Frontal Contributions to Memory Encoding Before and After Unilateral Medial Temporal Lobectomy

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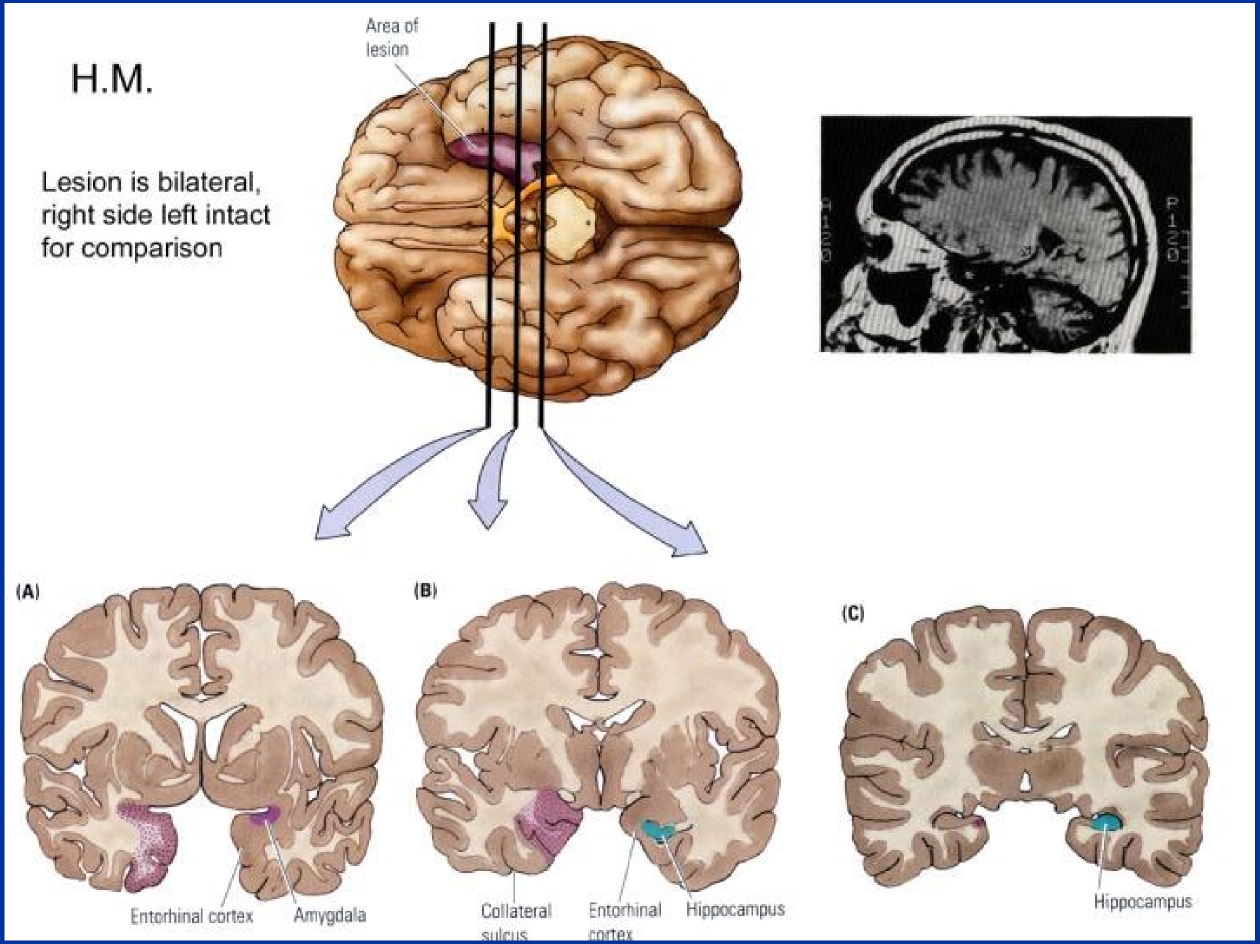
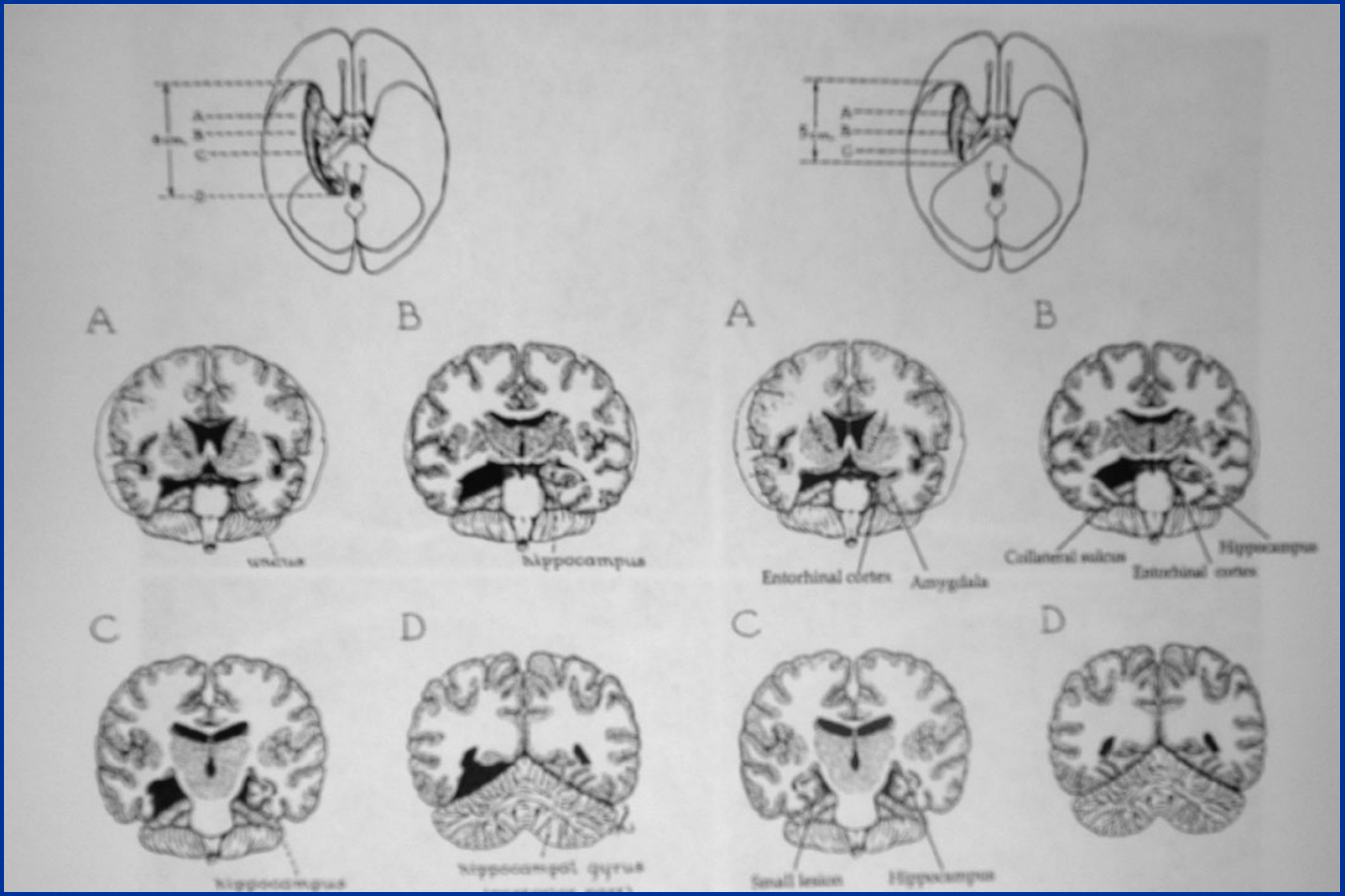
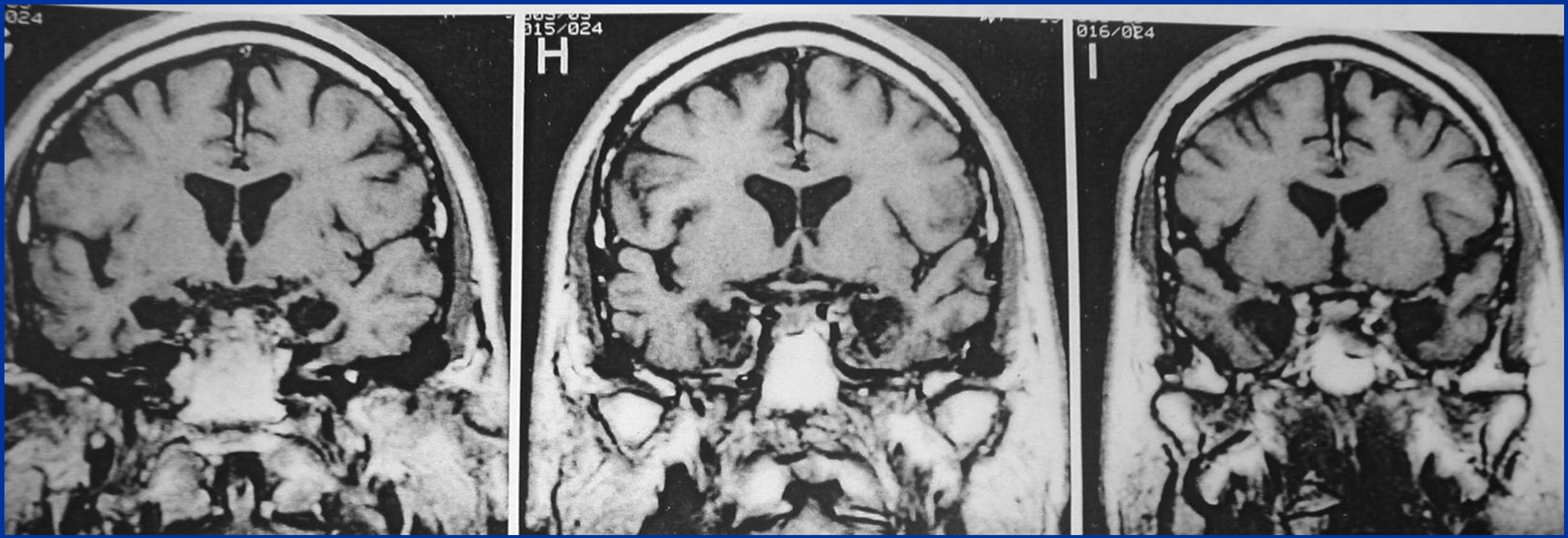
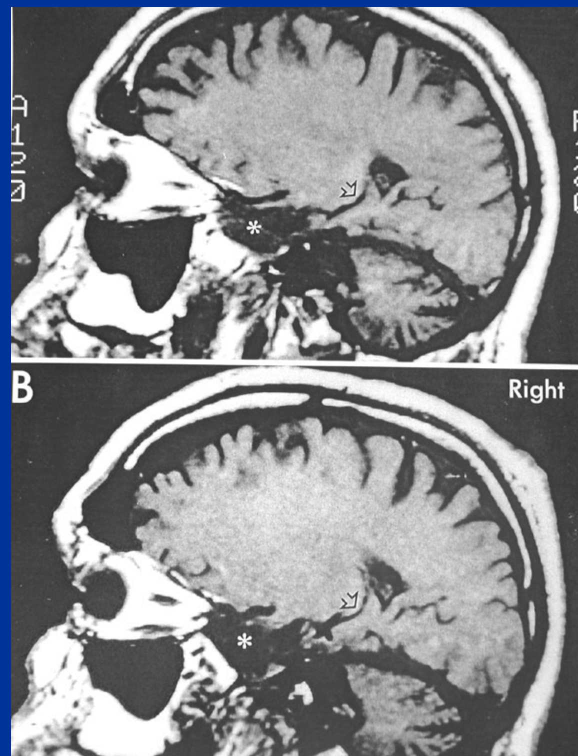
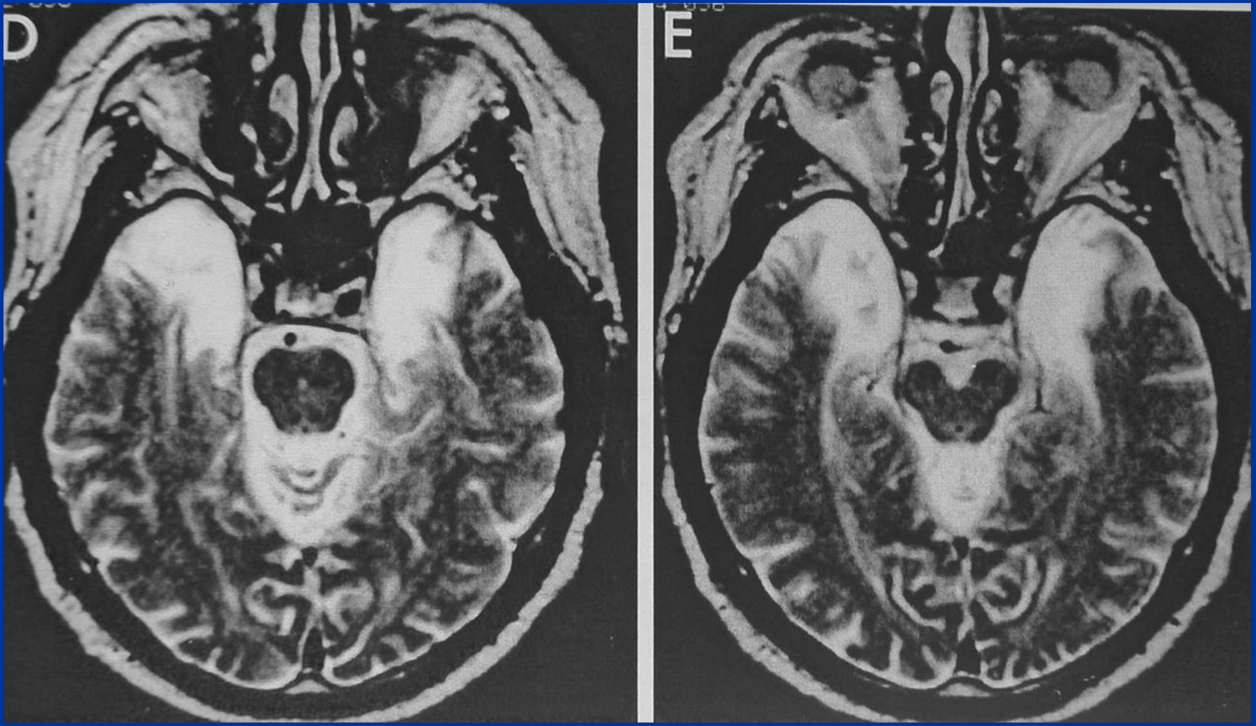
Episodic memory relies greatly on the presence of functioning medial temporal lobes




A
B
uncus
hippocampus
A
B
Entorhinal cortex
Amygdala
Collateral sulcus
Entorhinal cortex
Hippocampus
C
D
hippocampus
hippocampal gyrus
C
D
Small lesion
Hippocampus


024
015/024
H
016/024
I


B
Right


D
E

"…a grave loss of recent memory in those cases in which the medial temporal lobe resection was so extensive as to involve the major portion of the hippocampal complex bilaterally."

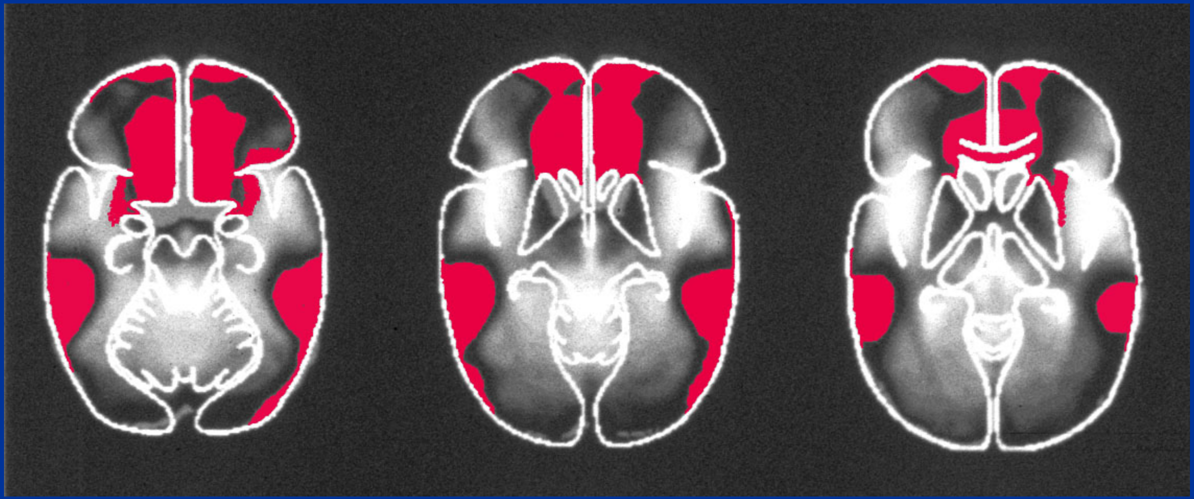
"After operation this young man [H.M.] could no longer recognize the hospital staff nor find his way to the bathroom, and he seemed to recall nothing of the day-to-day events of his hospital life."

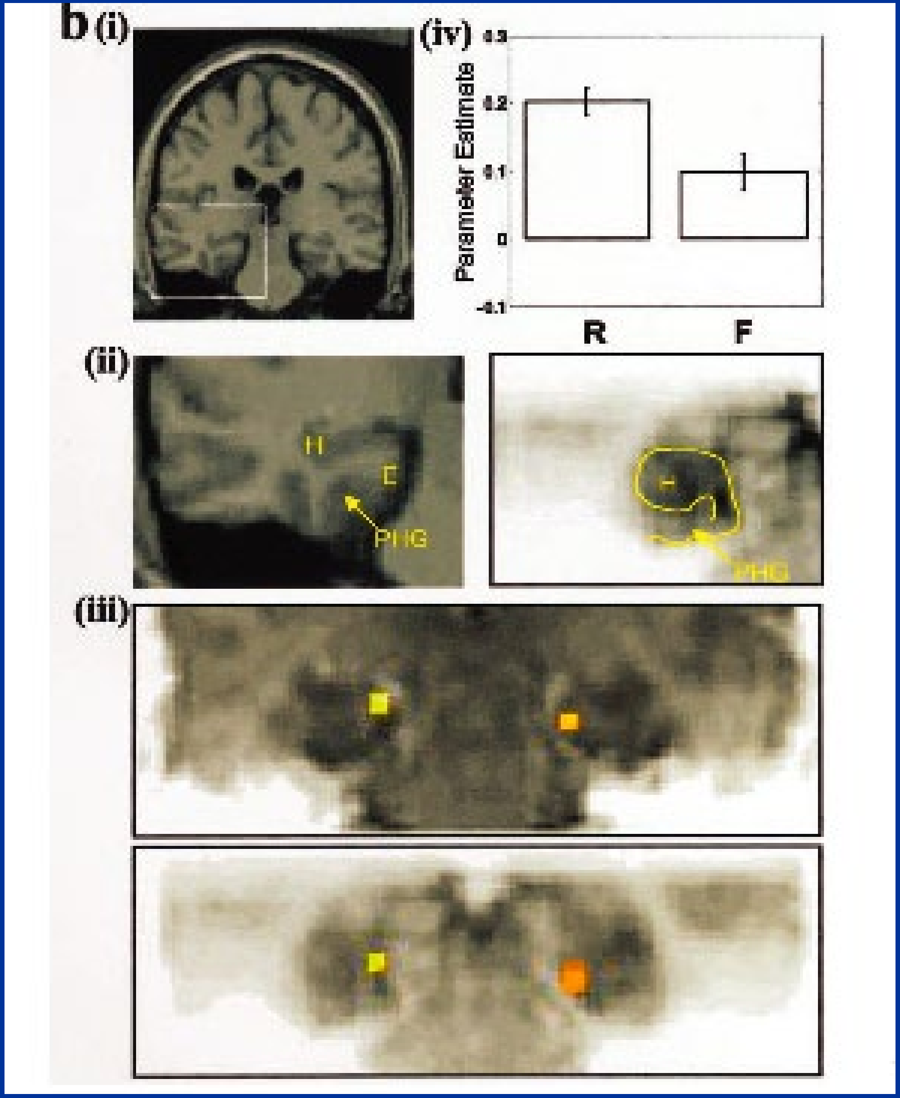
Scoville & Milner, 1957, *J. Neurol. Neurosurg. Psychiatr.*

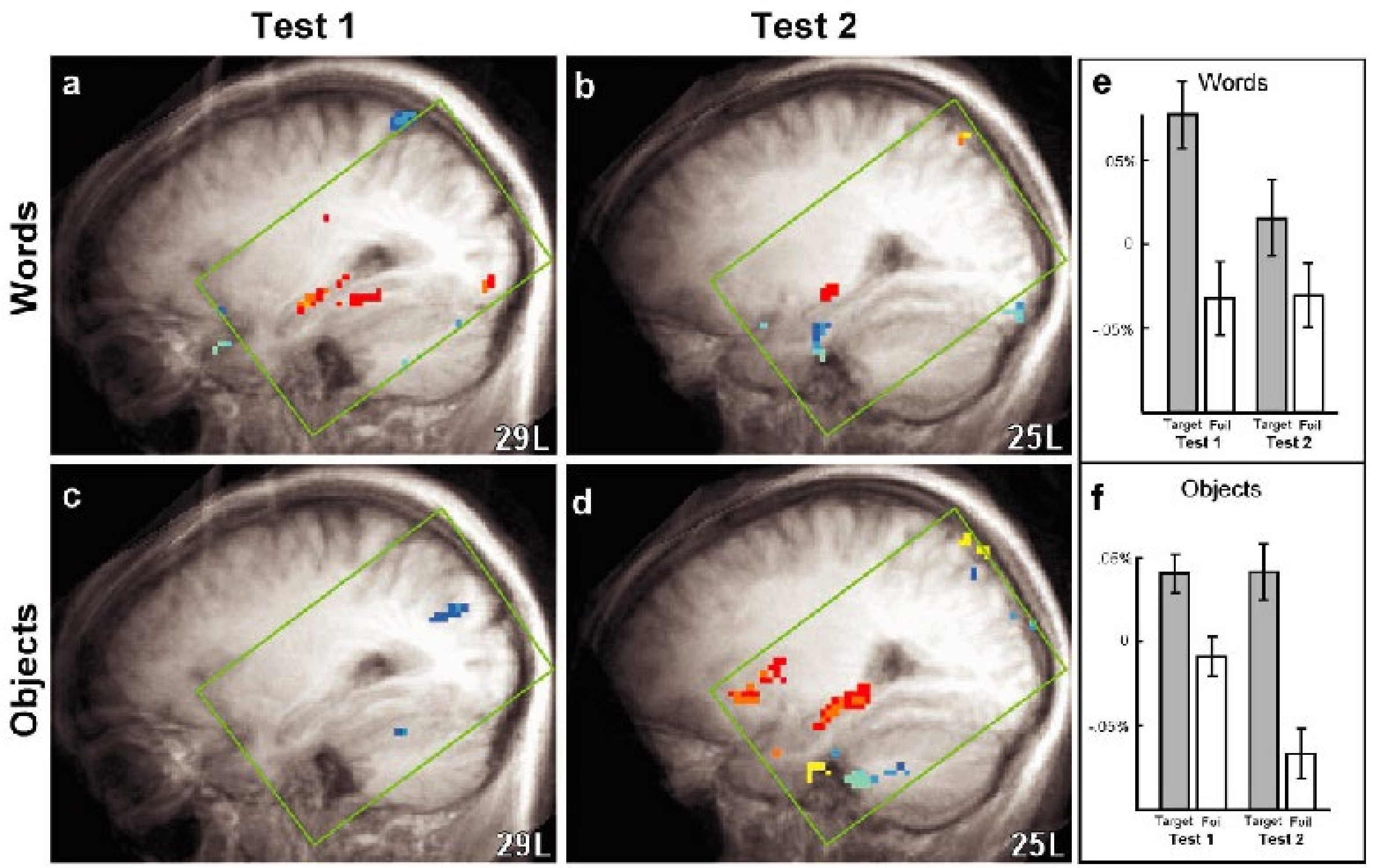
‘Word Stem’ memory-cued recall and Right Hippocampus

The *hippocampus* was not consistently seen in imaging studies of memory

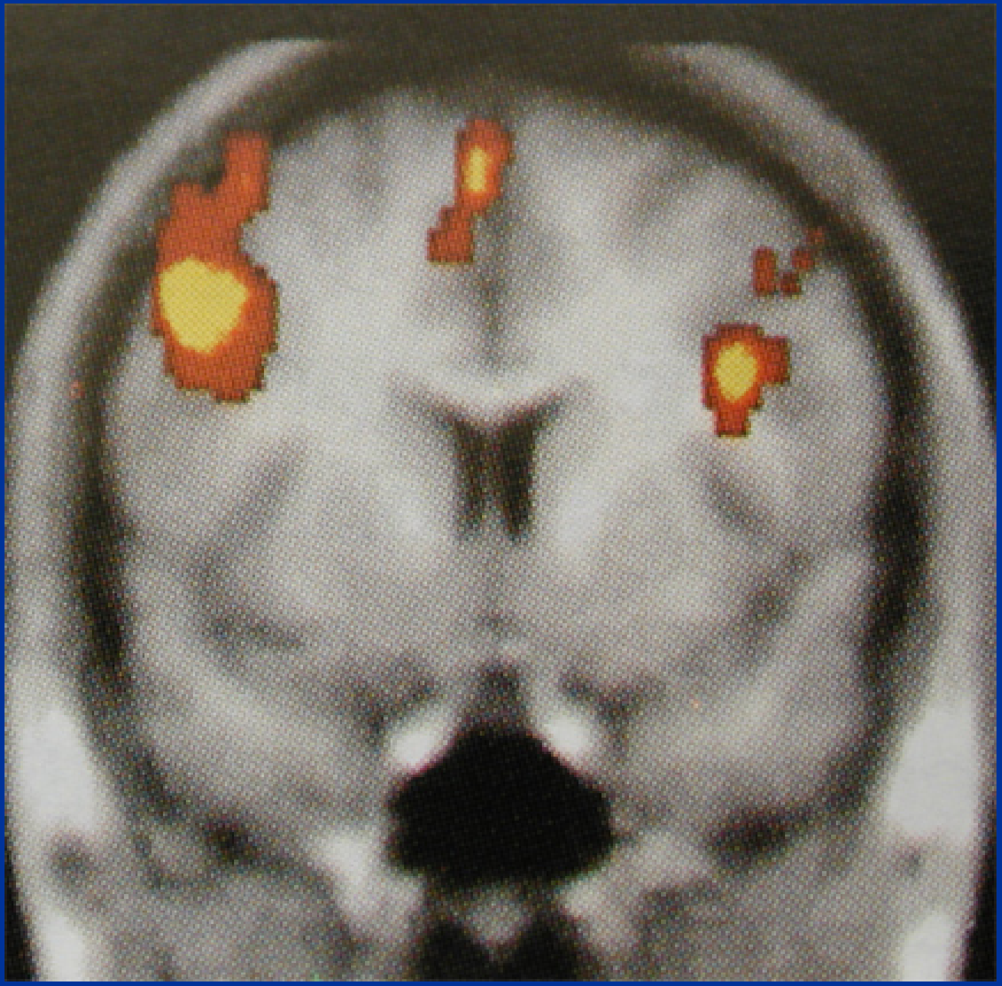
Areas of poor fMRI signal



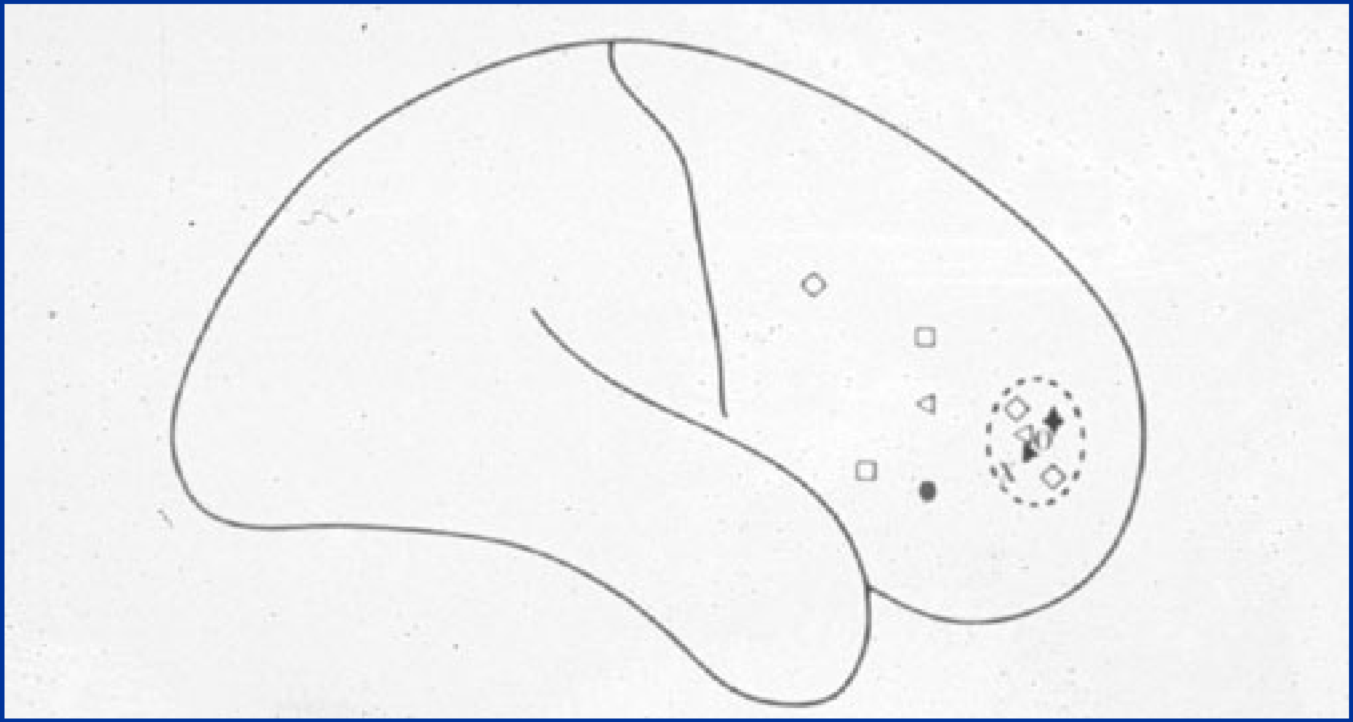

b
(i)
(iv)
Parameter Estimate
0.3
0.2
0.1
0
-0.1
R
F
(ii)
H
E
PHG
PHG
(iii)


Test 1
Test 2
Words
Objects
a
b
c
d
29L
25L
29L
25L
e
Words
.05%
0
-.05%
Target Foil
Test 1
Target Foil
Test 2
f
Objects
.05%
0
-.05%
Target Foil
Test 1
Target Foil
Test 2

Frontal Lobe and Memory

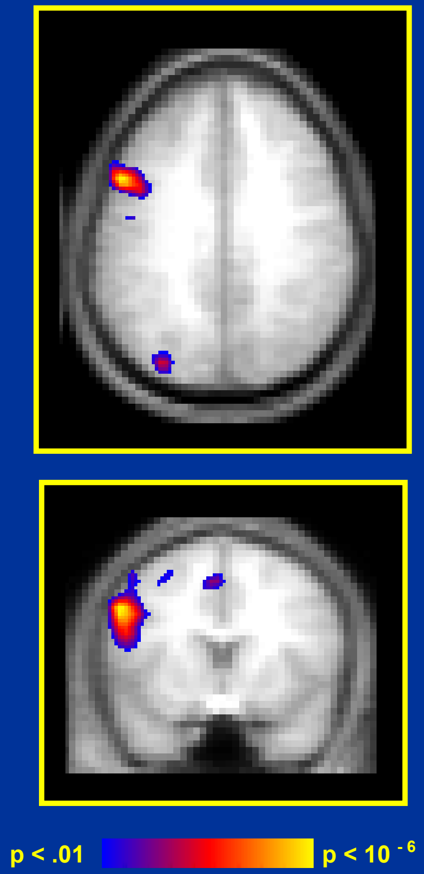


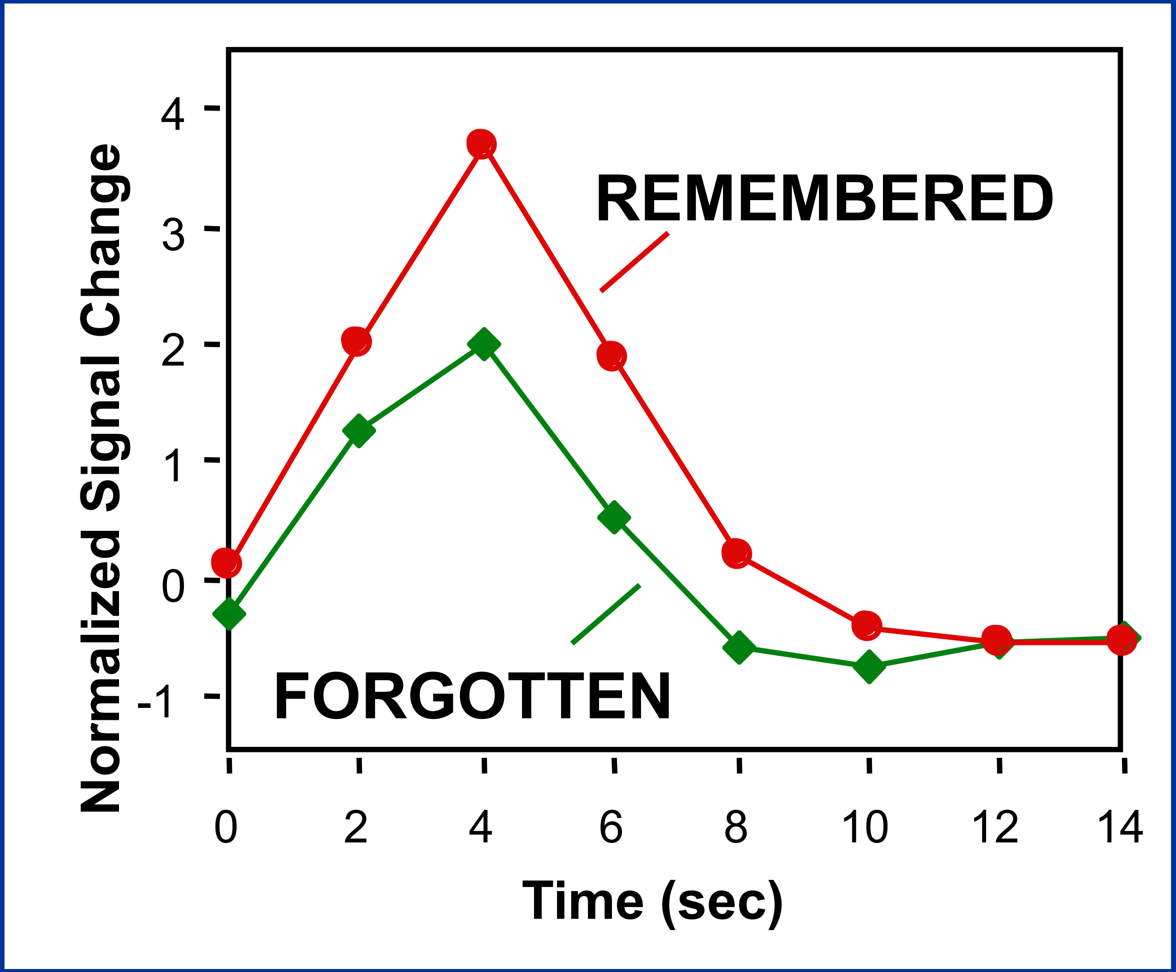
Many memory retrieval tasks activate frontal lobe



Regions of prefrontal cortex activate during encoding of both verbal and non-verbal material.

Moreover, their level of activation predicts subsequent memory.



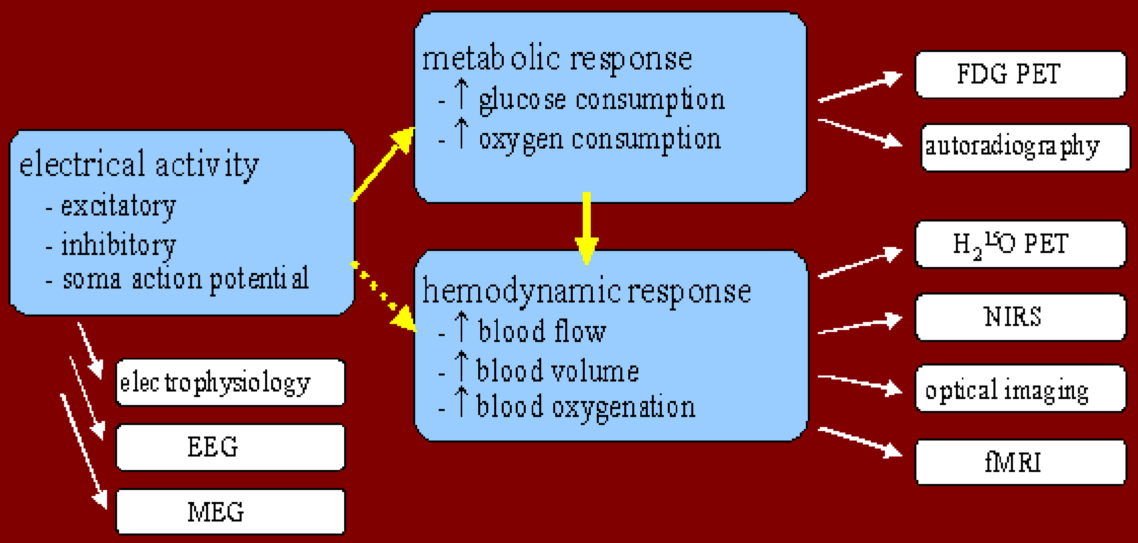


Wagner et al., 1998, *Science*

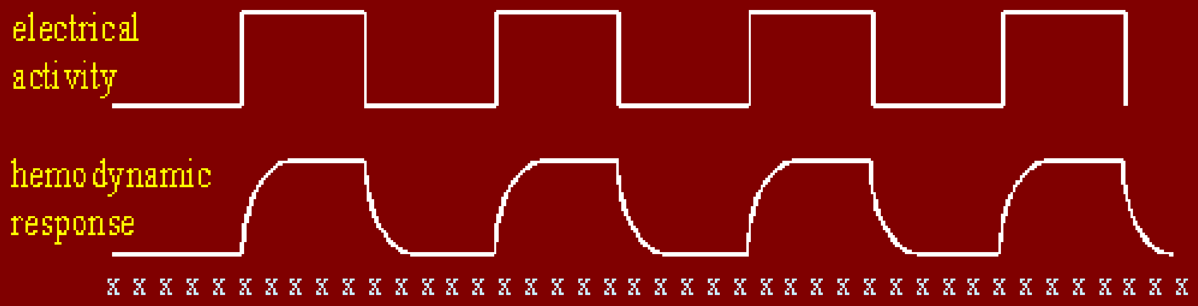
Functional imaging of memory

- Studies consistently activated the frontal lobe during encoding and retrieval tasks
- The hippocampus was rarely activated

Physiological Correlates of Brain Electrical Activity



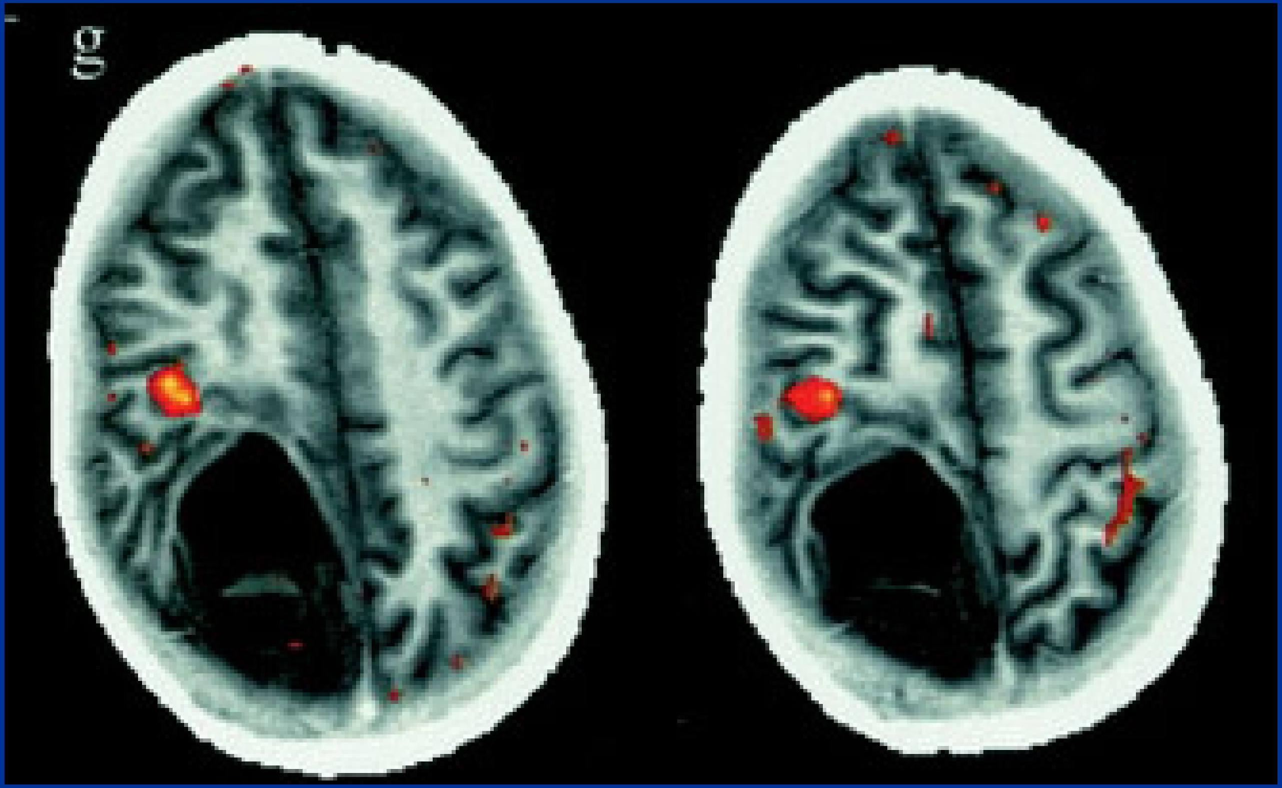
Functional MRI



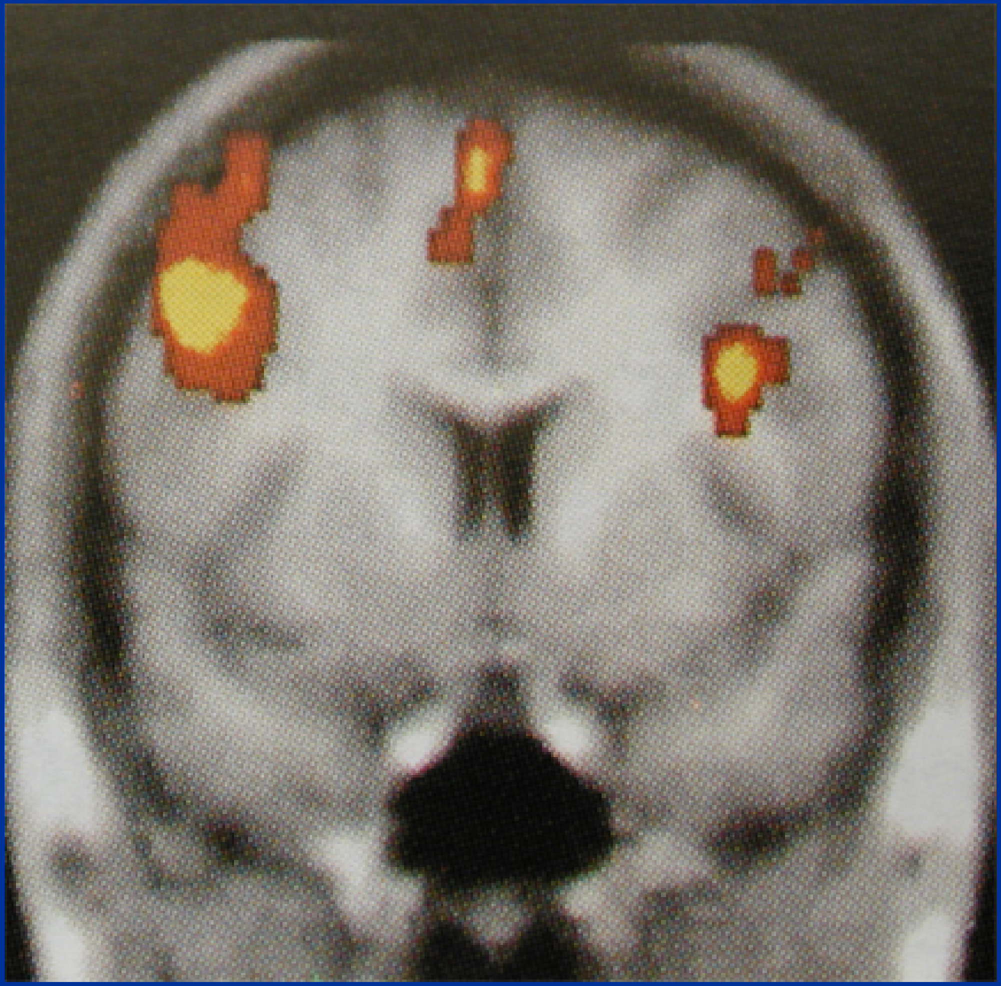
- need many samples of the brain
- need fast imaging capabilities
  - e.g. echo planar imaging
  - fast gradient coil
  - big disk!

Physiology: Summary

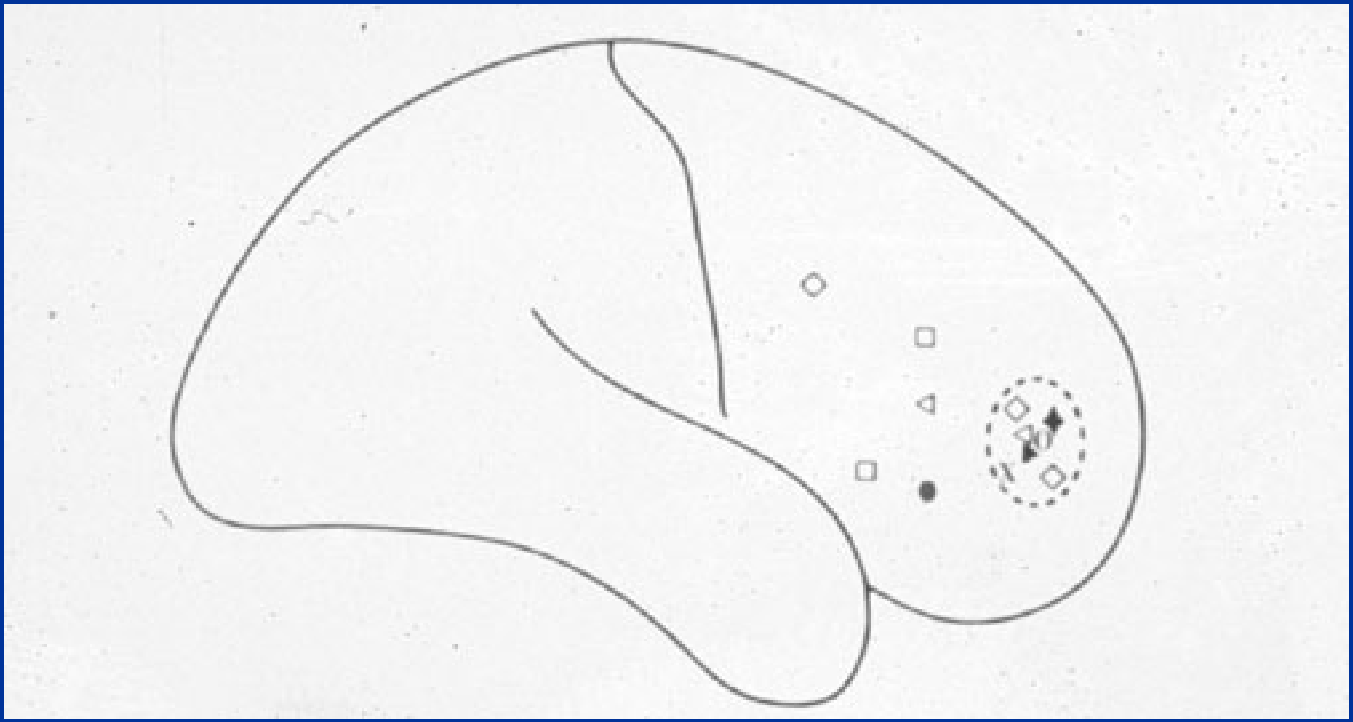
- increase in rCMRglu (20 – 40%)
  - seems to be mostly oxidative
- increase in $rCMRO_2$ (5 – 25%)
  - oxygen transport limited, but coupled: recent MR data suggests $\Delta CMRO_2 : \Delta CBF = 1:2$
- increase in rCBF (20 – 70%)
  - through increases in velocity rather than capillary recruitment
- increase in rCBV (5 – 30%)
  - mostly in venous vessels

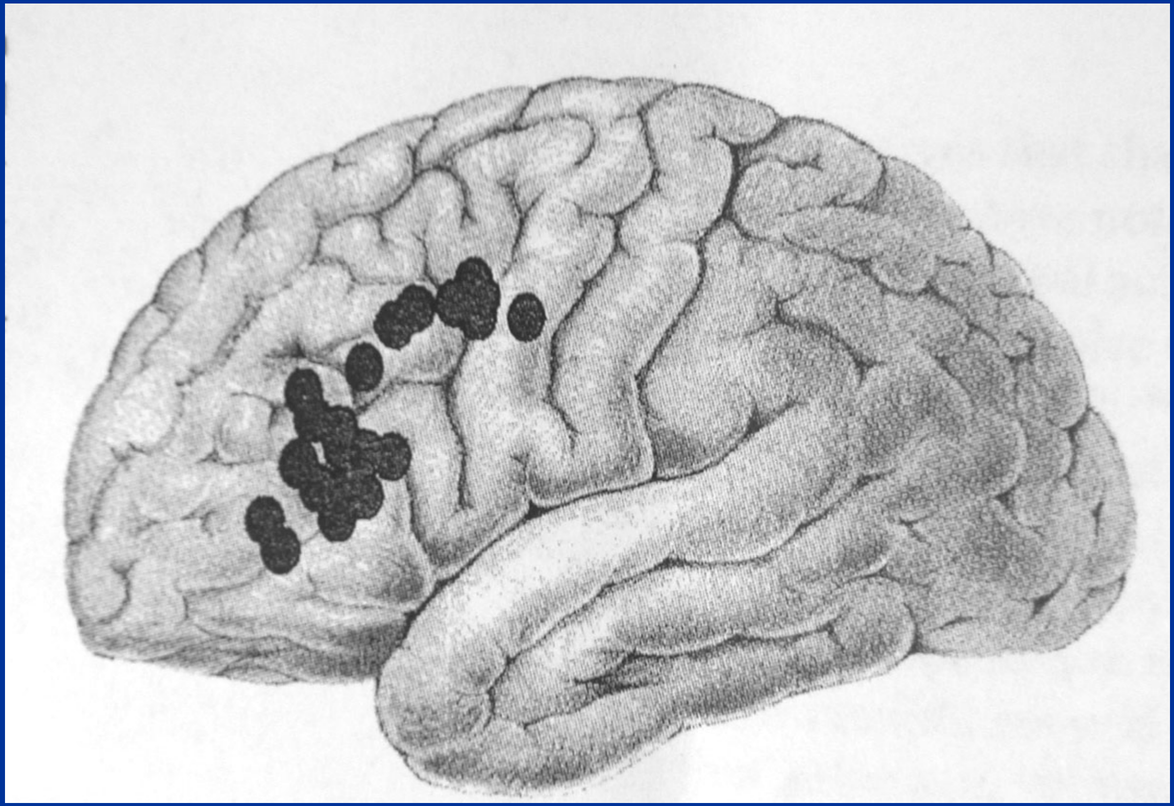


Frontal Lobe and Memory



Many memory retrieval tasks activate frontal lobe





Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 2016–2020, March 1994
Psychology

Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings

(frontal lobes/semantic memory/laterality)

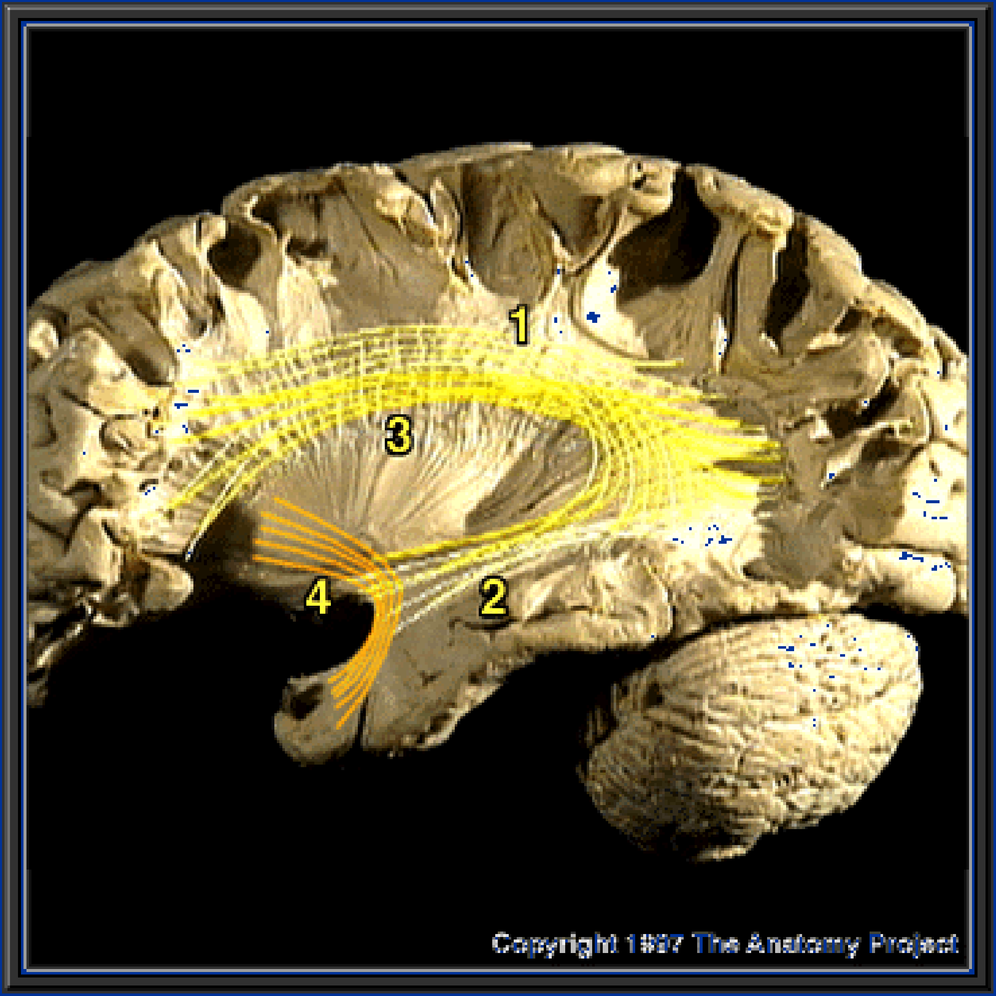
Endel Tulving*†, Shitij Kapur‡, Fergus I. M. Craik*†, Morris Moscovitch*†, and Sylvain Houle‡

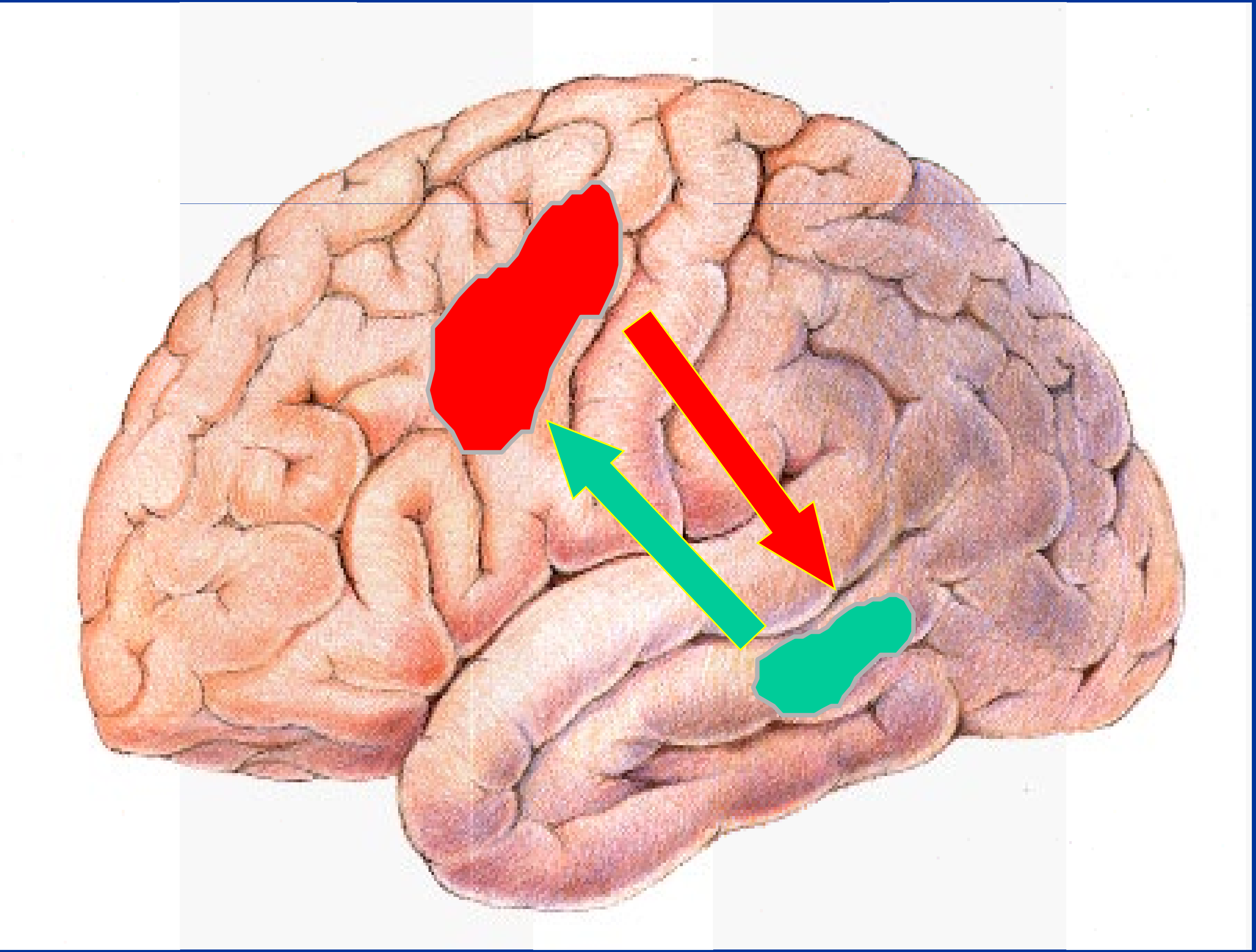
Table 1. Summary of PET findings with healthy human subjects concerning prefrontal activation associated with episodic memory encoding and retrieval processes

Study	Left	Right
Encoding		
Kapur *et al.* (14)	+	−
Petersen *et al.* (27)	+	−
Petersen *et al.* (30)	+	−
Frith *et al.* (31)	+	−
Frith *et al.* (32)	+	−
Wise *et al.* (33)	+	−
Raichle *et al.* (28)		
Trial 1	+	−
Trial 5	−	−
Buckner *et al.* (34)	+	−
Retrieval		
M.M. *et al.* (unpublished)		
Spatial Information	−	+
Object Information	−	+
Tulving *et al.* (16)	+	+
Squire *et al.* (35)	−	+
Buckner *et al.* (34)		
Different case	−	+
Auditory	−	+
Haxby *et al.* (36)	−	+
Jones–Gottman *et al.* (37)	−	+

Statistically significant evidence of prefrontal involvement is indicated by +, absence of similar evidence by −.

Brain Connections

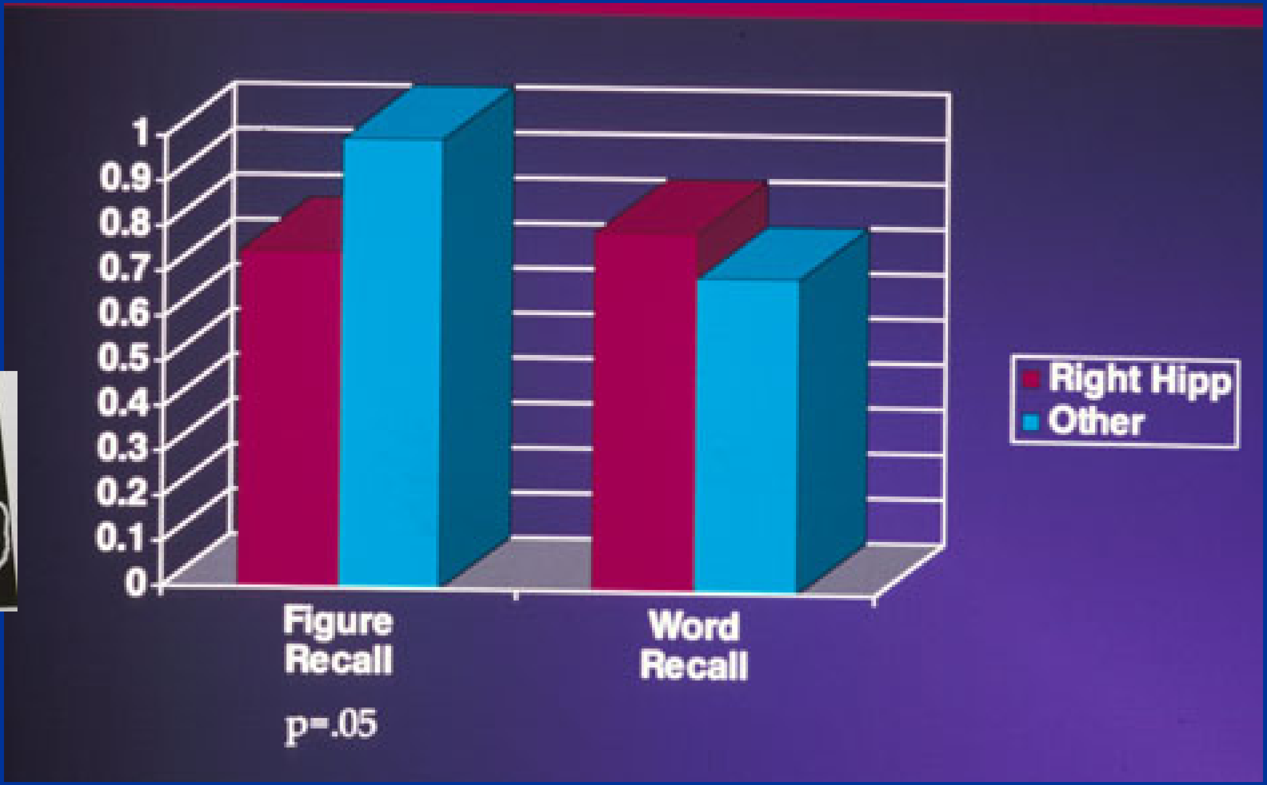




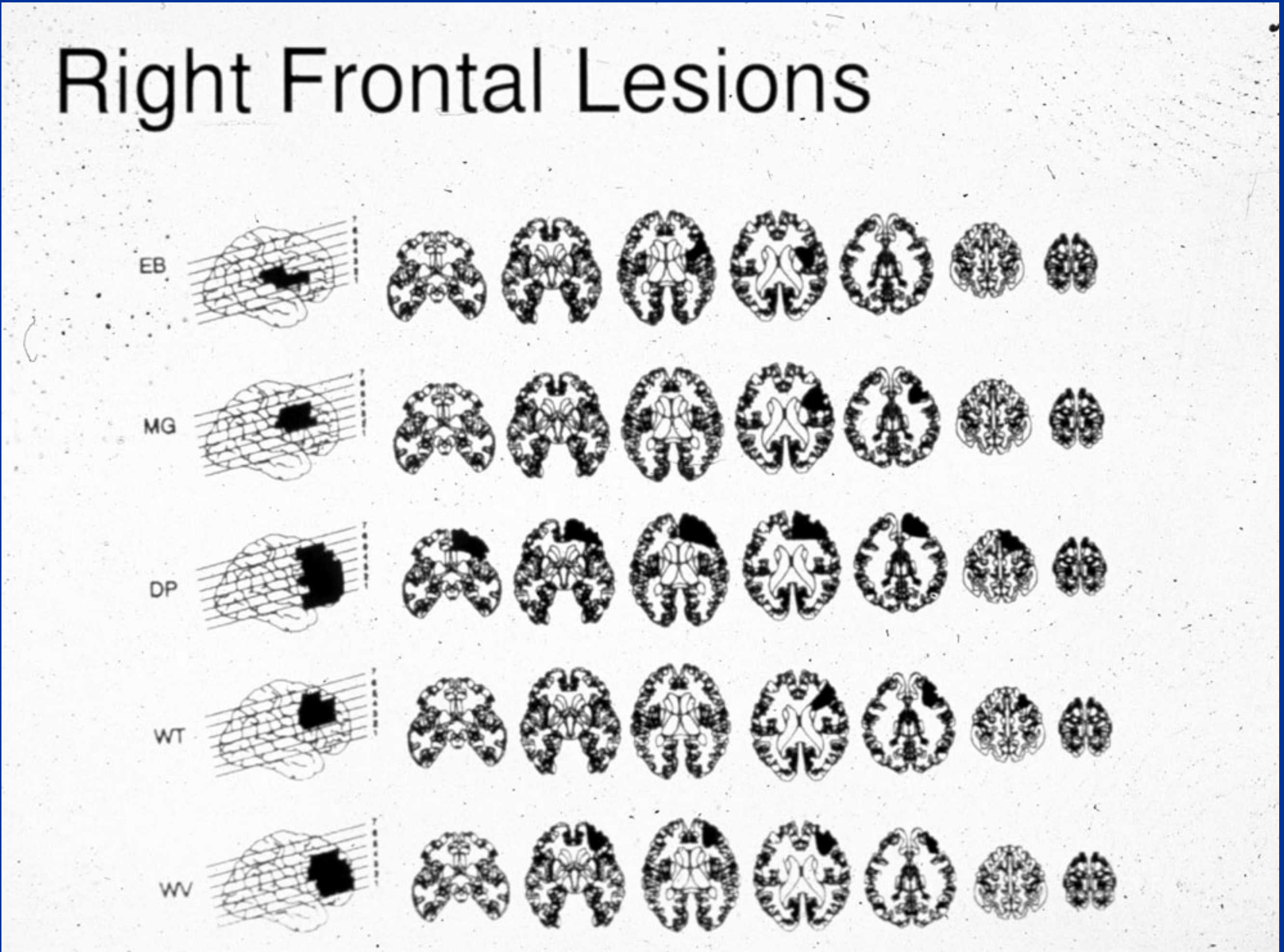
Memory

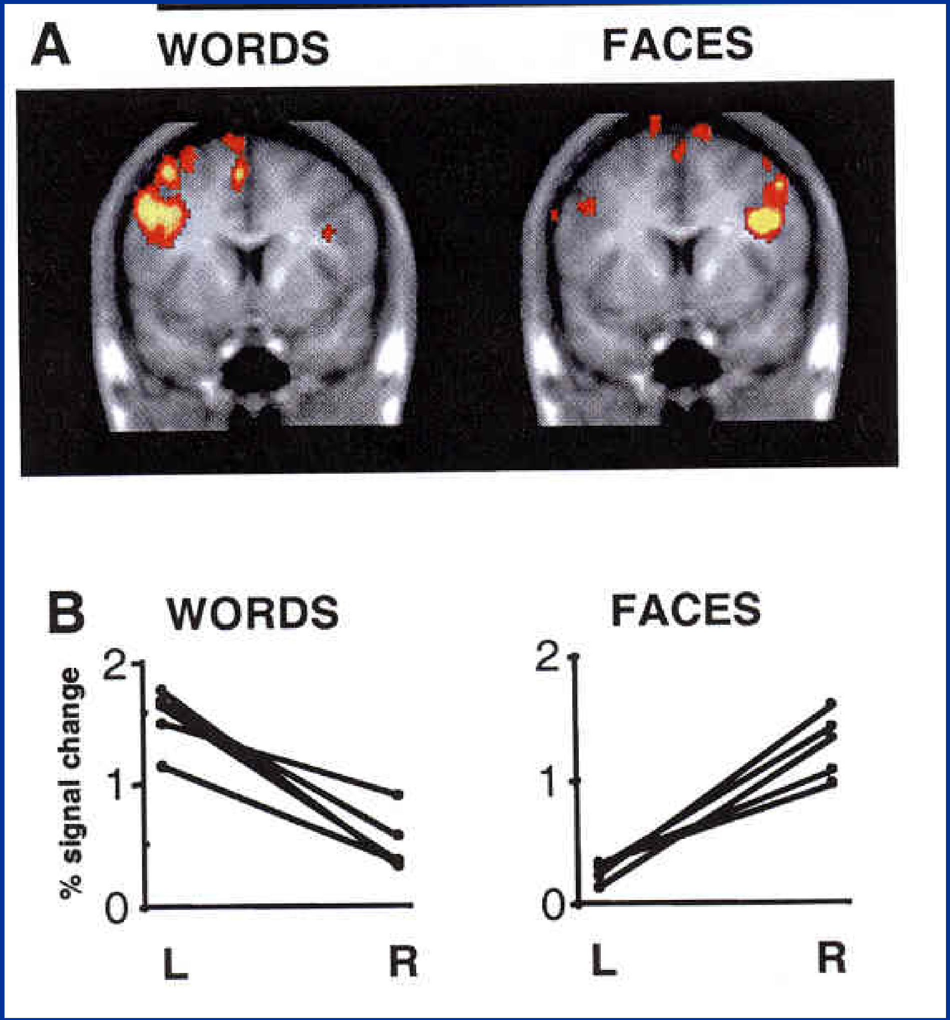
- Frontal activation > Medial Temporal lobe in fMRI literature
- Are frontal regions essential?
- Can MTL activation be useful?
- What is the significance of activation?

Functional MRI does not predict deficit

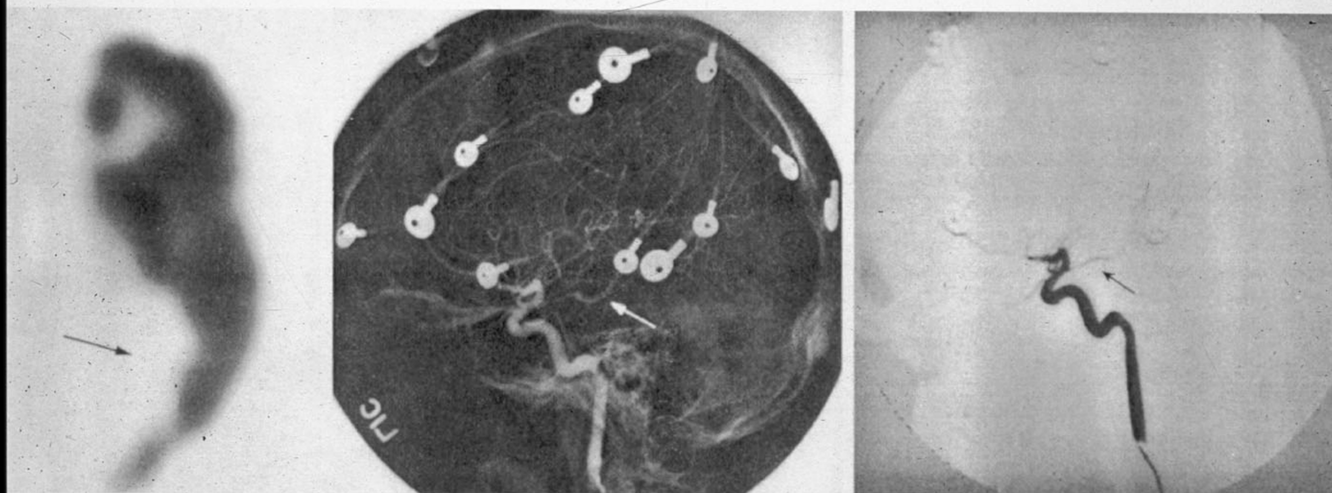


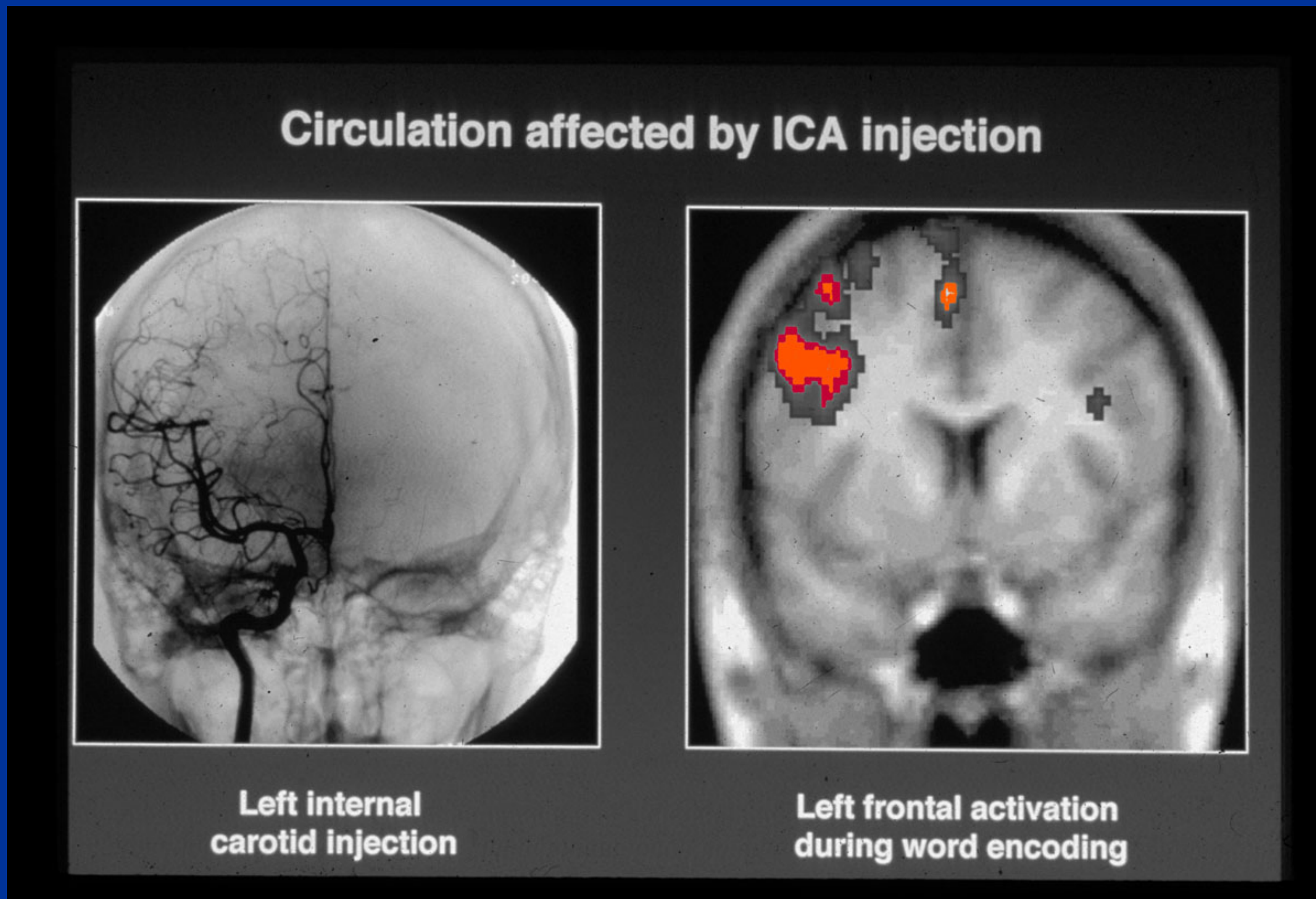
Lesions that do NOT impair retrieval



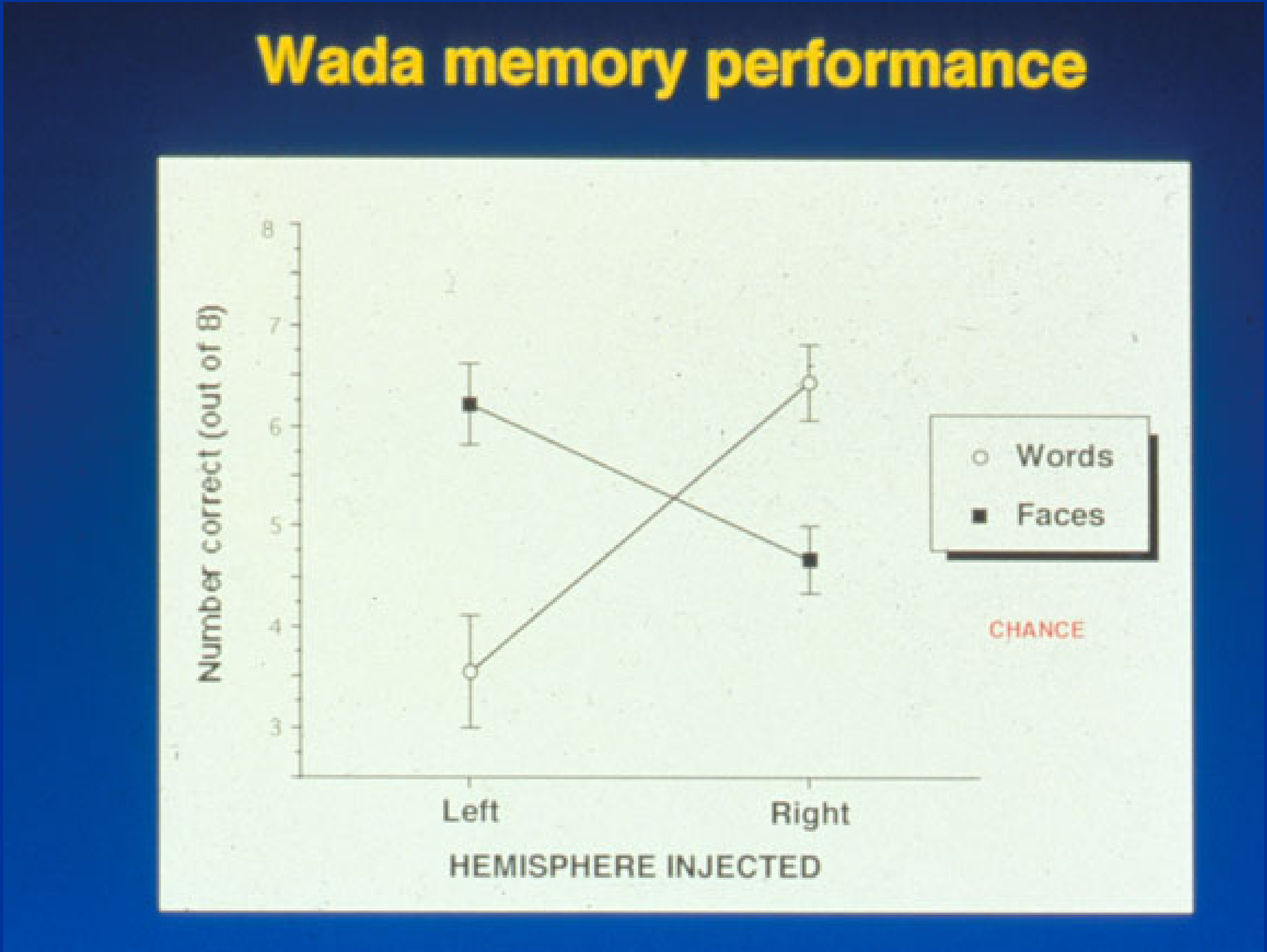

A
WORDS
FACES
B
WORDS
FACES
% signal change
2
1
0
L
R
2
1
0
L
R

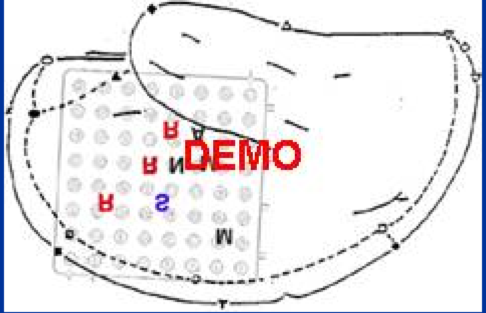
Distribution of ICA injection

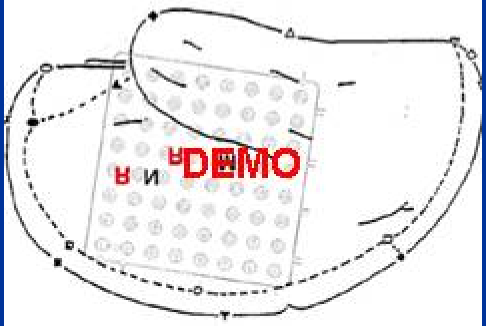


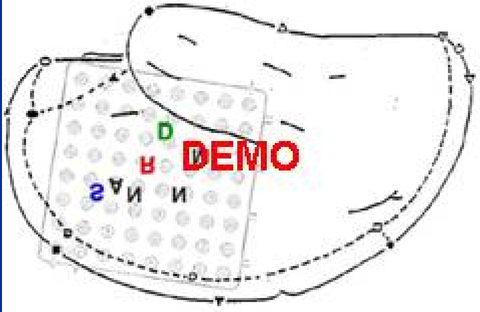

Circulation affected by ICA injection
Left internal carotid injection
Left frontal activation during word encoding

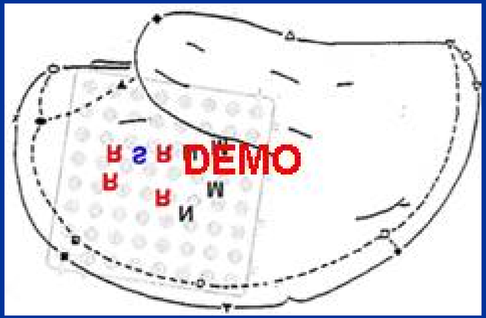
Memory formation







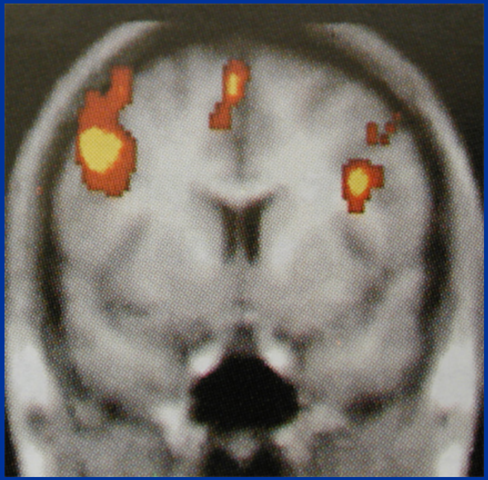


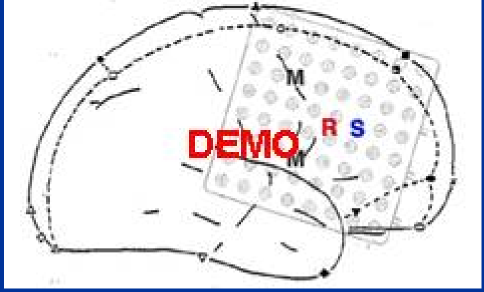


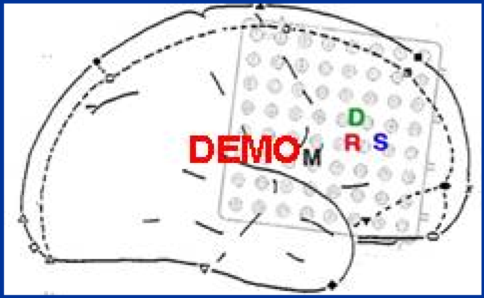
Mapping bilateral frontal sites during memory for pictures

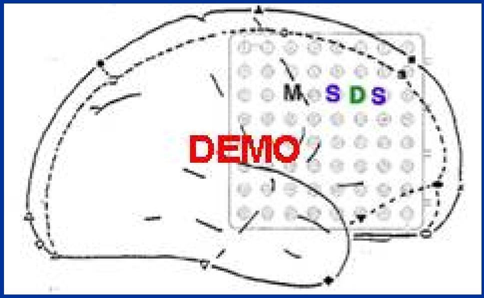
Both dominant and non-dominant sites

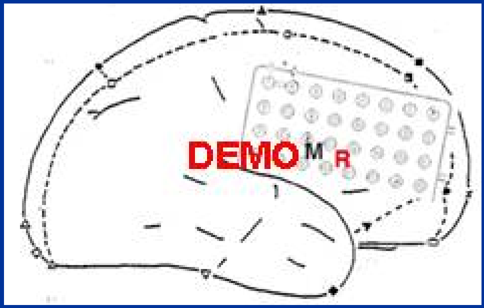
Consistent with fMRI literature



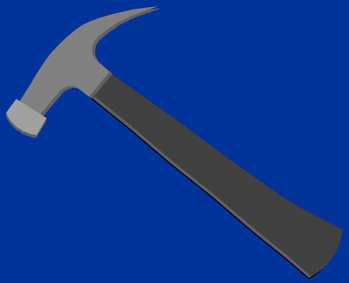








Cortical Stimulation Mapping



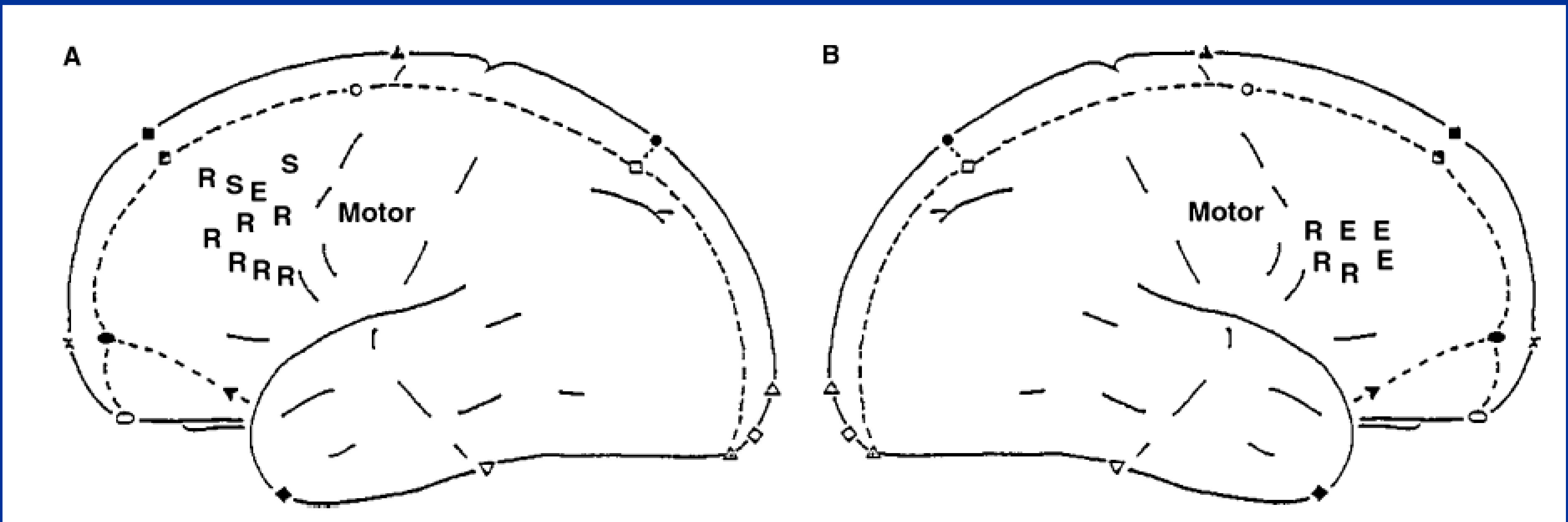
“Hammer”

Distractor sentence

Read Sentence

RECALL

“Hammer”



A
R
S
S
E
R
R
R
R
R
R
R
Motor
B
Motor
R
E
E
R
R
E

TEMPORAL LOBE EPILEPSY

- Temporal lobe epilepsy (TLE) is the most common form of epilepsy.

- Seizures are disabling, and difficult to control with medications.

- As a result, many TLE patients become potential candidates for epilepsy surgery.

- Surgery typically involves the antero-medial portion of the temporal lobe, unilaterally.

- For this reason, TLE patients represent a potentially optimal population in which to explore the interaction between frontal and temporal structures in memory encoding.

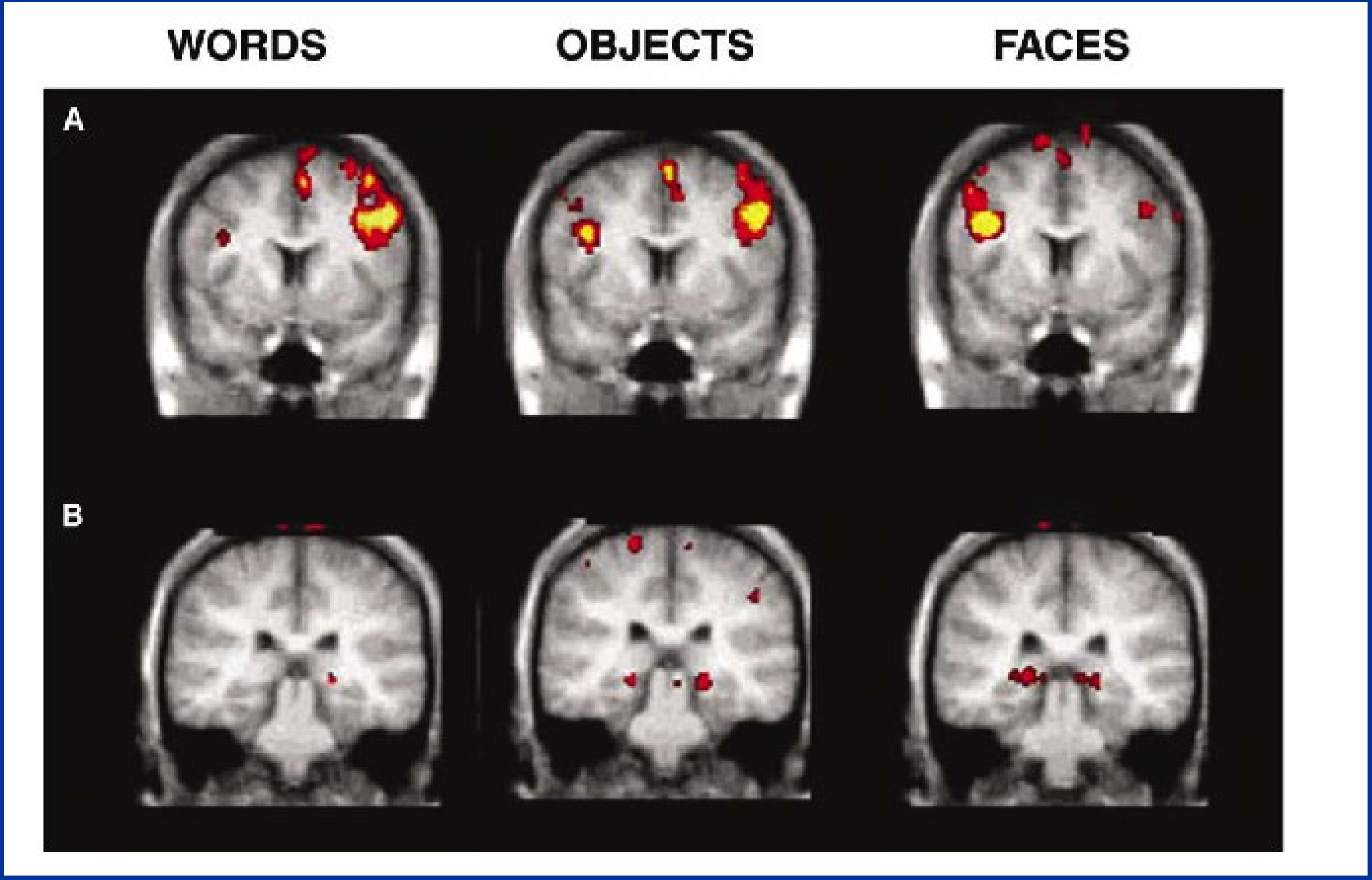
GOALS

- To explore the activity of frontal cortex during the encoding of verbal and non-verbal material *before* and *after* unilateral medial temporal lobectomy.

GOALS

• To explore the activity of frontal cortex during the encoding of verbal and non-verbal material *before* and *after* unilateral medial temporal lobectomy.

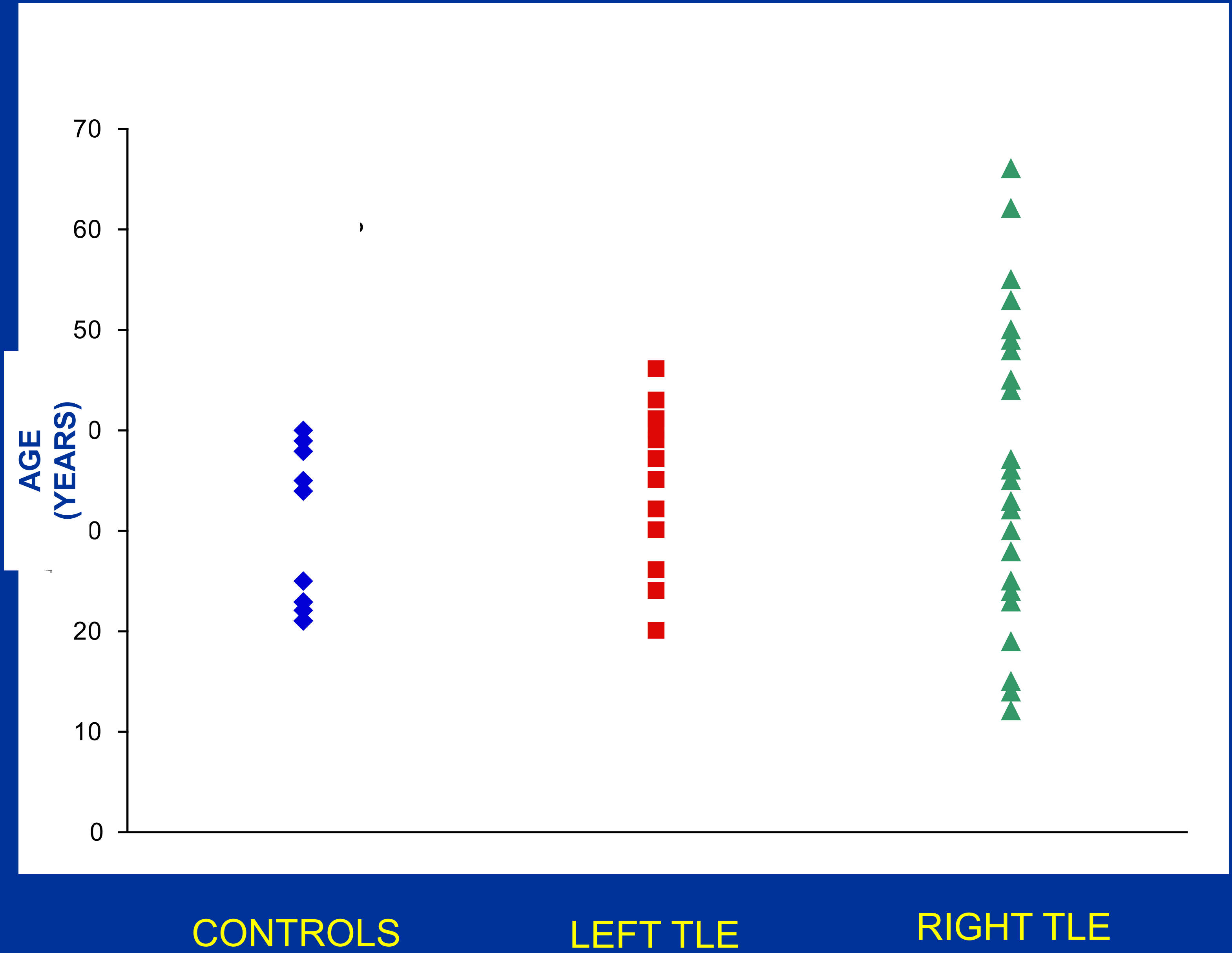
• To investigate the usefulness of frontal encoding activation levels as a predictor of memory deficits following unilateral medial temporal lobectomy.


WORDS
OBJECTS
FACES
A
B

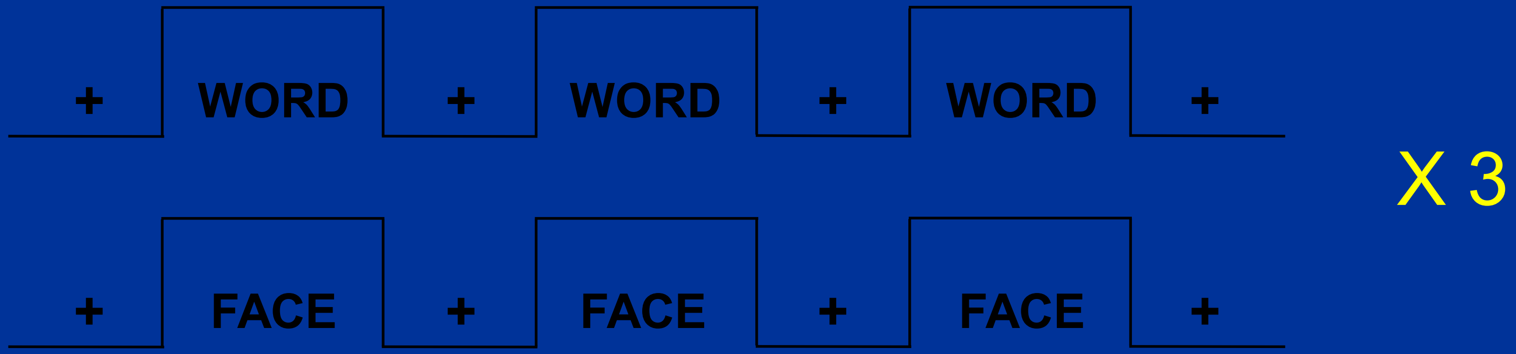
SUBJECTS

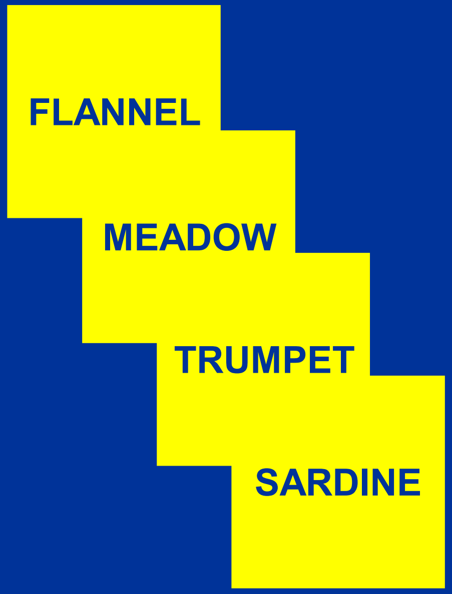
- 50 Patients with Temporal Lobe Epilepsy
  - mean age = 35.8 yrs
  - 21 M / 29 F
  - 5 left-handed
  - 37 participated in pre-operative fMRI session
  - 28 participated in post-operative fMRI session
  - of these, 15 (so far) have participated in both preop and postop fMRI sessions
- 12 Healthy Controls
  - mean age = 28.5 yrs
  - 7 M / 5 F
  - 1 left-handed

AGE DISTRIBUTION



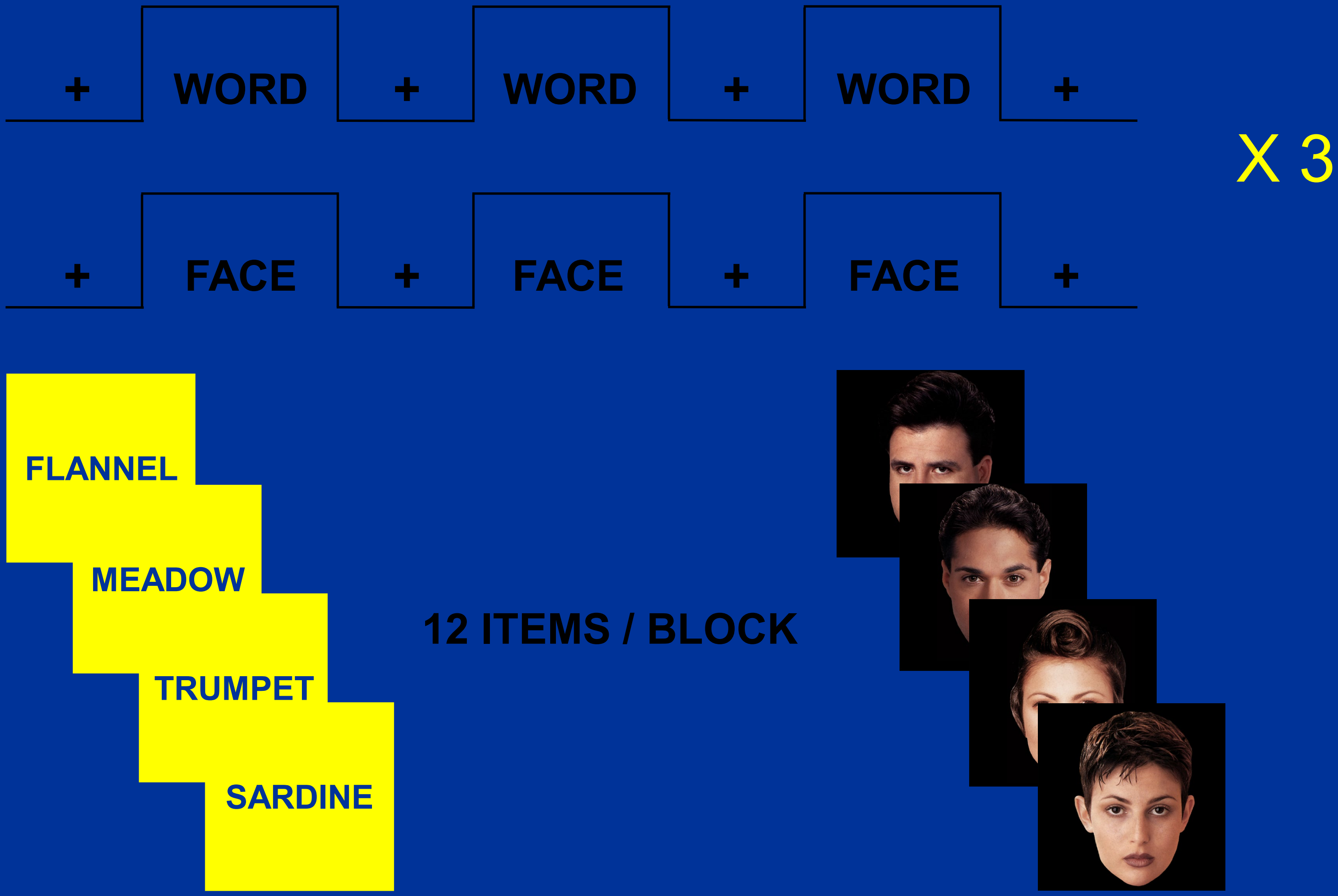
ENCODING (inside the scanner)





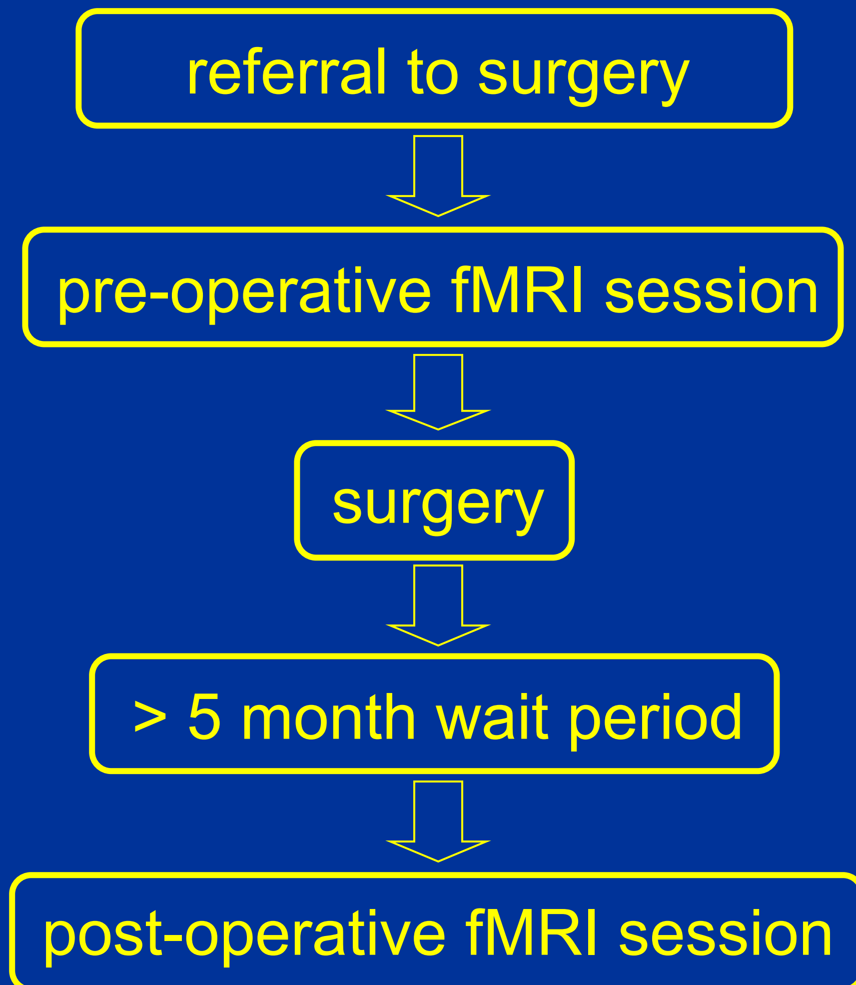
12 ITEMS / BLOCK

ENCODING (inside the scanner)



OLD/NEW RECOGNITION (outside the scanner)

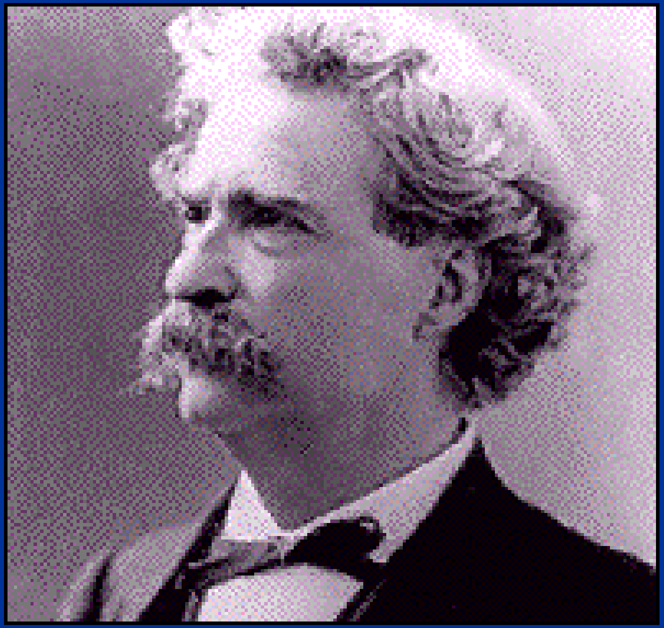
TIMELINE



referral to surgery
pre-operative fMRI session
surgery
> 5 month wait period
post-operative fMRI session

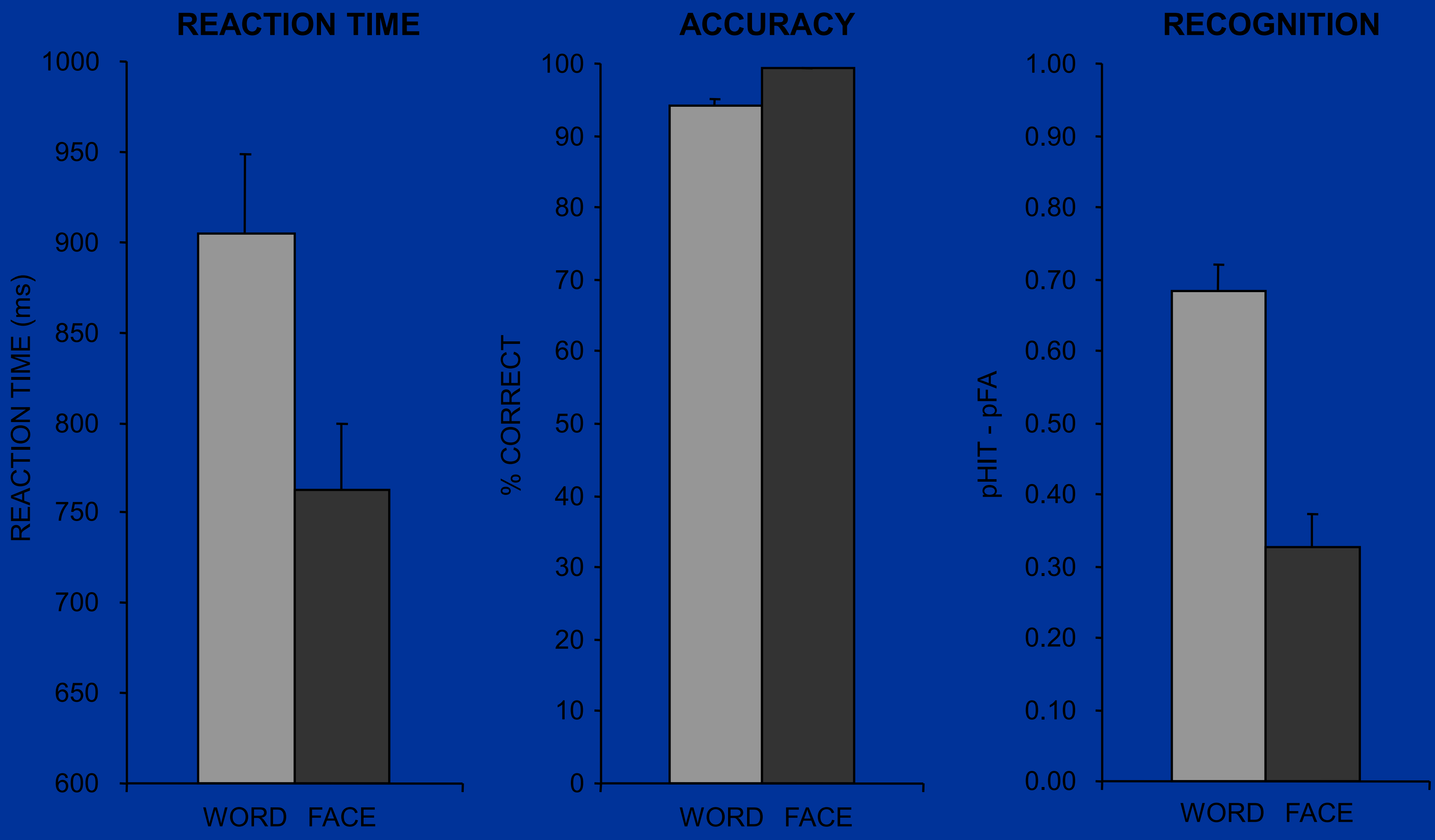
MR METHODS

- 1.5 Tesla BOLD fMRI (asymmetric spin echo)
- whole brain imaging (TR = 2.5 s, 16 axial slices, 8 mm thickness)
- six blocked runs (3 WORD, 3 FACE)
- analyzed using an implementation of the general linear model
- to allow accurate characterization of surgical resection 3 sets of MPRAGE images were acquired in each session

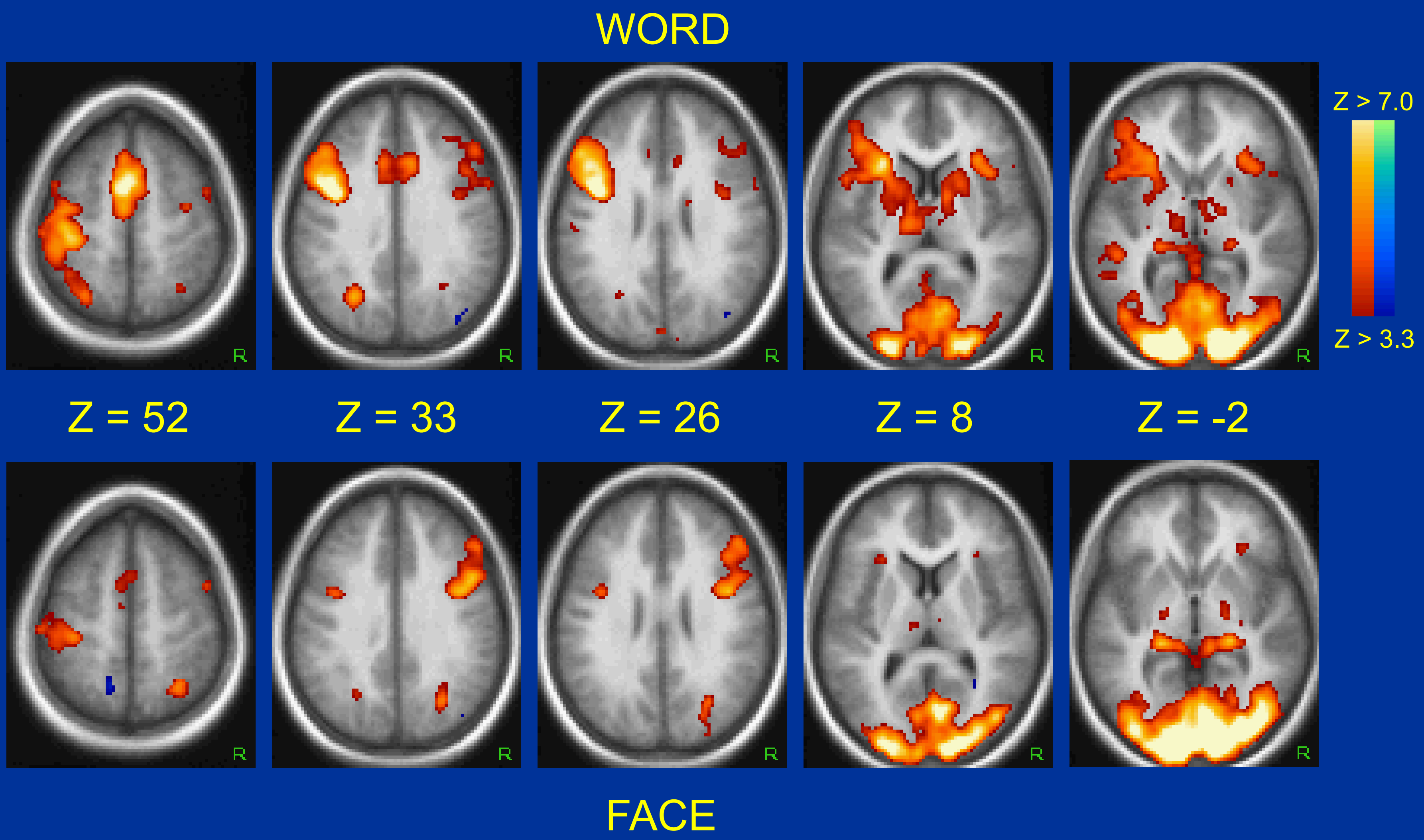


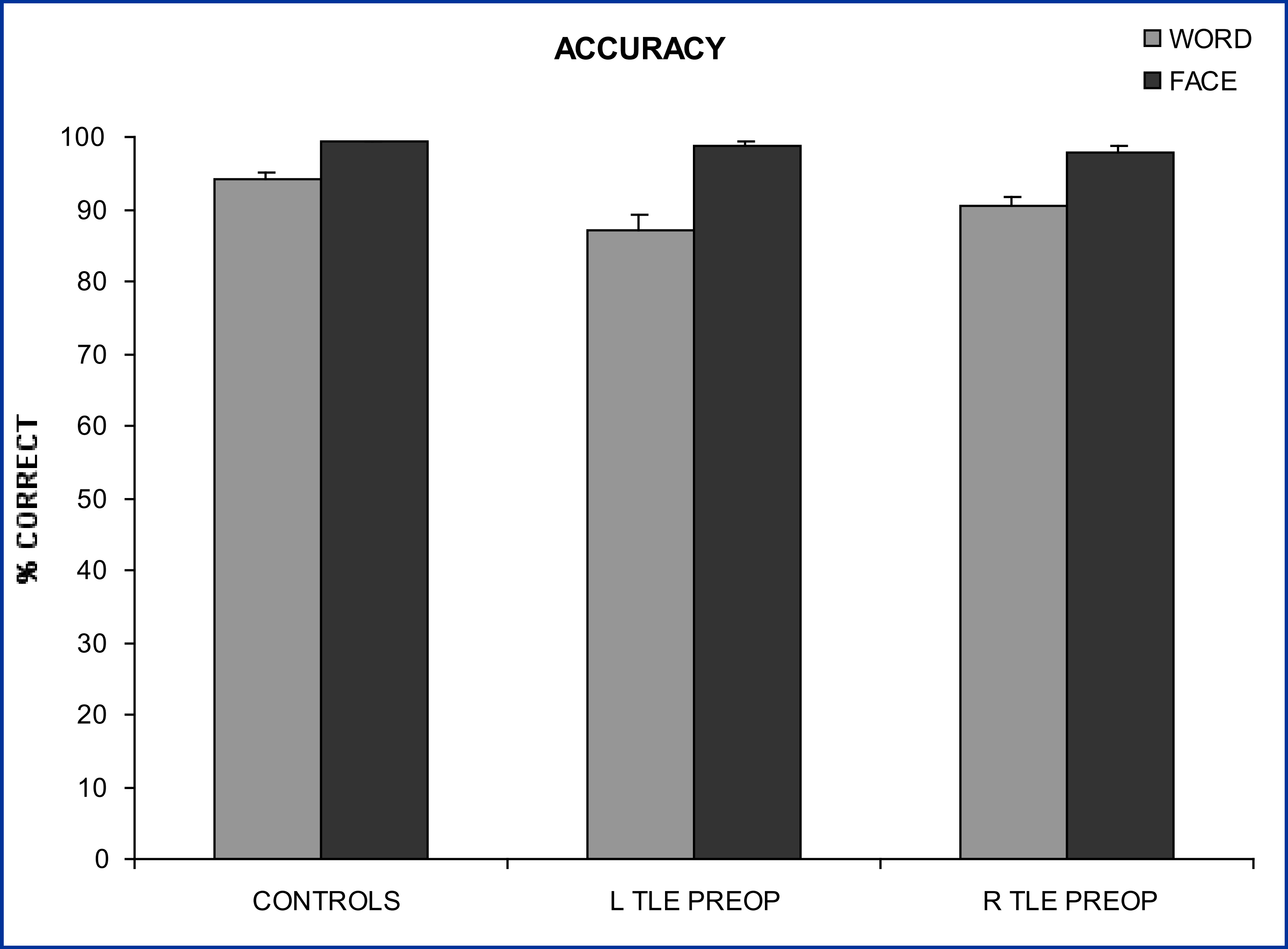
"There are lies, damn lies, and statistics"

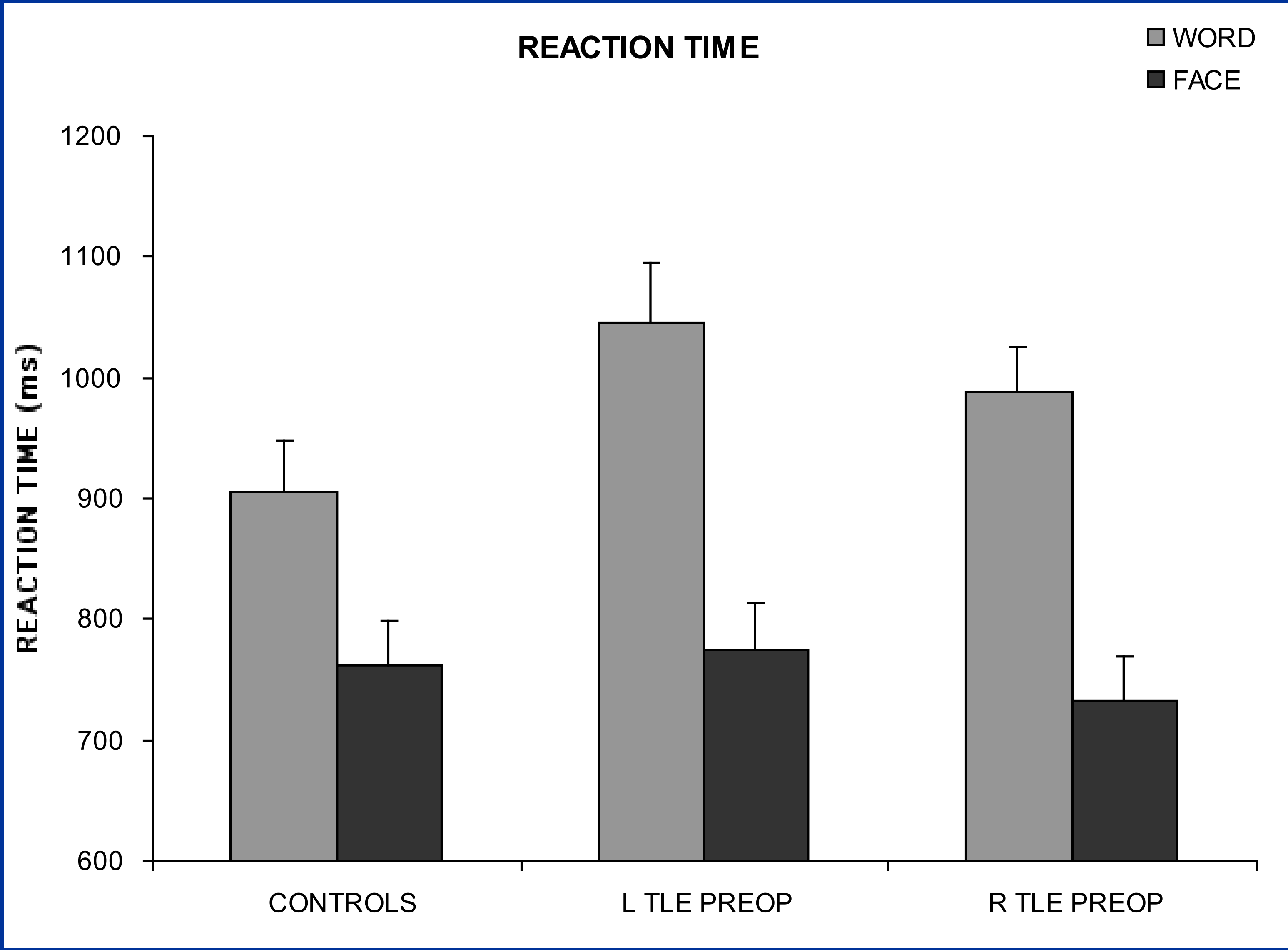
CONTROL BEHAVIOR

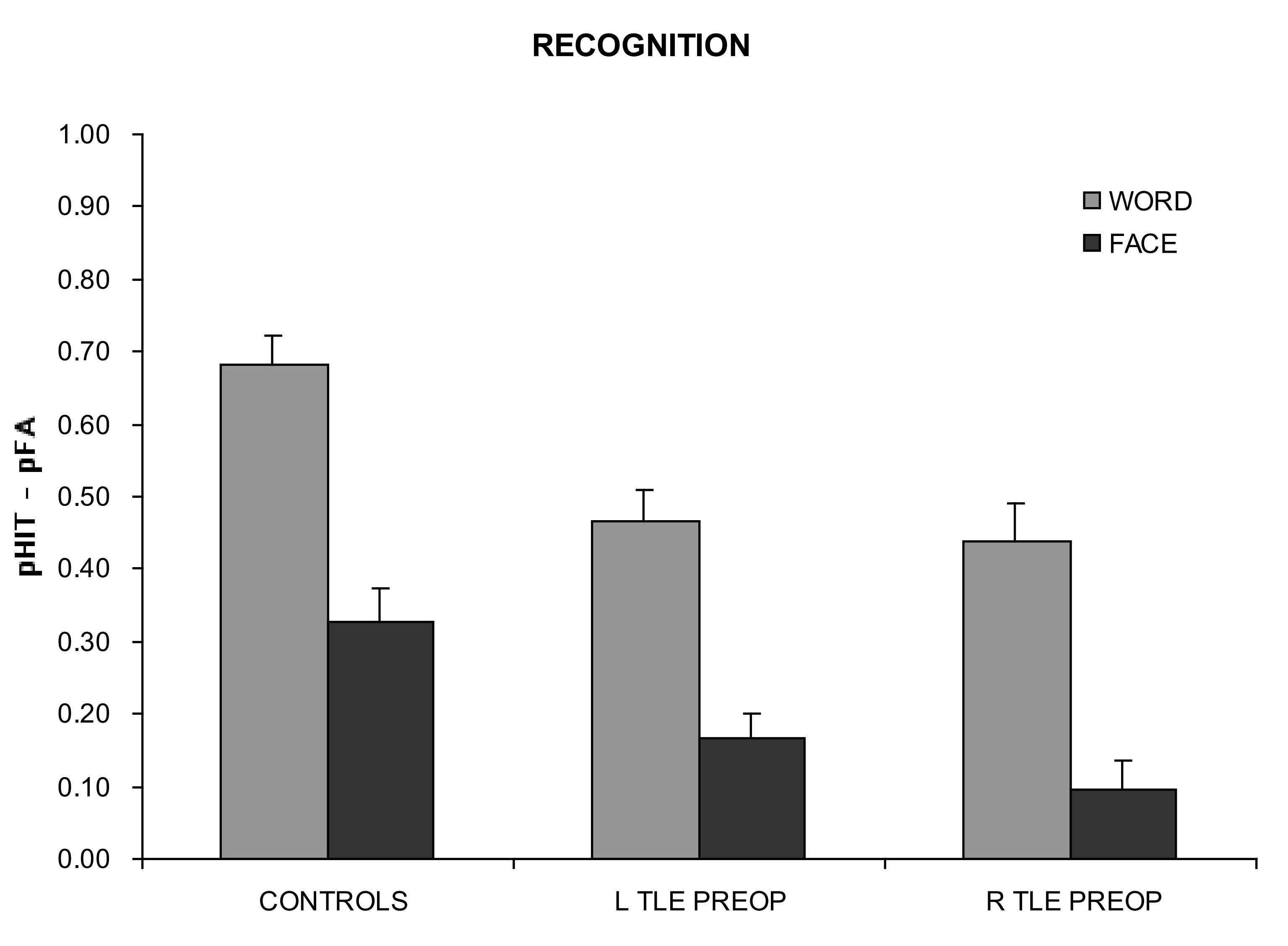


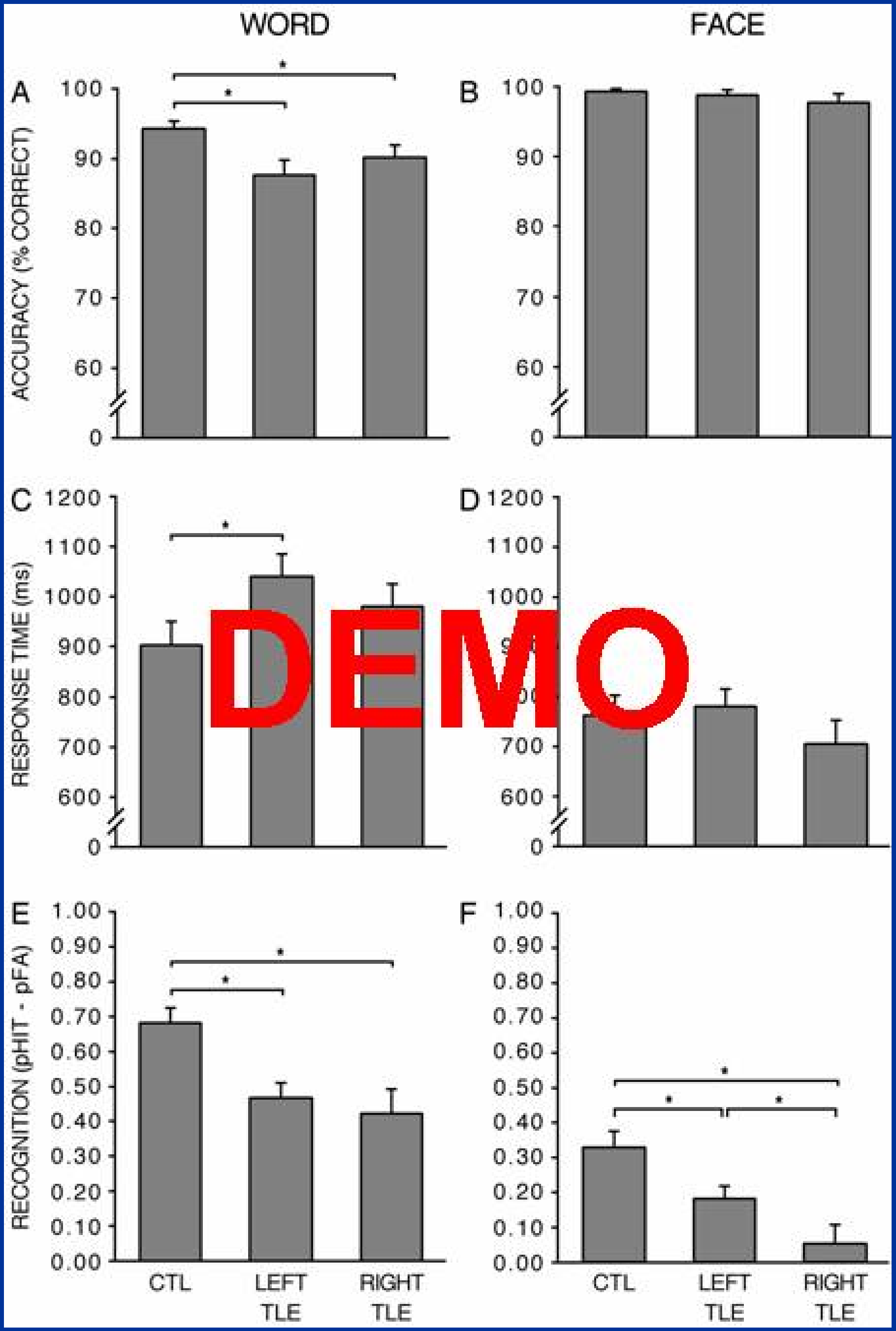
CONTROL ENCODING




ACCURACY
WORD
FACE
% CORRECT
100
90
80
70
60
50
40
30
20
10
0
CONTROLS
L TLE PREOP
R TLE PREOP


REACTION TIME
WORD
FACE
REACTION TIME (ms)
1200
1100
1000
900
800
700
600
CONTROLS
L TLE PREOP
R TLE PREOP

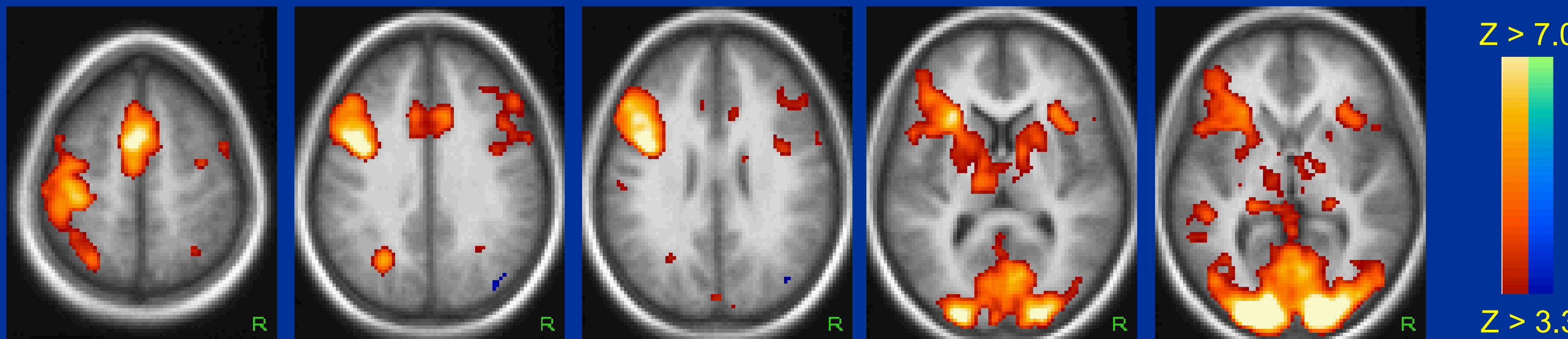

RECOGNITION
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
pHIT - pFA
WORD
FACE
CONTROLS
L TLE PREOP
R TLE PREOP



WORD
FACE
A
B
C
D
E
F
ACCURACY (% CORRECT)
RESPONSE TIME (ms)
RECOGNITION (pHIT - pFA)
CTL
LEFT TLE
RIGHT TLE
DEMO

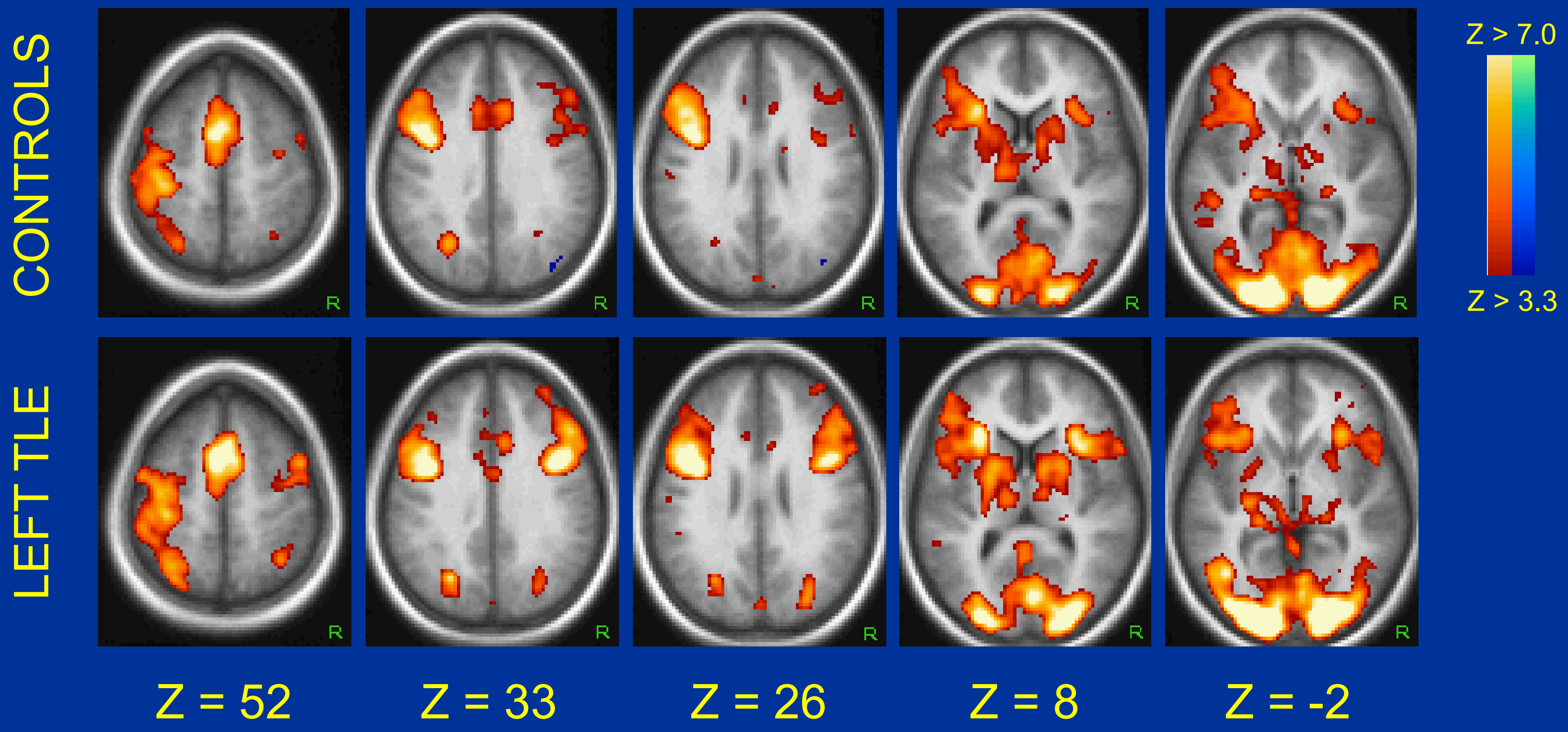
WORD TASK - PREOP

CONTROLS

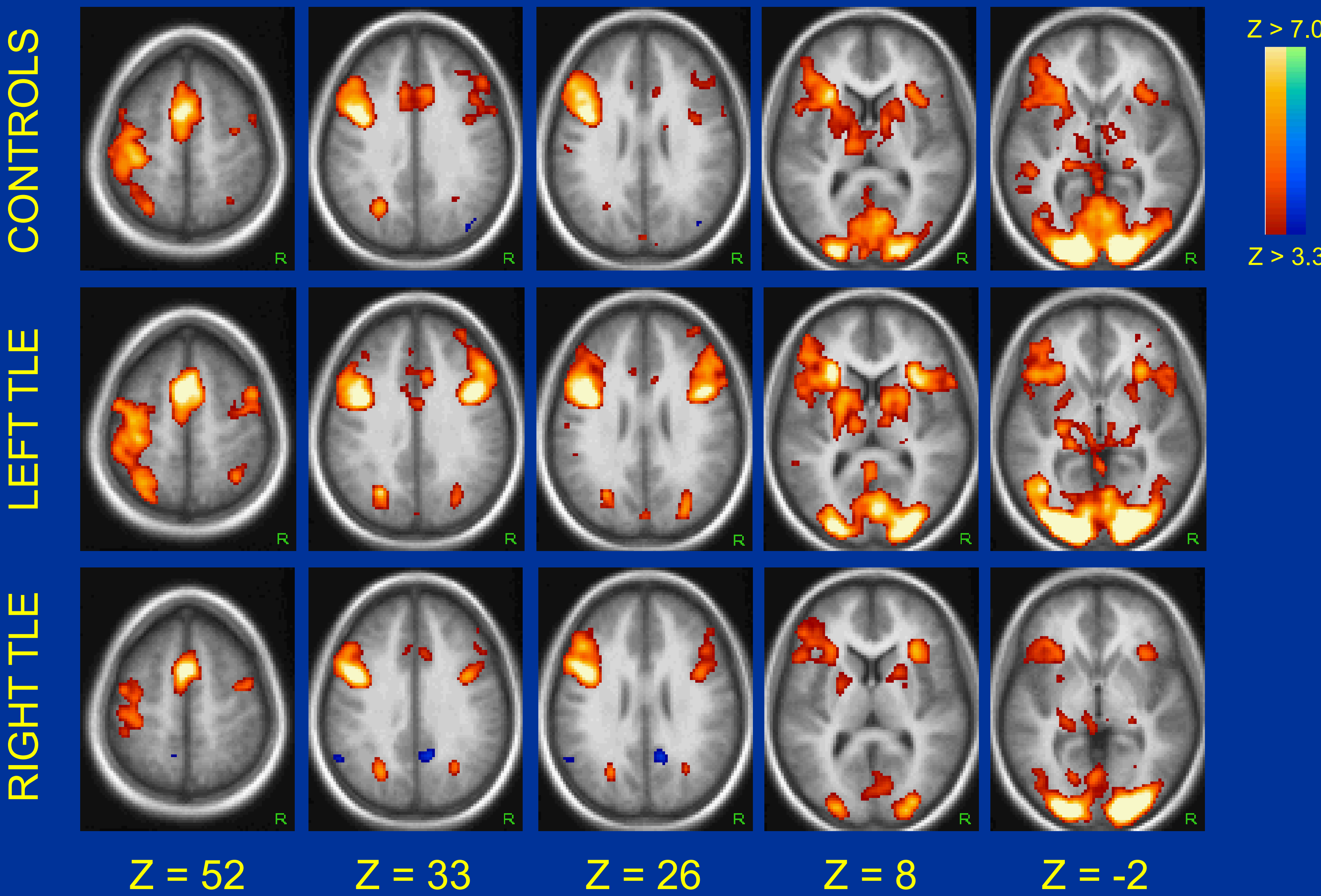


Z = 52　Z = 33　Z = 26　Z = 8　Z = -2

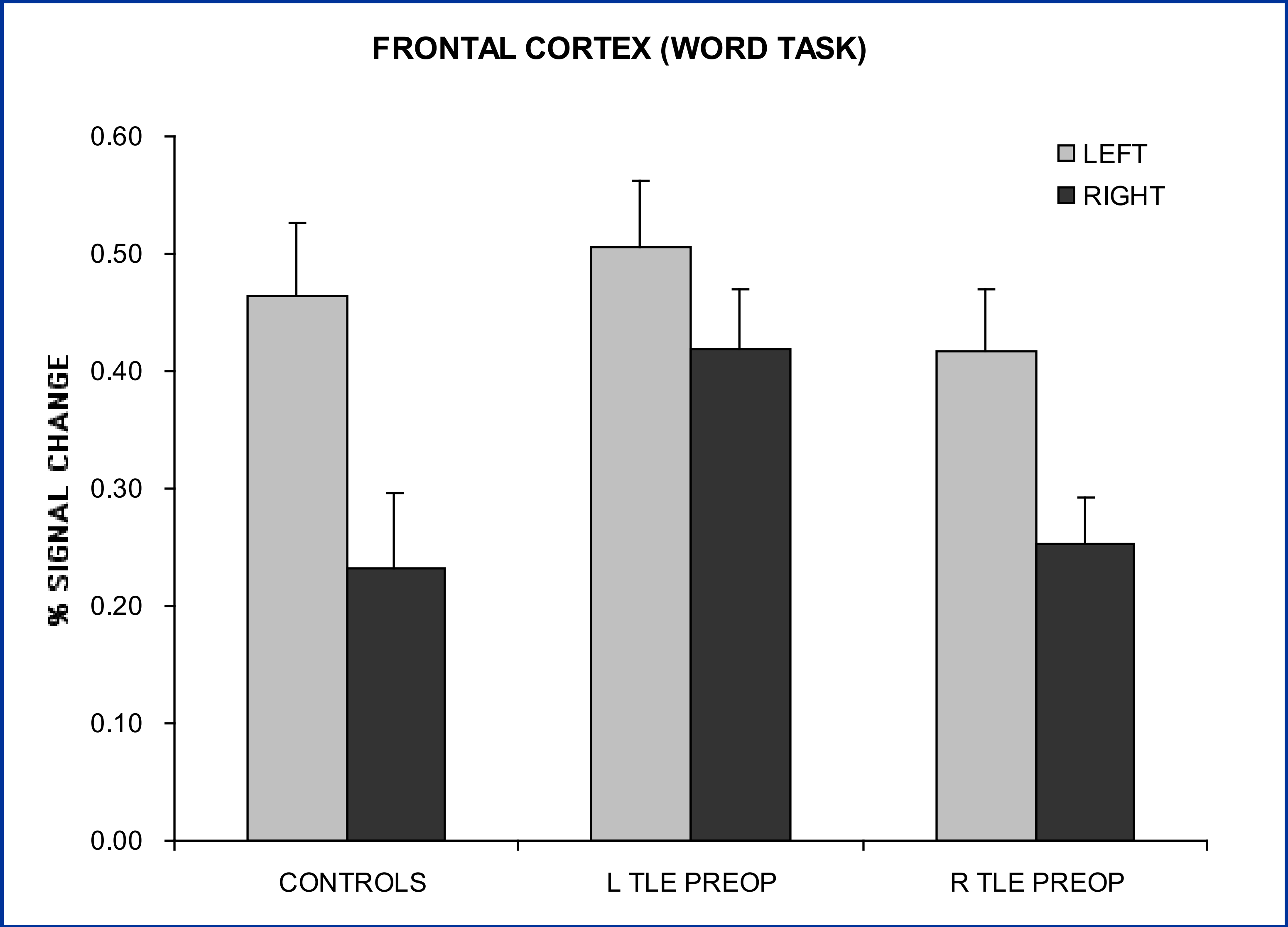
WORD TASK - PREOP



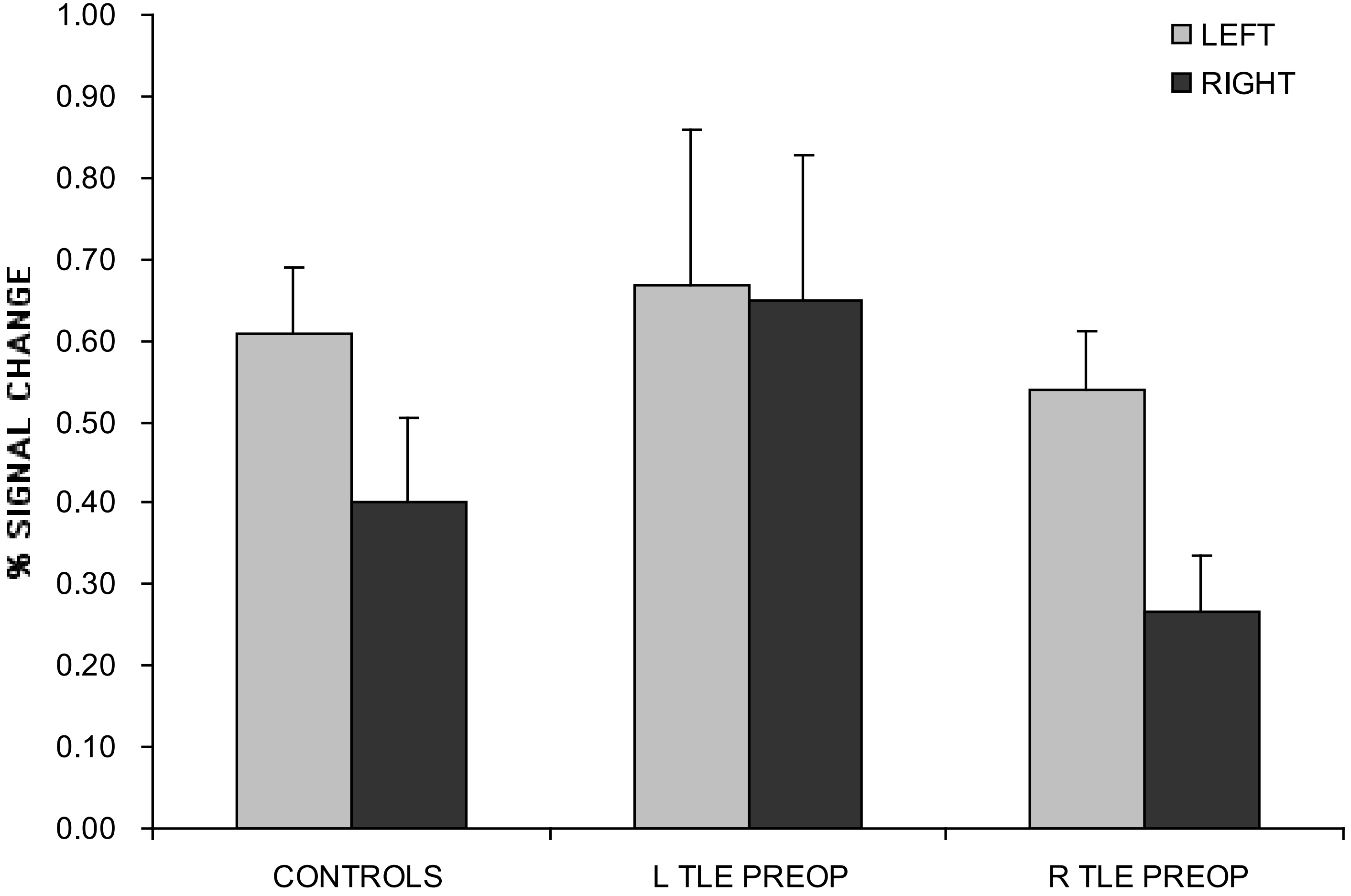
WORD TASK - PREOP



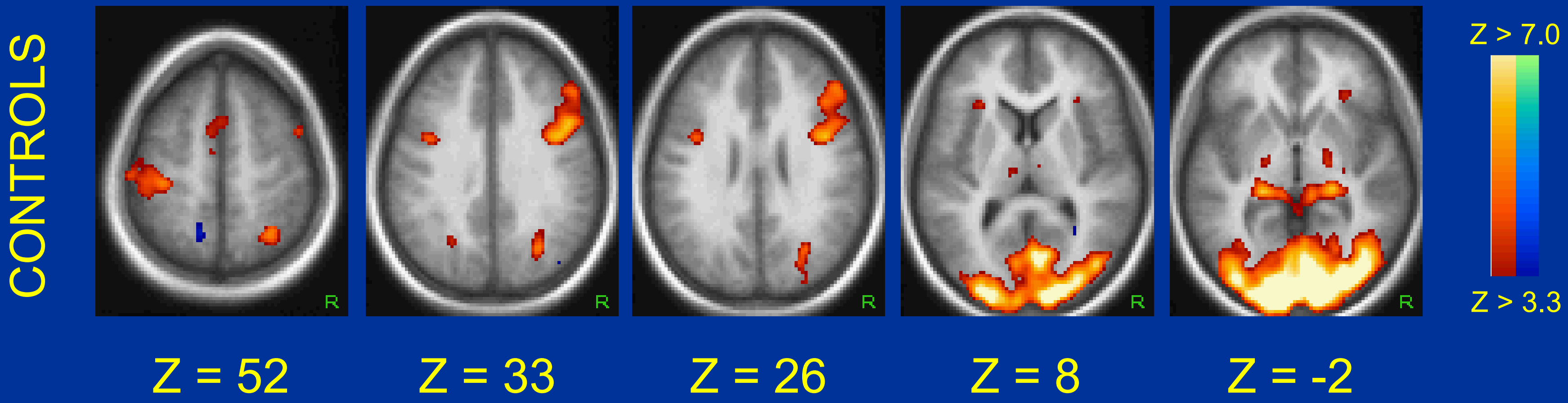

R


FRONTAL CORTEX (WORD TASK)
% SIGNAL CHANGE
0.60
0.50
0.40
0.30
0.20
0.10
0.00
LEFT
RIGHT
CONTROLS
L TLE PREOP
R TLE PREOP

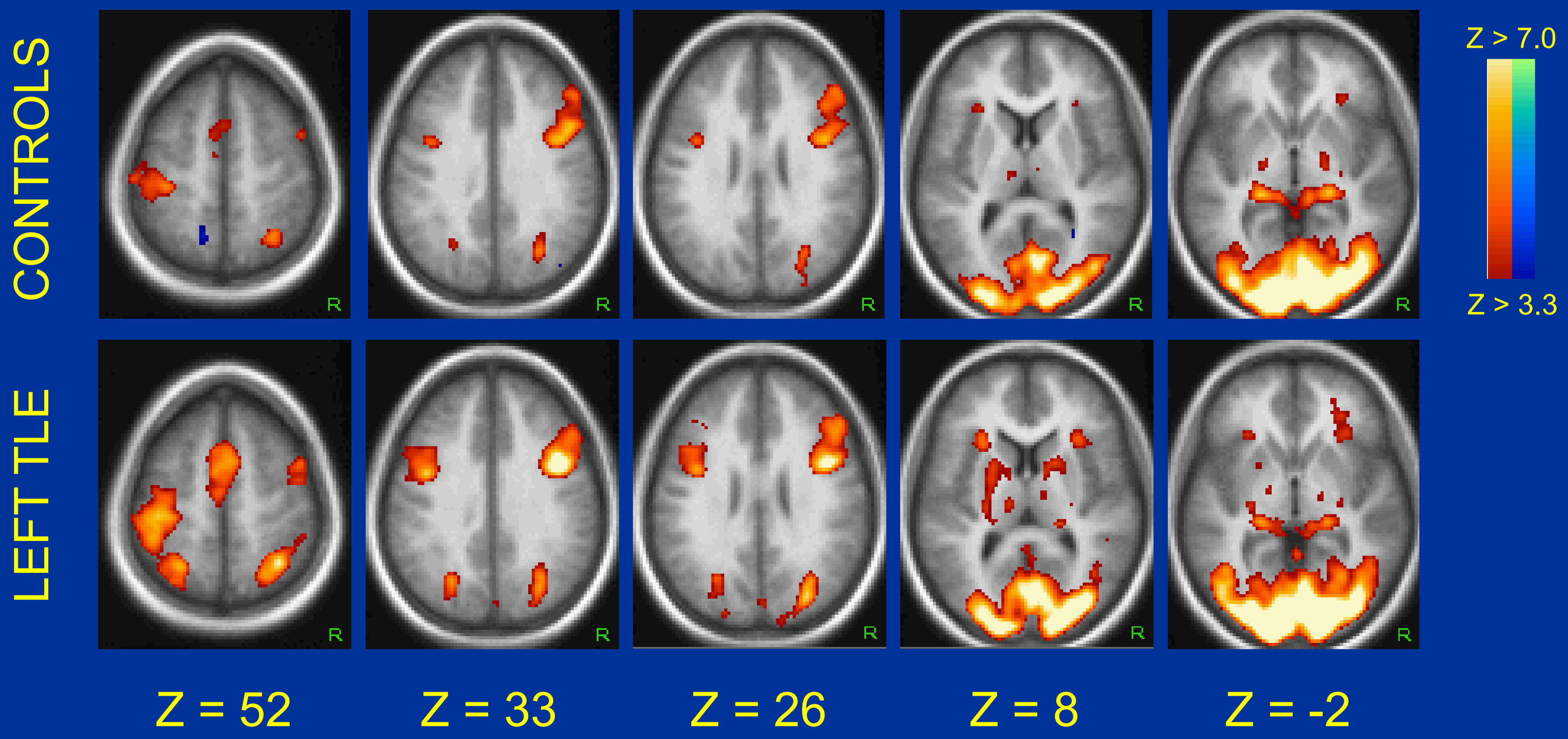
ANTERIOR FRONTAL CORTEX (WORD TASK)

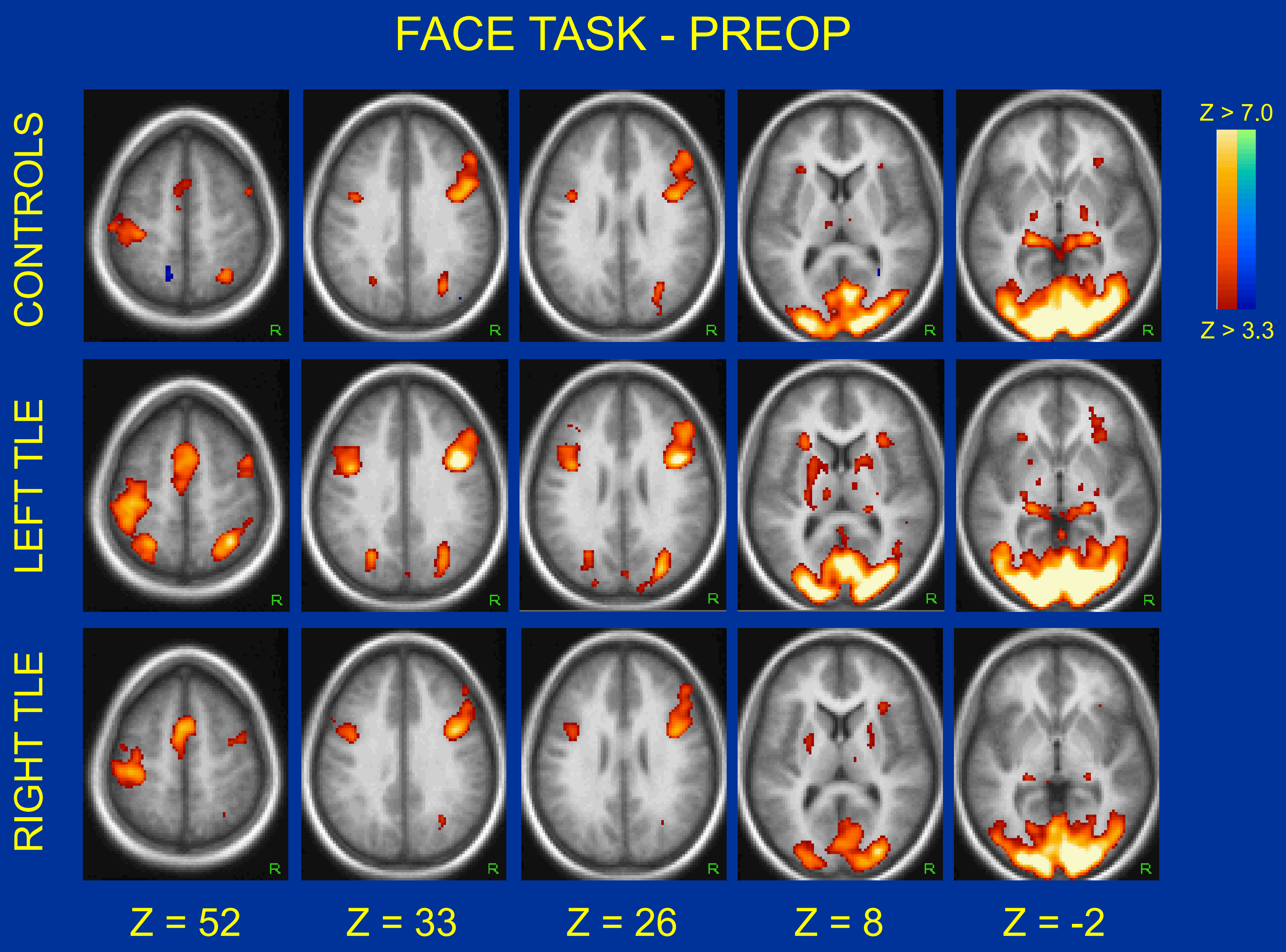


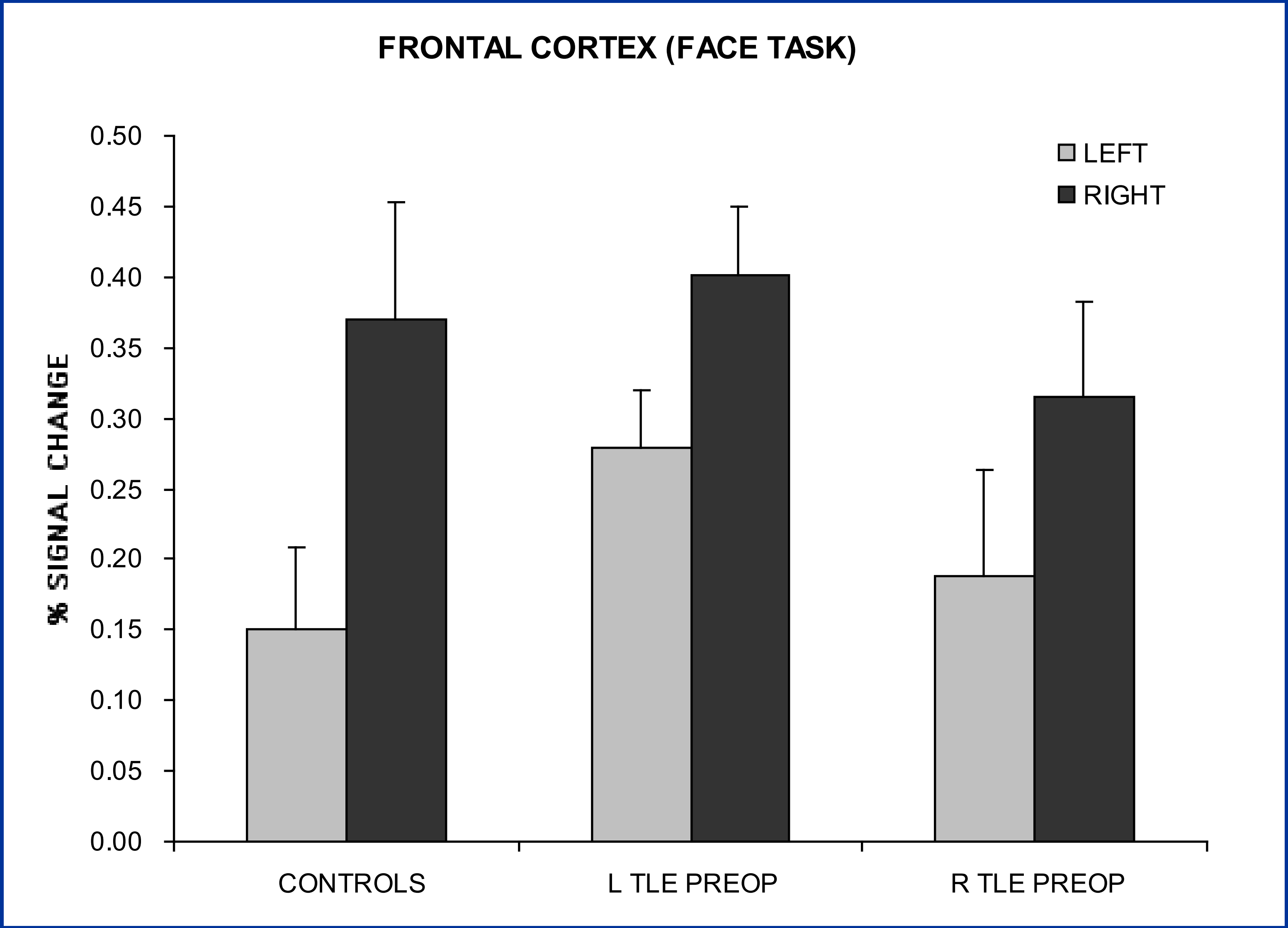
FACE TASK - PREOP



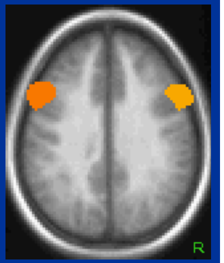
FACE TASK - PREOP

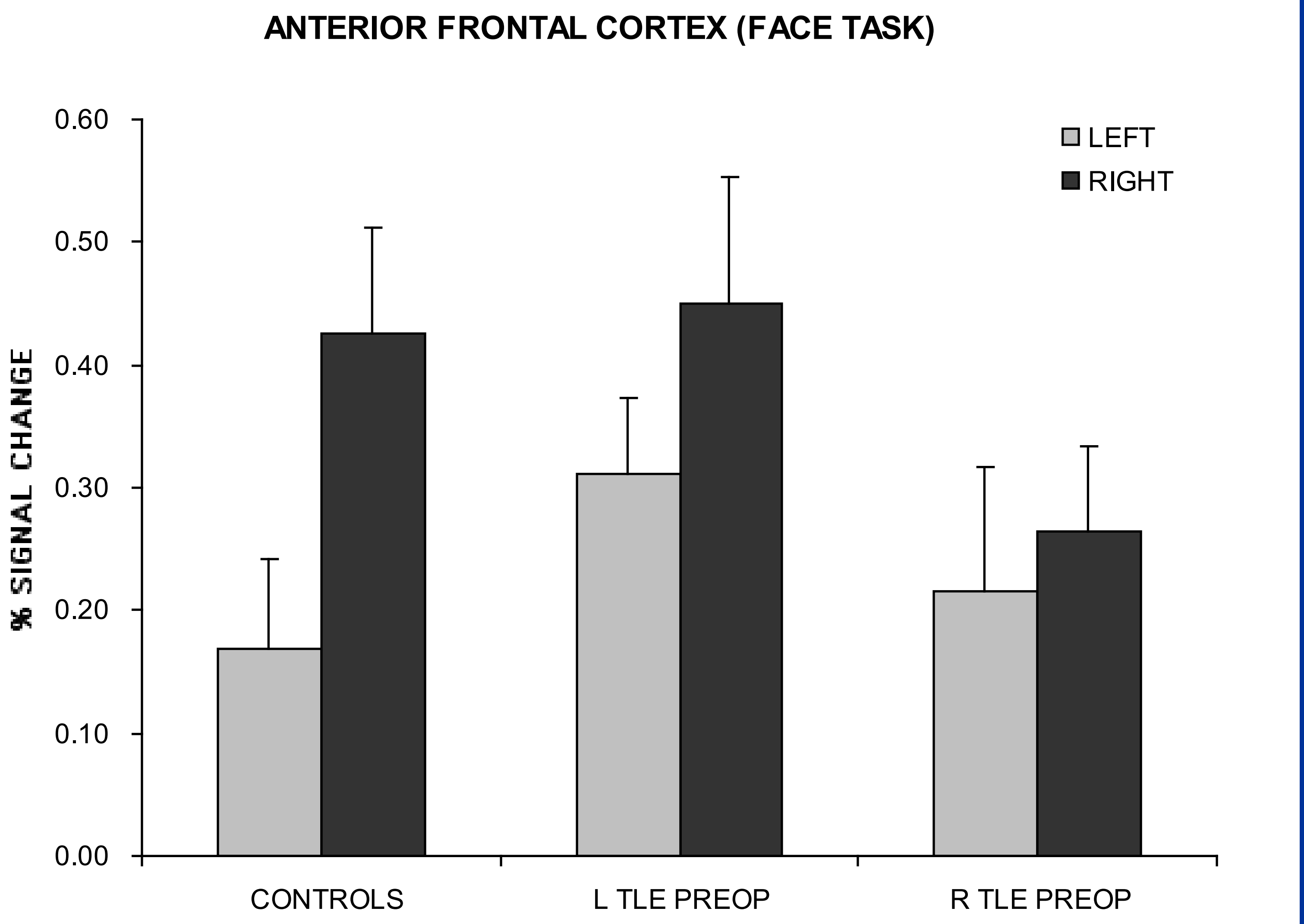



FACE TASK - PREOP
CONTROLS
LEFT TLE
RIGHT TLE
Z > 7.0
Z > 3.3
Z = 52
Z = 33
Z = 26
Z = 8
Z = -2



FRONTAL CORTEX (FACE TASK)
LEFT
RIGHT
% SIGNAL CHANGE
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
CONTROLS
L TLE PREOP
R TLE PREOP


R


ANTERIOR FRONTAL CORTEX (FACE TASK)
% SIGNAL CHANGE
0.60
0.50
0.40
0.30
0.20
0.10
0.00
LEFT
RIGHT
CONTROLS
L TLE PREOP
R TLE PREOP

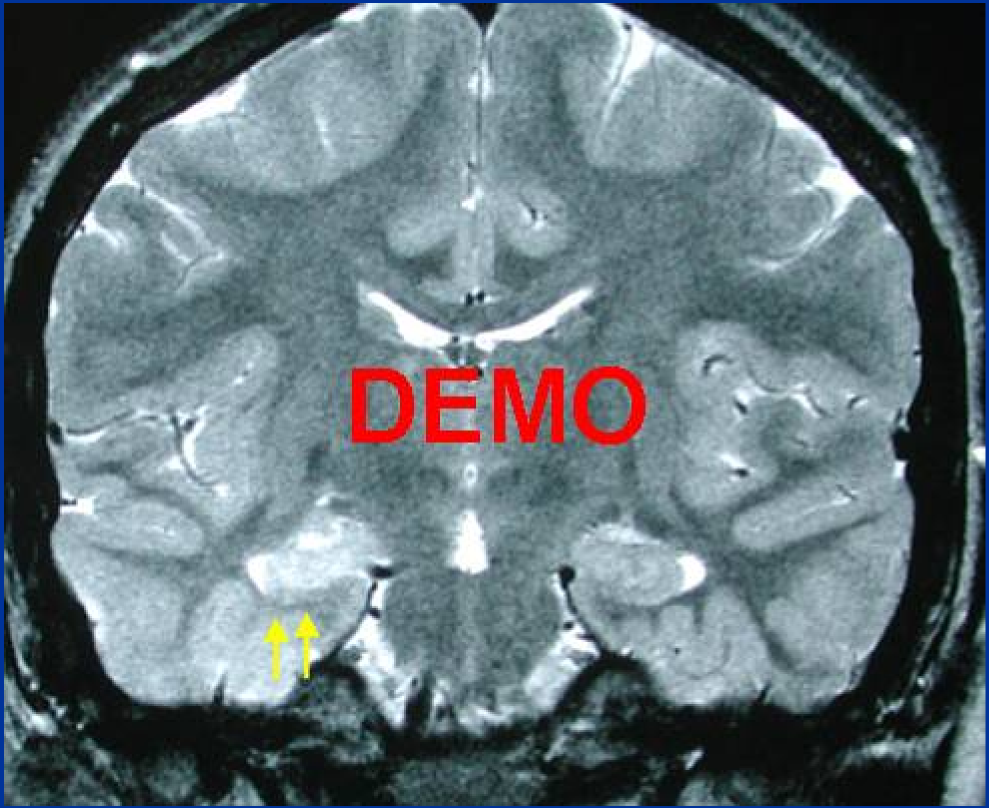
SUMMARY

- Preoperative TLE patients are behaviorally impaired in recognition as compared to controls, both in verbal and non-verbal domains.

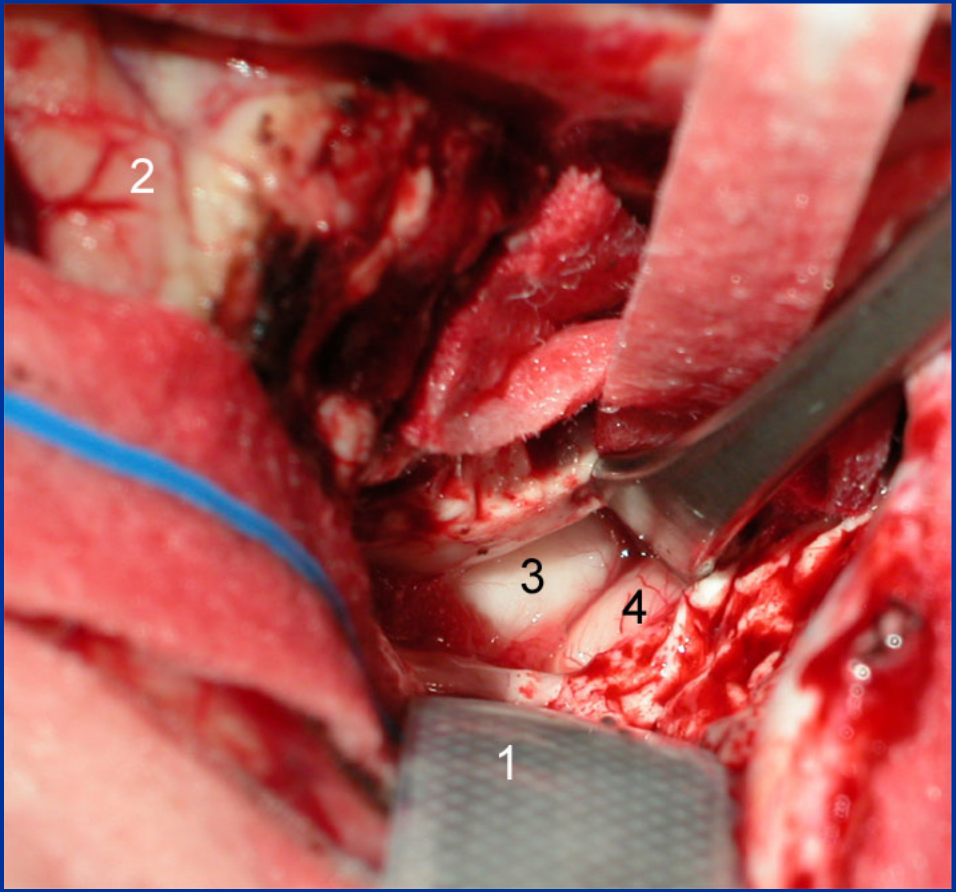
- At the same time, preoperative encoding activation in frontal cortex by-and-large resembles that of controls for both left and right TLE patients.

- Preoperative patients show a trend for reduced lateralization in frontal cortex (most significantly observed in L TLE patients when encoding verbal material).

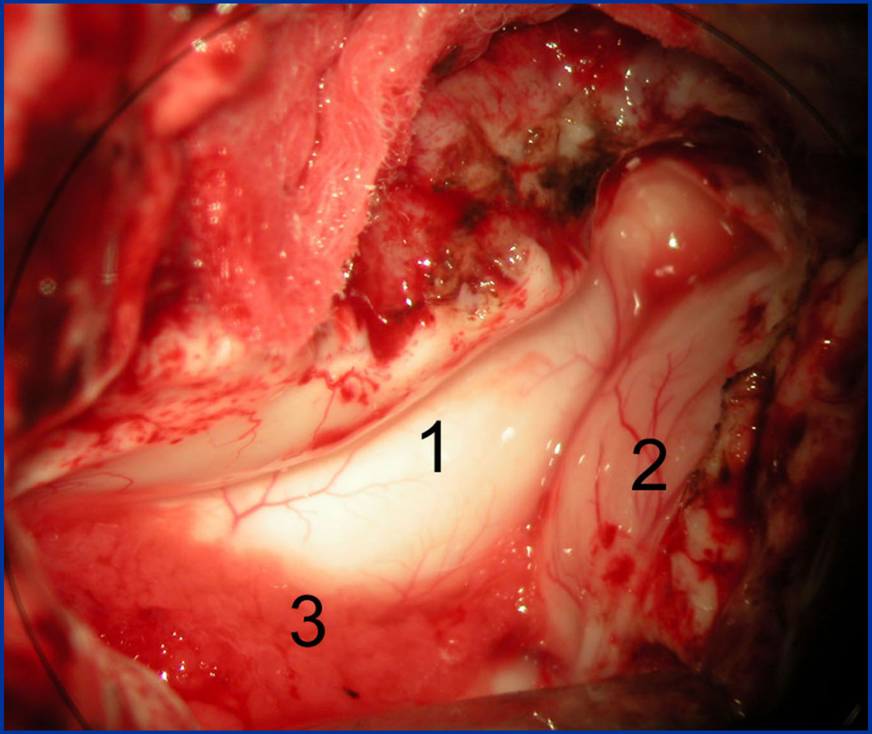

27
28
26
16'
1
7
14
23
24
22
21
18
10
4
11
13
6
11'
12
5


DEMO

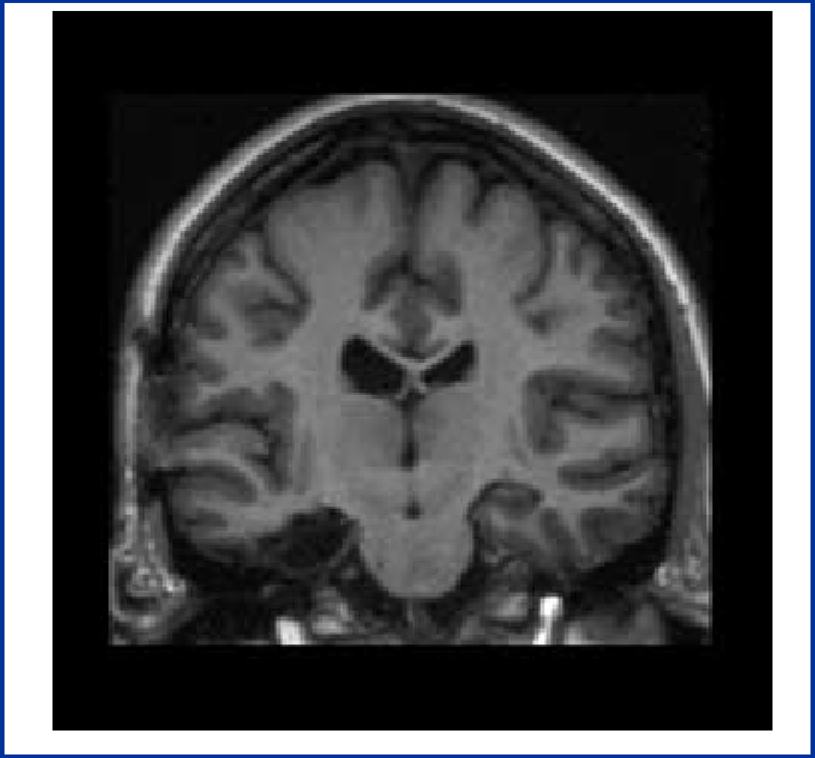
Surgery of the hippocampus

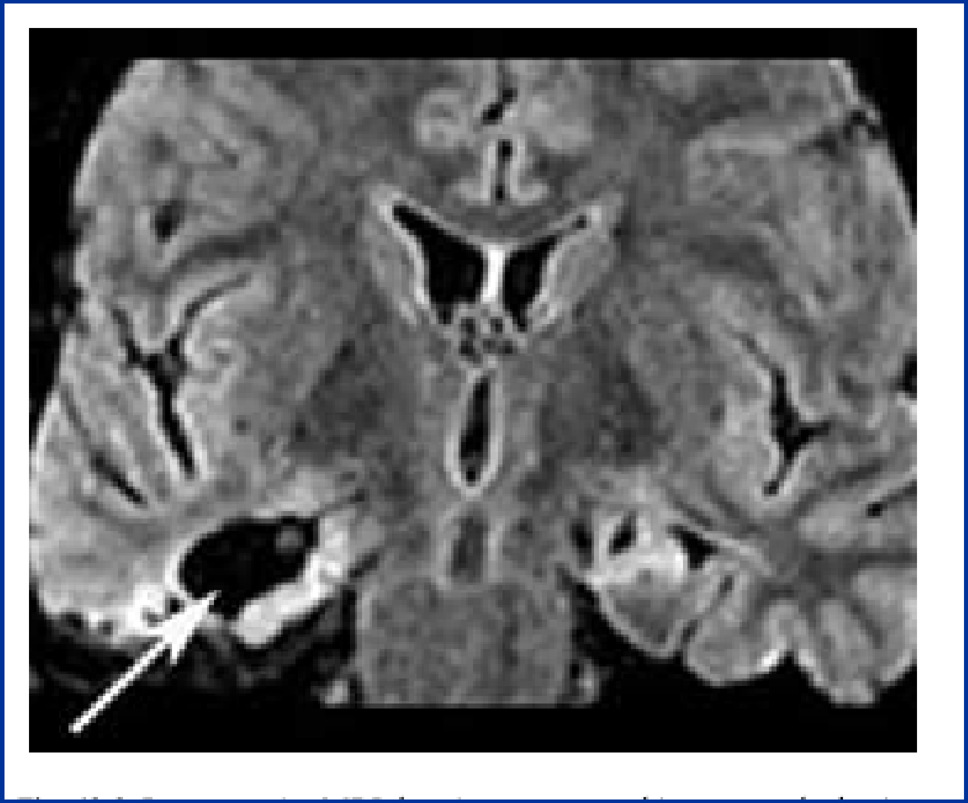


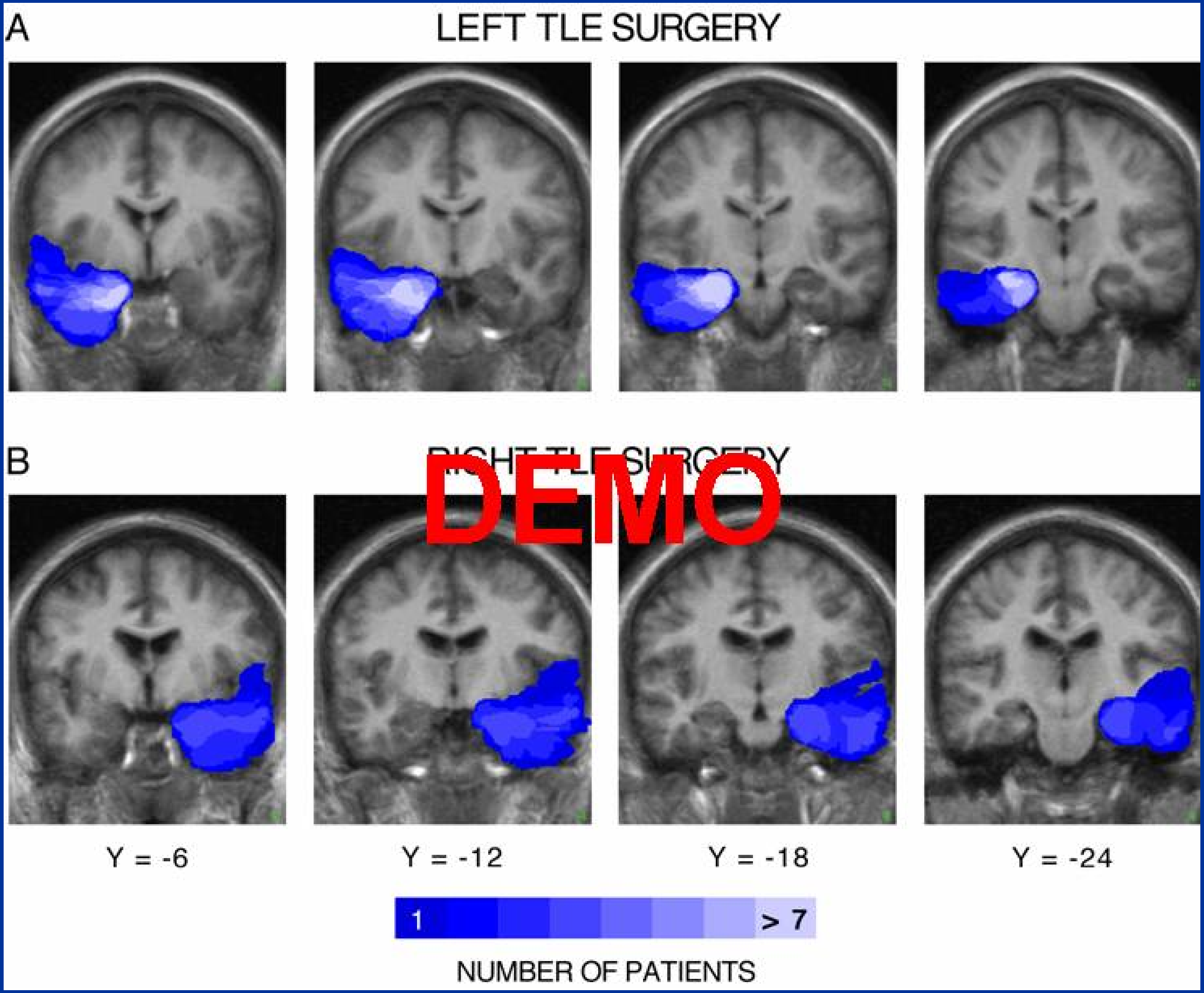
Hippocampus - surgery

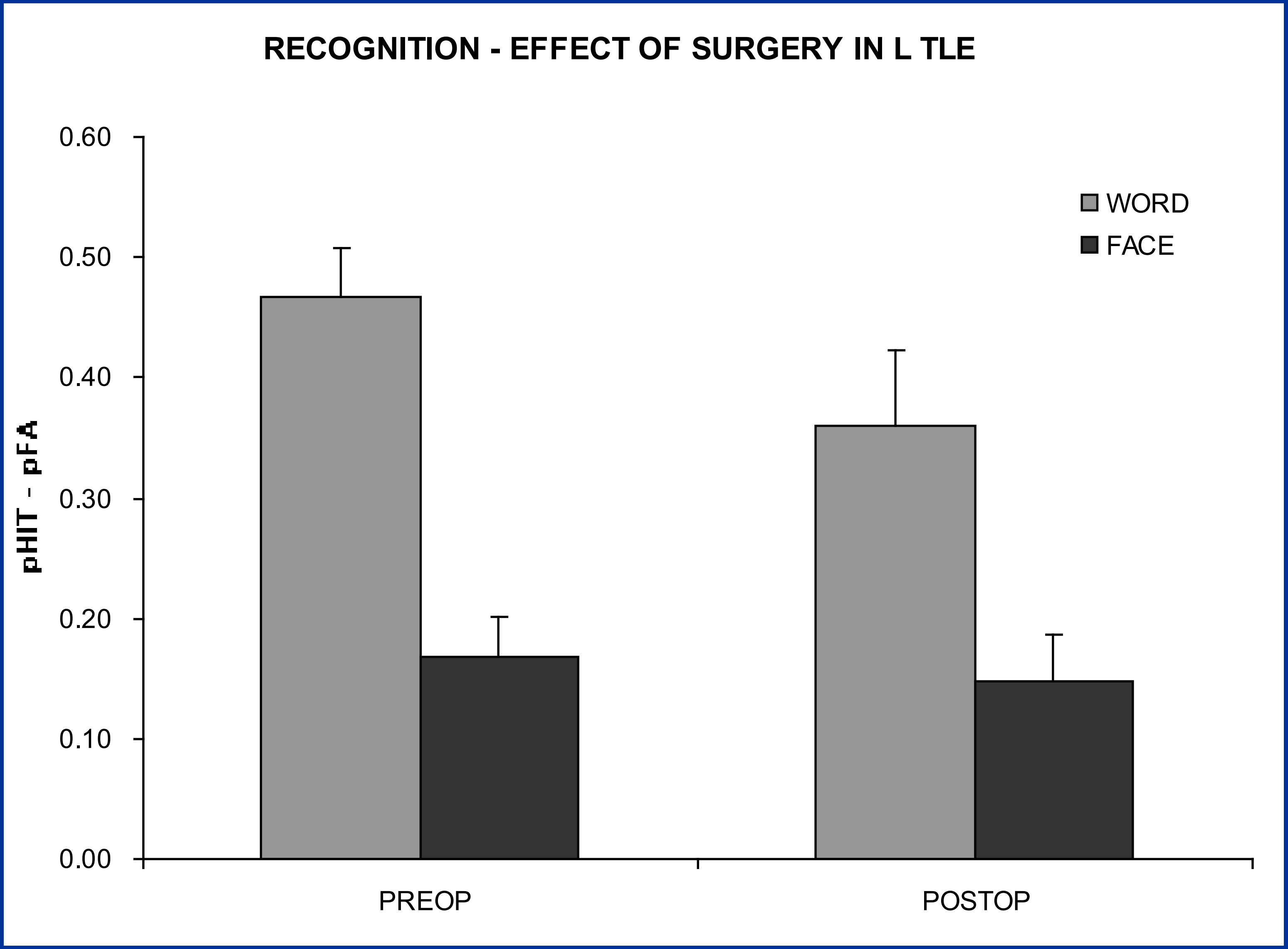


1
2
3
4
5

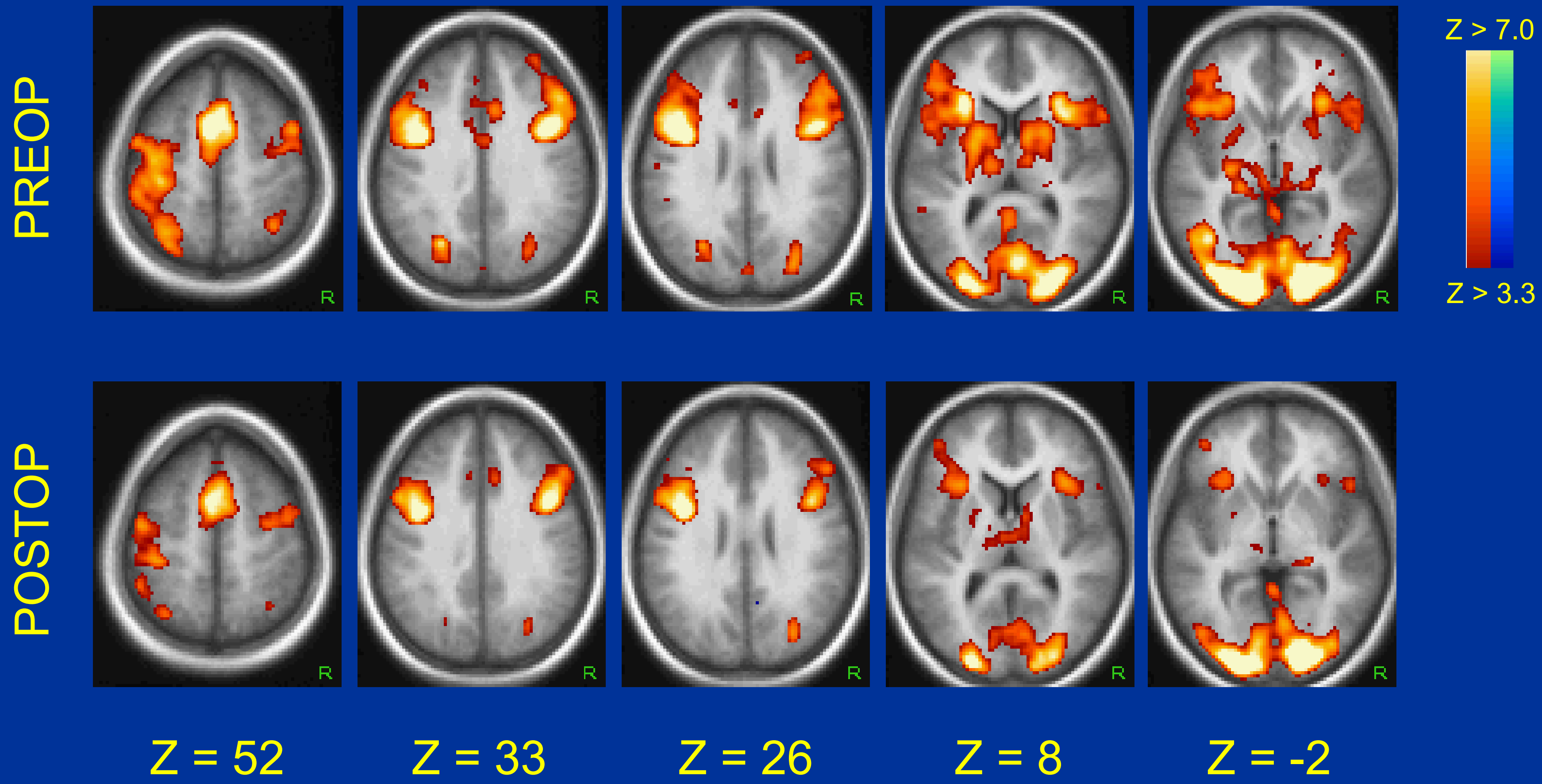



A
LEFT TLE SURGERY
B
RIGHT TLE SURGERY
Y = -6
Y = -12
Y = -18
Y = -24
1
> 7
NUMBER OF PATIENTS

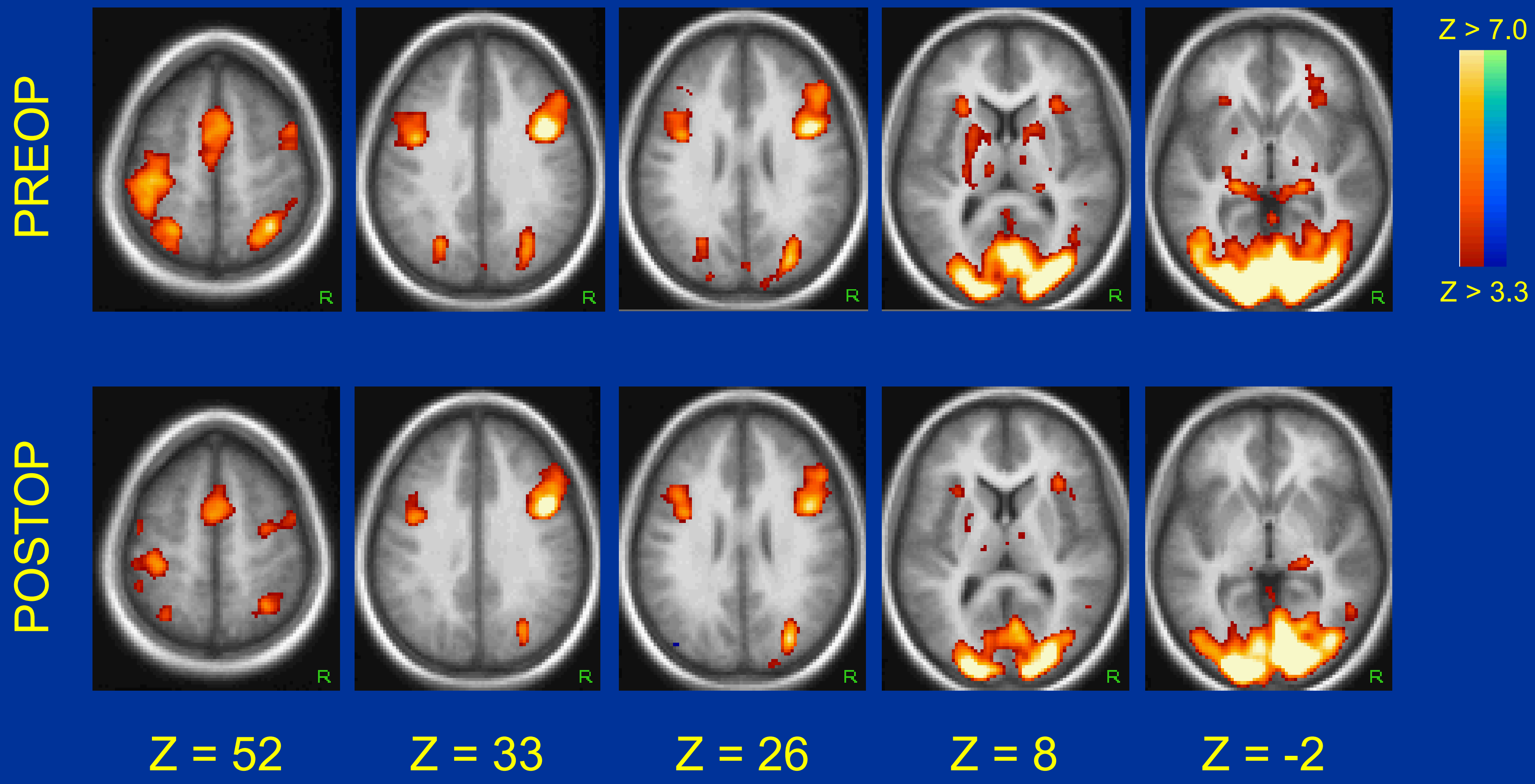


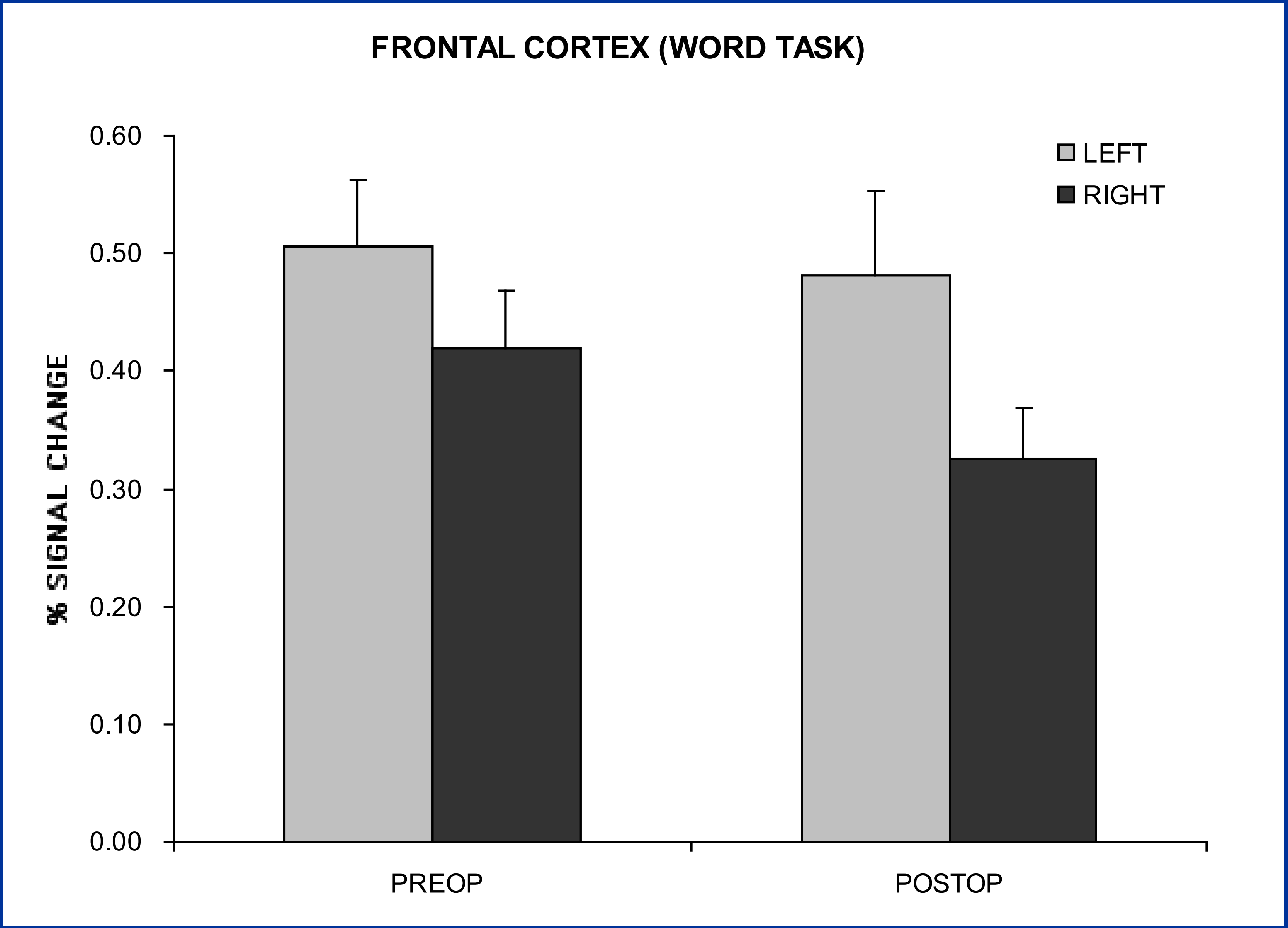
RECOGNITION - EFFECT OF SURGERY IN L TLE
0.60
0.50
0.40
0.30
0.20
0.10
0.00
pHIT - pFA
WORD
FACE
PREOP
POSTOP

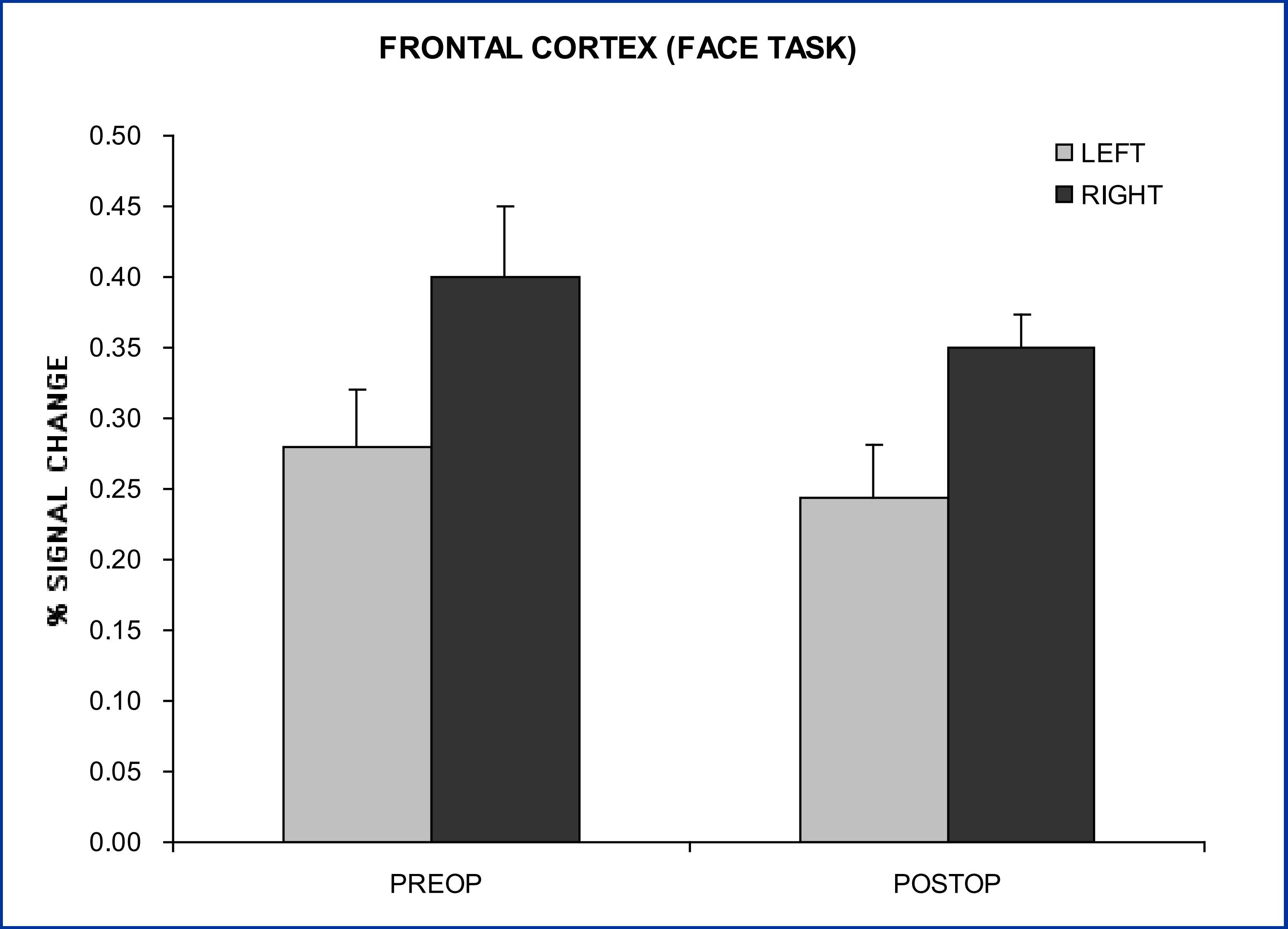
LEFT TLE - WORD TASK - PREOP/POSTOP

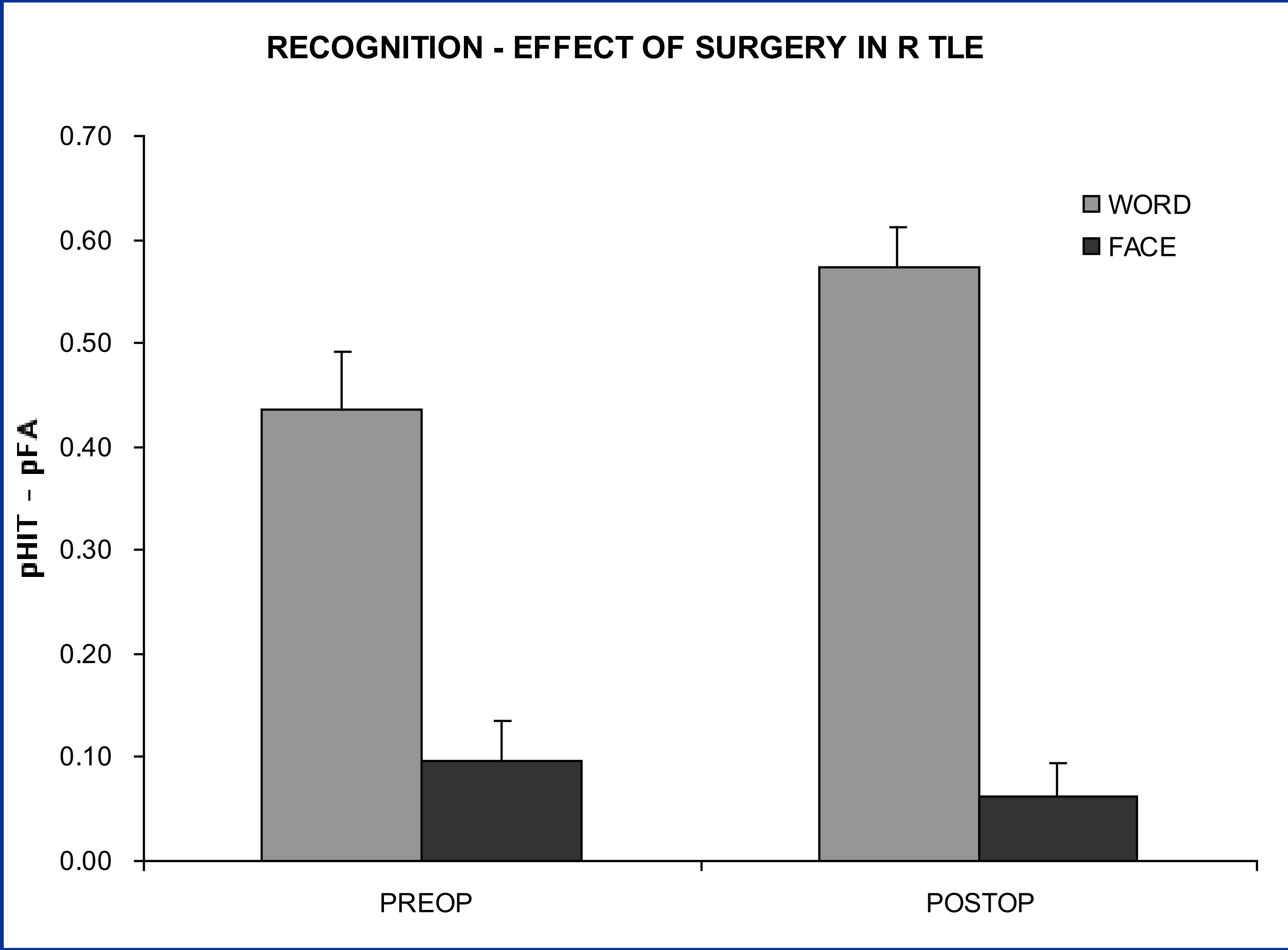


LEFT TLE - FACE TASK - PREOP/POSTOP

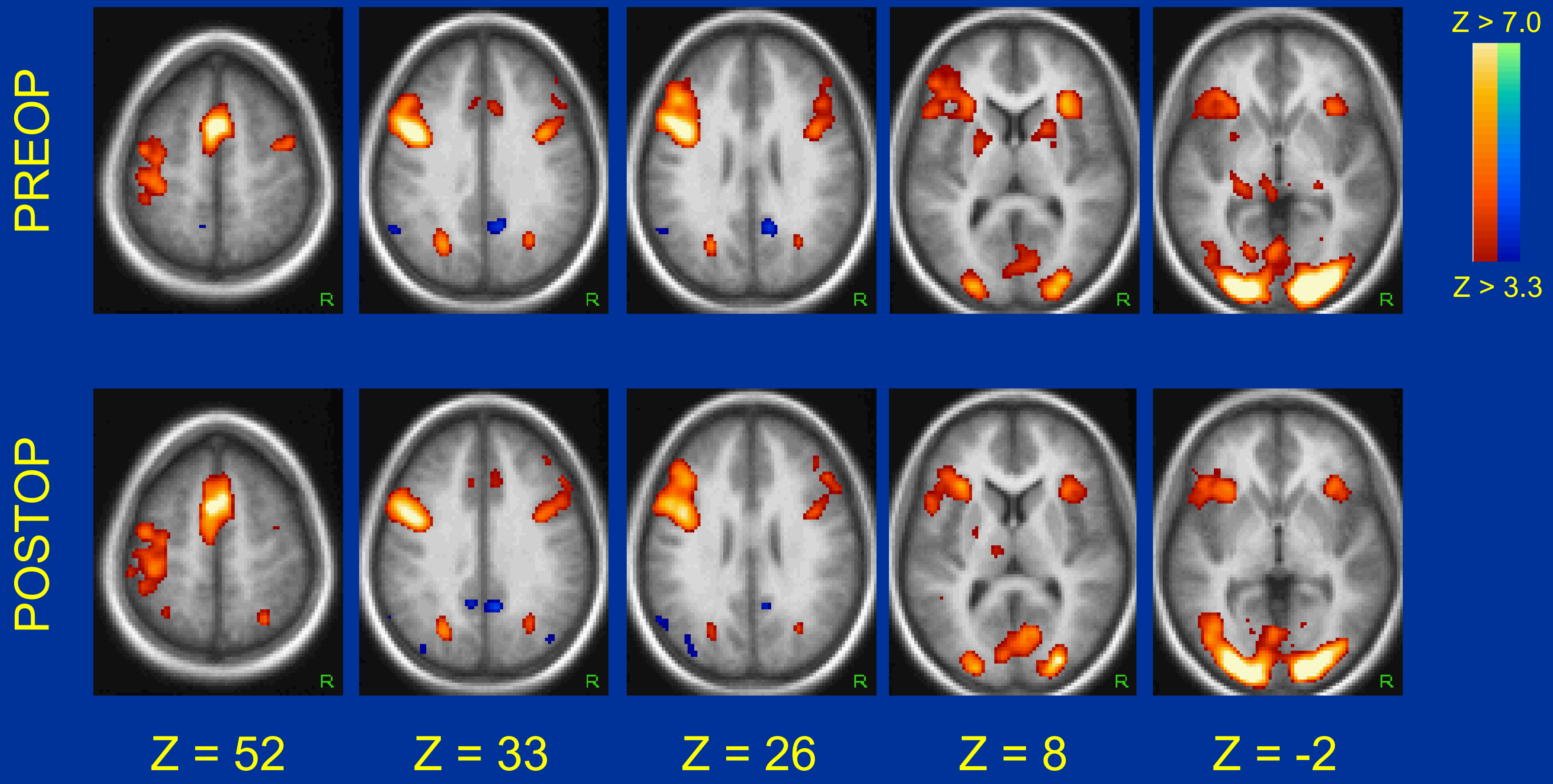



FRONTAL CORTEX (WORD TASK)
% SIGNAL CHANGE
0.60
0.50
0.40
0.30
0.20
0.10
0.00
LEFT
RIGHT
PREOP
POSTOP

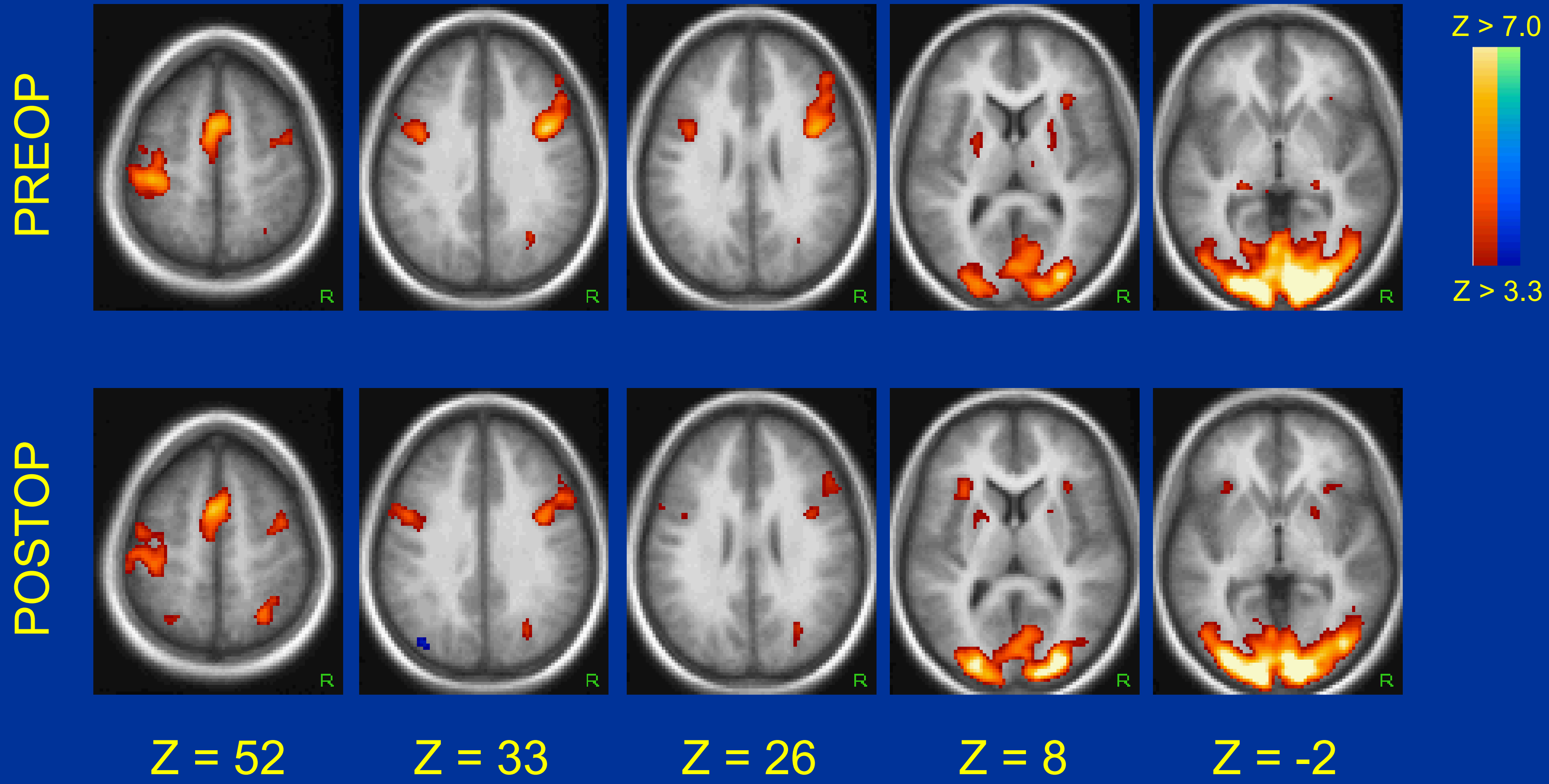

FRONTAL CORTEX (FACE TASK)
% SIGNAL CHANGE
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
LEFT
RIGHT
PREOP
POSTOP

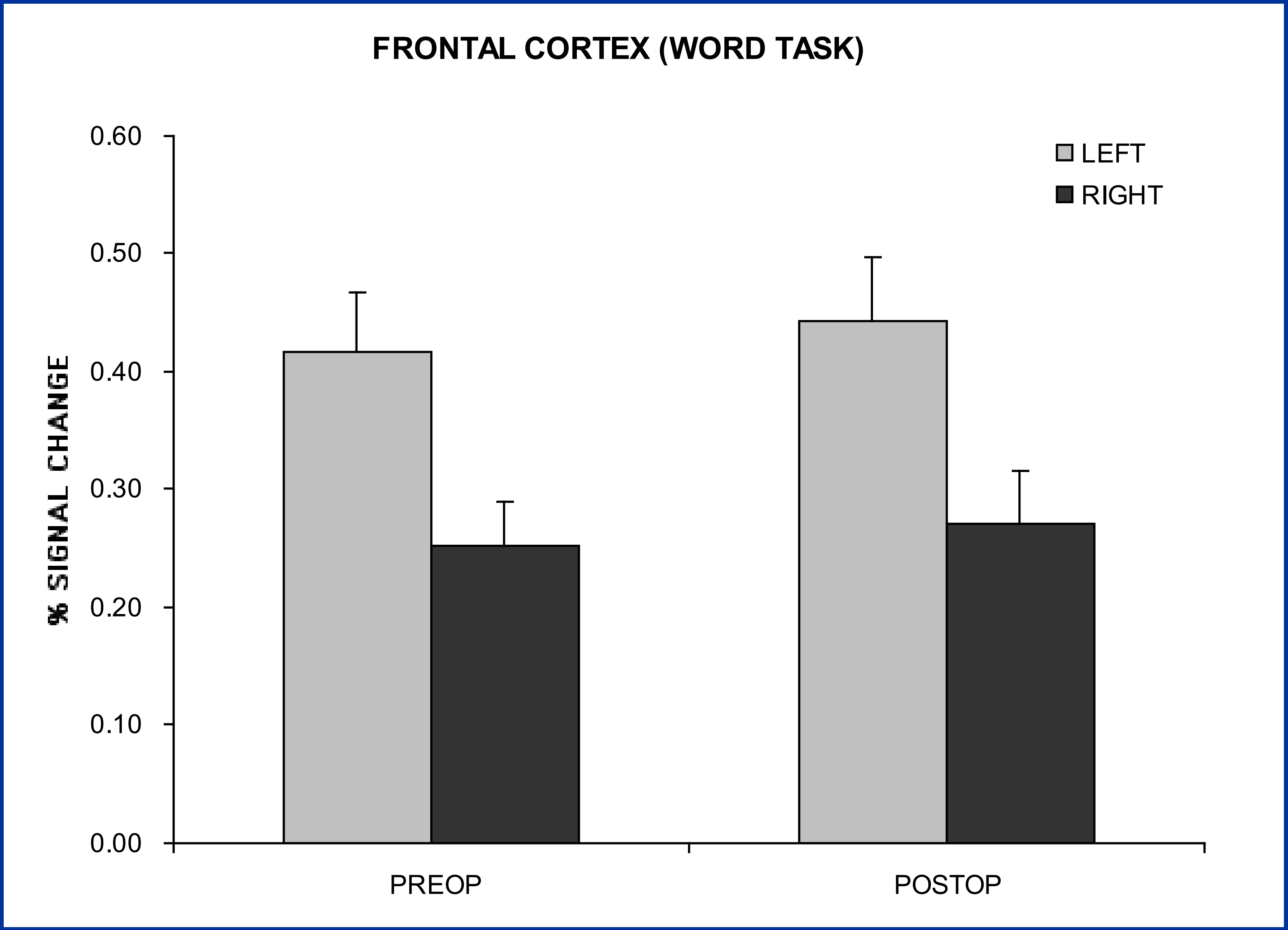

RECOGNITION - EFFECT OF SURGERY IN R TLE
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
pHIT - pFA
WORD
FACE
PREOP
POSTOP

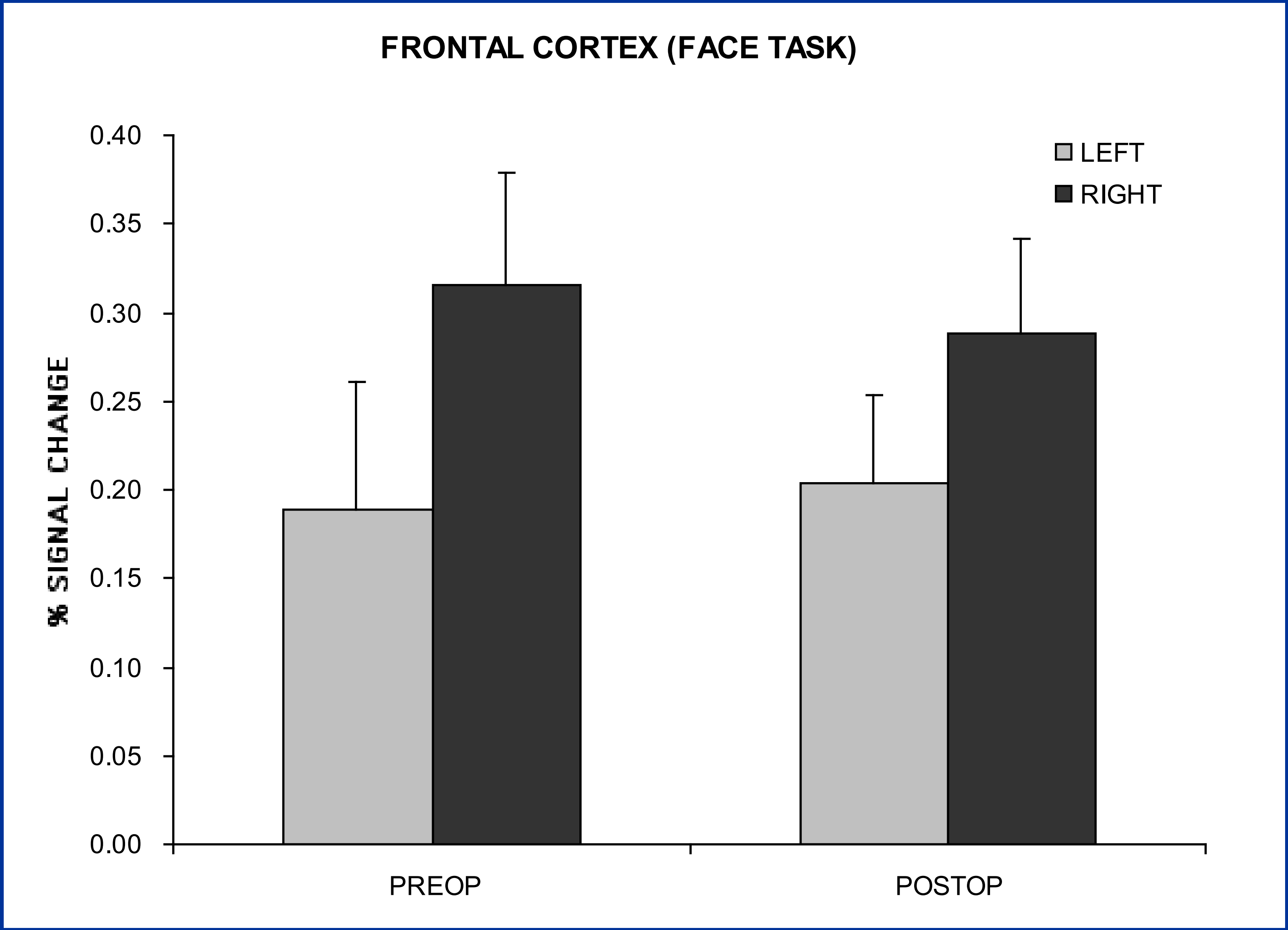
RIGHT TLE - WORD TASK - PREOP/POSTOP



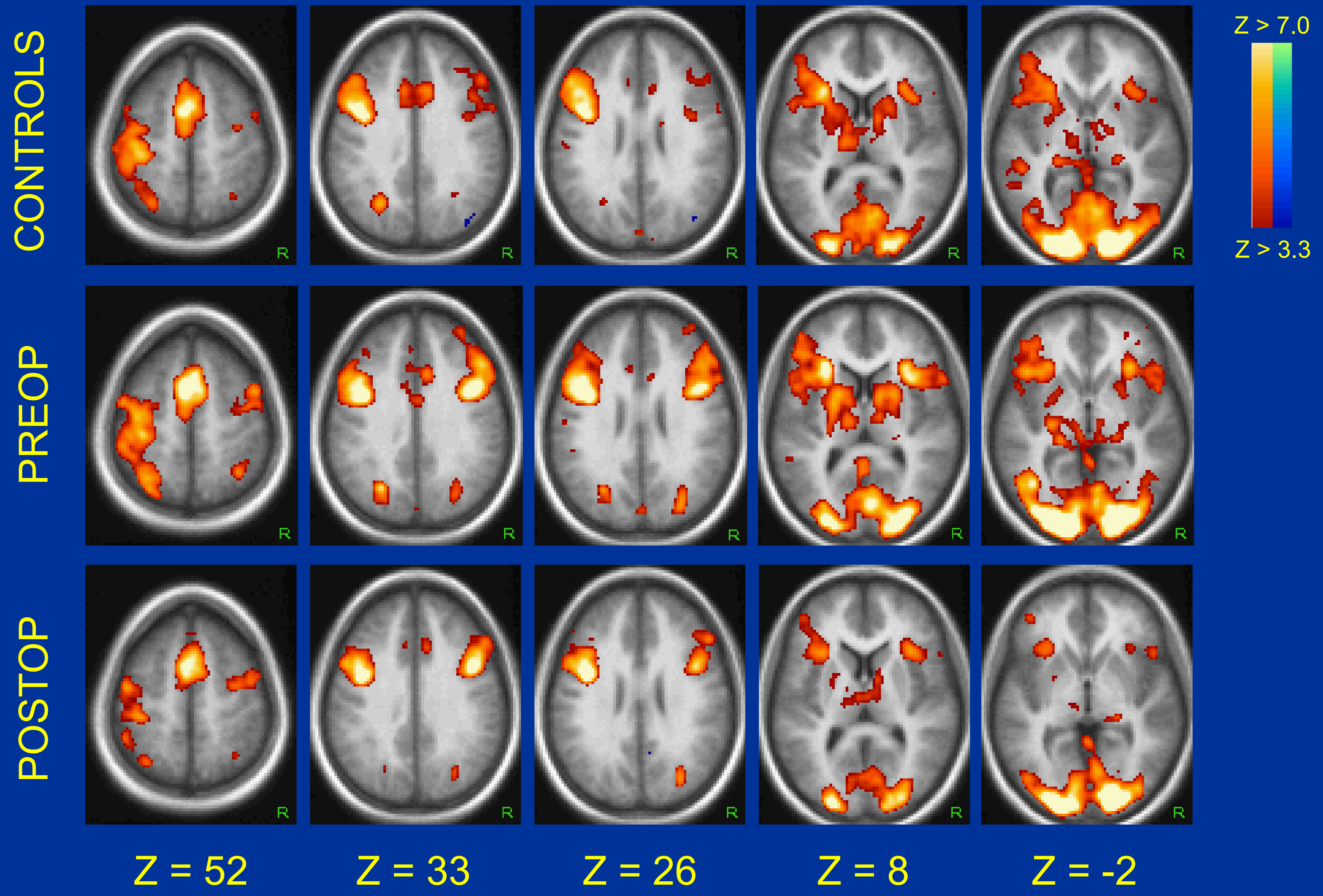
RIGHT TLE - FACE TASK - PREOP/POSTOP

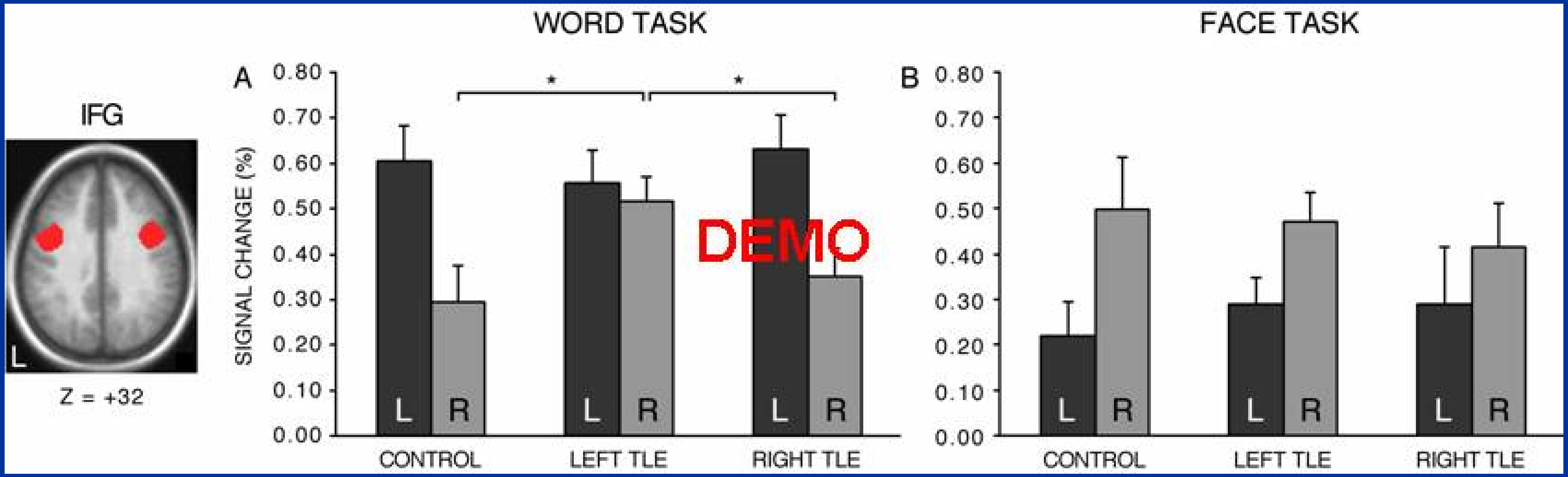



FRONTAL CORTEX (WORD TASK)
LEFT
RIGHT
% SIGNAL CHANGE
0.60
0.50
0.40
0.30
0.20
0.10
0.00
PREOP
POSTOP

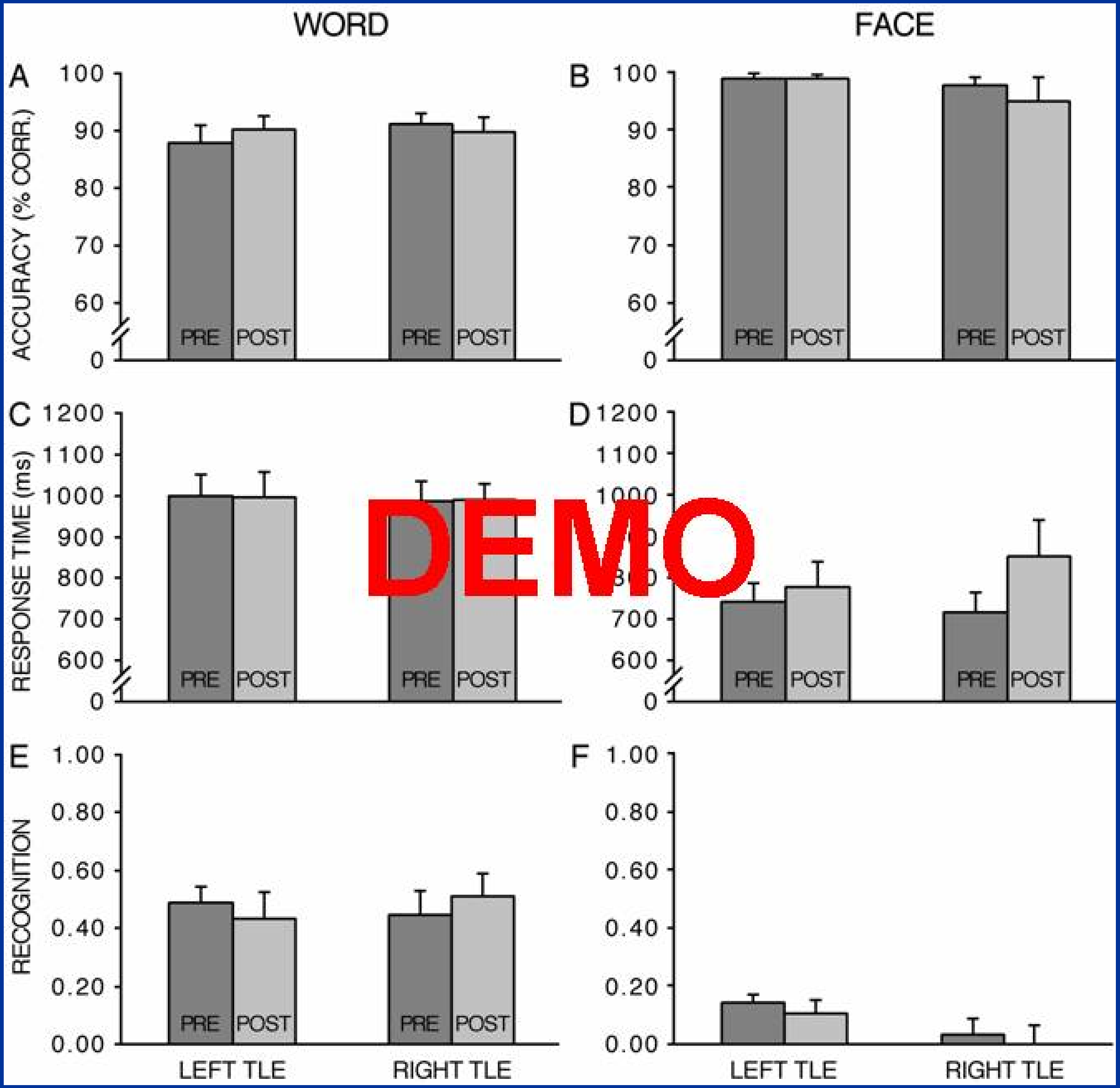

FRONTAL CORTEX (FACE TASK)
% SIGNAL CHANGE
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
LEFT
RIGHT
PREOP
POSTOP

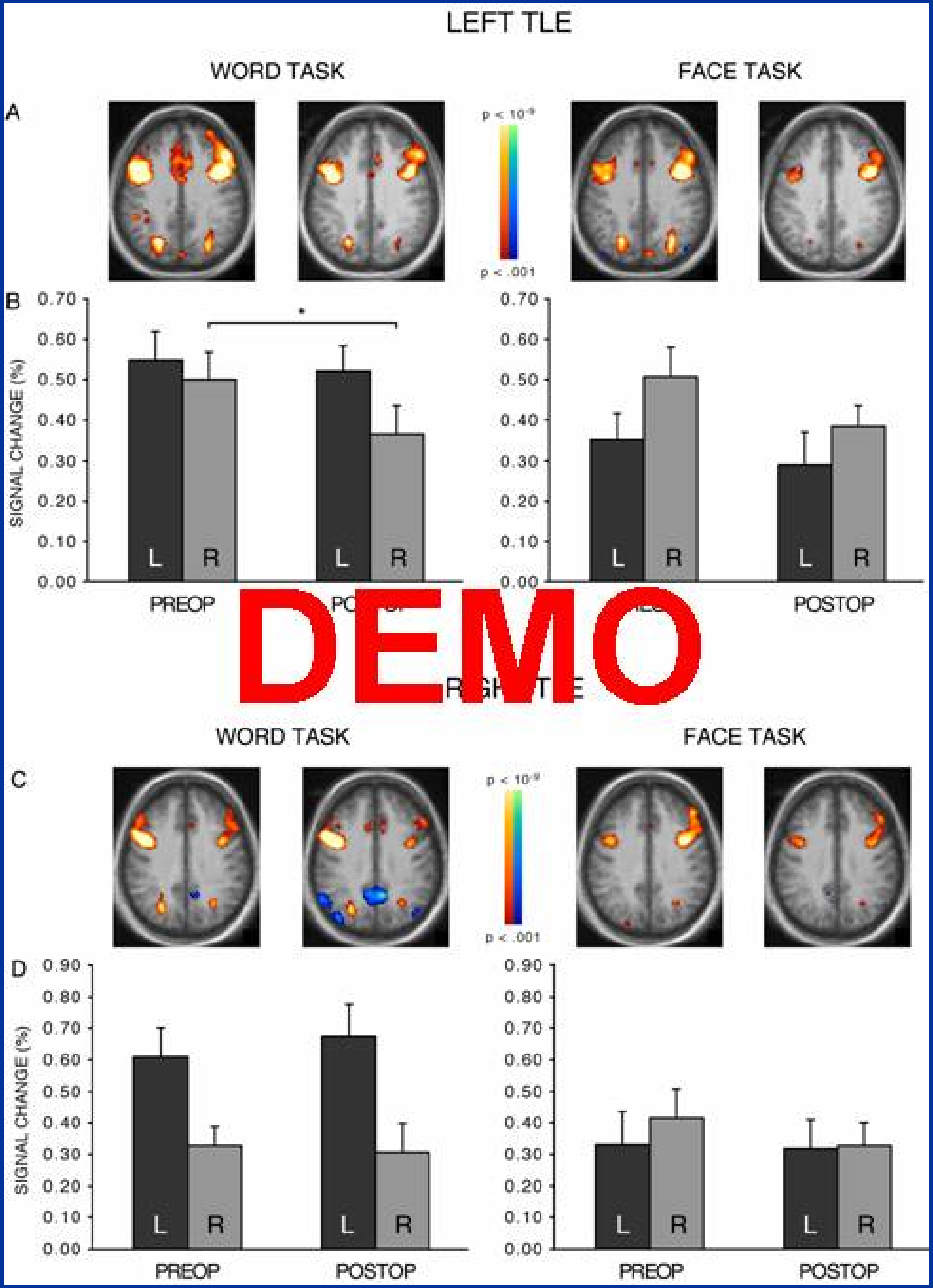
CONTROLS, LEFT TLE - WORD TASK





IFG
L
Z = +32
WORD TASK
A
FACE TASK
B
SIGNAL CHANGE (%)
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
*
*
L
R
CONTROL
LEFT TLE
RIGHT TLE
DEMO


WORD
FACE
A
B
C
D
E
F
ACCURACY (% CORR.)
RESPONSE TIME (ms)
RECOGNITION
100
90
80
70
60
0
1200
1100
1000
900
800
700
600
1.00
0.80
0.60
0.40
0.20
0.00
PRE
POST
LEFT TLE
RIGHT TLE
DEMO



LEFT TLE
WORD TASK
FACE TASK
A
p < 10-9
p < .001
B
SIGNAL CHANGE (%)
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
*
L
R
PREOP
POSTOP
DEMO
WORD TASK
FACE TASK
C
p < 10-9
p < .001
D
SIGNAL CHANGE (%)
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
L
R
PREOP
POSTOP

CONCLUSIONS

• TLE patients showed significant verbal and non-verbal memory impairment as compared to controls, *preoperatively*.

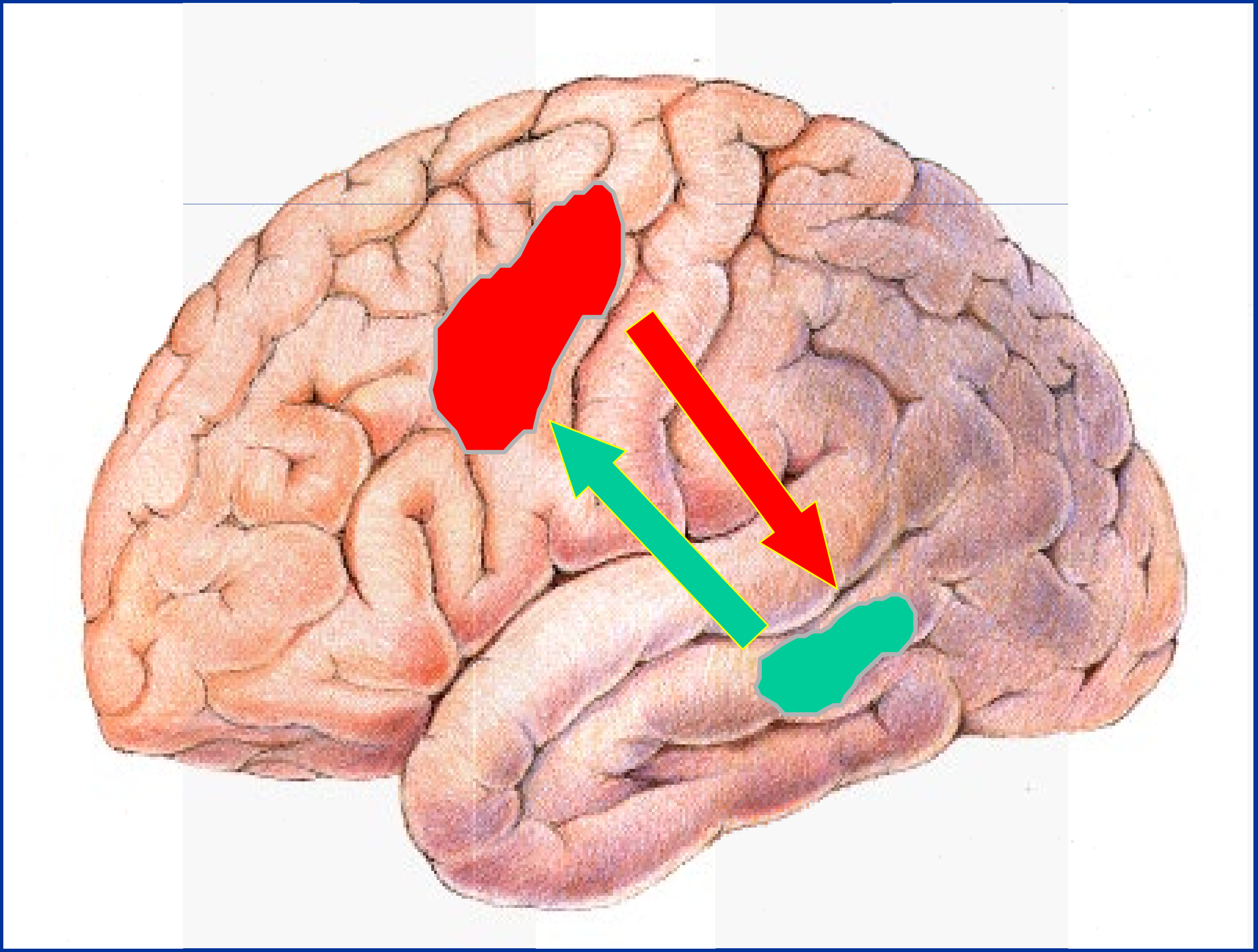
• In the face of this, activation levels in frontal regions near BA44/6 were essentially identical between preoperative TLE patients and controls for both verbal and non-verbal material (the greatest similarity being between controls and R TLE patients).

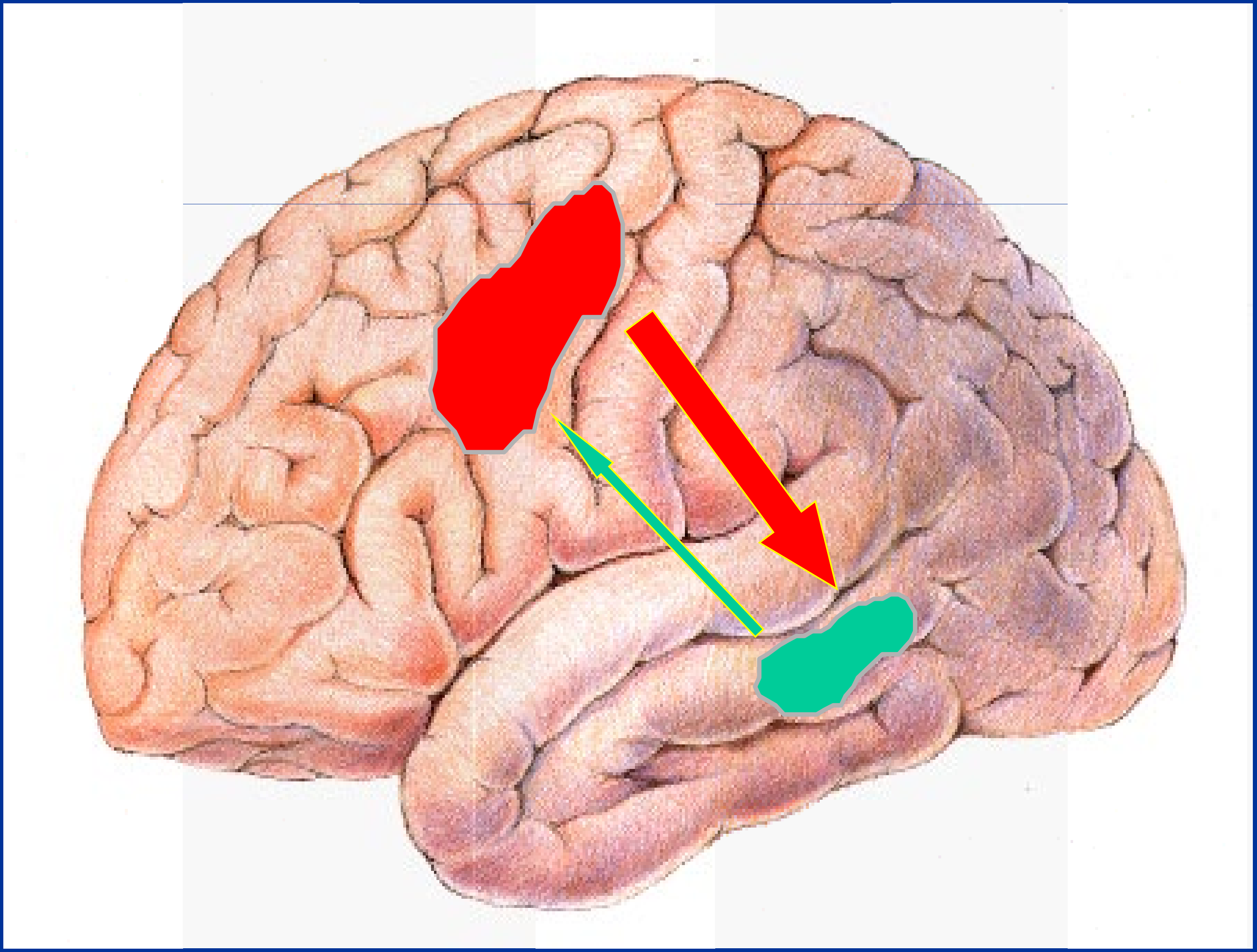
• Strikingly, surgery did not have a significant effect on recognition memory.

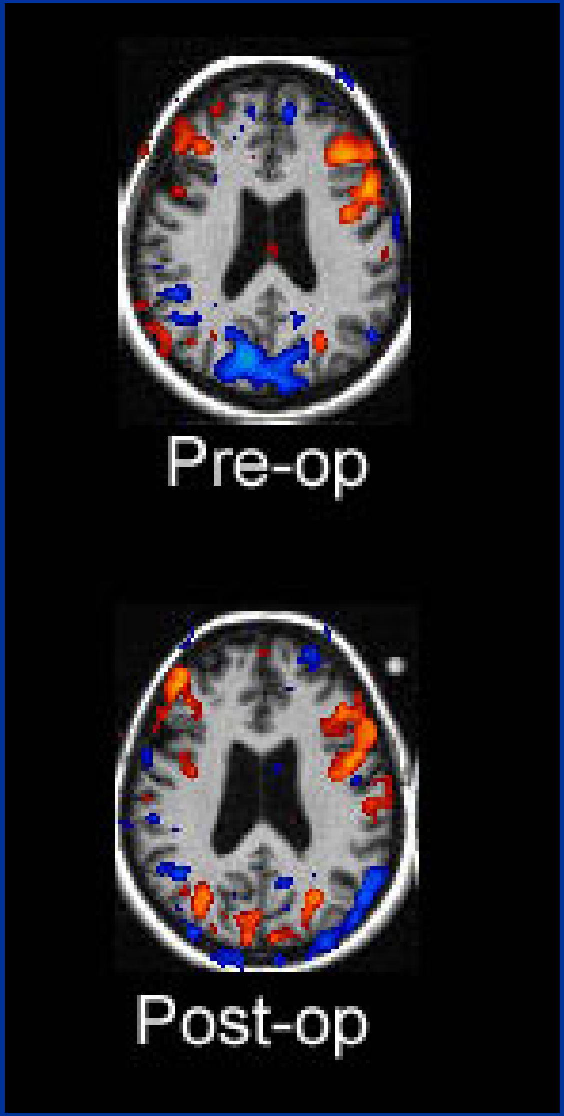
• Moreover, *postoperative* activation levels in frontal regions near BA44/6 were very similar to the levels observed preoperatively.

CONCLUSIONS

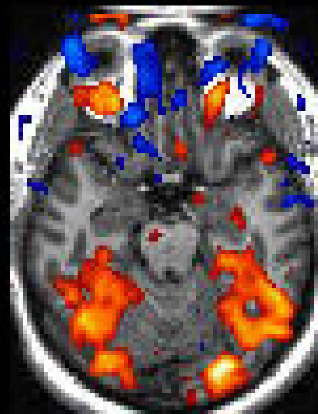
• Taken together, the observation that 1) epilepsy patients are significantly impaired in recognition memory, while 2) the levels of activity in frontal regions observed in such patients are essentially identical to those of healthy subjects both *before* and *after* unilateral removal of the medial temporal lobe, are strongly indicative of a one-directional interaction between frontal cortex and medial temporal structures in memory encoding.





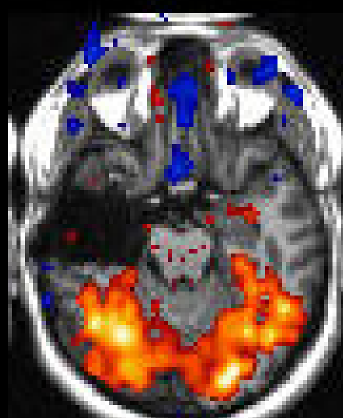


Preserved Frontal activation following temporal lobectomy



Pre-op

Temporal lobe activation

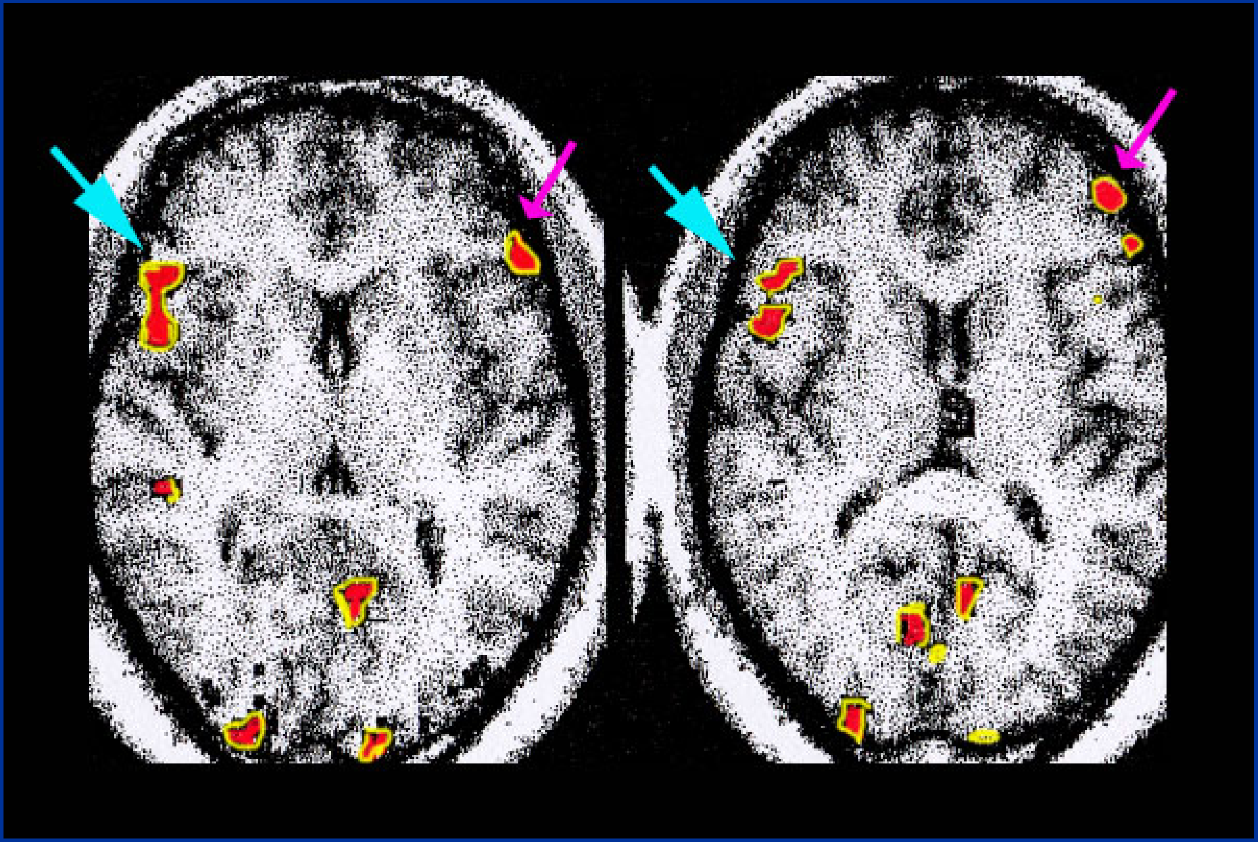


Post-op Right temporal lobectomy

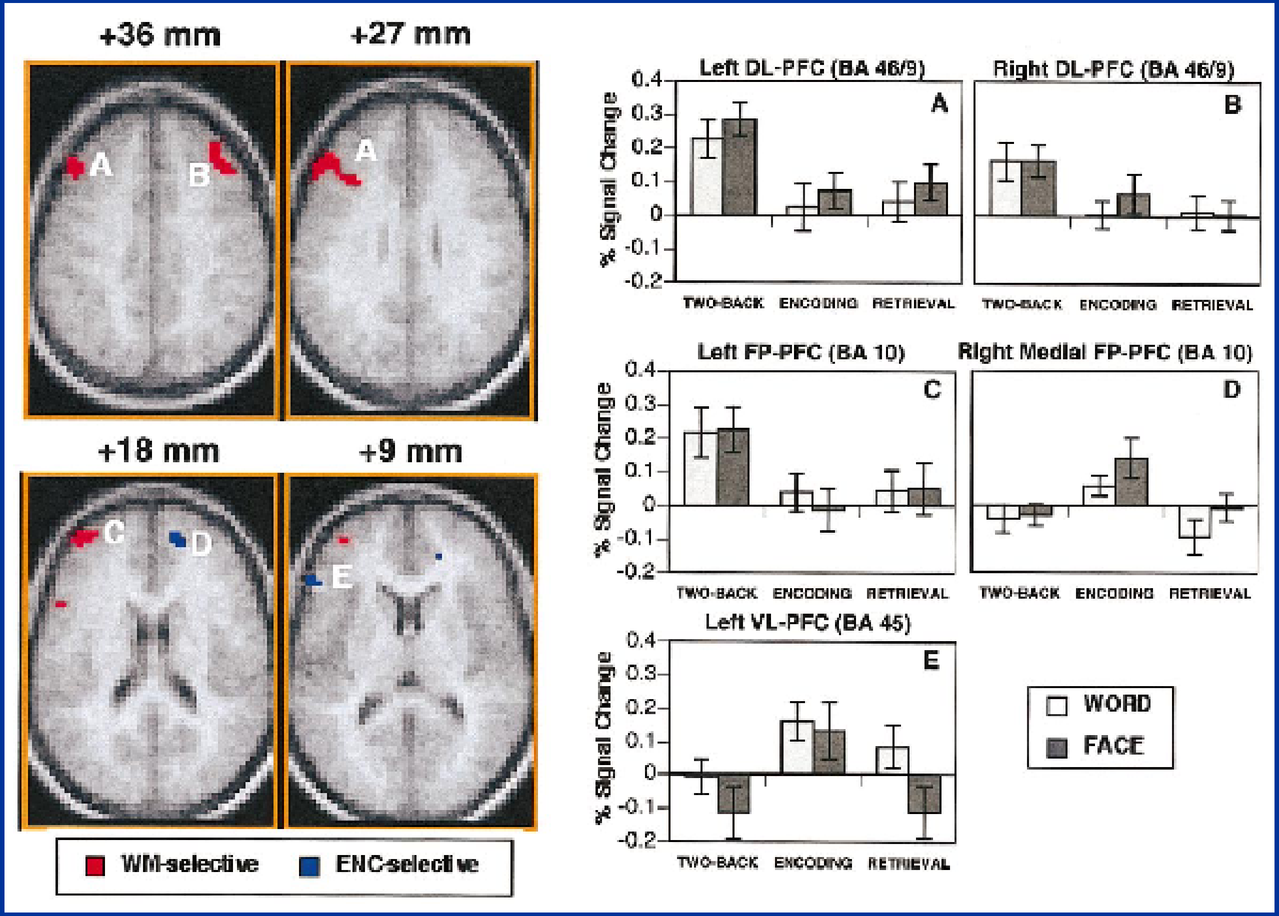
Memory and fMRI

- Memory formation can activate bilateral hippocampus
- ‘Unhealthy’ hippocampus may not activate
- Unclear if this will predict outcome
- Frontal lobe activation may predict Wada results

Frontal sites dissociate along with Wada lateralization



Is this all working memory?



Future studies

- Characterize post-op performance
- Functional MRI predictors of outcome?
- Non-memory correlates with fMRI?
- Stronger hippocampal activations, including *non-memory* tasks