PHENOMENOLOGY OF GLIOMA RESECTION IN THE DORSAL MEDIAL FRONTAL CORTEX

Running Title: Phenomenology of glioma resection in the dMFC

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Acknowledgements: This research was sponsored by grants to RLS from the County Council of Västerbotten, the Lion’s Cancer Research Foundation at Umeå University and the Sjöberg Foundation. The authors wish to express their gratitude to Research Nurse Kristin Nyman for help with this study.

Conflicts of interest: The authors have no conflicts of interest to declare.

Data Value Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.
Abstract:

Background: During the latest decades the hypothesis that the subjective experience of free will is determined by preconscious activity in the dominant dorsal medial frontal cortex (dMFC) has repeatedly challenged our commonly held concepts of moral responsibility.

Aims of the study: To investigate whether dMFC activity determines the sense of free will and to investigate effects of resections in this area on Quality of life (QoL).

Methods: A cohort of nine patients affected by transient declines in speech and movement skills after surgery involving the left dMFC answered questions about their postoperative, subjective experiences of volition in relation to symptoms. In eight cases resections were performed as part of glioma surgery and in the ninth case a meningioma adjacent to the dMFC was resected. In addition, a QoL questionnaire was administrated before and after surgery.

Results: None of the patients perceived the transient disabilities related to surgery as associated with a loss or absence of volition. No declines in QoL were detected after surgery. Two QoL domains showed improved function (motor dysfunction and future uncertainty).

Conclusions: The subjective sense of volition is not contingent on dMFC activity. Surgical resections of this area are not typically associated with declines in QoL.

Keyword: Higher cortical functions, Neurooncology, Quality of Life
Background:

In the early 1980s a series of experiments,[1] initiated a debate as to what extent preconscious activity in the dorsal Medial Frontal Cortex (dMFC) is the proximal cause of the subjective experience of conscious free will,[2, 3]. Subsequent studies have confirmed that this area of the brain is involved in self-reflection and action monitoring,[4, 5] and direct cortical stimulation of the dMFC in awake patients often creates an urge or intention to move contralateral parts of the body,[6]. If this means that the feeling of making a conscious decision is actually determined by preconscious dMFC activity, one fascinating implication could be that conscious free will and personal responsibility might be nothing but illusions,[7].

Surgical resections of the dMFC typically causes transient disturbances of the ability to speak, and/or to perform non stimulus driven motor actions in the contralateral part of the body, a phenomenon known as the Supplementary Motor Area (SMA-) Syndrome,[8]. In the present study we addressed the role of the dMFC in the subjective perceptions of volition by questioning patients who experienced postoperative SMA-syndromes about their experiences. In addition, we also evaluated effects of surgery amongst these patients with pre and postoperative measures of patient reported quality of life.

Methods:

Patients:

Eight patients consecutively operated for gliomas in the left dMFC by the last author (RLS) during 2015-2018 (Figure 1) were included. Two of the patients had previous resections done (in 2009 and 2013). These patients as well as another three of the included patients underwent a second extended resection during the study period. The mean age of patients at first surgery was 48.3 years (SD=13.6). Six patients had one or several preoperative epileptic seizures. None of the patients experienced postoperative seizures that we are aware of. One of the patients had a preoperative right arm paresis that improved after surgery. Pathological anatomical diagnosis was glioblastoma WHO IV in one case, oligodendroglioma WHO II in five cases and astrocytoma WHO II in two cases. All patients experienced various symptoms related to the SMA syndrome: One of the patients had a 3h period of akinetic mutism. Two patients had paresis of the right leg.
and arm combined with dysphasia, two had a mild paresis of the right hand and dysphasia, one had mild paresis of the right hand with no dysphasia and two patients had subclinical levels of paresis and dysphasia. All except one recovered from all clinically significant symptoms (one patient had a severe right arm paresis and a minor paresis of the right leg at 3 months post-op). Extents of resections for the glioma patients are described in figure 1.

In addition, we included a ninth patient (female, 64 years), operated on at our clinic in 2019. This patient experienced an unexpected SMA-syndrome after resection of a meningioma over the left dMFC.

**Quality of life**

The Quality-of-Life-Questionnaire (QLQ) C30,[9] and EORTC-BN20,[10] were administered to the patients 1-2 days before first surgery and between 4 weeks and approximately two years after the last surgery. For one patient who had her first surgery before 2015 preoperative QoL data obtained before the re-operation was used. Wilcoxon signed-rank test was used to study changes in pre and postoperative scores.

**Questionnaire regarding sense of volition during the SMA syndrome:**

For 4 patients the following questions were asked in the immediate postoperative period (1-2 days after surgery) during the SMA-syndrome. For 4 patients the questions were asked retrospectively (2-24 month after surgery) after the SMA-syndrome was resolved. For the last patient the questions were asked 1 month after surgery while discrete symptoms remained.

Questions were adjusted to the specific symptoms exhibited by the different patients. If several symptoms were prevalent the questions were asked about each symptom:

1. **During neurological exams as your impaired [speech/right arm motor function/right leg motor function, etc.] was observed, did you feel that your difficulties were caused by a lack of volition? (Yes/No).**

2. **Please grade your effort to comply with the demands to [speak/move your right arm/leg, etc.] during neurological exams on a scale between 1 and 10, where 1**
is no effort and 10 is a 100% maximal effort.

3. Please use the same method to grade your effort to move your healthy [arm/leg] during the neurological exam.

All patients answered all questions. However, one of the patients, who was asked questions retrospectively, remembered her motor dysfunction following surgery but not her dysphasia. Because of this, questions about her dysphasia where neither answered, nor included in further analyses.

Ethical considerations:

All surgeries were performed on clinical neuro-oncological grounds and patients gave informed consent to surgery according to standard clinical procedure. The publication of behavioral data and QoL data on patients was approved by the regional ethics committee at Umeå, Sweden (Dnr: 2016/479-3, Dnr, 2018-402-32M and Dnr, 2016/200-31). In addition, all patients gave informed written consent to participation in the study.

Results:

Sense of volition

All questions about volition were answered the same way by all patients. None of the nine patients reported a subjective experience of a lack of volition as influencing their impairments in motor and speech actions during the SMA syndrome. All patients reported maximal efforts (Mdn = 10) to comply with the demands of the physician during postoperative neurological exams. The same results were found for questions about movement on the non-affected side (Mdn = 10).

Quality of life

As can be seen in table 1 and figure 2, the eight glioma patients showed a significant improvement of mean quality of life regarding Future uncertainty (Pre-surgery Mdn = 45.83, Post-surgery Mdn = 4.17, Z = -2.53, p = 0.011) and Motor dysfunction (Pre-surgery Mdn = 27.78, Post-surgery Mdn = 0, Z = -2.02, p = 0.043) when pre surgical scores were compared with postoperative ones.
Discussion:

There are two main findings of the present study. The first one is that patients, after removal of the dMFC, unanimously reported an intact sense of volition and desire to cooperate during neurological exams even when affected by the SMA-syndrome.

The second is that surgery in this area does not seem to impair postoperative quality of life. On the contrary, despite the relatively small sample size, significant improvements between preoperative and postoperative outcome scores were seen for some of the sub scales.

The outcome variables of the present study were self-reported data. This was necessary because the variables of interest (sense of volition related to SMA-initiated activity and self-reported QoL) are to some extent subjective. From this also follows that just like autobiographical memories,[11,12] these reconstructions can theoretically be subject to influence and manipulation by a host of perceptive cognitive and social factors,[1,2].

Regarding sense of volition, the self-reports were collected during different circumstances. Five patients gave reports while under the influence of the SMA-syndrome, whereas four answered questions retrospectively. Eight of the patients had preoperatively been informed about the risk of an SMA-syndrome but the meningioma patient had not.

Even though perceptual phenomena, memory errors, situational demands or suggestion could all theoretically have influenced these patients’ self-reports in different directions their answers were remarkably consistent. The most parsimonious explanation for this would in our opinion be that the answers convey a subjective experience that is relatively stable across conditions amongst patients experiencing the SMA-syndrome. This interpretation also fits well with our clinical impression of the patients as cooperative and engaged during examinations, as well as with their willingness to comply with demands during examinations of their unaffected side.

Based on this, we understand our results as incompatible with the idea that the subjective sense of free will can be reduced to a secondary effect of preconscious neural activity in the dMFC. Instead our data would fit better with an understanding of the sense of volition as inferred based on multiple forms of conscious and unconscious sensory input,[13]. One source of such input might
be dMFC activity,[6] since this area appears to harbor a system for cognitive control,[14] that may be routinely utilized in order to achieve long term goals.

Finally, when it comes to the question whether surgery in this sensitive area can be motivated, our results are reassuring. Overall, the only significant changes between pre- and post-operative facets of quality of life in patients were for the better. One possible explanation for the improvements observed might be the reduced burden of epilepsy amongst these patients,[15]. Our sample size was admittedly small and the timing at which postoperative quality of life measurements were made varied greatly. Nevertheless, our results seem to clearly support the notion that resections of gliomas in the dominant dMFC should not be hindered by concerns for influencing patient’s quality of life.
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Table 1 | Self-reported Quality of life before and after surgery

|                          | Pre-op | Post-op | Z-value |
|--------------------------|--------|---------|---------|
| **Functional scales†**   |        |         |         |
| Physical function        | 93.33  | 90      | 0.00    |
| Role function            | 41.67  | 66.67   | -1.05   |
| Emotional function       | 50     | 83.33   | -1.56   |
| Cognitive function       | 83.33  | 91.67   | -0.41   |
| Social function          | 41.67  | 83.33   | -1.38   |
| **Symptom scales‡**      |        |         |         |
| Fatigue                  | 16.67  | 27.78   | -1.09   |
| Pain                     | 0      | 0       | -0.45   |
| Nausea and vomiting      | 0      | 0       | 0.00    |
| **Global health status†**|        |         |         |
| Future uncertainty       | 45.83  | 4.17    | -2.53*  |
| Visual disorder          | 0      | 0       | -1.73   |
| Communication deficit    | 11.11  | 0       | -0.95   |
| Motor dysfunction        | 27.78  | 0       | -2.02*  |
**Figure 1** | Size of resection in the 8 glioma patients

| Patient ID | Pat 1 | Pat 2 | Pat 3 | Pat 4 | Pat 5 | Pat 6 | Pat 7 | Pat 8 | M   | Std.  |
|------------|-------|-------|-------|-------|-------|-------|-------|-------|------|-------|
| Colour     |       |       |       |       |       |       |       |       |      |       |
| Posterior border to PCS**¹ | 0     | 4     | 6     | 5     | 6     | -4    | 8     | 0     | 3,13 | 4,05  |
| Anterior border to PCS**² | 49    | 19    | 44    | 48    | 28    | 44    | 33    | 36    | 37,63| 10,57 |
| Medial border to midline³ | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0     | 0,00 | 0,00  |
| Lateral border to midline⁴ | 28    | 11    | 26    | 25    | 11    | 44    | 29    | 20    | 24,25| 10,69 |
| Inferior border to cingulum⁵ | 1     | -1    | 1,0   | -4    | 6     | -3    | -3    | -0,63 | 3,25 |       |

*Yellow cross indicates the precentral sulcus, **Precentral sulcus, ¹Interrater reliability r=.71, ²Interrater reliability r=.996, ³Interrater reliability r=1, ⁴Interrater reliability r=.93, ⁵Interrater reliability r=.81
**Figure 2 | Self-reported Quality of life before and after surgery**

| Domains of Quality of life (QLQ-C30 & BN20) |
|--------------------------------------------|
| Physical function                         |
| Emotional function                        |
| Social function                           |
| Pain†                                     |
| Global health status                      |
| Visual disorder†                          |
| Motor dysfunction†‡                       |
| Role function                              |
| Cognitive function                        |
| Fatigue†                                  |
| Nausea and vomiting†                      |
| Future uncertainty†‡                      |
| Communication deficit†                    |

A higher score represents a higher function and Quality of Life. The score ranges from 0 to 100.
† Score has been inverted for increased legibility
* p = < .05