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Subcortical language and non-language mapping in awake brain surgery: the use of multimodal tests

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Abstract

Background Awake craniotomy is currently considered the gold standard to maximise the extent of resection and to minimise postoperative deficits in patients with supratentorial tumours near eloquent areas. In addition to direct electrical stimulation (DES) of the cortex, intraoperative subcortical mapping is increasingly used as it optimises the benefit-to-risk ratio by decreasing (permanent) postoperative neurological deficits. However, only little attention has been paid to subcortical mapping procedures and especially the tasks to be used.

Methods In this article, language and non-language testing at the subcortical level is described and discussed by means of three right-handed cases with a glioma in the left hemisphere. To assess subcortical functions, a multimodal test named the Quick Mixed Test was developed (QMT). Pre-, intra- and postoperative test results are described and discussed in detail. **Results** Based on the analysis of these preliminary observations, a number of clinical recommendations for intraoperative

subcortical mapping may be made: (1) the selection of a set of language and non-language tests needs to be tailored according to the functional corticosubcortical regions affected by the tumoral lesion and the patient's characteristics (job/hobby/daily life activities); (2) language and non-language tests should be presented in a multimodal and alternating way during subcortical stimulation since this approach enables screening various functions simultaneously or in a very short period of time and (3) spontaneous speech is a useful adjunct to standardised tests since it most resembles daily life conversation.

Conclusion Administration of multimodal tests during subcortical DES such as the experimental QMT may facilitate identification of eloquent pathways leading to avoidance of permanent neurological impairments.

Keywords Subcortical mapping · Direct electrical stimulation · Awake surgery · Glioma · Multimodal testing · Language mapping · Non-language mapping

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Introduction

Awake surgery with DES (direct electrical stimulation) is generally considered the 'gold standard' to map linguistic functions in patients with gliomas in eloquent regions [10, 12, 13, 21, 29, 44]. Since gliomas are highly invasive tumours that infiltrate the white matter tracts, intraoperative subcortical stimulation next to cortical stimulation is of crucial importance [2, 4, 13, 29, 43]. In addition, DTI (diffusion tensor imaging) is conducted in the preoperative phase to identify subcortical white matter tracts and to guide subcortical mapping with DES. However, DTI and subcortical stimulation are not yet routinely performed [12, 45, 48].

A growing number of studies has shown that the use of subcortical mapping decreases the number of permanent neurological deficits [1, 2, 15, 16, 20, 40]. Trinh et al. [45] found in 214 patients that subcortical injury identified with DES is an independent predictor of immediate and longer term (3 months) postoperative neurological deterioration (e.g. aphasia, hemiplegia) [8, 45]. The lack of recovery at 3 months postoperatively in patients with subcortical lesions could be explained by the limits of white matter plasticity [14]. This underscores the importance of subcortical mapping to preserve subcortical fiber tracts and their function.

Cortical mapping procedures have been extensively described in the literature [3, 12, 13, 29, 43]. A wide range of intraoperative language and non-language tasks has been used, [for reviews see 7, 12]. By contrast, subcortical mapping procedures have received only limited attention. Subcortical areas are usually mapped repeatedly along the pathway during tumour resection by means of similar electrical parameters and language tasks used at the cortical level [1, 20, 43]. Visual confrontational naming is generally applied during subcortical stimulation, but a number of studies show that white matter pathways also subserve a range of other linguistic processes [17, 19, 26–28, 34]. For instance, repetition tasks have been used to identify the arcuate fascicle (AF) [17, 31], reading tasks to identify the inferior longitudinal fascicle (ILF) [7, 28], semantic association tasks to identify the inferior fronto-occipital fascicle (IFOF) [7, 18] and famous face-naming tasks to identify the uncinate fascicle (UF) [34]. Only very few studies have focussed on non-language tasks for subcortical stimulation. A modified picture-naming task has been used to identify the visual pathways [24], a picture recognition task to identify the fornix tracts [5] and a line bisection task to identify the right superior longitudinal fascicle (SLF) [7]. Coello et al. [7] recommended a combined task with picture naming and continuous movement to identify language networks, sensorimotor pathways and attentional processing/working memory at the subcortical level.

Although the importance of subcortical mapping is generally acknowledged, no clear guidelines for subcortical testing exist. We aim to demonstrate the crucial importance of subcortical mapping by means of a multimodal test (QMT) built on a rapid alternation of language and non-language tasks in three right-handed patients with tumoral mass lesions in the left language-dominant hemisphere.

Methods

Patient group

Demographic and tumour characteristics of the three participants of this study are described in Table 1. All patients had presumed low-grade gliomas. As confirmed by anatomopathological examination of tumour specimen, foci

Table 1 Demographic characteristics and tumour- and treatment-related variables in three tumour patients

No.	Gender	Age	Education	EHI, HP	Location	Histological type	Grade*	Extent of resection	Preoperative treatment	Postoperative treatment
1	Male	41	15	+100/Right	Left temporoparietal	Astrocystoma	II–III	Partial	No	- Radiotherapy 60 Gy in 6 weeks; 180 cGy/day - Speech therapy
2	Male	46	14	+100/Right	Left frontotemporal	Astrocystoma	II–III	Partial	No	- Radiotherapy 54 Gy in 6 weeks; 180 cGy/day - Speech therapy
3	Male	53	10	+80/Right	L parieto-occipital	Oligoastrocytoma	II–III	Subtotal	No	- Radiotherapy 59.4 Gy in 6 weeks; 180 cGy/day - Speech therapy
Mean; SD		46.67 6.03	13.00 2.65							

No. Number of case, EHI Edinburgh Handedness Inventory, HP hand preference, SD standard deviation, Grade* according to the WHO classification system [36]

of grade III tumour tissue were found as well. None of the patients included had a sensorimotor impairment, a history of a medical or psychiatric condition known to affect cognitive functioning, severe preoperative cognitive/language disorders, severe hearing loss or a visual disorder. The study was approved by the Ethics Committee of the Free University of Brussels and the AZ Sint-Lucas hospital in Ghent. All patients gave written informed consent.

Neuroimaging and surgical procedure

Localisation of the tumour and extent of tumour resection were determined by means of pre- and postoperative T2-weighted magnetic resonance imaging (MRI). Preoperatively, functional MRI (fMRI) with a verb generation and finger-tapping task and DTI were performed. Postoperatively, anatomopathological analysis of the tumour specimen was conducted. An asleep-awake-asleep procedure with corticosubcortical mapping was performed [13]. Case 1 was operated in 2004, whereas the surgery of cases 2 and 3 took place in 2013.

Pre- and postoperative assessments

In the pre- and postoperative phase (6 weeks, 6 months) extensive neuropsychological investigations were carried out by means of standardised test batteries for language, memory, executive functions, visuoperception and the Dutch Linguistic Protocol (DuLIP) for awake brain surgery (see Table 2 for a description of tasks) [11]. Only a concise language examination was performed in case 1. At that time (2004), the Aachen Aphasia Test (AAT) [23] and Boston Naming Test (BNT) [30] were used. Based on the normative data, the test scores of the patients were transformed into z-values or percentiles to compare the performance of patients and healthy adults. Impairment was defined as a z-score ≥ -2 or a percentile < 2 (Tables 3 and 4) [33]. The intraoperative tests were practised in the preoperative phase. Only the items the patient was able to perform flawlessly in the preoperative phase were selected for intraoperative use.

Intraoperative assessments at the cortical level

In case 1, only counting and naming were used during cortical stimulation since this was the standard procedure in 2004. In the other cases, the selection of intraoperative tasks was tailor made based on the patient's characteristics (job, hobby, needs) and the tumour location. In addition to naming, another language task from the DuLIP (see the selection procedure in [11]) or a non-language task (e.g. calculation, line bisection) was selected if relevant.

Intraoperative assessments at the subcortical level

At the subcortical level, naming was continuously performed in case 1 whereas multimodal testing (i.e. assessing different modalities) via the Quick Mixed Test (QMT) and spontaneous speech was performed in cases 2 and 3.

The Quick Mixed Test (QMT)

The goal of the experimental QMT (unpublished) is to simultaneously and rapidly screen various functions at the subcortical level. A small test battery including language and/or non-language tasks was composed taking into account the functional neuroanatomy of the subcortical structures and their pathways as well as the patient's daily life activities (see case reports 2 and 3). The language tasks were selected from the standardised DuLIP tests (see the selection procedure in [11]). Non-language tasks were selected from the glioma literature (e.g. the line bisection task for right SLF [7]). Instead of performing the selected tasks consecutively (e.g. 25-item repetition, 25-item naming, 25-item calculation, 25-item line bisection) the items of the different tasks were mixed and displayed in an alternating way (Figs. 1 and 2). The subcortical areas of interest are repeatedly stimulated while performing the different tasks from the QMT. Since different functions are measured in a rapid and alternate manner, the cognitive ability to switch (executive functions/attention/concept shifting) is also examined [39]. The stimuli are presented every 4 s (accompanied by a beep) in a keynote presentation on a touch-screen device. As such motor function of the hand (by pointing and touching the screen) is assessed in parallel and simultaneously to language (e.g. during semantic picture out task = touching and naming the object that does not fit).

Spontaneous speech

Spontaneous speech production was also assessed during subcortical tumour resection. The examiner asks the patient to talk freely about the autobiographic topics (such as jobs, hobbies, family) selected during the preoperative phase. Assessment of spontaneous speech during the awake procedure is highly relevant since it not only resembles conversational speech in daily life but also implies the integration of different language processes (e.g. phonology, semantics and syntax) [35]. In addition, a conversation based on daily topics makes the patient feel at ease during the awake setting. To avoid postoperative speech deficits assessment of spontaneous speech appears to be essential especially if the lesion involves the supplementary motor area (SMA) [41, 42].

Table 2 Neuropsychological test protocol

Test	Cognitive abilities and description of task
Language	
Subtests of Aachen Aphasia Test	(AAT) [23]
Token test	Language comprehension, pointing to and manipulating geometric forms on verbal commands
Repetition	Repetition of phonemes, words and sentences
Naming	Word finding: naming objects, colours, situations
Reading	Reading aloud words and sentences
Language comprehension	Written and spoken comprehension of words and sentences, indicating the right picture
Boston Naming Test (BNT) [30]	Naming objects
Dutch Linguistic Intraoperative Protocol	(DuLIP) [11]
Phonological fluency	Flexibility of verbal phonological thought, producing words with a given letter (D, A, T) (1 min)
Semantic fluency	Flexibility of verbal semantic thought, producing words of a given category (e.g. animals) (1 min)
Verb fluency	Flexibility of verbal grammatical thought, producing verbs
Object naming (ON)	Word finding: naming objects (different frequency, imageability)
Action naming (AN)	Word finding, grammar: naming actions (different frequency, imageability)
Repetition	Repetition of words and sentences
Phonological odd word out	Phonological awareness: read aloud the word (out of 4 words) that does not fit phonologically
Semantic odd word out	Semantic judgment: read aloud the word (out of 4 words) that does not fit semantically
Semantic odd picture out	Semantic judgement and naming: name the object (out of 3 pictures) that does not fit semantically
Semantic association	Lexical-semantic processing: add a semantically related word to a list of 2 semantically related nouns
Semantic sentence completion	Reading, language dynamics: read the sentence out loud and complete in a meaningful way
Verb generation	Semantic association skills, grammar: produce verbs that are semantically related with the noun
Memory	
Digit span forward + backward [46]	Verbal learning of digits: repeat the list of digits forward; repeat the list of digits backwards
15-word test [47] (15 WT)	Verbal learning of words
Immediate	Immediate recall: learning a list of 15 words, 5 immediate recall
Recall	Delayed recall: learning a list of 15 words, 1 delayed recall
Recognition	Delayed recognition: learning a list of 15 words, 1 delayed recognition out of 30 words
Attention and executive functions	
Trailmaking Test A (TMTA) [25]	Visuomotor speed, attention: connecting numbers placed randomly in ascending order (timed)
Trailmaking Test B (TMTB)	Idem A + mental flexibility, divided attention: connecting alternating numbers and letters (timed)
Stroop I (SI) [25]	Mental speed, selective attention: reading colour words
Stroop II (S2)	Mental speed, selective attention: naming colours
Stroop III (SIII)	Mental speed, selective attention: naming colours of printed words denoting another colour
Visuoperceptive functions	
Subtests of RBANS [37]	Repeatable battery for the assessment of neuropsychological status
Line orientation	Visuoperceptual skills: orienting different angles using a reference figure with different oriented lines
Figure Copy	Visuoconstructive skills, graphomotor planning: copying a complex figure by drawing

Results

Case 1: no multimodal testing at the subcortical level

A 41-year-old right-handed male was admitted to hospital because of severe headaches associated with numbness of the right arm and leg. He had an educational level of 15 years and worked as headmaster of a primary school. A computed tomography (CT) scan of the brain revealed a tumour in the left posterior temporal region extending to the parietal lobe

(Fig. 3). Preoperative fMRI (during verb generation) showed activations in the left superior and middle temporal gyrus and in the inferior and middle frontal gyrus located at about 1 cm distance from the tumour borders. Preoperative language testing showed anomia for low frequency words (AAT naming test; $z=-1.70$; BNT naming test; $z=-1.87$). Erroneous answers included anomias and phonemic paraphasias but most commonly semantic paraphasias (Table 3).

Counting and naming (BNT) were used during cortical stimulation. Naming (BNT) and reading aloud (AAT) were

Fig. 1 Example of the Quick Mixed Test. Quick Mixed Test (QMT) consisting of four different tasks: repetition, object naming, calculation, line bisection

selected for subcortical stimulation (Table 4). Cortical stimulation of the left inferior frontal gyrus and the superior temporal gyrus induced speech arrests. During subcortical stimulation object naming did not deteriorate. However, spontaneous conversation was characterised by auditory comprehension deficits. The patient was not able to follow simple instructions such as “close your eyes” or “stick out your tongue”. Subcortical resection was therefore interrupted at the level of the ventricle.

Postoperative MRI of the brain (no images available) showed partial resection of the tumour in the posterior temporal area. Antomopathological analysis of the tumour specimen revealed an astrocytoma grade II with foci of grade III for which radiotherapy (60 Gy in 6 weeks; 180 cGy/day) was started (2 months postsurgery). After surgery, Wernicke’s aphasia was found consisting of fluent and empty speech with semantic paraphasias and comprehension deficits. Speech therapy was started (until 2 years postsurgery). Six weeks postsurgery defective results were found for the following subtests of the AAT: language comprehension ($z=-4.54$), token test ($z=-11.53$), naming ($z=-3.96$) and repetition ($z=-7.77$). Comprehension and repetition were more difficult for sentences than for words. Language assessments at 6 months postsurgery disclosed an improvement but the AAT subtest results were still abnormal (naming: $z=-3.48$; comprehension: $z=-2.29$; token: $z=-4.63$; repetition: $z=-4.68$) (Table 3). A residual moderate fluent aphasic disorder persisted at 1 year postsurgery and the patient was not able to work again.

Case 2: multimodal language testing in the language-dominant hemisphere

A 46-year-old right-handed computer scientist and teacher with an educational level of 14 years was admitted to hospital because of a generalised seizure. MRI of the brain disclosed a tumoral lesion in the left fronto-insulo-temporal area (Fig. 4a). DTI showed that the inferior frontal occipital fascicle (IFOF) was located close to the tumour. Preoperative fMRI (during verb generation) showed left hemisphere language dominance with activations including the inferior and middle frontal

Fig. 2 Slideshow of the Quick Mixed Test. Repetition of the word *crimineel* (criminal). Object naming: Dit is *een konijn* = This is a rabbit; calculation task (adding 2 and 11); line bisection task: point to the middle of the line; repetition of a sentence “*Ik ga naar de dokter*” (I

will go to the doctor). Object naming: Dit is *een bed* = This is a bed; calculation task (adding 3 and 8); line bisection task: point to the middle of the line

Fig. 3 Preoperative CT images of case 1. Preoperative CT scan images showing a tumoral lesion in the left temporal region surrounded by oedema and causing a midline shift to the right (a–b)

gyrus (expressive speech areas) and the superior and middle temporal gyrus (receptive speech areas). In the preoperative phase language testing disclosed an isolated deficit for verb fluency (perc <2). Cognitive testing revealed impaired memory (15-word test; immediate memory: $z = -2.80$ and recall: $z = -2.90$) (Table 5).

Based on the tumour location and the patient characteristics (preoperative cognitive level, job as a teacher requiring good language skills), a battery of linguistic tests from DuLIP was composed. Object naming and action naming (from DuLIP) were used during cortical stimulation. The following DuLIP language tasks were selected and embedded in a QMT for subcortical DES: verb generation and action naming (frontal areas); object naming, semantic picture out and semantic sentence completion (IFOF, temporal areas) (Table 4). During resection the QMT was alternated with spontaneous speech production. Disruption of motor speech was induced by DES of the precentral gyrus (speech arrest/dysarthria while naming) but not during stimulation of the inferior frontal gyrus (Broca's area). Disruption of receptive speech (delayed word retrieval during naming) followed DES of the superior and medial temporal gyrus. These findings contrast

with preoperative fMRI findings demonstrating activation of the inferior frontal gyrus during verb generation. During subcortical stimulation of the IFOF, semantic deficits were identified, consisting of comprehension problems for the semantic picture out task and semantic paraphasias during picture naming. As a consequence the resection was interrupted and a partial resection (more temporal than frontal) was performed as demonstrated on the postoperative MRI (Fig. 4b).

Postoperative anatomopathological analysis indicated grade II astrocytoma with grade III foci and radiotherapy was started at 2 months postsurgery (54 Gy in 6 weeks; 180 cGy/day). In the immediate postoperative phase, the patient presented with comprehension problems for complex instructions and delayed word retrieval for low frequency words (delayed answers during naming). Speech therapy was started (until 6 months postsurgery). Six weeks after surgery deviant scores were found for verb fluency, which is consistent with the findings in the preoperative phase (perc <2) and for the semantic odd word out task (perc <2). Memory problems had resolved. After 6 months only the verb fluency impairments persisted as in the preoperative phase (perc <2) (Table 5). The patient was able to successfully return to work again.

Table 3 Pre- and postoperative linguistic results for case 1

Tests	Case 1: raw scores (z-scores)		
	Preoperative results	Postoperative results (6 weeks)	Postoperative results (6 months)
Boston Naming Test	49 (−1.87)	43 (−3.74)*	45 (−3.12)*
Aachen Aphasia Test			
Token test	43 (−1.72)	16 (−11.53)*	35 (−4.63)*
Repetition	149 (2.54)	129 (−7.77)*	135 (−4.68)*
Naming	93 (−1.70)	76 (−3.96)*	80 (−3.48)*
Language comprehension	100 (−0.83)	62 (−4.54)*	85 (−2.29)*
Reading	30 (0.54)	28 (−0.49)	30 (0.54)

*Impaired result ($z\text{-score} \geq -2$)

Table 4 Selection of intraoperative tasks per case study

Case	Location MRI	Language dominance fMRI	Location DTI	Selection of intraoperative language and non-language tests
1	Left temporo-parietal	Left dominance	/	- Cortical: counting, naming* - Subcortical: naming, spontaneous speech*
2	Left fronto-temporal	Left dominance	Left IFOF	- Cortical: naming* - Subcortical: QMT > verb generation, naming*, semantic picture out*, semantic sentence completion
3	Left parieto-occipital	Bilateral dominance	Left AF, left SLF	- Cortical: naming*, calculation - Subcortical: QMT > repetition, semantic sentence completion*, calculation*, line bisection

UF Uncinate fascicle, AF arcuate fascicle, SLF superior longitudinal fascicle, *impaired during direct electrical stimulation

Case 3: multimodal language and non-language testing in the language-dominant hemisphere

A 53-year-old right-handed quality controller with an educational level of 10 years complained of progressive visual problems and memory disturbances. MRI of the brain revealed a left parietal tumour adjacent to the occipital lobe (Fig. 5a). DTI showed involvement of the AF and SLF. Preoperative fMRI (during verb generation) revealed activations in Broca's and Wernicke's area of both hemispheres. Concise preoperative cognitive testing yielded normal results (Table 5).

Not only the tumour location but also the patient's job was taken into account for the selection of intraoperative tasks. As a quality controller he had to check and count rails, requiring good visuospatial and calculation functions. In addition to the language tasks a line bisection task and calculation task were added. Naming (DuLIP) and calculation (experimental addition task) were assessed during cortical stimulation of parietal regions. The subcortical QMT consisted of a repetition task from DuLIP for AF and SLF testing, a semantic sentence completion task from DuLIP and a calculation task (experimental addition) for parietal regions, and a line bisection task

for parieto-occipital areas [38] (Table 4). Speech arrests were triggered after stimulation of the supramarginal gyrus. Anomia and delayed word retrieval were respectively found following stimulation of the angular gyrus and the postcentral gyrus. No calculation problems were found stimulating the angular gyrus. During subcortical stimulation of deeper parietal regions comprehensive reading (in the semantic sentence completion task) was slightly delayed and calculation problems (in addition task) arose. Consequently, the resection was interrupted.

Subtotal resection of the tumour is demonstrated on postoperative MRI (Fig. 5b). Antomopathological analysis of the tumour specimen revealed a grade II-III oligoastrocytoma and at 7 weeks postsurgery radiotherapy was started (59.4 Gy in 6 weeks; 180 cGy/day). In the acute postoperative phase the patient presented with slightly delayed comprehensive reading and calculation problems. These impairments resolved after 1 week. Speech therapy was started (until 6 months postsurgery). Language assessments at 6 weeks revealed distorted semantic fluency ($z=-2.43$). Cognitive testing showed defective verbal memory (immediate memory: $z=-2.00$ and recall: $z=-2.60$) and slow speed (Stroop I; $z=-2.70$). At 6 months postsurgery, remission of fluency problems was observed. Memory function

Fig. 4 Pre- and postoperative MRI images of case 2. **a** Preoperative MRI T2-weighted images disclosing a tumour in the left temporal area extending to the frontal and anterior insular region. **b** Postoperative MRI T2-weighted image showing the resection cavity in the left frontal area and tumour residue in the left insular lobe

Table 5 Pre- and postoperative neuropsychological results for cases 2 and 3

Tests	Case 2: raw scores (z-scores or P-scores)			Case 3: raw scores (z-scores or P-scores)		
	Preoperative	Postop 1	Postop 2	Preoperative	Postop 1	Postop 2
AAT						
Token test	49 (0.47)	48 (0.10)	49 (0.47)	48(0.10)	46 (−0.63)	48 (0.10)
DuLIP						
Phonological fluency	37(−0.10)	47 (1.20)	44 (0.60)	22(−1.10)	29 (−0.50)	27 (−0.70)
Semantic fluency	45(−0.28)	35(−1.15)	41(−0.63)	26(−1.65)	16 (−2.43)*	23 (−1.92)
Verb fluency	12<P 2*	18<P 2*	17<P 2*	11<P 7°	11<P 7°	12>P 7
Object naming	98>P 7	91<P 2	97>P 7	97>P 7	98>P 7	100>P 7
Action naming	56>P 7	56>P 7	57>P 7	57>P 7	58>P 7	59>P 7
Repetition	25>P 7	25>P 7	25>P 7	25>P 7	25>P 7	25>P 7
Semantic odd word out	24=P 7°	23=P 2*	25>P 7	25>P 7	21=P 7°	21=P 7°
Semantic odd picture out	25>P 7	24=P 2, 7°	24=P 2,7°	25>P 7	23<P 7°	25>P 7
Semantic association	22>P 7	21>P 7	22>P 7	23>P 7	17<P 7°	18<P 7°
Semantic sentence completion	50>P 7	49>P 7	50>P 7	49>P 7	46>P 7	49>P 7
Verb generation	49>P 7	49>P 7	50>P 7	48>P 7	46>P 7	48>P 7
15-word test						
Imprinting	28(−2.80)*	50(0.10)	49(0)	38(−1.00)	30 (−2.00)*	27 (−2.40)*
Recall	2(−2.90)*	10 (0.10)	10(0.10)	5(−1.50)	2 (−2.60)*	5 (−1.50)
Recognition	27	30	28	25	29	26
Digit span forward, backward	10(−1.33)	14(−0.33)	10(−1.33)	9 (−1.67)	12 (−1.00)	10 (−1.33)
Trailmaking test						
TMTA	30 (0.10)	25(0.70)	50(−1.60)	37 (0)	65 (−1.90)	47 (−0.80)
TMTB	49 (1.10)	64(0.30)	70(0)	123 (−1.10)	150 (−1.70)	202 (−2.50)*
Stroop test						
Stroop I	40 (0.10)	43(−0.40)	36(0.80)	57 (−1.70)	72 (−2.70)*	58 (−1.70)
Stroop II	40 (2.30)	43(−0.40)	41(2.10)	70 (−1.10)	83 (−1.80)	70 (−1.00)
Stroop III	85 (0.20)	81(0.50)	41(2.10)	128 (−1.20)	163 (−1.90)	150 (−1.70)
RBANS Visuosperception						
	(1.40)	(1.40)	(1.07)	(0.60)	(1.73)	(1.73)
Line orientation	19	19	18	17	20	20
Figure copy	20	20	20	20	20	20

Postop 1 6 weeks postsurgery, Postop 2 6 months postsurgery, Z-scores z-scores, P-scores percentile scores, AAT Aachen Aphasia Test, DuLIP Dutch Linguistic Intraoperative Protocol, TMT trailmaking test, RBANS repeatable battery for the assessment of neurological status, *impaired result (z-score ≥ -2 or percentile < 2)

Fig. 5 Pre- and postoperative MRI images of case 3. **a** Preoperative MRI T2-weighted image revealing a tumoral mass lesion in the left posterior parietal region. **b** Postoperative MRI T2-weighted image showing a tissue defect in the left posterior parietal area after tumour resection

improved but verbal immediate memory of words ($z=-2.40$) was still defective. Executive functioning was slightly impaired only for TMT version B ($z=-2.50$) (Table 5). Although the patient wanted to return to work, the management proposed that the patient should retire.

Discussion

Subcortical DES and DTI are promising techniques to reliably identify and preserve subcortical pathways in order to avoid permanent neurological damage after surgery [45, 48]. However, detailed information about appropriate and sensitive testing during subcortical mapping is scarce [7]. Therefore, the clinical use of the multimodal QMT in the (left) language-dominant hemisphere is illustrated in this article accompanied by some practical recommendations to facilitate subcortical mapping and testing.

Since there might be a trade-off between the extent of resection (EOR) and function preservation, a first recommendation is to carefully make a tailored set of subcortical tasks taking into account tumour characteristics (location, anatomofunctional analysis) as well as the patient's characteristics (jobs, hobby). Professionally active patients (as our cases) who intend to resume normal professional activities after the operation have a different individual onco-functional balance than older, retired patients [7, 22]. Discussing the possible postoperative deficits in relation to the EOR with the neurosurgical team and the patient and his/her family is of crucial importance. The selection of intraoperative tasks based on the tumour location is a(nother) complex procedure. According to the localisationist's view, specific tasks should be used for specific cortical/subcortical structures [6, 7, 11]. However, this perspective has been replaced by a hodotopical view, i.e. large-scale parallel, distributed cortico-subcortical networks subserve different functions in which brain plasticity mechanisms play an important role [7, 14]. Functions might be relocated and areas/pathways may be dispensable [8, 14]. Nevertheless, the plastic potential of the subcortical pathways is much more limited than that of the cortical areas since the white matter connectivity seems essential for network redistribution [14]. Studies showed that the functional repercussions of damage to the UF [19], the middle longitudinal fascicle (MLF) [9] and part of the ILF [28] can be compensated. By contrast, the structural integrity of the SLF, IFOF, CST and subcallosal fascicle needs to be preserved to prevent permanent functional neurological damage [2, 7, 32, 45]. Therefore, the functional role of these subcortical pathways needs to be assessed with appropriate tasks [11].

Because of these aforementioned dynamic networks connecting several regions with different (possibly relocated) functions, a multimodal approach for subcortical stimulation

and resection should be used (second recommendation). In addition to parallel testing, as suggested by Coello et al. [7], we propose performing an alternating test procedure with QMT for brain tumours in the (left) language-dominant hemisphere. Since language in the brain is subserved by a complex network single language tasks (such as naming) are not sufficient to reliably identify the possible range of functions of a particular brain region within the language network. The use of the QMT has several advantages. First, the QMT enables screening various language and non-language functions (instead of one) simultaneously (e.g. movement and naming in parallel) or in a short period of time (by alternating the tasks) as demonstrated in cases 2 and 3. In addition, task switching requires high-order cognitive functions (e.g. attention, working memory, executive function) [39] and can be monitored as well by the QMT. Second, as demonstrated in the case descriptions, a multimodal test such as the QMT is more sensitive than a single task approach based on counting or visual naming only. Case report 1 showed a false-negative result in the naming task during subcortical stimulation whereas positive results were obtained in case 2 and 3 using the QMT during subcortical mapping. As a consequence, subcortical pathways/structures were preserved in cases 2 and 3, avoiding permanent postoperative deficits. In agreement with the observations of Duffau [13] and Trinh et al. [45] transient postoperative impairments were found. By contrast, in case 1 a single language task was not able to identify the subcortical pathways. In this case, resection likely caused disruption of a crucial language tract (i.e. IFOF) resulting in longer term (1 year postsurgery) language deficits (Table 3). Therefore, visual naming tasks do not seem sensitive enough during subcortical stimulation of temporal regions. Moreover, the switching between different linguistic tasks (naming, reading aloud) was not fast enough to detect (language) deficits during subcortical stimulation. Third, the QMT can be used for various tumour locations since the selection of tasks can be adapted (see case reports).

The use of spontaneous speech next to multimodal tests is recommended during subcortical stimulation. Spontaneous speech allows testing of an integration of all language modalities (phonology, semantics, syntax, prosody), but also pragmatics and other cognitive functions (e.g. attention, working memory). It is the most natural form of speech in daily life and may be more natural to the patient. In addition, Satoer et al. [42] observed spontaneous speech deficits before and after surgery. No correlation was found between distorted spontaneous speech and other language tasks, underlining the additional value of spontaneous speech analyses. Intraoperative speech monitoring in case 1 confirmed these findings, as auditory comprehension deficits became evident during conversational speech. Spontaneous speech during tumoral lesion

resection in the SMA regions might be very helpful to evaluate language dynamics [41]. However, it is difficult to quantify spontaneous speech during surgery. Moreover, the patients might compensate for language problems (i.e. word-finding problems) in spontaneous speech because of strategic language behaviour. Therefore, we suggest alternating the QMT with spontaneous speech during subcortical stimulation and resection.

Limitations

The complexity of the QMT (over single tasks) has some disadvantages as well. First, QMT may be more demanding for the patient, which may induce false-positive results. The task in which the patient shows a deficit should be consecutively administered in isolation to control for an effect of fatigue. Awake sessions of more than 2 h should be avoided. Second, multimodal tasks require more cognitive effort (working memory, attention, executive functioning). The QMT is therefore only suited for patients with good preoperative cognitive performances. However, due to the typically slow growth of low-grade gliomas (i.e. 4 mm per year) allowing neural reorganisation (preoperative plasticity) [14], often no severe cognitive deficits but subtle impairments are noted when formally investigated by neuropsychological tests. Obviously, the QMT should be practised in the preoperative phase before use during an operation. Third, another limitation of presenting tasks in an alternative way is that a sensitive task is not used at the right moment and that the false-negative result induces a functional impairment. In order to avoid this risk, subcortical stimulation should be conducted during each subtest of the QMT in a certain area of interest. If impairments are found on a specific subtest, further examination should be conducted by administering the test in isolation. No tool exists that measures all relevant functions in parallel. Therefore, the QMT seems to be a valuable attempt to enable assessment of a limited number of functions in a rapid alternating way with a parallel response mode (e.g. motor and language by touching the screen).

Finally, the results of this exploratory study need to be carefully interpreted since only a limited number of cases was studied. Moreover, the first patient was operated on 8 years before the others. The worse outcome of case 1 is probably due to limited subcortical mapping and testing but might also be influenced by the fact that the DES technique in 2004 was not as developed as today. The positive influence of speech therapy on language recovery in patients 1, 2 and 3 is hard to define as no detailed information was available concerning the exact therapy programme and/or the therapy intensity.

Future directions

Pre-, intra- and postoperative data of large patient groups are needed to allow sound conclusions to be made about subcortical testing, mapping and outcome. In order to identify risk factors and to monitor rehabilitation, extensive neurocognitive assessments and a long-term follow-up of the patients are important to evaluate transient and permanent deficits as well as the impact on quality of life. To study the exact benefits of subcortical multimodal testing the outcome of a group of patients assessed by a multimodal approach has to be compared with the outcome of a consecutive single-task design. However, this issue might raise ethical concerns since a strong clinical impression exists that multimodal mapping enables safer resections.

Conclusion

Detailed information with regard to subcortical testing during awake neurosurgical interventions does not exist. The case descriptions in the current study, however, seem to show that intraoperative subcortical testing might be mandatory to guarantee a functionally beneficial postoperative outcome. The use of a tailored set of tasks taking into account the tumour location and patient's needs is recommended. We suggest screening various functions in a multimodal and alternating way using the QMT and spontaneous speech production. In addition, this kind of subcortical testing enables identifying subcortical structures and pathways and facilitates safe resection with preservation of function, an ultimate outcome measure in glioma patients to maintain quality of life.

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Conflicts of interest None.

Integrity of research and reporting This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The patient gave informed consent prior to the inclusion in the study.

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