Brain Stimulation 15 (2022) 87–95

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Jargonaphasia as a disconnection syndrome: A study combining white matter electrical stimulation and disconnectome mapping

Davide Giampiccolo [a, b], Sylvie Moritz-Gasser [b, c, d], Sam Ng [b, c], Anne-Laure Lemaître [b, c], Hugues Duffau [b, c, *]

[a] *Section of Neurosurgery, Department of Neurosciences, Biomedicine and Movement Sciences, University Hospital, Verona, Italy*
[b] *Department of Neurosurgery, Gui de Chauliac Hospital, Montpellier University Medical Center, Montpellier, France*
[c] *Team "Neuroplasticity, Stem Cells and Low-grade Gliomas," INSERM U1191, Institute of Genomics of Montpellier, University of Montpellier, Montpellier, France*
[d] *Department of Speech-Language Pathology, University of Montpellier, Montpellier, France*

A R T I C L E I N F O

Article history:
Received 11 September 2021
Received in revised form
16 October 2021
Accepted 14 November 2021
Available online 18 November 2021

Keywords:
Arcuate fasciculus
Jargon
Jargon aphasia
Phonology
Semantics
Brain mapping

A B S T R A C T

Background: In jargonaphasia, speech is fluent but meaningless. While neuropsychological evaluation may distinguish a neologistic component characterised by non-word production and a semantic component where pronounced words are real but speech is senseless, how this relates to the underlying white matter anatomy is debated.
Objective: To identify white matter pathways causally involved in jargonaphasia.
Methods: We retrospectively screened the intraoperative brain mapping data of 571 awake oncological resections using direct cortico-subcortical electrostimulation. Jargonaphasia was induced in 17 patients (19 sites) during a naming task. Stimulation sites were normalized to the Montreal Neurological Institute template space and used to generate individual disconnectome maps. Non-parametric voxelwise one and two sample t-tests were performed to identify the underlying white matter anatomy.
Results: Jargonaphasia was induced only during stimulation of the left hemisphere. No cortical stimulation generated jargonaphasia. Subcortical sites causally associated with jargonaphasia clustered in 3 regions: in the temporal lobe (middle to inferior temporal gyri; $n = 12$), in the parietal lobe (supramarginal gyrus; $n = 3$) and in the temporal stem ($n = 4$). Disconnectome analysis indicated the inferior-fronto-occipital fasciculus (IFOF) was damaged in both neologistic and semantic jargonaphasia, while the involvement of the arcuate fasciculus was specific to neologistic jargonaphasia.
Conclusion: For the first time, we show that jargonaphasia is induced by white matter stimulation, hinting at disconnection. As IFOF disconnection unites both variants, these may represent a continuum of disorders distinguished by semantic impairment. Conversely, damage to the arcuate fasciculus in addition to the IFOF is specific to neologistic jargonaphasia, thus suggesting a dual-disconnection syndrome.

1. Introduction

"Twas brillig, and the slithy toves
Did gyre and gimble in the wabe;
All mimsy were the borogoves,
And the mome raths outgrabe."

(Carroll L., The Jabberwock, 1871).

Language in the nonsense poem *The Jabberwock* may be considered among the first literary illustrations of jargon aphasia, or jargonaphasia, a clinical disorder where speech is fluent, but incomprehensible. The term "jargon" was first used by Hughlings-Jackson few years later to describe language in some patients that could articulate but not communicate. Two forms were described: the first was characterised by non-words (*"If he " says" anything, it is always " Yabby," or whatever his jargon may be; in reality he says*

* Corresponding author. Department of Neurosurgery, Gui de Chauliac Hospital, Montpellier University Medical Center, 80 Avenue Augustin Fliche, 34295, Montpellier, France.
E-mail address: h-duffau@chu-montpellier.fr (H. Duffau).

https://doi.org/10.1016/j.brs.2021.11.012

Abbreviations

STG	superior temporal gyrus
MTG	middle temporal gyrus
ITG	inferior temporal gyrus
vATL	ventral anterior temporal lobe
AF	arcuate fasciculus
IFOF	inferior fronto-occipital fasciculus
ILF	inferior longitudinal fasciculus
UF	uncinate fasciculus
DTI	diffusion tensor imaging
DES	direct electric stimulation

nothing with these utterances; they have no propositional value whatever.") [1]. In the second, the patient pronounced real words but dissociated from their meaning *("Sometimes the utterance is, what to a healthy person is, a word, as " man," " one," " awful". Such a word is, for use, no better than jargon in the mouth of the speechless patient; it is not a word to him; "man," as a recurring utterance, is not a symbol for a human being. The so-called word comes out, just as "yabby" does, and means no-more, means nothing.*") [1].

This distinction carries on in contemporary neologistic and semantic jargonaphasia. Neologistic jargonaphasia [2] (e.g. "Griblera" for "curtain") is a form identified by non-word production with peculiar legalities, especially in the phonological domain. Non-words respect phonotactics [3], are often phonologically related to the target words [4], and are composed of phonemes that reflect normal phoneme frequency in spoken language [5]. Conversely, pronunciation of real but contextually inappropriate words (e.g. the ottoman sits the sharpest) is characteristic of semantic jargonaphasia [2]. In this form, semantic deficits seem predominant, with comprehension being impaired across sensory modalities [6].

Neuropsychologically, neologistic and semantic jargon seem clearly distinguishable. However, dissociation of these two variants is less clear-cut in the clinical context. These forms of jargon can overlap or even co-occur [2] and it has been questioned whether these may instead represent a continuum [3,7,8]. This may be supported by their clinical progression: neologistic jargonaphasia commonly evolves in its semantic variant [9], with both recovering into void, anomic speech [3,7,10]. In this scenario, understanding the underlying anatomical substrates may clarify communalities and differences between these syndromes.

Recent voxel lesion-symptom mapping studies in stroke suggest that jargonaphasia is associated with damage to the temporo-parietal junction [11]. Large stroke damage implies white matter disconnection [12], and early studies proposed jargonaphasia to arise from disconnection of the arcuate fasciculus (AF) [3]. The AF (also described as long segment of the arcuate fasciculus), together with its indirect anterior/SLF-III and posterior segments (pAF) [13], represents a core dorsal network involved in phonological encoding. Its damage may therefore explain some of the phonological disorders classically associated with neologistic jargonaphasia. However, while the AF is often disconnected in ischemic stroke, the occurrence of jargonaphasia is rare and advocates for the involvement of a wider network. Other language pathways that map word to meaning within the ventral stream [14,15], such as the inferior fronto-occipital (IFOF), inferior longitudinal (ILF) and uncinate (UF) fasciculi, may therefore have relevance - particularly in those cases where semantic impairment is predominant.

Direct electrical stimulation in awake patients is the gold standard to identify functional anatomy *in vivo*, as it can causally target functional networks with unparalleled precision [16]. However, evidence for jargonaphasia during intraoperative stimulation is anecdotal [17] and cortical sites are reputed non-specific [18]. To our knowledge, subcortical stimulation leading to jargonaphasia has never been reported, hence the possible role of white matter disconnection is still unclear in this rare disorder.

In the current study, we took advantage of a unique cohort of patients who experienced jargonaphasia during awake neurosurgery while performing a naming task [16]. We investigated the prevalence and location of jargonaphasic responses induced by intraoperative stimulation at cortical and subcortical levels. In addition, we studied the underlying white matter pathways using connectome-based lesion-symptom methods [12] to analyse structural similarities and differences underlying this syndrome and its variants.

2. Material and methods

2.1. Participants

The study design was a retrospective case collection. We initially screened intraoperative stimulation data of 571 consecutive awake surgeries performed at our institution from 2015 to 2021. Of these, we selected patients meeting the following criteria: (i) at least one site inducing intraoperative jargonaphasia during a naming task in three non-consecutive trials, (ii) perioperative language assessment, (iii) a histologically-proven diffuse low-grade glioma to maintain homogeneity across the sample. Intraoperatively elicited semantic jargonaphasia consisted in reproducible (three non-consecutive stimulation trials) sequences of utterances (real words) that were semantically and contextually unrelated to the target word. Conversely, neologistic jargonaphasia was classified as reproducible (three non-consecutive stimulation trials) but unintelligible sequences of utterances (pseudoword or non-word) that replaced the target word.

2.2. Standard protocol approvals, registrations, and patient consents

The study proposal is in accordance with ethical standards of the Declaration of Helsinki and ethical standards of our institution (IRB registration number: 202000557). Our standard surgical approach includes awake craniotomy with stimulation mapping by means of direct electrostimulation. All patients provided written informed consent.

2.3. Surgical procedure and intraoperative mapping

The intraoperative mapping technique for cortical and subcortical function in patients undergoing awake craniotomy has been detailed in previous publications [19]. All surgeries were performed by the same surgeon (HD). Briefly, cortical stimulation was performed using a bipolar electrode with 5 mm spacing (0.5 mm diameter electrode tips, 60 Hz, biphasic stimulation, 1 ms pulse width duration, current amplitude 2–5 mA; stimulation duration less than 4 s; NIMBUS Stimulator, Newmedic, France) after tumour contours were determined using intraoperative ultrasonography. Cortical mapping started at 1.5 mA and increased of 0.5 mA steps of until reliable behavioural impairments (motor, articulatory, sensory) were induced. This optimal threshold was used throughout the mapping session. Intraoperative tasks were performed as a double-task (a behavioural task (Fig. 1) combined with rhythmic contralateral arm movement) [20]. An experienced speech therapist (SMG) performed the cognitive monitoring, which was blinded to the time of stimulation. Once resection proceeded subcortically, this was interrupted whenever behavioural impairments were

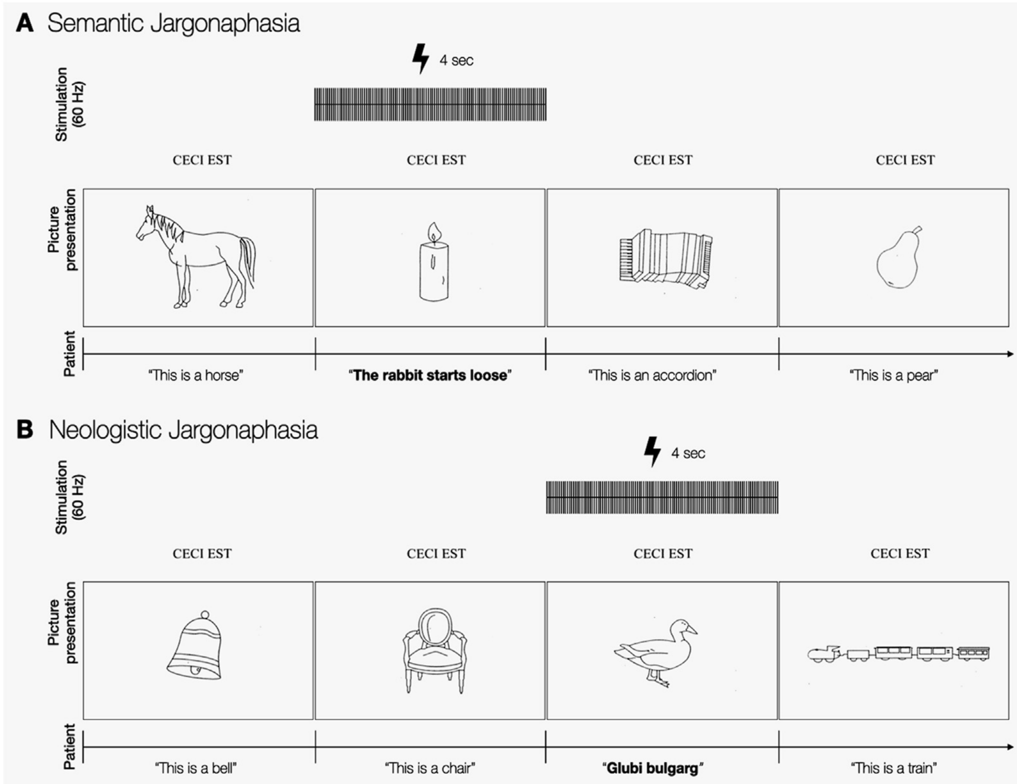

Fig. 1. Examples of jargonaphasia induced by DES during a naming taska
) Stimulation inducing semantic jargonaphasia during the second item presented (in bold). The stimulation was repeated on non-consecutive trails for consistency (not shown). b) Stimulation inducing neologistic jargonaphasia during the third item presented (in bold). The stimulation was repeated on non-consecutive trails for consistency (not shown).

induced by subcortical stimulation. After tumour removal, cortical and subcortical epicenters were identified with sterile number tags and a picture was acquired to allow offline data processing [21].

2.3.1. Mapping of jargonaphasia

For the purpose of this study, analysis of intraoperative data focused on the naming task (*Denomination Orale* (DO 80)) [22]. The DO 80 includes 80 black and white pictures belonging to various living and manufactured semantic categories to be named by the patient. Besides jargonaphasia, electrostimulation during awake surgery may induce different language disorders, such as anomia (inability to name a picture), articulation disorders (speech slurring through inhibition (relaxation) or disinhibition (dystonia) of orofacial movement), phonological paraphasia (the named picture is incorrect but phonologically related; e.g., "barana" instead of "banana") or semantic paraphasia (the named picture is incorrect but semantically related; e.g., "elephant" instead of "lion") [23]. Intraoperatively, the patient was asked to start with 'This is a … ' to distinguish anomia/jargonaphasia from articulation disorders. To ensure accurate evaluation of patients' intraoperative performance, a pre-operative examination was systematically carried out. The speech therapist started each individual trial and a sound signal indicated to the neurosurgeon that each item was to be displayed to the patient 500 ms later. Items were shown every 4 s and patients were tested throughout mapping and resection without interruption. Intraoperatively elicited semantic jargonaphasia consisted in reproducible (three non-consecutive stimulation trials) sequences of utterances that were semantically and contextually (e.g. "The rabbit starts loose" instead of "This is a candle") unrelated to the task performed when compared to the target word assessed preoperatively (Fig. 1a). Conversely, neologistic jargonaphasia was classified as reproducible (three non-consecutive stimulation trials) but unintelligible sequences of utterances (e.g. "Glubi Bulgarg" instead of "This is a duck") when compared to the target word assessed preoperatively (Fig. 1b). Other language or neuropsychological disorders co-occurring for a given stimulation site were recorded.

2.3.2. Extraoperative language and neuropsychological assessment

Naming abilities (DO 80), non verbal semantic associations (Pyramid and Palm tree test (PPTT)) [24], verbal fluency (number of non-repeated animals/non-repeated words starting with the letter "P" that could be pronounced within 2 min) and reading ability (ECLA 16+ composed of text reading reading of regular, irregular and pseudo-words) [25] were assessed preoperatively, postoperatively (2–4 days after surgery) and at a 3-months follow-up. This was accompanied by a qualitative evaluation of spontaneous speech. Additional neuropsychological tests were performed according to tumour location and clinical need. All language assessments were performed by the same experienced speech therapist (SMG). Performance raw scores were aligned to published French normative data (adjusted according to educational level, age, and sex) and converted into z-scores, considered impaired for values below −1.65.

2.4. Imaging acquisition and processing

Structural MRI datasets were collected preoperatively, postoperatively and at a follow-up of 3 months on a 3T MR imaging scanner (Skyra, Siemens Medical Systems, Erlangen, Germany), as part of the routine management protocol. For the purpose of the current work, standard gadolinium-enhanced isovolumetric T1-weighted images (repetition time 1.880/1.700 ms; echo time 3.4/2.5 ms; inversion time 1100/922 ms; field of view 256 × 256/250 × 250 mm; flip angle 15/9°; voxel size 1 × 1 × 1 mm^3 and 176 axial slices) were used. Fluid-attenuated inversion recovery (FLAIR) sequences were also acquired for each patient at each time point. The individual brain anatomy with the related resection cavity was normalized to a template of 152 patients (MNI; Montreal Neurological Institute) using an enantiomorphic normalization from SPM12. 3-month postoperative T1 MRI were used to exclude immediate postoperative brain-shift. As previously mentioned, MNI coordinates of each stimulation point were recorded using operative reports and intraoperative photographs. To increase the accuracy of this re-positioning work, a 3D pial-mesh reconstruction of each normalized 3-month postoperative MRI was generated using Brain VISA Software (Version 5.0, CEA I2BM, CATI Neuroimaging, France). This mesh allows a 3D navigation through anatomical structures and an automatic MNI coordinates-surface-matching of the 3D model with a high level of inter-rater reliability [26].

2.4.1. Disconnectome analysis

To investigate white matter pathways corresponding to different intraoperative impairments, a disconnectome analysis was performed using each stimulation site as ROI. Following normalization to MNI, a spherical volume of interest (VOI) with a 2.5 mm radius was centred on the coordinates of each effective site in each patient using MarsBaR. The sphere diameter was 5 mm to match the tip distance of the bipolar probe. The probability of disconnection induced by each stimulation was computed as a disconnectome map in BCBtoolkit software [12]. The maps were generated from the tractograms of 20 unrelated right-handed adults processed using High Angular Resolution Diffusion Imaging tractography (spherical deconvolution) from the 7T dataset of the Human Connectome Project. For each lesion, the tractograms were averaged together so that each voxel represented a probability of disconnection from 0 to 1 [12]. Each patient's disconnection profile was then used to investigate if disruption of specific white matter pathways were associated with language interference. To do so, non-parametric statistical comparisons were performed on disconnection maps using FSL's *randomise* with 5000 permutations and threshold-free cluster enhancement [27]. Family-wise error rate (FWE)-corrected one and two sample t-tests were used to assess which disconnection profiles were associated with each language impairment. To recognize the involved white matter tracts, we considered voxels significant at $p < 0.05$corrected based on the FSL-randomise contrast maps and white matter tracts from atlas computed on 1065 healthy subjects from the same 7T HCP dataset [28] were superimposed. Finally, a tractwise analysis using template tracts from the same 1065 7T HCP dataset (http://brain.labsolver.org/diffusion-mri-templates/tractography) was performed in DSI Studio to assess individual extent of white matter disconnection based on each resection cavity. Resection of more than 50% of streamlines was considered as disconnection.

2.5. Statistical analysis

Statistical analysis was performed using SPSS Statistics (16, IBM, Armonk, NY, USA). Normality of variable distribution was evaluated using a Kolmogorov-Smirnov test. Non-parametric voxel-based one and two sample t-tests were performed with FSL using threshold-free cluster enhancement and FWE-corrected[27]. A Wilcoxon signed-rank test was used to evaluate variation in language and neuropsychological performance at the different time-points.

2.6. Data and software availability

The clinical data is available on reasonable request to the first or last author. Software used for this study included: SPM12 (http://www.fil.ion.ucl.ac.uk/spm); MarsBaR (http://marsbar.sourceforge.net); ITK-SNAP (http://www.itksnap.org); BrainVISA (https://brainvisa.info/web/); DSI Studio (http://dsi-studio.labsolver.org/); MRIcron and MRIcroGL (https://www.nitrc.org); Surf Ice (https://www.nitrc.org/projects/surfice/); Cogent 2000 (http://www.vislab.ucl.ac.uk); FSL (https://fsl.fmrib.ox.ac.uk/fsl).

3. Results

3.1. Patients

Out of 571 patients, we identified 17 patients (9F, 14 right-handers, 38.7 ± 14.5 years old) that experienced intraoperative jargonaphasia. Of these, 11 patients experienced intraoperative neologistic jargonaphasia and 6 semantic jargonaphasia. All cases of jargonaphasia occurred during surgery in the left hemisphere (Fig. 2). Table 1 summarizes patients' sociodemographic and clinical data. In all patients, preoperative language assessment was normal.

3.2. Spatial distribution of stimulation sites inducing jargonaphasia

Jargonaphasia was never observed following cortical stimulation in the 571 patients screened. However, subcortical stimulation caused jargonaphasia in 17 patients (neologistic: 12; semantic: 7): two patients experienced this in two separate locations. Overall, jargonaphasia clustered in 3 regions: in the temporal lobe (middle to inferior temporal gyri; 12 sites), in the parietal lobe (supramarginal gyrus; 3 sites) and in the temporal stem (4 sites). Neologistic jargonaphasia sites were in the temporal lobe at the level of the middle/inferior temporal gyri (9 sites) and in the parietal lobe following its arching over the insula (3 sites). Semantic jargonaphasia occurred mostly at the level of the temporal stem (5 sites), or along the middle temporal gyrus (2 sites). 3D reconstructions as well as axial, coronal and sagittal sectional planes for subcortical sites inducing jargonaphasia have been provided in Fig. 2A.

3.3. Disconnectome analysis

Disconnectome maps were generated from the stimulation sites inducing jargonaphasia. Overall, a non-parametric one sample *t*-test showed that intraoperative jargonaphasia occurred when stimulation was applied to fibres of the arcuate fasciculus (AF), the posterior segment of the arcuate fasciculus (pAF) and the inferior fronto-occipital fasciculus (IFOF) ($p < 0.05_{\text{corrected}}$; 5000 permutations). Variant-specific non-parametric one-sample *t*-test showed that sites associated with neologistic jargonaphasia were significantly linked to the same tracts: AF, pAF, and IFOF ($p < 0.05_{\text{corrected}}$; 5000 permutations), whereas semantic jargonaphasia sites were significantly associated with the IFOF only ($p < 0.05_{\text{corrected}}$; 5000 permutations) (Fig. 3). This was confirmed by a non-parametric two-sample *t*-test which indicated that the AF and its posterior segment were significantly more associated with neologistic jargonaphasia than semantic jargonaphasia ($p < 0.05_{\text{corrected}}$; 5000 permutations) (Suppl. Fig. 1).

3.4. Postoperative assessment and resection analysis

Immediately (2–4 days) following surgery, language ability was significantly impaired in all domains across patients (on average falling below 3 standard deviations in the French normative values)

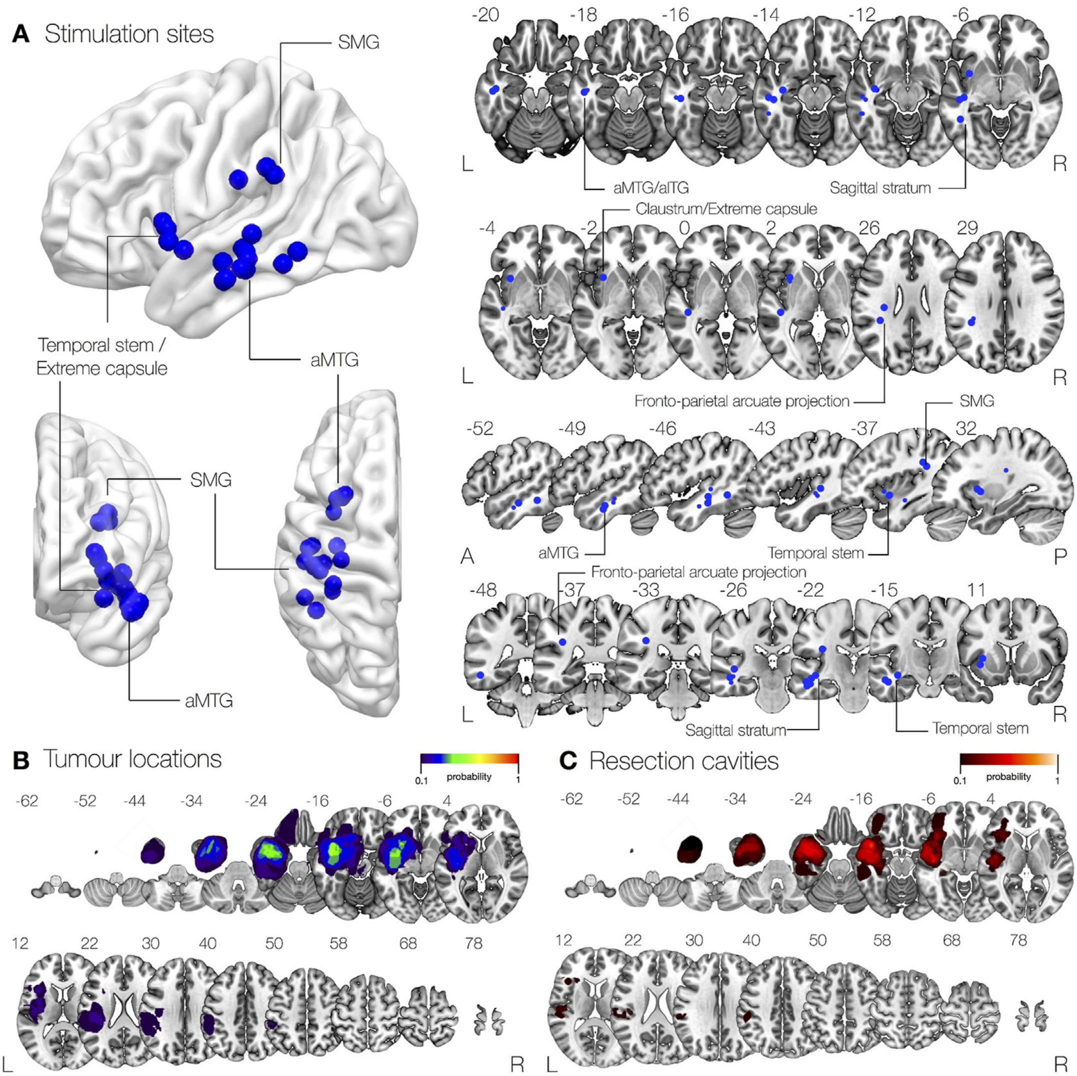

Fig. 2. Spatial distribution of jargonaphasia sites, tumour and cavity locationsa
) On the left, tridimensional reconstruction of sites inducing jargonophasia, represented as blue spheres. On the right, sectional anatomy with sites for jargonaphasia indicated as blue spheres. These were enlarged for better visualisation. b) Distribution of tumour locations. c) Distribution of resection locations. aMTG: anterior middle temporal gyrus: aITG: anterior inferior temporal gyrus; SMG: supramarginal gyrus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Demographic; anatomical and stimulation data relating to patient cohort.

No	Sex	Age	YoE	H	Side	Type of Jargon	Type of Lesion	No of Surgery	Tumour location	Tumour (cc)	Resection (cc)	MNI coordinates (x; y; z)
1	M	27	9	R	L	semantic	LGG	1	I	12.28	13.6	−30.8;13.5; 5.5
2	F	18	12	R	L	neologistic	LGG	1	TI	76.6	66.06	a)-47.5;-25;-10.1; b) −52;-22;-14
3	M	35	12	R	L	neologistic	LGG	1	FI	36.4	15.6	−33.5;22; 25.5
4	M	35	12	R	L	neologistic	LGG	2	TI	175.4	91.7	−46;-48;- 7
5	F	68	12	R	L	neologistic	LGG	1	T	9.1	10.7	−47;-24;-15
6	M	26	15	R	L	neologistic	LGG	1	P	56.8	27.3	−37.4;-37.7; 27.6
7	M	37	14	R	L	neologistic	LGG	1	T	22.7	14.9	−53.5;-42;-12.5
8	F	56	ND	R	L	neologistic	LGG	1	P	15.48	11.1	−36.9; −34.1; 31
9	F	38	17	R	L	semantic	LGG	1	TI	44	47.9	−41; −23; 5.5
10	F	48	15	R	L	semantic	LGG	3	F	28.12	34.2	−32.4;11.4; 2.4
11	F	34	14	R	L	semantic	LGG	1	FI	125	116.3	−35;-14;-13
12	F	65	14	R	L	neologistic	LGG	1	T	20.4	27.2	−45;-15;-19
13	M	27	17	R	L	semantic	LGG	1	TI	26.3	27.4	−37.5;4;-6.9
14	M	19	12	L	L	neologistic	LGG	1	T	95.3	96	−45;-24; −7
15	M	40	9	L	L	neologistic	LGG	2	TI	66.3	62.4	−48.1;-13.9; −20
16	F	50	12	L	L	semantic	LGG	1	FI	57.5	35.1	a)-32.1; 12.4; 3.3 b) −35.1;11;-3
17	F	36	14	R	L	neologistic	LGG	1	I	17.8	7.9	−44; −27; 1

YoE: Years of education: Hand: handedness; LGG: Lower grade glioma.

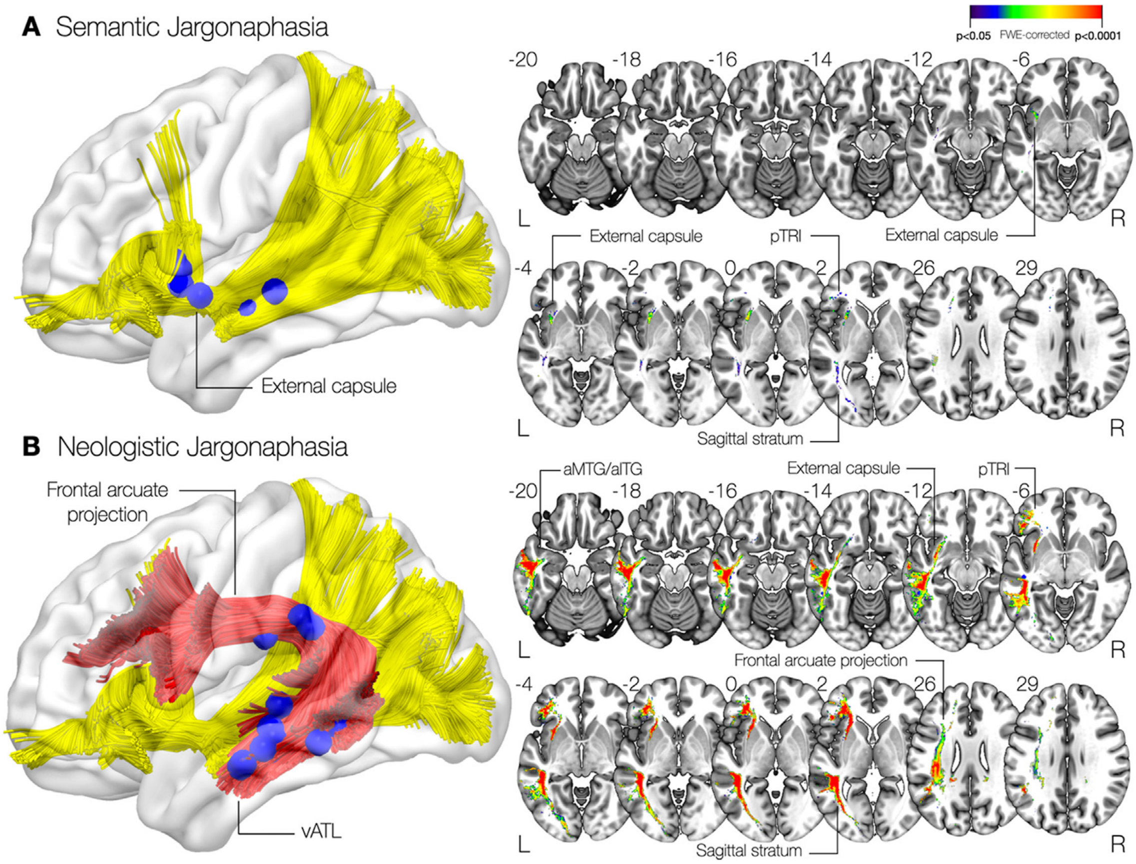

Fig. 3. Disconnectome analysis for sites inducing semantic and neologistic jargonaphasia
a) Disconnectome analysis for sites inducing semantic jargonaphasia indicated a role for superficial (temporal) and deep (parietal) layers of the IFOF (in yellow) b) Disconnectome analysis for sites inducing neologistic jargonaphasia indicated a role for superficial (temporal) and deep (parietal) layers of the IFOF, but also for projections of the arcuate fasciculus which were specific for this variant (IFOF: yellow; Arcuate fasciculus: red). Most represented white matter tracts have been dissected using a template from high-angular-resolution diffusion MRI data of 1065 healthy subjects within the 7T Human Connectome Project (HCP) database [26]. *Blue spheres: sites for intraoperative jargonaphasia. aMTG: anterior middle temporal gyrus: aITG: anterior inferior temporal gyrus; pTRI: pars triangularis; vATL: ventral anterior temporal lobe.* (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(Table 2). All patients who had experienced intraoperative neologistic jargonaphasia produced frequent phonological paraphasias in spontaneous speech at this immediate postoperative timepoint, and neologistic jargonaphasia itself was present in three patients (Table 3). Semantic paraphasias and/or perseverations were present during spontaneous speech in both groups (all patients with semantic and 5 patients with neologistic jargonaphasia). At the 3-month follow-up, overall language ability reverted to normal except for a worsening in text reading in 7 patients (Wilcoxon signed-rank: $z = -2.04$; $p < 0.041$). Data on perioperative and follow-up language and neuropsychological assessment are shown respectively in Table 2 and Supplementary Table 1, data on spontaneous speech is reported in Table 3.

Finally, a tractwise analysis using template tracts was performed to investigate proximity and extent of disconnection of the AF, its posterior segment and the IFOF in each patient (Table 4). The ILF and the uncinate fasciculus were also included as controls. Overall, the arcuate fasciculus was preserved in 15 patients (close or within the resection cavity in 9) and disconnected in two patients. Interestingly, in these two patients only the anterior/middle inferior temporal projections were disconnected with preservation of the tract core and the superior temporal projections. The IFOF was disconnected in 1 patient and preserved in 16 patients (close or within the resection cavity in 14 patients). The posterior segment was never resected but laid in proximity of the cavity in 2 patients. Conversely, the ILF and the uncinate were resected in most patients (ILF: 6/11 patients; Uncinate: 8/11 patients).

4. Discussion

Direct electrical stimulation in awake neurosurgical patients represents the most reliable method to causally assess function of language pathways [29]. In this study, we reviewed intraoperative stimulation data of 571 awake surgeries to show that direct stimulation caused jargonaphasia in only 17 patients. This is, to our knowledge, the largest intraoperative dataset for this disorder to date. Furthermore, we showed for the first time that jargonaphasia occurred following subcortical stimulation, indicating this rare language dysfunction may reflect a transient disconnection of subcortical white matter anatomy. Therefore, we used disconnectome lesion-symptom methods [12] to identify networks involved in neologistic and semantic jargonaphasia. On one hand, our results advocate for a continuum among variants of jargonaphasia determined by common subcortical damage. Disconnection of the IFOF, a main ventral pathway linking word to meaning, may represent a core anatomical substrate for both variants, thus justifying the historical classification of jargonaphasia as a comprehension disorder. Critically, damage to this white matter pathway may underlie not only language: cognitive impairments distinctive of both semantic and neologistic jargonaphasia, such as

Table 2
Perioperative and follow-up language assessment.

Task	Average z-score	SD
Phonologic fluency		
Preoperative	−0.37	1.04
Immediate postoperative	−2.55	1.22
3 Mo Follow-up	−0.87	1.25
Semantic fluency		
Preoperative	−0.04	0.92
Immediate postoperative	−1.98	1.38
3 Mo Follow-up	−0.02	1.16
Pyramids and Palm Tree test (PPTT)		
Preoperative	−0.47	1.06
Immediate postoperative	−2.49	5.79
3 Mo Follow-up	−0.32	1.49
Denomination Orale (DO 80)		
Preoperative	0.13	0.76
Immediate postoperative	−6.34	11.29
3 Mo Follow-up	−0.16	1.7
Text Reading		
Preoperative	−0.17	1
Immediate postoperative	−3.92	2.27
3 Mo Follow-up	−2.27	2.71
Word reading (regular)		
Preoperative	0.16	0.73
Immediate postoperative	−4.64	8.04
3 Mo Follow-up	−0.4	2.54
Word reading (irregular)		
Preoperative	−0.1	2.95
Immediate postoperative	−3.11	4.85
3 Mo Follow-up	−1.01	4.1
Word reading (non-words)		
Preoperative	0.15	1.02
Immediate postoperative	−3.93	4.68
3 Mo Follow-up	−1.28	3.4

deficits in self-monitoring, may also be determined by IFOF dysfunction. On the other hand, however, our results also emphasized distinctions marked by damage to the AF and pAF, core dorsal connections linking word to action. When stimulation and hence disconnection of the IFOF co-occurred with that of the AF and its posterior segment, jargonaphasia was characterised by production of non-words, with phonological disorders in this variant determined by dual-disconnection.

A distinction between neologistic and semantic jargonaphasia has been long debated [2,3,7,8]. While some are in favour of a sharp division of these two components [2], others have proposed they may represent a continuum characterised by progressive recovery of real word production [3,7,9]. Comprehension disorders have been shown to characterise both forms of jargonaphasia [3,8,30], suggesting these may have a shared neuropsychological background. Shared disconnection of the IFOF may anatomically underlie comprehension deficits in both neologistic and semantic jargonaphasia. By connecting the occipital, temporal and parietal lobe with the frontal lobe [31,32], the IFOF represent a critical ventral stream pathway passing through the external capsule [14]. Stimulation sites clustering along the course of the IFOF, within the temporal lobe but also in the parietal lobe, suggest involvement of both its superficial and deep layers [26,31]. Damage to these projections supporting verbal and non-verbal semantics [26,33] may thus underlie verbal and non-verbal comprehension disorders in jargonaphasia. Hence, disconnection of the IFOF may induce a breakdown of semantic associations in both neologistic and semantic jargonaphasia impacting comprehension and potentially production, with sentences becoming meaningless regardless of words pronounced being real or not. These clinical signs may thus represent a spectrum of disorders, as suggested by clinical examination and recovery pattern [3,7,9].

It has been proposed that jargonaphasia may exceed language dysfunction and represent “an intersection of impaired language and cognitive systems” [34]. Cognitive impairments in jargonaphasia may be determined by damage to the IFOF. Patients suffering from jargonaphasia are classically unaware of their jargon and fail to correct it [2,8,35]. This seems specific to their own speech, as they are aware of the jargon of others [36,37], which may suggest a concurrent deficit in self-evaluation. Recent evidence from intraoperative stimulation has shown that transient disconnection of the IFOF prevents self-evaluation, with patients reporting high confidence in having performed correctly an incorrect task [21]. This is common in jargonaphasia, where glaring noun abnormalities are often pronounced with confidence (e.g. patient reporting *‘Ha I was looking for that word since yesterday’* after jargon [5]). Damage to the IFOF resulting in self-evaluation dysfunction may thus represent a critical insult in jargonaphasia, as it may not only impair error monitoring [2], but also prevent rehabilitation through correction [37]. Similarly, subcortical stimulation of the IFOF has been linked to verbal perseveration, an inappropriate repetition of a previously pronounced word or phoneme [38]. Perseveration is considered a hallmark feature of both semantic and neologistic variants in jargonaphasia, and has been associated with jargonaphasia severity [8]. Disconnection of the IFOF may underlie both types: its isolated impairment may be sufficient for perseveration of single words, while added damage to phonological pathways such as the AF may be necessary for phoneme perseveration [37].

Table 3
Immediate postoperative evaluation of spontaneous speech.

No	Type of Jargon	Neologistic paraphasia	Semantic paraphasia	note
1	semantic		++	
2	neologistic	+		
3	neologistic	+++		immediate jargonaphasia recovered at follow-up
4	neologistic	++	+	
5	neologistic	+	+	
6	neologistic	+++		
7	neologistic	+	+	perseverations
8	neologistic	++		
9	semantic	+	++	
10	semantic		++	bilingual
11	neologistic	++	++	
12	neologistic	++	++	
13	semantic		++	
14	neologistic	++		immediate jargonaphasia and jargonagraphia recovered on the 2nd day postoperative
15	neologistic	+++		immediate jargonaphasia, perseverations recovered at follow-up
16	semantic		+	perseverations
17	neologistic	+		

Table 4
Pattern of white matter disconnection in the cohort of patients.

No	Type	AF	% AF	IFOF	% IFOF	PS	% PS	ILF	% ILF	UNC	% UNC
1	semantic	-	0.00%	bordered	48.13%	-	0.00%	-	0.00%	bordered	19.04%
2	neologistic	bordered	26.58%	bordered	49.01%	-	0.00%	**disconnected**	**85.94%**	**disconnected**	**95.20%**
3	neologistic	bordered	2.37%	bordered	0.00%	-	0.00%	-	0.15%	-	0.00%
4	neologistic	**disconnected**	**62.73%**	**disconnected**	**59.83%**	bordered	6.17%	**disconnected**	**99.87%**	**disconnected**	**95.20%**
5	neologistic	bordered	8.15%	bordered	21.38%	-	0.00%	**disconnected**	**83.56%**	**disconnected**	**94.29%**
6	neologistic	**disconnected**	**87.51%**	-	0.00%	bordered	9.52%	-	0.00%	-	0.00%
7	neologistic	bordered	45.76%	bordered	1.46%	-	0.00%	bordered	28.06%	-	0.00%
8	neologistic	bordered	0.00%	-	0.00%	-	0.00%	-	0.00%	-	0.00%
9	semantic	bordered	7.91%	bordered	46.09%	-	0.00%	**disconnected**	**82.48%**	**disconnected**	**95.20%**
10	semantic	*resected preoperatively	-	*resected preoperatively	-	-	-	-	-	-	-
11	neologistic	bordered	0.00%	bordered	48.07%	-	0.00%	bordered	0.00%	**disconnected**	**99.88%**
12	neologistic	bordered	0.05%	bordered	3.53%	-	0.00%	**disconnected**	**51.58%**	**disconnected**	**93.99%**
13	semantic	bordered	3.72%	bordered	0.39%	-	0.00%	bordered	30.53%	bordered	10.26%
14	neologistic	bordered	18.67%	bordered	41.32%	-	0.00%	**disconnected**	**79.82%**	**disconnected**	**92.37%**
15	neologistic	bordered	9.64%	bordered	31.90%	-	0.00%	**disconnected**	**86.62%**	**disconnected**	**95.20%**
16	semantic	-	0.00%	bordered	39.78%	-	0.00%	bordered	0.48%	bordered	12.80%
17	neologistic	bordered	5.62%	bordered	34.56%	-	0.00%	bordered	9.17%	-	0.00%

Disconnected tracts are shown in bold. % indicates percentage of disconnection. AF: Arcuate fasciculus; IFOF: inferior fronto-occipital fasciculus; PS: Posterior segment of the Arcuate fasciculus; ILF inferior longitudinal fasciculus; UNC: Uncinate fasciculus.

Our results also support anatomical explanations for differences in these neuropsychological profiles. In our study, intraoperative stimulation of the AF and its posterior segment was specific to neologistic jargonaphasia. Stimulation sites for this variant clustered along the AF in the middle-inferior temporal gyri and in the inferior parietal arching along the insula. The involvement of the AF is consistent with deficits in phonological processing and therefore its disconnection has been long theorised to underlie neologistic jargonaphasia, even before the advent of diffusion imaging [3,39]. However, damage to the AF is common in stroke and its selected disconnection is generally associated with conduction aphasia [40], rather than jargonaphasia. Therefore, while the AF is linked to this variant, its isolated disconnection may be insufficient to produce neologistic jargonaphasia. Interestingly, neologistic jargonaphasia occurred whenever the IFOF and AF were in close proximity, which may suggest a dual stimulation could have occurred. This differed from semantic jargonaphasia where the majority of stimulation sites were located in the temporal stem, far from arcuate projections. In this perspective, neologistic jargonaphasia – but not semantic jargonaphasia - may result from disruption of the flow of information taking place along both the IFOF and the AF, possibly reflecting a dual-disconnection syndrome.

Dual-disconnection of the AF and the IFOF may account for neuropsychological peculiarities of neologistic jargonaphasia, especially deficits in phonological self-monitoring. Although phonological self-monitoring disorders are well-established in neologistic jargonaphasia, there is disagreement whether they would arise from an impairment in cognition or in speech production [2]. On one hand, they may reflect a cognitive deficit where error awareness/self-evaluation is impaired, and therefore correction is intact but prevented [2]. On the other hand, these may underlie a language deficit where production-based correction (such as lexico-semantic 'clean-up' of disrupted phonological output through repetition in '*conduite d'approche*') is damaged [41,42]. Dual-disconnection of the AF and IFOF may underlie both conditions: IFOF damage may prevent self-evaluation of incorrect phonological output associated to an insult of the arcuate fasciculus, however, it may also prevent semantic correction of non-word associated with failure of phonological encoding after AF disconnection.

Our study has some limitations. First, diffuse low-grade gliomas (LGGs) are renowned for their neuroplastic reorganisation. Therefore, we cannot rule out that these results may reflect a unique feature of reorganisation in this patients' cohort. However, the heterogenous distribution of tumour locations in the patient cohort makes this unlikely. In addition, it has been recently shown that the white matter has low plastic potential, which argues against white matter tracts reconfiguration induced by the lesion [43]. Third, our results suggest that the IFOF, AF and pAF may be particularly relevant for jargonaphasia. However, these may not be unique. Further studies with a larger cohorts will address this issue. It is noteworthy, however, that our disconnectome analysis excluded a role for the ILF and the UF.

To conclude, jargonaphasia has been described since Hughlings-Jackson, but the underlying anatomy reflecting it has been to date elusive. Using a methodology that enables causal structure-function inferences, the present study suggests a continuum between variants of jargonaphasia where well-established deficits in language, such as comprehension, but also in cognition, such as self-evaluation and perseveration, may be structurally instantiated by disconnection of the IFOF. On the other side, it shows that phonological disorders specific to neologistic jargonaphasia may be determined by dual-disconnection of the arcuate fasciculus and its posterior segment in addition to the IFOF. Beyond the implications of these studies in anatomical models of jargonaphasia, a better understanding of its pathophysiology may allow for more specific and effective rehabilitation [8].

Funding

The authors have no funding to disclose.

CRediT authorship contribution statement

Davide Giampiccolo: Investigation, Conceptualization, Software, Visualization, Methodology, Formal analysis, Writing – original draft. **Sylvie Moritz-Gasser:** Investigation, Conceptualization, Data curation, Methodology, Writing – review & editing. **Sam Ng:** Investigation, Methodology, Software, Formal analysis, Writing – review & editing. **Anne-Laure Lemaître:** Investigation, Data curation, Methodology, Writing – review & editing. **Hugues Duffau:** Project administration, Methodology, Conceptualization, Data curation, Methodology, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.11.012.

References

[1] Hughlings-Jackson J. On affections of speech from disease of the brain. Brain 1879;2:203–22.
[2] Marshall J. Jargon aphasia: what have we learned? Aphasiology 2006;20:387–410.
[3] Kertesz A, Benson DF. Neologistic jargon: a clinicopathological study. Cortex 1970;6:362–86.
[4] Moses MS, Nickels LA, Sheard C. Disentangling the web: neologistic perseverative errors in jargon aphasia. Neurocase 2004;10:452–61.
[5] Cohen L, Verstichel P, Dehaene S. Neologistic jargon sparing numbers: a category-specific phonological impairment. Cogn Neuropsychol 1997;14:1029–61.
[6] Marshall J, Pring T, Chiat S, Robson J. When ottoman is easier than chair: an inverse frequency effect in jargon aphasia. Cortex 2001;37:33–53.
[7] Alajouanine T. Verbal realization in aphasia. Brain 1956;79:1–28.
[8] Marshall J. Therapy for people with jargon aphasia. Aphasia rehabilitation: Clinical challenges; 2018.
[9] Hough MS. Treatment of Wernicke's aphasia with jargon: a case study. J Commun Disord 1993;26:101–11.
[10] Robson J, Marshall J, Pring T, Chiat S. Phonological naming therapy in jargon aphasia: positive but paradoxical effects. J Int Neuropsychol Soc 1998;4:675–86.
[11] Pilkington E, Keidel J, Kendrick LT, Saddy JD, Sage K, Robson H. Sources of phoneme errors in repetition: perseverative, neologistic, and lesion patterns in Jargon Aphasia. Front Hum Neurosci 2017;11:1–14.
[12] Thiebaut de Schotten M, Foulon C, Nachev P. Brain disconnections link structural connectivity with function and behaviour. Nat Commun 2020:11.
[13] Catani M, Jones DK, Ffytche DH. Perisylvian language networks of the human brain. Ann Neurol 2005;57:8–16.
[14] Saur D, Kreher BW, Schnell S, et al. Ventral and dorsal pathways for language. Proc Natl Acad Sci Unit States Am 2008;105:18035–40.
[15] Duffau H, Moritz-Gasser S, Mandonnet E. A re-examination of neural basis of language processing: proposal of a dynamic hodotopical model from data provided by brain stimulation mapping during picture naming. Brain Lang 2014;131:1–10.
[16] Duffau H. Stimulation mapping of white matter tracts to study brain functional connectivity. Nat Rev Neurol 2015;11:255–65.
[17] Ojemann G, Mateer C. Human language cortex: localization of memory, syntax, and sequential motor-phoneme identification systems. Science 1979;205:1401–3.
[18] Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere. J Neurosurg 1989;108:411–21.
[19] Duffau H, Gatignol P, Denvil D, Lopes M, Capelle L. The articulatory loop: study of the subcortical connectivity by electrostimulation. Neuroreport 2003;14:2005–8.
[20] Herbet G, Duffau H. Revisiting the functional anatomy of the human brain: toward a meta-networking theory of cerebral functions. Physiol Rev 2020;100:1181–228.
[21] Ng S, Herbet G, Lemaitre A-L, Moritz-Gasser S, Duffau H. Disrupting self-evaluative processing with electrostimulation mapping during awake brain surgery. Sci Rep 2021;11:9386.
[22] Metz-Lutz M, Kremin H, Deloche G, et al. Standardisation d'un test de denomination orale : controle des effects de l'age, du sexe et du niveau de scolarite chez des sujets adultes normaux. Rev Neuropsychol 1991;1:73–95.
[23] Duffau H, Gatignol P, Mandonnet E, Peruzzi P, Tzourio-Mazoyer N, Capelle L. New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. Brain 2005;128:797–810.
[24] Howard D, Patterson KE. The pyramids and Palm trees test: a test of semantic access from words and pictures. Bury St. Edmunds: Thames Valley Test Company; 1992.
[25] Gola-Asmussen C, Lequette C, Pouget G, Rouyer C, Zorman M. ECLA-16+. Evaluation des compétences en lecture chez l'adulte de plus de 16 ans. CogniSciences; 2010.
[26] Roux A, Lemaitre A, Deverdun J, Ng S, Duffau H, Herbet G. Combining electrostimulation with fiber tracking to stratify the inferior fronto-occipital fasciculus. Front Neurosci 2021;15:1–12.
[27] Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. Neuroimage 2014;92:381–97.
[28] Yeh FC, Panesar S, Fernandes D, et al. Population-averaged atlas of the macroscale human structural connectome and its network topology. Neuroimage 2018;178:57–68.
[29] Duffau H, Gatignol P, Mandonnet E, Capelle L, Taillandier L. Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with Grade II glioma in the left dominant hemisphere. J Neurosurg 2008;109:461–71.
[30] Buckingham HW, Kertesz A. A linguistic analysis of fluent aphasia. Brain Lang 1974;1:43–61.
[31] Sarubbo S, De Benedictis A, Maldonado IL, Basso G, Duffau H. Frontal terminations for the inferior fronto-occipital fascicle: anatomical dissection, DTI study and functional considerations on a multi-component bundle. Brain Struct Funct 2013;218:21–37.
[32] Sarubbo S, De Benedictis A, Merler S, et al. Structural and functional integration between dorsal and ventral language streams as revealed by blunt dissection and direct electrical stimulation. Hum Brain Mapp 2016;37:3858–72.
[33] Herbet G, Moritz-Gasser S, Duffau H. Electrical stimulation of the dorsolateral prefrontal cortex impairs semantic cognition. Neurology 2018;90:e1077–e1084..
[34] Purcell R, Lambon Ralph MA, Sage K. Investigating the language, cognition and self-monitoring abilities of speakers with jargon output. Aphasiology 2019;33:1095–113.
[35] Kinsbourne M, Warrington EK. Jargon aphasia. Neuropsychologia 1963;1:27–37.
[36] Marshall J, Chiat S, Robson J, Pring T. Calling a salad a federation: an investigation of semantic jargon. Part 2 - Verbs. J Neurolinguistics 1996;9:251–60.
[37] Marshall J, Robson J, Pring T, Chiat S. Why does monitoring fail in jargon aphasia? Comprehension, judgment, and therapy evidence. Brain Lang 1998;63:79–107.
[38] Mandonnet E, Herbet G, Moritz-Gasser S, Poisson I, Rheault F, Duffau H. Electrically induced verbal perseveration: a striatal deafferentation model. Neurology 2019;92:e613–21.
[39] Hillis AE, Boatman D, Hart J, Gordon B. Making sense out of jargon. Neurology 1999;53:1813. LP – 1813.
[40] Forkel SJ, Rogalski E, Drossinos Sancho N, et al. Anatomical evidence of an indirect pathway for word repetition. Neurology 2020;94:e594–606.
[41] Ueno T, Lambon Ralph MA. The roles of the “ventral” semantic and “dorsal” pathways in conduite d'approche: a neuroanatomically-constrained computational modeling investigation. Front Hum Neurosci 2013;7:1–7.
[42] Nadeau SE. Phonology: a review and proposals from a connectionist perspective. Brain Lang 2001;79:511–79.
[43] Herbet G, Maheu M, Costi E, Lafargue G, Duffau H. Mapping neuroplastic potential in brain-damaged patients. Brain 2016;139:829–44.