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REVIEW

The supplementary motor area syndrome: a neurosurgical review

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Abstract

The supplementary motor area (SMA) syndrome is a frequently encountered clinical phenomenon associated with surgery of the dorsomedial prefrontal lobe. The region has a known motor sequencing function and the dominant pre-SMA specifically is associated with more complex language functions; the SMA is furthermore incorporated in the negative motor network. The SMA has a rich interconnectivity with other cortical regions and subcortical structures using the frontal aslant tract (FAT) and the frontostriatal tract (FST). The development of the SMA syndrome is positively correlated with the extent of resection of the SMA region, especially its medial side. This may be due to interruption of the nearby callosal association fibres as the contralateral SMA has a particular important function in brain plasticity after SMA surgery. The syndrome is characterized by a profound decrease in interhemispheric connectivity of the motor network hubs. Clinical improvement is related to increasing connectivity between the contralateral SMA region and the ipsilateral motor hubs. Overall, most patients know a full recovery of the SMA syndrome, however a minority of patients might continue to suffer from mild motor and speech dysfunction. Rarely, no recovery of neurological function after SMA region resection is reported.

Keywords Literature review · SMA syndrome · Glioma surgery

Introduction

The supplementary motor area (SMA) syndrome is a well-known phenomenon after dorsomedial prefrontal lobe surgery. The SMA region is a common hotspot for low-grade glioma (LGG) development and the syndrome is thus most frequent after oncological resections [16]. Although the syndrome has an overall favourable prognosis and most patients make a full recovery, the acute phase after surgery burdens the patient, their families and the neurosurgeon. However the syndrome is widely known by specialists, various aspects, not at least the favourable prognosis, remain enigmatic. This paper therefore aims to review some aspects of the SMA syndrome and will discuss the following points: (1) the anatomy and function of the SMA region; (2) the white matter connectivity of the SMA region; (3) the clinical aspects of the SMA syndrome; (4) the mechanisms of neuroplasticity associated with SMA syndrome remission.

Material and methods

Design

A systematic review of the literature was performed according to the PRISMA statement [45]. The PubMed (1946–2021) and Embase (1972–2021) databases were consulted for data screening and extraction. Only clinical articles, reviews or textbook chapters written in English were considered for inclusion. The last database search was performed on March 28, 2021. In addition, references of included papers were screened for potentially relevant data using the snowball method.

Search strategy

The search strategy was designed to include peer-reviewed papers reporting on the clinical aspects of the supplementary motor area syndrome after medial prefrontal lobe surgery or direct electrical stimulation.

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The search strings for both PubMed and Embase were constructed by the first author. The following MeSH terms were used searching the Medline database: Humans; Brain Neoplasms/surgery; Glioma/surgery; Motor cortex/surgery; Prefrontal Cortex/surgery; Brain Mapping; Electric Stimulation; Neurosurgical Procedures/adverse effects; Postoperative Complications; Recovery of Function/physiology; Speech; Mutism; Speech disorders; Motor Skills Disorders; Movement; Paresis; Sensation; Psychomotor Performance (Appendix).

The following Emtree terms were used searching the Embase database: Human; Neurosurgery; Glioma; Motor Cortex; Electrostimulation; Neurological Complication; Postoperative Complication; Functional Connectivity; Motor Dysfunction; Motor Performance, Paralysis; Supplementary Motor Area Syndrome; Speech Disorder; Speech; Language; Functional Status (Appendix).

After removing duplicates in the PubMed and Embase databases, the selection of eligible references was performed by the first and fourth author. The records were screened based on the article title, followed by the abstract and if needed full text.

Results

The combined search strings yielded 57.053 hits. After removing duplicates, 31.574 hits remained which were screened using the title and if necessary abstract reading. Of these articles, 36 were retained for full-text analysis and 28 were finally included. Half of these 28 included papers were found in both the Medline and Embase databases, seven only in the Medline database and four only in the Embase database. Finally, three papers were found using the snowball method. Eight papers were dismissed due to superfluous or irrelevant content (see Fig. 1).

Discussion

Anatomy and function of the SMA region

The supplementary motor area (SMA) is part of the motor system of the prefrontal cortex [41]. It is located on the dorsomedial aspect of the superior frontal gyrus with the prefrontal sulcus and primary motor cortex (PMC) as the

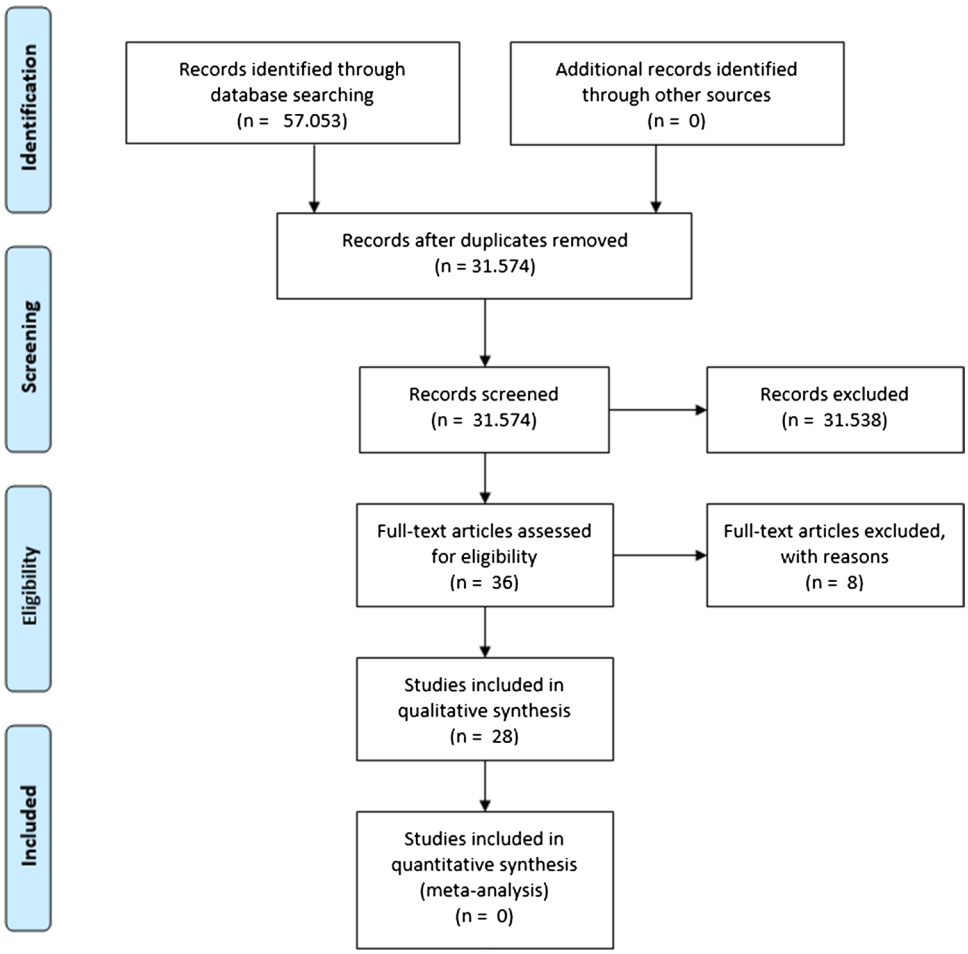

Fig. 1 The PRISMA flow diagram

posterior border. Medially, the SMA is limited by the cingulate sulcus. The rostral and lateral borders of the region are anatomically less well defined. The lateral border of the SMA was located 15 mm from the midline in a meta-analysis published by Mayka et al. based on functional imaging [40]. The superior frontal sulcus might therefore be used as a surgical landmark for the lateral border of the SMA as was suggested earlier by the work of Talairach et al. [56]. The rostral limit of the SMA region is surgically undefined as there are no clear anatomical landmarks available anterior to the prefrontal sulcus. Vorobiev et al. found nevertheless a rostral cytoarchitectonic limit of the SMA region 20 mm anterior of the vertical line transversing the anterior commissure (VCA-line) [62]. These results were later confirmed by Mayka et al. [40].

Historically, Hughlings Jackson was the first in 1858 to conceive the motor system to be organized in various hierarchical levels of control [48]. The primary motor cortex acts as the simple executioner to directly innervate the lower motor neurons located in the anterior grey matter of the brain stem and spinal cord. The rostral prefrontal cortex is at the top of the motor system where the most complex and abstract motor actions are formed. Anatomically and functionally, the SMA region is interlocked between these two neural networks. As such, the SMA complex can be seen as a gateway between the more rostral systems of executive function and the PMC [54].

The SMA region is part of a larger brain network mediating what is called *domain-general sequence processing* in various cognitive functions [11]. In motor function specifically, the SMA determines the particular order in which a motor sequence has to be executed by the lower hierarchical level of the PMC. The sequencing does however not only refer to the exact chain of motor commands, but to its timely execution as well. The former was illustrated by injecting a GABA agonist in the SMA region of monkeys. The animals were perfectly capable of executing simple motor functions, but had impaired execution of more complex sequences of motor actions [53]. Sequence processing is however not unique for the brain motor system and the SMA does provide this function for other cognitive systems too. In language for example, the SMA is involved in determining the exact sequence of letters, syllables and words to construct sentences in spoken and written language [11]. The same is true for music processing, in which the SMA is shown to be active during music listening, generation and improvisation [11]. This illustrates the multitude of applications of the same network function of the SMA region in various cognitive functions of the human brain, in contrast to the more simple *domain-specific* functions of hierarchically lower brain networks such as the PMC.

A second function of the SMA remains more enigmatic and might be related to the negative motor network of the brain [20, 47]. This motor network seems to be responsible for inhibition of motor actions during their execution. Direct electrical stimulation of cortical regions in the negative motor network, so called negative motor areas (NMA), therefore results in speech arrest or arrest of motor action [20, 47]. These NMAs are located in the frontal lobe but might have a less well-defined somatotopy in comparison to the better known positive motor areas [47]. Rech et al. showed nevertheless several clusters of NMAs in the precentral gyrus grouped in face, upper and lower limb regions [47]. Functional connectivity analysis showed marked connectivity with the SMA region [47]. These findings are in line with earlier neuroscientific papers using functional imaging methods. Toma et al. for example showed a marked increase in SMA region activity in preparing and executing voluntary motor relaxation using fMRI [58]. Various studies reported furthermore negative motor actions in the SMA region itself using direct electrical stimulation [20].

The SMA region can be subdivided into different functional subregions with a clear somatotopic organization following a rostrocaudal direction. The SMA region can be divided in a rostral pre-SMA region and a caudal SMA proper using the before mentioned VCA-line [62]. This subdivision does not only have a cytoarchitectonic basis, but functional repercussions as well [27, 30, 62, 65]. The pre-SMA is associated with complex task processing and has shown more complex language-associated functions in the dominant hemisphere [34, 41, 49]. The more caudal SMA proper is linked to motor processing and has a clear somatotopic organization [33]. Fried et al. showed by stimulating grid electrodes placed in the SMA cortex that a lower limb representation at the caudal border and face representation at the rostral end of the SMA proper exists [23]. These findings were later confirmed using functional imaging and astute clinical observation [22, 37, 39, 52].

White matter connectivity of the SMA region

Given the more complex domain-general processing functions of the SMA in multiple functional brain networks, it is not surprising the region has rich white matter connections to different parts of the brain. These connections are mediated by various association, commissural and projection fibres.

Association fibres

Superficial U-fibres connect the SMA region with the PMC, the middle frontal gyrus lateral and the cingulum medial [3, 61]. The most prominent of these arcuate fibres forms

a projection to the hand knob of the precentral gyrus [61]. This may well correspond to the frequently encountered gyral bridges of the precentral sulcus connecting the gyrus with the prefrontal cortex [24]. The superior longitudinal fascicle (SLF I) connects the SMA region with the superior parietal lobule; minor contributions to the inferior fronto-occipital fascicle (IFOF) might depart from the superior frontal gyrus as well [3, 4, 55].

The frontal aslant tract (FAT) connects the pre-SMA and rostral SMA proper to the inferior frontal gyrus and deserves special attention in this review. This white matter bundle projects more specifically to the opercular part of the IFG and runs obliquely to the SLF and IFOF fibres [5, 61]. Functionally, as can be expected from its anatomical relation to the IFG, the FAT is related to speech production [13]. Catani et al. were the first to describe a negative relation between dominant FAT integrity and verbal fluency in patients with primary progressive aphasia [6]. Illustrative was a case study published by Chernoff et al. in which a patient with postoperative damage to the left FAT showed marked reduction in verbal fluency but no semantic or phonemic paraphasias [9]. These results were consistent with a larger series of patients published by Kinoshita et al. in which the distance of the postoperative resection cavity correlated with verbal fluency problems. Interestingly, the authors did not find significant speech problems in patients with non-dominant right-sided lesions and concluded that resection of the non-dominant FAT is probably safe [32]. Intraoperative awake direct stimulation of the dominant FAT evokes speech arrest and stuttering during surgery by inducing a transient disconnection between the SMA region and the IFG [25, 29, 32, 59]. This is in line with the projected connection between the SMA and the earlier mentioned negative motor network [47]. However, direct postoperative problems with verbal fluency should be anticipated after resection of the dominant FAT, a substantial if not full recovery may be expected on the longer term [25, 29, 32, 63]. To conclude, the FAT forms a third major contribution to the speech network apart from the dorsal phonologic and ventral semantic streams [8, 63].

A second white matter tract, the frontostriatal tract (FST) or subcallosal fascicle, connects the pre-SMA to the caudate nucleus of the striatum and is part of the internal and external capsules [3, 32, 61]. Duffau et al. were the first to present results of direct electrical stimulation of the FST during surgery. They found a consistent reduction in spontaneous speech with dysarthria or anarthria [18]. Duffau therefore called it the final common pathway in the language network necessary for motor execution of language [14]. Furthermore, the FST is part of the negative motor network as electrical stimulation could induce negative motor responses [32]. This might be mediated by direct contributions of the NMAs in the precentral gyrus to the FST [47].

Commissural fibres

The SMA region has strong interconnections with the contralateral hemisphere via the corpus callosum. These commissural fibres are mainly located in the rostrum and anterior body of the corpus callosum and run lateral to the cingulum [3, 61]. Baker et al. argue moreover the existence of a crossed FAT fibre bundle consisting of non-homologues fibres connecting the SMA with the contralateral premotor cortex in the middle frontal gyrus [2].

Projection fibres

Finally, an estimated one-tenth to one-third of the fibres within the corticospinal tract originate in the SMA region [21, 41]. The exact role of these pyramidal fibres remains uncertain but various hypotheses were postulated [21]. Experiments in monkeys revealed direct innervation of the anterior grey horn of the medulla by SMA projections; however, the densest SMA projections terminated in the intermediate grey zone thus innervating predominantly inhibitory interneurons [38]. This might reflect the role of the SMA in more complex motor functions by modulating the excitability of spinal motor neurons [38]. As such, the negative motor network might for example mediate its function through stimulation of inhibitory spinal interneurons by the SMA leading to a suppression of lower motor neurons [21].

Clinical aspects of the SMA syndrome

The SMA syndrome often occurs after medial prefrontal lobe surgery. It has a favourable evolution in three stages as was first described by Laplane et al. [36]. In the direct postoperative period, there seems to be a global akinesia in the contralateral hemicorpus with a mild hypotonia and diminished to normal stretch reflexes [21, 33, 36]. If the dominant frontal lobe is violated, a reduction in spontaneous speech (not seldom frank mutism) with normal comprehension may be seen; paraphasia or dysnomia are however absent [33, 36]. Remarkably, Duffau et al. showed the onset of the SMA syndrome may not occur immediately after resection of the SMA region [17]. After a short latency period of some days, a progressive recovery is to be expected. Muscular strength and tonus recover quickly, but a decrease in spontaneous movements of the affected limb wanes more slowly [33, 36]. Spontaneous speech reappears suddenly, although patients may suffer from speech fluency problems during longer periods of time [7, 19, 34, 36]. After weeks to months, a near full recovery is to be expected; a minority of patients might however continue to suffer from mild motor and speech dysfunction. Nakajima et al. found more specifically that the severity of motor paralysis on the seventh postoperative day correlated positively with time to full clinical recovery [42]. Intriguingly, Baker

et al. described two SMA syndrome cases in which no clinical recovery was found on long-term follow-up [2]. Although literature concerning an irreversible SMA syndrome is scant, surgeons should be aware of its rare occurrence.

The incidence of SMA syndrome after dorsomedial prefrontal lobe surgery varies widely in the literature: 23–100% [52]. Interestingly thus, not *all* patients who undergo resection of the SMA region develop neurological deficits in the postoperative period [28, 49, 50]. Various reports have therefore tried to identify presurgical risk factors in the development of SMA syndrome. Overall, the extent of SMA resection plays an important role in the development of (transient) postoperative deficits [64]. Russell et al. found an extent of resection > 90% of the SMA region to be associated with a higher incidence of SMA syndrome development [50]. In particular, resection of the SMA proper, posterior to the VCA-line, is a major risk factor [31]. This was elegantly confirmed and illustrated by Ibe et al. who showed that resection of the SMA proper and left (dominant) pre-SMA is associated with the development of the SMA syndrome (see Fig. 2) [26]. More intriguing, various studies describe an increased risk of SMA syndrome when trespassing the medial part of the SMA and adjacent cingulate gyrus [26, 28, 31, 42]. These findings are in accordance with a series published by Tate et al. in which a frequent morbidity of tumour resection in the middle cingulate gyrus (MCC) was the SMA syndrome due to medial SMA region trespassing but not SMA resection [57]. Damage to this region is however not only related to the risk of SMA syndrome, but implies a more protracted recovery as well (see Fig. 3) [42].

Mechanisms of neuroplasticity associated with SMA syndrome remission

According to the hodotopical paradigm, motor function is not confined to strictly definable cortical regions in the brain, but rather depending on large-scale white matter connections between the PMC, premotor regions, negative motor regions and the parietal lobules [12, 15]. Otten et al. showed major functional connectivity between these various regions using resting-state fMRI in normal subjects [44]. Interestingly, they showed an identical brain network architecture in brain tumour patients with normal motor function, albeit with an increased mean connectivity between the cortical hubs [44]. Brain tumour patients with preoperative motor deficits however had a marked decrease in interhemispheric but preserved intrahemispheric connectivity in comparison to controls [44]. When patients with new postoperative motor deficits were followed in time, a correlation between regain in motor function and increase in average brain connectivity was found [44]. Otten et al. therefore concluded that motor functions return as brain motor networks restore to preoperative conditions by redistribution of network functions to other cortical areas, including the contralateral hemisphere [44].

These findings were confirmed specifically in SMA syndrome patients suffering from postoperative motor deficits by Vassal et al. They found a significant decrease in inter- but not intrahemispheric connectivity after resection of the SMA region for LGG [60]. At 3 months, when the patients had made a full clinical recovery, the authors found an increased interhemispheric connectivity in comparison to the direct postoperative values (see Fig. 4) [60]. Overall, both studies agreed on an inverse correlation of interhemispheric connectivity with preoperative motor deficits and a positive correlation with clinical recovery [44, 60].

The contralateral, healthy SMA region plays a major role in functional restoration of neurologic function [1, 10, 46]. Slow growth of a LGG is associated with brain plasticity allowing resections of historically considered eloquent brain regions. Clinical research showed an increase in contralateral SMA activity on fMRI when a tumour progressively

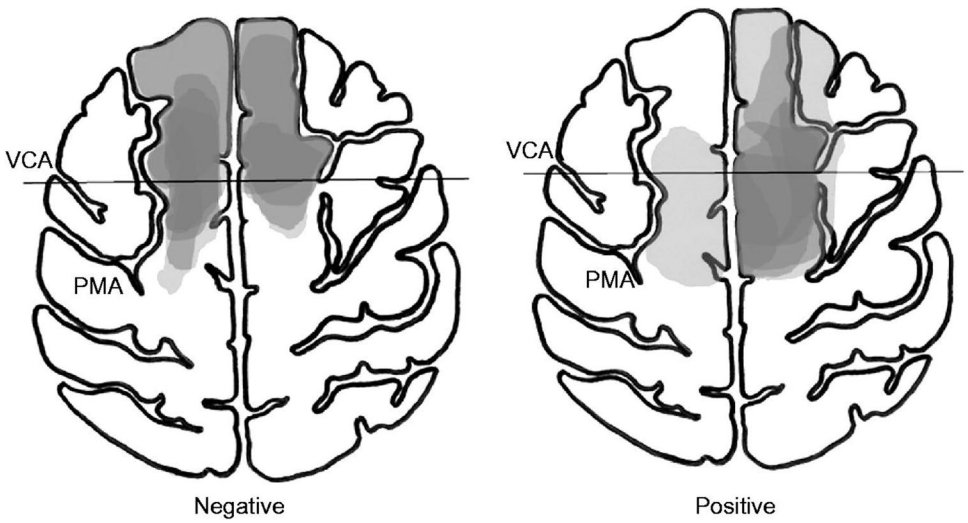

Fig. 2 Schematic representation of tumour resections. The extent of tumour resection is indicated as the shaded area, and transferred to a schematic axial brain section. Negative (left): diagram obtained in patients without postoperative neurological deficits. Positive (right): diagram obtained with postoperative deficits. PMA = primary motor area; VCA = vertical commissure anterior [26]. Reprinted with permission

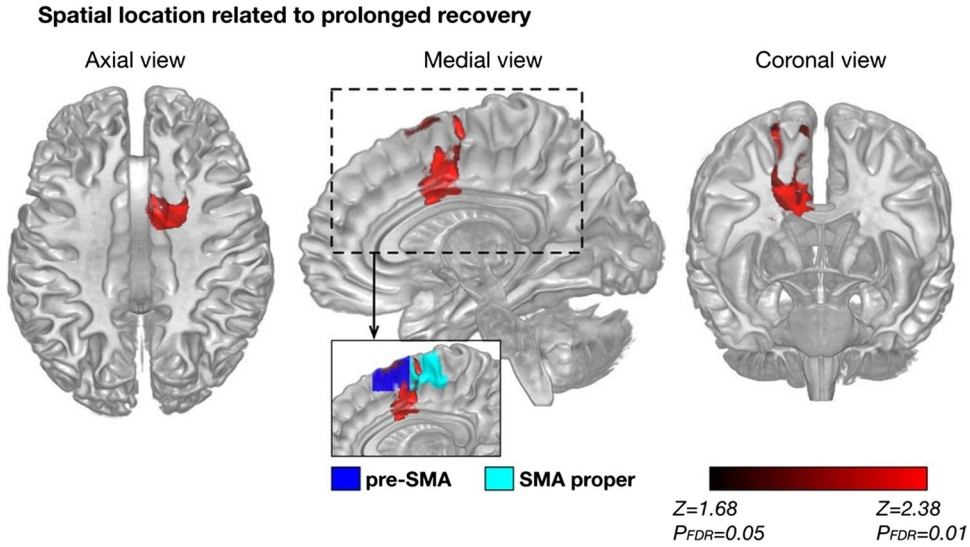

Fig. 3 Factors related to delayed recovery from SMA syndrome. The statistical map from voxel-based lesion-symptom analysis shows only the voxels that were significant with a false discovery rate-controlled threshold (p = 0.05:z = 1.68). The largest significant cluster was located on the cingulate cortex and its deep regions [42]. Reprinted with permission

seized the ipsilateral homologue [35, 51]. In other words, brain plasticity allows compensation of ipsilateral functional loss due to tumour invasion by recruiting the contralateral SMA region using dens interhemispheric connections. When a SMA syndrome eventually does occur postoperatively, these compensatory mechanisms fail to sustain the global motor network, partially because of loss of interhemispheric connectivity due to interruption of the associative callosal fibres. This may explain the above-mentioned observations that especially resection of the medial aspects of the SMA region and cingulum are associated with the development of a motor deficit [26, 31, 42]. The callosal commissural fibres are in fact closely related to the medial SMA region and cingulate gyrus and are probably disconnected when trespassing the region leading to a decrease in interhemispheric connectivity. Baker et al. furthermore argue these callosal fibres might be directly related to the development of a permanent neurological deficit after resection [2]

Interestingly, the preoperative recruitment of the contralateral SMA was associated with an earlier and faster clinical recovery of the SMA syndrome [35]. Furthermore, Oda et al. showed a direct connection between the contralateral SMA and ipsilateral PMC in patients with SMA syndrome using DTI tractography. The strength of this connection was related to a favourable postoperative neurological course [43].

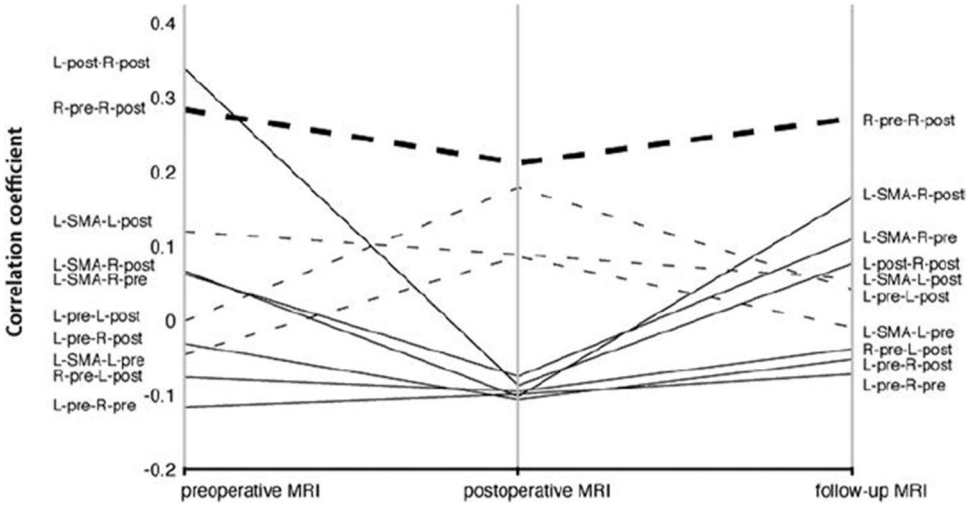

Fig. 4 Longitudinal evolution plot of inter- and intrahemispheric correlations in the sensorimotor network. The time course of all intrahemispheric (dashed lines) and interhemispheric (continuous lines) correlation coefficients within the sensorimotor network are presented. For purposes of this study, right (R) is always the lesional hemisphere, and left (L) the healthy hemisphere. The temporary decreases in interhemispheric correlations between the healthy-side SMA and the contralateral motor areas and between the 2 postcentral regions are statistically significant (Kruskal–Wallis test performed on z-transformed correlation coefficients). post = postcentral gyrus; pre = precentral gyrus [60]. Reprinted with permission

Conclusion

The SMA syndrome is a frequently encountered clinical phenomenon associated with surgery of the dorsomedial prefrontal lobe. The SMA has a rich interconnectivity with other cortical regions and subcortical structures. The development of the SMA syndrome is positively correlated with the extent of resection of the SMA region. Clinical recovery is related to contralateral SMA region mobilization through a dens interhemispheric callosal connectivity. As these fibres appear crucial in the recovery phase, surgical interruption seems the major risk factor for SMA syndrome development and might even be responsible for long-term motor dysfunction. In developing optimal surgical strategies for SMA lesions, it is crucial to know which patients will develop the syndrome and if these deficits will remain permanent or not. Future research should directly address the question of irreversibility as today's literature on the topic is very limited. Current evidence nevertheless points to a key role of the corpus callosum and adjacent white matter tracts underneath the cingulum. Trespassing the region should be done cautiously as development of a profound SMA syndrome with delayed if not incomplete recovery is to be expected. The surgeon hence should count in patient-specific factors such as tumour status when pursuing a full SMA resection, especially on the dominant side. Overall, one should realize SMA surgery can from time to time become a treacherous endeavour as the current scientific literature does not fully elucidate its various pitfalls.

Appendix

Search string used in PubMed:

1. Humans
2. Brain Neoplasms/surgery
3. Glioma/surgery
4. Motor cortex/surgery
5. Prefrontal Cortex/surgery
6. Brain Mapping
7. Electric Stimulation
8. 2 or 3 or 4 or 5 or 6 or 7
9. 1 and 8
10. Neurosurgical Procedures/adverse effects
11. Postoperative Complications
12. Recovery of Function/physiology
13. Speech
14. Speech disorders
15. Mutism
16. Motor Skills Disorders
17. Movement
18. Paresis
19. Sensation
20. Psychomotor Performance.
21. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 9 and 21

Search string used in Embase:

1. Human
2. Neurosurgery
3. Glioma
4. Motor Cortex
5. Electrostimulation
6. 2 or 3 or 4 or 5
7. 1 and 6
8. Neurological Complication
9. Postoperative Complication
10. Functional Connectivity
11. Motor Dysfunction
12. Motor Performance
13. Paralysis
14. Supplementary Motor Area Syndrome
15. Speech Disorder
16. Speech
17. Language
18. Functional Status.
19. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 7 and 19

Author contribution H. Pinson – literature search, writing manuscript.
J. Van Lerbeirghe – writing manuscript, proof reading.
D. Vanhauwaert – writing manuscript, proof reading.
O. Van Damme – literature search.
G. Hallaert – writing manuscript, proof reading.
JP. Kalala – proof reading.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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