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Published in:
Brain and Language

DOI:
[10.1016/j.bandl.2014.10.011](https://doi.org/10.1016/j.bandl.2014.10.011)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

De Witte, E., Satoer, D., Robert, E., Colle, H., Verheyen, S., Visch-Brink, E., & Mariën, P. (2015). The Dutch Linguistic Intraoperative Protocol: A valid linguistic approach to awake brain surgery. *Brain and Language*, 140, 35–48. <https://doi.org/10.1016/j.bandl.2014.10.011>

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The Dutch Linguistic Intraoperative Protocol: A valid linguistic approach to awake brain surgery

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ARTICLE INFO

Article history:

Accepted 25 October 2014

Available online 17 December 2014

Keywords:

Awake surgery

Intraoperative language testing

Language mapping

Brain tumour

Direct electrical stimulation

Corticosubcortical mapping

Standardised test battery

ABSTRACT

Intraoperative direct electrical stimulation (DES) is increasingly used in patients operated on for tumours in eloquent areas. Although a positive impact of DES on postoperative linguistic outcome is generally advocated, information about the neurolinguistic methods applied in awake surgery is scarce. We developed for the first time a standardised Dutch linguistic test battery (measuring phonology, semantics, syntax) to reliably identify the critical language zones in detail. A normative study was carried out in a control group of 250 native Dutch-speaking healthy adults.

In addition, the clinical application of the Dutch Linguistic Intraoperative Protocol (DuLIP) was demonstrated by means of anatomo-functional models and five case studies. A set of DuLIP tests was selected for each patient depending on the tumour location and degree of linguistic impairment. DuLIP is a valid test battery for pre-, intraoperative and postoperative language testing and facilitates intraoperative mapping of eloquent language regions that are variably located.

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1. Introduction

Intraoperative language mapping during awake surgery is considered to be the 'gold standard' since a positive impact of direct electrical stimulation (DES) on postoperative linguistic outcome is generally advocated (De Witt Hamer, Robles, Zwinderman, Duffau, & Berger, 2012; Duffau, Moritz-Gasser, & Gatignol, 2009; Ilmberger et al., 2008; Pereira et al., 2009; Sanai & Berger, 2010; Sanai, Mirzadeh, & Berger, 2008; Spina et al., 2010). DES enables to identify critical cortical and subcortical language areas and pathways, which cannot be resected without post-operative language deficits (De Witt Hamer et al., 2012; Duffau, 2007; Duffau, Lopes, et al., 2005; Spina et al., 2010). During DES, picture naming (Metz-Lutz et al., 1991) and counting are commonly used as language paradigms (Bertani et al., 2009; Duffau, 2007). However, this approach, in which word-finding abilities and automatic speech are investigated in a restricted way, does not cover the integral variety of expressive and receptive language functions,

necessary for an adequate communication. Verb–noun association tasks, auditory and visual comprehension tasks, repetition, reading, and writing tasks are occasionally used in experimental settings and some studies described a more tailored selection taking into account tumour location (Bello et al., 2007, 2008; Bertani et al., 2009; Duffau et al., 2003; Duffau, Lopes, et al., 2005) (for a review see De Witte & Mariën, 2013). As a result, test batteries including specific and sensitive tasks are needed for intraoperative language testing in order to preserve language function. Polczynska (2009) suggested three sets of 'home made' tasks consisting of: (1) 'grammar-focused tests', (2) 'non-dominant right-hemisphere tests', and (3) 'tests for subcortical stimulation'. Coello et al. (2013) proposed a minimal common protocol consisting of language tasks such as picture naming, semantic association and reading. In the study of Miceli, Capasso, Monti, Santini, and Talacchi (2012), the following language tasks were included to assess lexical-semantic processing: naming (both objects and actions), lexical decision (both auditory and visual) and word–picture matching (nouns and verbs, auditory and visual). Papagno et al. (2012) suggested a neuropsychological battery (Milano-Bicocca Battery MIBIB) to assess cognition (language, memory, executive functions, apraxia, spatial cognition) in low-grade glioma's pre- and

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postoperatively. Intraoperatively, they use naming of objects, actions and people. However, in general little is known about the feasibility, the construction, the validity of the tasks, and no normative data are available. The selection of the type of language paradigms during DES procedures is of crucial importance because of its direct effect on clinical outcome (Hamberger, Seidel, Mckhann, Perrine, & Goodman, 2005). Therefore the sensitivity of each language task used during DES needs to be investigated (Satoer et al., 2012; Talacchi, Santini, Savazzi, & Gerosa, 2011; Talacchi et al., 2012; Teixidor et al., 2007). We attempted to achieve this goal by developing for the first time a Dutch standardised neurolinguistic test battery for awake surgery in critical language areas. The language test battery, called DuLIP (Dutch Linguistic Intraoperative Protocol) includes a variety of phonological, semantic, syntactic and articulatory tests, standardised in a healthy control population of 250 neurologically healthy adults (see part 2 and 3). The clinical use of DuLIP in awake surgery is illustrated with a 'location-function-task' model and this model is applied to select an appropriate intraoperative language test battery to assess linguistic functions in patients with tumoural lesions in eloquent areas (see part 4).

2. Methods

2.1. Procedure

The first two authors of this manuscript and a group of master level students in clinical linguistics, speech and language pathology and clinical psychology were trained to administer the set of linguistic tests of the DuLIP, consisting of one object naming test, four phonological tests (repetition words, phonological odd word out, phonological fluency, phonological sentence judgment), eight semantic tests (semantic odd word out, semantic picture out, semantic association, sentence completions (closed and broad context), semantic fluency animals + jobs, semantic sentence judgment), five syntactic¹ tests (action naming, verb generation, syntactic fluency, syntactic sentence judgment I & II) and one articulatory test (verbal diadochokinesis). 250 healthy volunteers participated in the normative study. All test data were quantitatively (see statistics) and qualitatively analysed.

2.2. Subjects

250 healthy adult volunteers entered the normative study for the DuLIP. Inclusion criteria consisted of (1) Dutch as a mother tongue, (2) no (history of) cardiovascular, neurological, psychiatric, or developmental language and/or speech disorders, (3) no toxic substance abuse (no drug or alcohol abuse), (4) normal vision, (5) normal hearing, (6) no use of sleep medication, psychopharmaca or neuroleptic drugs, and (7) a score above 24/30 on the Mini Mental State Examination (MMSE) (generally accepted cut-off for impairment is 23; Crum, Anthony, Bassett, & Folstein, 1993; Folstein, Folstein, & McHugh, 1975) (<http://faculty.pepperdine.edu/shimels/Courses/Files/MMSE.pdf>). The participants were informed about the goals of the project and gave a written informed consent. The study was approved by the ethical committee of the Vrije Universiteit Brussel. The number of participants per age group was defined on the basis of current statistics about the prevalence of supratentorial tumours in the Flemish adult population (30% between 18 and 49 years, 55% between 50 and 74 years, 15% 75 years or older (Van Eycken & De Wever, 2006). Both male (18–92 y) and female (18–86 y) participants were included. We recruited subjects from a variety of culturally and philosophically different organizations over different rural and urban regions in

Table 1

Demographic characteristics of the 250 healthy participants.

Demographics	Mean (median)	SD	Range
(A) Age, education, MMSE (mean, SD, range)			
Age in years	51.29 (54.00)	19.81	18–92
Education in years	13.78 (14.00)	3.27	6–23
MMSE	29.16 (30.00)	1.18	24–30
Demographics	Groups	Number of subjects	Percentage
(B) Gender, age, education, province, handedness groups			
Gender	M	101	40.40
	F	149	59.60
Age	18–54 y	129	51.60
	55+ y	121	48.40
Education level	≤12 y	104	41.60
	>12 y	146	58.40
Province	West Flanders	44	17.60
	East Flanders	114	45.60
	Antwerp	20	8.00
	Flemish Brabant	40	16.00
	Limburg	32	12.80
Handedness	L	13	5.20
	A	8	3.20
	R	229	91.60

(A) Legend: SD = standard deviation; MMSE = Mini Mental State Examination.

(B) Legend: M = male, F = female, y = year, L = left-handed, A = ambidexter (Laterality Quotient ≥ −40 en ≤ +40), R = right-handed.

Belgium (provinces: West-Flanders, East-Flanders, Antwerp, Flemish Brabant, Limburg). The demographic data of the healthy participants are summarised in Table 1.

2.3. Test administration, registration and correction

The tests were administered in an identical order. Practice items were included to ensure that participants understood the task. Visual stimuli were presented in a powerpoint presentation on a laptop screen (Table 2). A division was made between tasks for use during DES stimulation within 4 s (A) and tasks for use during resection (no time restriction) (B). Since corticostimulatory stimulation may maximally last 4 s, all language tasks should ideally be performed within this time frame. However, certain tasks measuring important language aspects such as the fluency tasks (language initiation) and judgment tasks (language perception) are not feasible within 4 s. Since these tasks provide valuable information they were included in the protocol and used during resection in between stimulations. Of course, the tasks for stimulation (A) are also very relevant to apply during resection. Test items for use during DES were presented every 4 s accompanied by a beep called 'laser sound'. To avoid fatigue the DuLIP protocol was assessed in two parts (A & B) at two different test moments. The total length of both assessments (heteroanamnesis, EHI, MMSE, DuLIP) was 1.5 h. The answers were recorded verbatim and transcribed. One point was given if the target answer was correctly produced and within the given time frame. Self-corrections were allowed if given within the 4 s time frame. One repetition of an auditory task on request of the participant was allowed. The accuracy of the scoring of the tests was checked by one of the first two authors and was based on qualitative terms agreed on a priori. Uncertainties regarding the correctness of test items were discussed in group with the other authors until a consensus was reached.

2.4. Description of tests

The phonological, semantic, syntactic, naming tasks and articulatory task of the DuLIP are presented in Table 2. Taking into account the constraints of the awake procedure (fixed position, limited time) we carefully selected existing language tests

¹ The term syntax is used to define tasks that measure grammatical aspects.

Table 2

Intraoperative linguistic tasks from DuLIP.

Timing of assessment(s)	Linguistic level	Task	Stimuli (examples)
DURING DES (in 4 s)	Phonology	– repetition of words:	– <i>discussie</i> (discussion)
		• repetition of 3-syllabic words with alternating word accents	– <i>wortel</i> (carrot)
		• repetition of 2-syllabic words	– <i>individu</i> (individual)
		• repetition of words with phonemic similarities	– <i>programma</i> (programme)
		• repetition of words with consonant clusters	– <i>wijn, pijn, lijn, kat</i> (wine, pain, line, cat) → answer <i>kat</i> (cat)
	Semantics	– reading with phonological odd word out ^a	– <i>been, arm, raam, voet</i> (leg, arm, window, foot) → answer <i>raam</i> (window)
		– reading with semantic odd word out ^a	– pictures of ‘borstel, hond, kat’ (brush, dog, cat) → answer <i>borstal</i> (brush)
		– semantic association task ^a	– <i>auto, fiets ...</i> (car, bike ...) → answer e.g. <i>bus</i>
		– sentence completion (semantically induced sentences) ^a	– <i>Hij snijdt met een ...</i> (He cuts with a ...) → answer e.g. <i>mes</i> (knife)
		– verb generation ^a	– <i>bal</i> (ball) → <i>gooien/werpen</i> (to throw)
NOT DURING DES	Syntax	– action naming (3rd person singular, transitive verbs), 60 actions ^a (RUG-Vrije Universiteit Brussel)	– <i>de man ...</i> (the man ...) → answer e.g. <i>loopt</i> (e.g. runs) → picture of a man who is running
		– verbal diadochokinesis test	– repeat/papapa/, /pataka/, /papopu/, /pafpafpaf/, /dafnaflaf/, /pafpofpuf/, /pafpaspaf/ (5x)
		– object naming, 100 objects ^a	– black and white drawings of objects
			<i>Dit is ...</i> (this is) → answer <i>hond</i> (dog) → picture of a dog
			– <i>De hokkel eet een gersie.</i> (The hokkel eats a gersie.) → ‘hokkel’, ‘gersie’ non-existing words
	Semantics	– phonological fluency	– Letters D, A, T
		– semantic sentence judgment	– <i>De gieter smeert een boterham.</i> (The watering-can prepares a sandwich.) → wrong sentence
		– semantic fluency	– animals/jobs
		– sentence completion (less semantically induced sentences) ^a	– <i>Om 5 uur ...</i> (At 5 O'clock...) → possible answer: <i>ga ik naar huis</i> (I go home)
		– syntactic sentence judgment	– <i>Er was over niets meer van het scheerapparaat.</i> (There was over nothing left of the razor) → wrong word order
		– verbal fluency (verbs)	– verbs

^a Presented with powerpoint slides.

(i.e. phonological fluency & semantic fluency, see below for a description), adapted language tasks (e.g. naming task) and composed new tasks (e.g. semantic picture out) to include in the DuLIP protocol. The Dutch databases CELEX (Baayen, Piepenbrock, & van Rijn, 1993), SUBTLEX-NL (Keuleers, Brysbaert, & New, 2010) and Positiewoordenboek (Weijters, 1983) were used to control for the linguistic variables frequency, imageability (Van Loon-Vervoorn, 1989), word length, word form (see linguistic variables per test). As a rule, non-compound singular nouns were selected, and words that could evoke emotional reactions such as ‘sadness, brain, death’ were avoided. Per test, detailed information is given regarding the design of the items and the linguistic variables within the linguistic levels to be assessed. The qualitative terms to consider a test item as correct or incorrect were also described. In addition, we attempted to motivate the selection of tasks in relation to lesion location.

A. Tasks performed during DES within a time frame of 4 s per item

A.1. Phonological tests

A.1.1. Repetition of words

The aim of the word repetition task is to assess word production according to the phonological input- and output route. Participants were instructed to repeat 2 or 3-syllable words. In the awake setting 3-syllable words are easier to catch by the patient and the neurosurgeon than 2-syllable words because of the varying intonational pattern in Dutch. A list of 125 3-syllable words with varying syllable stress was composed, containing stimuli such as, *oefening* (exercise), *discussie* (discussion), *avontuur* (adventure). 125 2-syllable words were used in the task to allow examination of patients

who are not able to repeat 3-syllable words due to e.g. pre-existing language problems. The word list consists of different complexity levels. To increase the degree of articulatory and phonological complexity, we included words without consonant clusters (75 words for 3 syllable list, 100 words for 2 syllable list) (e.g. *mandarijn* – mandarine) and words with consonant clusters (e.g. *projectiel* – projectile) (50 words for 3 syllable list, 25 words for 2 syllable list) as well as phonologically similar words without consonant clusters (40 words) (e.g. *karamel* – caramel) and with consonant clusters (10 words) (e.g. *crimineel* – criminal). Phonologically or semantically related words were not consecutively presented to avoid perseveration. Studies have shown that words with similar phonemes (especially vowels) and words with consonant clusters are more prone to errors (Nespoulous & Moureau, 1998; Shattuck-Hufnagel & Klatt, 1980).

Repetition processes can be distorted after stimulation of the left arcuate fascicle (AF) but also after stimulation of the left inferior supramarginal gyrus (Maldonado, Moritz-Gasser, & Duffau, 2011; Moritz-Gasser & Duffau, 2013).

A.1.2. Reading with phonological odd word out

The aim of this phonological selection task is to assess phonological awareness via the lexical input route. Participants covertly read a list of four one-syllable words (25 slides) presented on a laptop screen and read aloud the word that does not phonologically fit (Fig. 1A). In order to present words with equal consonant clusters, the syllable structure of each of the items was controlled. Evidence in the literature on low grade gliomas shows that the insula, the inferior supramarginal gyrus, the AF and the inferior longitudinal fascicle (ILF) are crucially involved in phonological decision (Bello et al., 2007; Maldonado et al., 2011; Moritz-Gasser & Duffau,

bal (ball) hal (hall) val (fall) weg (road) A	been (leg) arm (arm) raam (window) voet (foot) B	C
bus auto ... (bus car ...) D	De bakker verkoopt ... (The baker sells ...) E	De man ... (The man ...) F

Fig. 1. (A) Reading with phonological odd word out. The target item is *weg* (road) because it is the only word that does not rhyme on -al (bal, hal, val); (B) reading with semantic odd word out. The target item is *raam* (window) because it is not semantically related to the three others representing body parts i.e. *been* (leg), *arm* (arm), *voet* (foot); (C) naming with semantic picture out. The target item is *borstel* (brush) because it does not belong to the semantic category (animals) to which the other two pictures (dog, cat) belong; (D) semantic association task. The target item is a semantically related word such as *fiets* (bike) or *trein* (train) that fits within the same semantic category transport. *Weg* (road) is an incorrect target answer although it is semantically related it is not a means of transport; (E) sentence completion (closed context). Possible target answer is *brood* (bread): *De bakker verkoopt brood* (The baker sells bread). *De bakker verkoopt schoenen* (The baker sells shoes) is an incorrect answer; (F) action naming. The target item is *loopt* (synonyms such as *rent*, *holt* are also correct): *De man loopt* (The man runs).

2013). In this task the occipital lobe is also involved since the presented words need to be read (Gras-Combe, Moritz-Gasser, Herbert, & Duffau, 2012; Richardson, Seghier, Leff, Thomas, & Price, 2011).

A.2. Semantic tests

A.2.1. Reading with semantic odd word out

The aim of this test is to assess semantic judgment via the lexical visual input route. Verbal semantic knowledge, semantic processing and reading are assessed. These functions may be distorted after stimulation of the temporal (posterior and superior) regions, the prefrontal (orbitofrontal and dorsolateral) regions (Duffau, Gatignol, et al., 2005), the parietal regions (Roux et al., 2004) and the occipital regions (Gras-Combe et al., 2012; Richardson et al., 2011). At the subcortical level stimulation of the uncinate fascicle (UF), the ILF (Bello et al., 2007), and the inferior fronto-occipital fascicle (IFOF) may result in disruption of semantic judgment (Bello et al., 2007; Duffau, Gatignol, et al., 2005; Moritz-Gasser, Herbert, & Duffau, 2013). Participants are instructed to read aloud the word that does not semantically fit in a list consisting of 4 one-syllabic or 4 two-syllabic words (25 items) (Fig. 1B).

A.2.2. Naming with semantic odd picture out

The aim of this test is to assess non-verbal semantic judgment and naming. As in the semantic odd word out task, semantic knowledge and processing is assessed but pictures (Snodgrass & Vanderwart, 1980) are used instead of written words. Therefore, this task can be used to stimulate temporal, prefrontal regions as well as for the IFOF and the ILF (Moritz-Gasser et al., 2013). Participants name the picture that does not semantically fit in a series consisting of 3 black and white drawings of objects and animals (25 items) (Fig. 1C). Two of the three pictures belong to the same semantic category.

A.2.3. Semantic association task

The aim of this test is to assess lexical-semantic processing. Reading, semantic knowledge and generating words according a given concept are assessed. As a result this task may be relevant

for DES in posterior as well as frontal brain regions and to map the IFOF (Coello et al., 2013). Participants add a semantically related word to a list of two semantically related nouns consisting of 1 or 2 syllables (25 items) (Fig. 1D).

A.2.4. Sentence completion (closed context)

The aim of the test is to assess the production of parts of speech elicited by a specific context and to measure reading, language dynamics and production of semantically and syntactically appropriate speech. Participants read sentences out loud and complete it in a meaningful way (25 items) (Fig. 1E). Reduction of spontaneous speech has been found after stimulation of the supplementary motor area (Fontaine, Capelle, & Duffau, 2002), Broca's area, the insula and the subcallosal fascicle and the ILF (Bello et al., 2007).

A.3. Syntactic tests

A.3.1. Action naming

The test aims to assess syntactic (and semantic) processing. On each slide a short introductive phrase is presented that has to be completed with a finite verb in the third person singular depicted by black and white drawings of an action (Fig. 1F). The reading aloud of the introductive phase is used to ensure that distorted verb naming is not due to seizures induced by the stimulation.

Verb assessment in the third person present singular allows on-line monitoring of the grammatical processes of person and number agreement between the subject and the action verb. Specific action naming sites are mainly identified in Broca's area and in the posterior midfrontal region (Lubrano, Filleron, Demonet, & Roux, 2014). Test items are presented in 3 blocks of 20 items (60 items in total) followed by a resting period. The selection of items was based on a cooperative study between Roelien Bastiaanse (University of Groningen) and Peter Mariën (Vrije Universiteit Brussel) (Rofes, 2012).

A.3.2. Verb generation

Verb generation is commonly used during function Magnetic Resonance Imaging (fMRI) to locate Broca's area (Engström, Ragnehed, Lundberg, & Söderfeldt, 2004). The test aims to assess

semantic association as well as syntactic competence and can be used during stimulation of the perisylvian regions (Bertani et al., 2009; Bizzi et al., 2008). Participants produce verbs that are semantically related with the singular nouns presented on a laptop screen (50 items). The stimuli were selected from 'Spreektaal, Woordfrequenties in Gesproken Nederlands' (De Jong, 1979), which contains lists of words most frequently used in spoken Dutch. Next to frequency and morphological category, two other selection criteria were used to sample the nouns: imageability and word length. Sixty highly imageable nouns of maximally 2 syllables were selected from the corpus. Ten items were deleted from the final list because in Dutch some (typically associated) target verbs strongly relate to the morphological form of the item due to an identical wordstem (e.g. fiets-fietsen (bike-to bike), spel-spelen (play-to play)). If they were included, the patient only had to add ' -en', which is too easy.

A.4. Verbal diadochokinesis test

The verbal diadochokinesis test aims to investigate the planning and coordination abilities of the motor speech system. It is a sensitive task to assess articulation which is generally represented in the inferior frontal gyrus, frontal ventral premotor areas and anterior insular regions. Because of its limited plasticity these regions should be preserved during surgery (Van Geemen, Herbet, Moritz-Gasser, & Duffau, 2013). In addition, the test can be used during subcortical stimulation of the part of the superior longitudinal fascicle (SLF) that connects the supramarginal gyrus with the ventral premotor cortex (Maldonado et al., 2011) as well as the corticospinal tract (CST) (Bello et al., 2007). Participants repeat 9 sequences of monosyllables as fast as possible 5 times in a row. Both alternating (alternating different phonemes) (DAF PAF LAF) and sequential diadochokinesis (repeating identical phonemes) (PAF PAF PAF) are used.

A.5. Object naming

Object naming is typically applied during intraoperative mapping with DES (for a review see De Witte & Mariën, 2013). Naming errors have been described after stimulations in the left perisylvian regions and frontal premotor cortex and subcortically in the AF, ILF, IFOF, subcallosal fascicle, UF (Bello et al., 2007; Coello et al., 2013; Moritz-Gasser & Duffau, 2013). Specific object naming sites are mainly localised in Broca's area and the temporal cortex (Lubrano et al., 2014).

The aim of this visual object naming task is to assess word retrieval. Participants name 100 black and white drawings of objects and animals depicted on the screen after producing an introductive phrase 'dit is een ... (this is a ...)'. The introductive phase is used for intraoperative condition to ensure that distorted naming is not due to seizures induced by the stimulation. Black and white drawings were selected from Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 1983; Mariën, Mampaey, Vervaeke, Saerens, & De Deyn, 1998), the Dutch versions of the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA-NL 52) (Bastiaanse, Bosje, & Visch-Brink, 1995), ATP (Auditief Taalbegripsprogramma) (Bastiaanse, 2010) and Graded Naming Test (GNT) (Warrington, 1997). Both living and non-living things are included in the test since they may activate different regions (Martin & Chao, 2001). High, middle and low frequent words were selected and different word lengths were used. As such the task allows assessment and manipulation of lexical retrieval and phonological encoding. Test items were randomly presented in blocks of 25 followed by a resting period.

B. Tasks performed with no time frame

B.1. Phonological tests

B.1.1. Phonological fluency

The aim of this test requiring generating words with a given phoneme is to assess flexibility of phonological thought and internal driven language which are typically located in the frontal areas (Baldo, Schwartz, Wilkins, & Dronkers, 2006) involving the supplementary motor areas (Satoer, Kloet, Vincent, Dirven, & Visch-Brink, 2013). Participants produce within one minute as many words as possible beginning with a particular phoneme. The phonemes D, A, T were chosen (Schmand, Groenink, & van den Dungen, 2008).

B.1.2. Phonological sentence

The aim of this test is to assess phonological awareness by discriminating between auditorily presented phonologically correct and incorrect sentences ($n = 30$) including non-words (e.g. *De hokkel eet een gersie* – The *hokkel* eats a *gersie*). The stimuli were homemade. Phonological decoding and verbal short-term memory are measured. No comparable task has been reported in the literature so far. This task could be informative to assess function of the language areas in the middle posterior temporal area (Hickok, 2012) and at the subcortical level including the AF, SLF and the ILF (Bello et al., 2007; Maldonado et al., 2011; Moritz-Gasser & Duffau, 2013).

B.2. Semantic tests

B.2.1. Semantic fluency

The aim of this task is to assess word generation within a specific conceptual category measuring the semantic knowledge represented in temporal areas (Baldo et al., 2006). The participants have to produce in one minute as many words as possible within a given semantic category. The semantic categories animals and jobs were chosen according to the data collection of Luteijn and Barelds (2004) in a Dutch population (GIT I, II).

B.2.2. Judgment of semantically anomalous and correct sentences

The aim of this test is to assess via the auditory input route, semantic awareness, knowledge and comprehension, by discriminating between semantically correct and incorrect sentences ($n = 50$) with violations of semantic selection restrictions (e.g. *De gieter smeert een boterham* – The watering-can prepares a sandwich). This task can be used for temporal cortical and subcortical areas (Bello et al., 2007; Bertani et al., 2009; Pereira et al., 2009; Santini et al., 2012). The sentences were based on BOX part 6 of Visch-Brink and Bajema (2001).

B.2.3. Semantic sentence completion (broad context)

The aim of the task is to assess speech production within a sentence frame with obligatory and less obligatory parts of speech. It measures reading, language dynamics, and production of semantically (and syntactically) appropriate speech. The task can be used in the supplementary motor area, the temporoparietal regions, the insula, the subcallosal fascicle and the ILF (Bello et al., 2007; Fontaine et al., 2002). Subjects read out loud 25 sentences, which have to be completed in a meaningful way. A phrase instead of a single word (see A.2.4) has to be added and the sentence has to be grammatically correct (with conjugated verbs). For example *Om 5 uur rijdt de buurman naar zijn werk* (At 5 O'clock the

neighbour drives to his work) is a correct answer. *Samen met Lies lopen* (*Running together with Lies*) is not a correct sentence in Dutch. In contrast to the sentences of subtest A.2.4, the sentences included in this task do not strongly trigger a particular semantic response but allow a diversity of answers.

B.3. Syntactic tests

B.3.1. Syntactic fluency

The aim of this task is to assess the flexibility of syntactic thought mainly organised in frontal areas (inferior, middle) but also in the parietal lobe (Ardila, 2012). The subject has to produce within one minute as many verbs as possible.

B.3.2. Syntactic sentence judgment

This task aims to assess syntactic awareness in frontal areas by discriminating between syntactically correct and incorrect sentences. Twenty-five stimulus sentences were selected from the *Werkwoorden-en Zinnentest* (WEZT) (Bastiaanse, Maas, & Rispens, 2000) (e.g. *De hond heeft de man geslaan* – The dog has beaten the man) and 25 sentences were home-made. The home-made sentences included word order errors (e.g. *Er was over niets meer van het scheerapparaat* – There was over nothing left of the raser), 8 sentences with verb inflection errors (e.g. *Wij was van plan naar de film te gaan* – We was planning to go to the movie) and 2 sentences with incorrect pronouns (e.g. *Dat is niet van jullie, dat is van wij* – This is not from you, this is from we).

2.5. Statistics

The data obtained in the cohort of 250 healthy participants were analysed with SPSS Statistics (v. 22). The dependent variables included the number of correct answers per test. For the analyses of the results, two gender groups (male, female), two age groups and two education groups were compared. The age groups were divided according to the median, i.e. 54 (18–54 y, >55 y). Education groups consisted of less or equal to 12 years of education and more than 12 years of education. The choice to present the data in this way was based both on content and statistical criteria. There is a lot of discussion about the age at which cognitive decline starts, however, a lot of researchers suggest somewhere around the age of 55 (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). Since more than 12 years of education implies continuation of education after the age of 18 years (bachelor or master degree), this cross over point is frequently used in normative studies (Miatton, Wolters, Lannoo, & Vingerhoets, 2004). From the statistical point of view, this division of age and education allows for group comparisons with sufficient power ($p > .80$).

The non-parametric Mann–Whitney U test was used to measure the effects of age/education/gender on the ordinal test scores. A p -value of $\leq .00089948$ (Sidak, 1967) was used as criterion of significance since multiple testing was involved (19×3 for age, education, gender) (see Appendix 1). The normative data were split for, age, education and/or gender if these groups differed significantly. Mean, median, ranges and cut-off scores were then calculated per linguistic test both at the level of the entire group and at the level of age/education combinations (see Appendices 2–4). We defined the cut-off scores according to the generally accepted method in clinical practice: i.e. the raw scores that go together with percentile 7 (equal to standard deviation 1.5.) (clinically impaired) and percentile 2 (equal to standard deviation 2.0) (pathologically impaired) (Palmer, Boone, Lesser, & Wohl, 1998).

With respect to object and action naming we additionally performed a picture naming agreement study (Kemmerer & Tranel, 2000). Therefore, the data were classified into correct and incorrect

responses. First, we accounted for the percentages of correct answers of each item and excluded items with less than 80% of picture-name agreement from further analysis. After the naming agreement study 100 out of 150 test items were used for object naming and 60 out of 100 items were included for action naming.

3. Results

No significant difference in mean age ($p = 0.369$) and mean years of education ($p = 0.061$) was found between the male and female participants of this study. In general, the healthy subjects with a normal cognitive level obtained high scores and a ceiling effect was found for all tasks but the fluency tasks (Appendix 1). The tasks that elicited most errors in the study population were the naming tasks, and some of the semantic tasks: the semantic odd word out task, the semantic sentence completion task (broad context) and the semantic association task. However, these tasks still have an accuracy rate (number of correct items divided by total number of items multiplied by 100) of more than 90% except for the semantic association task (83.44%). The semantic association task turned out to be the most difficult task with a lot of ‘delayed answers’ (not within 4 s = error) (see Appendices 2–4).

For most of the DuLIP tasks there was a significant effect of age (18–54, 55 y) (the higher the age, the lower the scores) and years of education (≤ 12 y, >12 y) (the higher the education level, the higher the scores), whereas gender groups (M, F) did not differ significantly (Appendix 1). There were some exceptions. No significant differences were observed between age/education/gender groups on the subtest ‘verbal diadochokinesis accuracy’. No significant effect was found for education effect in the semantic sentence completion task (closed context) ($p = .001$) and no significant effect for age was found in the phonemic judgment task ($p = .029$), but the p -value was smaller than the generally used alpha .05 in both tasks.

4. Clinical application of DuLIP in tumour population

4.1. Procedure

To illustrate the clinical use of the DuLIP protocol the pre-, intra- and postoperative data of 5 patients with tumours in different eloquent brain areas are demonstrated. In the pre- and postoperative phase (6 weeks and 6 months postsurgery), the DuLIP Protocol is administered together with tasks for the other cognitive (memory, attention, visuosperception, execution) functions (2 h of testing divided into two test moments). The normative data and especially the cut-off scores are used to define the presence and severity of a pre- and/or postoperative language impairment.

In the intraoperative phase, the asleep–awake–asleep procedure with corticosubcortical mapping is performed (Duffau, 2007). The mean time of the awake procedure is one hour and a half. For intraoperative testing, an individual-tailored battery of language tasks from DuLIP is composed based on the patient’s characteristics (preoperative language level, job) and the tumour characteristics (location) (Coello et al., 2013). If relevant, other cognitive tasks or non-language tasks are selected. The tailored test battery is practised in the preoperative phase. The items the patient is unable to perform correctly in the preoperative assessments are left out of the set for intraoperative testing to ensure that the errors in the awake setting are due to cortical stimulation and not caused by a pre-existing deficit (Duffau, 2007). It is generally accepted that transient language deficits occurring during 3 stimulations (with subsequent normalisation) is sufficient to ensure that the stimulated site is essential for language processing. The selection of appropriate language tasks taking into account the

tumour location is a complex process since speech and language are represented in parallel, distributed and interactive corticosubcortical networks (Catani & Thiebaut de Schotten, 2008; Coello et al., 2013; Hickok, 2012) (see Section 4.2).

4.2. Task selection per cortical site and subcortical pathway

The construction of anatomoclinical correlations in patients with brain tumours is difficult given the fact that brain plasticity mechanisms play an important role (Duffau, 2008, 2009, 2013). Based on the available literature, studies and clinical practice we constructed models that broadly represent the functions and preferred language tasks per cortical site (Fig. 2, Table 3) and subcortical pathway (Fig. 3, Table 4) of the (left) language

dominant hemisphere. These models may form the starting-point for the selection of language tasks in patients with brain tumours. In addition to the frequent use of naming tasks, other language task from the DuLIP may be selected based on the cortical and subcortical areas involved (e.g. semantic sentence completion in the SMA area, repetition for AF) (see Section 4.3). During cortical stimulation the tasks can be applied in serial order depending on the location of the stimulation (e.g. verb generation in frontal area, semantic picture out in temporal area). At the subcortical level, we suggest to apply tasks in parallel (e.g. semantic picture out and motor function by touching the item on the screen) and alternating order (switching between different tasks) to not overlook any function since subcortical pathways connect several cortical and subcortical areas.

Fig. 2. Per coloured cortical site the function(s) and most suitable language tasks from the DuLIP are shown in Table 3. (B) Ant = anterior; Med = medial; Post = posterior; SMG = supramarginal gyrus; ANG = angular gyrus; a = anterior; p = posterior; LAT = lateral; sup = superior; inf = inferior.

Table 3
Selection of DuLIP tasks per cortical site.

Frontal Regions	Function(s)	Intraoperative language tasks from DuLIP
inferior frontal gyrus	Articulatory processing/ syntax/ (writing)	Verbal diadochokinesis, repetition/ verb generation, action naming
posterior midfrontal gyrus	Action naming/ (writing)	Action naming
supplementary motor area (posterior superior frontal gyrus)	Language initiation	Sentence completion (closed and broad context), fluency
precentral gyrus	Motor network	Repetition, verbal diadochokinesis
Temporal Regions	Function	Intraoperative language tasks
posterior superior temporal gyrus	semantics, auditory comprehension, naming living objects	semantic picture out, semantic judgment, object naming
middle posterior superior temporal sulcus	Phonological network	Phonological odd word out, phonological judgment
middle inferior temporal gyrus	Lexical interface (link phonological – semantic information), naming non-living objects	Semantic judgment, object naming
anterior middle temporal gyrus	Famous face naming, (memory)	Naming
Parietal Regions	Function(s)	Intraoperative language tasks
supramarginal gyrus (SMG)	Reading, naming, semantics, (memory)	Reading + sentence completion, semantic association, naming
angular gyrus (ANG)	Reading, writing, (calculation)	Reading + sentence completion

4.3. Case reports

4.3.1. Case 1

A 48-year-old right-handed (Edinburgh Handedness Inventory (EHI) = +100; Oldfield, 1978) man with an educational level of 13 years developed a seizure and right sensory-motor syndrome after a period with paroxysms of severe headaches and dizziness. MRI and Diffusion Tensor Imaging (DTI) of the brain revealed a tumour in the left inferior frontal gyrus, near to Broca's area (Fig. 4AB), the UF, AF and frontal part of the IFOF. Preoperative functional MRI using a verb generation task and finger tapping task showed bilateral activation. Preoperative language testing revealed impaired results for phonological (Raw Score (RS) = 22; <Percentile (Pc) 2) and syntactic fluency (RS = 9; <Pc 2) and verb generation (RS = 40/50; <Pc 2). For intraoperative use, the verb generation (selection of correct items) and repetition task were selected because of the involvement of the inferior frontal gyrus and AF. Semantic association and object naming task were included to identify the IFOF and UF (Table 5). Cortical stimulation of inferior and middle frontal gyrus did not induce language deficits. Facial/hand sensations and motor reactions of face/hand were elicited respectively after and before the central gyrus. During subcortical stimulation and tumour resection no language deficits were found. Postoperative MRI demonstrates a partial resection (Berger,

Deliganis, Dobbins, & Keles, 1994) in the frontal lobe (Fig. 4CD and added in Table 5). At 6 weeks and 6 months postsurgery the DuLIP protocol was repeated and no aggravation of language occurred. As in the preoperative phase phonological (RS = 23; <Pc 2) and syntactic fluency (RS = 7; <Pc 2) were reduced 6 weeks postsurgery. Six months postsurgery improvement was noticed but defective results for phonological (RS = 24; <Pc 2) and syntactic fluency (RS = 13; <Pc 2) were still present.

4.3.2. Case 2

A tumoural mass lesion in the left temporal lobe extending to the insula and opercular regions was identified in a 64-year old right-handed (EHI + 80) woman with an educational level of 19 years (Fig. 5AB). She was admitted to the hospital because of a grand mal seizure with right hemiparesis and language problems.

Fig. 3. Per subcortical pathway the function(s) and suitable language tasks from the DuLIP are shown in Table 4.

Fig. 4. Case 1 – preoperative axial T2-weighted MR of the brain disclosing a tumoural mass lesion in the left prefrontal lobe encroaching upon the precentral gyrus of the left hemisphere, close to Broca's area (A and B). Postoperative axial T2-weighted MR brain images demonstrating the resection cavity in the prefrontal lobe (C and D).

Table 4
Selection of DuLIP tasks per subcortical pathway.

Subcortical pathways	Function(s)	Intraoperative language tasks from DuLIP
subcallosal fascicle	Initiation of speech	Fluency, sentence completion
inferior fronto-occipital fascicle	Semantics, reading, judgment	Semantic association, semantic odd word/picture out, semantic judgment
inferior longitudinal fascicle	Reading Phonology/semantics	Reading + sentence completion, naming
superior longitudinal fascicle (arcuate fascicle)	Articulatory processing/ Phonology	Verbal diadochokinesis, repetition/ phonological odd word out
uncinate fascicle	Famous face naming, semantics	Naming, semantic odd picture out
corticospinal tract	Motor speech	Verbal diadochokinesis, repetition

Fig. 5. Case 2 – preoperative axial T2-weighted MR of the brain demonstrating a tumoural mass lesion involving the left medial and posterior insular region extending to the anterior pole of the left temporal lobe, with compression of the left lateral ventricle (A and B). Postoperative axial T2-weighted MR brain images showing partial resection of the tumour in the left anterior pole of the temporal lobe (C and D).

Fig. 6. Case 3 – preoperative axial T2-weighted MR of the brain showing a tumoural resection cavity in the medial and anterior prefrontal area of the left hemisphere close to the premotor and supplementary motor area (A). Significant regrowth of the tumour is shown with invasion of the corpus callosum and extension to the prefrontal right hemisphere (B). Postoperative axial T2-weighted MR brain images demonstrating enlargement of the resection cavity in the left anterior frontal area with a for/backward diameter of 7 cm and a transversal diameter of 4.7 cm (C and D).

She regularly complained of word findings problems, memory problems and visual, auditory and tactile hallucinations. DTI indicated that the CST, the AF and IFOF were located adjacent to the tumour. Preoperative fMRI (verb generation) showed left hemisphere language dominance and a mass lesion encroaching upon Broca's area and Wernicke's area.

Preoperatively, in-depth examination of linguistic functions disclosed defective results for semantic fluency of animals (RS = 12; <Pc 2). Consequently, an intraoperative test battery was composed. The verb generation and action naming task were selected for stimulation of the frontal areas (insular region), the repetition task for stimulation of the AF. The semantic tasks (semantic picture out, semantic sentence judgment, object naming) were selected for stimulation of the posterior areas (Wernicke's area) and the IFOF (Table 5).

During cortical stimulation, essential language areas were identified in the inferior frontal gyrus (speech arrests during action naming) and in the anterior middle temporal gyrus (delay, speech

arrest during object naming). Subcortical stimulation triggered phonological paraphasias and word finding problems at the boarders of the AF (repetition task) and IFOF (semantic picture out task). Resection was interrupted when the insula was reached. Postoperative MRI showed partial resection of the tumour in the left anterior pole of the temporal lobe (Fig. 5CD).

At 6 weeks postsurgery, in addition to the disorder in semantic fluency, which was still present, a number of novel language deficits were observed including object naming (RS = 61/100; <Pc 2), action naming (RS = 32/60; <Pc 2) and comprehension problems indicated by the semantic sentence judgment score (RS = 42/50; <Pc 2). She also presented with fluency problems (phonological: RS = 12; <Pc 2; semantic: RS = 9; <Pc 2; syntactic (RS = 12; <Pc 7). At 3 months postsurgery, the word finding difficulties, expressed in object and action naming and perception problems disappeared. Language fluency improved but remained impaired for semantic fluency of animals (RS = 11; <Pc 2) as was in the preoperative phase.

Table 5
Selection of intraoperative DuLIP tasks per case study.

Case	Location MRI	Location fMRI	Location DTI	Intraoperative language tests	Extent of resection ^a
1	L inferior frontal gyrus	Bilateral activation	UF, IFOF, AF	Repetition, verb generation, object naming, semantic association	Partial
2	L temporoinsular	L dominance	CST, IFOF, AF	Repetition, verb generation, naming (actions + objects), semantic picture out, semantic sentence judgment	Partial
3	L frontal, SMA	L dominance	IFOF, CST, SLF	Fluency, semantic sentence completion, repetition, verbal diadochokinesis	Subtotal
4	L temporoparietal	L dominance	CST, AF, IFOF	Repetition, semantic picture out, semantic sentence judgment, reading + semantic sentence completion, object naming	Subtotal
5	L parietooccipital	R dominance	AF, SLF	Reading + semantic sentence completion, semantic picture out, naming, repetition, phonological odd word out (calculation, vision)	Subtotal

Legend: Nr = Number of case, SMA = supplementary motor area, L = left, R = right, UF = Uncinate Fasciculus, AF = Arcuate Fasciculus, SLF = Superior Longitudinal Fasciculus, CST = corticospinal tract.

^a According to the classification from Berger et al. (1994).

4.3.3. Case 3

A 38-year-old right-handed (EHI = +100) man with an educational level of 12 years underwent repeat surgery after regrowth of a tumoural lesion in the left frontal lobe close to the supplementary motor area (SMA) and the premotor cortex (Fig. 6AB). DTI showed involvement of the SLF and IFOF. The CST was adjacent to the tumour. fMRI (verb generation, finger tapping) revealed left hemisphere language dominance with activations in the superior and middle temporal gyrus and the inferior and middle frontal gyrus. In the preoperative phase, no linguistic problems were identified. The selected tasks from DuLIP for intraoperative mapping were fluency tasks and semantic sentence completion (SMA, premotor cortex, IFOF) and repetition & verbal diadochokinesis (SLF, CST) (see Table 5). During cortical stimulation of the left precentral and inferior frontal gyrus no linguistic deficits were found. Subcortical stimulation in the vicinity of the CST resulted during repetition tasks in speech arrests and motor reactions of the right hand. After stimulation and resection near the SMA initiation difficulties appeared during the sentence completion task. On the postoperative MRI a subtotal enlarged resection was found in the left anterior frontal area (Fig. 6CD). In the acute phase after surgery a dynamic aphasia (characterised by a selective disorder in the spontaneous speech) typical for an SMA syndrome was found. Extensive testing at 6 weeks revealed marked phonological (RS = 15; <Pc 2), semantic (animals: RS = 13; <Pc 2), and syntactic fluency (RS = 4; <Pc 2) problems. At six months postsurgery, reassessment of language functions disclosed normal results.

4.3.4. Case 4

A 34-year-old left-handed (EHI –66, 67) man with an educational level of 16 years was transferred to the hospital following a grand mal seizure. MRI of the brain revealed a tumoural mass lesion in the left temporoparietal lobe (Fig. 7AB). DTI indicated that the AF and CST were relocated upwards due to mass effects (AF to cranial, CST to anterior) and that the IFOF was involved.

Fig. 7. Case 4 – preoperative axial T2-weighted MR of the brain demonstrating a tumoural mass lesion in the left lateral ventricle extending to the temporoparieto-occipital region (A). A slight midline shift to the right and dilatation of the left lateral ventricle are observed (B). Postoperative axial T2-weighted MR brain images showing the resection cavity in the left temporoparietal area (4–2 cm) (C and D).

Preoperative fMRI (verb generation, finger tapping) in this left-handed patient showed left hemisphere language dominance. Wernicke's area was located close to the posterior part of the tumour. Preoperatively, in-depth examination of linguistic functions was entirely normal. Semantic tasks (semantic picture out, semantic sentence judgment), reading task (reading + semantic sentence completion), naming (object) and repetition were included in the intraoperative test battery for these eloquent regions and pathways (Table 5). Cortical stimulation elicited speech arrests in the inferior frontal gyrus (during repetition) and anomia and delayed word retrieval in the medial and inferior temporal gyrus (during naming). The preoperative fMRI disclosing activation in Wernicke's area did not correlate with the positive intraoperative stimulation points (superior and middle temporal gyrus). During subcortical stimulation, word finding problems (during semantic picture out task) and delayed word retrieval (during semantic sentence completion) were found at the borders of the IFOF and phonological paraphasia at the borders of the AF (during repetition). Resection was stopped according to these functional boundaries, consequently subtotal resection was found on postoperative MRI in the left temporoparietal area (Fig. 7CD).

In the first week after surgery, the patient could speak fluently but in a clinical examination some naming and comprehension problems at a linguistic complex level were noticed. At 6 weeks postsurgery, the following DuLIP tasks were severely impaired: object naming (RS = 78/100; <Pc 2), action naming (RS = 48/60; <Pc 2), semantic fluency (animals) (RS = 14; <Pc 2), syntactic fluency (RS = 18; <Pc 2), semantic odd word out (RS = 15; <Pc 2), semantic picture out (RS = 23/25; <Pc 2) and semantic sentence judgment (RS = 46/50; <Pc 2). After six months the naming and semantic deficits resolved and only mild fluency problems persisted in speech (syntactic fluency was still disturbed: RS = 18; <Pc 2).

4.3.5. Case 5

A 53-year-old right-handed (EHI = +80) man with an educational level of 10 years complained of visual problems (troubled sight) and progressive memory problems. MRI of the brain revealed a left posterior parietal glioma (Fig. 8AB). DTI showed that the tumour was adjacent to the AF (that connects Broca's and Wernicke's area) and involved the anterior and posterior indirect segment of the SLF (Catani & Mesulam, 2008). Preoperative fMRI (verb generation, finger tapping) showed reversed, right hemisphere language dominance. Concise preoperative language testing yielded normal results except for slight semantic fluency deficits (animals: RS: 16; <Pc 7). Phonological tasks (phonological odd word out, repetition) were used during surgery when the AF was approached, whereas semantic and reading tasks (semantic picture out, semantic sentence completion, naming) were selected for DES in the parietal regions. Non-language tasks such as calculation (self-made) and a line bisection task were added (Roux et al., 2011). Speech arrest and dysarthria was triggered after stimulation in the area located between the left angular gyrus and supramarginal gyrus (semantic picture out). Anomia was found following stimulation of the posterior middle temporal gyrus. Delayed word retrieval was found after stimulation of the junction between the postcentral gyrus and supramarginal gyrus. Paresthesias of the right hand were elicited by stimulation near the postcentral gyrus. During subcortical stimulation to inferior reading was slightly delayed (semantic sentence completion) and calculation problems for complex tasks occurred during stimulation of the deeper parietal regions. Consequently, the resection was interrupted and a subtotal resection was confirmed in the posterior parietal lobe on the postoperative MRI (Fig. 8CD).

In the first days after surgery the patient presented with delayed reading and calculation problems. Language assessments

Fig. 8. Case 5 – preoperative axial T2-weighted MR brain of the brain disclosing a tumoural mass lesion in the left posterior parietal lobe (A and B). Postoperative axial T2-weighted MR brain images reveals subtotal tumour resection in the left parietooccipital area (C and D).

at 6 weeks revealed defective scores for semantic fluency (RS = 16; <Pc 2) and reading & semantic sentence completion (RS = 18; <Pc 2). At six months postsurgery, remission of fluency, reading and calculation problems was observed.

5. Discussion

This study reports the rationale, development, standardisation and application of DuLIP, the first Dutch linguistic test battery for pre-, intra- and postoperative use in awake brain surgery. DuLIP includes tasks that relate to a broad variety of linguistic levels and modalities and as such allows assessment of various linguistic functions in detail. The normative data and clinical application of DuLIP as well as some limitations and future needs are discussed in the sections below.

5.1. Normative data of DuLIP

Quantitative analysis of data showed a ceiling effect for all but one of the linguistic tests (fluency tasks). The target answers in the fluency tasks were numerous and there was no maximum score. In contrast to the other linguistic tasks more variance between subjects was found. Since the primary objective of DuLIP is the selection of a set of relevant tasks and test items in the preoperative phase, DuLIP was constructed in such a way that patients with mild to moderate aphasia could perform to some degree all tasks within 4 s. Consequently, normal participants obtained high scores (De Witte & Mariën, 2013). As expected, task performance differed significantly according to age and education. The higher the age the lower the test score and the lower the education level the lower the scores. In various studies similar findings have been found (Brucki, 2004; Mariën et al., 1998; Mathuranath, 2003; Snitz, 2009; Zec, Burkett, Markwell, & Larsen, 2007). According to the Sidak correction, education did not significantly effect performance on the semantic sentence completion task (closed context) ($p = .001$) and age did not have a significant effect on the phonemic

judgment task ($p = .029$). A significant difference, however, was obtained when using a p -value of 0.05. Therefore, cut-off scores were calculated in all four categories (age/education groups) for every DuLIP task (except for verbal diadochokinesis task which did not show any age or education effect).

Qualitative analysis of the data revealed that the few errors made by the control group could not be systematically related to specific items. Therefore, no items were deleted after standardisation. Only for the semantic association task the percentage of correct answers was below 90% (83.44%) and the most frequent mistakes were delayed responses. This task seems to be the most difficult one since intact reading, semantic knowledge and language initiation are necessary to produce the target answer within 4 s. Moreover, as is the case for all DuLIP tasks this test also relies on memory, attention and executive function.

5.2. Clinical application of DuLIP

The normative data allow to analyse and compare the pre- and postoperative results of the patient group with the norm group. Intraoperative selection of DuLIP tasks was based on the preoperative patient level and recent insights in the functional neuroanatomy subserving linguistic processes in brain tumour populations. Although neural language representation is a complex phenomenon and subject to brain plasticity mechanisms, some guidelines might be proposed regarding structure-to-function relations at the cortical and subcortical level. For cortical tumours located in dominant frontal brain regions, phonology, syntax and language initiation should be assessed. For tumours located in dominant temporal regions, semantic tasks that measure both comprehension and production seem indispensable (e.g. semantic picture out task). For tumours situated in the dominant parietal regions, semantic tasks and reading tests add valuable information (see Fig. 2, Table 3). Since the plastic potential of the white matter is limited (Duffau, 2013) and subcortical injury is an independent predictor of postoperative neurological deficits (Trinh et al., 2013), subcortical mapping is even more important. As the IFOF, ILF, SLF, CST and subcallosal fascicle are essential language pathways involved in respectively semantics, reading, phonology, motor speech, language initiation, an appropriate set of DuLIP tests should be selected (see Fig. 3, Table 4). We have restricted to the (left) dominant language hemisphere, however, the right hemisphere is also involved in language functions such as prosody and processing unfamiliar sentences that contain distant semantic relationships (Polczynska, 2009). Polczynska (2009) therefore suggested two types of tests for the non-dominant right hemisphere (1) tests investigating alternative meanings of words and broader semantic relationships, (2) affective prosody tests.

As demonstrated in the case descriptions, DuLIP may be a useful and reliable tool in the pre-, intra- and postoperative phase of awake surgery. Preoperatively, no linguistic deficits were found in cases 3 and 4 which may be due to typically slow growth of low-grade gliomas allowing neural reorganisation (preoperative plasticity). Cases 1, 2 and 5 presented verbal fluency problems which is in agreement with a large outcome study of Satoer et al. (2014). Intraoperative corticosubcortical stimulation induced language deficits in all but one case (case 1). In three out of the four cases (case 1, 2, 4) intraoperative findings did not correlate with preoperative fMRI results. As a consequence, the surgical strategy had to be adapted. The absence of a strong correlation between fMRI and DES findings in our cases highlights the importance of intraoperative stimulation and testing. Postoperatively, the extent of the resection was calculated and subtotal and partial resections were performed. The cases in which essential language sites were identified intraoperatively (cases 2–5) developed transient language deficits at 6 weeks postsurgery. In agreement with the

observations of Duffau (2007) and Trinh et al. (2013) the postoperative linguistic impairments in these patients resolved after 6 months. Naming and verbal fluency were most frequently impaired and seem to be sensitive parameters to identify (Sato et al., 2012, 2014). To conclude, the selected DuLIP tasks were feasible in the pre-, intra- and postoperative phase and elicited language deficits during stimulation.

5.3. Limitations of the study

Some tasks should be refined in order to better assess the function targeted. The phonological odd word out task might be too easy since some answers can be visually identified without using phonological knowledge (e.g. bal, hal, val, weg). A solution might be inclusion of items with no transparent phonology/orthography correspondence, such as 'jack', in Dutch rhyming on 'bek' and 'vrek', but not on 'dak' (e.g. bek, jack, vrek, dak) or to present the items auditorily. The syntactic fluency and verb generation tasks are not pure syntactic tasks but also measure lexical semantics. However, they rely more strongly on syntactic processing than semantic fluency as verb lemmas contain more information, may be harder to retrieve, and require more grammatical encoding than noun lemmas (Bastiaanse & van Zonneveld, 2004). The action naming task is a more efficient task to assess grammatical processing since the verb needs to be inflected in a short sentence. The semantic association task seems to be a difficult task to perform within 4 s even in the normal population and under normal conditions. Therefore, this task appears to be more suitable during tumour resection (and not during stimulation) at the subcortical level to control the semantic level.

Since only 5 case studies were included in this study no sound conclusions can be drawn regarding the most sensitive tasks for pre-, intra- and postoperative testing. As the total DuLIP protocol takes 1h30 to perform, the total of pre- and postoperative cognitive assessments require two test moments. In comparison to naming, application of a selection of DuLIP tasks does not substantially prolong the awake procedure. The intraoperative cortical procedure is only increased with a few minutes since in general only one additional task is required to identify positive language sites. During subcortical stimulation the selected tasks are presented in alternation which does not lead to a substantial prolongation of the surgical time.

5.4. Future directions

In order to improve current knowledge on anatomoclinical correlations and sensitivity of the DuLIP tasks (inter-location-sensitivity and pre- and postoperative sensitivity), a longitudinal neurolinguistic follow-up study in a large patient group is needed. Results from these studies will shed light on the most sensitive DuLIP tasks and only these tasks will be further administered. Future studies using the DuLIP protocol during pre- and postoperative fMRI assessments may be relevant for both clinical (e.g. to plan or to exclude the possibility of awake surgery) and scientific purposes (e.g. to study linguistic processes, anatomoclinical correlations, brain plasticity mechanisms). Since verb generation and naming tasks are often used as fMRI language paradigms (Ojemann, Ojemann, & Lettich, 2002; Smits, Visch-Brink, Schraa-Tam, Koudstaal, & van der Lugt, 2006), the DuLIP protocol might be used in future research to define the most sensitive tasks for preoperative fMRI. However, it should be noted that the correlation between preoperative fMRI and intraoperative DES is poor for language (66%). As a result preoperative fMRI cannot be reliably used without the combination with DES to make critical surgical decisions (Roux et al., 2003).

To identify the exact benefits of the DuLIP protocol, the outcome of a group of patients in which a set of DuLIP tests is used versus a matched control group of patients in which only naming is assessed should be studied. Retrospective studies or comparisons of methods between neurosurgical departments should be conducted to further investigate this issue. Although the normative data of the DuLIP set can only be used in the Dutch-speaking part of Belgium and the Netherlands, the tasks, however, may be adapted to different languages.

Apart from language and sensorimotor functions, higher-order cognitive functions (e.g. memory, attention/executive functioning, spatial awareness, calculation) and visual functions should also be (briefly) tested in awake procedures (see case 5) in order to ward the postoperative outcome and Quality of Life of the patient (Coello et al., 2013; Duffau, 2010).

6. Conclusion

In this study a set of linguistic tasks (DuLIP) to assess a variety of linguistic functions during awake surgery was carefully constructed and standardised in a cohort of 250 Dutch healthy controls. With DuLIP, a valid linguistic test battery and methodologically sound instrument has become available to reliably evaluate linguistic functions in the pre-, intra- and postoperative phase of awake surgery. Based on the tumour localisation (preoperative neuroimaging data) and the patient's personal characteristics (preoperative language level, job), DuLIP allows a tailored selection per patient. This valid linguistic approach enhances the reliability of the neurosurgical procedure and patient outcome.

Acknowledgments

Elke De Witte is a Ph.D. fellow of the Research Foundation – Flanders (FWO). Steven Verheyen is a postdoctoral fellow of the Research Foundation – Flanders (FWO).

We want to thank Prof. Dr. Roelien Bastiaanse and Drs. Adria Rofes for their cooperation in the development and analysis of the action naming task.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bandl.2014.10.011>.

References

- Ardila, A. (2012). Interaction between lexical and grammatical language systems in the brain. *Physics of Life Reviews*, 9(2), 198–214. <http://dx.doi.org/10.1016/j.plrev.2012.05.001>.
- Baayen, R. H., Piepenbrock, R., & van Rijn, H. (1993). *The CELEX lexical database (CD-ROM)*. Philadelphia, PA: Linguistic Data Consortium, University of Pennsylvania.
- Baldo, J. V., Schwartz, S., Wilkins, D., & Dronkers, N. F. (2006). Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *Journal of the International Neuropsychological Society: JINS*, 12(6), 896–900. <http://dx.doi.org/10.1017/S1355617706061078>.
- Bastiaanse, R., Bosje, M., & Visch-Brink, E. G. (1995). *PALPA: De Nederlandse versie (PALPA: The Dutch version)*. Hove: Lawrence Erlbaum.
- Bastiaanse, R. (2010). *ATP: Auditief Taalbegripsprogramma complete set*. Houten, The Netherlands: Bohn Stafleu van Logum.
- Bastiaanse, R., Maas, E., & Rispens, J. (2000). *Werkwoorden-en Zinnentest. WEZT*. Lisse, The Netherlands: Swets Test Publishers.
- Bastiaanse, R., & van Zonneveld, R. (2004). Broca's aphasia, verbs and the mental lexicon. *Brain and Language*, 90(1–3), 198–202. [http://dx.doi.org/10.1016/S0093-934X\(03\)00432-2](http://dx.doi.org/10.1016/S0093-934X(03)00432-2).
- Bello, L., Gallucci, M., Fava, M., Carrabba, G., Giussani, C., Acerbi, F., et al. (2007). Intraoperative subcortical language tract mapping guides surgical removal of gliomas involving speech areas. *Neurosurgery*, 60(1), 67–82.
- Bello, L., Gambini, A., Castellano, A., Carrabba, G., Acerbi, F., Fava, E., et al. (2008). Motor and language DTI Fiber Tracking combined with intraoperative

- subcortical mapping for surgical removal of gliomas. *NeuroImage*, 39(1), 369–382.
- Berger, M. S., Deliganis, A. V., Dobbins, J., & Keles, G. E. (1994). The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. *Cancer*, 74(6), 1784–1791.
- Bertani, G., Fava, E., Casaceli, G., Carabba, G., Casarotti, A., Papagno, C., et al. (2009). Intraoperative mapping and monitoring of brain functions for the resection of low-grade gliomas: Technical considerations. *Neurosurgical Focus*, 27(4).
- Bizzi, A., Blasi, V., Falini, A., Ferrolli, P., Cadioli, M., Danesi, U., et al. (2008). Presurgical functional MR imaging of language and motor functions: Validation with intraoperative electrocortical mapping. *Radiology*, 248(2), 579–589. <http://dx.doi.org/10.1148/radiol.2482071214>.
- Brucki, S. M. D. (2004). Category fluency test: Effects of age, gender and education on total scores, clustering and switching in Brazilian Portuguese-speaking subjects. *Brazilian Journal of Medical and Biological Research*, 37(12), 1771.
- Catani, M., & Mesulam, M. (2008). The arcuate fasciculus and the disconnection theme in language and aphasia: History and current state. *Cortex; A Journal Devoted to the Study of the Nervous System and Behavior*, 44(8), 953–961. <http://dx.doi.org/10.1016/j.cortex.2008.04.002>.
- Catani, M., & Thiebaut de Schotten, M. (2008). A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex; A Journal Devoted to the Study of the Nervous System and Behavior*, 44(8), 1105–1132. <http://dx.doi.org/10.1016/j.cortex.2008.05.004>.
- Coello, A. F., Moritz-Gasser, S., Martino, J., Martinoni, M., Matsuda, R., & Duffau, H. (2013). Selection of intraoperative tasks for awake mapping based on relationships between tumor location and functional networks. *Journal of Neurosurgery*, 119(6), 1380–1394. <http://dx.doi.org/10.3171/2013.6.JNS122470>.
- Crum, R. M., Anthony, J. C., Bassett, S. S., & Folstein, M. F. (1993). Population-based norms for the Mini-Mental State Examination by age and educational level. *JAMA: The Journal of the American Medical Association*, 269(18), 2386–2391.
- De Jong, E. D. (Ed.). (1979). *Spreektaal: Woordfrequenties in gesproken Nederlands*. Utrecht, The Netherlands: Boh, Scheltema & Holkema.
- De Witt Hamer, P. C., Robles, S. G., Zwinderman, A. H., Duffau, H., & Berger, M. S. (2012). Impact of intraoperative stimulation brain mapping on glioma surgery outcome: A meta-analysis. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 30(20), 2559–2565. <http://dx.doi.org/10.1200/JCO.2011.38.4818>.
- De Witte, E., & Mariën, P. (2013). The neurolinguistic approach to awake surgery reviewed. *Clinical Neurology and Neurosurgery*, 115(2), 127–145. <http://dx.doi.org/10.1016/j.clineuro.2012.09.015>.
- Duffau, H. (2007). Contribution of cortical and subcortical electrostimulation in brain glioma surgery: Methodological and functional considerations. *Neurophysiologie Clinique/Clinical Neurophysiology*, 37, 373–382.
- Duffau, H. (2008). The anatomo-functional connectivity of language revisited new insights provided by electrostimulation and tractography. *Neuropsychologia*, 46(4), 927–934.
- Duffau, H. (2009). Surgery of low-grade gliomas: Towards a “functional neurooncology”. *Current Opinion in Oncology*, 21(6), 543–549.
- Duffau, H. (2010). Awake surgery for nonlanguage mapping. *Neurosurgery*, 66(3), 523–528.
- Duffau, H. (2013). The huge plastic potential of adult brain and the role of connectomics: New insights provided by serial mappings in glioma surgery. *Cortex; A Journal Devoted to the Study of the Nervous System and Behavior*. <http://dx.doi.org/10.1016/j.cortex.2013.08.005>.
- Duffau, H., Capelle, L., Denvil, D., Sichez, N., Gatignol, P., Taillandier, L., et al. (2003). Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: Functional results in a consecutive series of 103 patients. *Journal of Neurosurgery*, 98(4), 764–778.
- Duffau, H., Gatignol, P., Mandonnet, E., Peruzzi, P., Tzourio-Mazoyer, N., & Capelle, L. (2005). New insights into the anatomo-functional connectivity of the semantic system: A study using cortico-subcortical electrostimulations. *Brain*, 128, 797–810.
- Duffau, H., Lopes, M., Arthuis, F., Bitar, A., Sichez, J., Van Effenterre, R., et al. (2005). Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: A comparative study between two series without (1985–96) and with (1996–2003) functional mapping in the same institution. *Journal of Neurology Neurosurgery and Psychiatry*, 76(6), 845–851.
- Duffau, H., Moritz-Gasser, S., & Gatignol, P. (2009). Functional outcome after language mapping for insular World Health Organization Grade II gliomas in the dominant hemisphere: Experience with 24 patients. *Neurosurgical Focus*, 27(2).
- Engström, M., Ragnehed, M., Lundberg, P., & Söderfeldt, B. (2004). Paradigm design of sensory-motor and language tests in clinical fMRI. *Neurophysiologie Clinique = Clinical Neurophysiology*, 34(6), 267–277. <http://dx.doi.org/10.1016/j.neucli.2004.09.006>.
- Folstein, M., Folstein, S., & McHugh, P. (1975). Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189–198.
- Fontaine, D., Capelle, L., & Duffau, H. (2002). Somatotopy of the supplementary motor area: Evidence from correlation of the extent of surgical resection with the clinical patterns of deficit. *Neurosurgery*, 50(2), 297–303.
- Gras-Combe, G., Moritz-Gasser, S., Herbet, G., & Duffau, H. (2012). Intraoperative subcortical electrical mapping of optic radiations in awake surgery for glioma involving visual pathways. *Journal of Neurosurgery*, 117(3), 466–473. <http://dx.doi.org/10.3171/2012.6.JNS111981>.
- Hamberger, M. J., Seidel, W. T., Mckhann, G. M., Perrine, K., & Goodman, R. R. (2005). Brain stimulation reveals critical auditory naming cortex. *Brain*, 128(11), 2742–2749.
- Hickok, G. (2012). The cortical organization of speech processing: Feedback control and predictive coding the context of a dual-stream model. *Journal of Communication Disorders*, 45(6), 393–402. <http://dx.doi.org/10.1016/j.jcomdis.2012.06.004>.
- Ilmberger, J., Ruge, M., Kreth, F.-W., Briegel, J., Reulen, H.-J., & Tonn, J.-C. (2008). Intraoperative mapping of language functions: A longitudinal neurolinguistic analysis. *Journal of Neurosurgery*, 109(4), 583–592.
- Kaplan, E. F., Goodglass, H., & Weintraub, S. (1983). *The Boston naming test* (2nd ed.). Philadelphia: Lea and Febiger.
- Kemmerer, D., & Tranel, D. (2000). Verb retrieval in brain-damaged subjects: 1. Analysis of stimulus, lexical, and conceptual factors. *Brain and Language*, 73(3), 347–392. <http://dx.doi.org/10.1006/brln.2000.2311>.
- Keuleers, E., Brysbaert, M., & New, B. (2010). SUBTLEX-NL: A new measure for Dutch word frequency based on film subtitles. *Behavior Research Methods*, 42(3), 643–650. <http://dx.doi.org/10.3758/BRM.42.3.643>.
- Lubrano, V., Filleron, T., Demonet, J.-F., & Roux, F.-E. (2014). Anatomical correlates for category-specific naming of objects and actions: A brain stimulation mapping study. *Human Brain Mapping*, 35(2), 429–443. <http://dx.doi.org/10.1002/hbm.22189>.
- Luteijn, F., & Barelids, D. (2004). *Groninger Intelligentie Test II (GIT II)*. Amsterdam, The Netherlands: Pearson.
- Maldonado, I. L., Moritz-Gasser, S., & Duffau, H. (2011). Does the left superior longitudinal fascicle subserve language semantics? A brain electrostimulation study. *Brain Structure and Function*, 216(3), 263–274. <http://dx.doi.org/10.1007/s00429-011-0309-x>.
- Mariën, P., Mampaey, E., Vervaeke, A., Saerens, J., & De Deyn, P. P. (1998). Normative data for the Boston Naming Test in native Dutch-speaking Belgian elderly. *Brain and Language*, 65(3), 447–467. <http://dx.doi.org/10.1006/brln.1998.2000>.
- Martin, A., & Chao, L. L. (2001). Semantic memory and the brain: Structure and processes. *Current Opinion in Neurobiology*, 11(2), 194–201. [http://dx.doi.org/10.1016/S0959-4388\(00\)00196-3](http://dx.doi.org/10.1016/S0959-4388(00)00196-3).
- Mathuranath, P. S. (2003). Effects of age, education and gender on verbal fluency. *Journal of Clinical and Experimental Neuropsychology*, 25(8), 1057.
- Metz-Lutz, M. N., Kremin, H., Deloche, G., Hannequin, D., Ferrand, L., & Perrier, D. (1991). Standardisation d'un test de dénomination orale: Contrôle des effets de l'âge, du sexe et du niveau de scolarité chez les sujets adultes normaux. *Rev de Neuropsychol*, 1, 73–95.
- Miatton, M., Wolters, M., Lannoo, E., & Vingerhoets, G. (2004). Updated and extended Flemish normative data of commonly used neuropsychological tests. *Psychologica Belgica*, 44(3), 189–216.
- Miceli, G., Capasso, R., Monti, A., Santini, B., & Talacchi, A. (2012). Language testing in brain tumor patients. *Journal of Neuro-Oncology*, 108(2), 247–252. <http://dx.doi.org/10.1007/s11060-012-0810-y>.
- Moritz-Gasser, S., & Duffau, H. (2013). The anatomo-functional connectivity of word repetition: Insights provided by awake brain tumor surgery. *Frontiers in Human Neuroscience*, 7. <http://dx.doi.org/10.3389/fnhum.2013.00405>.
- Moritz-Gasser, S., Herbet, G., & Duffau, H. (2013). Mapping the connectivity underlying multimodal (verbal and non-verbal) semantic processing: A brain electrostimulation study. *Neuropsychologia*, 51(10), 1814–1822. <http://dx.doi.org/10.1016/j.neuropsychologia.2013.06.007>.
- Nespoulous, J.-L., & Moureau, N. (1998). “Repair strategies” and the production of segmental errors in aphasia: Epenthesis vs. syncope in consonantal clusters. In E. Visch-Brink & R. Bastiaanse (Eds.), *Linguistic levels in aphasiology* (pp. 133–145). San Diego-London: Singular Publishing Group.
- Ojemann, J. G., Ojemann, G. A., & Lettich, E. (2002). Cortical stimulation mapping of language cortex by using a verb generation task: Effects of learning and comparison to mapping based on object naming. *Journal of Neurosurgery*, 97(1), 33–38. <http://dx.doi.org/10.3171/jns.2002.97.1.0033>.
- Palmer, B. W., Boone, K. B., Lesser, I. M., & Wohl, M. A. (1998). Base rates of “impaired” neuropsychological test performance among healthy older adults. *Archives of Clinical Neuropsychology*, 13(6), 503–511. [http://dx.doi.org/10.1016/S0887-6177\(97\)00037-1](http://dx.doi.org/10.1016/S0887-6177(97)00037-1).
- Papagno, C., Casarotti, A., Comi, A., Gallucci, M., Riva, M., & Bello, L. (2012). Measuring clinical outcomes in neuro-oncology. A battery to evaluate low-grade gliomas (LGG). *Journal of Neuro-Oncology*, 108(2), 269–275. <http://dx.doi.org/10.1007/s11060-012-0824-5>.
- Pereira, L. C. M., Oliveira, K. M. L., Abbate, G. L., Sugai, R., Ferreira, J. A., & Motta, L. A. (2009). Outcome of fully awake craniotomy for lesions near the eloquent cortex: Analysis of a prospective surgical series of 79 supratentorial primary brain tumors with long follow-up. *Acta Neurochirurgica*, 151(10), 1215–1230.
- Polczynska, M. (2009). New tests for language mapping with intraoperative electrical stimulation of the brain to preserve language in individuals with tumors and epilepsy: A preliminary follow-up study. *Poznan Studies in Contemporary Linguistics*, 45(2), 261–279.
- Richardson, F. M., Seghier, M. L., Leff, A. P., Thomas, M. S. C., & Price, C. J. (2011). Multiple routes from occipital to temporal cortices during reading. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 31(22), 8239–8247. <http://dx.doi.org/10.1523/JNEUROSCI.6519-10.2011>.
- Rofes, A. (2012). *The verb in sentence context test: Standardization and application in awake neurosurgery*. Unpublished master dissertation. University of Groningen, Groningen.

- Rönnlund, M., Nyberg, L., Bäckman, L., & Nilsson, L.-G. (2005). Stability, growth, and decline in adult life span development of declarative memory: Cross-sectional and longitudinal data from a population-based study. *Psychology and Aging*, 20(1), 3–18. <http://dx.doi.org/10.1037/0882-7974.20.1.3>.
- Roux, F.-E., Boulanouar, K., Lotterie, J.-A., Mejdoubi, M., LeSage, J. P., & Berry, I. (2003). Language functional magnetic resonance imaging in preoperative assessment of language areas: Correlation with direct cortical stimulation. *Neurosurgery*, 52(6), 1335–1347.
- Roux, F.-E., Dufor, O., Lauwers-Cances, V., Boukhatem, L., Brauge, D., Draper, L., et al. (2011). Electrostimulation mapping of spatial neglect. *Neurosurgery*, 69(6), 1218–1231.
- Roux, F., Lubrano, V., Lauwers-Cances, V., Tremoulet, M., Mascott, C., & Demonet, J. (2004). Intra-operative mapping of cortical areas involved in reading in mono- and bilingual patients RID B-3227-2008. *Brain*, 127, 1796–1810.
- Sanai, N., & Berger, M. S. (2010). Intraoperative stimulation techniques for functional pathway preservation and glioma resection. *Neurosurgical Focus*, 28(2), E1.
- Sanai, N., Mirzadeh, Z., & Berger, M. S. (2008). Functional outcome after language mapping for glioma resection. *New England Journal of Medicine*, 358(1), 18–27.
- Santini, B., Talacchi, A., Squintani, G., Casagrande, F., Capasso, R., & Miceli, G. (2012). Cognitive outcome after awake surgery for tumors in language areas. *Journal of Neuro-Oncology*. <<http://www.ncbi.nlm.nih.gov/pubmed/22350433>>.
- Satoer, D., Kloet, A., Vincent, A., Dirven, C., & Visch-Brink, E. (2013). Dynamic aphasia following low-grade glioma surgery near the supplementary motor area: A selective spontaneous speech deficit. *Neurocase*. <http://dx.doi.org/10.1080/13554794.2013.841954>.
- Satoer, D., Visch-Brink, E., Smits, M., Kloet, A., Looman, C., Dirven, C., et al. (2014). Long-term evaluation of cognition after glioma surgery in eloquent areas. *Journal of Neuro-Oncology*, 116(1), 153–160. <http://dx.doi.org/10.1007/s11060-013-1275-3>.
- Satoer, D., Vork, J., Visch-Brink, E., Smits, M., Dirven, C., & Vincent, A. (2012). Cognitive functioning early after surgery of gliomas in eloquent areas. *Journal of Neurosurgery*, 117(5), 831–838. <http://dx.doi.org/10.3171/2012.7.JNS12263>.
- Schmand, B., Groenink, S. C., & van den Dungen, M. (2008). Letterfluency: Psychometrische eigenschappen en Nederlandse normen. *Tijdschrift voor Gerontologie en Geriatrie*, 39(2), 64–74. <http://dx.doi.org/10.1007/BF03078128>.
- Shattuck-Hufnagel, S., & Klatt, D. H. (1980). How single phoneme error data rule out two models of error generation. In V. A. Fromkin (Ed.), *Errors in linguistic performance: Slips of the tongue, ear, pen, and hand* (pp. 35–46). New York-London-Toronto-Sydney-San Francisco: Academic Press.
- Sidak, Z. K. (1967). Rectangular confidence regions for the means of multivariate normal distributions. *Journal of the American Statistical Association*, 62, 626–633.
- Smits, M., Visch-Brink, E., Schraa-Tam, C. K., Koudstaal, P. J., & van der Lugt, A. (2006). Functional MR imaging of language processing: An overview of easy-to-implement paradigms for patient care and clinical research. *Radiographics: A Review Publication of the Radiological Society of North America Inc*, 26(Suppl. 1), S145–S158. <http://dx.doi.org/10.1148/rg.26si065507>.
- Snitz, B. E. (2009). Effects of age, gender, education and race on two tests of language ability in community-based older adults. *International Psychogeriatrics*, 21(6), 1051.
- Snodgrass, J. G., & Vanderwart, M. (1980). A standardized set of 260 pictures: Norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology: Human Learning and Memory*, 6(2), 174–215.
- Spena, G., Nava, A., Cassini, F., Pepoli, A., Bruno, M., D'Agata, F., et al. (2010). Preoperative and intraoperative brain mapping for the resection of eloquent-area tumors. A prospective analysis of methodology, correlation, and usefulness based on clinical outcomes. *Acta Neurochirurgica*, 152(11), 1835–1846.
- Talacchi, A., d'Avella, D., Denaro, L., Santini, B., Meneghelli, P., et al. (2012). Cognitive outcome as part and parcel of clinical outcome in brain tumor surgery. *Journal of Neuro-Oncology*, 108(2), 327–332. <http://dx.doi.org/10.1007/s11060-012-0818-3>.
- Talacchi, A., Santini, B., Savazzi, S., & Gerosa, M. (2011). Cognitive effects of tumour and surgical treatment in glioma patients. *Journal of Neuro-Oncology*, 103(3), 541–549.
- Teixidor, P., Gatignol, P., Leroy, M., Masuet-Aumatell, C., Capelle, L., & Duffau, H. (2007). Assessment of verbal working memory before and after surgery for low-grade glioma. *Journal of Neuro-Oncology*, 81(3), 305–313.
- Trinh, V. T., Fahim, D. K., Shah, K., Tummala, S., McCutcheon, I. E., Sawaya, R., et al. (2013). Subcortical injury is an independent predictor of worsening neurological deficits following awake craniotomy procedures. *Neurosurgery*, 72(2), 160–169. <http://dx.doi.org/10.1227/NEU.0b013e31827b9a11>.
- Van Eycken & De Wever (2006). *Cancer incidence and survival in Flanders, 2000–2001*. Brussels: Flemish Cancer Registry Network (VLK).
- Van Geemen, K., Herbet, G., Moritz-Gasser, S., & Duffau, H. (2013). Limited plastic potential of the left ventral premotor cortex in speech articulation: Evidence from intraoperative awake mapping in glioma patients. *Human Brain Mapping*. <http://dx.doi.org/10.1002/hbm.22275>.
- Van Loon-Vervoorn, W. A. (1989). *Eigenschappen van basiswoorden*. Lisse, The Netherlands: Swets and Zeitlinger.
- Visch-Brink, E., & Bajema, I. (2001). *BOX. Lexicaal semantische afasitherapie*. Amsterdam, The Netherlands: Pearson.
- Warrington, E. K. (1997). The graded naming test: A restandardisation. *Neuropsychological Rehabilitation*, 7(2), 143–146.
- Weijters, T. (1983). *Positiewoordenboek van de Nederlandse Taal*. Lisse, The Netherlands: Swets and Zeitlinger.
- Zec, R. F., Burkett, N. R., Markwell, S. J., & Larsen, D. L. (2007). A cross-sectional study of the effects of age, education, and gender on the Boston Naming Test. *The Clinical Neuropsychologist*, 21(4), 587–616. <http://dx.doi.org/10.1080/13854040701220028>.