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Strandberg, Maria; Mannfolk, Peter; Stenberg, Lars; Källén, Kristina

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Verbal encoding fMRI paradigm adds complementary information to cerebral language lateralization

Maria Strandberg[1*], Peter Mannfolk[2], Lars Stenberg[2] and Kristina Källén[1]

[1]Department of Neurology, Department of Clinical Sciences, Lund, Skåne University Hospital, SE-221 85 Lund, Sweden,
[2]Diagnostic Radiology, Department of Clinical Sciences, Lund, Skåne University Hospital, SE-221 85 Lund, Sweden.

*Corresponding author:
Maria Strandberg
maria.strandberg@med.lu.se

Editors approved:

Vinay Parikh
Temple University, USA

Kamilla Bargiel-Matusiewicz
University of Warsaw, Poland

Abstract

Title: Verbal encoding fMRI paradigm adds complementary information to cerebral language lateralization.

Purpose: To explore two conceptually different fMRI paradigms' ability to lateralize language.

Methods: A verbal encoding paradigm and a word generation task were performed by six patients (four right-handed) with therapy-resistant temporal lobe epilepsy (TLE), and by ten healthy individuals (five right-handed). FMRI laterality indices (LI) and laterality curves for the anterior cerebral language regions were calculated. Typical lateralization was defined as left-hemisphere dominance, and a typical as bilateral or right-hemisphere dominance.

Results: Both paradigms showed predominantly left-sided activation in the anterior language regions, with typical contralateral cerebellar activity. Thirteen out of sixteen subjects showed concordant language lateralization results for both paradigms. Two subjects, both left-handed, showed discordant language lateralization results. Laterality curves added information for individual subjects with uncharacteristic results. The verbal encoding task showed overall more widespread activation compared to the word generation task.

Conclusion: Our results indicate valid language lateralization obtained by the fMRI verbal encoding paradigm for right-handed subjects. This offers the opportunity to simultaneously study two cognitive functions, language and verbal encoding, using one task. TLE is a network disease which predisposes afflicted patients to cortical re-organization and inserting uncertainties regarding hemisphere dominance. Atypical language representation in connection with left-handedness should be interpreted with caution irrespective of which paradigm is chosen.

Keywords: TLE, fMRI, handedness, lateralization index, language lateralization

Introduction

The spatial resolution of functional magnetic resonance imaging (fMRI) makes it possible to study cerebral language activation patterns. Language lateralization is probably the most investigated aspect in fMRI research and the relative contribution from each hemisphere is often reported as a lateralization index (LI). Accurate determination of language lateralization is essential prior to temporal lobe epilepsy (TLE) surgery aiming at the dominant hemisphere, as patients are at risk for decline in verbal memory and naming post-operatively. FMRI is currently the imaging method of choice, as it has shown 80-90% concordance compared to the invasive intracarotid amobarbital test (IAT) [1,2]. A recent paper has even suggested that fMRI may be more sensitive than IAT to

right hemisphere processing [3].

In addition to language deficits, epilepsy surgery can cause post-operative decline in other cognitive domains such as memory, and more specifically, in verbal memory [4,5]. Binder et al., [6] have published very interesting results showing that fMRI language LIs in frontal areas have the strongest predictive value for verbal memory outcome following temporal lobe resection. The underlying hypothesis is that language processes and verbal encoding co-lateralize, a theory that is supported by other researchers [7-10].

In 2010, we [11] published a study where healthy right-handed subjects performed a verbal encoding paradigm, which was subsequently used to study verbal memory. The task visualized levels of processing – deep and shallow encoding - for incidental learning and it elicited MTL activation during encoding [11]. It was designed to be used as a clinically applicable fMRI test for assessment of verbal memory capacity in the medial temporal lobes (MTL) in an epilepsy surgery setting. The paradigm produced fMRI activation not only in areas essential for encoding processes, but also in anterior language areas. Fourteen of the 15 right-handed healthy subjects showed left lateralized activity in this area. As verbal encoding involves the interpretation of verbal stimuli, this is not surprising. However, the extent of the activation was intriguing, and motivated further exploration of its mechanism and utility. Based on Binder's theory, we hypothesized that our verbal encoding paradigm could lateralize language similarly to a commonly used word generation task.

The word generation task, also known as "verbal fluency", is often used in the evaluation of language laterality [12-14]. It has been shown to lateralize to a stronger degree compared to other paradigms [15,16], and it has good concordance with IAT results [17]. Nevertheless, researchers have suggested that the human language has two diverse dimensions that depend upon different brain areas and are based on different types of learning supported by different neuroanatomic networks [18] motivating further investigation of various methods to study language systems.

The aims of the current study were primarily to explore the concordance between a verbal encoding paradigm and a commonly used word generation paradigm in a group of subjects and TLE patients with mixed handedness. Secondly, we wanted to examine if the verbal encoding paradigm can provide complementary lateralization information, possibly contributing to additional understanding of the cortical language and memory networks, at an individual level in a clinical setting.

Methods
Subjects
Six Swedish-speaking patients with therapy-resistant temporal lobe epilepsy (2 females; 2 left-handed; median age 33 yrs; range 24-58 yrs) and ten healthy Swedish-speaking volunteers (2 females; 5 left-handed; median age 38 yrs; range 25-62 yrs) without history of neurological or psychiatric illness were recruited for the study (**Table 1**). The patients were all therapy-

Table 1. Demographic data and laterality indices.

Subject	Sex/Age	Handedness	Word generation	Verbal encoding
1	F/62	Right	0.71	0.4
2	M/38	Right	0.49	0.39
3	M/50	Right	0.74	0.39
4	M/40	Right	0.82	0.77
5	M/38	Right	0.72	0.45
6	M/50	Left	0.69	0.67
7	M/31	Left	0.73	-0.44
8	F/25	Left	-0.5	-0.52
9	M/36	Left	-0.77	0.06
10	M/31	Left	0.79	0.13
11	M/58	Right	0.71	0.73
12	F/27	Right	0.77	0.51
13	M/37	Right	0.6	0.58
14	M/24	Right	0.56	0.35
15	M/44	Left	0.49	0.76
16	F/29	Left	0.7	-0.34

Overall mean laterality indices for each subject (n=16; no 1-10 healthy controls, 11-16 TLE patients) A positive value means a left-lateralization and a negative value right-lateralization. LI greater than 0.1 were classified as left lateralized and LI less than 0.1 were classified as atypical (i.e., bilateral or right-lateralized activation).

refractory temporal lobe epilepsy patients under investigation for temporal lobe resection and already scheduled to perform the clinically used fMRI paradigm for language lateralization as part of their pre-surgical work-up (**Table 2**). An experienced neuroradiologist reviewed structural MRI scans, and no pathological changes were detected on the morphological images acquired during the fMRI scans for the healthy subjects. For patients, no *additional* pathology, other than reported with clinical data in **Table 2**, was found. In non-lesional patients (subjects 11, 12 and 13) lobar diagnosis was made using invasive EEG-recordings and/or subtraction ictal single-photon emission computed tomography (SPECT) co-registered to MRI (SISCOM). Handedness for all included subjects was classified according to the Edinburgh Handedness Questionnaire [19].

The study was approved by the Lund University Ethics Committee, with all subjects giving their written informed consent.

FMRI-task experimental design
Word generation task
The subjects were shown different letters projected subsequently on a screen. Letters were shown during five blocks of 20 seconds each, where every active block was followed by a 20 second resting period. During the active period, subjects were asked to silently generate words beginning with the visualized letter

Table 2. Additional clinical data for the TLE patients.

Nr	Age at disease onset	Age at fMRI	AED at time of fMRI*	Sz/EEG onset	Structural MRI pathology
11	46 yrs	49 yrs	VPA, LTG	Right Temporal Lobe	--
12	13 yrs	25 yrs	LTG	Left Temporal Lobe	--
13	32 yrs	35 yrs	VPA	Left Temporal Lobe	--
14	19 yrs	23 yrs	VPA, LTG	Left Temporal Lobe	Possible left cortical dysplasia/DNET temporal lobe
15	28 yrs	41 yrs	CBZ	Right Temporal Lobe	Right temporal lobe hippocampal sclerosis
16	13 yrs	27 yrs	VPA, LTG	Left Temporal Lobe	Possible cortical dysplasia right parahippocampal gyrus

*Antiepileptic drugs during time of fMRI: (VPA: Valproic acid; LTG: Lamotrigin; CBZ: Carbamazepine)

until a cross appeared in the center of the screen. In the resting condition, participants were asked to fixate on the cross.

Verbal encoding task

During scanning, subjects were presented with 192 nouns. Each noun had two letters underlined, and subjects were asked to perform one of two alternating tasks. In the deep encoding task, subjects were asked to decide if the word was pleasant or not (e.g., BIKE. In the shallow encoding task, the subjects were asked whether the underlined letters were in alphabetical order or not (e.g., PADDLE).

The paradigm was based upon neuropsychological research exploring the encoding process. Stimulus material processed in an elaborate meaning-based manner, so called deep processing, has shown to be better remembered compared to when the same stimulus material is processed with an emphasis on perceptual features, so called shallow processing. This is the main effect of the encoding task, levels-of-processing (LOP-effect), a robust encoding effect in human memory [20-22].

Subjects indicated their answer—yes or no—by pressing a button on a mouse pad. Answers were logged and served as confirmation of task compliance and basic behavioral data. The 192 words consisted of 96 words for deep encoding and 96 words for shallow encoding. Each word was presented for 4.25 sec followed by a 2 sec pause; they were randomly presented in blocks of eight subsequent deep and shallow encoding tasks, respectively (i.e., each block lasted 50 seconds). The words were presented in a total of three scan sessions, with eight blocks in each session. The scan time for each session was 6:54 min each, with a 1 min pause between each session.

E-prime software (Psychology Software Tools, Inc., Pittsburgh, USA) was used for the presentation and timing of the stimuli, and for the collection of response data. The font was equal for both scans.

MRI scanning

Magnetic resonance imaging was performed using either a 3T Siemens Magnetom Allegra MR unit (verbal encoding paradigm for subject 1-4) or a 3 T Philips Achieva MR unit (all remaining scans) with a standard quadrature head coil. Prior to the study, careful trials using the verbal encoding paradigm deemed this paradigm robust enough to produce similar activation with either unit, i.e., a non-camera-specific paradigm. A GRE-EPI pulse sequence (matrix size 64×64, TE=30 ms, TR=3000 ms, FoV=192 mm, 49 slices, slice thickness=3 mm, 0.9 mm slice gap for verbal fluency and 0.0 mm slice gap for verbal memory interleaved slice acquisition) was used for functional imaging. 3D T1-weighted and FLAIR (T2-weighted) sequences were used to obtain images for anatomical overlay of functional activation maps and to exclude pathology.

Pre-processing and statistical analysis

All data analysis was performed using MATLAB (Mathworks, Natick, MA). Preprocessing and statistical analysis was performed with the SPM5 software package (Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm). Preprocessing included motion correction, where images were realigned to the first image to correct for movement-related variance, as well as slice time correction. Furthermore, normalization into standard Montreal Neurological Institute (MNI) space was performed using an EPI template [23,24]. Finally, the images were then spatially smoothed with an 8-mm isotropic Gaussian kernel to fulfill the assumptions of Gaussian random field theory [25].

Statistical analysis of all fMRI data was performed using the general linear model, yielding statistical parametric maps of task-related activation. Onset vectors for the verbal memory paradigm were created from the logged data of each participant's recognition test corresponding to two possible event types (i.e., deep encoding and shallow encoding).

For the word generation task, a single onset vector (active state) was created from the onsets of the five blocks of word generation. The BOLD time course was modeled by convolving the onset vectors with the SPM5 canonical hemodynamic response function (HRF).

The results of this study were based on the analysis of the following contrasts:

1. Word generation task: The active state (word generation) was contrasted against the resting state (fixating on a cross).
2. Verbal encoding task: The deep encoding trials ("pleasant or not pleasant?") were contrasted against the shallow encoding trials ("correct alphabetical order or not?").

The resulting contrast images were entered into a second-level random-effects analysis. The statistical parametric maps were thresholded at p<0.001, uncorrected for multiple comparisons. This threshold was chosen to reduce the occurrence of false negatives, and it is the threshold used in clinical practice in our department. It is also the threshold used in the original study [11].

Laterality assessment

Laterality indices were calculated using the LI-toolbox running within the SPM environment. A bootstrap algorithm was applied in order to calculate robust LIs at different thresholds. The algorithm is described in detail in the original article [26], and has been applied previously in similar studies [11,27,28]. The result is a lateralization index between −1 and +1, where an overall LI mean greater than 0.1 was classified as left lateralized and an overall LI mean less than 0.1 was classified as atypical (i.e., right-lateralized or with a bilateral activation pattern). This classification was based on a study published in 2006 [29,30]. The limits were maintained to facilitate comparison to our previous study using the verbal encoding paradigm [11]. The LI toolbox also produces laterality curves based on laterality indices for a range of consecutive thresholds without the necessity of a pre-defined cut-off. A single LI represents the curve, but the curve in itself visualizes the range of activation effects.

Prior to the LI calculation procedure, a mask for analysis of activation within regions of interest (ROI) was constructed. The ROI was drawn symmetrically; that is, it contained the same structures in both hemispheres. Symmetry with respect to the exact number of voxels included in the LI calculation was ensured by a mask weighting factor, which was applied to the ROI within the LI toolbox.

An experienced neuroradiologist drew the ROI, and it is routinely used in our department for clinical lateralization of language. The ROI was drawn on the MNI template and then applied to all subjects in the MNI space. It includes the inferior frontal gyrus, the main part of the middle frontal gyrus, and the dorsolateral pre-frontal cortex. This includes Broca's area and its homologue in the right hemisphere.

Results

All participants were able to complete the fMRI tasks during scanning. Due to severe motion artifacts noted before analysis of activation data, two scanning sessions for two of the healthy volunteers were repeated (word generation only).

Activation results

Table 3 shows the most important sites of overall activation for the two paradigms in the fourteen subjects with typical left-dominant language: nine right-handed and five left-handed.

For the word generation task, group activation showed a typical pattern of activation for language with activity primarily in the left hemisphere with expected contra-lateral cerebellar activation (**Figure 1**).

Whole-brain analysis at the group level for the verbal encoding paradigm showed strong activation in the left superior temporal gyrus, the right inferior temporal gyrus, and the left middle frontal gyrus. These brain regions are associated with frontal and temporal language areas. Contra-lateral activation was seen in the right cerebellum. The group activation was more widespread and bilateral for the verbal encoding paradigm, and more localized to traditional anterior language areas for the word generation task (**Figure 1**).

Lateralization indices (LI) and laterality curves

FMRI indices are shown in **Table 1**. For the verbal encoding paradigm, 12 participants showed predominantly left-sided

Table 3. Functional neuroimaging results.

Word generation task					Verbal encoding task				
X	Y	Z	Anatomical structure	Z-score	X	Y	Z	Anatomical structure	Z-score
27	-63	-33	R Culmen	5.18	-39	15	-39	L BA 38	5.91
15	-69	-51	R Inferior semi-lunar lobule	5.07	39	-81	-42	R Pyramis	5.52
-33	-63	57	L BA 7	4.62	-6	18	66	L BA 6	5.13
-30	-66	45	L Superior parietale lobule	4.17	51	0	-36	R BA 20	4.83
39	27	-12	R Inferior frontal gyrus	4.58	-12	36	45	L Middle frontal gyrus	4.68
-6	18	45	L BA 32	4.55	-6	-51	21	L Posterior cingulated	4.62
0	27	39	L Frontal superior medial lobe	4.32	-48	-69	30	L BA 39	4.35
0	21	54	L Superior frontal gyrus	4.04	54	33	-6	R Inferior frontal gyrus	4.14
-3	-15	-21	Midbrain	4.51	24	-15	-21	R Parahippocampal gyrus	4.06
-42	18	-9	L Inferior frontal gyrus	4.20	-12	42	51	L Superior frontal gyrus	4.06

Statistical contrast maps were thresholded at p<0.001 uncorrected; T=3.8. Coordinates correspond to selected activated clusters of interest, not all activated areas in the wholebrain analysis. The listed coordinates refer to peaks in larger clusters of activation where anatomic structures of importance are listed in the text. Coordinates are given in MNI stereotaxic space. BA refer to Brodmann areas. L–Left hemisphere, R–Right hemisphere.
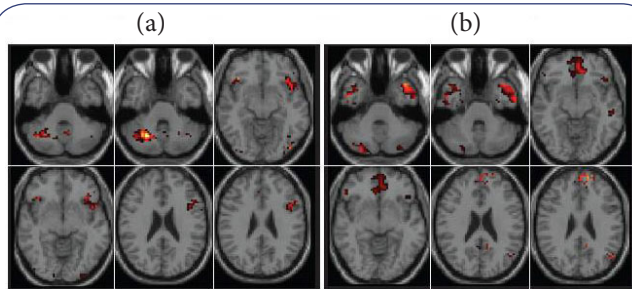
Figure 1. The picture shows the overall group activation patterns (i.e., group maps) for:
(**a**) Word generation paradigm
(**b**) Verbal encoding paradigm
In order to facilitate the comparison between individual and group data the anatomic MRI sections presenting group data are equal to the sections presenting individual data in **Figure 4**.

activity (defined as LI >0.1), and four participants showed atypical (predominantly right-sided or bilateral; defined as LI <0.1). Concordance between the two paradigms was seen in 9 out of 9 right-handed subjects. **Figure 1** shows a graphic illustration of concordance versus discordant language lateralization in all 16 participants, divided according to handedness and if the subjects were patients or not. Four subjects' (7, 9, 10 and 16) indices and bars (**Table 1**; **Figure 2**) evoke immediate attention. Subjects 7 and 16 (patient), both left-handed, showed discordance between LI for word generation (typical, left-sided dominance) and LI for verbal encoding (atypical, right-sided dominance).

Figure 3 shows the individual laterality curves for the two paradigms without further categorization, but with information about trend and range of activation effects. Subjects 9 and 10 had right-lateralized LI in the word generation task analysis, and bilateral activity without significant lateralization during the verbal encoding task. The LI curve for subject 9-for the verbal encoding task - indicates equal use of both hemispheres with a slight trend toward the left hemisphere until very high thresholds where activation deviates towards the right hemisphere. If the whole curve is taken in account for index calculation results show
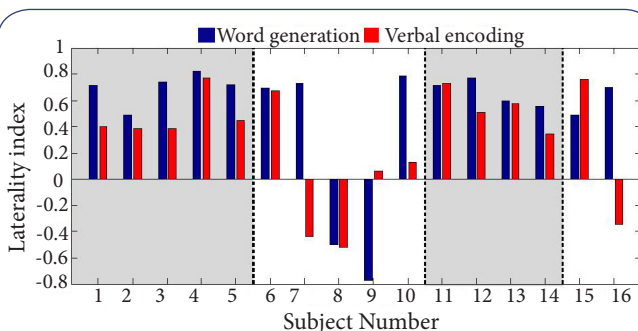
Figure 2. Individual laterality indices for all subjects are shown in bars: blue bars correspond to activation from word generation, red bars from verbal encoding. Grey backgrounds encompass dexterous individuals and white background non-dexterous individuals.
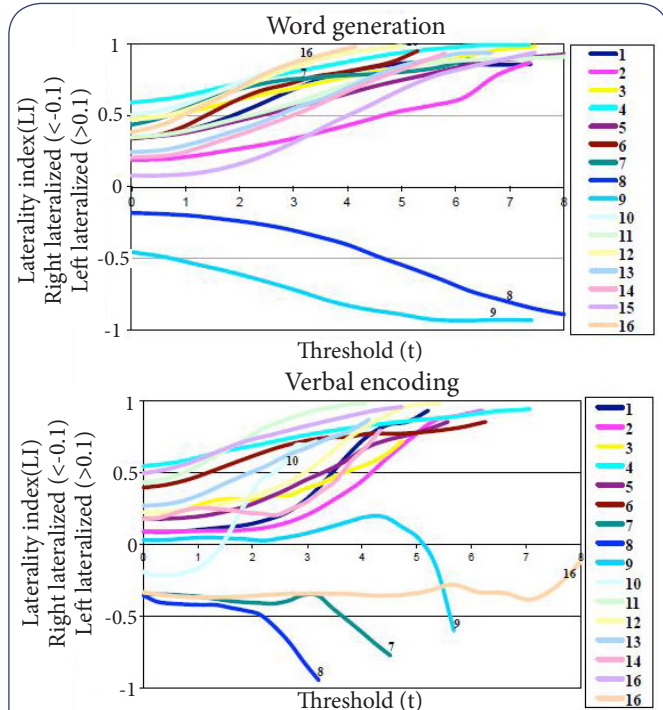
Figure 3. The individual laterality curves for all subjects, each represented with their own colour: one for each paradigm. The curves for the word generation paradigm clearly show the left lateralization for all but two subjects. For the verbal encoding paradigm, the left-sided dominance is also obvious, with the exception of four subjects where the curves offer information that complements the single lateralization index. Range of activation effects can be studied for both paradigms.

a non-lateralizing index. The LI curve for subject 10 deviates toward left lateralization.

Discussion

The assessment of language lateralization in our study showed significant concordance between a standard word generation paradigm and a verbal encoding paradigm through ROI analysis in anterior language areas at a group level (13/16 subjects). All right-handed subjects were left lateralized (9/9) while language representation in connection with left-handedness showed concordant lateralization for 4/7 subjects. Laterality curves illustrated a variety of activation effects for verbal encoding and indicated a bilateral language representation for 1/7 left-handed subject.

The combination of tasks in order to visualize different aspects of a cognitive process has previously been proposed, but in the context of the subject performing one task after another [31-33]. To assess two connected cognitive functions, language and memory, using a single fMRI paradigm is attractive not only because it demands less scanner time, but also because it potentially offers more information. Analysis of complex connections between higher cerebral functions including general activation patterns can probably contribute to further
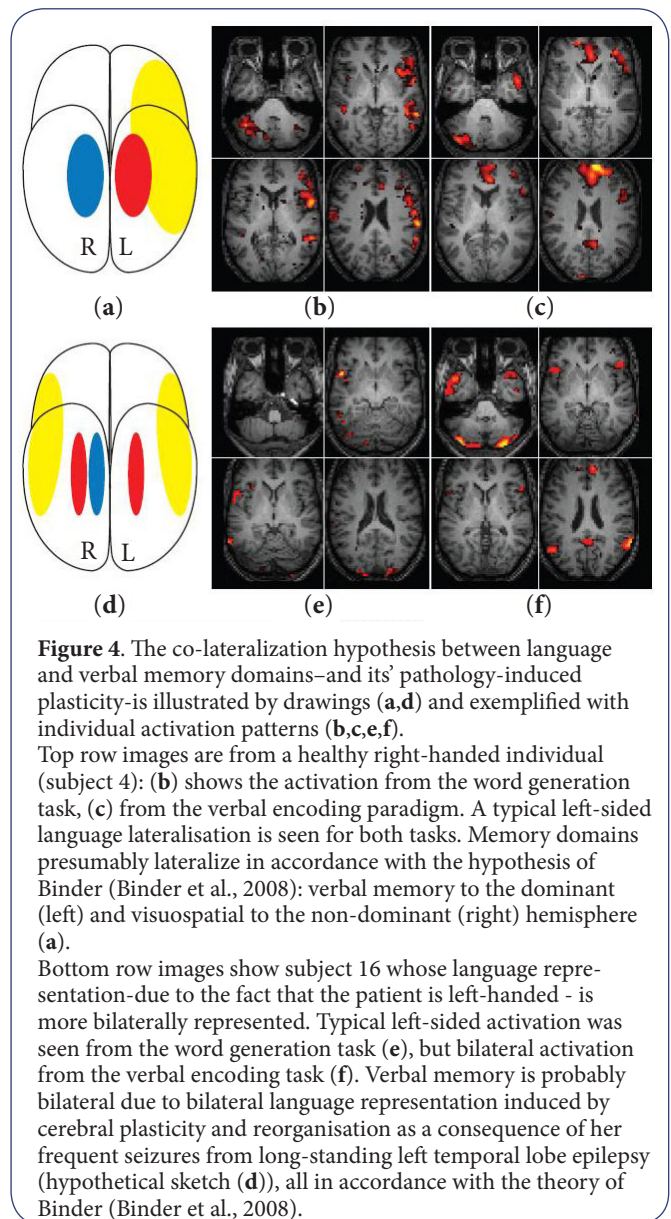
understanding of the brain networks. A *combined* fMRI *task*, *one* complex task demanding input from several cognitive abilities, can *theoretically* activate bilateral networks to a higher extent than two separate ones. Verbal encoding visualized by fMRI showed a widespread activation extending towards posterior as well as to frontal language areas. However, a more pronounced component of network activation results in less distinct lateralization, evaluated by lateralization indices, which makes the word generation task more attractive for standard clinical purposes.

Difficulty in lateralizing language using the fMRI technique largely pertains to individuals with atypical handedness [29]. Furthermore, atypical language representation involves a wide range of patterns difficult to classify consistently across centers [34,35], partly explaining the commonly used, but very unspecific nomenclature: typical (left-sided) versus atypical (i.e., right-sided or bilateral representation).

Figure 4 illustrates two examples pertaining to the co-lateralization hypothesis of verbal memory and language where subject 16 serves as an example of network shift following long-standing therapy-resistant epilepsy. Subject 16, a young woman with refractory left-sided temporal lobe epilepsy, showed discordant data that merits further thought. Intra-cranial EEG recordings using electrodes (strip and depth electrodes) covering the temporal lobes bilaterally revealed initiation of seizures on the left side. Structural MRI indicated probable cortical dysplasia in the right lateral temporal gyrus.

Left TLE with frequent seizures affecting the dominant temporal lobe poses a risk for progressive decline in verbal memory function. However, instead of memory decline, repeated neuropsychological testing revealed intact verbal memory over time (2009, 2010, 2011 and 2014) in this patient. Verbal encoding and retention were normal and unaffected over time (measured by the Claeson-Dahl Verbal Learning Test and the Boston Naming Test [36]). Within these psychometric tasks, she performed 0.6 standard deviations (SD) and 1 SD respectively above normal for list learning (immediate recall and delayed recall respectively). Using the visuospatial task (Rey Complex Figure Task), she performed consistently with -0.9 SD for immediate recall, -1 SD for delayed recall and 0.42 in a face recognition task. All values were deemed within the range of expected, normal capacity. This raised concerns regarding her language dominance being lateralized to the left as was indicated by her word generation task. Word generation LI indicated typical left-hemisphere dominance, whereas verbal encoding LI indicated atypical dominance (**Figures 2** and **3**). A possible explanation for the LI discrepancy is that the left-sided epileptic focus had induced a more active verbal encoding process in the right temporal lobe, despite suspected structural pathology on the right side. Thus, the encoding LI may reveal this patient's possible atypical hemisphere dominance.

Figure 2 illustrates the general difficulties in lateralizing language in non-dexterous individuals, as some subjects have concordant, but somewhat ambiguous results, i.e., subject no's

Figure 4. The co-lateralization hypothesis between language and verbal memory domains–and its' pathology-induced plasticity-is illustrated by drawings (**a**,**d**) and exemplified with individual activation patterns (**b**,**c**,**e**,**f**).

Top row images are from a healthy right-handed individual (subject 4): (**b**) shows the activation from the word generation task, (**c**) from the verbal encoding paradigm. A typical left-sided language lateralisation is seen for both tasks. Memory domains presumably lateralize in accordance with the hypothesis of Binder (Binder et al., 2008): verbal memory to the dominant (left) and visuospatial to the non-dominant (right) hemisphere (**a**).

Bottom row images show subject 16 whose language representation-due to the fact that the patient is left-handed - is more bilaterally represented. Typical left-sided activation was seen from the word generation task (**e**), but bilateral activation from the verbal encoding task (**f**). Verbal memory is probably bilateral due to bilateral language representation induced by cerebral plasticity and reorganisation as a consequence of her frequent seizures from long-standing left temporal lobe epilepsy (hypothetical sketch (**d**)), all in accordance with the theory of Binder (Binder et al., 2008).

9 and 10. Both subjects were left lateralized for word generation and by our definition subject 10 for verbal encoding as well, although by a very small margin. Their laterality curves for verbal encoding differed from each other. Subject 10's verbal encoding curve convincingly deviates towards left lateralization at high thresholds, thus rendering concordance with the clearly left lateralized curve for word generation. The verbal encoding LI curve for subject 9 indicates a bilateral activation pattern, which is, by our definition atypical (atypical=bilateral), but not equal to the word generation curve (atypical=right lateralized) (**Figure 2**). Based on the curves subject 9 was judged not concordant.

A complicating, but not unforeseen, factor in our study was that patients were included regardless of handedness, whereas healthy subjects were included with knowledge of their handedness.

TLE patients are predisposed to cortical re-organization, which inserts an uncertainty concerning expected hemisphere dominance. About 70% of healthy non-right-handed persons have left hemisphere dominance for language compared to 95% of healthy right-handed persons [37,38]. Optimally patients should have been included based on their true laterality of language established by IAT and/or language testing during direct cortical stimulation. As both investigations poses a risk for complications they are not routinely applied for dexterous handed patients. The key limitation in our study is the low number of study subjects. The study subjects (healthy and TLE patients) are few with a higher incidence of atypical handedness than expected in the normal population. The number of participants in the study limited the possibilities for statistical analysis.

In order to study activation patterns at a group level, we did create one main group: subjects (healthy and TLE patients) with typical left-hemisphere dominance from visual assessment of word generation (all but subjects 8 and 9). A similar categorization has been done previously [39].

Our intention was to explore and evaluate the concordance between two paradigms aiming at language lateralization, without intent to replace one with the other. We conclude that overall concordance was 81% when all subjects were included and 100% in dexterous-handed subjects illustrating the overlap between the two paradigms. The discordance in itself is informative and supports previous reports stating that subjects with greater likelihood of atypical language representation should be investigated more carefully, using more than one language paradigm [40]. The discordant individual patient LI data seen in the non-dexterous-handed group served as basis for a hypothetical discussion regarding cognitive network re-organization reflecting the nature of TLE as a network disease. Laterality curves potentially add complementary information to both paradigms, particularly for low numerical indices. The word generation paradigm is probably superior as a tool to lateralize language in fMRI trials. However, as the verbal encoding paradigm offers at least partial evaluation of two cognitive functions-language and memory-our results may add to the understanding of cortical networks if this approach is further investigated. Not only can memory be studied through language, but possibly also the other way around: language can be studied through memory. Future studies are needed to determine the clinical relevance and usefulness of this association.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
MST and KKÄ designed the study and wrote the manuscript. MST recruited the patients and gathered the clinical data. PM was involved in collection of and analyzed all the fMRI data. LS reviewed all morphological MRI scans and made visual assessments of fMRI data.

Acknowledgement

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