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 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.”

‘Word Stem’ memory-cued recall and Right Hippocampus
The *hippocampus* was not consistently seen in imaging studies of memory.
Areas of poor fMRI signal
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

- electrical activity
  - excitatory
  - inhibitory
  - soma action potential

- hemodynamic response
  - ↑ blood flow
  - ↑ blood volume
  - ↑ blood oxygenation

- metabolic response
  - ↑ glucose consumption
  - ↑ oxygen consumption

- electrophysiology
  - EEG
  - MEG

- imaging techniques
  - FDG PET
  - Autoradiography
  - H₂¹⁵O PET
  - NIRS
  - Optical imaging
  - fMRI
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 rCMRO₂ (5 – 25%)
  - oxygen transport limited, but coupled: recent MR data suggests ΔCMRO₂: ΔCBF = 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
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>
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<th>Table 1. Summary of PET findings with healthy human subjects concerning prefrontal activation associated with episodic memory encoding and retrieval processes</th>
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<tr>
<td>Encoding</td>
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<tr>
<td>Kapur <em>et al.</em> (14)</td>
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<td>Petersen <em>et al.</em> (27)</td>
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<td>Trial 1</td>
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<td>Buckner <em>et al.</em> (34)</td>
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<tr>
<td>M.M. <em>et al.</em> (unpublished)</td>
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<td>Spatial Information</td>
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<td>Tulving <em>et al.</em> (16)</td>
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<td>Different case</td>
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<td>Haxby <em>et al.</em> (36)</td>
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Statistically significant evidence of prefrontal involvement is indicated by +, absence of similar evidence by -.
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
Distribution of ICA injection
Circulation affected by ICA injection

Left internal carotid injection

Left frontal activation during word encoding
Memory formation

Wada memory performance

Number correct (out of 8)

HEMISPHERE INJECTED

CHANCE

Words
Faces
Mapping bilateral frontal sites during memory for pictures

Both dominant and non-dominant sites

Consistent with fMRI literature
Cortical Stimulation Mapping

Distractor sentence: "Hammer"

Read Sentence: "Hammer"

RECALL: "Hammer"
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.
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• 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.
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
ENCODING (inside the scanner)

+ WORD + WORD + WORD +

+ FACE + FACE + FACE +

FLANNEL
MEADOW
TRUMPET
SARDINE

12 ITEMS / BLOCK
ENCODING (inside the scanner)

+ WORD + WORD + WORD +

+ FACE + FACE + FACE +

X 3

FLANNEL
MEADOW
TRUMPET
SARDINE

12 ITEMS / BLOCK

OLD/NEW RECOGNITION (outside the scanner)
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 ENCODING

Z = 52
Z = 33
Z = 26
Z = 8
Z = -2

WORD

FACE
ACCURACY

CONTROLS

L TLE PREOP

R TLE PREOP

% CORRECT

WORD

FACE
Reaction Time

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<thead>
<tr>
<th></th>
<th>Controls</th>
<th>L TLE PREOP</th>
<th>R TLE PREOP</th>
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<tr>
<td>WORD</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>FACE</td>
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</table>

Reaction Time (ms)
DEMO
WORD TASK - PREOP

CONTROLS

Z = 52  Z = 33  Z = 26  Z = 8  Z = -2
WORD TASK - PREOP

CONTROLs

LEFT TLE

Z = 52
Z = 33
Z = 26
Z = 8
Z = -2
ANTERIOR FRONTAL CORTEX (WORD TASK)

% SIGNAL CHANGE

CONTROLS  L TLE PREOP  R TLE PREOP

LEF T  RIGHT

0.00  0.10  0.20  0.30  0.40  0.50  0.60  0.70  0.80  0.90  1.00
FACE TASK - PREOP

Z > 3.3

Z > 7.0

CONTROLS

Z = 52

Z = 33

Z = 26

Z = 8

Z = -2
FACE TASK - PREOP

CONTROLS
Z = 52  Z = 33  Z = 26  Z = 8  Z = -2

LEFT TLE
Z > 3.3  Z > 7.0
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).
Surgery of the hippocampus
Hippocampus - surgery
RECOGNITION - EFFECT OF SURGERY IN L TLE

- PREOP
- POSTOP

WORD
FACE
LEFT TLE - FACE TASK - PREOP/POSTOP

PREOP

Z = 52
Z = 33
Z = 26
Z = 8
Z = -2

POSTOP

Z > 3.3
Z > 7.0
CONTROLS, LEFT TLE - WORD TASK

PREOP

POSTOP

Z = 52
Z = 33
Z = 26
Z = 8
Z = -2
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