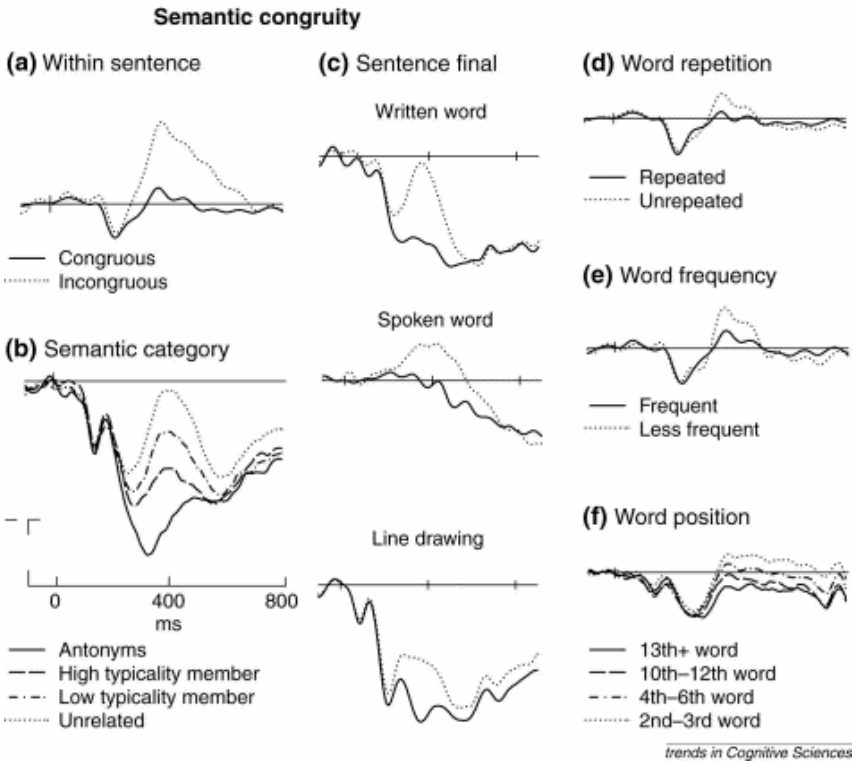
N400: Neural Generators

Functional Significance

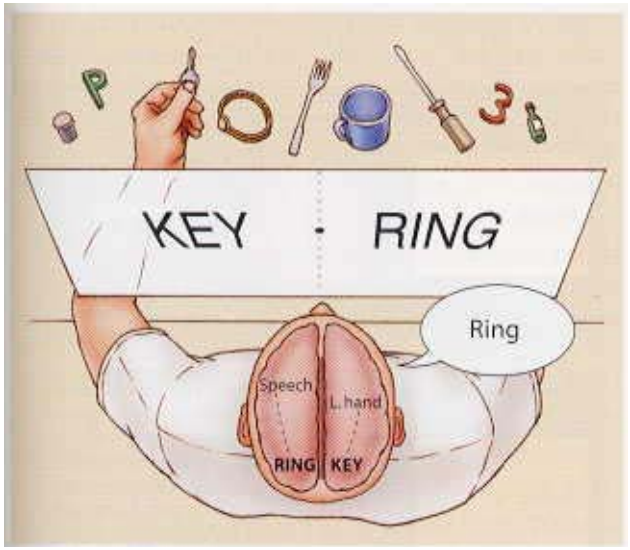
- N400 index of difficulty retrieving conceptual knowledge associated with a word
- Depends on
  - Representation of word itself
  - Contextually activated knowledge



Identifying Neural Generators

- ERPs from patients with well-characterized damage to the brain
- fMRI
- Intracranial Recording
- MEG

Commissurotomy Patients



- Corpus callosi severed in surgical treatment of epilepsy
- Information in right visual hemifield processed almost exclusively by LH
  - Vice versa for LVF/RH
- Behavior of these patients points to strong left lateralization of language function

Kutas, Hillyard & Gazzaniga (1988)

- Experimental Paradigm
  - Sentence context spoken
  - Last word presented visually in left & right hemifields
    - Both congruous, both incongruous, mixed cong/incong
- Context effects differed among patients
  - RVF/LH completions context effects for all patients
  - LVF/RH completions context effects only in patients with RH speech capability
- Scalp distribution of context effects
  - Words presented to ‘speaking’ hemisphere elicited N400 context effects evident over both sides of scalp
  - Words presented to ‘mute’ hemisphere yield no context effects
- N400 probably more dependent on LH generators

Patients with RH Lesions

- ERPs to second word of spoken word pairs
- RH stroke patients with lesions around the Sylvian sulcus
- N400 to strongly associated pairs relatively normal
- N400 to weakly associated pairs smaller than in controls

Strongly Associated Word Pairs

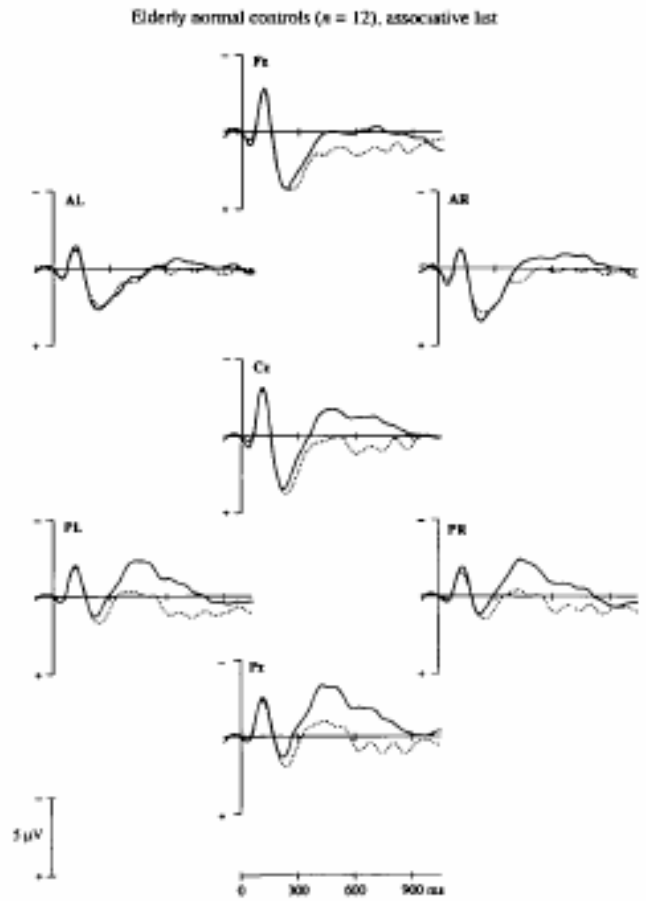


Fig. 4 Grand average ERPs for the elderly normal controls (n = 12) to the unrelated targets (continuous line) and the related targets (dotted line) in the associative list.

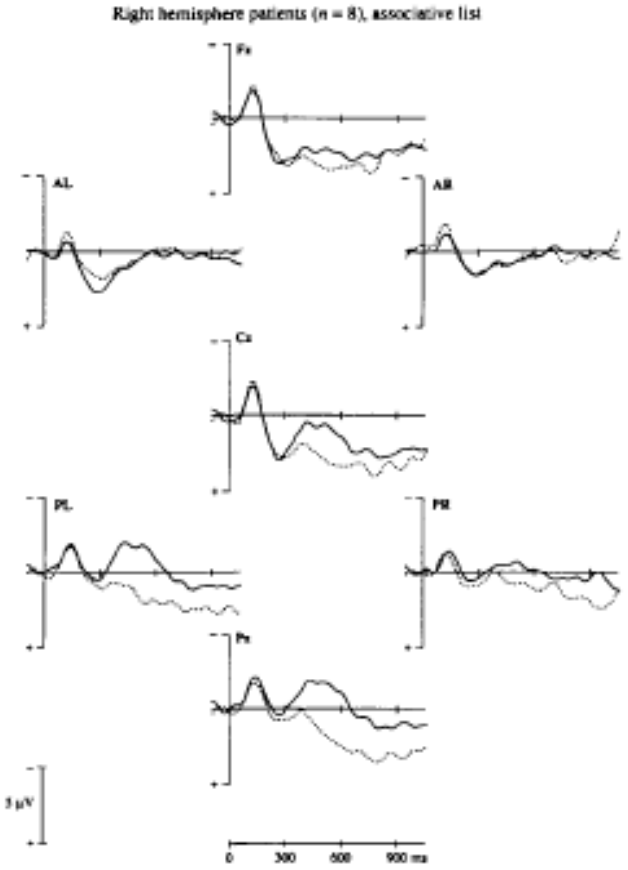


Fig. 10 Grand average ERPs for the patients with a right hemisphere lesion (n = 8) to the unrelated targets (continuous line) and the related targets (dotted line) in the associative list.

Weakly Associated Word Pairs

Age-matched Controls

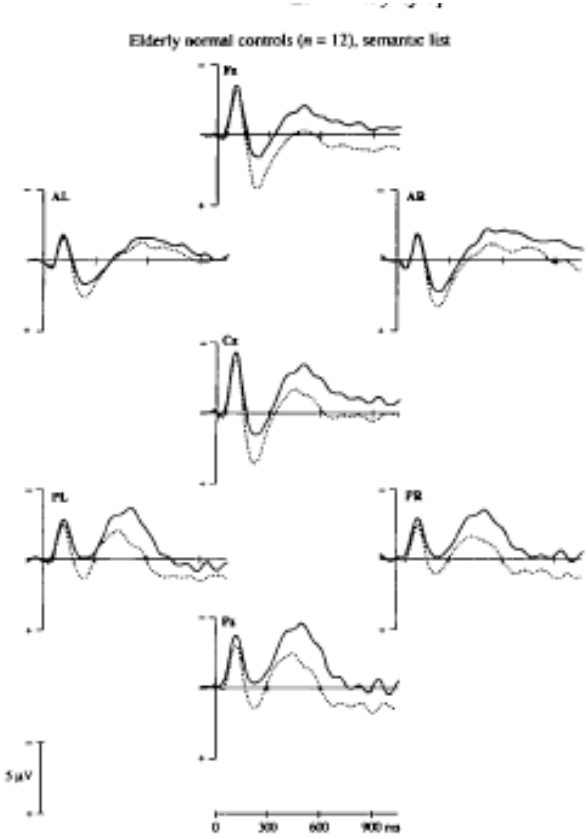


Fig. 5 Grand average ERPs for the elderly normal controls (n = 12) to the unrelated targets (continuous line) and the related targets (dotted line) in the semantic list.

RH Stroke Patients

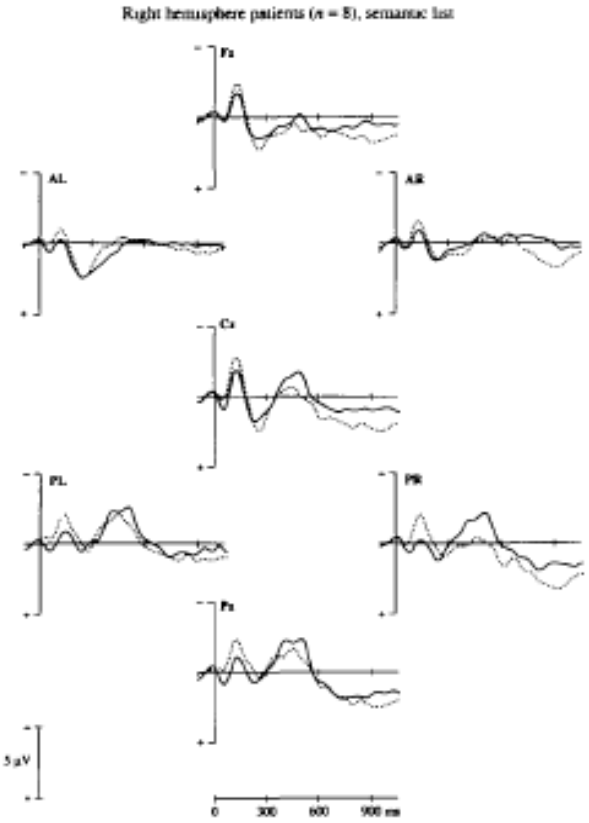


Fig. 11 Grand average ERPs for the patients with a right hemisphere lesion (n = 8) to the unrelated targets (continuous line) and the related targets (dotted line) in the semantic list.

Patients with RH Lesions

- ERPs to second word of spoken word pairs
- Stroke patients with lesions around the Sylvian sulcus
- N400 to strongly associated pairs relatively normal
- N400 to weakly associated pairs smaller than in controls
- **What does this suggest about neural generators of the N400?**
  - *Is it consistent with the study of split-brain patients?*

Anterior vs. Posterior Lesions (of the LH)

- N400 reduction more associated with *posterior* lesions than *anterior* lesions
- Amplitude of N400 context effects correlates well with patients' language comprehension ability as assessed on other tests

Broca's Aphasics

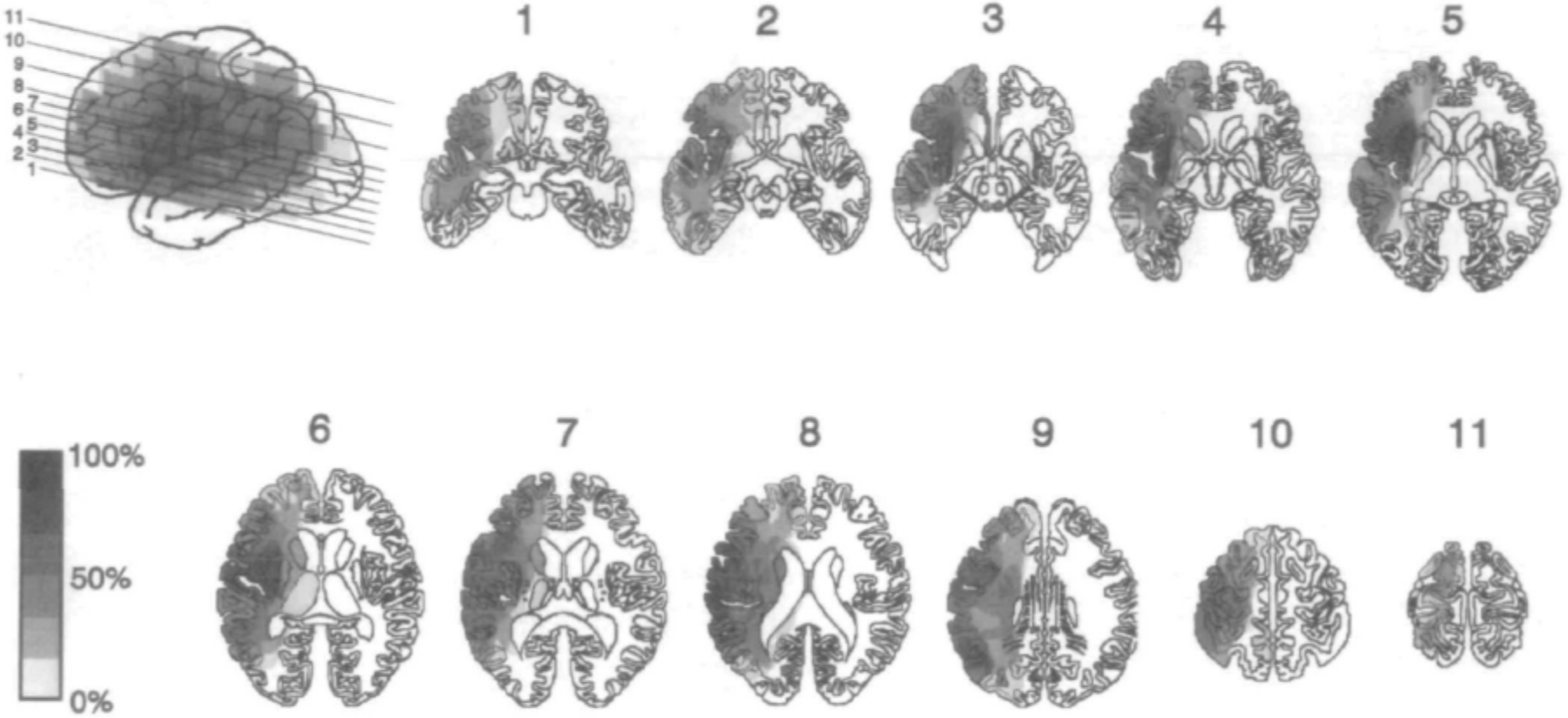


Fig. 1 Lesion extent of the Broca's aphasics. Lesions determined by available CT-scans or MRI-scans from individual patients were transcribed onto templates 0° to the canthomeatal line. These lesion data were then read into a reconstruction program. The digitized data were averaged to generate the group lesion densities. The 11 lines through the lateral reconstruction indicate the 11 axial sections. The shading scale indicates the percentage of patients with damage in the corresponding area. Lesions were averaged over 10 Broca's aphasics.

Wernicke's Aphasics

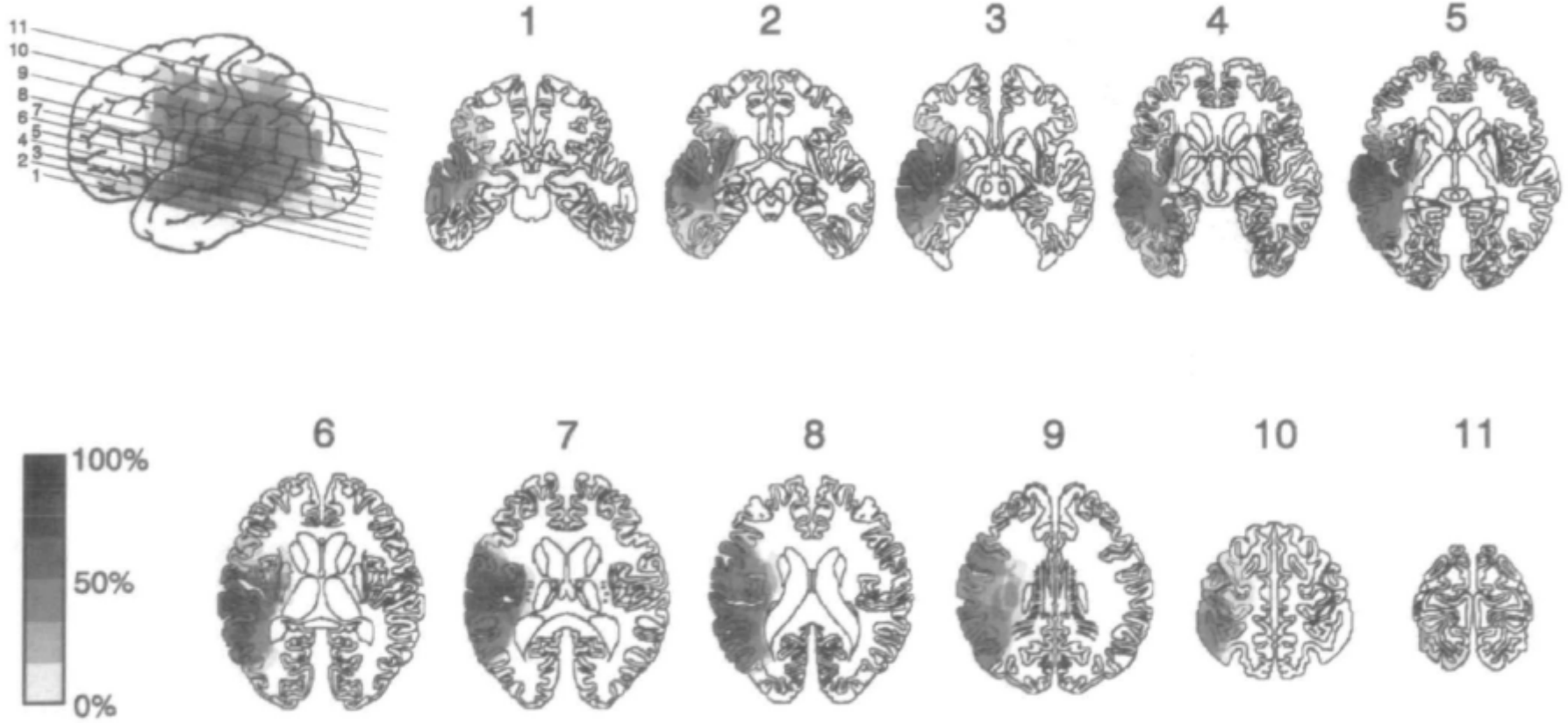


Fig. 2 Lesion extent of the Wernicke's aphasics (n = 7). For details *see* Fig. 1 legend.

Associative Priming

Broca's Aphasics

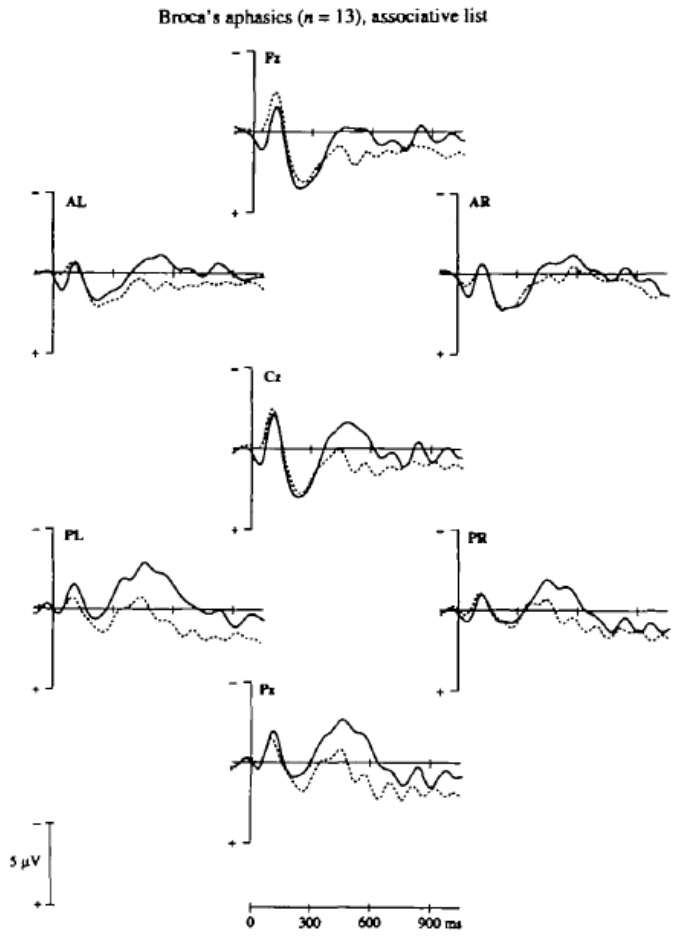


Fig. 6 Grand average ERPs for the Broca's aphasics (n = 13) to the unrelated targets (continuous line) and the related targets (dotted line) in the associative list.

Wernicke's Aphasics

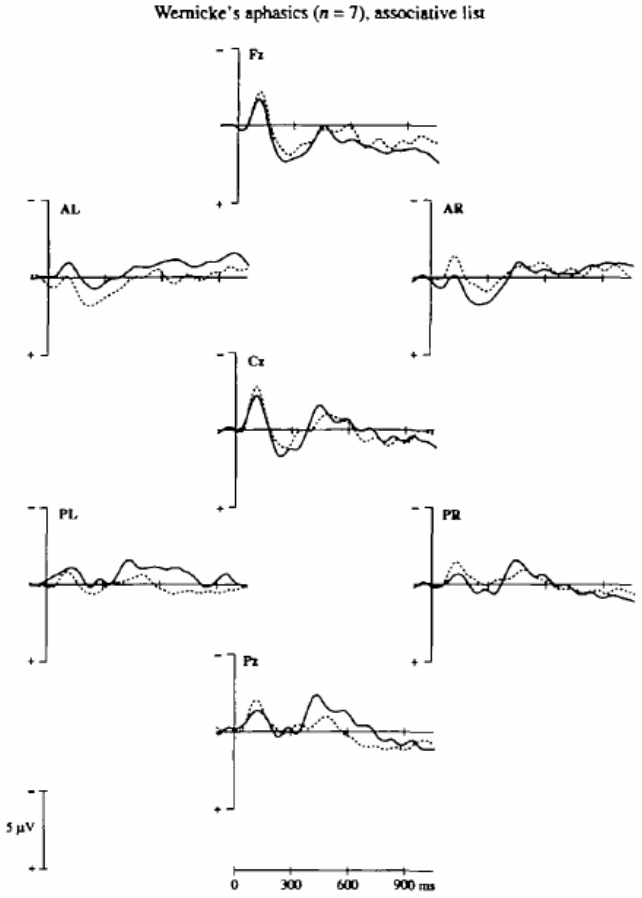
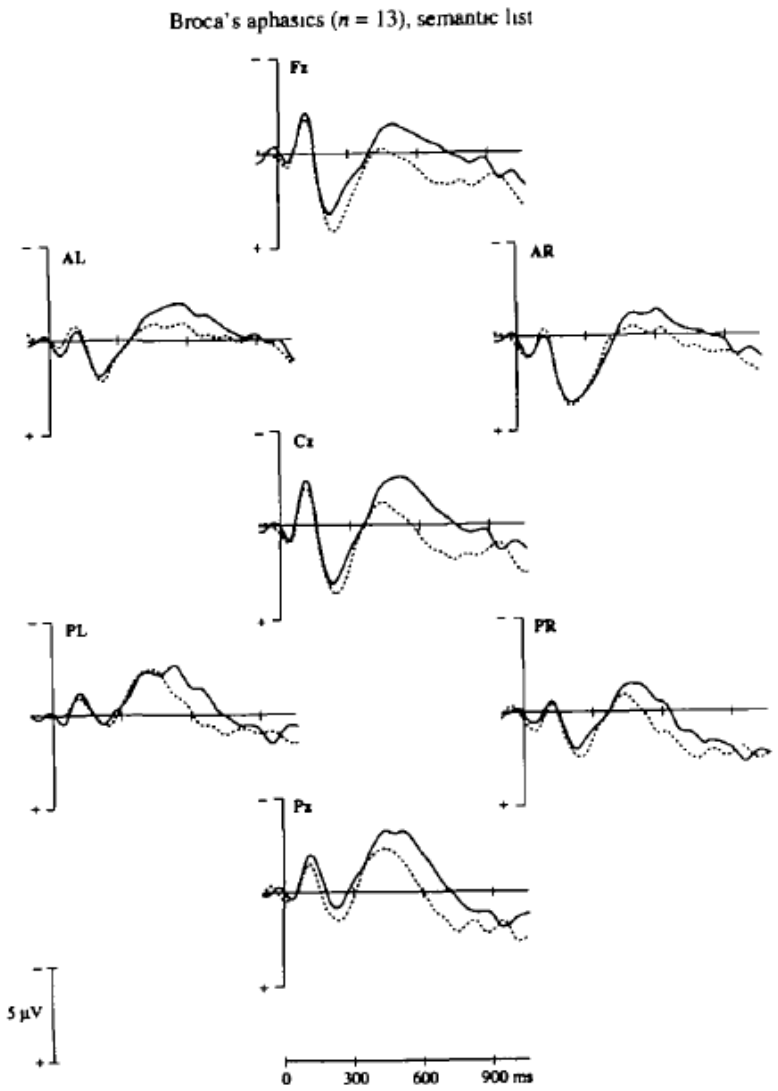


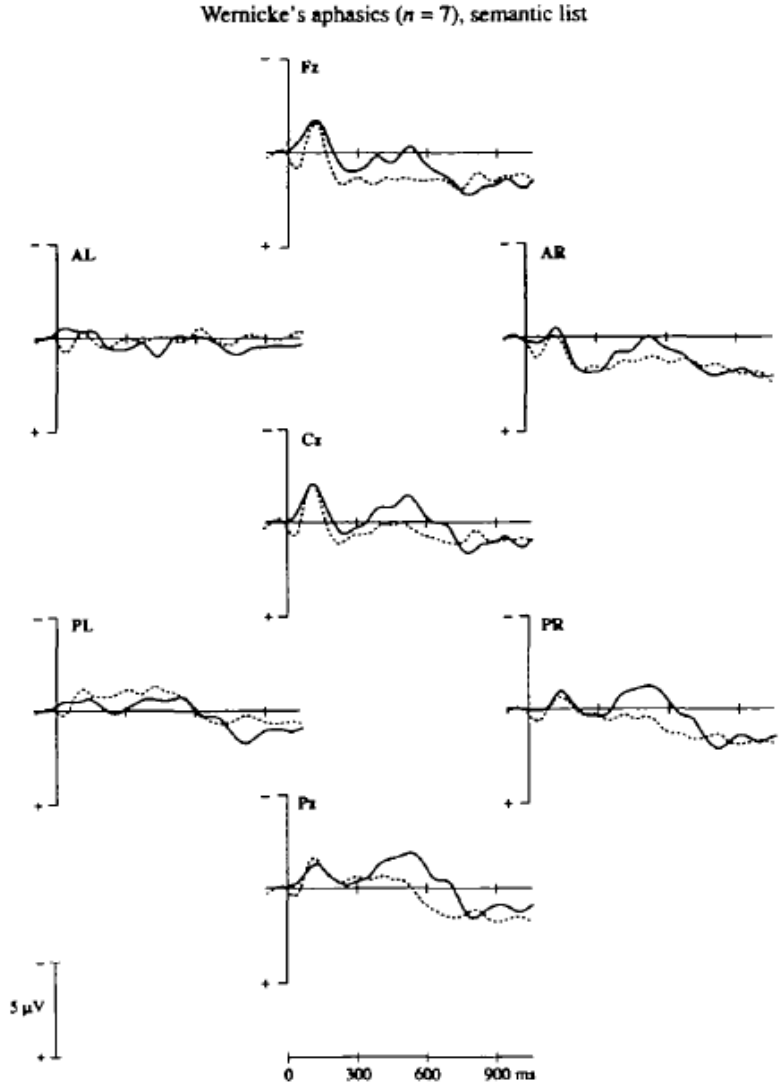
Fig. 8 Grand average ERPs for the Wernicke's aphasics (n = 7) to the unrelated targets (continuous line) and the related targets (dotted line) in the associative list.

Weakley Related Word Pairs

Broca's Aphasics



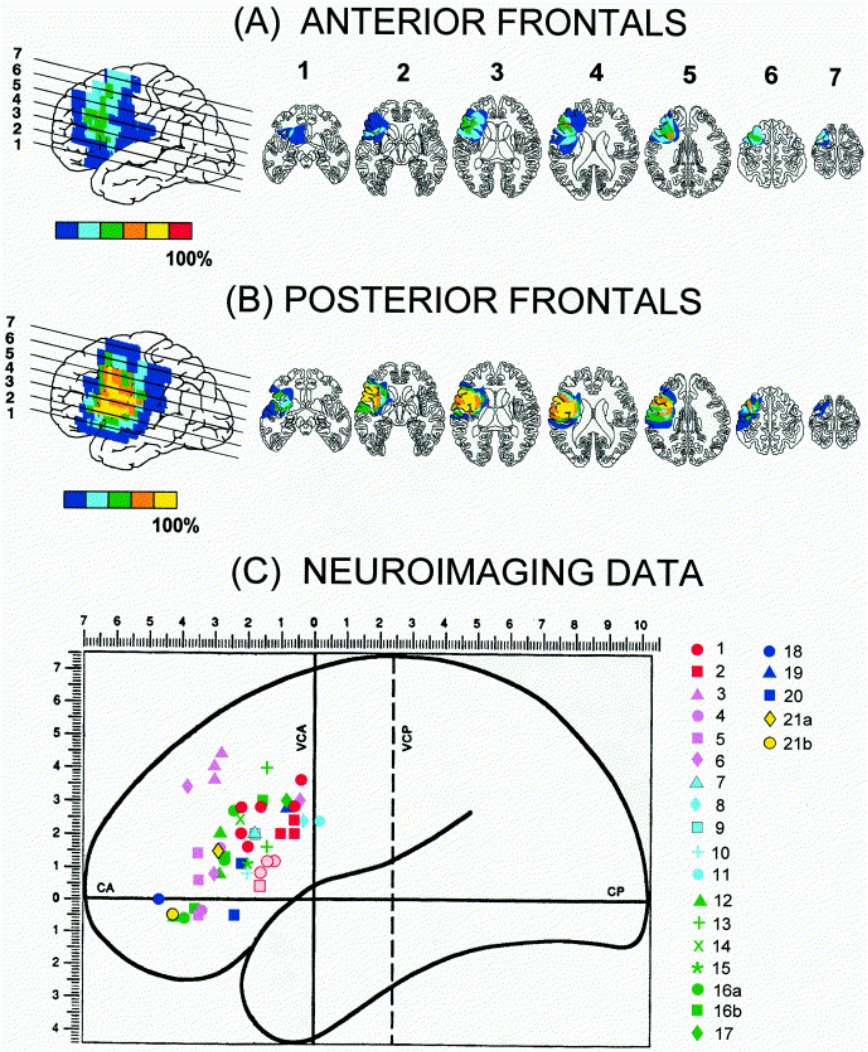
Wernicke's Aphasics



Anterior vs. Posterior Lesions

- N400 reduction more associated with *posterior* lesions than *anterior* lesions
  - ***What does this suggest about the generators?***
  - ***Is that necessarily the case?***
- Amplitude of N400 context effects correlates well with patients' language comprehension ability as assessed on other tests
  - ***What does this tell us?***
  - ***Does it have implications for the questions above?***

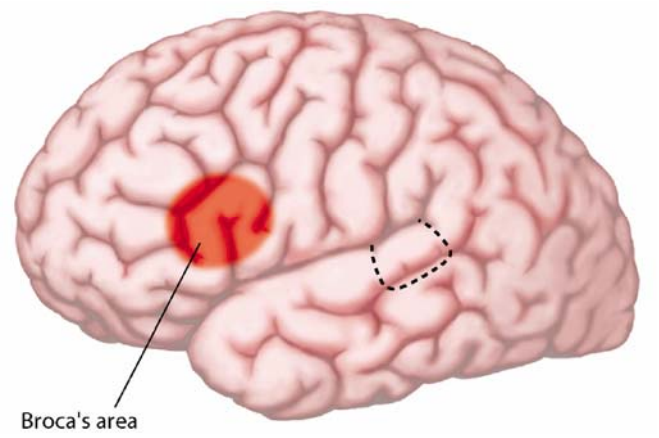
Swick, unpublished data

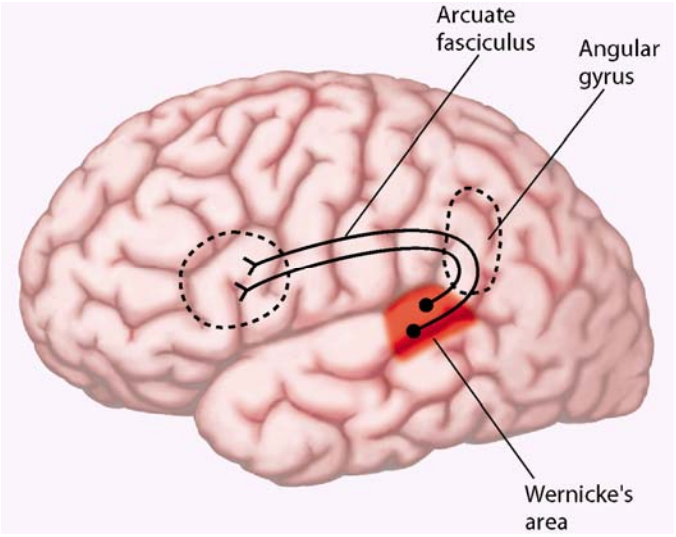


- N400 sentence context effect present in frontal lesion patients
- Subsequent positivity not evident in patients' ERPs but present in healthy controls

fMRI

- Divergent pattern of activation due to manipulations of semantic context
- Left superior temporal gyrus in 7/12 experiments
- Left inferior frontal gyrus in 8/12 experiments





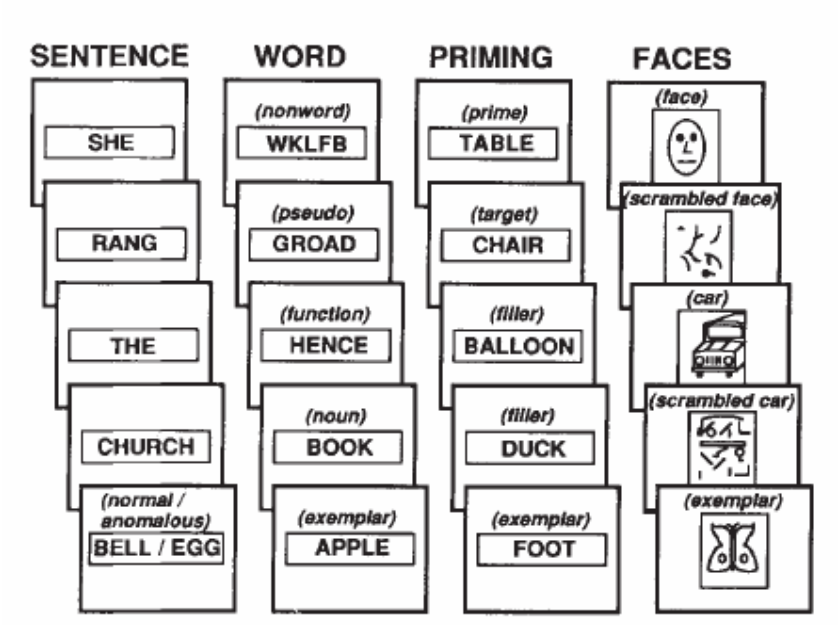
EEG/fMRI

- Both methods sensitive to relatively low frequency neural activity
  - EEG ERPs direct manifestation of electrochemical communication between neurons
  - fMRI indirect manifestation of neural activity via oxygen consumption
- Signal:Noise Considerations
  - In both methods, some brain activity easier to detect than others
  - EEG/ERPs limited by configuration of sources
  - fMRI limited by capillary density
- Phase Resetting vs. More Activity
  - Amplitude of ERP component can reflect degree of activity or degree of *phase-locked* activity
  - fMRI signal presumably more sensitive to degree of activity
  - ERP components due to phase resetting (by the stimulus) would not affect oxygen consumption so would not be detectable with fMRI
  - Non-timelocked activity in EEG won't be evident in ERP (but will in frequency analysis) but should be detectable with fMRI

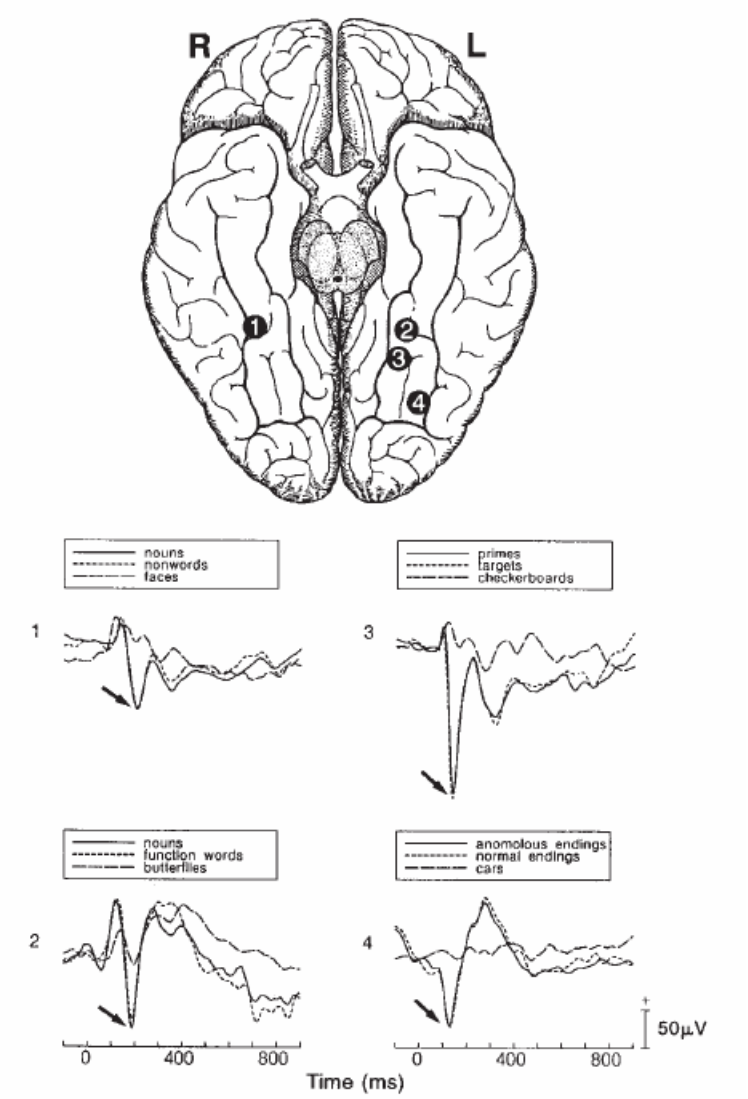
Intracranial ERPs

- In principle, same limitations of localization due to volume conduction
- In practice, fantastic localization is possible with multiple electrodes
- If locally generated ERP component
  - larger than in adjacent structures and
  - changes amplitude and polarity over short distances
  - THEN that component is generated locally
- Limitations
  - Done in epileptic patients who may have irregular brain organization
  - Electrode placement determined by clinical not theoretical issues so certain brain regions over-sampled (temporal lobe) while others under-sampled

Nobre & McCarthy (1994)



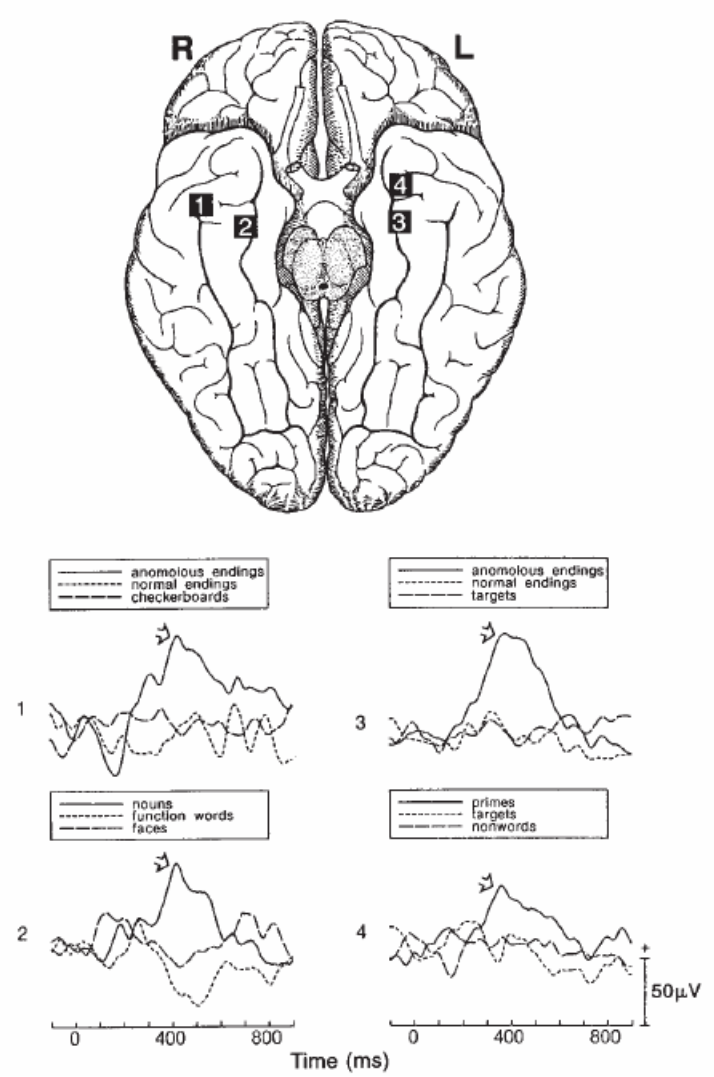
N200 in posterior fusiform cortex



- Electrode 1
  - Response to nouns and nonwords
  - No response to faces
- Electrode 2
  - Response to nouns and function words
  - No response to butterflies
- Electrode 3
  - Response to primes and targets
  - No response to checkerboards
- Electrode 4
  - Response to anomalous and normal sentence endings
  - No response to cars

P400 in anterior fusiform

- Electrode 1
  - Anomalous Endings: Big P400
  - Normal Endings: nada
  - Checkerboards: nada
- Electrode 2
  - Nouns: Big P400
  - Function Words: negativity
  - Faces: attenuated version of function words
- Electrode 3
  - Anomalous Endings: Big P400
  - Normal Endings: zilch
  - (primed) Targets: zilch
- Electrode 4
  - Primes: medium P400
  - (primed) Targets: less P400
  - Nonwords: niente



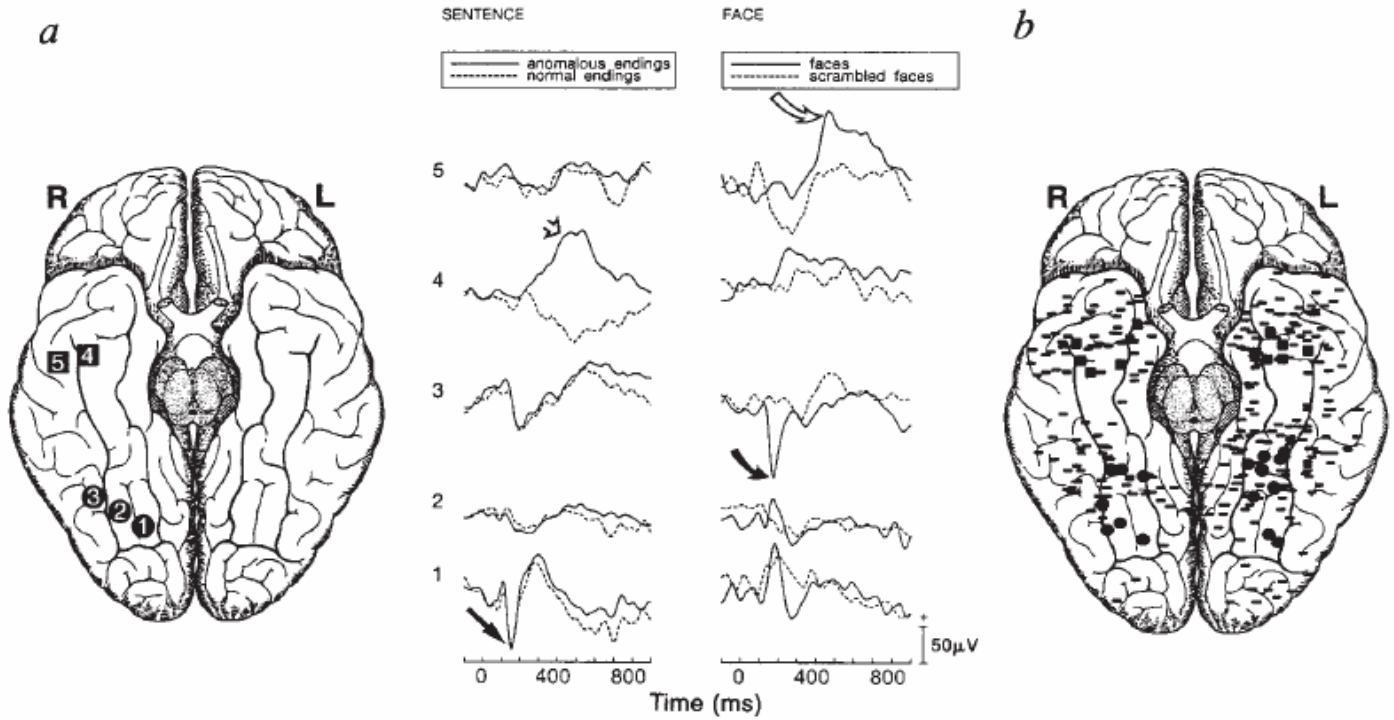


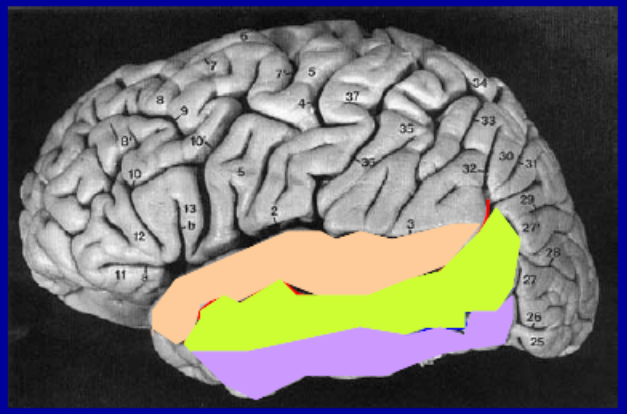
FIG. 4 Modularity and modulation of letter-string ERPs. *a*, Recordings from the sentence task are compared with recordings from the face task in a patient. A letter-string N200 (arrow) was observed at electrode location 1 in the posterior fusiform gyrus. In contrast, location 3 of the same electrod strip recorded a face N200 (curved arrow) in the inferior temporal gyrus. A letter-string P400 (open arrow) was elicited at location 4 in the anterior fusiform gyrus, while a face P400 (curved open arrow) was elicited at location 5 in the anterior inferior temporal gyrus. The letter-string N200 was not sensitive to priming in sentences, whereas the letter-string P400 was markedly reduced. As in previous reports[14,24], the face N200 and P400 were specific to faces. The sensitivity of the face P400 to context is at present unknown. *b*, Electrode locations of letter-string N200 (●), letter-string P400s (■), and locations where letter-strings did not elicit selective ERPS (−) are shown for all patients. Mean Talairach locations[29] were: N200 left, X=G.18, Y=Ic.05; N200 right, X=H.03, Y=rc.00; P400 left, X=E.21, Y=Ib.46; P400 right, X=E.43, Y=rc.17.

Inferior Temporal Lobe Anatomy…

Superior and Inferior Temporal Sulci

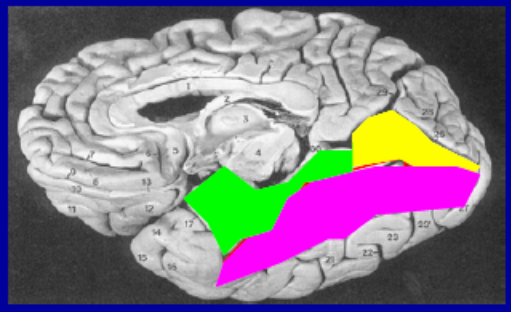
Superior Temporal Sulcus (red)
-divides superior temporal gyrus (peach) from middle temporal gyrus (lime)

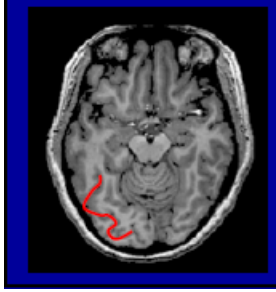
Inferior Temporal Sulcus (blue)
-not usually very continuous
-divides middle temporal gyrus from inferior temporal gyrus (lavender)

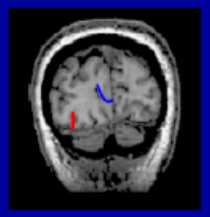


Collateral Sulcus

-divides lingual (yellow) and parahippocampal (green) gyri from fusiform gyrus (pink)







McCarthy et al. (1995)

- Recorded ERPs from intracranial electrodes as epileptic patients read sentences
- 8-12 word sentences, half of which ended as expected and half of which ended unexpectedly

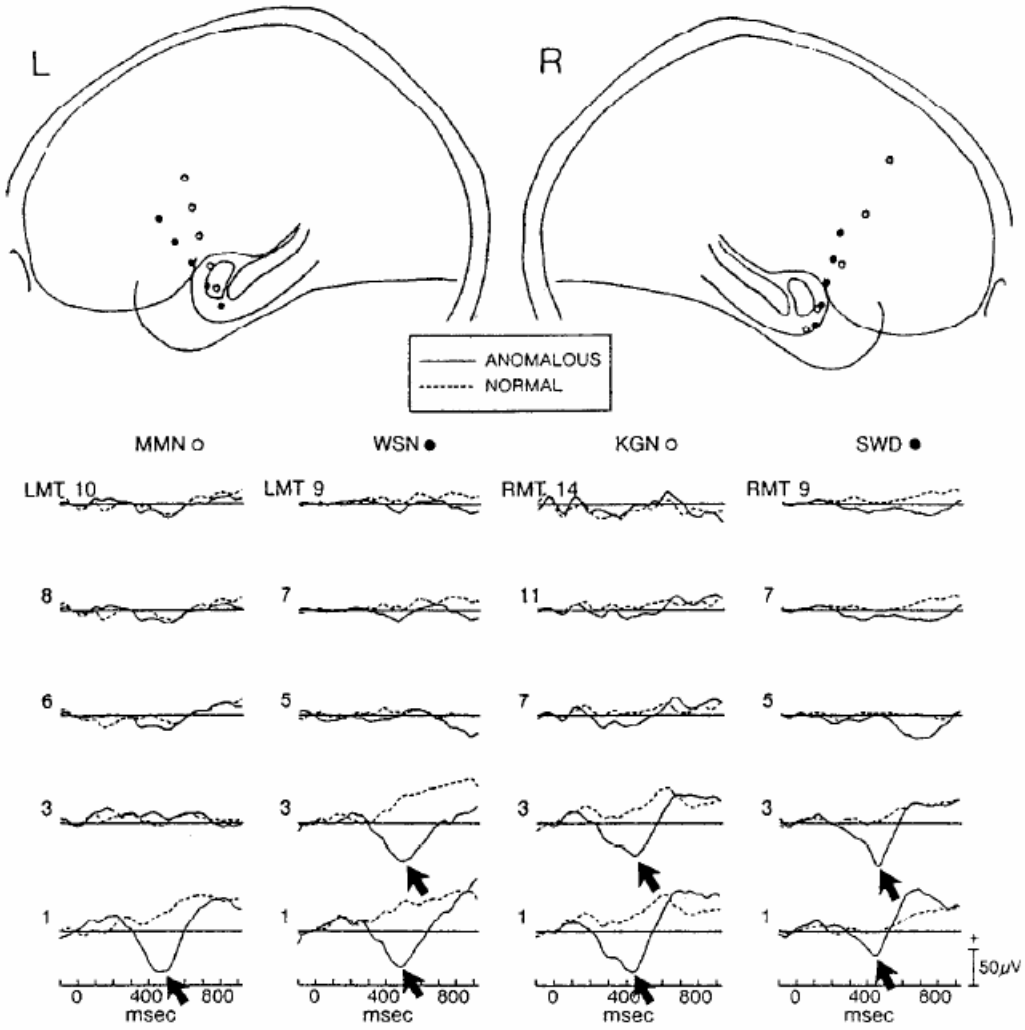
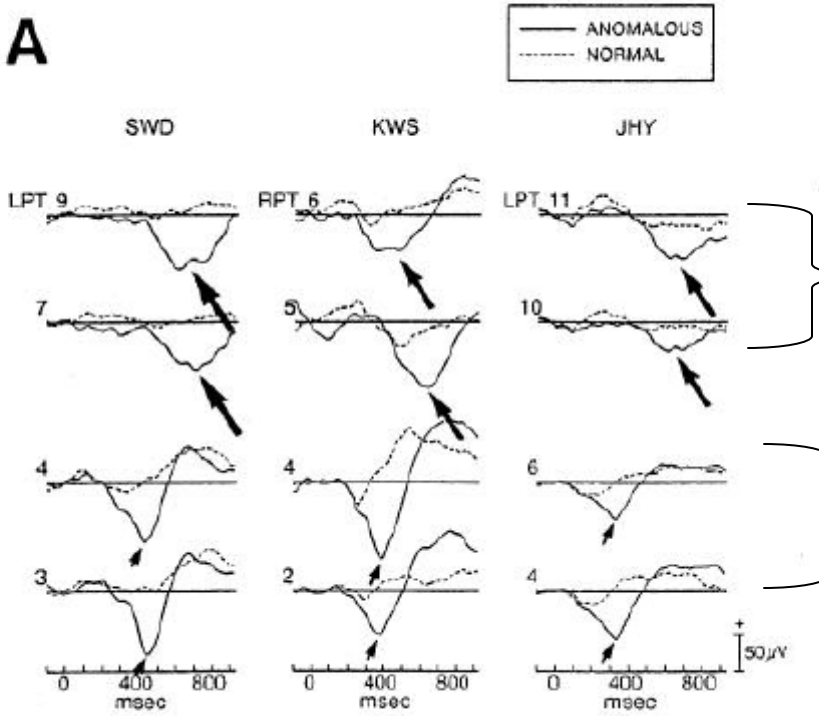


Figure 1. ERPs elicited by ANOMALOUS (*solid line*) and NORMAL sentence-ending words and recorded from electrodes along the left (*LMT*) or right midtemporal (*RMT*) probes are shown superimposed. Each column represents data from a single patient with ERPs from the most superior electrode at the top of each column. This same electrode order is maintained in the inset overlays taken from the atlas of Talairach and Szikla (1967) in which the schematic outlines of the hippocampus and amygdala are shown. Unless otherwise noted, the waveforms in this and all following figures comes from right-handed patients. The data from patients MMN (*open circle*) and WSN (left-handed, *closed circle*) were obtained from the left hemisphere, and the data from patients KGN (*open circle*) and SWD (*closed circle*) were obtained from the right hemisphere. The *black arrows* indicate the AMTL N400s that were distributed focally near the amygdala.

AMTL-N400 vs. Hippocampal P300

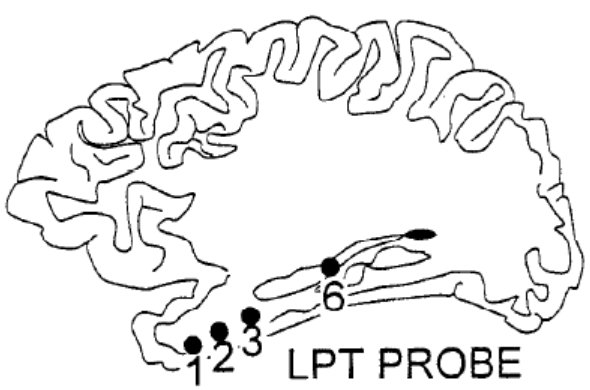


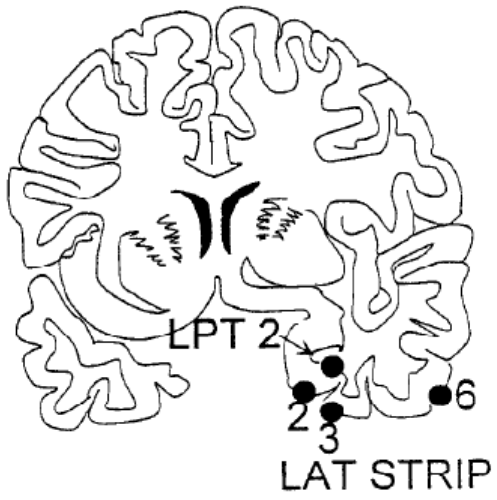
Electrodes within the hippocampus

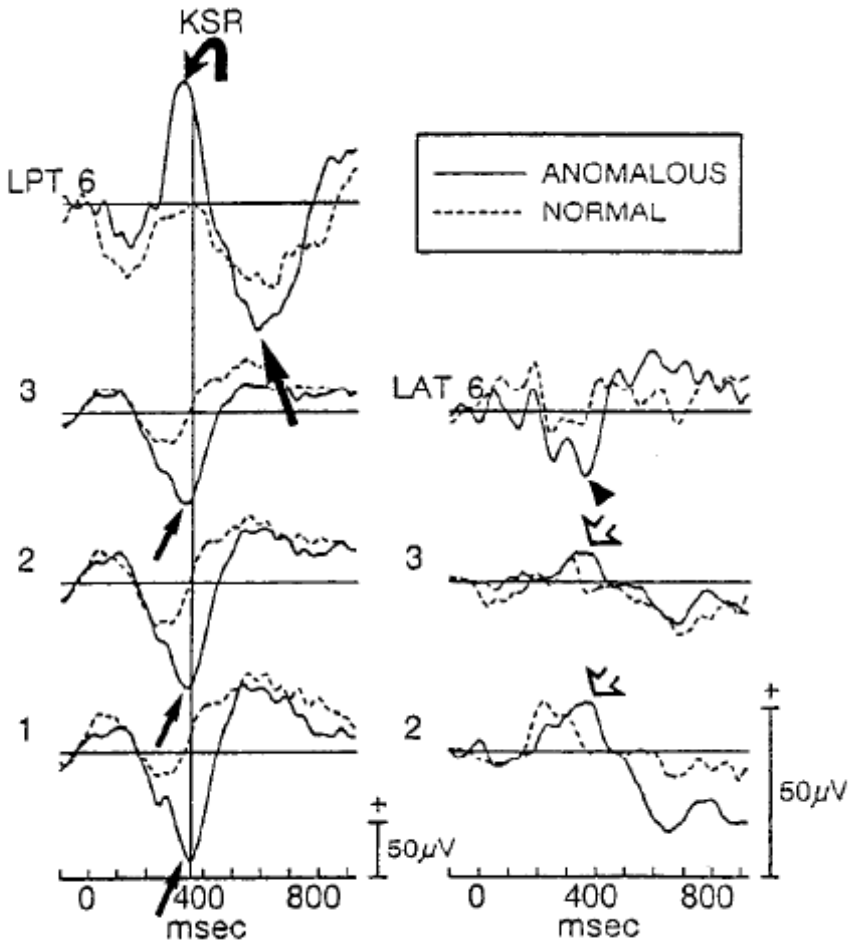
Electrodes near the amygdala

- Hippocampal P300s elicited in a variety of categorization tasks
- Distinct from AMTL-N400 in timing and location

LPT 3 – lateral amygdala, LPT2 – collateral sulcus, LPT 6 – hippocampus
LAT 2 & 3 – collateral sulcus, LAT 6 – inferior temporal gyrus







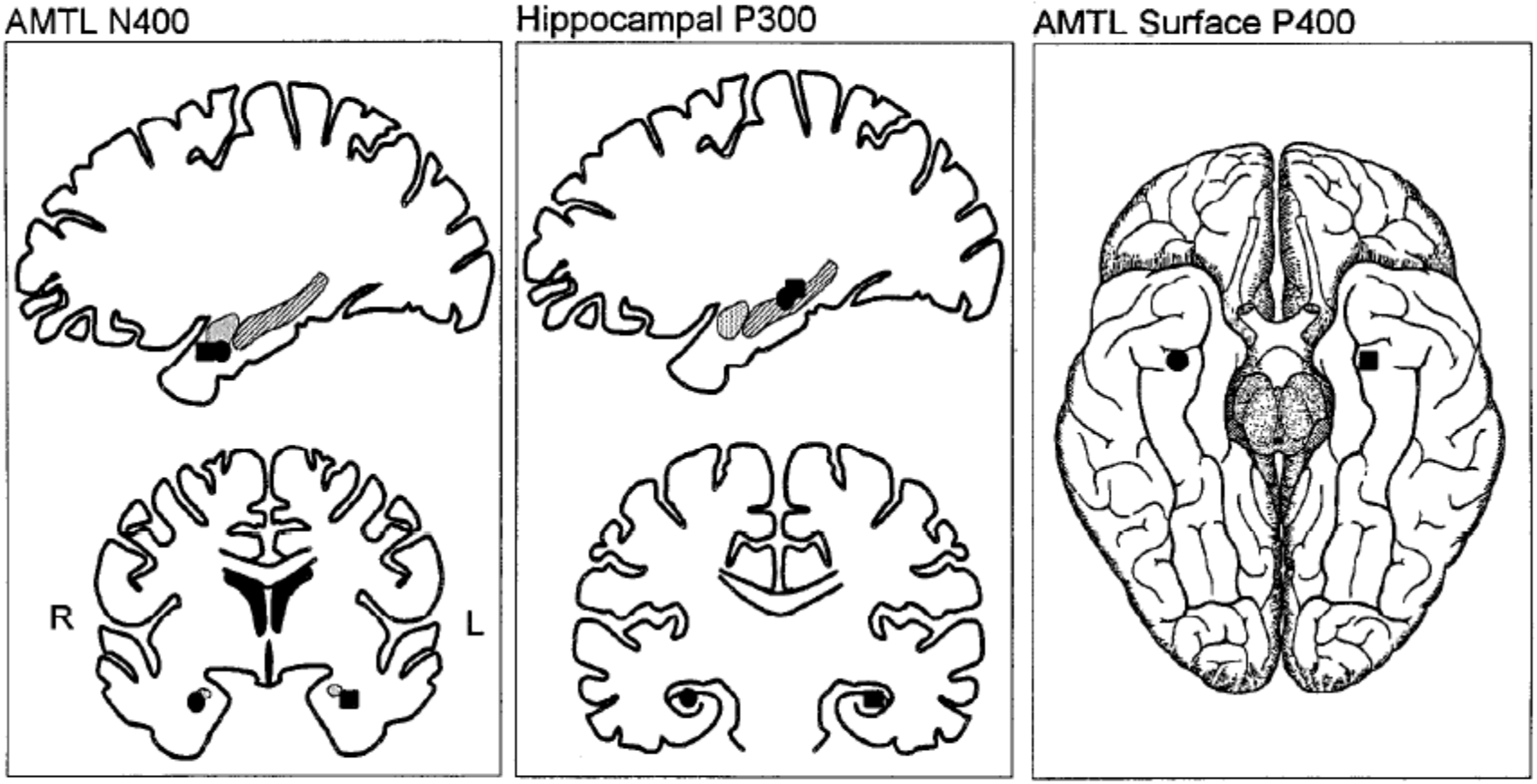


Figure 10. Median Talairach locations for the ERPs discussed in the text are depicted. Left and right hemisphere locations are indicated by *squares* and *circles,* respectively. Locations of ERPs recorded from depth probes are shown using sagittal and coronal planes. Locations of cortical surface ERPs are shown on the inferior surface of the brain. AMTL N400, shown in the *left column,* was located in the anterior border of the amygdala. Hippocampal P300, shown in the *middle column,* was located within the midbody of the hippocampus. The cortical surface AMTL P400, shown in the *right column,* was located laterally to the colateral sulcus in the anterior fusiform gyrus.

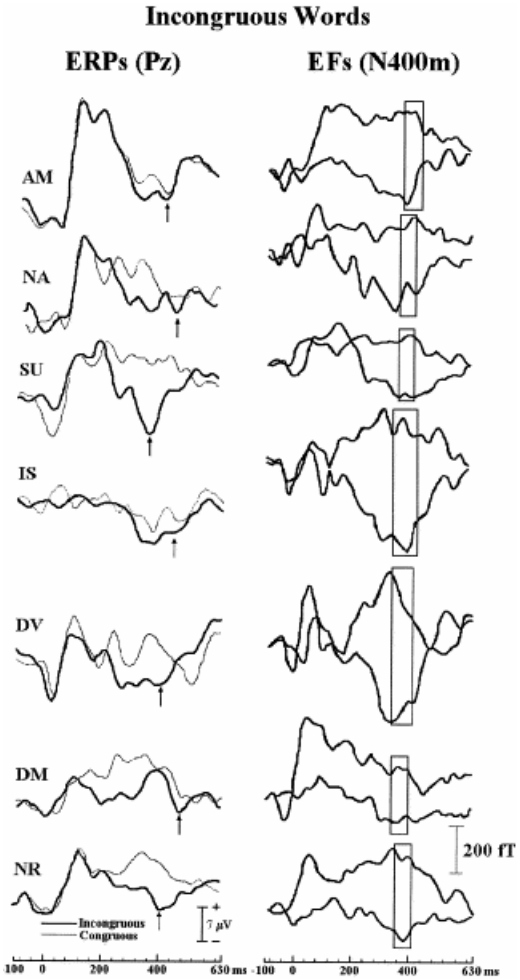
Summary

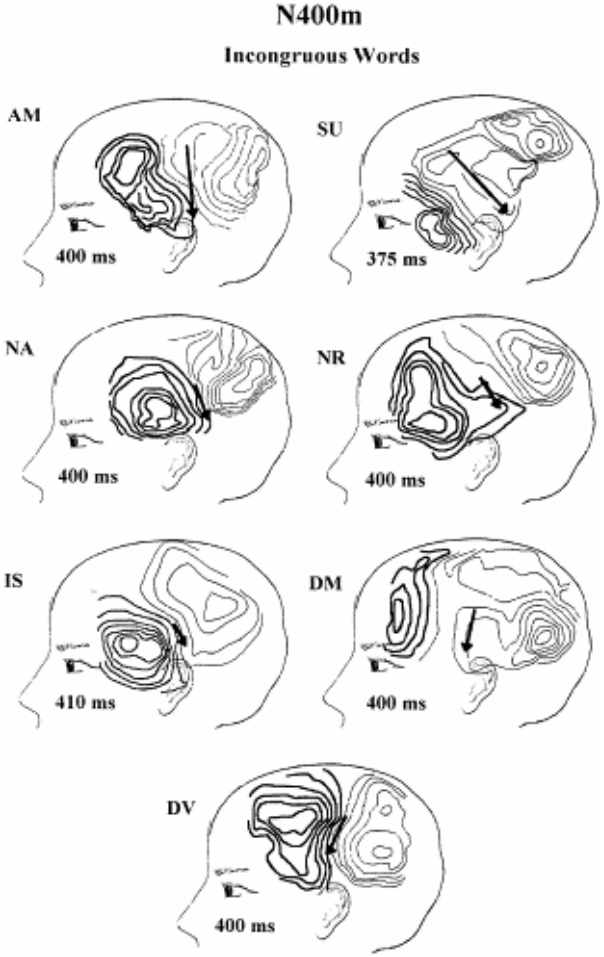
- AMTL-N400 recorded from medial temporal lobe sites
  - Evident in amygdala and adjacent white matter
  - Largest just anterior to hippocampus
- Different activity in hippocampus proper
- P400 recorded from anterior fusiform gyrus and parahippocampal gyrus
- Small amplitude N400 recorded from lateral sites on the inferior & middle temporal gyri
- Generated in cortex near collateral sulcus, especially anterior fusiform and parahippocampal gyri

MEG

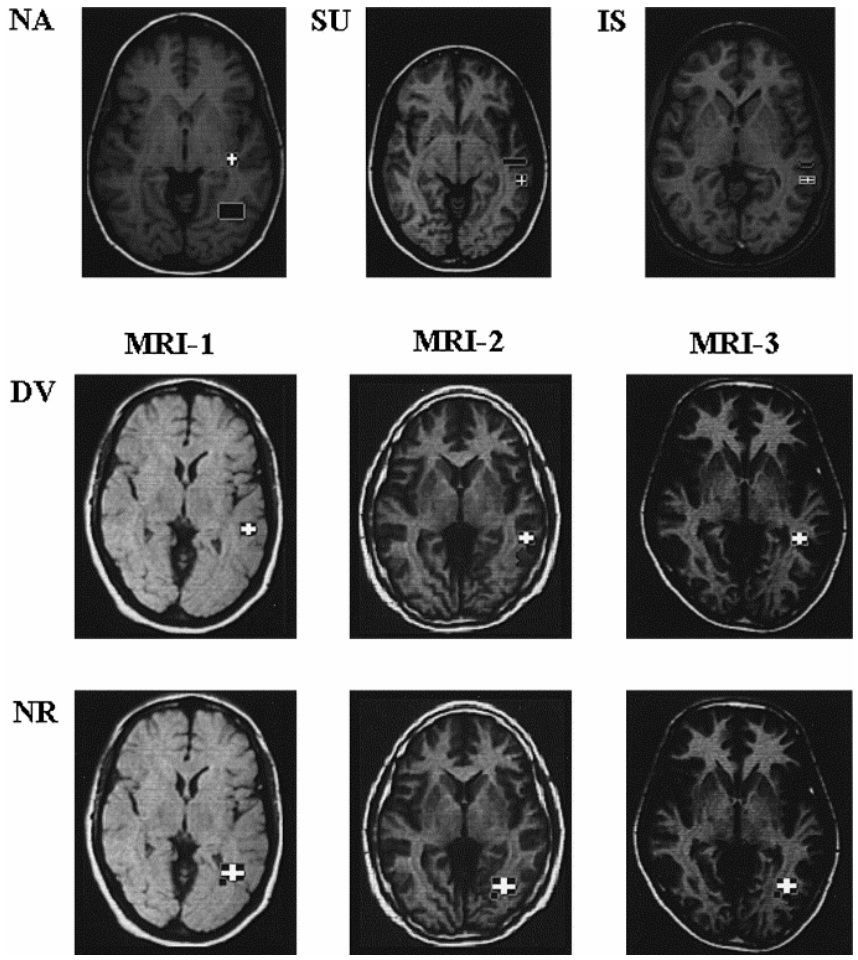
- Impact of sentence context manipulation tested in 4 studies
  - Simos et al. (1997)
  - Kwon et al. (2005)
  - Helenius, et al. (1998)
  - Helenius, et al. (2005)

Simos, et al. (1997)

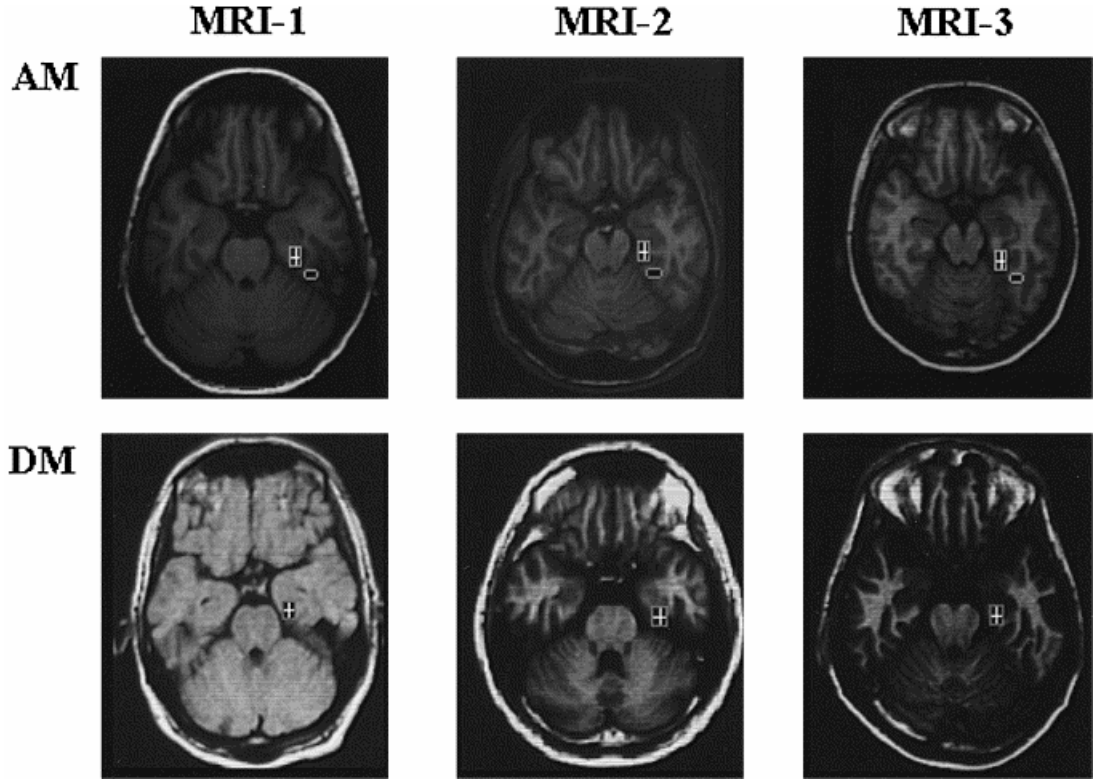




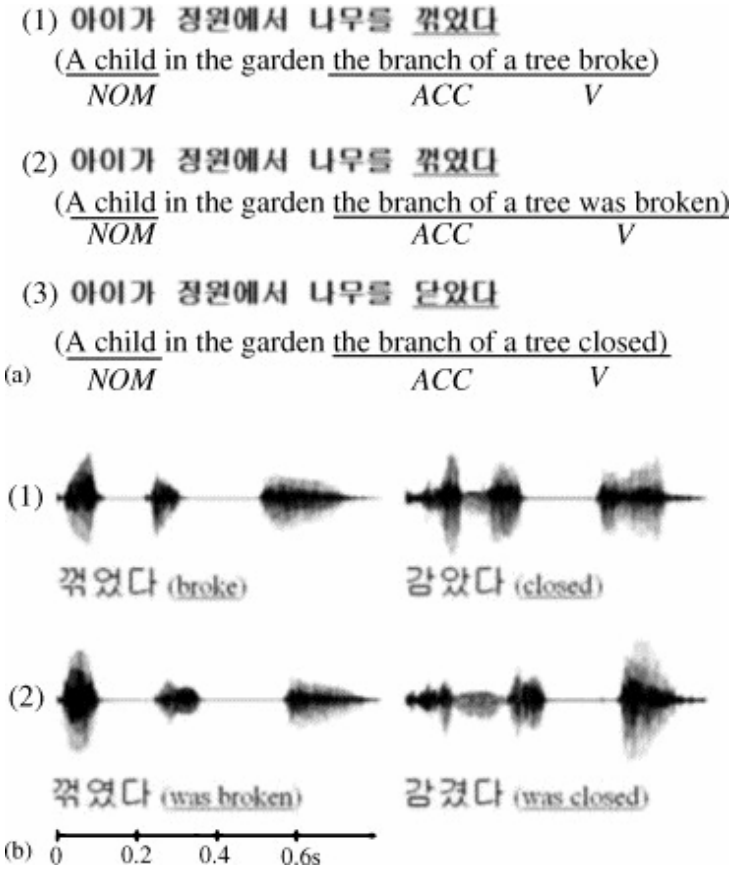
Middle Temporal Gyrus



Hippocampus, Parahippocampal Gyrus

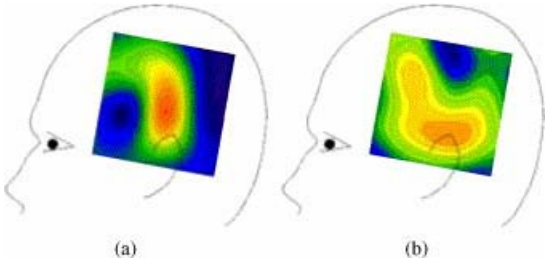


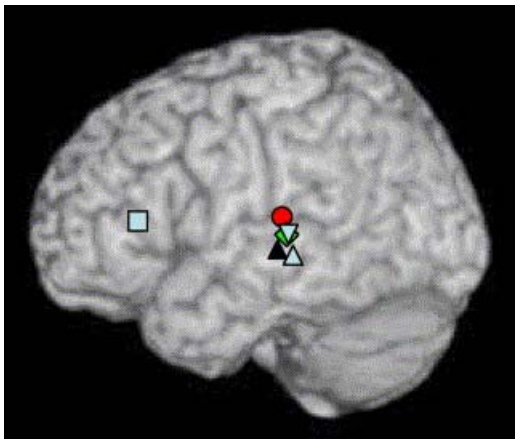
Kwon, et al. (2005)



Kwon, et al. (2005)

400 ms 600 ms





Semantic Violation

- ECD for 400 ms dipole indicated by green diamond (underneath blue triangle)
  - Superior temporal gyrus (just inferior to auditory cortex)
- ECD for 600 ms dipole indicated by black triangle
  - Middle temporal gyrus

Helenius et al. (1998)

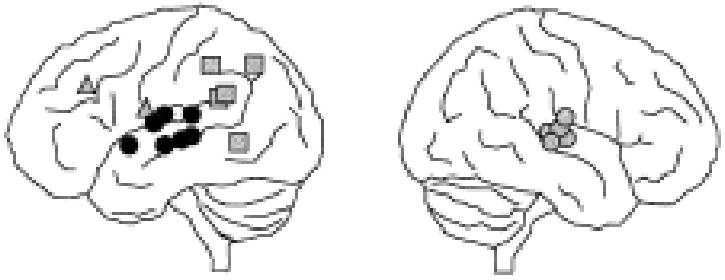
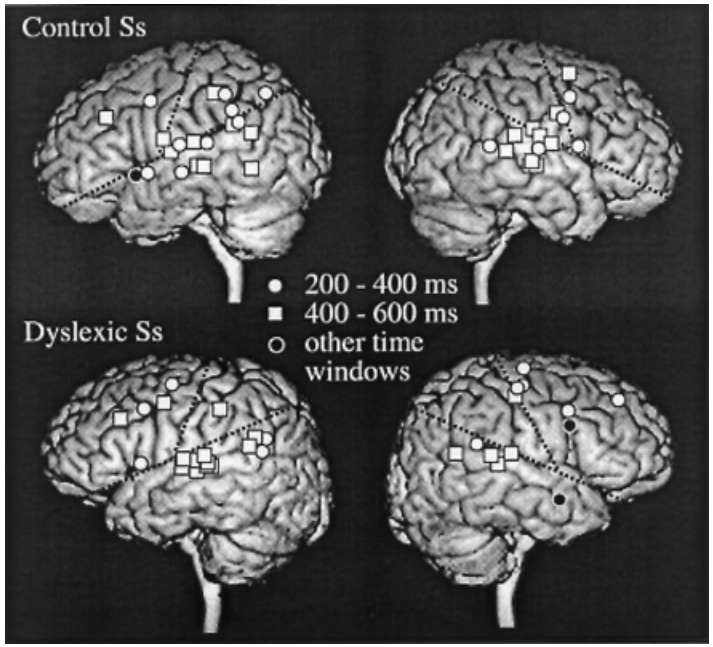


Fig. 2 Cortical loci displaying a reliable congruity effect combined from all subjects. Sources located in the left superior temporal cortex are plotted as black dots; for the one subject with two sources in this region, the later activation is shown in white. Two subjects showed a congruity effect in the left frontal lobe instead (grey triangles), and five subjects had an additional source around the posterior end of the sylvian fissure (grey squares). In five subjects the posterior end of the right superior temporal gyrus also produced signals sensitive to sentence congruity (grey circles). Dipoles were located on the schematic brain with the help of individual MRI (available for seven subjects) and/or using sources of auditory and hand somatosensory responses as functional landmarks (see Method). For easy visualization, dipoles were projected to the surface of the schematic brain; the sources represented by black dots were located on average 16 mm below the outer surface of the brain. The sources displayed were required to have a maximum amplitude exceeding 5 nAm and to show a difference of at least twice the prestimulus noise level between responses to anomalous (and/or phonological) and probable sentence endings.

- Left superior temporal cortex
  - All subjects
- Inferior frontal lobe
  - 2 subjects
- Temporal-parietal junction
  - 5 subjects
- RH superior temporal gyrus
  - 5 subjects

Helenius & colleagues (2005)



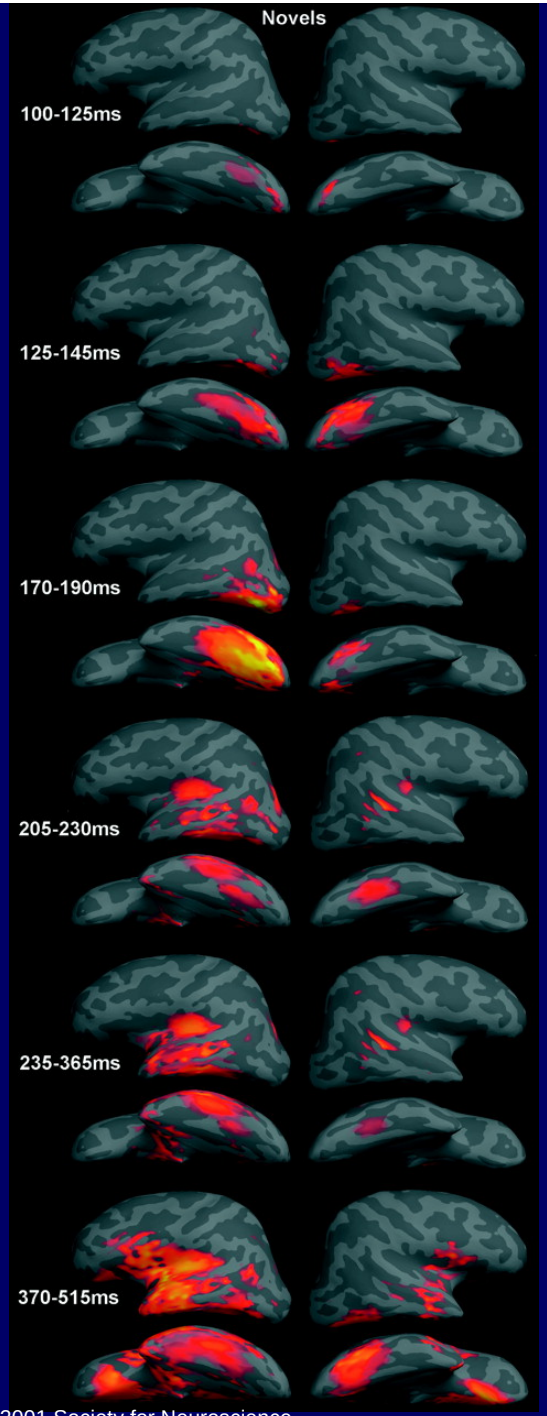
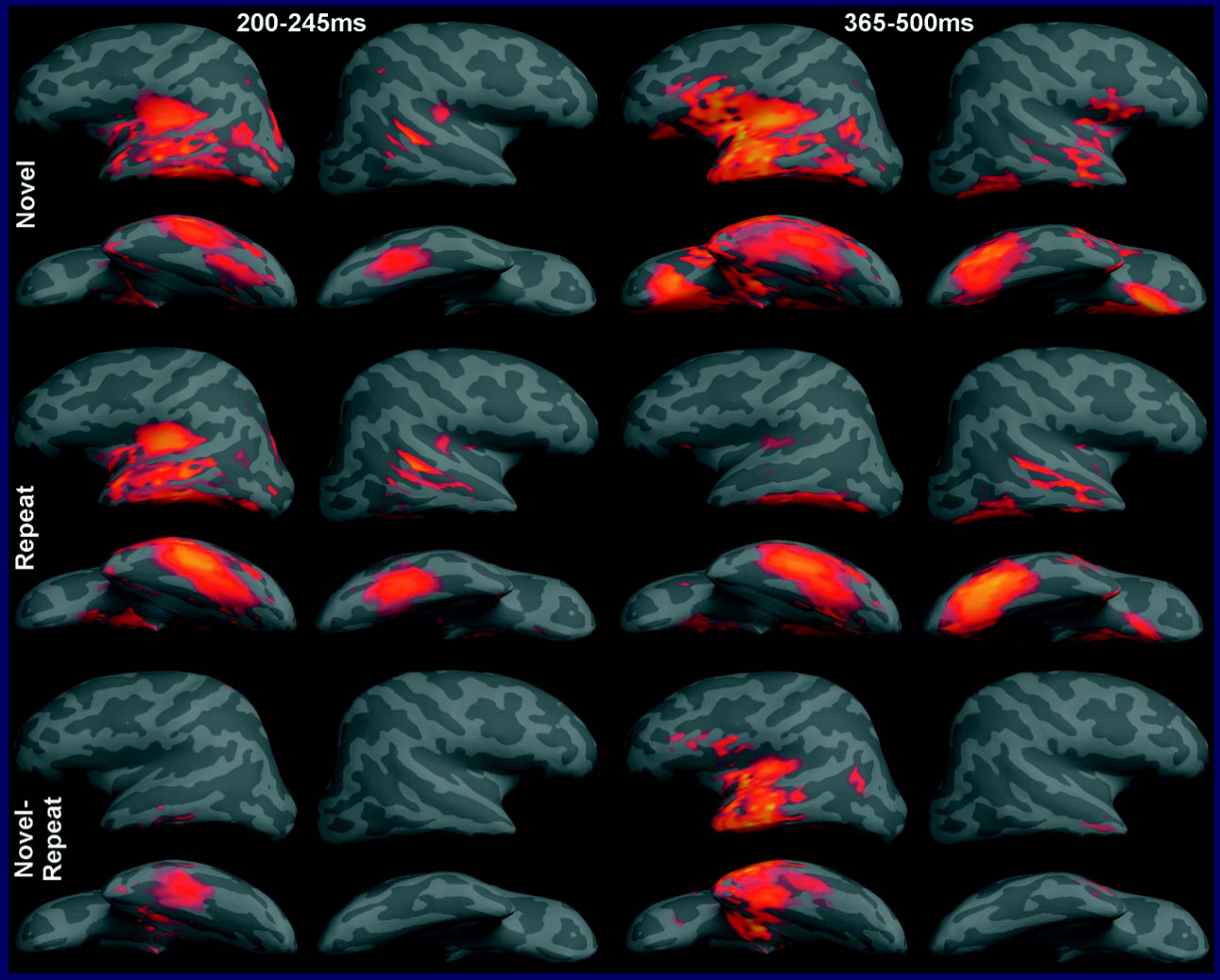


Figure 2.

Dhond, R. P. et al. J. Neurosci. 2001;21:3564-3571

Figure 3.



Dhond, R. P. et al. J. Neurosci. 2001;21:3564-3571

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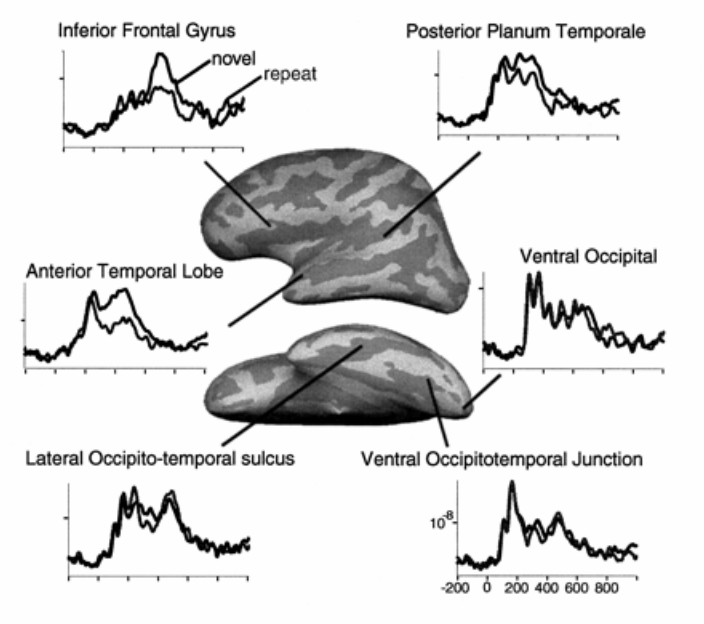
Tracing the repetition effects through the brain…



- Occipital regions active early
  - Not modulated by repetition
- Anterior temporal lobe regions active slightly later
  - Modulated by repetition
- Inferior frontal gyrus activation shortly after that
  - Modulated by repetition