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Caregivers' quality of life and psychological health in response to functional, cognitive, neuropsychiatric and social deficits of patients with brain tumour: 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 with 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 5 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.

Strengths and limitations of this study

► 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 behavioural tests rather than subjective evaluation measures.
► In addition to examining the effect of the tumour grade, the study will also consider its location (ie, region and hemisphere).
► In order to better understand the specifics for caregivers of patients with glioma, 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.

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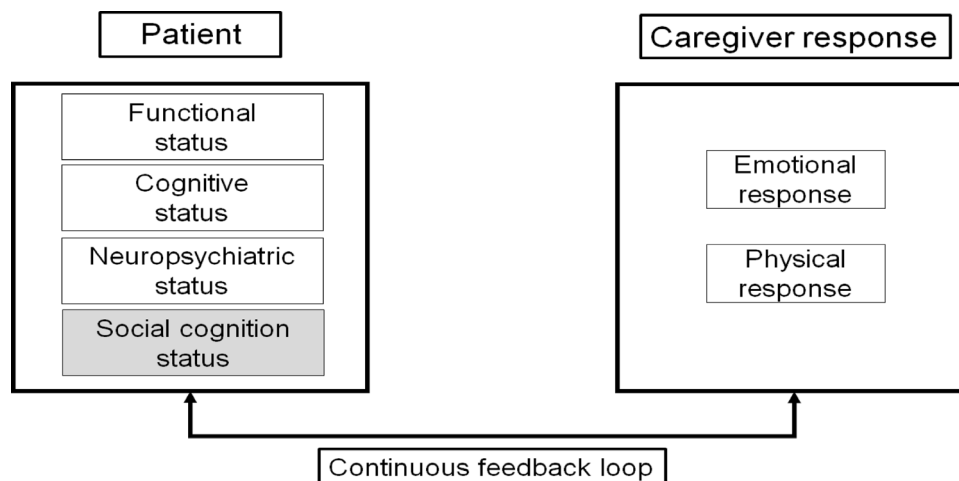
Figure 1 Adaptation of Sherwood *et al*'s[5] model of the links between patients' deficits and caregivers' responses. In addition to the influence of the functional, neuropsychiatric and cognitive status of the patients, their social cognition status has been integrated.

(eg, 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 with 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 (ie, 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 tumour 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 (eg, emotional traits) and external (eg, 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 behavioural and personality changes, which can lead to reduced emotional awareness,[17] impulsiveness and aggressive behaviour, 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 effect,[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 favour 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 (1) investigating the functional, cognitive and neuropsychiatric deficits of patients, (2) integrating the social cognition status of patients and (3) focusing on the caregivers' quality of life as well as their mental health (ie, burden, anxiety, depression). The secondary aims of the study are: (4) to examine the impact of patients' awareness of their social deficits on caregivers, (5) 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).

METHODS/DESIGN
Participants
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.

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 (eg, Parkinson's);
3. Addiction to any harmful substance (eg, alcohol);
4. Major psychiatric disorders (eg, schizophrenia);
5. tumours 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 tumours treated (currently or in the past) with curative intent.

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 with 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.

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 centre usually come from large areas in the region, and may have very different sociocultural backgrounds, which implies considerable sociodemographic and socioprofessional diversity.

One hundred and eighty patients, 180 caregivers and 60 healthy controls will be recruited (ie, 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 patients with primary brain tumour

versus patients with other cancers (*Cohen's d*=0.63; α=0.05; 1-β=0.95).

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 (1) the participants are allowed to quit the study whenever they want to (2) we assure the anonymity of the data and (3) 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 between 1 and 999. The clinical research associate will be in charge of filling in the sociodemographic data for the study. Patients and caregivers will be tested separately and individually at the hospital by the investigator of the study.

MEASURES
Caregiver
Demographic information
The caregivers' sociodemographic data will be collected such as age, sex, family situation and their relationship to the patient. Information about socioeducational and socioeconomic levels will also be gathered (study level, profession and professional situation).

Autoevaluative questionnaires
Anxiety and depression
The '**Hospital Anxiety and Depression Scale**'[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 healthcare, 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**'[32] (French version[33]) questionnaire assesses the caregiver's perceived burden. The questionnaire consists of 24 items measuring five 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 four 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**'[36] (French version[37]) evaluates the patient's autonomy perceived by the caregiver. Five competency domains are assessed: daily living activities, behavioural 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 (ie, 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 with 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.

Patients
Demographic information
The caregivers' sociodemographic data will be collected such as age, sex and family situation. Information about

socioeducational and socioeconomic 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 tumour location, its grade, period in time since surgery, type of surgery (biopsy, partial resection and full resection), Karnofsky Performance Score, type of adjuvant treatment (radiotherapy, type of chemotherapy) and radiological response to adjuvant treatment according to the Response **Assessment** in Neuro-Oncology (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 test,[40] the complex Rey figure,[41] the trail making test[42] and Raven's coloured progressive matrices.[43]

Their functional status will be measured by the Karnofsky Index and their neuropsychiatric status by the Mini-International Neuropsychiatric Interview[44]. Finally, their social status will be measured by validated tasks such as faux pas and mental states decoding[45–48] and by autoevaluative questionnaires (IRI,[34] Trait Emotional Intelligence Questionnaire (TEIQue),[49] Inventory of Interpersonal Problems (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 (ie, 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 recognise 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

Interpersonal Reactivity Index([IRI34]**)** is a multidimensional 28-item questionnaire of empathy. As previously mentioned, it includes four 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 Inventory of Interpersonal Problems-64[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-centred, cold/distant, socially inhibited, non-assertive, overly accommodating, self-sacrificing and intrusive/needy.

Two meetings of 1 hour and 30 min each will be held within 2 weeks to reduce concentration and attentional difficulties, especially for grade IV patients. To avoid dropouts, 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.

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 20 software.

The sociodemographic, socioprofessional, socioeducational and clinical data will be presented in recapitulative and contingency tables summarising 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 (1) investigating the functional, cognitive and neuropsychiatric deficits of the patients, (2) integrating the social cognition status of the patients and (3) focusing on the caregivers' quality of life as well as their mental health (ie, 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 (ie, 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: (4) to examine the impact of patients' awareness of their social deficits on caregivers (5) to test whether the grade of the gliomas modulates patients' deficits (and their impact on the caregivers' state) and (6) 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 with 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 with 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 ($p > 0.10$), mean comparisons will be carried out by analysis of variance for an independent sample; if not, non-parametrical tests will be applied.

DISCUSSION

This comprehensive empirical study aims to contribute to a better understanding of the factors that are hypothesised 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 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[14][15]) and affective disorders such as anxiety, depression or emotional awareness[53][54]. However, despite the direct consequences of the tumour on the functional, cognitive and affective deficits of patients, tumours may also lead to social deficits, which have rarely been examined to date. Although they have been rather minimised, social deficits are particularly relevant in patients with cancer who frequently report loneliness and social isolation. Therefore, impairments in understanding and inferring the mental states of others (eg, belief, intention, emotion, perception) can

be damaging for patients' social interactions as they are known to worsen social isolation, loneliness and social support[55][56]. Consequently, in addition to the social disruption due to the cancer itself (eg, stigma, social isolation), we hypothesise 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 tumours have to deal with both oncological and neurological sequels,[5] which may potentiate their difficulties. Specifically, compared with 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[2][13][18] or coping strategies[57] particularly affect caregivers.

Therefore, from a theoretical perspective, the study will (1) provide a comprehensive overview of patients' deficits, (2) test the conceptual model of Sherwood et al[5] and (3) 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 with 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, temporoparietal junction). Patients whose cognitive deficits are too serious may not be able to complete all the tasks (eg, 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 still examine the impact of patients' deficits on caregivers' health, the investigators will adapt the examination by facilitating the administration of some tasks (eg, 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 patients with cancer or palliative patients[59] and more recently for caregivers of patients with a glioma.[60] This intervention, which provides psychoeducation 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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