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Phonological Short-Term Memory Networks Following Recovery from Landau and Kleffner Syndrome

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Abstract

Landau-Kleffner syndrome (LKS) is a rare acquired aphasia occurring in otherwise healthy children, together with spike-wave discharges predominating over superior temporal regions and activated by sleep. Although the outcome of language abilities is variable, a residual impairment in verbal short-term memory (STM) is frequent. This STM deficit might be related to the persistent dysfunction of those temporal lobe regions where epileptic discharges were observed during the active phase of the disorder. We tested this hypothesis by measuring brain activation during immediate serial recall of lists of 4 words, compared to single word repetition, using $H_2{}^{15}O$ positron emission tomography (PET), in 3 LKS patients after recovery and in 14 healthy controls. The patients (TG, JPH, and DC) had shown abnormally increased or decreased glucose metabolism in left or right superior temporal gyrus (STG) at different stages during the active phase of their disease. At the time of this study, the patients were 6-10 years from the active phase of LKS. Results showed that Patients JPH and DC had impaired performance in the STM condition, whereas TG showed near normal performance. PET data showed that JPH and DC activated significantly less than controls left and right posterior STG. TG, having near normal STM performance, showed increased activity in the posterior part of the right STG. These data suggest that impaired verbal STM at late outcome of LKS might indeed be related to a persistent decrease of activity in those posterior superior temporal gyri that were involved in the epileptic focus during the active phase. *Hum. Brain Mapping 19:133-144, 2003.*

Key words: verbal short-term memory; PET; Landau-Kleffner; epilepsy; aphasia

INTRODUCTION

We explored the relationship between persistent deficits in phonological short-term memory (STM) in late outcome of Landau-Kleffner Syndrome (LKS) and abnormal activation of superior temporal gyri (STG) and adjacent cortex. LKS, initially described by Landau and Kleffner in 1957, is a rare epileptic condition occurring between ages 3 and 8 years [Landau and Kleffner, 1957]. Receptive aphasia, characterized by severe deficits in auditory comprehension, represents the most common feature of the active phase in LKS. In many cases, it is the first symptom preceding the epileptic manifestations and subsequent expressive language impairments. Although overt epileptic seizures are not present in all LKS children, the receptive language difficulties are associated with disturbed EEG recordings, characterized by spike-wave discharges (SWD) originating from left or right temporal regions and increasing in frequency during sleep, leading to an aspect of continuous spike-wave discharges during slow sleep (CSWS). The EEG abnormalities disappear at the age of 12 or 13 [Dugas et al., 1982; Paquier et al., 1992]. While recovery of receptive and productive language is variable, a very consistent finding is a deficit in phonological short-term memory (STM) performance, even in patients showing relatively good language recovery [Grote et al., 1999; Metz-Lutz et al., 1999a,b; Plaza et al., 2001; Robinson et al., 2001; Soprano et al., 1994]. Indeed, Metz-Lutz et al. [1999a] investigated STM performance for words and nonwords in six LKS patients 8 months to 6 years after recovery and observed persistent difficulties in word span, non-word repetition, and sentence repetition. Soprano et al. [1994] also showed that digit span performance was more depressed than performance in other language tasks in LKS patients several months after recovery. Grote et al. [1999] and Robinson et al. [2001] showed that LKS patients, who had recovered normal or near normal language function, still displayed impaired verbal STM, as evidenced by difficulties in verbatim and ordered recall of sentence, letter, or digit lists. The persisting phonological STM impairment might indeed be responsible for

residual language difficulties in verbal comprehension, phonological judgment, and articulation.

Most importantly, the phonological STM impairment at late outcome of LKS might be related to persisting dysfunction of those superior temporal regions that were involved in the epileptic focus during the active phase of LKS [Metz-Lutz et al., 1999b, 2001]. Firstly, during the active phase of LKS, functional neuroimaging has shown abnormal perfusion of left, right, or bilateral superior and middle temporal gyri in LKS patients during sleep and wakefulness [Da Silva et al., 1997; Guerreiro et al., 1996; Maquet et al., 1995]. Secondly, ^{18}FDG-PET studies conducted in four patients during and after the active phase of LKS showed that STG and adjacent perisylvian cortex that had been hypermetabolic during LKS became hypo-metabolic after recovery of LKS, suggesting possible long-lasting dysfunction in these brain regions [Maquet et al., 1995]. Furthermore, a persistent one-ear extinction has been observed on dichotic listening tasks at late outcome of LKS (several years after normalization of EEG recordings) [Metz-Lutz et al., 1999b, 2001]. The dichotic extinction involved the channel contralateral to the side where SWDs were predominant during the active epileptic period [Metz-Lutz et al., 1997; Plaza et al., 2001]. Disturbances in late components of auditory evoked potentials observed in five LKS patients after recovery also suggest a permanent focal dysfunction in the temporal cortex concerned by epileptic activity during the active phase of epilepsy [Wioland et al., 2001].

We compared brain activation associated with phonological STM in patients who have recovered from LKS, relative to healthy normal controls, and investigated whether depressed STM performance in late outcome of LKS is linked to abnormal activation at the level of STG. We hypothesized that (1) LKS patients would show an abnormal pattern of brain activation for phonological STM compared to controls; (2) abnormal brain activation would primarily concern brain regions that were affected by the focal epileptic activity during the active phase of LKS, i.e., mainly superior temporal regions; and (3) activation in STG would be most abnormal in the patients with the most impaired STM performance.

SUBJECTS AND METHODS Subjects

The Ethics Committees of the Faculty of Medicine of the University of Liège and of the Strasbourg University Hospital (CCPPRB Alsace, N.l, Strasbourg) approved the study. Written informed consent was obtained from the patients and their family and from all control subjects according to the declaration of Helsinki.

The control population consisted of 14 young, right-handed, drug-free, healthy volunteers without significant medical, surgical or psychiatric history (8 males, 6 females; mean age was 22 years, range 19-26 years).

All patients previously suffered from LKS. Table I summarizes their main characteristics. Their clinical history has been reported in detail in a previous ^{18}FDG-PET study of resting brain metabolism during an earlier period of the disease [Maquet et al. 1995] (DC refers to Patient 3, TG to Patient 4, and JPH to Patient 5). During the active phase of LKS, all patients presented SWDs originating in the left or right temporal lobes and evolving to CSWS during slow sleep (see Table I). ^{18}FDG-PET scanning during the active phase showed increased glucose metabolism in right STG and adjacent perisylvian cortex for Patients TG and DC, and decreased glucose metabolism in bilateral superior and middle temporal gyri and adjacent perisylvian cortex in Patient JPH (see Table I). At recovery, decreased glucose metabolism was observed in STG and adjacent perisylvian cortex for Patients TG and JPH; no data were available for Patient DC. During the active phase, all patients had shown severe language disorders, marked by an auditory agnosia and/or severe auditory verbal comprehension deficits, as well as profound impairments in articulation, naming and syntax, leading to global aphasia in Patients TG and JPH. As the first symptom of LKS were either language impairments (TG) or epileptic seizures (JPH and DC), the delay between first symptoms and diagnosis of LKS varied from 5 months (TG) to 48 months (DC) and 22 months (JPH). Cortisone was introduced after at least one unsuccessful antiepileptic drug treatment (see Table I). A detailed phonological and lexico-semantic language and STM follow-up testing was performed subsequent to the present PET activation study (Table II). Results showed normal performance in word repetition, in vocabulary comprehension and production, and in sentence comprehension; some residual difficulties were observed for non-word repetition in Patients JPH and DC. Most importantly, the patients showed significantly impaired performance in verbal STM tasks, this deficit being most pronounced in Patients JPH and DC. At the time of the present study, all patients were free of anti-epileptic drug for at least 5 years and free of seizures for at least 7 years.

Positron emission tomography scanning

PET data were obtained on a CTI 951 16/32 scanner (Siemens, Erlangen). The subject's head was stabilised by a thermoplastic facemask secured to the head holder (Truscan Imaging, MA), and a venous catheter was secured in a left antebrachial vein. A transmission scan measured attenuation correction. Data were reconstructed using a

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Hanning filter (cut-off frequency:

0.5 cycle/pixel) and corrected for attenuation and background activity. Twelve $H_2{}^{15}O$ scans were acquired at 8-minute intervals in 3-D mode. Each scan consisted of two frames: a 30-sec background frame and a 90-sec frame. The slow intravenous water infusion began just before the second frame in order to observe the head curve rising within the first 10 sec of this frame. For each scan, 6-8 mCi (222-296 MBq) were injected, in 5 ml saline, over a period of 20 sec. The infusion was totally automated.

Cognitive tasks

Two different verbal repetition tasks were performed during the scans: single word repetition (REP) and repetition of sequences of four words (MEM). A pool of 240 French words was selected from the Brulex database [Content et al., 1990] with the following criteria: the items were disyllabic concrete nouns of high frequency and imageability. Mean word length was 616 msec (SD 71 msec). From these items, 6 lists containing 20 single words and 6 lists containing five sequences of four words were constructed and recorded on a computer disk by a native French female speaker. No item was repeated within or between the different lists. Stimuli were presented through headphones. For repetition of four-word sequences, each word was presented at a rate of 1 item every 1,500 msec; after the last item of each sequence, subjects were allocated a response time of 5,700 msec to recall the four words in correct serial order. After response time, a sine-wave tone of 300 msec (frequency: 950 Hz) announced the next sequence that began 1,000 msec after the tone. For single-word repetition, items were presented at a rate of 1 item every 3,000 msec; subjects had to repeat each stimulus immediately after presentation. In order to keep the single-word lists and four-word sequences as similar as possible, except STM load, the sine-wave tones were also presented five times at random positions in the single-word lists. The six lists for single word and the six lists for four-word repetition were presented in random order, except that two lists from the same condition could not be presented at two consecutive trials. Subjects' responses were recorded on a tape microphone. For single word repetition, number of correct repetitions was determined for each subject. For four-word sequence repetition, the number of items recalled in correct serial position and recalled independently of correct serial position was determined. Subjects were trained on each cognitive task before the PET session. Before each acquisition, the instructions were repeated. The task began 10 sec prior to the second scan frame. Subjects kept their eyes closed while ambient light and noise were kept to a minimum.

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TABLE I. Clinical features of the LKS patient group

Patient	Age at onset of LKS (yr)	Age at introduction of cortisone (yr)	Epileptic focus[a]	^{18}FDG-PET active phase[b]	^{18}FDG-PET at recovery[b]	Duration of aphasia with epilepsy[c]	Main aphasic features during active epilepsy
TG	5.3	7.0	R temporal	6.1 yr, during sleep: R superior temporal increase	*7.7* yr, during sleep: bilateral superior temporal and perisylvian decrease	22 mo.	Severe auditory agnosia evolving to severe global aphasia with signed language communication
JPH	3.0	8.2	L temporal	6.3 yr, during sleep: L superior and middle temporal and perisylvian decrease 7.5 yr, during sleep: R superior and middle temporal and bilateral perisylvian decrease	8.8 yr, during wakefulness: L superior and middle temporal, and perisylvian decrease 11.8 yr, during sleep: L middle temporal decrease 11.8 yr, during wakefulness: L superior temporal and perisylvian decrease	46 mo.	Global aphasia with auditory agnosia and signed language communication
DC	6.0	11.5	R temporal	10.1 yr, during sleep: R superior and middle temporal perisylvian, orbital and lateral frontal increase; 10.1 yr, during wakefulness: R superior and middle temporal perisylvian, orbital and lateral frontal increase; L perisylvian decrease		30 mo.	Increasing difficulties in auditory verbal comprehension; non-fluent oral language with anomia and phonetic disintegration

[a] Predominant (higher amplitude and frequency) SWDs on wake EEG and CSWS on sleep EEG recordings.

[b] Summary of main results published by Maquet et al., 1995.

[c] From onset of language disorder to recovery of verbal functions concomitant with the normalisation of waking and sleep EEG following treatment with cortisone.

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TABLE II. Performance in language, verbal and visuo-spatial STM tasks, as well as standardized scores on Wechsler Intelligence scales, 7-10 years after recovery of LKS

	Patient		
	TG	**JPH**	**DC**
Delay after recovery of LKS (yr)	8	10	7
Phonological processing			
Single word repetition (correct repetitions, %)	92	100	95
Single non-word repetition (correct repetitions, %)	87	48[a]	67[a]
Lexico-semantic processing			
Picture naming (Bachy 90; pictures correctly named, %)	88	93	92
Receptive vocabulary (EVIP) [Dunn, Thériault-Whalen & Dunn, 1981], standardized score	112	109	109
Oral sentence comprehension (E.CO.S.SE) [Lecoq, 1993], incorrect trials (n)	4	5	7
Written sentence comprehension (E.CO.S.SE) [Lecoq, 1993], incorrect trials (n)	4	1	5
Verbal short-term memory			
Digit span[b]	5	4[a]	4[a]
Short word span[b]	4	3[a]	3[a]
Long word span[b]	4	3[a]	3[a]
Phonologically dissimilar word span[b]	5	4[a]	3[a]
Phonologically similar word span[b]	3[a]	3[a]	3[a]
Visuo-spatial short-term memory			
Block tapping test [Corsi, 1972]	7	5	5
Wechsler Intelligence Scales (WAIS-R) [Wechsler, 1989]			
Verbal IQ	117	80	85
Performance IQ	144	110	101
Total IQ	134	93	91

[a] Performances < 2 SD to control group.

[b] For each STM condition, lists of increasing length were presented (2-7 items for words, 2-9 items for digits); there were three trials for each list length; span level was determined as the longest list length at which at least two trials were correctly recalled.

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Data analysis

Data were analysed using statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) implemented in MATLAB (Mathworks Inc., Sherborn, MA). Scans from each subject were realigned [Friston et al., 1995a], transformed into a standard stereotactic space, and smoothed using a 16-mm full-width-half-maximum (FWHM) isotropic kernel [Friston, 1997]. In patients, PET data were co-registered to their Tl-weighted MRI scan [Friston et al., 1995a]. The condition and subject (block) effects were estimated according to the general linear model at each voxel [Friston et al., 1995b]. Global flow normalization was performed by proportional scaling. The design matrix included patients' and controls' scans and the number of errors as confound. This additional regressor was added to account for the difference in performance between subjects and patients. To test hypotheses about regionally specific condition effects, the parameter estimates were compared using linear compounds or contrasts. A subtraction analysis first identified the cerebral areas supporting verbal STM in the control population [MEM-REP]. We then looked for areas that would be *less* activated during performance of the STM task in each patient compared to the control population [group (patient vs. controls) by condition (MEM vs. REP) interaction]. Finally, a similar interaction analysis identified areas that were significantly *more* activated during performance of the STM task in each patient compared to controls. The resulting set of voxel values for each contrast, constituting an SPM of the *t* statistic (SPM{t}), was transformed in Z distribution (SPM{Z}), with a statistical threshold of $P = 0.001$. STG regions more or less activated in the STM condition in patients were explored more specifically by creating an inclusive mask of those STG and adjacent perisylvian regions where glucose metabolism had been abnormal during the active phase of the disease and by limiting search volume to these regions, based on the regions reported in Maquet et al. [1995]. The STG regions of interest were delineated on the coreg-istered and normalized MRI scans of each patient and included, for Patient TG the right STG, for JPH the right and left STG, and for Patient DC the right STG. Furthermore, given our a priori knowledge on the involvement of ventral, lateral, and dorsal prefrontal, posterior superior temporal, inferior parietal, insular, cingulate, cerebellar, and subcortical (lentiform nuclei, thalamus, caudate nucleus) regions in verbal STM, activation in these regions was considered significant at $P < 0.05$, corrected for small search volume (sphere = 10 mm) on the published coordinates in these studies [Becker et al., 1994, 1999; Collette et al., 2001; D'Esposito, 2001; Fiez et al., 1996; Grasby et al., 1993; Henson et al., 2000; Jonides et al., 1998; Paulesu et al., 1993; Rypma et al., 1999; Rypma and D'Esposito, 1999; Salmon et al., 1996; Smith and Jonides, 1998].

Magnetic resonance imaging

High resolution Tl-weighted structural MRI (voxel size: 0.96 X 0.96 X 1.35 mm) was performed the day of the PET study in each patient (1.5 T Magnetom Imager, Siemens, Erlangen).

RESULTS

Behavioural data

In the single word condition (REP), controls and LKS patients had no difficulty to repeat back the different words (Controls: 100%; TG: 99%; JPH: 99%; DC: 97%). In the four-word condition (MEM), Patients DC and JPH showed a large decrease in performance compared to controls, especially when counting words recalled in correct serial position; Patient TG's STM performance, although not completely in the normal range, was very close to normal performance (controls: mean = 99.7%, SD = 0.6, for item recall; mean = 99.7%, SD = 0.6, for serial position; TG: 97 and 93%, respectively; JPH: 80 and 40%, respectively; DC: 95 and 73%, respectively).

Imaging data

Brain regions activated in the STM condition in control subjects

Significant increases in brain activity were observed, at corrected levels, bilaterally in the inferior prefrontal cortex (BA 44, 47), the middle frontal gyri (BA 10, 46, 6), the insula, the superior temporal gyrus

(BA 38/22), the inferior parietal lobule (BA 40), the left inferior occipital gyrus (BA 19), the anterior cingulate cortex (BA 24/32), the cerebellum and in subcortical structures (left putamen and thalamus, as well as left caudate nucleus). Coordinates of peak activation foci and corresponding Z-scores are reported in Table III.

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Interaction analysis: brain regions less activated in the STM condition for TG, JPH, DC compared to the controls

For Patient TG, no voxel remained significant at corrected statistical thresholds. A right midtemporal region (BA 21/38) was significant at $P < 0.001$, uncorrected. For Patient JPH, decrease in brain activation compared to controls was observed bilaterally in the perisylvian cortex. This region included the left anterior superior temporal gyrus (BA 38), the lateral part of the right posterior superior temporal gyrus (BA 22), and the right inferior parietal gyrus (BA 40). The right middle frontal gyrus (BA 6) was also significantly less active than in controls in the STM condition. Further decreases of activation, at uncorrected *P* levels, were observed in the right orbital gyrus (BA 11), the left post-central gyrus (BA 1/2/3) and the left insula. For DC, brain response to STM task was also bilaterally decreased in the perisylvian area, as compared to normal subjects. This region included the posterior superior temporal gyrus bilaterally (BA 42/22), the right inferior parietal lobule (BA 40), and left Broca's area (BA 44/6). The posterior cingulate cortex was also less activated than in controls (BA 30). Coordinates of peak activation foci and corresponding Z-scores for corrected P-levels are reported in Table IV. Activation foci rendered on the patients 3-D co-registered MRI scans are presented in Figure 1.

Interaction analysis: brain regions more activated in the STM condition for TG, JPH, and DC compared to the controls

For Patient TG, increased brain activity was observed in the right posterior temporo-parietal area, including the superior temporal gyrus (BA 42) and the inferior parietal lobule (BA 40), as well as in the left putamen. Additional increases of activation were observed in the superior frontal gyrus (BA 10) and the posterior cingulate (BA 30/31), at $P < 0.001$, uncorrected. For Patient JPH, a significant interaction was observed in the anterior cingulate cortex (BA 24/32). Increased activity was also observed in the right medial and the inferior frontal gyrus (BA 6/32, BA 46/ 10). For Patient DC, a significant interaction was observed in the right middle frontal gyrus (BA 46/45) and the medial frontal gyrus (BA 10). At uncorrected *P* levels, activation was observed in the left anterior middle temporal gyrus (BA 21) and the right inferior parietal lobule (BA 39). Coordinates of peak activation foci and corresponding Z-scores for corrected *P* levels, are reported in Table IV. Activation foci rendered on the patients 3-D co-registered MRI scans are presented in Figure 1.

DISCUSSION

Before discussing the implications of our patients' data, we briefly comment on the activation pattern for phonological STM processing found in the control subjects. Past functional neuroimaging studies have shown that bilateral dorsal, lateral, and ventral prefrontal cortex, insula, premotor cortex and posterior parietal cortex, posterior and superior temporal cortex as well as cingular, cerebellar and subcortical regions (lentiform nucleus, thalamus, caudate nucleus), in left or both hemispheres, are activated during STM tasks for verbal information [Becker et al., 1994, 1999; Collette et al., 2001; D'Esposito, 2001; Fiez et al., 1996; Grasby et al., 1993; Henson et al., 2000; Jonides et al., 1998; Paulesu et al., 1993; Rypma et al., 1999; Rypma and D'Esposito, 1999; Salmon et al., 1996; Smith and Jonides, 1998]. Posterior parietal cortex is thought to be involved in passive storage processes while prefrontal cortex is considered to be involved in rehearsal of the verbal information that is passively stored in posterior brain regions [Collette et al., 2001; Paulesu et al., 1993; Salmon et al., 1996; Smith and Jonides, 1998]. In the present study, we observed activations of the inferior and middle frontal regions, the insula, the superior temporal gyrus bilaterally, the right parietal gyrus, the left inferior occipital gyrus, the cingulate cortex, the cerebellum as well as left putamen, thalamus, and caudate nucleus. These results are indeed largely consistent with the previous studies. The only major difference was that the activation was bilateral in this study while in previous studies activation had been predominantly left-sided. This difference might be due to the stimulus set used; in this study, we presented highly imageable and frequent words while in other studies single consonants were mainly used. The bilateral activation might be due to the visual semantic content of our stimuli that has been shown to activate both left and right hemispheres [e.g., Pulver-müller, 1999].

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TABLE III. Fixed-effect analysis for activation in the STM condition compared to single word repetition for the control group

	Stereotaxic coordinates			
Brain area	***x***	***y***	**z**	**Z**
Inferior frontal gyrus L (BA 47)	-50	30	-22	4.77[a]
Inferior frontal gyrus R (BA 47)	63	21	-8	5.24[a]
	36	18	1	5.03[a]
Inferior frontal gyrus R (BA 44)	67	14	1	5.04[a]
Middle frontal gyrus L (BA 10/46)	-36	49	18	3.89[b]
Middle frontal gyrus R (BA 10/46)	38	44	16	5.47[a]
Middle frontal gyrus R (BA 6)	34	1	53	4.82[a]
Superior temporal gyrus L (BA 38)	-48	26	-28	4.30[a]
Superior temporal gyrus R (BA 38)	59	20	-18	4.85[a]
Inferior parietal gyrus L (BA 40)	-24	-49	37	4.07[b]
Inferior parietal gyrus R (BA 40)	34	-37	31	5.25[a]
Inferior occipital gyrus L (BA 19)	-51	-78	-5	5.36[a]
Anterior cingulate (BA 24/32)	-8	16	32	3.65[b]
	-4	28	22	3.33[b]
Insula L	-22	16	-1	4.18[b]
	-22	-20	19	3.36[b]
Insula R	30	22	4	4.78[a]
Putamen L	-24	14	4	4.41[b]
Caudate Nucleus	-20	14	16	3.97[b]
Cerebellum R	2	-47	-8	3.87[b]

[a] $P < 0.001$, corrected for multiple comparisons ($P < 0.05$). [b] $P < 0.001$, small volume correction ($P < 0.05$).

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TABLE IV. Brain regions less or more activated in the LKS patients compared to controls for the STM condition

Brain regions less activated in the LKS patients	Stereotaxic coordinates				Brain regions more activated in the LKS patients	Stereotaxic coordinates			
	x	*y*	z	Z		*x*	*y*	z	Z
Patient TG					Patient TG				
No voxel reached statistical threshold					Superior temporal gyrus R (BA 42)	65	-22	18	3.22[b]
					Inferior parietal lobule R (BA 40)	67	-22	29	3.38[b]
					Putamen L	-34	-17	1	3.04[b]
Patient JPH					Patient JPH				
Middle frontal gyrus R (BA 6)	32	-3	52	3.90[b]	Inferior frontal gyrus R (BA 46/10)	50	51	3	3.44[b]
					Medial frontal gyrus R (BA 6/32)	16	14	45	3.80[b]
Superior temporal gyrus L (BA 38)	-20	20	-30	3.22[b]	Anterior cingulate (BA 24/32)	-12	30	10	4.97[a]
Superior temporal gyrus R (BA 22/42)	73	-28	14	3.44[b]					
Inferior parietal gyrus R (BA 40)	69	-27	38	3.03[b]					
Patient DC					Patient DC				
Inferior frontal gyrus L (BA 44/6)	-55	4	11	3.20[b]	Middle frontal gyrus R (BA 45/46)	57	25	25	4.64[a]
					Medial frontal gyrus L (BA 10)	-1	54	7	3.15[b]
Superior temporal gyrus L (BA 42)	-65	-23	14	3.44[b]					
Superior temporal gyrus R (BA 22)	63	-3	9	3.96[b]					
Superior temporal gyrus R (BA 22)	44	-27	5	3.73[b]					
Inferior parietal lobe R (BA 40)	42	-33	31	3.07[b]					
Posterior cingulate (BA 30)	-12	-50	17	3.34[b]					

[a] $P \leq 0.001$, corrected for multiple comparisons ($P \leq 0.05$). [b] $P \leq 0.001$, small volume correction ($P \leq 0.05$).

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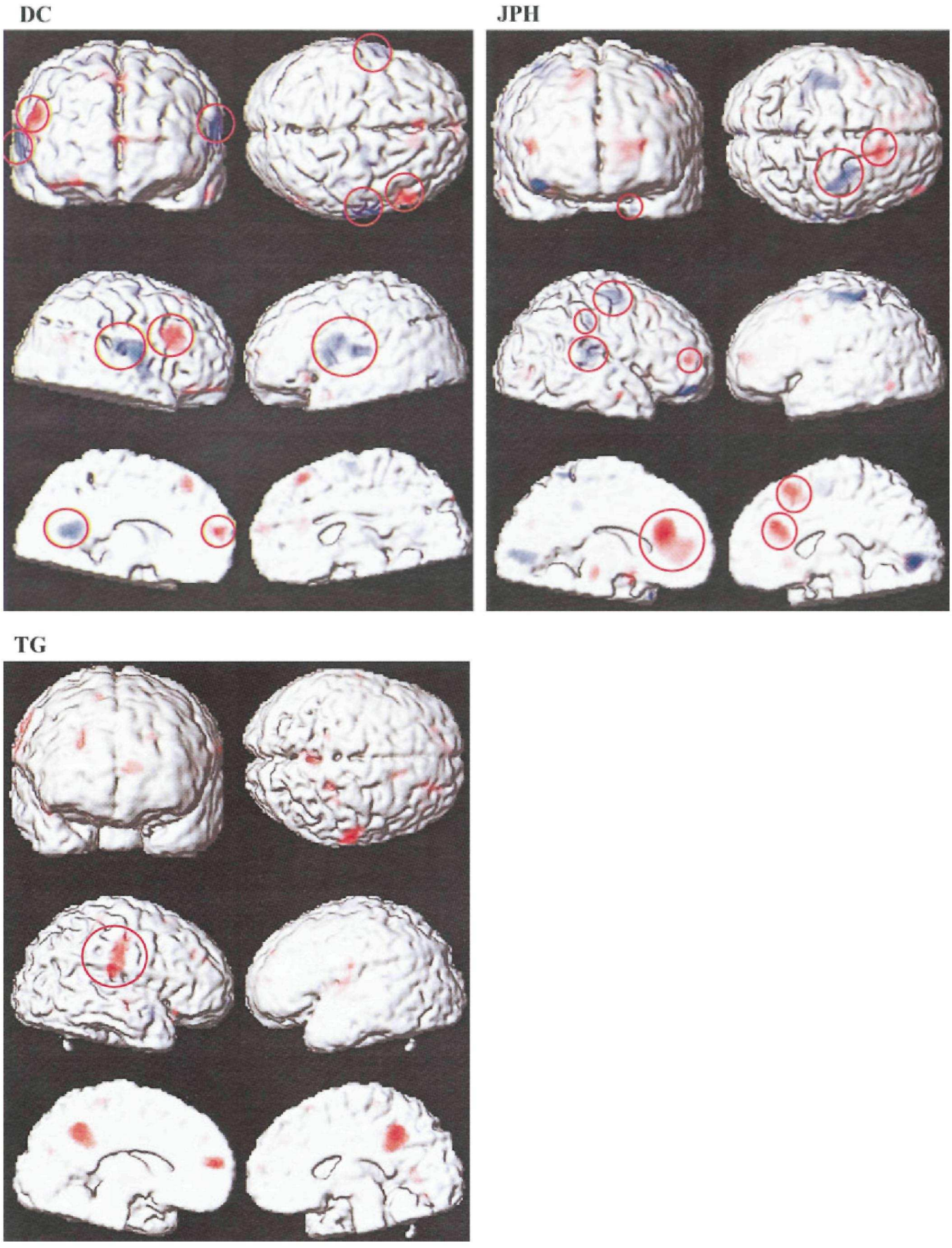

Figure I.

Brain regions less or more activated in the STM condition for patients DC, JPH and TG, rendered on their 3-D

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MRI scans (P < 0.01, uncorrected). Regions more activated are indicated in red; regions less activated are indicated in blue. The red circles indicate regions of interest that remain significant after small volume corrections. Two sources of information guided the selection of regions of interest: (I) the previous neuroimaging data of patients DC, JPH, and TG, showing abnormal glucose metabolism in superior temporal gyri during the active phase of LKS and during recovery [Maquet et al., I995]; and (2) published neuroimaging results for verbal STM tasks in healthy controls (see description in the text).

As for the patients, two points deserve a detailed discussion: (1) how do the present activation patterns compare with previous metabolic abnormalities in the STG and adjacent perisylvian cortex, and (2) how do they relate to the persistent STM impairment? First, there is a clear relationship between the hypermeta-bolic and hypometabolic regions during the active phase of the LKS and the present brain activation pattern during a STM task. During the active phase of LKS, Patient JPH had shown decreased glucose uptake in the left superior and middle temporal regions, as well as reduced glucose uptake bilaterally in superior temporal regions several months later. In the present study, we observed reduced activity in the anterior portion of the left STG and in the right STG, extending to adjacent perisylvian cortex. Regarding Patient DC, he had shown during the active phase increased glucose metabolism in the right middle and superior temporal regions and decreased glucose metabolism in the left perisylvian cortex. In the present study, diminished activity bilaterally in the superior temporal cortex, extending to the adjacent perisylvian cortex was observed. Finally, during the active phase of LKS, Patient TG had shown a very focal increase in glucose metabolism at the level of the right STG, which became hypometabolic several months later. In the present study, slightly reduced activity in the anterior part of the right midtemporal gyrus was observed for STM processing, several years after recovery of LKS (although only at uncorrected *P* levels). The results suggest that late outcome of LKS may indeed be characterized by long-lasting dysfunction of superior temporal gyri and adjacent perisylvian areas that had been dysfunctional during the active phase of epilepsy.

Secondly, Patients JPH and DC had very important difficulties in STM processing whereas Patient TG had near normal performance in the STM task. Indeed, the first two patients showed decreased activation in bilateral STG and adjacent perisylvian cortex, whereas decreased activation was found only in a small portion of the right STG in Patient TG. Most importantly, the patients with significantly reduced STM performance presented reduced activation of posterior STG, while TG showed increased activity in the right posterior STG and adjacent inferior parietal cortex. These data strongly suggest that the impaired STM performance in Patients DC and JPH might be related to decreased activity in the posterior part of the STG, and the better performance in TG to increased activity in the same region.

Now, what might be the precise role of the posterior part of the STG in verbal STM tasks? This region seems to be activated only when verbal information (single letters, letter or phoneme strings, or words) has to be processed in STM, but not for spatial or visual information. Some authors have argued that the posterior superior temporal cortex simply reflects perception and identification of the phonemes [Binder et al., 2000; Henson et al., 2000; Paulesu et al., 1993; Scott et al., 2000]. However, recent data suggest that the lateral part of the posterior STG might also be more directly implicated in short-term storage processes for phonological information, while simple perception of sub-lexical phonological information is restricted to regions in the anterior and posterior superior temporal sulcus [Binder et al., 2000]. Indeed, Hughes et al. [2001] repeatedly presented, to epileptic patients, a same consonant-vowel (CV) syllable at regular inter-stimulus intervals (ISI); sometimes, the CV syllable did not occur at the expected ISI. Intracranial ERP recordings showed that the posterior and lateral part of the bilateral STG specifically responded to the repetition of CV syllables, and, most importantly, was activated at the moment when the CV was expected to occur, even if it was not presented. This response to expected, but not necessarily really presented phonological information suggests that the posterior part of the STG had stored a temporary representation of the phonological event, which permitted to predict the occurrence of phonological information. Thus, activation of the posterior STG in the study by Hughes et al. [2001] was not related to basic perception processes, but rather to some form of short-term storage for phonological information. Similarly, Giraud and Price [2001], Grasby et al. [1993], and Wise et al. [2001] proposed that the posterior STG might be specifically implicated in temporary storage of phonological information. The function of this temporary phonological representation in the STG could be to form an "interface" representation, the time necessary to forward the perceived phonological information to further processing levels, like semantic long-term memory or further verbal STM processing in frontoparietal regions. The data of the present study seem to support this role for the posterior part of the STG in verbal STM tasks, by snowing reduced activity in posterior STG in those patients showing the greatest impairment in the verbal STM tasks, and increased activity in the same area for Patient TG showing relatively normal STM performance.

Furthermore, the storage of such "interface" representations in the posterior STG might be especially important when the capacity of the fronto-parietal verbal STM network is reduced. In that case, this reduced capacity

would only allow a very limited number of verbal information (1-2 items) to enter the fronto-parietal STM system at the same time; for the remaining items, the "interface" representation would have to remain activated until these items can enter the fronto-parietal STM system. In that case, Patients DC and JPH, who had the worst STM performance, might also have a reduced capacity of the frontoparietal verbal STM network. Accordingly, decreased activation in two regions of the fronto-parietal STM network was observed in Patients DC and JPH, the right inferior parietal lobule (Patients DC and JPH) and left Broca's area (Patient DC). Moreover, Patient DC showed a strong increase in activity in the right middle frontal gyrus (BA 46/45), while Patient JPH showed an important increase of activity in the anterior cingulate cortex, and some increase in the right inferior prefrontal cortex outside Broca's area (BA 46/ 10). These activations probably reflect strategic and attentional efforts implemented in order to compensate for the reduced STM storage capacities related to decreased activity in posterior STG and in the frontoparietal STM network in DC and JPH.

The proposed interactions between temporary interface representations in the posterior STG and reduced capacities of the fronto-parietal STM system might also explain why we did not observe greater posterior STG activation in the STM condition compared to single word repetition in controls (although there was some greater activation in anterior superior temporal gyri regions). The STM load achieved by four word lists, and used in this study, is indeed below the word span level for normal adults (normally 5-6 words) and does probably not exceed the capacities of the fronto-parietal STM system. Hence, construction of "interface" representations in the posterior STG was probably not much needed in controls. This relatively low STM load had actually been chosen on purpose to take into account the STM difficulties of the LKS patients.

Finally, could the STM difficulties and reduced activation in posterior STG for Patients DC and JPH not more simply be explained by a deficit in phonological speech perception processes? Recent neuroimaging studies have shown that phoneme perception and identification is related to activation of the bilateral superior temporal *sulcus* [Binder et al., 2000; Binder and Price, 2001; Jäncke et al., 2002; Scott et al., 2000]. In Patients JPH and DC, abnormal activity was confined to the lateral part of the posterior STG, identified by Hughes et al. [2001] and Wise et al. [2001] as being implicated in temporary storage processes of phonological information, and did not include the superior temporal sulcus supposed to be implicated in phonological perception processes. However, we must remain cautious as the cortical architecture in our patients might have changed relative to normal subjects, as a result of cortical plasticity during recovery from LKS. Nevertheless, our behavioural data showed that single word perception was quite normal in all patients, demonstrating that DCs and JPH's phonological identification processes were at least sufficient to permit correct perception and identification of word stimuli used in the present STM task and thus are not likely to explain their difficulties in the verbal STM tasks.

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