers (Figure 1). Moreover, these impairments may be intensified from the deleterious effect of treatments and associated treatment (e.g., anti-epileptic medication) [11] which may also worsen mental and physical health of the caregiver.

In relation to the functional deficits, patients with gliomas present motor and/or sensory deficits, visual disorders, speech difficulties, as well as neurological impairment [12]. Sherwood et al. [12] argue that assisting the patient with activities of daily living is not without consequences. Indeed, the caregiver often reduces their own leisure, social and working periods to increase time spent with the patient. This could have an impact on the caregiver's emotional experience and quality of life. In terms of the patients' cognitive difficulties, gliomas alter normal functioning such as executive, attention and memory deficits [13,14].These may increase the workload of the caregiver as the patients can be unable to hold onto information and to make decisions. Therefore, the caregiver is often alone in making important decisions, pertaining to the treatment of the disease, the housekeeping or also for example education of the children [5]. Some neuropsychiatric symptoms such as high levels of distress, irritability and anxiety among patients [5] can lead to fatigue and emotional difficulties for the caregiver due to the need for constant attention by the patient. Indeed, managing patient's depression and negative feelings can be more difficult than physical care [15]. Finally, patients affected with glioma present particular behavioural and personality changes, which can lead to impulsiveness and aggressive behaviour, and thus increase caregivers' feelings of distress. For instance, diminution of their social abilities together to the social stigma associated with cancer diagnosis may lead to patients' and caregivers' social isolation [16,17].

So far, only few studies have been conducted to examine the direct links between patients' cognitive, neuropsychiatric and functional status and caregivers' psychological health. These studies revealed that the neuropsychiatric status of the patient is associated with caregivers' burden, negative affect [12,18,19], mental health [20], and psychological well-being [21]. However, the effects of functional and cognitive deficits are less clear. Indeed, while some data suggest that patient's functional status impact caregiver's burden, anxiety and perceived health [2,12] other studies showed no association [22,23]. Regarding the effect of cognitive status, studies found either association with caregiver's perceived quality of life [23] or no association [12]. Furthermore, patients sometimes underestimate their psychological problems and interpersonal problems which may increase the anxiety of the caregivers [24].

Taken together, these preliminary findings are in favour of a direct link between patients' neuropsychiatric deficits and caregivers difficulties. However, the results are more inconsistent in terms of the role of cognitive and functional deficits, mainly accounted by different shortcomings. First, only few studies [12,18,21] examined the comprehensive model

of Sherwood (i.e., functional, cognitive, and neuropsychiatric status). Second, most studies evaluated only one caregiver's measure whereas the caregiver's life is impacted at different levels (e.g., quality of life, depression, anxiety, burden), which all require to be examined. Third, we argue that in addition to its functional, neuropsychiatric and cognitive alterations, gliomas may also impair patients' social cognition, which has been so far underestimated. Social cognition is the study of the way individuals understand others and themselves [25]. We argue that the social dimension should be considered as important as the functional, cognitive or neuropsychiatric deficits. Indeed, patients' social cognition impairments may impair their social functioning, leading them and their caregiver to social isolation [16,17]. So far, only few studies examined this question and have all revealed social impairments such as deficits to decode other's mental states [26,27]. Because caregiver's isolation has been associated with lower social support and increased distress [10], we argue that it is crucial to integrate the social dimension as a predictor of poor mental health in caregivers.

This study thus aims to examine for the first time the Sherwood et al.'s [5] model in a comprehensive way by (i) investigating the functional, cognitive and neuropsychiatric deficits of the patients, (ii) integrating the social cognition status of the patient, and (iii) by focusing on the caregivers' quality of life as well as their mental health (i.e., burden, anxiety, depression). The secondary aims of the study are: (iv) to examine the impact of patients' awareness of their social deficits on caregivers, (v) to test whether the localization and the grade of the glioma (grade III and IV vs. grade II) modulate patient's deficits (and their impact on caregivers' state) and (vi) to evaluate whether caregivers have higher levels of depression and anxiety than healthy controls.

2. Methods/Design

The study has obtained the approval of the local Faculty ethical committee. The study does not involve products mentioned in article L.5311-1 of the French Code of Public Health and does not imply any changes in the medical care received by the patients. The study will begin in April 2017 and will end in 2020.

2.1. Participants

2.1.1. Caregivers

To be included in the study, caregivers must be over 18 years old. They must be fluent in French and sign an informed consent to participate in the study. They have to be designated by the patient as their caregiver. Furthermore, the patients must have approved the participation of their caregiver. Participants who do not meet the inclusion criteria will be excluded.

Other exclusion criteria for the caregiver are:

1) being paid to take care of the patient;

2) presenting any psychological, cognitive or physical impairment which does not allow the caregiver to complete the questionnaire

3) being under guardianship.

2.1.2. Patients

Patients must be over 18 years old. They must be fluent in French and sign an informed consent to participate in the study. Patients must be affected by supratentorial gliomas of grade II to grade IV, according to WHO classification, histologically proven with either biopsy, partial or total removal. Patients have to be cover by the French social security. Patients who do not meet the inclusion criteria will not be included.

Other exclusion criteria are:

1) any previous cerebral pathology, trauma (with a loss of consciousness) or any treatment that could have lead to cognitive or physical impairments

2) other chronic neurological diseases (e.g;, Parkinson)

3) addiction to any noxious substance (e.g., alcohol)

4) major psychiatric disorders (e.g., schizophrenia)

5) tumours classified as pilocytic astrocytoma

6) infratentorial gliomas

7) patients unable to complete questionnaires

8) the presence of other malignant tumours treated with curative intent within 5 years (with the exception of basal cell carcinoma of the skin and carcinoma in situ of the cervix)

2.1.3. Control participants

To be included in the study, control must be over 18 years old. They must be fluent in French and sign an informed consent to participate in the study. Exclusion criteria for the control participants are presenting any psychological, cognitive or physical impairment which does not allow them to complete the questionnaires according the researchers of the study. The anxiety and depression levels of the caregivers will be compared to the anxiety and depression levels of this healthy group.

2.2. Number of patients and sample representativeness

All participants will be recruited at the Department of Neuro-Oncology of Lille University Medical Center, which is the main institution in charge of glioma treatment in the North of France (Nord-Pas-de-Calais region). Patients treated in this center usually come from large

areas in the region, and may have very different sociocultural histories, which implies considerable socio-demographic and socio-professional diversity.

One hundred and twenty patients, 120 caregivers as well as 60 healthy controls will be recruited (i.e., 60 low grade patients, 60 caregivers of low grade patients, 60 high grade patients, 60 caregivers of high grade patients and 60 health subjects). This cohort size was based on effect sizes found in Aoun et al.'s [6] study that compared quality of life of caregiver's of primary brain tumor patients vs patients with other cancers (*d-Cohen* = 0.63; α=.05; 1-β=.95).

2.3. Procedure

Based on medical screening by the investigator at the admission, all the patients complying with all the selection criteria will be included in the study. The investigator will describe the study to the patient and, if the latter agrees, the investigator will give information letter and ask the patient to sign the informed consent form. The main information of the consent form are (i) that the participants are allowed to quit the study whenever they want to (ii) that we assure the anonymity of the data and that (iii) their participation to the study is independent from their treatments.

After obtaining the patient's consent about his/her participation, the study will be presented to the caregiver designed as such by the patient. Subsequently, the caregiver complying with all the selection criteria will be contacted. It is only when the caregiver's consent will be signed that the patient-caregiver pair will be included. The patient and their caregiver will then be given an identification and random number comprised between 1 and 999. The clinical research associate will be in charge of filling the socio-demographic data for the study. Patients and caregivers will be test separately and individually at the hospital by the investigator of the study.

2.4. Measures
2.4.1. Caregiver

Demographic

The caregivers' socio-demographics data will be collected such as age, sex, family situation, and their relationship to the patient. Furthermore, information about socio-educational and socioeconomic levels will also be gathered (study level, profession and professional situation).

Auto-evaluative questionnaire

Anxiety and depression: The "Hospital Anxiety and Depression Scale" (HADS, [28]; French Version: [29]) is used to measure emotional distress through depression and anxiety levels.

This scale is composed of 14 items measuring depression (7 items) and anxiety (7 items). Each response is scored on a scale that ranges from 0 to 3 (3 indicates higher symptom frequencies). Scores for each subscale range from 0 to 21 which may be either normal (0-7), moderate (8-10) or indicating a depression and/or anxiety disorder (11-21).

Quality of life: The "CareGiver Oncology Quality of Life" (CarGOQoL, [30]) questionnaire has been developed to evaluate the cancer caregiver's quality of life. It is a 29-item, multidimensional and self-administered questionnaire. The CarGOQOL comprises 10 subscales indicating psychological well-being, burden, relationship with health care, administration and finances, coping, physical well-being, self-esteem, leisure time, social support, and private life. Participants are invited to estimate their quality of life on a 5-point Likert scale ranging from 1 (Never/Not at all) to 5 (Always/Widely). The global score ranges from 0 to 100. Higher scores indicate good quality of life.

Burden: The "Caregiver Reaction Assessment" (CRA, [31]; French version: [32]) questionnaire assesses the caregiver's perceived burden. The questionnaire consists in 24 items measuring 5 subscales: impact on disrupted schedule, financial problems, lack of family support, health problems and the impact on self-esteem. Caregivers have to indicate their level of agreement using a 5-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). For each subscale, a score is calculated by taking the average of the items. Higher scores indicate a greater impact (either beneficial or detrimental).

Questionnaires about the patient

Perceived level of empathy: The Interpersonal Reactivity Index (IRI, [33]; French version: [34]) has been modified and adapted for the present study. subscales: personal distress, empathic concern, fantasy and perspective taking. Participants are asked to indicate the extent to which each item describes them on a 5-point Likert scale ranging from 0 (does not describe me well) to 4 (describes me very well). In this study, caregivers are instructed to evaluate the empathy abilities of the patient on a 5-point Likert scale ranging from 0 (does not describe the patient well) to 4 (describes the patient very well). Higher score indicate that the caregiver perceives the patient as highly empathic. The calculation of the score for each subscale is by the average of the items that compose it.

Patient's autonomy : The « Patient Competency Rating Scale » (PCRS, [35]; French Version; [36]) evaluates the patient's autonomy perceived by the caregiver. Five competency domains are assessed: daily living activities, behavioral and emotional functions, cognitive

and physical abilities. The caregiver has to estimate the patient's capacity through 30 items on a 5 point Likert-scale ranging from 1 (he/she cannot do) to 5 (he/she can do it easily). Higher scores indicate greater autonomy. Furthermore, in order to enable us to examine the evolution of these abilities (i.e., comparison of the patient's competencies before and after the disease) we added a dimension such that for each item, the caregiver is asked to indicate whether compared to before the disease, (1) it is more difficult for the patient, (2) it has not changed or (3) whether it is easier for the patient to accomplish the activity. Lower scores indicate a reduced autonomy.

2.4.2 Patients

Demographic information

The caregivers' socio-demographic data will be collected such as age, sex and family situation. Furthermore, information about socio-educational and socioeconomic levels will also be gathered (study level, profession and professional situation).

Clinical data

At inclusion, patients will have a detailed clinical assessment. The following parameters will be determined: gender, age, the presence of any previous or current cerebral pathology, cerebral trauma or cancer, initial neurological symptoms, complete physical examination, initial tumor location, its grade, date of the initial surgery, type of surgery treatment (biopsies, partial resection, complete resection), Karnofsky performance score (KPS), type of adjuvant treatment (radiotherapy, type of chemotherapy), radiological response to adjuvant treatment according to RANO assessment [37]. The hemineglect will be evaluated by the Line Section Task [38], their cognitive status will be investigated by the test of Montreal Cognitive Assessment - MoCA [39], the Complex Rey Figure [40] and the Trail Making Test [41]. Their functional status will be measured by the Karnofsky index and their neuropsychiatric status by the Mini-International Neuropsychiatric Interview (MINI, [42]). Finally, the social status will be measured by validated tasks such as Faux-pas, false beliefs and mental states decoding [43–46] and by auto-evaluative questionnaires (IRI, [33]; TEIQue, [47]; IIP-64, [48]).

2.5. Analyses

Patient and their caregiver's data will be matched. Once the patient exclusion criteria have been checked, statistical analyses will be performed with SPSS software.

The sociodemographic, socio-professional, socio-educational and clinical data will be presented in recapitulative and contingency tables summarizing the descriptive statistics (means, frequencies, percentages, SDs) depending on whether the variables are categorical or continuous.

This main aims of the study consisted in examining for the first time the Sherwood et al.'s [5] model in a comprehensive way by (i) investigating the functional, cognitive and neuropsychiatric deficits of the patients, (ii) integrating the social cognition status of the patient, and by (iii) focusing on the caregivers' quality of life as well as their mental health (i.e., burden, anxiety, depression).

In order to test the associations between patients' status and caregivers' quality of life and psychological health, we will conduct Pearson's correlations between these variables. We expect moderate significant correlations between patients' neuropsychiatric and social disorders and caregivers' reports of poor quality of life and mental health. Hierarchical linear regressions will also be conducted to examine the weight of each status (functional, cognitive, neuropsychiatric, and social) on caregiver's functioning. Results may show significant regression weights of patient's neuropsychiatric and social deficits on caregiver's quality of life and mental health (i.e., burden, anxiety and depression) beyond the functional and cognitive deficits.

The secondary aims of the study are: (iv) to examine the impact of patients' awareness of their social deficits on caregivers (v) to test whether the grade of the gliomas (high vs. low) modulates patient's deficits (and their impact on caregivers' state) and (vi) to evaluate whether caregivers have higher levels of depression and anxiety than healthy controls. To examine whether the awareness of the patients about their own social deficits also affects the caregiver experience, a delta will be calculated between the patients' IRI scores and the IRI scores reported by the caregiver. Results may show significant regression weight of the effect of the delta and the caregiver's scores. We expect that higher delta scores will predict deteriorated quality of life and psychological health.

Finally, we will examine whether the impact of functional, cognitive, neurophysiciatric and social deficits on caregivers' scores is modulated by the tumor grade gliomas. We expect that the patients' impairments may be stronger for high grade gliomas (grade III and IV) compared to low grade gliomas (grade II). Furthermore, we expect that caregivers of patient with a more advanced grade of the disease (III, IV) may present higher burden, anxiety and depression levels together with lower quality of compared to reports of caregivers of patients with low grade glioma (II). Finally, we expect that caregivers will present higher levels of depression and anxiety than healthy subjects. If the data distribution follows a normal distribution and if the variance equality is revealed ($p>.10$), mean comparisons will be carried out by ANOVA test for an independent sample, if not, nonparametric tests will be applied.

3. Discussion

This comprehensive empirical study aims to contribute to a better understanding of the factors that are hypothesized to influence the quality of life and mental health of the caregivers of adults with primary malignant brain tumours. Specifically, the unique feature of this study is that it will overcome previous shortcomings by examining in a comprehensive way the patients' characteristics together with caregivers' quality of life and mental health. In respect to patients' psychological deficits, previous studies have mainly focused on the effect of gliomas (localization, treatments, grade) on cognitive alterations (executive, attention, memory; e.g., [13,14]) and affective disorders such as anxiety, depression or emotional awareness (e.g., [49,50]). However, despite the direct consequences of the tumour on the functional, cognitive and affective deficits of the patients, tumours may also lead to social deficits which have been so far rather unexamined. Although they have been so far minimized, social deficits are particularly relevant in cancer patients who frequently report loneliness and social isolation. Therefore, impairments in understanding and inferring other's mental states (e.g., belief, intention, emotion, perception) can be deleterious for patients' social interactions as they are known to worsen social isolation, loneliness, and social support (e.g., [51,52]). Consequently, in addition to the social disruption due to the cancer itself (e.g., stigma; social isolation) we hypothesize that glioma may impair social cognition abilities which are supposed to preserve patients from loneliness [51]. The present study is thus innovative because it examines several domains that are frequently affected by the glioma and because it relies on measures of patients' social deficits.

In respect to the caregivers, although they are all particularly exposed to health problems [3], caregivers of adults with primary malignant brain tumours have to deal with both oncological and neurological sequels [5], which may potentiate their difficulties. Specifically, compared to other caregivers, they report greater strain, fatigue, lower well-being and impaired social functioning [6,20]. Despite the specific vulnerability of this population, only few studies have examined which patients' impairments (e.g., [2,12,21]) or coping strategies [53] were particularly affecting caregivers.

Therefore, from a theoretical perspective, the study will allow (i) to have a comprehensive overview of patients' deficits, (ii) to test the conceptual model of Sherwood et al. [5] and (iii) to assess the social dimension in terms of the impact of gliomas on mental states and emotions processing. This study will thus enable to identify the factors that particularly affect the caregivers and to understand in which way. It will also evaluate the influence of localization and grade (low vs high), with the hypothesis that patients with high grade gliomas compared to low grade gliomas will present more social deficits, especially if the tumours are located in regions associated with social cognition (eg., anterior and posterior cingulate cortex, medial prefrontal cortex, temporo-parietal junction).

From a clinical perspective, this study will provide support to medical professionals to focus on the caregivers that are at risk of developing mental and physical health troubles according to the patients' deficits. Indeed, it will allow professionals to be aware of which patients' deficits have the more deleterious impact on caregivers. On the long run, if the data support the hypotheses, we aim to set up future interventions targeting the difficulties encountered by the caregivers as well as rehabilitation of patients' main deficits. Specifically, while there exists only recent support for positive effect of multidisciplinary rehabilitation on patients' cognition [54], some interventions exist for caregivers of cancer or palliative patients (e.g., [55]) and more recently for caregivers of patients with a glioma [56]. This intervention which provides psycho-education about the patients' symptoms and aims to improve caregivers' ability to cope with the demands they have to face has shown positive effect on their feeling of mastery [56]. Improving the caregiver's quality of life and affective state may have a double impact: on the one hand it can help them to better cope with the disease of the patients and on the other hand it can lead them to better taking care of the patient.

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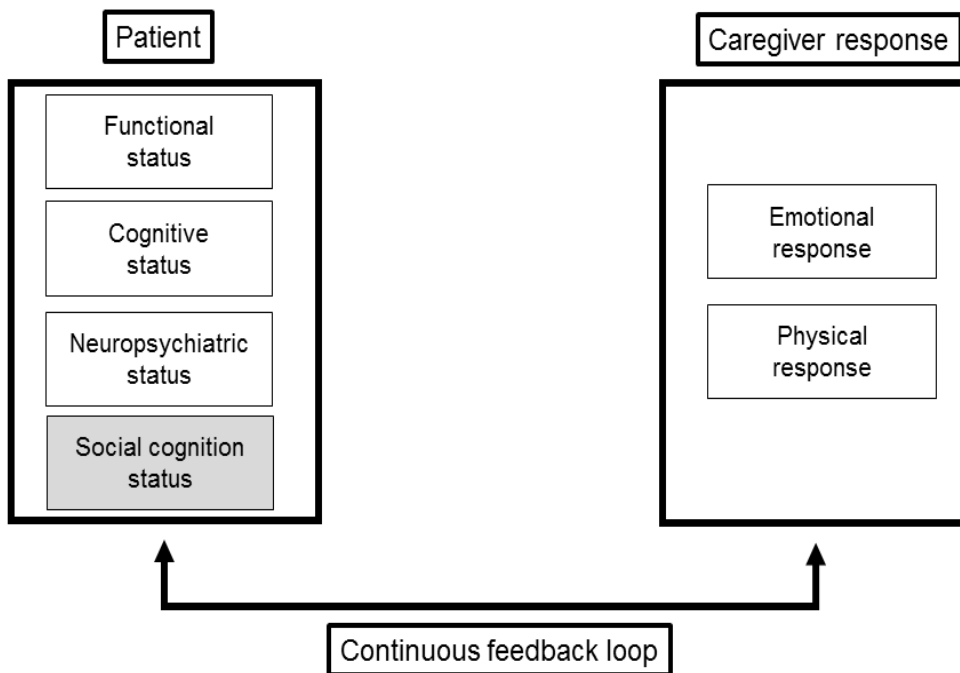
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Figure 1:

Adaptation of the Sherwood et al.'s [5] *model of the links between patient's deficits and caregiver's responses. In addition to the influence of the functional, neuropsychiatric and cognitive status of the patients, their social cognition status has been integrated.*

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Caregivers' quality of life and psychological health in response to brain tumor patients'

functional, cognitive, neuropsychiatric and social deficits: protocol for a cross sectional study

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Abstract

Introduction: Patients with gliomas generally present cognitive, neuropsychiatric and functional deficits. Although previous research showed that their caregivers present a poor quality of life and a poor mental health, only few studies have tested in a comprehensive way which deficits/preserved abilities predominantly impact their caregivers. Furthermore, only a few studies have focused on the social impact of gliomas, which may also deteriorate the caregivers' quality of life. Therefore, this cross sectional study aims to investigate which patients' impairments are particularly deleterious for the caregivers and whether the histological characteristics of the gliomas also affect their quality of life.

Methods and analysis: In order to examine these research questions, this study intends to include 180 patients (60 patients with grade II gliomas; 60 patients with grade III gliomas, 60 patients with a grade IV gliomas), their caregivers and 60 healthy controls. While patients will complete a full battery of cognitive, neuropsychiatric, functional and social tests, caregivers will complete questionnaires about their quality of life, depression, anxiety and burden. Patients performances and caregivers' reports of depression and anxiety will be compared to the scores of healthy controls. Eventually, our aim will be to provide specific care support to reduce patients' deficits together with the improvement of caregivers' difficulties.

Ethics and dissemination: The study has obtained the approval of the local Faculty ethicsl committee ("Comité d'éthique en sciences comportementales"; 2016-5-S41 and 2015-3-S37). On completion of the study, data will be kept by Université de Lille for five years before they are destroyed. Study findings will be disseminated through peer-reviewed journal publications and conference presentations with no reference to a specific individual.

Main strengths and limitations

- This study is the first to examine the additional role of patients' interpersonal deficits on the caregivers' quality of life and mental health
- In contrast to previous research, this study is based on behavioral tests rather than subjective evaluation measures.
- In addition to the examination of the effect of tumor grade, the study will also consider its localisation (i.e., region and hemisphere).
- In order to better understand the specifics for caregivers of glioma patients further studies will have to compare caregivers of patients who suffer from gliomas with caregivers of patients who suffer from another form of cancer.
- Future studies should examine objective measures of physical health among caregivers

1. Introduction

Caregivers are one of the main actors in patients' health. Indeed, 55% of persons who are disabled rely at least partly on other people's informal care and support [1]. Caregiving can range from physical help in daily living, personal care, financial help, medical or emotional and social support [2]. The caregiver could be a relative (e.g., child, spouse) or a friend designated as caregiver by themselves or referred to as such by the patient.

Previous findings clearly showed that independently of the patient's disease, caregivers often report distress, fatigue, and burden [3]. Nevertheless, the deleterious impact of being a caregiver may also differ based on the symptoms, treatments and prognosis of the disease. Caregivers of adult patients affected with glioma are a specific subset of caregivers because they are particularly exposed to mental and physical disorders [4–6], compared to caregivers of patients with others cancers (e.g. lung, breast), these carers have significantly higher adjusted mortality, report higher levels of strain and lower levels of mental well-being [6–8]. This could be explained by the fact that they have to take care of patients with both *oncological* and *neurological* issues [9]. The interaction between both these conditions may particularly increase their difficulties due to several causes. Compared to people who are carrying for individuals with other health disabilities, they have to take care of patients with reduced life expectancy and to cope with prolonged and diverse treatments as well as an uncertain prognosis [10].

Furthermore, in addition to these serious characteristics of the disorder itself (i.e., poor prognosis, healthcare costs), the functional, cognitive and neuropsychiatric impairments presented by patients may directly impact the caregivers' state [5]. According to Sherwood and al.'s [5] conceptual model, these impairments influence the emotional and physical responses among caregivers (simplified model: Figure 1). The model also suggests that the deleterious effect of treatments and poorly available resources either personal or external [11] may also worsen the mental and physical health of the caregiver. This model is based on the Lazarus' model of Stress and Coping ([12]), which suggests a stressor leads a person to consider it in terms of primary (relevance for one's goals) and secondary appraisals (coping strategies), which will then determine the person's stress response. In the conceptual model of Sherwood and collaborators, the diagnosis of a brain tumor refers to the stressor, which will lead the caregiver to evaluate the demands associated with the patient's functional, cognitive and neuropsychiatric deficits (primary appraisal) as well as the available resources, both internal (e.g., emotional traits) and external (e.g., social, financial supports) (secondary appraisal). The conceptual model of Sherwood is thus theoretically grounded and of great relevance as it aims to examine the predictors together with the protective factors of caregiver's difficulties.

In relation to the *functional* deficits, patients with gliomas present motor and/or sensory deficits, visual disorders, speech difficulties, as well as neurological impairment [13], which may increase the time spent with the patient and thus reduce the caregiver's own leisure, social and working periods [13]. In terms of the patients' *cognitive* difficulties, gliomas alter normal functioning such as executive, attention and memory deficits [14,15], which may increase the workload of the caregiver as the patients can be unable to hold onto information and to make decisions. Therefore, the caregiver is often alone in making important decisions, pertaining to the treatment of the disease, the housekeeping or the education of the children [5]. Finally, some *neuropsychiatric* symptoms such as high levels of distress, irritability and anxiety among patients [5] can lead to fatigue and emotional difficulties for the caregiver due to the need for constant attention by the patient. Managing patient's depression and negative feelings can be even more difficult than physical care [16]. Finally, patients affected with glioma present particular behavioural and personality changes, which can lead to reduce emotional awareness [17], impulsiveness and aggressive behaviour, and thus increase caregivers' feelings of distress [18].

So far, only few studies have been conducted to examine the direct links between patients' cognitive, neuropsychiatric and functional status and the caregivers' psychological health. These studies revealed that the neuropsychiatric status of the patient is associated with caregivers' burden, negative affect [13,19,20], mental health [21], and psychological well-being [18]. However, the effects of functional and cognitive deficits are less clear. Indeed, while some data suggest that patient's functional status impact the caregiver's burden, anxiety and perceived health [2,13] other studies showed no association [22,23]. Regarding the effect of cognitive status, studies found either association with the caregiver's perceived quality of life [23] or no association [13]. Furthermore, patients sometimes underestimate their psychological and interpersonal problems which may increase the anxiety of the caregivers [24].

Taken together, these preliminary findings are in favour of a direct link between patients' neuropsychiatric deficits and caregivers' difficulties. However, the results are more inconsistent in terms of the role of cognitive and functional deficits, mainly accounted by different shortcomings. First, only few studies [13,19,25] examined the comprehensive model of Sherwood. Second, we argue that in addition to its functional, neuropsychiatric and cognitive alterations, gliomas may also impair patients' social cognition, which has been so far underestimated. Social cognition is the study of the way individuals understand others and themselves [26]. We argue that the social dimension should be considered as important as the functional, cognitive or neuropsychiatric deficits. Indeed, patients' social cognition impairments may impair their social functioning, leading them and their caregiver to social isolation [20,27]. So far, only a few studies examined this question and have all revealed

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social impairments such as deficits to decode other's mental states [17,28]. Because a caregiver's isolation has been associated with lower social support and increased distress [8], we argue that it is crucial to integrate the social dimension as a predictor of poor mental health in caregivers.

This study thus aims to examine for the first time the Sherwood et al.'s [5] model in a comprehensive way by (i) investigating the functional, cognitive and neuropsychiatric deficits of the patients, (ii) integrating the social cognition status of the patient, and (iii) by focusing on the caregivers' quality of life as well as their mental health (i.e., burden, anxiety, depression). The secondary aims of the study are: (iv) to examine the impact of patients' awareness of their social deficits on caregivers, (v) to test whether the localization and the grade of the glioma (grade II,III and IV) modulate patient's deficits (and their impact on the caregivers' state).

2. Methods/Design

2.1. Participants

2.1.1. Caregivers

To be included in the study, caregivers must be over 18 years old. They must be fluent in French and sign an informed consent to participate in the study. They have to be designated by the patient as their caregiver. Furthermore, the patients must have approved the participation of their caregiver. Participants who do not meet the inclusion criteria will be excluded.

Other exclusion criteria for the caregiver are:

1) being paid to take care of the patient;
2) presenting any psychological, cognitive or physical impairment which does not allow the caregiver to complete the questionnaire
3) being under guardianship.

2.1.2. Patients

Patients must be over 18 years old. They must be fluent in French and sign an informed consent to participate in the study. Patients must be affected by supratentorial gliomas of grade II to grade IV, according to WHO classification, histologically proven with either biopsy, partial or total removal. Patients have to be covered by the French social security. Patients who do not meet the inclusion criteria will not be included.

Other exclusion criteria are:

1) any previous cerebral pathology, trauma (with a loss of consciousness) or any treatment that could have lead to cognitive or physical impairments

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2) other chronic neurological diseases (e.g;, Parkinson)

3) addiction to any noxious substance (e.g., alcohol)

4) major psychiatric disorders (e.g., schizophrenia)

5) tumors classified as pilocytic astrocytoma, because they are mainly infratentorial (rather than supratentorial) and are Grade I.

6) infratentorial gliomas

7) patients unable to complete questionnaires

8) the presence of other malignant tumours treated (currently or in the past) with curative intent.

2.1.3. Control participants

To be included in the study, controls must be over 18 years old. They must be fluent in French and sign an informed consent to participate in the study. Exclusion criteria for the control participants are presenting any psychological, cognitive or physical impairment which does not allow them to complete the questionnaires according the researchers of the study. The anxiety and depression levels of the caregivers will be compared to the anxiety and depression levels of this healthy group. The control group will also complete the patients' tasks and questionnaires in order to compare their difficulties to a normal population. The control group will also allow us to examine whether patients and caregivers present greater levels of depression and anxiety. The control group will be matched in terms of age, gender and education.

2.2. Number of patients and sample representativeness

All participants will be recruited at the Department of Neuro-Oncology of Lille University Medical Center, which is the main institution in charge of glioma treatment in the North of France (Nord-Pas-de-Calais region). Patients treated in this center usually come from large areas in the region, and may have very different sociocultural histories, which implies considerable socio-demographic and socio-professional diversity.

One hundred and eighty patients, 180 caregivers as well as 60 healthy controls will be recruited (i.e., 60 grade II patients and their caregivers, 60 grade III patients and their caregiver, 60 grade IV patients and their caregiver, and 60 health subjects). This cohort size was based on effect sizes found in Aoun et al.'s [6] study that compared quality of life of the caregivers of primary brain tumor patients vs patients with other cancers ($d\text{-}Cohen$ = 0.63; α=.05; 1-β=.95).

2.3. Procedure

Based on medical screening by the investigator at the admission, all the patients complying with all the selection criteria will be included in the study. The investigator will describe the study to the patient and, if the latter agrees, the investigator will give the information letter and ask the patient to sign the informed consent form. The main information on the consent form is (i) that the participants are allowed to quit the study whenever they want to (ii) that we assure the anonymity of the data and that (iii) their participation to the study is independent from their treatments.

After obtaining the patient's consent about his/her participation, the study will be presented to the caregiver designated as such by the patient. Subsequently, the caregiver complying with all the selection criteria will be contacted. It is only when the caregiver's consent will be signed that the patient-caregiver pair will be included. The patient and their caregiver will then be given an identification and random number comprised between 1 and 999. The clinical research associate will be in charge of filling the socio-demographic data for the study. Patients and caregivers will be tested separately and individually at the hospital by the investigator of the study.

2.4. Measures

2.4.1. Caregiver

Demographic

The caregivers' socio-demographics data will be collected such as age, sex, family situation, and their relationship to the patient. Furthermore, information about socio-educational and socioeconomic levels will also be gathered (study level, profession and professional situation).

Auto-evaluative questionnaire

Anxiety and depression: The "Hospital Anxiety and Depression Scale" (HADS, [29]; French Version:[30]) is used to measure emotional distress through depression and anxiety levels. This scale is composed of 14 items measuring depression (7 items) and anxiety (7 items). Each response is scored on a scale that ranges from 0 to 3 (3 indicates higher symptom frequencies). Scores for each subscale range from 0 to 21 which may be either normal (0-7), moderate (8-10) or indicating a depression and/or anxiety disorder (11-21).

Quality of life: The "CareGiver Oncology Quality of Life" (CarGOQoL, [31]) questionnaire has been developed to evaluate the cancer caregiver's quality of life. It is a 29-item, multidimensional and self-administered questionnaire. The CarGOQOL comprises 10 subscales indicating psychological well-being, burden, relationship with health care, administration and finances, coping, physical well-being, self-esteem, leisure time, social

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support, and private life. Participants are invited to estimate their quality of life on a 5-point Likert scale ranging from 1 (Never/Not at all) to 5 (Always/Widely). The global score ranges from 0 to 100. Higher scores indicate good quality of life.

Burden: The "Caregiver Reaction Assessment" (CRA, [32]; French version: [33]) questionnaire assesses the caregiver's perceived burden. The questionnaire consists of 24 items measuring 5 subscales: impact on disrupted schedule, financial problems, lack of family support, health problems and the impact on self-esteem. Caregivers have to indicate their level of agreement using a 5-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). For each subscale, a score is calculated by taking the average of the items. Higher scores indicate a greater impact (either beneficial or detrimental).

Questionnaires about the patient

Perceived level of empathy: The Interpersonal Reactivity Index (IRI, [34]; French version: [35]) has been modified and adapted for the present study. It includes 4 subscales: personal distress, empathic concern, fantasy and perspective taking. Participants are asked to indicate the extent to which each item describes them on a 5-point Likert scale ranging from 0 (does not describe me well) to 4 (describes me very well). In this study, caregivers are instructed to evaluate the empathy abilities of the patient on a 5-point Likert scale ranging from 0 (does not describe the patient well) to 4 (describes the patient very well). Higher score indicate that the caregiver perceives the patient as highly empathic. The calculation of the score for each subscale is by the average of the items that compose it.

Patient's autonomy : The « Patient Competency Rating Scale » (PCRS, [36]; French Version; [37]) evaluates the patient's autonomy perceived by the caregiver. Five competency domains are assessed: daily living activities, behavioral and emotional functions, cognitive and physical abilities. The caregiver has to estimate the patient's capacity through 30 items on a 5 point Likert-scale ranging from 1 (he/she cannot do) to 5 (he/she can do it easily). Higher scores indicate greater autonomy. Furthermore, in order to enable us to examine the evolution of these abilities (i.e., comparison of the patient's competencies before and after the disease) we added a dimension such that for each item, the caregiver is asked to indicate whether compared to before the disease, (1) it is more difficult for the patient, (2) it has not changed or (3) whether it is easier for the patient to accomplish the activity. Lower scores indicate a reduced autonomy.

2.4.2 Patients

Demographic information

The caregivers' socio-demographic data will be collected such as age, sex and family situation. Furthermore, information about socio-educational and socioeconomic levels will also be gathered (study level, profession and professional situation).

Clinical data

At inclusion, patients will have a detailed clinical assessment. The following parameters will be determined: gender, age, the presence of any previous or current cerebral pathology, cerebral trauma or cancer, initial neurological symptoms, complete physical examination, initial tumor location, its grade, distance in time from surgery, type of surgery (biopsy, partial resection and full resection), Karnofsky performance score (KPS), type of adjuvant treatment (radiotherapy, type of chemotherapy), radiological response to adjuvant treatment according to RANO assessment [38]. The hemineglect will be evaluated by the Line Section Task [39], their cognitive status will be investigated by the test of Montreal Cognitive Assessment - MoCA [40], the Complex Rey Figure [41], the Trail Making Test [42] and the Raven's Colored Progressive Matrices [43].

Their functional status will be measured by the Karnofsky index and their neuropsychiatric status by the Mini-International Neuropsychiatric Interview (MINI, [44]). Finally, their social status will be measured by validated tasks such as Faux-pas, mental states decoding [45–48] and by auto-evaluative questionnaires (IRI, [34]; TEIQue,[49] IIP-64, [50]).

Faux-pas Task: In this task, participants have to answer several questions based on 20 verbal scenarios that either describe a faux-pas (i.e., when someone unintentionally offends another person by saying something that should not be said) or a control situation. The scores are based on participants' abilities to detect the faux pas, to understand it and its non intentionality [45].

Mental states decoding: Participants will be instructed to detect the emotional state that is expressed by a facial expression (disgust, anger, fear, sadness, happiness). These emotions will be expressed at various intensities in order to evaluate whether patients need more perceptual information to accurately recognize the emotion (0%, 30%; 70%, and 100%) [51]. In other tasks, participants will be asked to decode complex affective mental states and to mention to what extent they are sharing the affective state of the person displayed in the picture [47,52]. Finally, a non verbal task (based on pictures) will be used to examine the ability to detect the intentionality of characters [48].

Questionnaires

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The Interpersonal Reactivity Index [34] is a multidimensional 28-item questionnaire of empathy. As previously mentioned, it includes 4 subscales: personal distress, empathic concern, fantasy and perspective taking. Participants are asked to indicate the extent to which each item describes them on a 5-point Likert scale ranging from 0 (does not describe me well) to 4 (describes me very well).

The Trait Emotional Intelligence Questionnaire – Short form [49] is a 30-item questionnaire that measures trait emotional intelligence. It requires participants to estimate their abilities in indentifying, understanding, regulating and using emotions in oneself and others.

The Questionnaire Inventory of Interpersonal Problems - 64 items [50] examines interpersonal difficulties. Participants are asked to indicate on a Likert scale (0: not at all to 4: extremely) the extent to which they encounter problems in terms Domineering/Controlling; Vindictive/Self-Centered, Cold/Distant, Socially Inhibited, Nonassertive, Overly Accommodating, Self-Sacrificing, and Intrusive/Needy.

We are planning two meetings of 1 hour and 30 minutes each within 2 weeks to reduce concentration and attentional difficulties, especially for grade IV patients. To avoid drop outs, the meetings will be arranged when they are visiting the doctor at the hospital and when it is not too inconvenient for the patients in terms of mobility and availability.

2.5. Analyses

Patient and their caregiver's data will be matched. Once the patient exclusion criteria have been checked, statistical analyses will be performed with SPSS software.

The sociodemographic, socio-professional, socio-educational and clinical data will be presented in recapitulative and contingency tables summarizing the descriptive statistics (means, frequencies, percentages, SDs) depending on whether the variables are categorical or continuous.

This main aims of the study consist in examining for the first time the Sherwood et al.'s [5] model in a comprehensive way by (i) investigating the functional, cognitive and neuropsychiatric deficits of the patients, (ii) integrating the social cognition status of the patient, and by (iii) focusing on the caregivers' quality of life as well as their mental health (i.e., burden, anxiety, depression).

In order to test the associations between patients' status and caregivers' quality of life and psychological health, we will conduct Pearson's correlations between these variables. We expect moderate significant correlations between patients' neuropsychiatric and social disorders and caregivers' reports of poor quality of life and mental health. Hierarchical linear regressions will also be conducted to examine the weight of each status (functional, cognitive, neuropsychiatric, and social) on caregiver's functioning. The lesion volume, the distance in time from surgery and the type of surgery (biopsy, partial resection and full resection) will be entered in the first step as control factors. Results may show significant regression weights of patient's neuropsychiatric and social deficits on caregiver's quality of life and mental health (i.e., burden, anxiety and depression) beyond the functional and cognitive deficits and the abovementioned controlled factors. Furthermore, in order to examine whether the data fit with the model, we will use path analysis (AMOS).

The secondary aims of the study are: (iv) to examine the impact of patients' awareness of their social deficits on caregivers (v) to test whether the grade of the gliomas modulates patient's deficits (and their impact on the caregivers' state) and (vi) to evaluate whether caregivers have higher levels of depression and anxiety than healthy controls. To examine whether the awareness of the patients about their own social deficits also affects the caregiver experience, a delta will be calculated between the patients' IRI scores and the IRI scores reported by the caregiver. Results may show significant regression weight of the effect of the delta and the caregiver's scores. We expect that higher delta scores will predict deteriorated quality of life and psychological health.

Finally, we will examine whether the impact of functional, cognitive, neurophysiciatric and social deficits on caregivers' scores is modulated by the tumor grade gliomas. We expect that the patients' impairments may be stronger for high grade gliomas (grade III and IV) compared to low grade gliomas (grade II). Furthermore, we expect that caregivers of patient with a more advanced grade of the disease (III, IV) may present higher burden, anxiety and depression levels together with lower quality of life compared to reports of caregivers of patients with low grade glioma (II). Finally, we expect that caregivers will present higher levels of depression and anxiety than healthy subjects. If the data distribution follows a normal distribution and if the variance equality is revealed (*p>.10*), mean comparisons will be carried out by ANOVA test for an independent sample, if not, nonparametric tests will be applied.

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3. Ethics and dissemination

The study has obtained the approval of the local Faculty ethics committee ("Comité d'éthique en sciences comportementales"; 2016-5-S41 and 2015-3-S37). The study does not involve products mentioned in article L.5311-1 of the French Code of Public Health and does not imply any changes in the medical care received by the patients. The study will begin in April 2017 and will end in 2020. On completion of the study, data will be kept by Université de Lille for five years before they are destroyed. Study findings will be disseminated through peer-reviewed journal publications and conference presentations with no reference to a specific individual.

4. Discussion

This comprehensive empirical study aims to contribute to a better understanding of the factors that are hypothesized to influence the quality of life and mental health of the caregivers of adults with primary malignant brain tumours. Specifically, the unique feature of this study is that it will overcome previous shortcomings by examining in a comprehensive way the patients' characteristics together with caregivers' quality of life and mental health. In respect to patients' psychological deficits, previous studies have mainly focused on the effect of gliomas (localization, treatments, grade) on cognitive alterations (executive, attention, memory; e.g., [14,15]) and affective disorders such as anxiety, depression or emotional awareness (e.g., [53,54]). However, despite the direct consequences of the tumour on the functional, cognitive and affective deficits of the patients, tumours may also lead to social deficits which have been so far rather unexamined. Although they have been so far minimized, social deficits are particularly relevant in cancer patients who frequently report loneliness and social isolation. Therefore, impairments in understanding and inferring other's mental states (e.g., belief, intention, emotion, perception) can be deleterious for patients' social interactions as they are known to worsen social isolation, loneliness, and social support (e.g., [55,56]). Consequently, in addition to the social disruption due to the cancer itself (e.g., stigma; social isolation) we hypothesize that glioma may impair social cognition abilities which are supposed to protect patients from loneliness [55]. In this research we aim to overcome several limitations of previous studies [13,19,21,22] that examined the effect of the patient's functional, cognitive, and/or neuropsychiatric status on caregiver symptoms. Specifically, we aim to overcome the non investigation of patient's social deficits, the reliance on caregivers' evaluation and/or non-experimental measures of patient's deficits. The present study is thus innovative because it examines several domains that are frequently affected by the glioma and because it relies on measures of patients' social deficits.

In respect to the caregivers, although they are all particularly exposed to health problems [3], caregivers of adults with primary malignant brain tumours have to deal with both oncological and neurological sequels [5], which may potentiate their difficulties. Specifically, compared to other caregivers, they report greater strain, fatigue, lower well-being and impaired social functioning [6,21]. Despite the specific vulnerability of this population, only few studies have examined which patients' impairments (e.g., [2,13,18]) or coping strategies [57] were particularly affecting caregivers.

Therefore, from a theoretical perspective, the study will allow (i) to have a comprehensive overview of patients' deficits, (ii) to test the conceptual model of Sherwood et al. [5] and (iii) to assess the social dimension in terms of the impact of gliomas on mental states and emotions processing. This study will thus enable to identify the factors that particularly affect the caregivers and to understand in which way. It will also evaluate the influence of localization and grade (II, III and IV), with the hypothesis that patients with grade IV gliomas compared to grade II gliomas will present more social deficits, especially if the tumours are located in regions associated with social cognition (eg., anterior and posterior cingulate cortex, medial prefrontal cortex, temporo-parietal junction). Patients with too serious cognitive deficits may not be able to complete all tasks (e.g., aphasia may prevent patients to complete verbal social tasks such as the faux-pas task). However, in order to avoid any selection bias and to still examine the impact of patients' deficits on caregivers' health, the investigators will adapt the examination by facilitating the administration of some tasks (e.g., reading the questionnaires with the patient) and/or by removing tasks that require too many cognitive abilities.

From a clinical perspective, this study will provide support to medical professionals to focus on the caregivers that are at risk of developing mental and physical health troubles driven by the patients' deficits. Indeed, it will allow professionals to be aware of which patients' deficits have the more deleterious impact on caregivers. In the long run, if the data support the hypotheses, we aim to set up future interventions targeting the difficulties encountered by the caregivers and the rehabilitation of patients' main deficits. Specifically, while there exists only recent support for the positive effect of multidisciplinary rehabilitation on patients' cognition [58], some interventions exist for caregivers of cancer or palliative patients (e.g., [59]) and more recently for caregivers of patients with a glioma [60]. This intervention which provides psycho-education about the patients' symptoms and aims to improve caregivers' ability to cope with the demands they have to face has shown positive effect on their feeling of mastery [60]. Improving the quality of life and affective state of caregivers may have a double impact: on the one hand it can help them to better cope with the disease of the patient and on the other hand it can lead them to better taking care of the patient.

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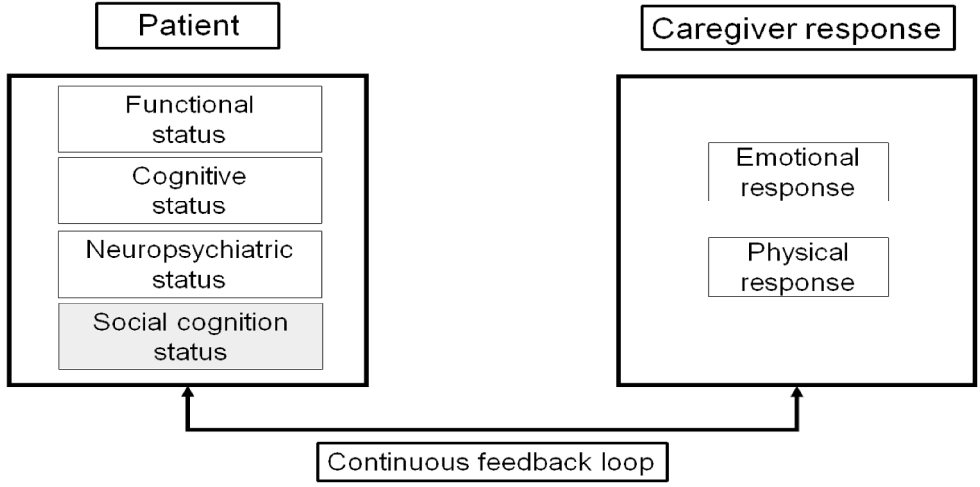
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Figure 1: *Adaptation of the Sherwood et al.'s* [5] *model of the links between patient's deficits and caregiver's responses. In addition to the influence of the functional, neuropsychiatric and cognitive status of the patients, their social cognition status has been integrated.*

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Caregivers' quality of life and psychological health in response to brain tumor patients' functional, cognitive, neuropsychiatric and social deficits: protocol for a cross sectional study

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Caregivers' quality of life and psychological health in response to brain tumor patients'

functional, cognitive, neuropsychiatric and social deficits: protocol for a cross-sectional study

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Abstract

Introduction: Patients with gliomas generally present cognitive, neuropsychiatric and functional deficits. Although previous research has shown that their caregivers present a poor quality of life and poor mental health, only a few studies have tested in a comprehensive way which deficits/preserved abilities of patients predominantly impact their caregivers. Furthermore, only a few studies have focused on the social impact of gliomas, which may also damage the caregivers' quality of life. Therefore, this cross-sectional study aims to investigate which patients' impairments are particularly deleterious for the caregivers and whether the histological characteristics of the gliomas also affect their quality of life.

Methods and analysis: In order to examine these research questions, this study intends to include 180 patients (60 patients with grade II gliomas, 60 patients with grade III gliomas, and 60 patients with grade IV gliomas), their caregivers and 60 healthy controls. While patients will complete a full battery of cognitive, neuropsychiatric, functional and social tests, caregivers will complete questionnaires about their quality of life, depression, anxiety and burden. Patients' performances and caregivers' reports of depression and anxiety will be compared to the scores of healthy controls. Eventually, our aim will be to provide specific care support both to reduce patients' deficits and alleviate caregivers' difficulties.

Ethics and dissemination: The study has obtained the approval of the local Faculty ethics committee ("Comité d'éthique en sciences comportementales"; 2016-5-S41 and 2015-3-S37). On completion of the study, data will be kept by Lille University for five years before they are destroyed. Study findings will be disseminated through peer-reviewed journal publications and conference presentations with no reference to a specific individual.

Main strengths and limitations

- This study is the first to examine the additional role of patients' interpersonal deficits in their caregivers' quality of life and mental health

- In contrast to previous research, this study is based on behavioral tests rather than subjective evaluation measures.

- In addition to examining the effect of the tumor grade, the study will also consider its location (i.e., region and hemisphere).

- In order to better understand the specifics for caregivers of glioma patients, further studies will have to compare caregivers of patients who suffer from gliomas with caregivers of patients who suffer from another form of cancer.

- Future studies should examine objective measures of physical health among caregivers.

1.   Introduction

Caregivers are one of the main actors in patients' health. In fact, 55% of people with a disability rely at least partly on other people's informal care and support [1]. Caregiving can range from physical help with daily living, personal care, financial help, medical or emotional and social support [2]. The caregiver may be a relative (e.g., child, spouse) or a friend designated as a caregiver by themselves or referred to as such by the patient.

Previous findings have clearly shown that independently of the patient's disease, caregivers often report distress, fatigue, and burden [3]. Nevertheless, the damaging impact of being a caregiver may differ based on the symptoms, treatments and prognosis of the disease. Caregivers of adult patients affected with glioma are a specific subset of caregivers because they are particularly exposed to mental and physical disorders [4–6], compared to caregivers of patients with other cancers (e.g., lung, breast). These carers have significantly higher adjusted mortality, report higher levels of strain and lower levels of mental well-being [6–8]. This could be explained by the fact that they have to take care of patients with both *oncological* and *neurological* issues [9]. The interaction between these two conditions may particularly increase their difficulties for several reasons. Compared to people who are caring for individuals with other health disabilities, they have to take care of patients with reduced life expectancy and cope with prolonged and diverse treatments as well as an uncertain prognosis [10].

In addition to these serious characteristics of the disorder itself (i.e., poor prognosis, healthcare costs), the functional, cognitive and neuropsychiatric impairments presented by patients may directly impact the caregivers' state [5]. According to Sherwood et al.'s [5] conceptual model, these impairments influence the emotional and physical responses of caregivers (simplified model: Figure 1). The model also suggests that the damaging effect of treatments and poorly available resources, either personal or external [11], may also worsen the mental and physical health of the caregiver. This model is based on the Lazarus model of Stress and Coping ([12]), which suggests that a stressor leads a person to consider it in terms of primary (relevance to one's goals) and secondary (coping strategies) appraisals, which then determine the person's stress response. In the conceptual model of Sherwood and collaborators, the diagnosis of a brain tumor refers to the stressor, which will lead the caregiver to evaluate the demands associated with the patient's functional, cognitive and neuropsychiatric deficits (primary appraisal) as well as the available resources, both internal (e.g., emotional traits) and external (e.g., social and financial support) (secondary appraisal). The conceptual model of Sherwood is thus theoretically grounded and of great relevance as it aims to examine the predictors together with the protective factors of the caregiver's difficulties.

In relation to the *functional* deficits, patients with gliomas present motor and/or sensory deficits, visual disorders, speech difficulties, as well as neurological impairment [13], which may increase the time spent with the patient and thus reduce the caregiver's own leisure, social and working periods [13]. In terms of the patients' *cognitive* difficulties, gliomas alter normal functioning such as executive, attention and memory deficits [14,15], which may increase the workload of the caregiver as the patient may be unable to hold onto information and make decisions. Therefore, the caregiver is often alone in making important decisions, pertaining to the treatment of the disease, the housekeeping or the education of children [5]. Finally, some *neuropsychiatric* symptoms such as high levels of distress, irritability and anxiety among patients [5] can lead to fatigue and emotional difficulties for the caregiver due to the patient's need for constant attention. Managing the patient's depression and negative feelings can be even more difficult than physical care [16]. Finally, patients affected with glioma present particular behavioral and personality changes, which can lead to reduced emotional awareness [17], impulsiveness and aggressive behavior, and thus increase the caregivers' feelings of distress [18].

To date, only a few studies have been conducted to examine the direct links between the patients' cognitive, neuropsychiatric and functional status and the caregivers' psychological health. These studies have revealed that the neuropsychiatric status of the patient is associated with the caregiver's burden, negative affect [13,19,20], mental health [21], and psychological well-being [18]. However, the effects of functional and cognitive deficits are less clear. For example, while some data suggest that the patient's functional status impacts the caregiver's burden, anxiety and perceived health [2,13] others show no association [22,23]. Regarding the effect of cognitive status, studies have found either association with the caregiver's perceived quality of life [23] or no association [13]. Furthermore, patients sometimes underestimate their psychological and interpersonal problems, which may increase the anxiety of the caregivers [24].

Taken together, these preliminary findings favor a direct link between patients' neuropsychiatric deficits and caregivers' difficulties. However, the results are more inconsistent in terms of the role of cognitive and functional deficits, mainly accounted for by various shortcomings. First, only a few studies [13,19,25] have examined the comprehensive model of Sherwood. Second, we argue that, in addition to their functional, neuropsychiatric and cognitive alterations, gliomas may also impair patients' social cognition, which has so far been underestimated. Social cognition is the study of the way individuals understand others and themselves [26]. We argue that the social dimension should be considered as important as the functional, cognitive and neuropsychiatric deficits. In fact, patients' social cognition impairments may hinder their social functioning, leading them and their caregivers to social isolation [20,27]. To date, only a few studies have examined this question and all have

revealed social impairments, such as deficits in decoding the mental states of others [17,28]. Because a caregiver's isolation has been associated with less social support and increased distress [8], we argue that it is crucial to include the social dimension as a predictor of poor mental health in caregivers.

This study thus aims to examine Sherwood et al.'s [5] model for the first time in a comprehensive way by (i) investigating the functional, cognitive and neuropsychiatric deficits of patients, (ii) integrating the social cognition status of patients, and (iii) focusing on the caregivers' quality of life as well as their mental health (i.e., burden, anxiety, depression). The secondary aims of the study are: (iv) to examine the impact of patients' awareness of their social deficits on caregivers, (v) to test whether the location and grade of the glioma (grade II, III or IV) modulate patients' deficits (and their impact on the caregivers' state).

2. Methods/Design

2.1. Participants

2.1.1. Caregivers

To be included in the study, caregivers must be over 18 years old and fluent in French. They have to be designated by the patient as their caregiver and sign an informed consent to participate in the study. Furthermore, the patients must approve the participation of their caregiver. Participants who do not meet these inclusion criteria will be excluded.

Other exclusion criteria for the caregiver are:

1) being paid to take care of the patient;
2) presenting any psychological, cognitive or physical impairment, which prevents the caregiver from completing the questionnaire;
3) being under guardianship.

2.1.2. Patients

Patients must be over 18 years old and fluent in French. They have to sign an informed consent to participate in the study. Patients must be affected by supratentorial gliomas of grade II to grade IV, according to the WHO classification, histologically proven by either biopsy, or partial or total removal. Patients have to be covered by French social security. Patients who do not meet these inclusion criteria will be excluded.

Other exclusion criteria are:

1) any previous cerebral pathology, trauma (with loss of consciousness) or any treatment that could have led to cognitive or physical impairments;
2) other chronic neurological diseases (e.g., Parkinson's);
3) addiction to any harmful substance (e.g., alcohol);

4) major psychiatric disorders (e.g., schizophrenia);

5) tumors classified as pilocytic astrocytoma, because they are mainly infratentorial (rather than supratentorial) and are grade I;

6) infratentorial gliomas;

7) patients unable to complete the questionnaires;

8) the presence of other malignant tumors treated (currently or in the past) with curative intent.

2.1.3. Control participants

To be included in the study, controls must be over 18 years old and fluent in French. They have to sign an informed consent to participate in the study. Exclusion criteria for the control participants are presenting any psychological, cognitive or physical impairment that prevents them from completing the questionnaires according to the researchers of the study. The anxiety and depression levels of the caregivers will be compared to the anxiety and depression levels of this healthy group. The control group will also complete the patients' tasks and questionnaires in order to compare their difficulties to those of a normal population. The control group will also enable us to examine whether patients and caregivers present greater levels of depression and anxiety. The control group will be matched in terms of age, gender and education.

2.2. Number of patients and sample representativeness

All participants will be recruited at the Department of Neuro-Oncology of Lille University Medical Center, which is the main institution in charge of glioma treatment in Northern France (Nord-Pas-de-Calais region). Patients treated in this center usually come from large areas in the region, and may have very different socio-cultural backgrounds, which implies considerable socio-demographic and socio-professional diversity.

One hundred and eighty patients, 180 caregivers and 60 healthy controls will be recruited (i.e., 60 grade II patients and their caregivers, 60 grade III patients and their caregivers, 60 grade IV patients and their caregivers, and 60 healthy subjects). This cohort size is based on effect sizes found in Aoun et al.'s [6] study, which compared the quality of life of caregivers of primary brain tumor patients vs. patients with other cancers (*Cohen's d* = 0.63; α = .05; 1-β = .95).

2.3. Procedure

Based on medical screening by the investigator during admission, all patients complying with all the selection criteria will be included in the study. The investigator will describe the study to the patient and, if the latter agrees, the investigator will give them the information letter

and ask the patient to sign the informed consent form. The main information provided on the consent form is that (i) the participants are allowed to quit the study whenever they want to (ii) we assure the anonymity of the data and (iii) their participation in the study is independent of their treatments.

After obtaining the patient's consent to his/her participation, the study will be presented to the caregiver designated as such by the patient. Subsequently, the caregiver complying with all the selection criteria will be contacted. It is only when the caregiver's consent form is signed that the patient-caregiver pair will be included. The patient and their caregiver will then be given a random identification number comprised between 1 and 999. The clinical research associate will be in charge of filling in the socio-demographic data for the study. Patients and caregivers will be tested separately and individually at the hospital by the investigator of the study.

2.4. Measures
2.4.1. Caregiver
Demographic information

The caregivers' socio-demographic data will be collected such as age, sex, family situation, and their relationship to the patient. Information about socio-educational and socio-economic levels will also be gathered (study level, profession and professional situation).

Auto-evaluative questionnaires

Anxiety and depression: The "Hospital Anxiety and Depression Scale" (HADS, [29]; French Version:[30]) is used to measure emotional distress through depression and anxiety levels. This scale is composed of 14 items measuring depression (7 items) and anxiety (7 items). Each response is scored on a scale that ranges from 0 to 3 (3 indicates higher symptom frequencies). Scores for each subscale range from 0 to 21, which may be either normal (0-7), moderate (8-10) or indicate a depression and/or anxiety disorder (11-21).

Quality of life: The "CareGiver Oncology Quality of Life" (CarGOQoL, [31]) questionnaire was developed to evaluate the cancer caregiver's quality of life. It is a 29-item, multidimensional and self-administered questionnaire. The CarGOQOL comprises 10 subscales indicating psychological well-being, burden, relationship with health care, administration and finances, coping, physical well-being, self-esteem, leisure time, social support, and private life. Participants are invited to estimate their quality of life on a 5-point Likert scale ranging from 1 (Never/Not at all) to 5 (Always/Widely). The overall score ranges from 0 to 100. Higher scores indicate a good quality of life.

Burden: The "Caregiver Reaction Assessment" (CRA, [32]; French version: [33]) questionnaire assesses the caregiver's perceived burden. The questionnaire consists of 24 items measuring 5 subscales: impact on disrupted schedule, financial problems, lack of family support, health problems and impact on self-esteem. Caregivers have to indicate their level of agreement using a 5-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). For each subscale, a score is calculated by taking the average of the items. Higher scores indicate a greater impact (either beneficial or detrimental).

Questionnaires about the patient

Perceived level of empathy: The "Interpersonal Reactivity Index" (IRI, [34]; French version: [35]) has been modified and adapted for the present study. It includes 4 subscales: personal distress, empathic concern, fantasy and perspective taking. Participants are asked to indicate the extent to which each item describes them on a 5-point Likert scale ranging from 0 (does not describe me well) to 4 (describes me very well). In this study, caregivers are instructed to evaluate the empathy abilities of the patient on a 5-point Likert scale ranging from 0 (does not describe the patient well) to 4 (describes the patient very well). Higher scores indicate that the caregiver perceives the patient as highly empathic. The calculation of the score for each subscale is the average of the items that compose it.

Patient's autonomy: The "Patient Competency Rating Scale" (PCRS, [36]; French version; [37]) evaluates the patient's autonomy perceived by the caregiver. Five competency domains are assessed: daily living activities, behavioral and emotional functions, cognitive and physical abilities. The caregiver has to estimate the patient's capacity through 30 items on a 5-point Likert scale ranging from 1 (he/she cannot do it) to 5 (he/she can do it easily). Higher scores indicate greater autonomy. Furthermore, in order to examine the evolution of these abilities (i.e., comparison of the patient's competences before and after the disease), we have added a dimension such that for each item, the caregiver is asked to indicate whether compared to before the disease, (1) it is more difficult for the patient, (2) it has not changed or (3) it is easier for the patient to accomplish the activity. Lower scores indicate a reduced autonomy.

2.4.2 Patients

Demographic information

The caregivers' socio-demographic data will be collected such as age, sex and family situation. Information about socio-educational and socio-economic levels will also be gathered (study level, profession and professional situation).

Clinical data

At inclusion, patients will receive a detailed clinical assessment. The following parameters will be determined: gender, age, the presence of any previous or current cerebral pathology, cerebral trauma or cancer, initial neurological symptoms, complete physical examination, initial tumor location, its grade, period in time since surgery, type of surgery (biopsy, partial resection and full resection), Karnofsky performance score (KPS), type of adjuvant treatment (radiotherapy, type of chemotherapy), and radiological response to adjuvant treatment according to the RANO assessment [38]. The hemineglect will be evaluated by the Line Section Task [39] while their cognitive status will be investigated by the Montreal Cognitive Assessment - MoCA - test [40], the Complex Rey Figure [41], the Trail Making Test [42] and Raven's Colored Progressive Matrices [43].

Their functional status will be measured by the Karnofsky index and their neuropsychiatric status by the Mini-International Neuropsychiatric Interview (MINI, [44]). Finally, their social status will be measured by validated tasks such as faux-pas and mental states decoding [45–48] and by auto-evaluative questionnaires (IRI, [34]; TEIQue,[49] IIP-64, [50]).

Faux-pas Task: In this task, participants have to answer several questions based on 20 verbal scenarios that describe either a faux-pas (i.e., when someone unintentionally offends another person by saying something that should not be said) or a control situation. The scores are based on participants' abilities to detect the faux-pas, to understand it and its lack of intentionality [45].

Mental states decoding: Participants will be instructed to detect the emotional state expressed by a facial expression (disgust, anger, fear, sadness, happiness). These emotions will be expressed at various intensities in order to evaluate whether patients need more perceptual information to recognize the emotion accurately (0%, 30%; 70%, and 100%) [51]. In other tasks, participants will be asked to decode complex affective mental states and to mention to what extent they share the affective state of the person displayed in the picture [47,52]. Finally, a non-verbal task (based on pictures) will be used to examine the ability to detect the intentionality of characters [48].

Questionnaires

The Interpersonal Reactivity Index [34] is a multidimensional 28-item questionnaire of empathy. As previously mentioned, it includes 4 subscales: personal distress, empathic concern, fantasy and perspective taking. Participants are asked to indicate the extent to

which each item describes them on a 5-point Likert scale ranging from 0 (does not describe me well) to 4 (describes me very well).

The Trait Emotional Intelligence Questionnaire – Short form [49] is a 30-item questionnaire that measures trait emotional intelligence. It requires participants to estimate their abilities in identifying, understanding, regulating and using emotions in themselves and others.

The Questionnaire Inventory of Interpersonal Problems - 64 items [50] examines interpersonal difficulties. Participants are asked to indicate on a Likert scale (0: not at all to 4: extremely) the extent to which they encounter problems in terms of Domineering/Controlling, Vindictive/Self-Centered, Cold/Distant, Socially Inhibited, Nonassertive, Overly Accommodating, Self-Sacrificing, and Intrusive/Needy.

Two meetings of 1 hour and 30 minutes each will be held within 2 weeks to reduce concentration and attentional difficulties, especially for grade IV patients. To avoid drop outs, the meetings will be arranged when patients are visiting their doctor at the hospital and when it is not too inconvenient for them in terms of mobility and availability.

2.5. Analyses

Data from patients and their caregivers will be matched. Once the patient exclusion criteria have been checked, statistical analyses will be performed with SPSS software.

The socio-demographic, socio-professional, socio-educational and clinical data will be presented in recapitulative and contingency tables summarizing the descriptive statistics (means, frequencies, percentages, SDs) depending on whether the variables are categorical or continuous.

The main aim of this study is to examine Sherwood et al.'s [5] model for the first time in a comprehensive way by (i) investigating the functional, cognitive and neuropsychiatric deficits of the patients, (ii) integrating the social cognition status of the patients, and (iii) focusing on the caregivers' quality of life as well as their mental health (i.e., burden, anxiety, depression).

In order to test the associations between patients' status and caregivers' quality of life and psychological health, Pearson's correlations will be conducted between these variables. We expect moderate significant correlations between patients' neuropsychiatric and social disorders and caregivers' reports of poor quality of life and mental health. Hierarchical linear regressions will also be conducted to examine the weight of each status (functional,

cognitive, neuropsychiatric, and social) on caregiver's functioning. The lesion volume, the period in time since surgery and the type of surgery (biopsy, partial resection and full resection) will be entered in the first step as control factors. Results may show significant regression weights of the patient's neuropsychiatric and social deficits on the caregiver's quality of life and mental health (i.e., burden, anxiety and depression) beyond the functional and cognitive deficits and the abovementioned controlled factors. Furthermore, in order to examine whether the data fit with the model, path analysis (AMOS) will be used.

The secondary aims of the study are: (iv) to examine the impact of patients' awareness of their social deficits on caregivers (v) to test whether the grade of the gliomas modulates patients' deficits (and their impact on the caregivers' state) and (vi) to evaluate whether caregivers have higher levels of depression and anxiety than healthy controls. To examine whether the patients' awareness of their own social deficits also affects the caregivers' experience, a delta will be calculated between the patients' IRI scores and the IRI scores reported by the caregivers. Results may show significant regression weights of the effect of the delta and the caregiver's scores. We expect that higher delta scores will predict poorer quality of life and psychological health.

Finally, we will examine whether the impact of functional, cognitive, neuropsychiatric and social deficits on caregivers' scores is modulated by the glioma grade. We expect that the patients' impairments may be stronger for high-grade gliomas (grades III and IV) compared to low-grade gliomas (grade II). Furthermore, we expect that caregivers of patients with a more advanced grade of the disease (III, IV) may present higher burden, anxiety and depression levels together with a lower quality of life compared to caregivers of patients with a low-grade glioma (II). Finally, we expect that caregivers will present higher levels of depression and anxiety than healthy subjects. If the data distribution follows a normal distribution and if variance equality is revealed (*p>.10*), mean comparisons will be carried out by ANOVA test for an independent sample; if not, nonparametric tests will be applied.

3. Ethics and dissemination

The study has obtained the approval of the local Faculty ethics committee ("Comité d'éthique en sciences comportementales"; 2016-5-S41 and 2015-3-S37). The study does not involve products mentioned in article L.5311-1 of the French Code of Public Health and does not imply any changes in the medical care received by the patients. The study will begin in April 2017 and will end in 2020. On completion of the study, data will be kept by Lille University for five years before they are destroyed. Study findings will be disseminated through peer-

reviewed journal publications and conference presentations with no reference to a specific individual.

4. Discussion

This comprehensive empirical study aims to contribute to a better understanding of the factors that are hypothesized to influence the quality of life and mental health of the caregivers of adults with primary malignant brain tumors. Specifically, the unique feature of this study is that it will overcome previous shortcomings by examining, in a comprehensive way, the patients' characteristics together with the caregivers' quality of life and mental health. With respect to patients' psychological deficits, previous studies have mainly focused on the effect of gliomas (location, treatments, grade) on cognitive alterations (executive, attention, memory; e.g., [14,15]) and affective disorders such as anxiety, depression or emotional awareness (e.g., [53,54]). However, despite the direct consequences of the tumor on the functional, cognitive and affective deficits of patients, tumors may also lead to social deficits, which have rarely been examined to date. Although they have been rather minimized, social deficits are particularly relevant in cancer patients who frequently report loneliness and social isolation. Therefore, impairments in understanding and inferring the mental states of others (e.g., belief, intention, emotion, perception) can be damaging for patients' social interactions as they are known to worsen social isolation, loneliness, and social support (e.g., [55,56]). Consequently, in addition to the social disruption due to the cancer itself (e.g., stigma, social isolation), we hypothesize that gliomas may impair social cognition abilities that are supposed to protect patients from loneliness [55]. In this research, we aim to overcome several limitations of previous studies [13,19,21,22] that examined the effect of the patient's functional, cognitive, and/or neuropsychiatric status on caregiver symptoms. Specifically, we aim to counteract the lack of investigation of patients' social deficits, the reliance on caregivers' evaluation and/or the non-experimental measures of patients' deficits. The present study is thus innovative because it examines several domains that are frequently affected by gliomas and because it relies on measures of patients' social deficits.

With respect to the caregivers, although they are all exposed to health problems [3], caregivers of adults with primary malignant brain tumors have to deal with both oncological and neurological sequels [5], which may potentiate their difficulties. Specifically, compared to other caregivers, they report greater strain, fatigue, lower well-being and impaired social functioning [6,21]. Despite the specific vulnerability of this population, only a few studies have examined which patients' impairments (e.g., [2,13,18]) or coping strategies [57] particularly affect caregivers.

Therefore, from a theoretical perspective, the study will (i) provide a comprehensive overview of patients' deficits, (ii) test the conceptual model of Sherwood et al. [5] and (iii) assess the social dimension in terms of the impact of gliomas on mental states and emotion processing. It will enable the factors that particularly affect caregivers, and in which way, to be identified and understood. It will also evaluate the influence of location and grade (II, III and IV), with the hypothesis that patients with grade IV gliomas compared to grade II gliomas will present more social deficits, especially if the tumors are located in regions associated with social cognition (e.g., anterior and posterior cingulate cortex, medial prefrontal cortex, temporo-parietal junction). Patients whose cognitive deficits are too serious may not be able to complete all the tasks (e.g., aphasia may prevent patients from completing verbal social tasks such as the faux-pas task). However, in order to avoid any selection bias and to examine still the impact of patients' deficits on caregivers' health, the investigators will adapt the examination by facilitating the administration of some tasks (e.g., reading the questionnaires with the patient) and/or by removing tasks that require too many cognitive abilities.

From a clinical perspective, this study will provide support to medical professionals to focus on the caregivers who are at risk of developing mental and physical health disorders driven by the patients' deficits. Indeed, it will enable professionals to be aware of which patients' deficits have the more damaging impact on caregivers. In the long run, if the data support the hypotheses, we aim to set up future interventions targeting the difficulties encountered by caregivers and the rehabilitation of patients' main deficits. Specifically, while there is only recent support for the positive effect of multidisciplinary rehabilitation on patients' cognition [58], there are some interventions for caregivers of cancer or palliative patients (e.g., [59]) and more recently for caregivers of patients with a glioma [60]. This intervention, which provides psycho-education about the patients' symptoms and aims to improve caregivers' ability to cope with the demands they have to face, has shown positive effects on their feeling of mastery [60]. Improving the quality of life and affective state of caregivers may have a double impact: on the one hand, it can help them to cope better with the patient's disease and, on the other hand, it can lead them to take better care of the patient.

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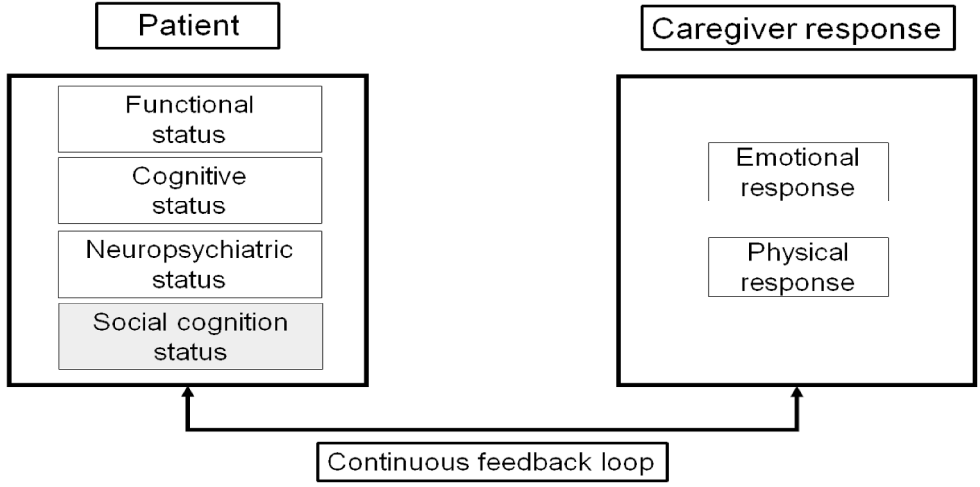
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Figure 1: *Adaptation of Sherwood et al.'s* [5] *model of the links between patients' deficits and caregivers' responses. In addition to the influence of the functional, neuropsychiatric and cognitive status of the patients, their social cognition status has been integrated.*

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