Language and the Brain: Evidence from Dementia

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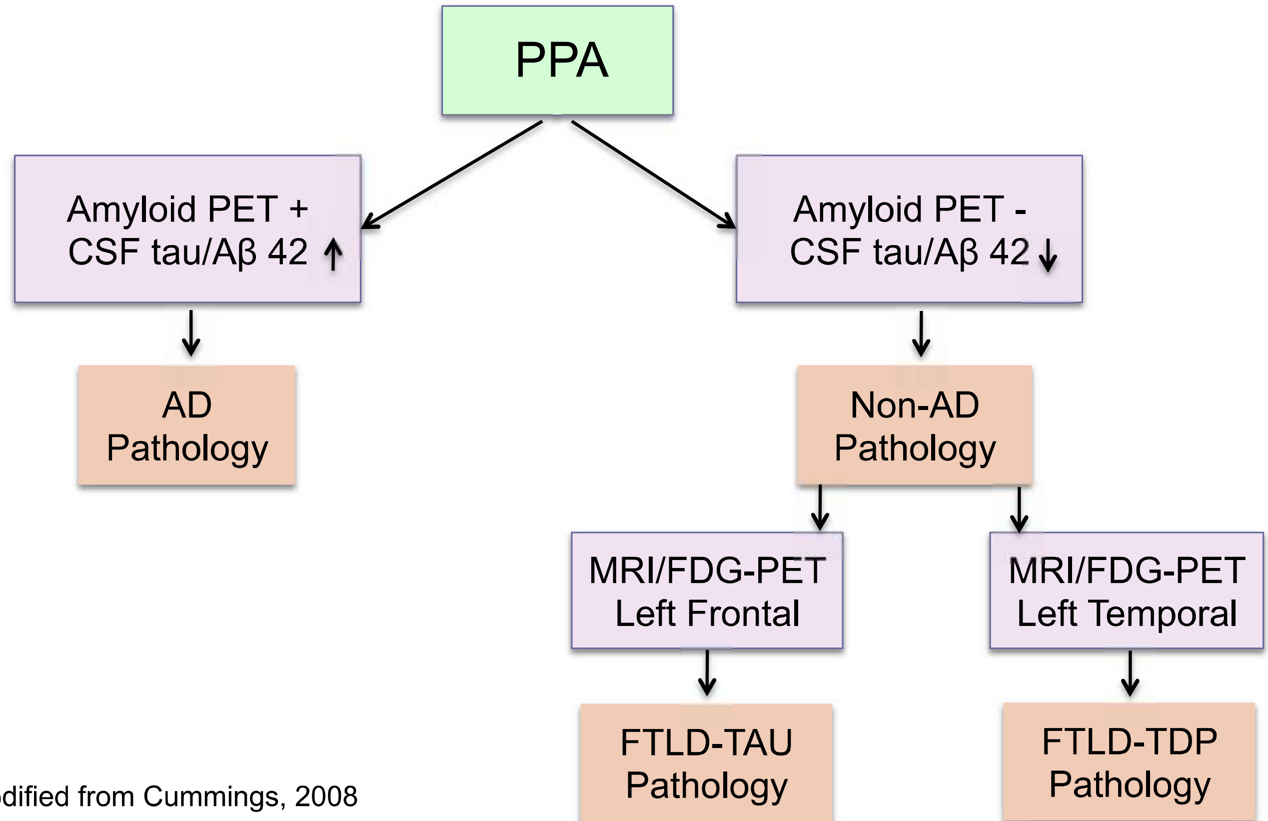
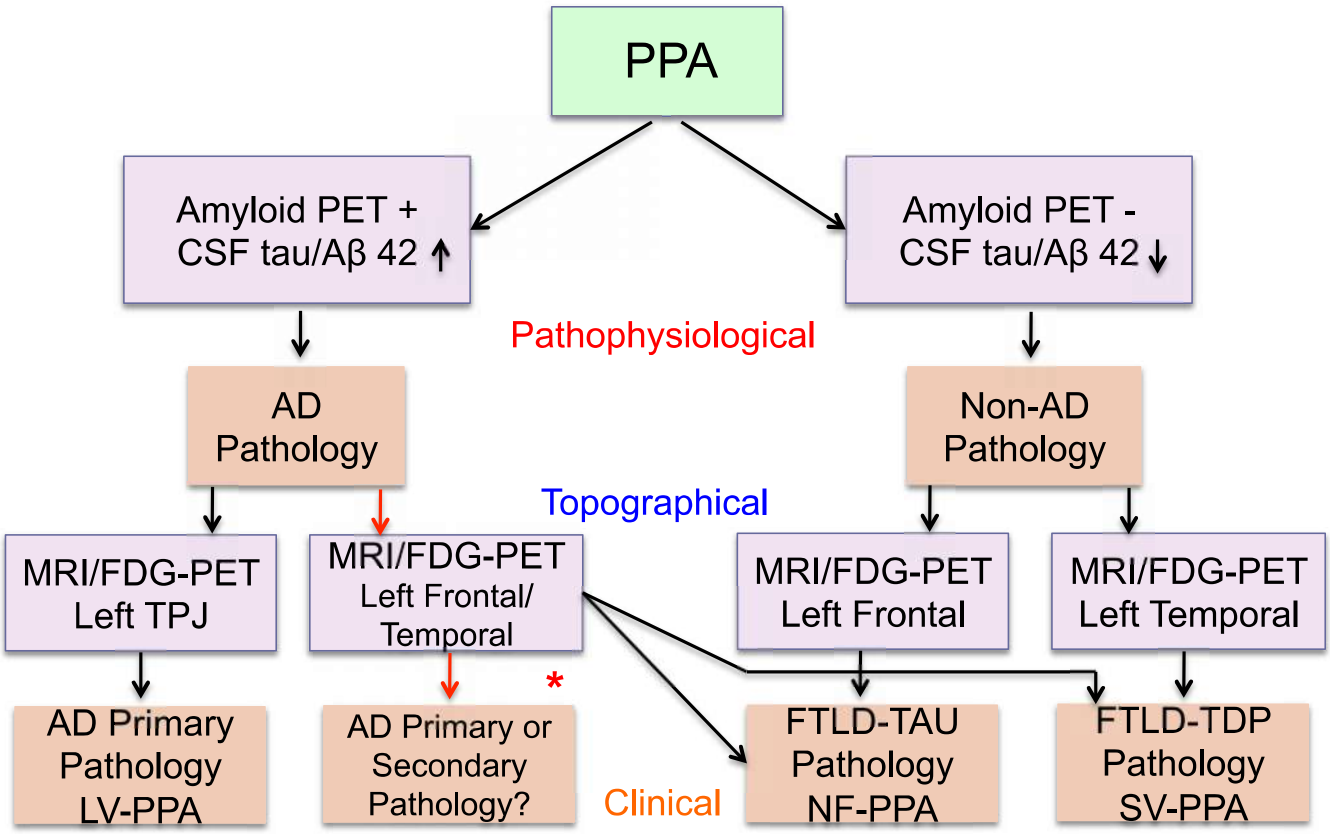
PPA in the Age of Biomarkers



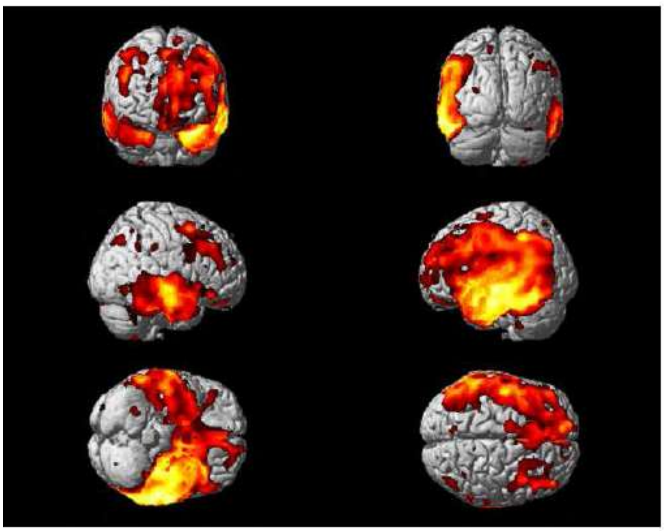
Modified from Cummings, 2008

Diagnosis of PPA Using Biomarkers

Modified from Cummings, 2008



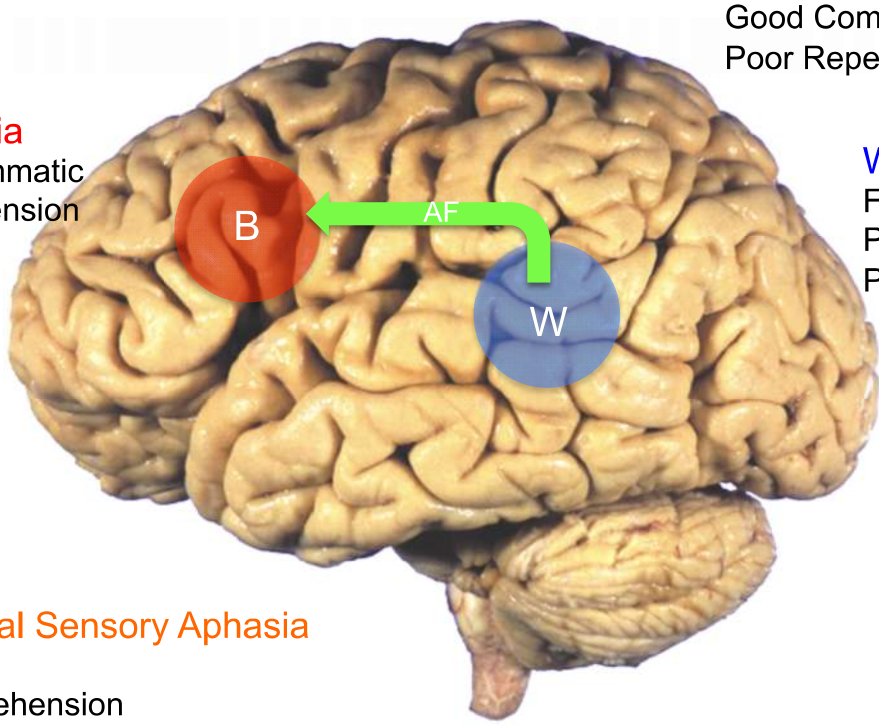
Evidence for Dual-Pathway Models of Language: Functional Neuroanatomy of Speech Production and Comprehension



Language and the Brain Circa 1885

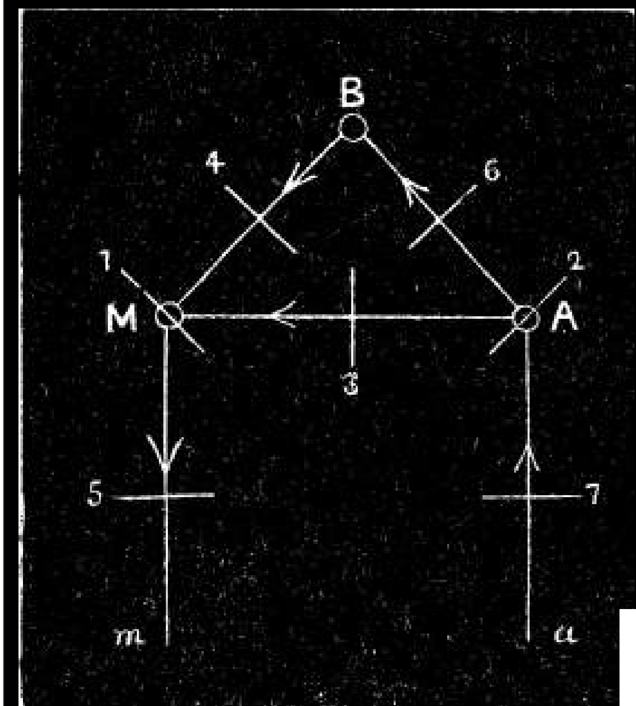
Broca's Aphasia
Nonfluent/Agrammatic
Good Comprehension
Poor Repetition

Transcortical Sensory Aphasia
Fluent
Poor Comprehension
Preserved Repetition

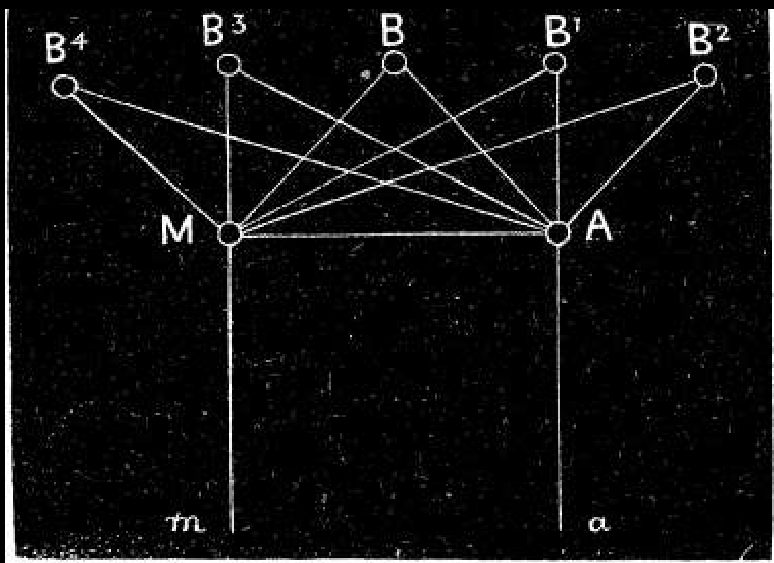


Conduction Aphasia
Fluent
Good Comprehension
Poor Repetition

Wernicke's Aphasia
Fluent
Poor Comprehension
Poor Repetition



Lichtheim, 1885

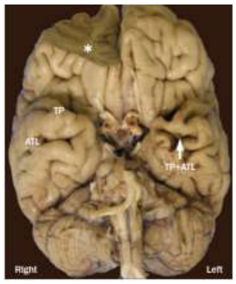


We shall further have to deal with the course of the inner and outer commissures of M and A. Though in the diagram B is represented as a sort of centre for the elaboration of concepts, this has been done for simplicity's sake; with most writers, I do not consider the function to be localised in one spot of the brain, but rather to result from the combined action of the whole sensorial sphere. Hence the point B should be distributed over many spots; and the commissures M B and A B, would not form two distinct and separate paths, but consist of converging radiations from various parts of the cortex to the points A and M (see Diagram 7, p. 478). This admission

On the relationship between senile cerebral atrophy and aphasia*[1]

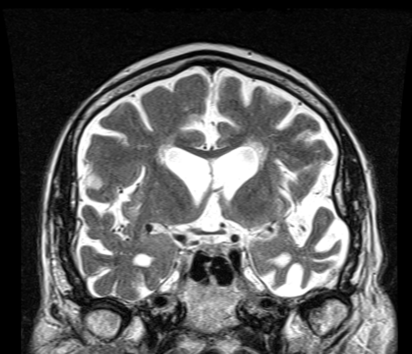
1892

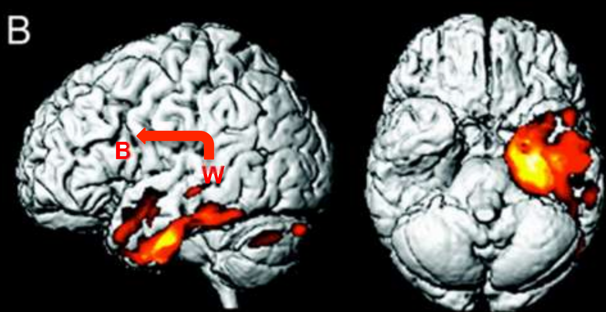
Translated by
D. M. GIRLING and G. E. BERRIOS

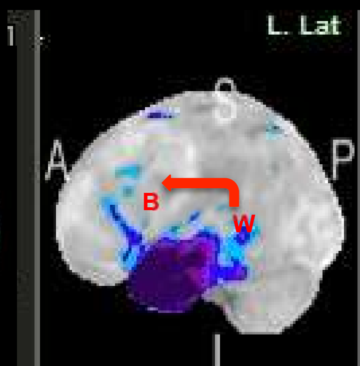


- Progressive fluent aphasia, with impaired comprehension and naming
- Preserved motor speech and repetition
- Language profile similar to transcortical sensory aphasia (Wernicke/Lichtheim)
- ”…pronounced atrophy of the gyri of the left hemisphere, particularly of the left temporal lobe…the origin of the disturbance is in the second and third left temporal gyri.”
- “…it seems right to state that a more or less sharply *circumscribed* type of aphasia may exist at a particular point in time and be related to *circumscribed*, perhaps simple atrophic, brain changes.”

Semantic Dementia or Semantic Variant of Primary Progressive Aphasia (svPPA)

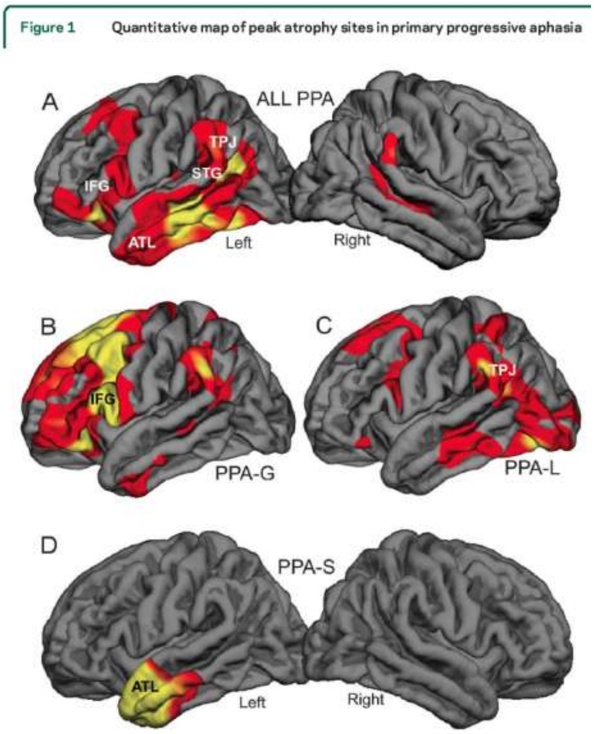




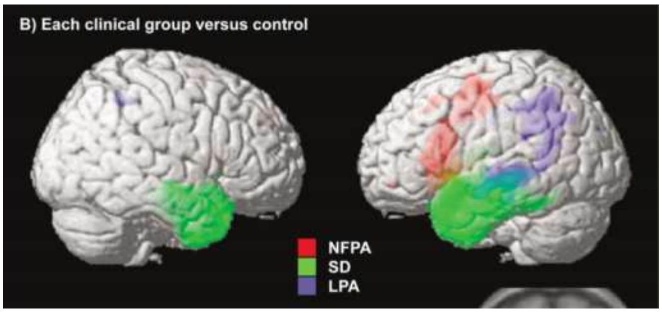


Comprehension Impairment without Damage to Wernicke’s area

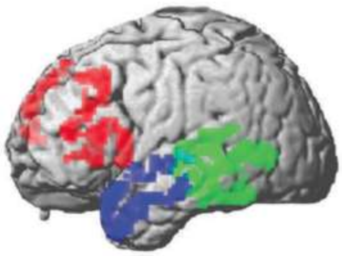
PPA Variants and the Language Network



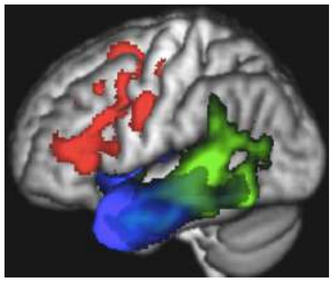
Mesulam, 2013



Gorno-Tempini et al., 2004

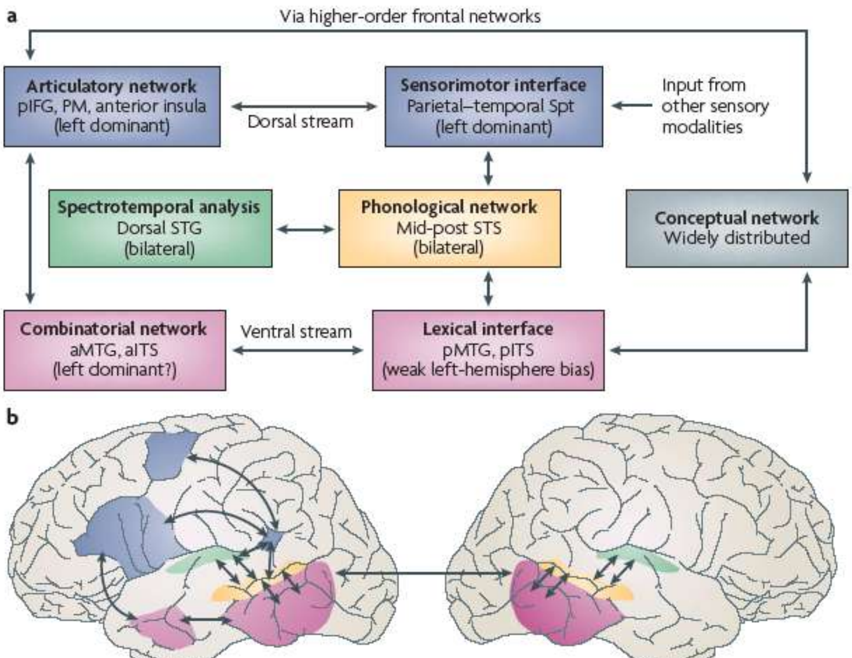


Grossman, 2010



Henry, Wilson, & Rapcsak, 2013

Dual-Pathway Model of Language

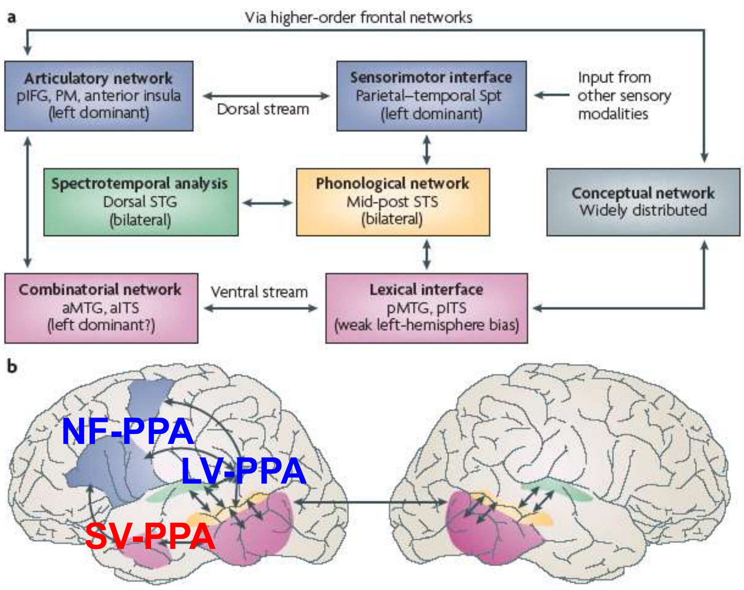


Hickok & Poeppel, 2007

Dorsal Pathway: mapping phonological representations to articulatory networks for **speech production** (sensory-motor integration), also implicated in **phonological short-term memory** and phonological awareness

Ventral Pathway: mapping phonological representations to semantic networks for **speech comprehension**

PPA Variants within the Dual-Pathway Model of Language



Hickock & Poeppel, 2007

Dorsal Pathway: Grammar, Motor Speech, Phonology,

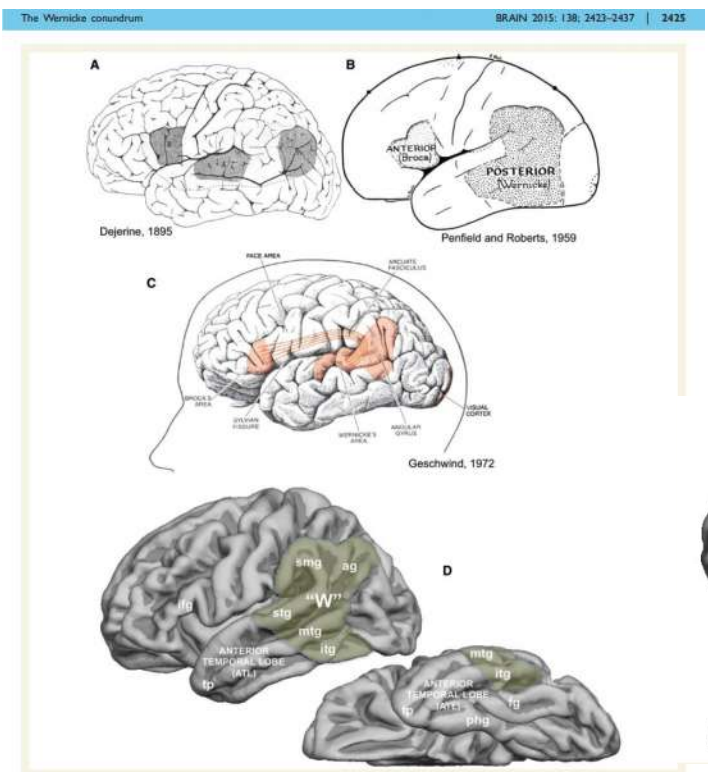
Nonfluent/Agrammatic PPA: Broca's
Logopenic Variant PPA: Conduction
Good Comprehension

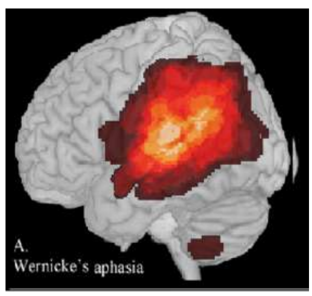
Ventral Pathway: Semantics

Semantic Variant PPA: Transcortical Sensory
Poor comprehension

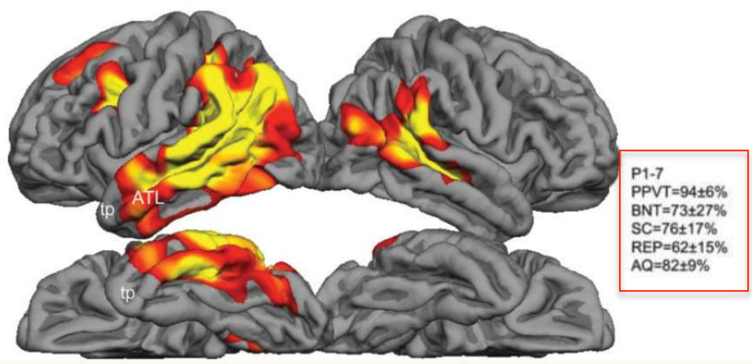
PPA variant of Wernicke's aphasia?
Fluent
Poor repetition
Poor comprehension

Is Wernicke's Area Critical for Language Comprehension?



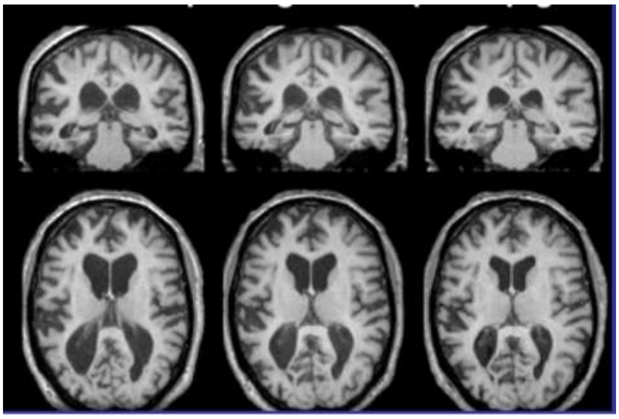


Robson et al., 2012



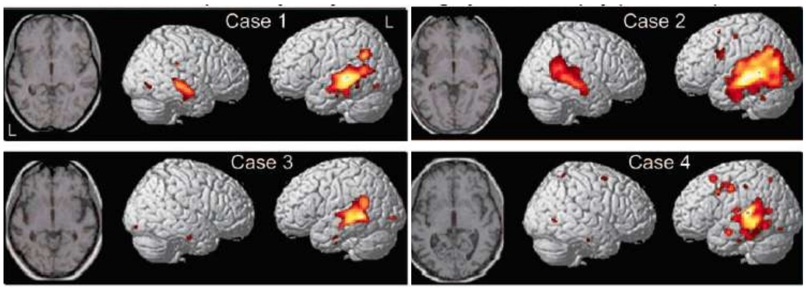
Mesulam, 2015

Logopenic Variant PPA: Neuroimaging



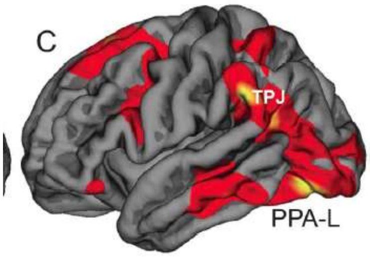
Rohrer et al., 2009

Structural MRI

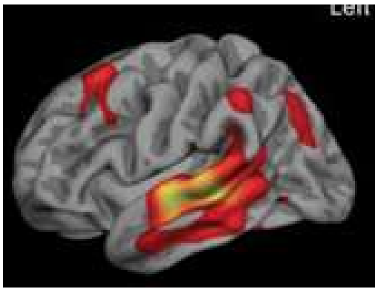


Gorno-Tempini et al., 2008

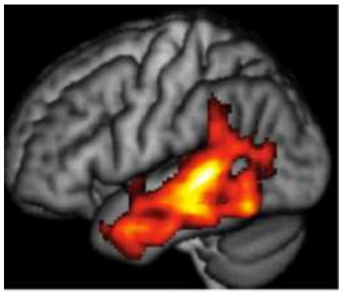
VBM/Cortical Thickness



Mesulam, 2013

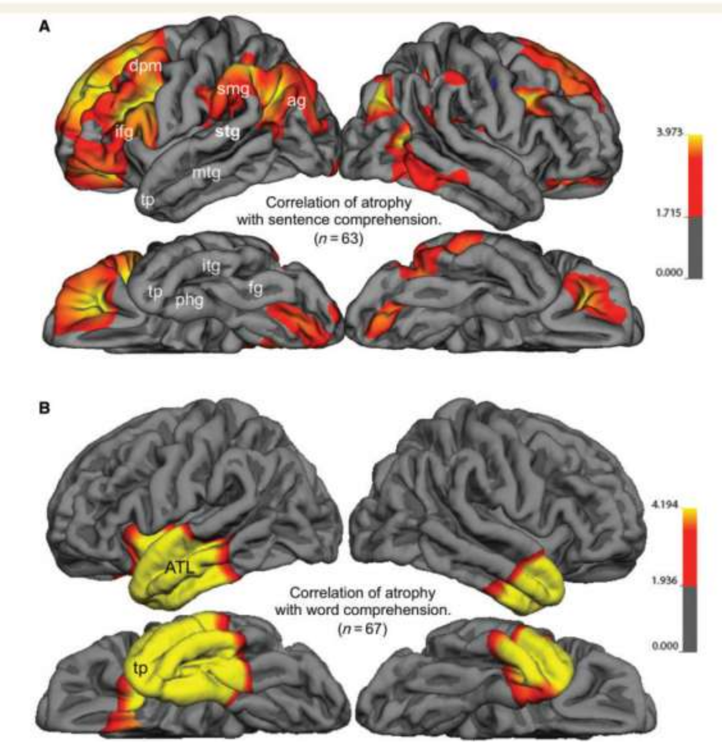


Dickerson, 2011



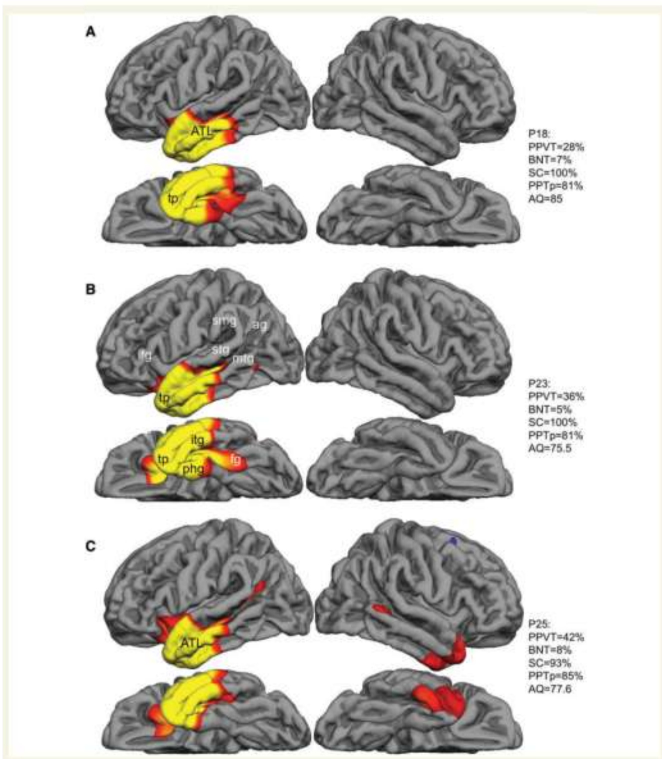
Wilson et al., 2010

Distinct Neural Correlates of Sentence vs. Single Word Comprehension in PPA



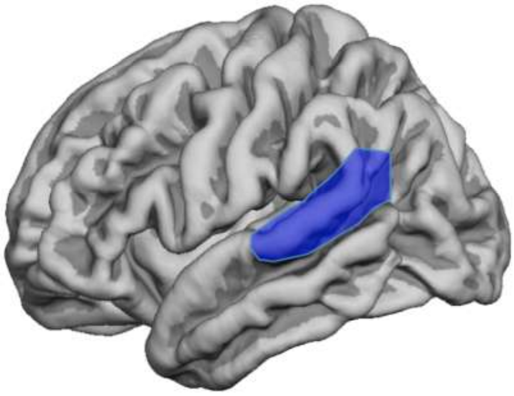
Mixed Group

Mesulam, 2015



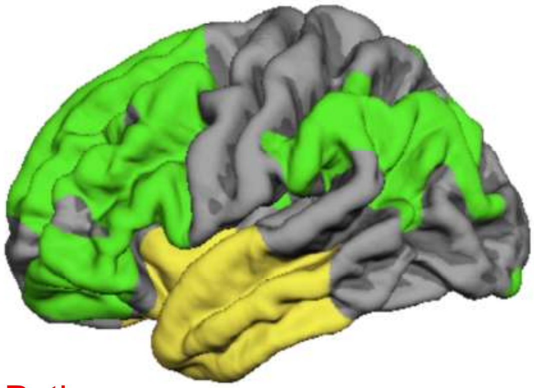
svPPA

Stroke



Classic location of Wernicke's area, considered critical for both word and sentence comprehension.

Dorsal Pathway



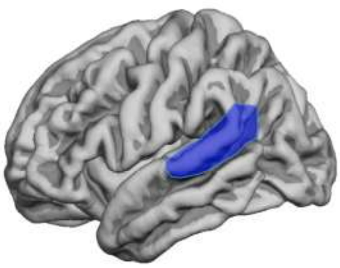
Ventral Pathway

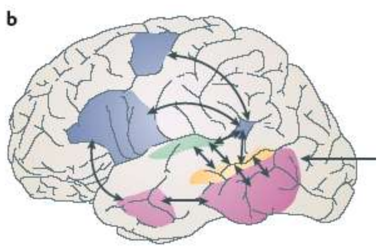
Investigation in PPA shows that sentence comprehension (green) and word comprehension (yellow) are controlled by different areas. There is only partial overlap with the classic location of Wernicke's area.

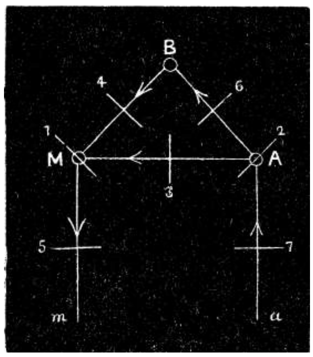
Based on Mesulam, 2015

Wernicke's Aphasia: Dual Deficit/Double Disconnection Involving Dorsal (Speech Production, Repetition, Phonological STM, Sentence Comprehension) and Ventral Language Pathways (Single Word Comprehension)
Severe Damage to Phonological Representations in STG/STS (Wernicke's area) Critical for Both Speech Production and Comprehension

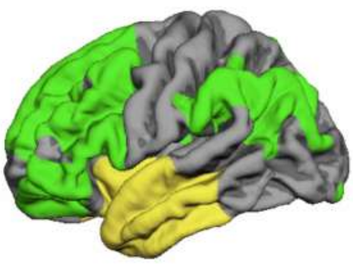
STG/STS Phonological Hub or Interface

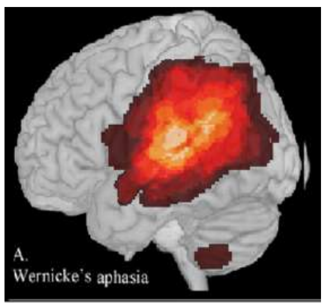






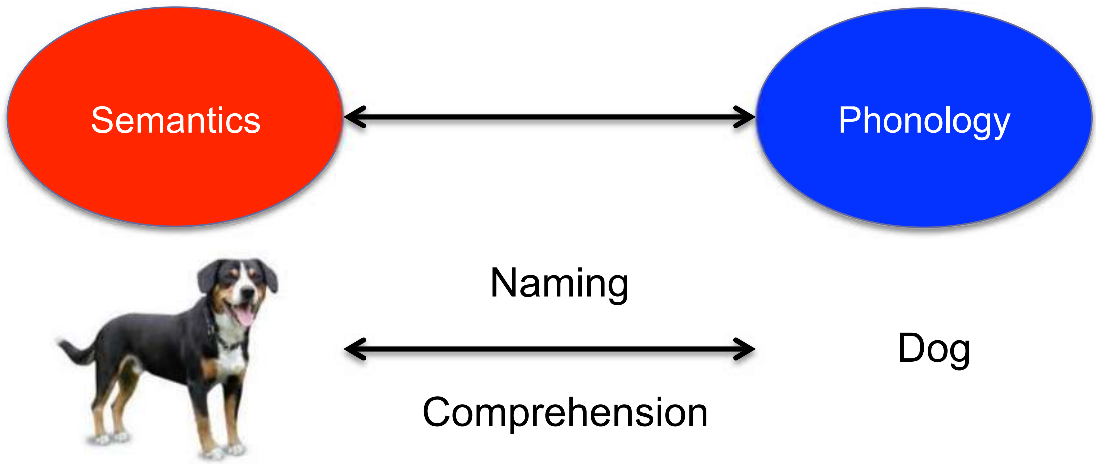
Sentence Comprehension



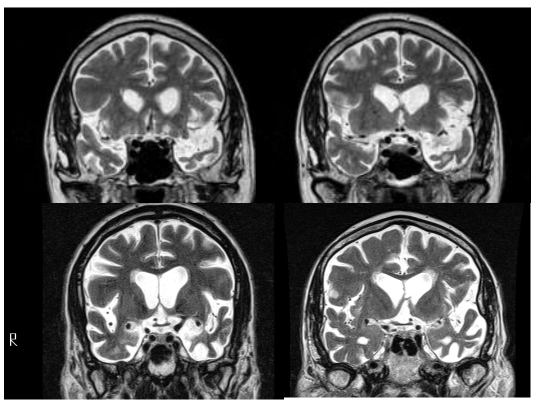


Single Word Comprehension

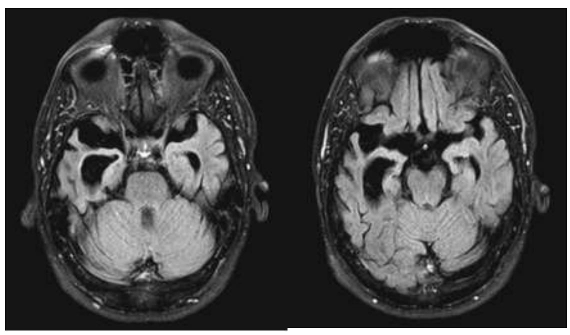
Evidence Regarding the Organization of Lexical-Semantic Knowledge in the Brain and the Interaction between Words and their Meanings



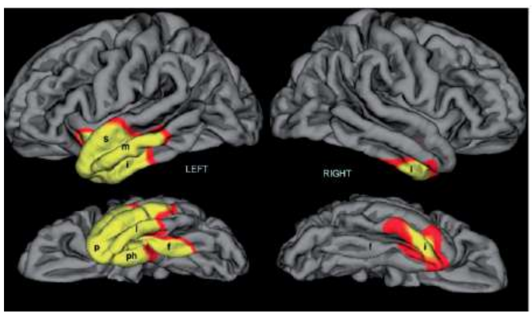
Semantic Variant PPA: Neuroimaging



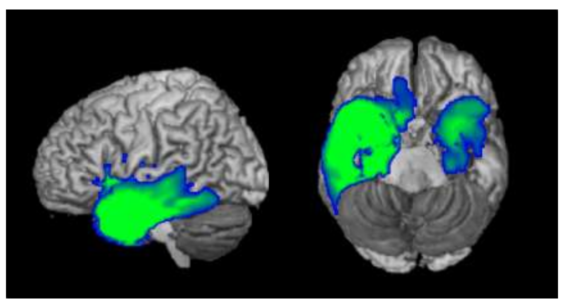
Structural MRI



VBM/Cortical Thickness

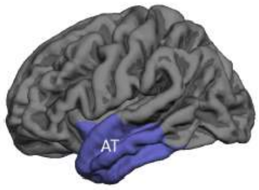


Mesulam et al., 2009

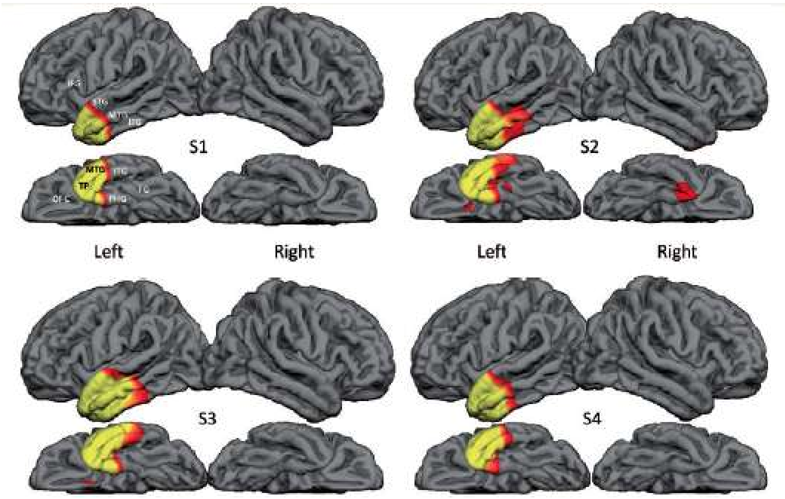


Henry et al., 2011

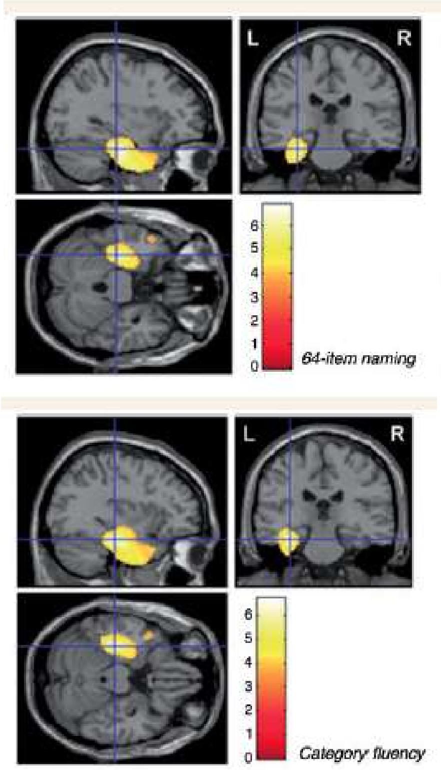
Semantic Variant PPA: Lesion-Deficit Correlations
Verbal Tasks: Left ATL Involved in Naming and Comprehension



Word Comprehension
Rogalski et al., 2011

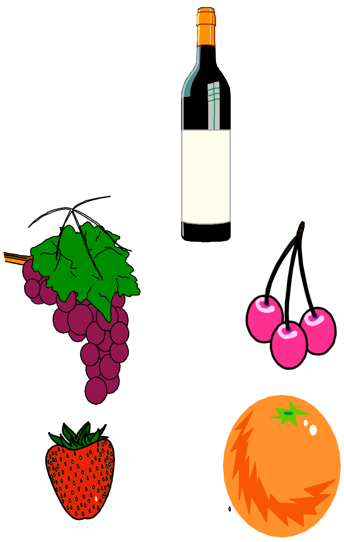


Naming
Mesulam et al., 2013



Mion et al., 2012

Semantic Variant PPA: Impaired Verbal and Nonverbal Knowledge of Objects/People Consistent with Multimodal Semantic Deficit



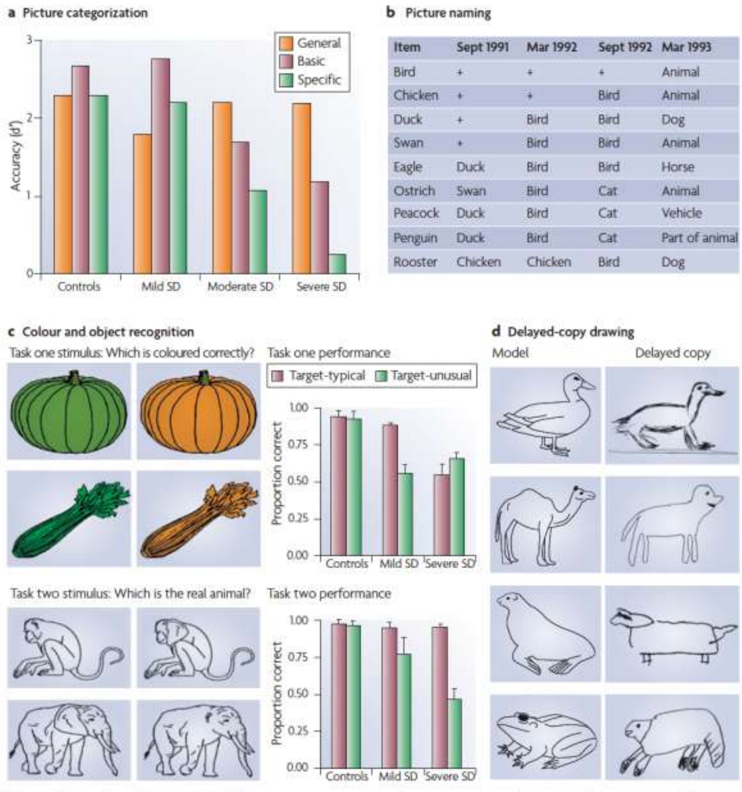
key

window table

mirror door

car

Levels of Specificity: Preservation of General/Categorical Relative to Specific/Individuating Semantic Information in SD



Item	Sept 1991	Mar 1992	Sept 1992	Mar 1993
Bird	+	+	+	Animal
Chicken	+	+	Bird	Animal
Duck	+	Bird	Bird	Dog
Swan	+	Bird	Bird	Animal
Eagle	Duck	Bird	Bird	Horse
Ostrich	Swan	Bird	Cat	Animal
Peacock	Duck	Bird	Cat	Vehicle
Penguin	Duck	Bird	Cat	Part of animal
Rooster	Chicken	Chicken	Bird	Dog

Patterson, 2007

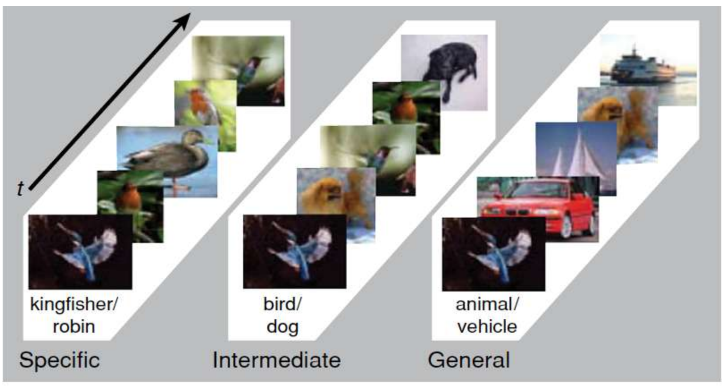


Figure 1. Some examples of the stimuli used and a schematic of the block design. On each trial, a word was viewed, followed by a picture, and the subjects were asked to indicate whether the picture matched the word.

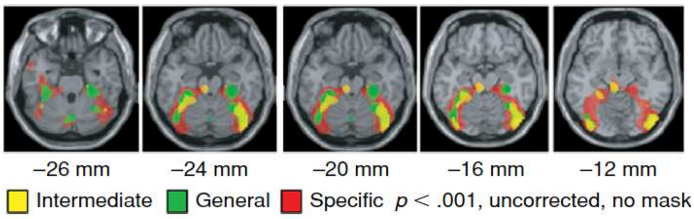


Figure 3. Experimental conditions significantly activated above baseline. Extent of temporal lobe activation was significant at $p < .001$, uncorrected, for the whole brain in the contrast of specific classification with baseline (red), intermediate classification with baseline (yellow), and general classification with baseline (green).

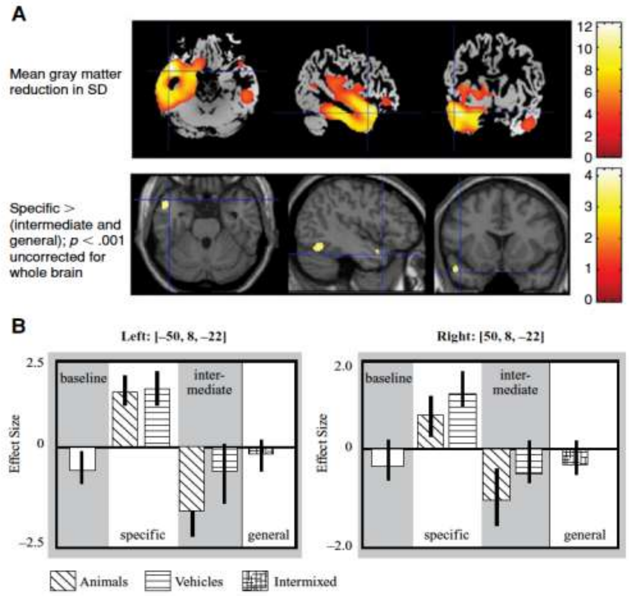
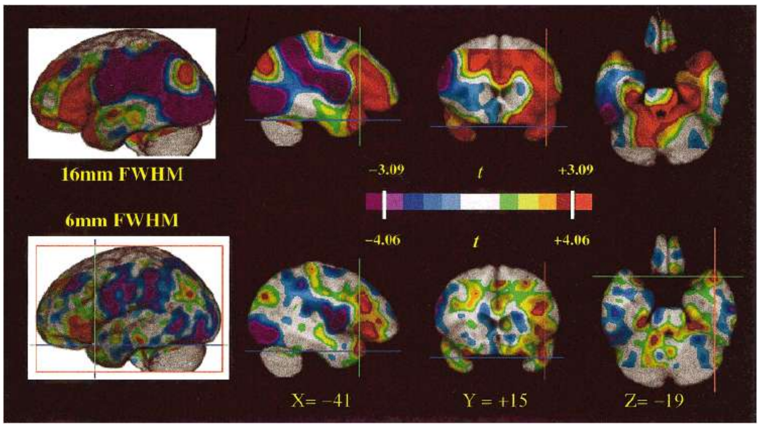
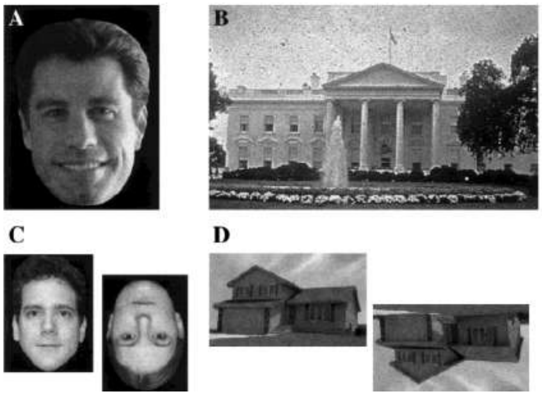


Figure 2. Localization of atrophy and activation. (A) Top row: Mean gray matter reduction for 6 patients with semantic dementia (SD). The peak was identified at [−44, 14, −27]; a volume of 8 mm around this peak and the corresponding region in the right hemisphere were defined as regions of interest for the PET analysis. The crosshairs indicate the peak of activation from the functional imaging study contrasting specific with intermediate and general categorization. Bottom row: Whole-brain activation for healthy controls significant at $p < .001$, uncorrected, contrasting the specific with the intermediate and general categorization conditions. A corresponding peak in the right hemisphere did not surmount the whole-brain threshold but fell within the region of interest and was statistically reliable with small-volume correction. The crosshairs indicate the peak of maximal atrophy from the volumetric analysis of SD data. (B) Mean-centered effect sizes (percentage of regional blood flow change) at the left and right peaks for the six different stimulus conditions in our experiment: specific categorization for animals and for vehicles, intermediate categorization for animals and vehicles, general categorization, and the baseline task. The effect was observed for both animal and vehicle scans.

Rogers et al., 2006





Grabowski et al., 2001

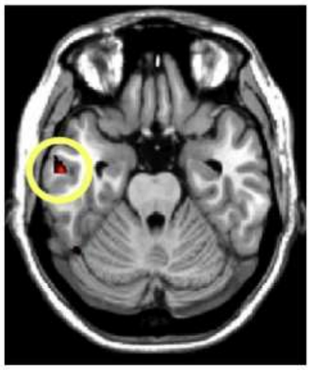


Fig. 3. Pattern of activation in the comparison [SC>GC]. The left ATL was activated by

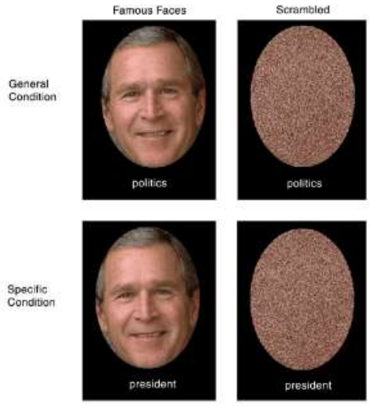


Fig. 1. Illustration of the experimental design and the stimuli.

Brambati et al. , 2010

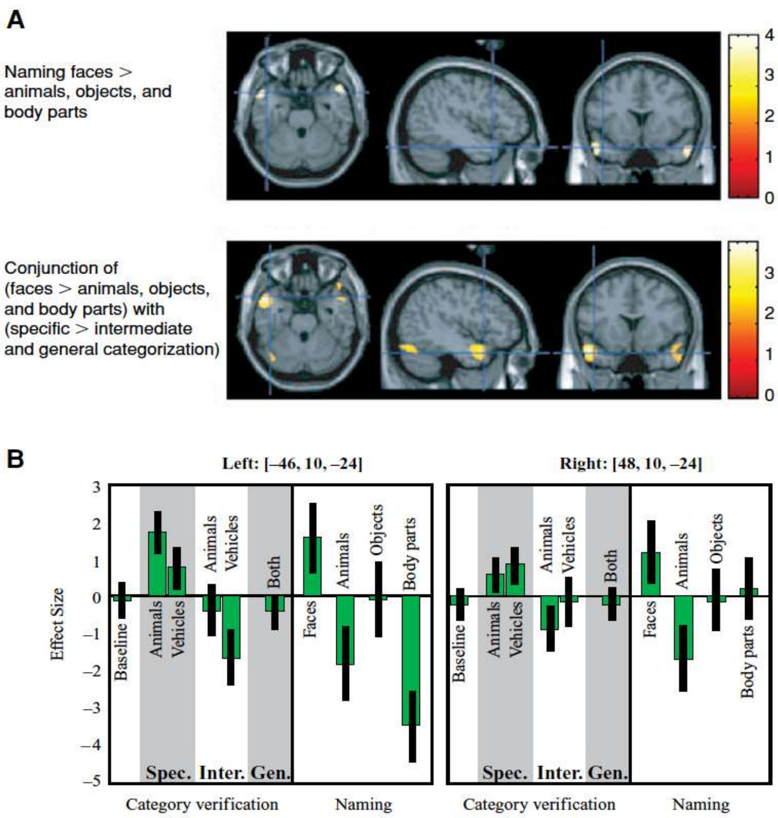
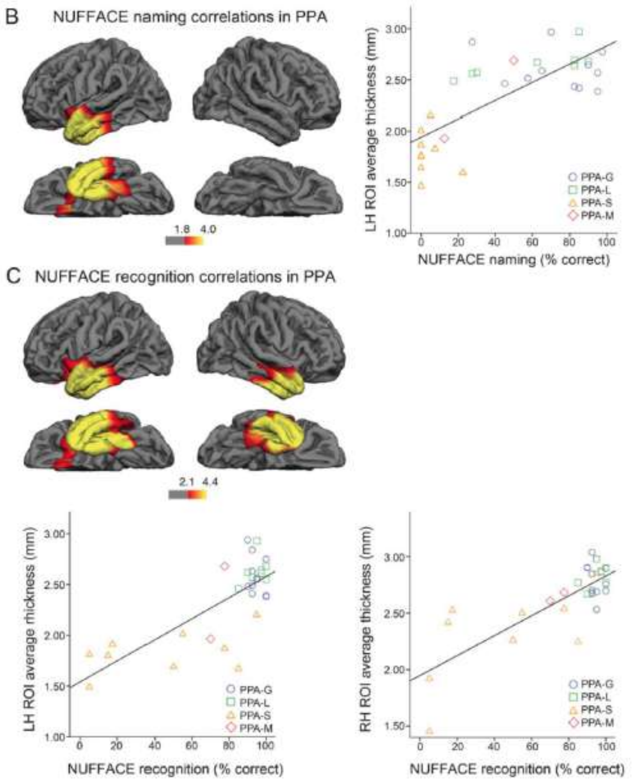


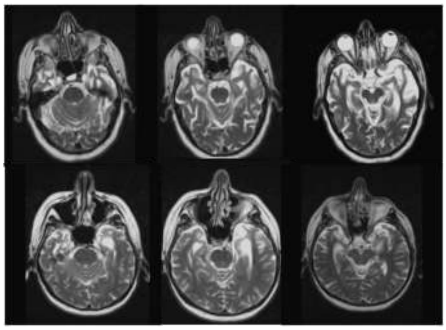
Figure 4. Naming faces versus objects, animals, and body parts. (A) Top: Silent naming of unique faces versus nonunique items (animals, objects, and body parts) from Gorno-Tempini, Cipolotti, and Price (2000). Bottom: Conjunction of (specific > general categorization) from the present study and (naming faces > naming animals, objects, and body parts) from Gorno-Tempini et al. (2000). Note that, in the case of the conjunction, the color scale for the *t* values relates to the minimal *t*. (B) Mean centered effect sizes (percentages of regional blood flow change) at the peak voxel.

Rogers et al., 2006

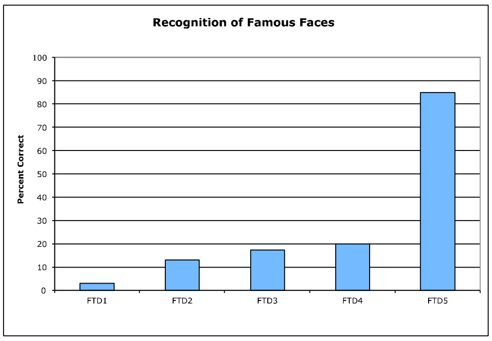
Semantic Variant PPA: Lesion-Deficit Correlations
Famous Person Knowledge and ATL

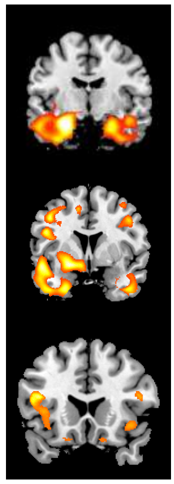


Gefen et al., 2013

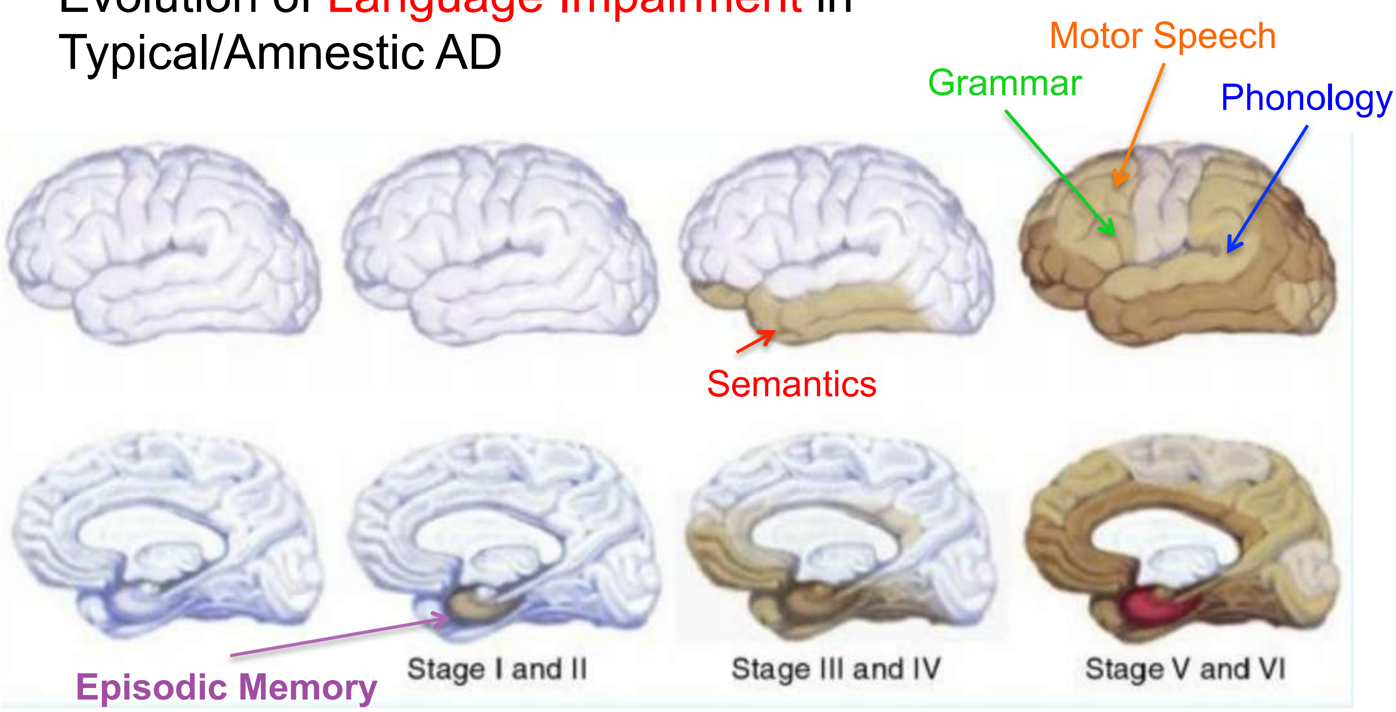


Rapcsak, 2013





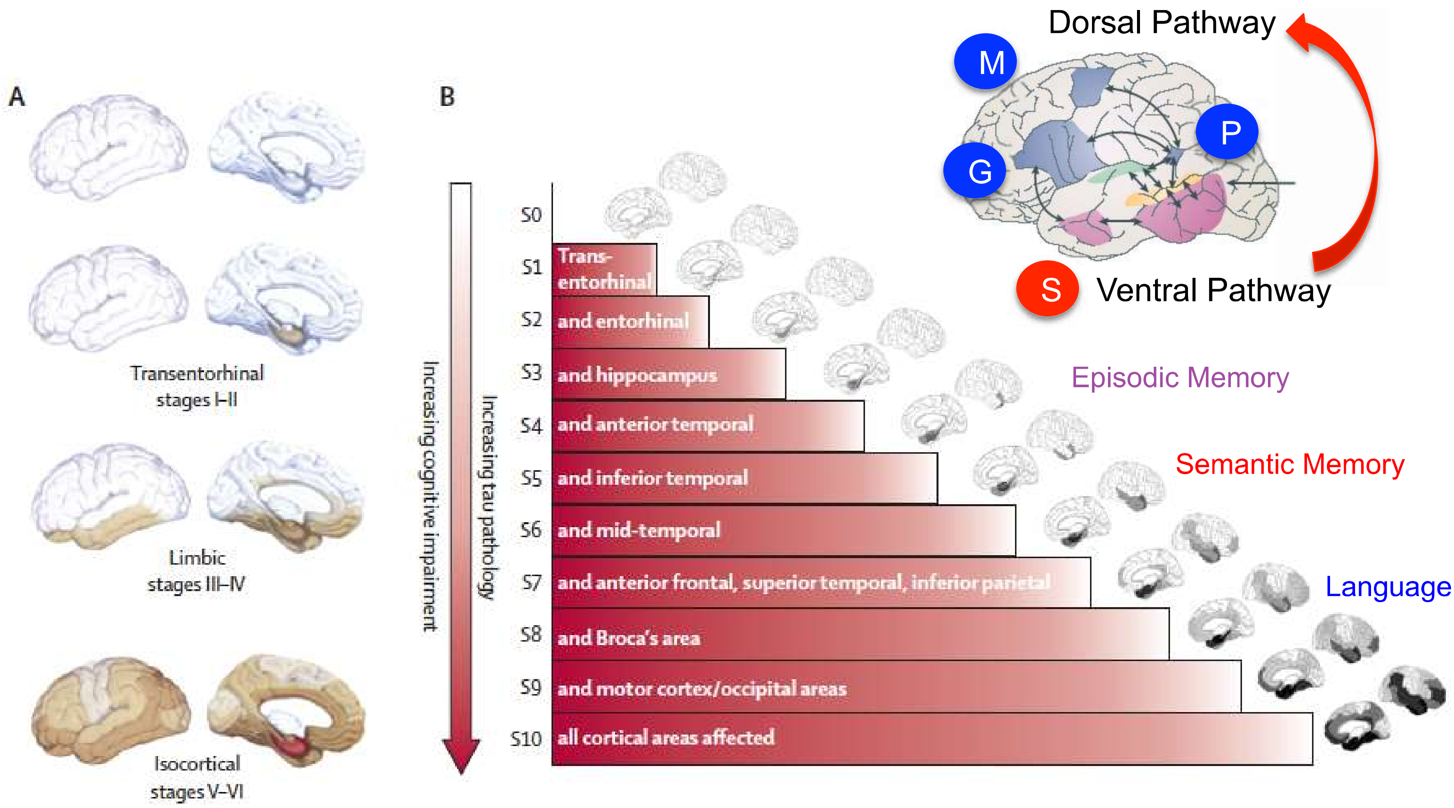
Evolution of Language Impairment in Typical/Amnestic AD



Transentorhinal Limbic Isocortical

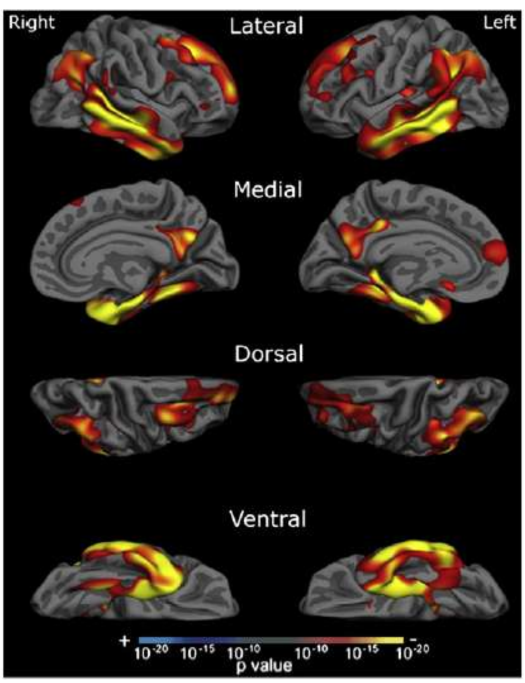
Braak Stages: Neurofibrillary Tangles/Tau-Mediated Neurodegeneration

Ventral Pathway: Semantics/Naming, Verbal Fluency, Comprehension
Dorsal Pathway: Phonology, Grammar, Motor Speech

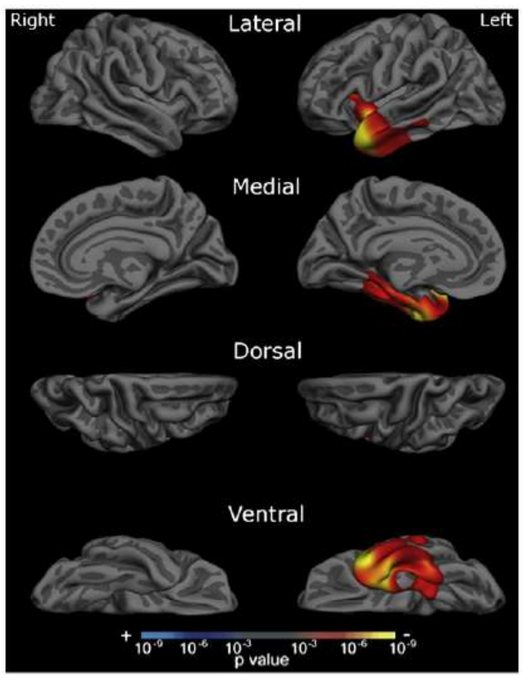


Modified from Villemagne et al., 2015

Neural Correlates of Anomia in AD



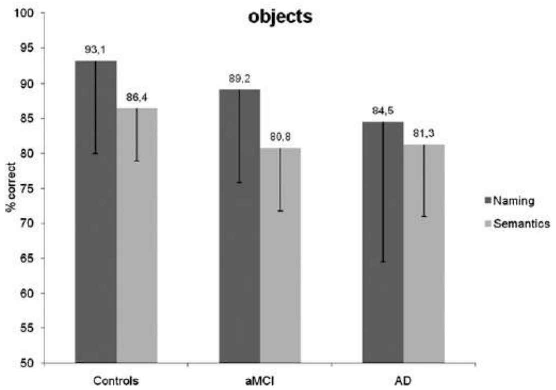
Cortical Atrophy

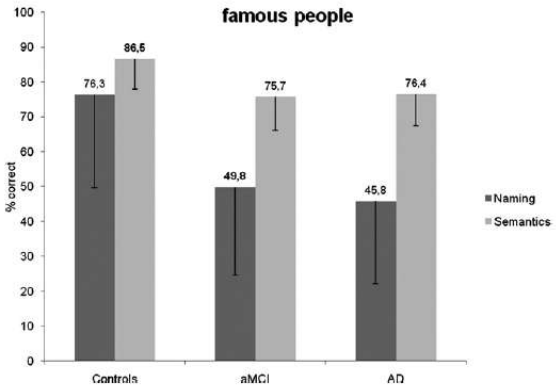


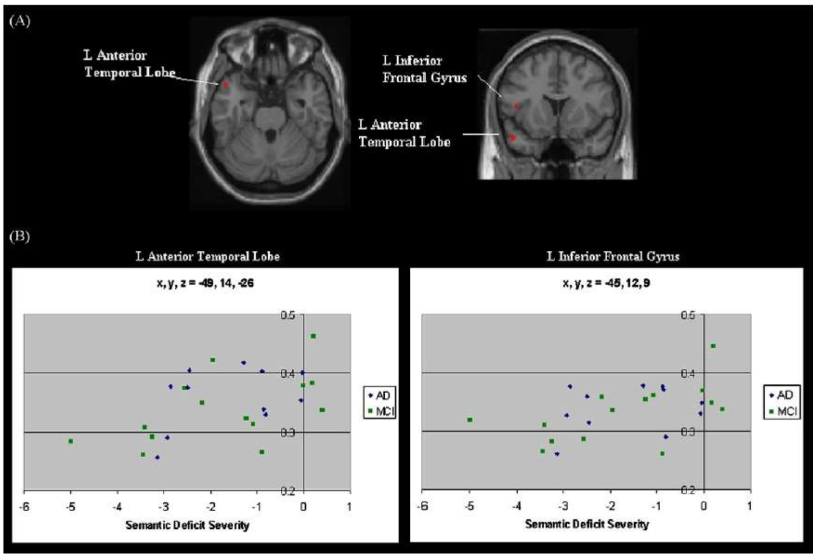
Correlations of Atrophy with Naming

Domoto-Reilly et al., 2012

Impaired Semantic Knowledge of Objects and People is Associated with Left Anterior Temporal Lobe Atrophy in AD

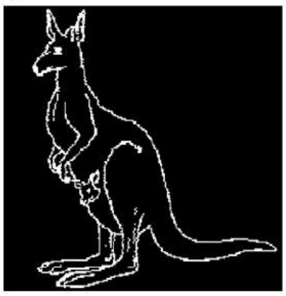


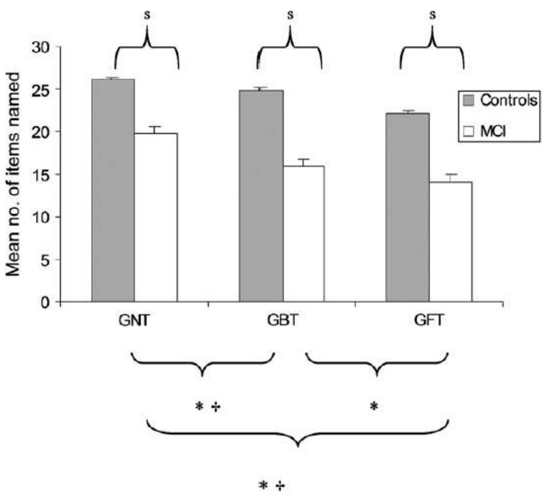




Joubert et al., 2010 (n=31; aMCI = 15, early AD = 16)

Impaired Naming of Objects, Famous People, and Buildings in MCI

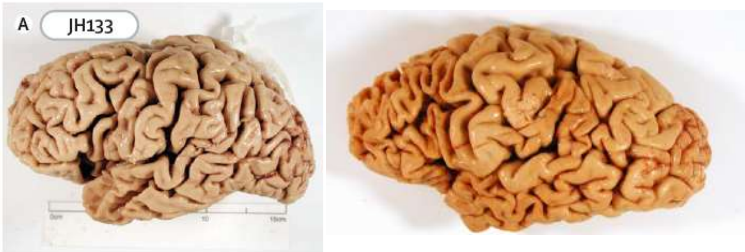


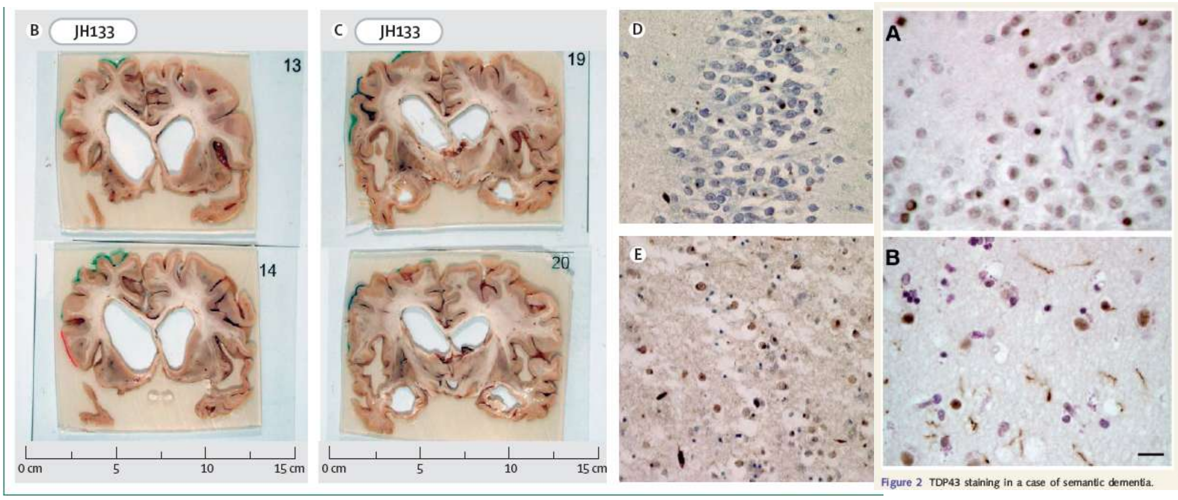


Ahmed et al., 2008

Semantic Variant PPA: Neuropathology

- FTLD-TDP (70-80)%
    - AD
        - FTLD-TAU





Hodges & Patterson, 2007/Hodges et al., 2010

Category-Specific Semantic Deficits: Living vs. Nonliving

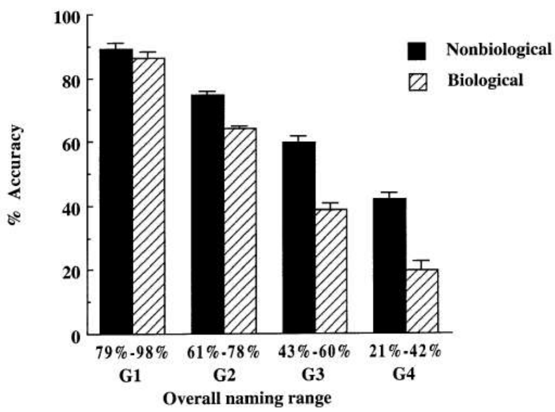
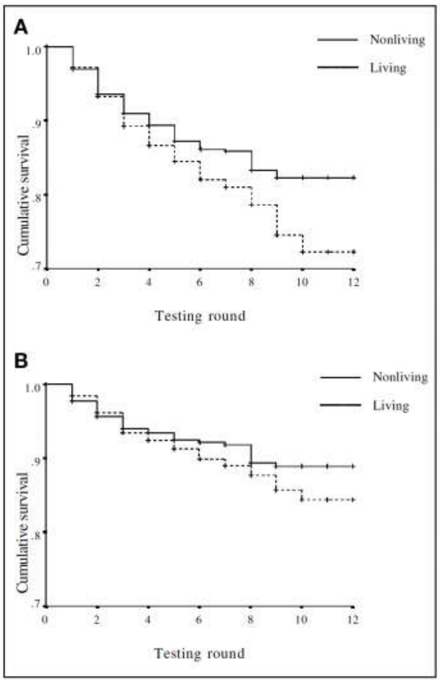


Fig. 1. Mean naming accuracy of DAT/MCI participants on nonbiological and biological items at successive ranges of overall naming impairment.

Whatmough et al., 2003

AD



Garrard et al., 2001

Category-Specific Semantic Deficits: Living vs. Nonliving

Brambati et al., 2006

Libon et al., 2013

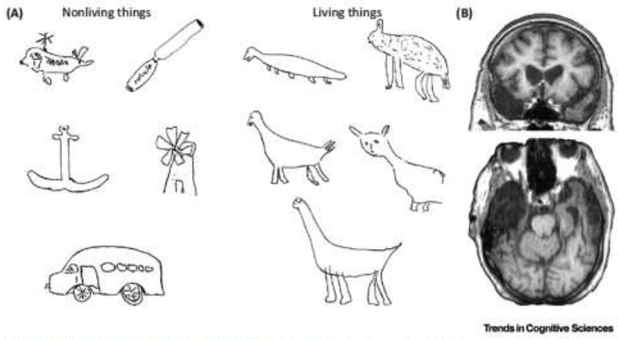
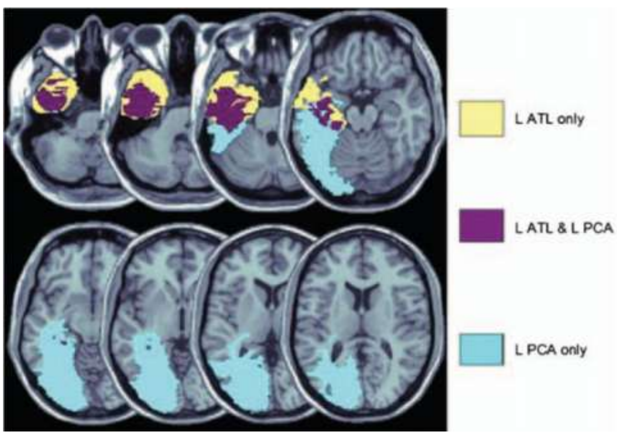


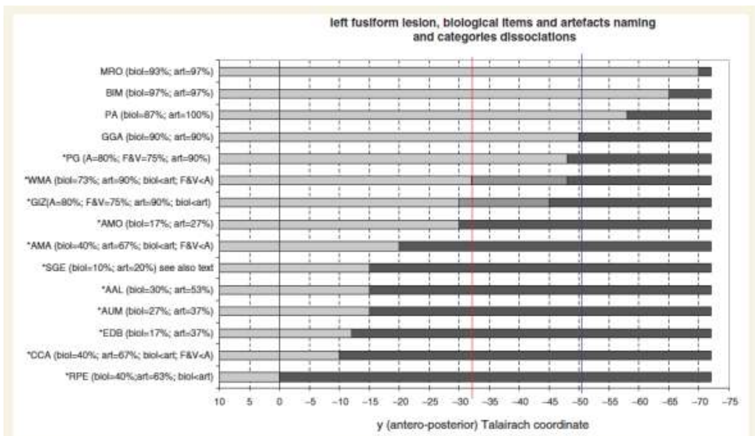
Figure 2. The Nature of Category-Specific Deficits. (A) Drawings from patient SE of common objects of living and nonliving things, showing a clear absence of distinctive feature information for living things and a preservation of details for nonliving things. Nonliving objects, top left to bottom right; helicopter, chisel, anchor, windmill, bus. Living objects; crocodile, zebra, duck, penguin, camel. Reproduced from [17] with permission from Taylor and Francis. (B) MRI scan from patient SE showing extensive damage in the right anterior temporal lobe (ATL; image shown in radiological convention, previously unpublished).

Patient	Disease	Naming		Word–picture matching	
		Living	Non-living	Living	Non-living
JBR	HSVE	0.16	0.63	0.31	0.97
JH	HSVE	0.53	0.72	0.63	0.97
RC	HSVE	0.22	0.66	0.38	0.88
YW	HSVE	0.59	0.84	0.66	0.88
Mean		0.38	0.71	0.49	0.92

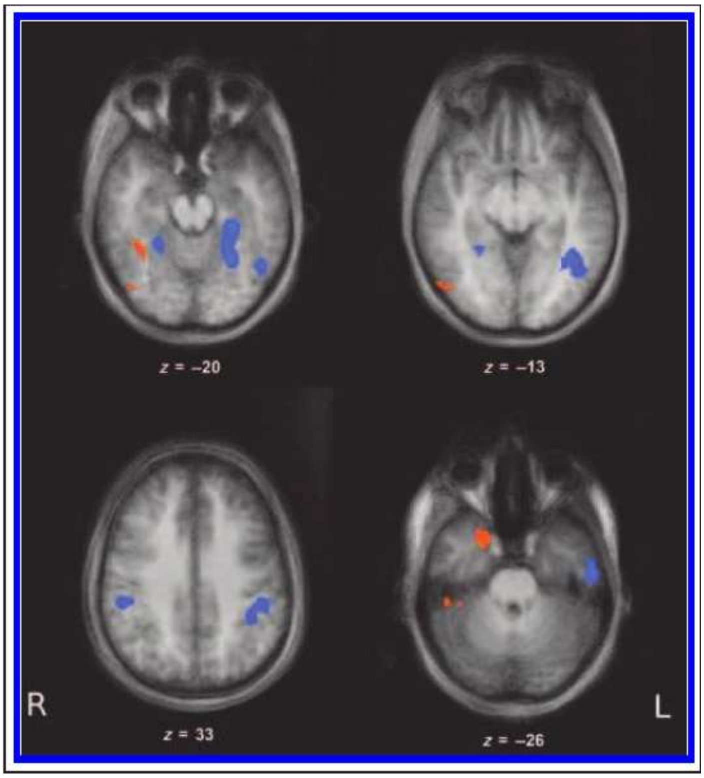
Herpes Simplex Viral Encephalitis
Clarke et al, 2016; Lambon Ralph, 2007

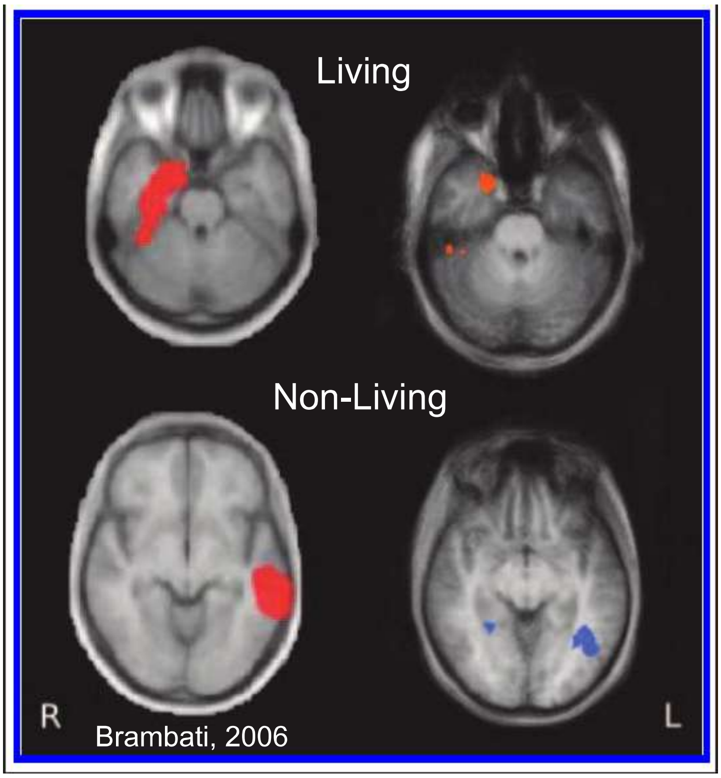


Antonucci et al., 2008



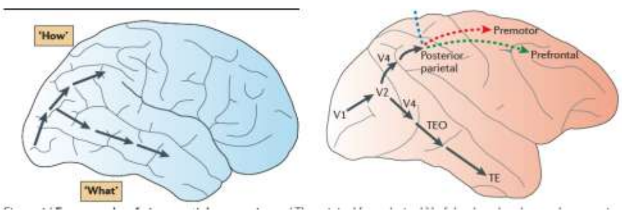
Capitani et al., 2009





fMRI
Red: living/animals ventral,
Blue: nonliving/tools ventral plus dorsal

Anzellotti et al., 2011



Kravitz., 2011

Figure 1. The 131 object images used in the current study. The order of images matches that of the representational dissimilarity matrices presented in Figure 2.

Clarke & Tyler, 2014

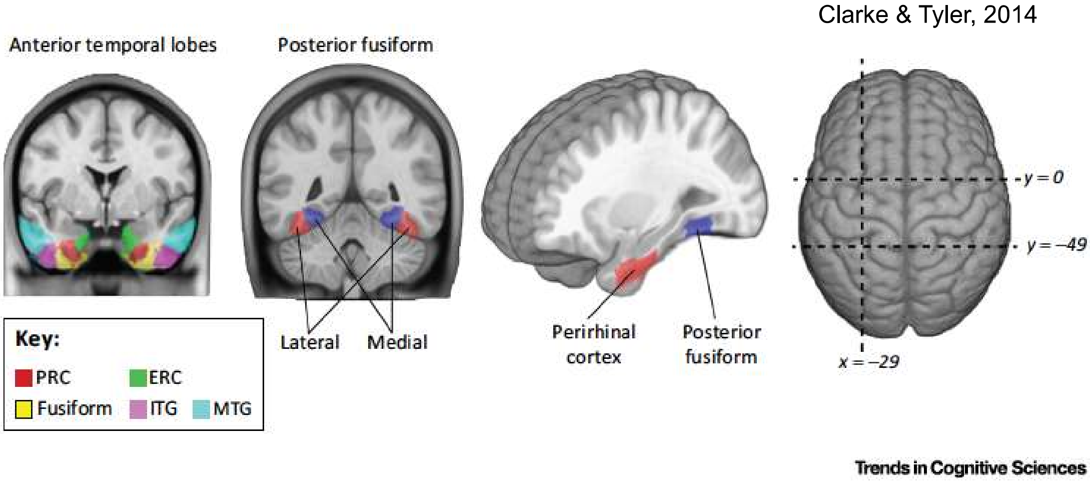
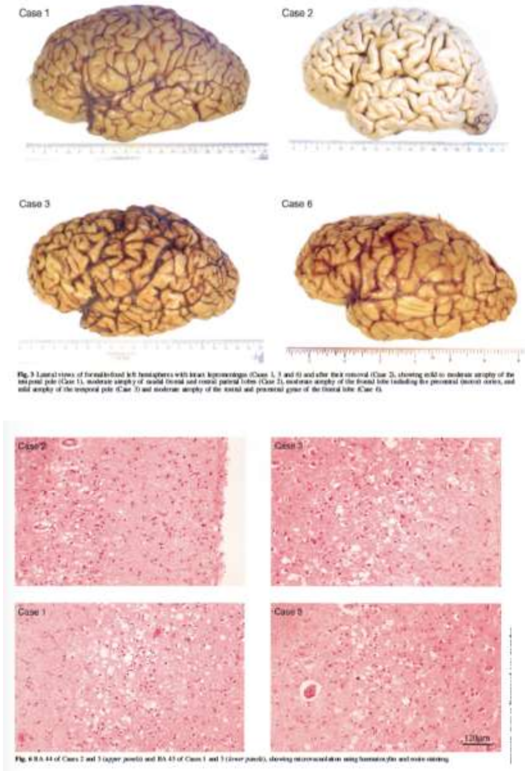


Figure 1. Regions Supporting Conceptual Processing in the Anterior and Posterior Ventral Visual Pathway.

Clarke & Tyler, 2016

Category-Specific Semantic Deficits: Verbs vs. Nouns

IFG:
BA 44/45



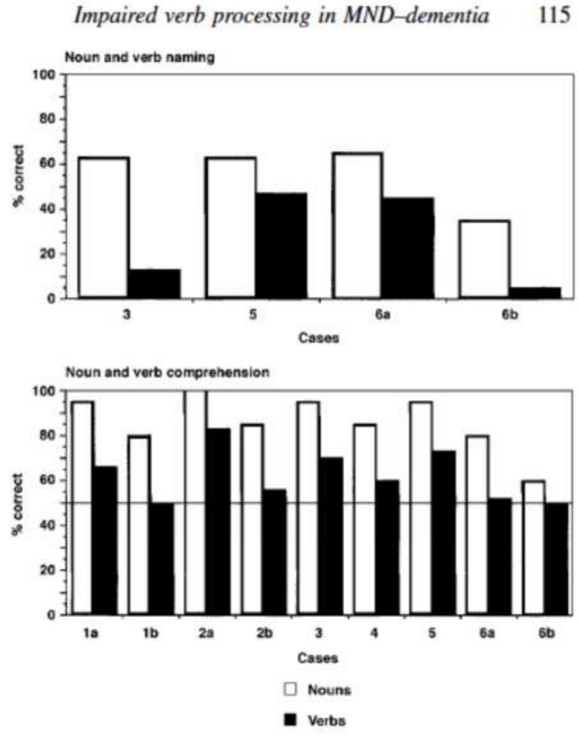
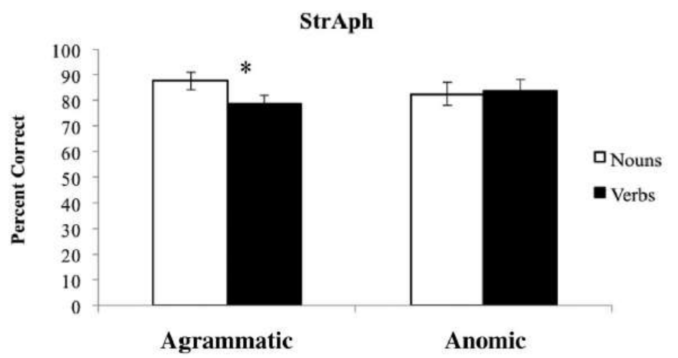
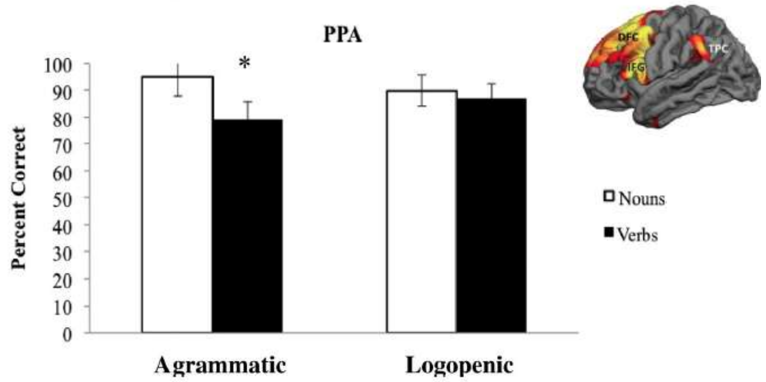


Fig. 8 Noun and verb naming (*upper panel*) and comprehension

Bak et al., 2001





ıre 2. Production of nouns and verbs for stroke aphasia (StrAph) (top graph) and primary progressi... asia (PPA) participant groups (lower graph).

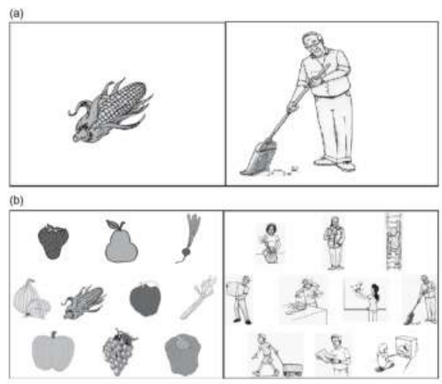
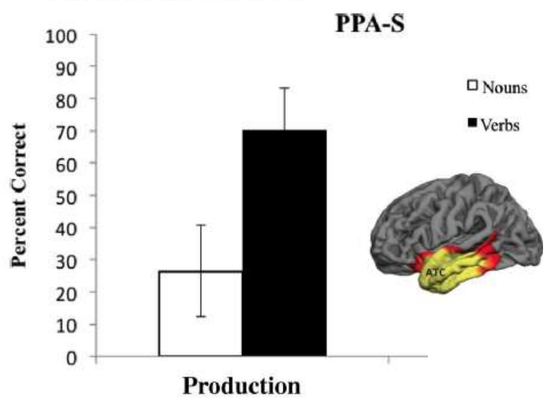


Figure 1. (A) Picture stimuli used to test production of the noun corn and the verb sweep. (B) Stimuli used to test comprehension of the noun corn and the verb sweep.



Thompson et al., 2012

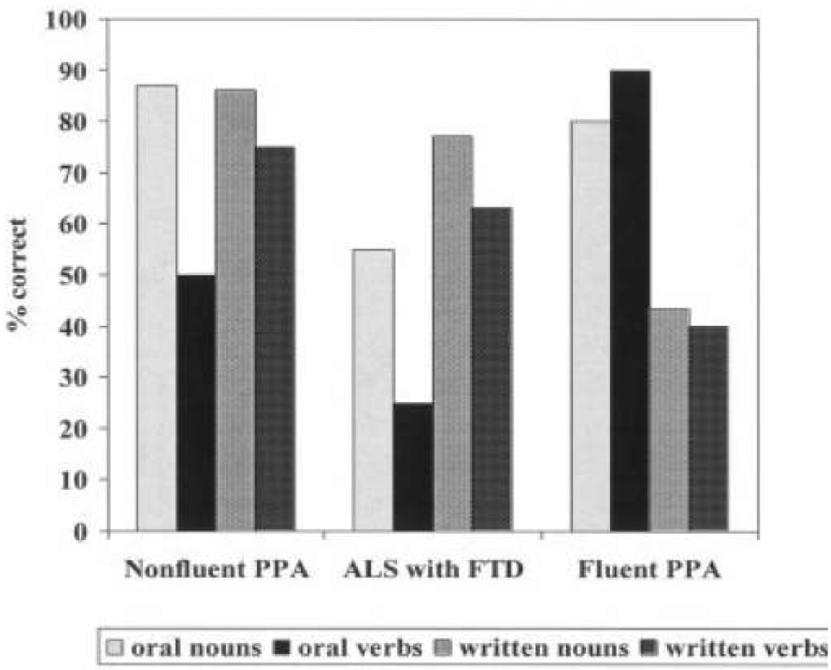


Fig 1. Median scores for oral and written naming in each group. PPA = primary progressive aphasia; ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia.

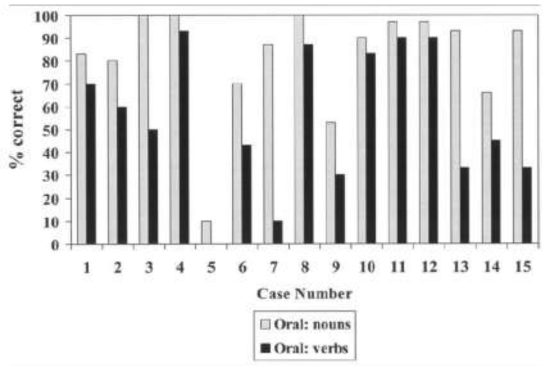


Fig 2. Individual scores for oral naming of nouns and verbs in patients with nonfluent primary progressive aphasia.

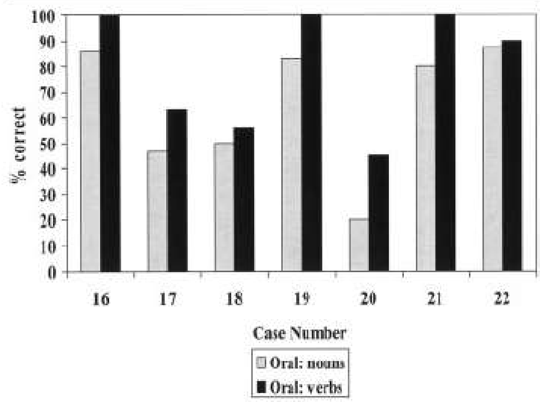
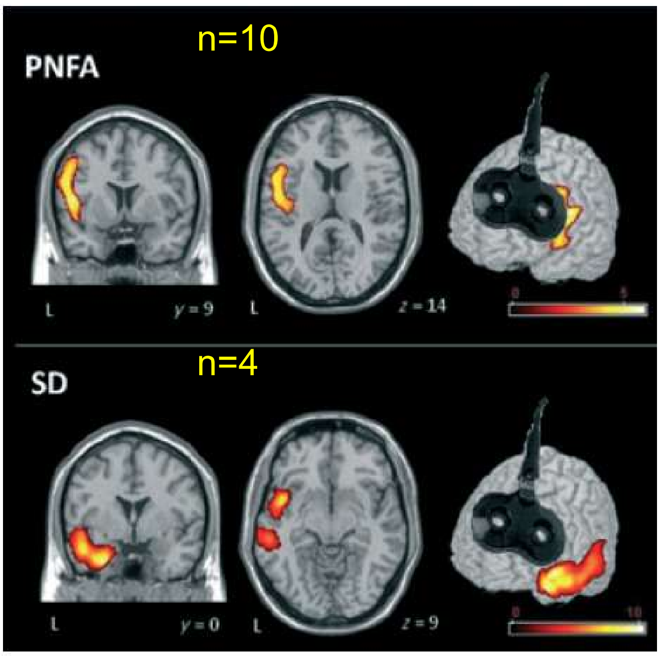
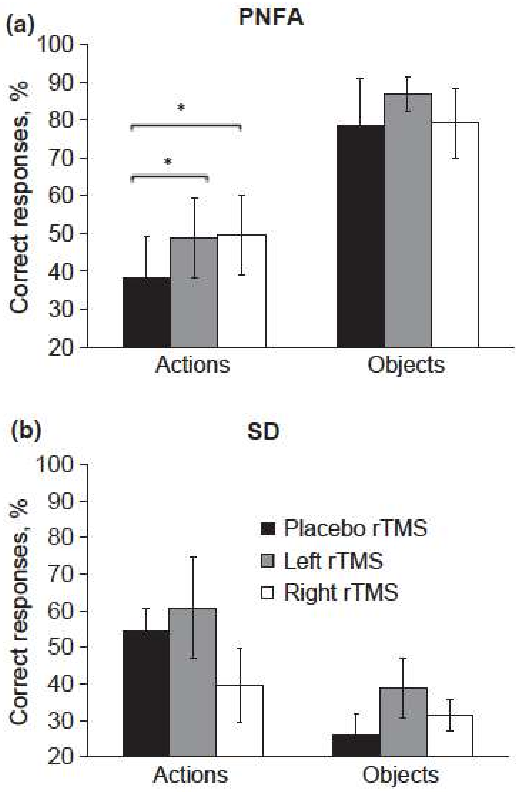


Fig 4. Individual scores for oral naming of nouns and verbs in patients with fluent primary progressive aphasia.

Hillis et al., 2004





Cotelli et al., 2012

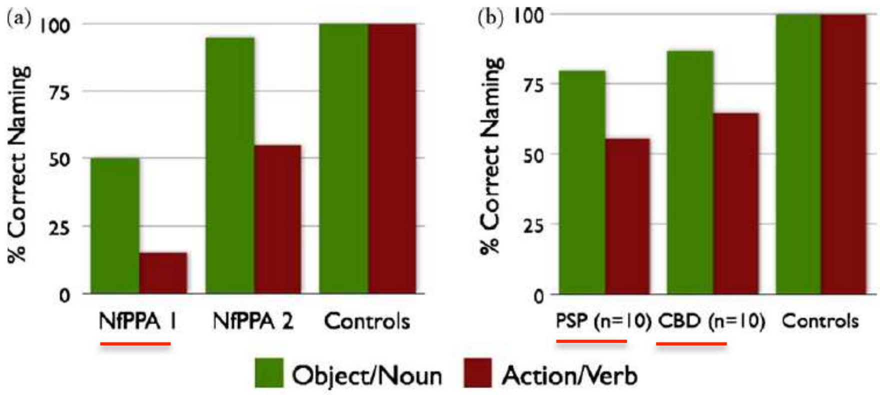


Fig. 5. Object and action naming for two patients suffering from Non-fluent Progressive Primary Aphasia (NfPPA) and matched controls (panel a); groups of Progressive Supranuclear Palsy (PSP) and Corticobasal Degenration (CBD) and matched controls (panel b); data from Cotelli et al. (2006).

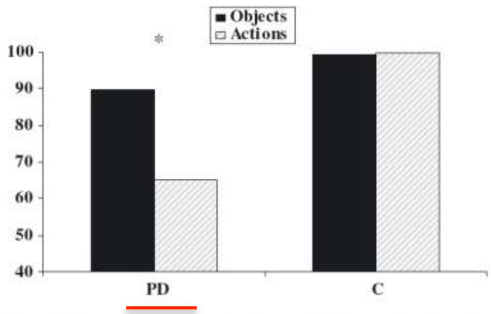
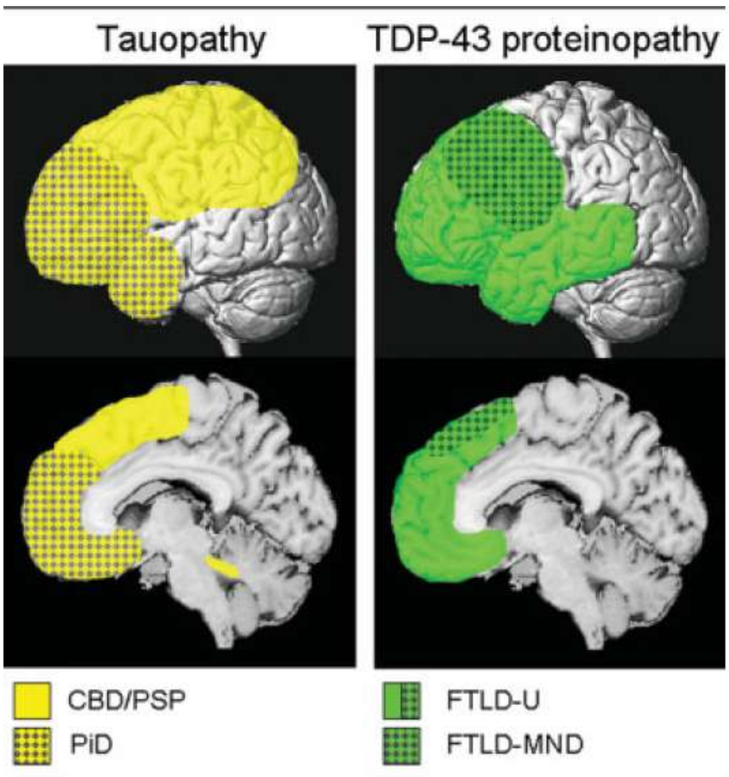


Figure 2 Mean scores for oral action and object naming in each group. PD: Parkinson's disease, C: control subjects. Results are expressed as mean of percentage of correct responses. *Action–object naming, $P < 0.05$.

Cotelli et al., 2007

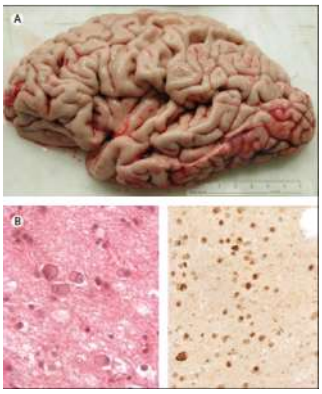


Josephs et al., 2008

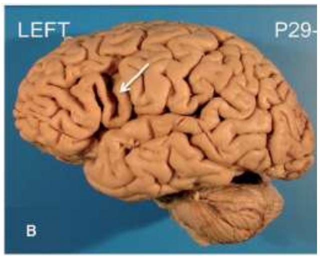
Nonfluent/Agrammatic PPA: Neuropathology

- FTLD-TAU (60-70%)
  - Pick's Disease (PiD)
  - Corticobasal Degeneration (CBD)
    - Asymmetrical rigidity, limb apraxia, alien hand, dystonia, myoclonus
  - Progressive Supranuclear Palsy (PSP)
    - Vertical gaze palsy, axial rigidity, frequent falls
  - Strong association between apraxia of speech and extrapyramidal disorders (CBD and PSP)
- FTLD-TDP
  - Agrammatism without apraxia/motor speech disorder
  - Association with motor neuron disease (ALS)
    - Muscle weakness, wasting, fasciculations, bulbar symptoms, upper motor neuron signs
- AD neuropathology

Verbs < Nouns



PiD (Grossman, 2012)



CBD (Mesulam et al., 2014)

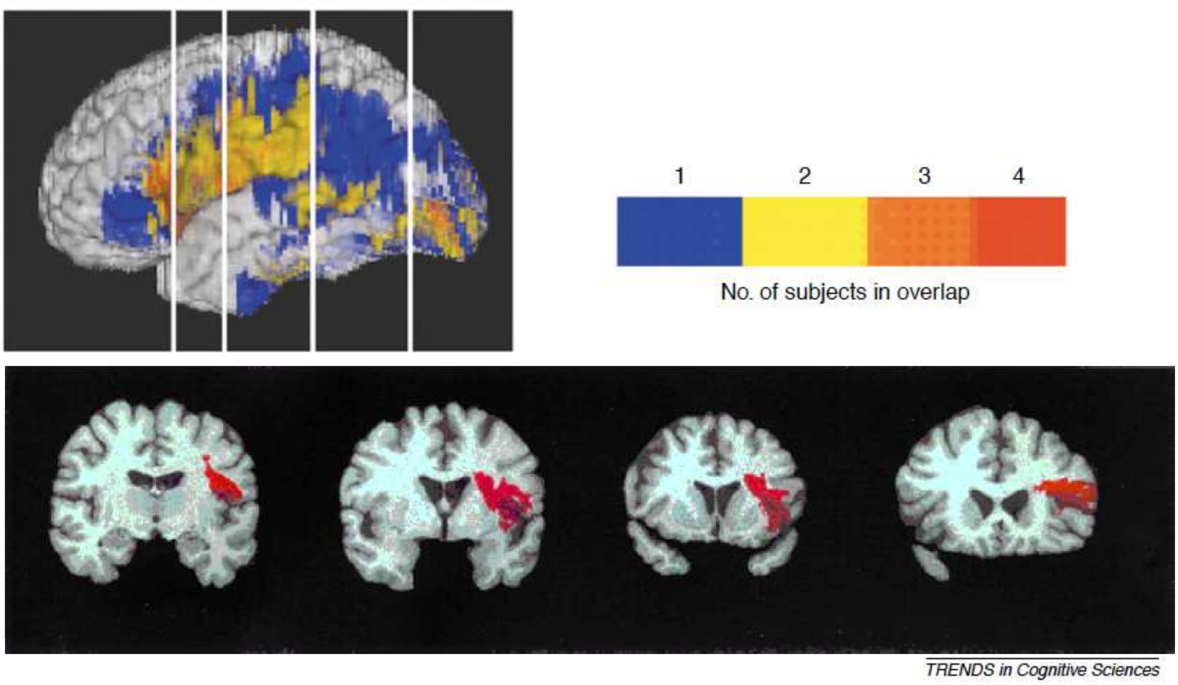


Fig. 3. Areas of lesion overlap in 13 subjects with disproportionate impairments in action naming, relative to naming of concrete entities. The figure shows three regions of maximal overlap: (1) the left frontal operculum, underlying white matter, and anterior insula; (2) the left mesial occipital cortex; and (3) the paraventricular white matter underneath the supramarginal gyrus and posterior temporal region. The color bar indicates the number of subjects in the overlap. Reproduced with permission from Ref. [26].

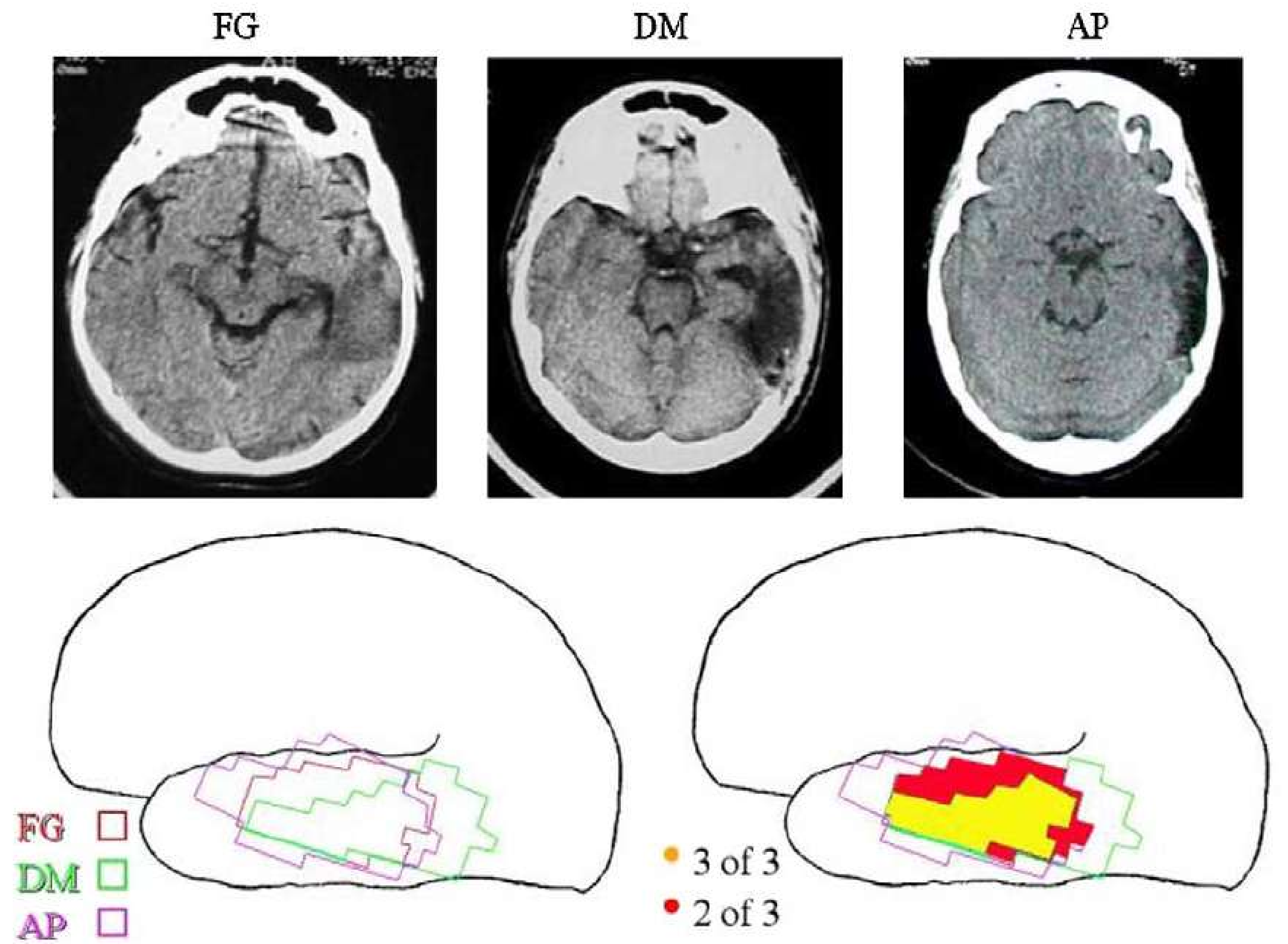


Fig. 1. Noun-impaired patients with temporal lesion (three patients): single lesions and overlap areas.

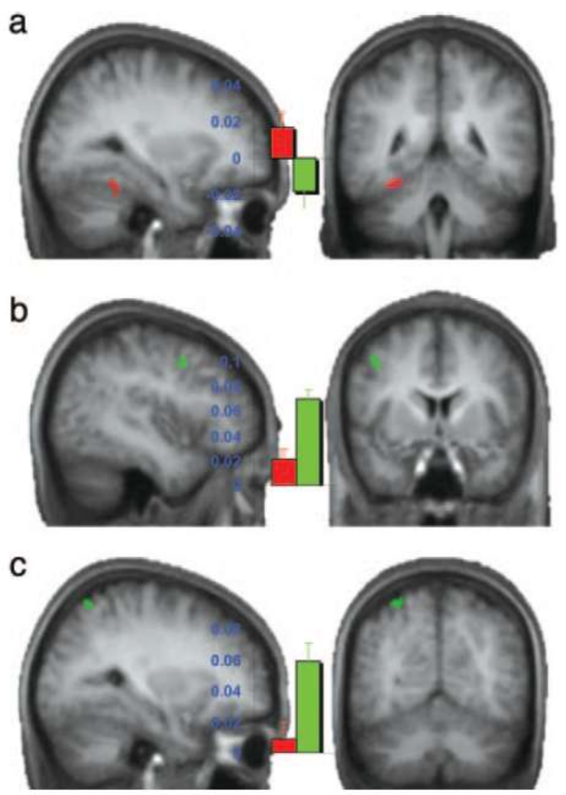
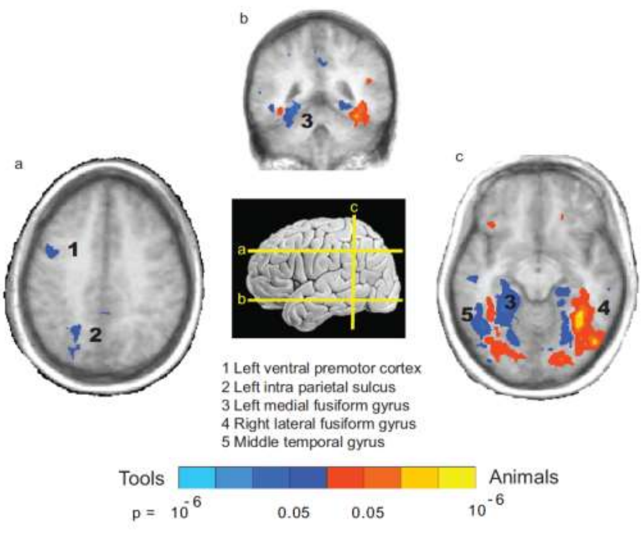
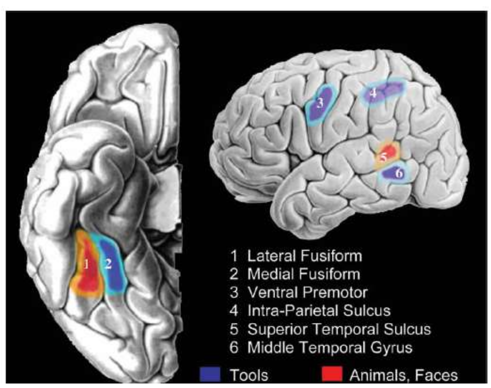


Fig. 2. Brain regions showing consistent patterns of selective event-related activation for nouns (red) and verbs (green) across all three experiments. (*a*)

Shapiro et al., 2006



Mahon & Caramazza, 2009



Caramazza & Mahon, 2006

frontocentral cortex activation to
action words, phrases and sentences

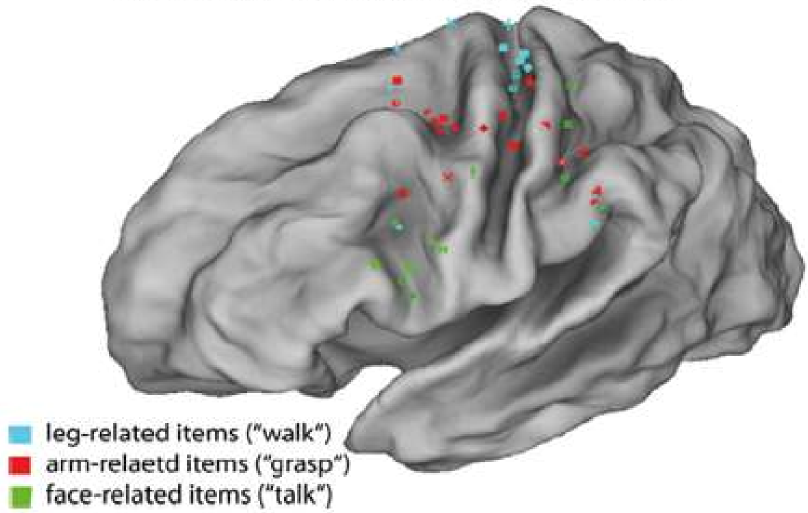
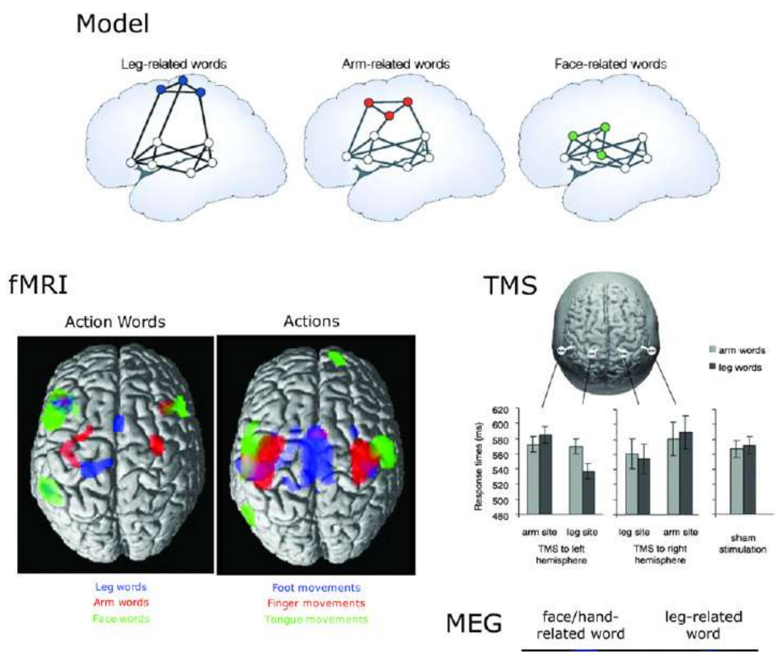
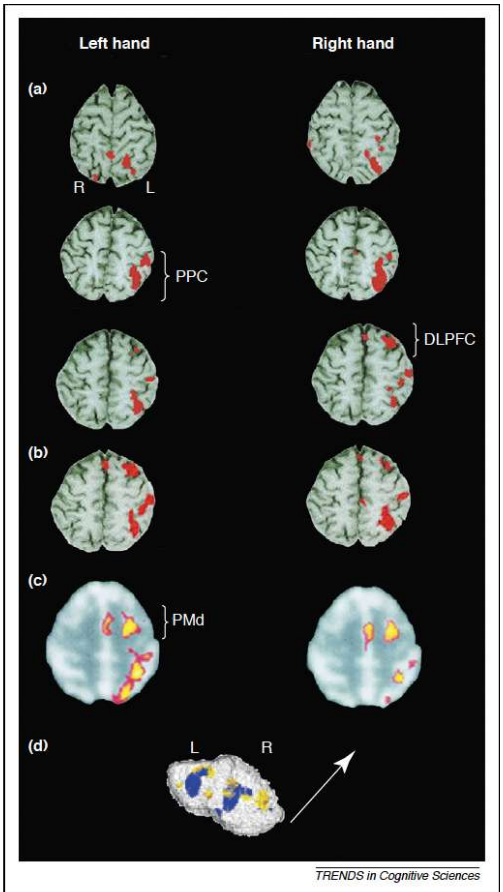


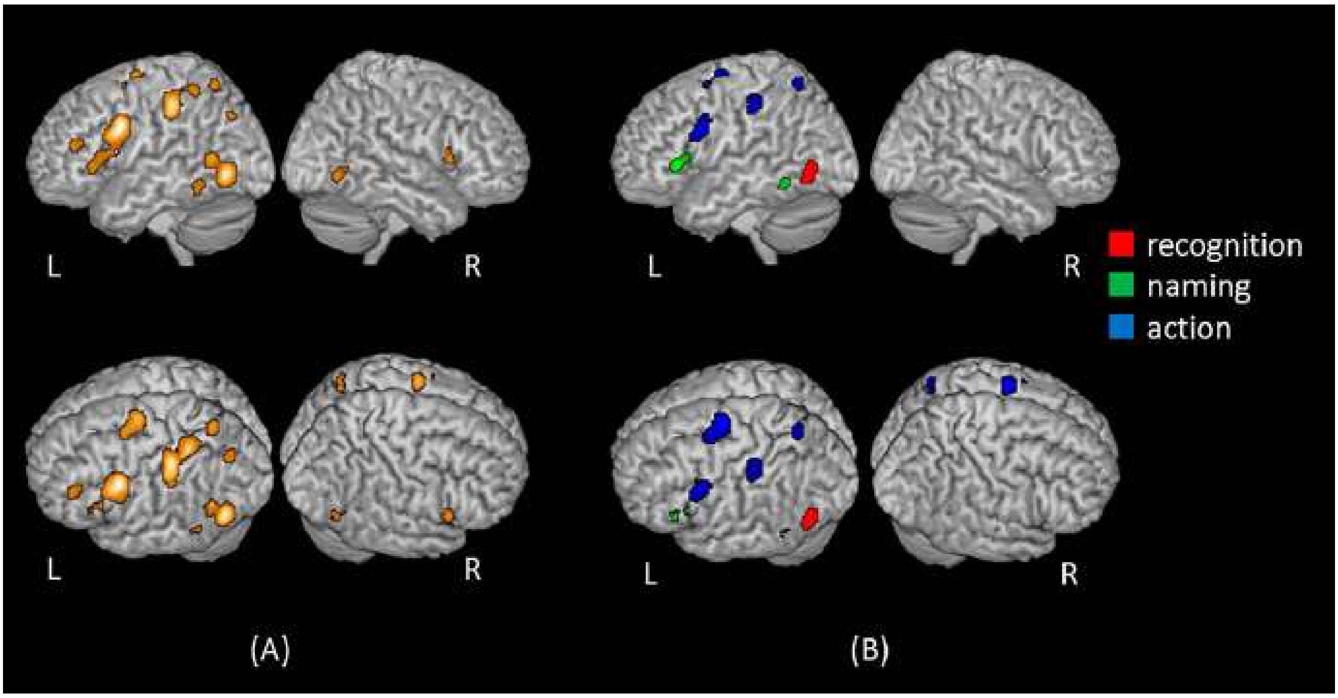
Fig. 7. Manifestation of the sign-action link in motor system activation to action words. Maximal activation foci reported by a range of fMRI studies targeting the processing of verbs and nouns typically used to speak about face-, arm- or leg-actions ("talk", "grasp", "walk") and that of food and tool nouns whose referent objects afford mouth- or hand-actions. Activation foci for face-, arm- and leg-items are shown in green, red and blue, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).
From Carota, Moseley and Pulvermüller (2012).



Kiefer & Pulvermuller, 2012



Johnson-Frey, 2004



Ishibashi et al., 2016

G. Vigliocco et al. / Neuroscience and Biobehavioral Reviews 35 (2011) 407–426

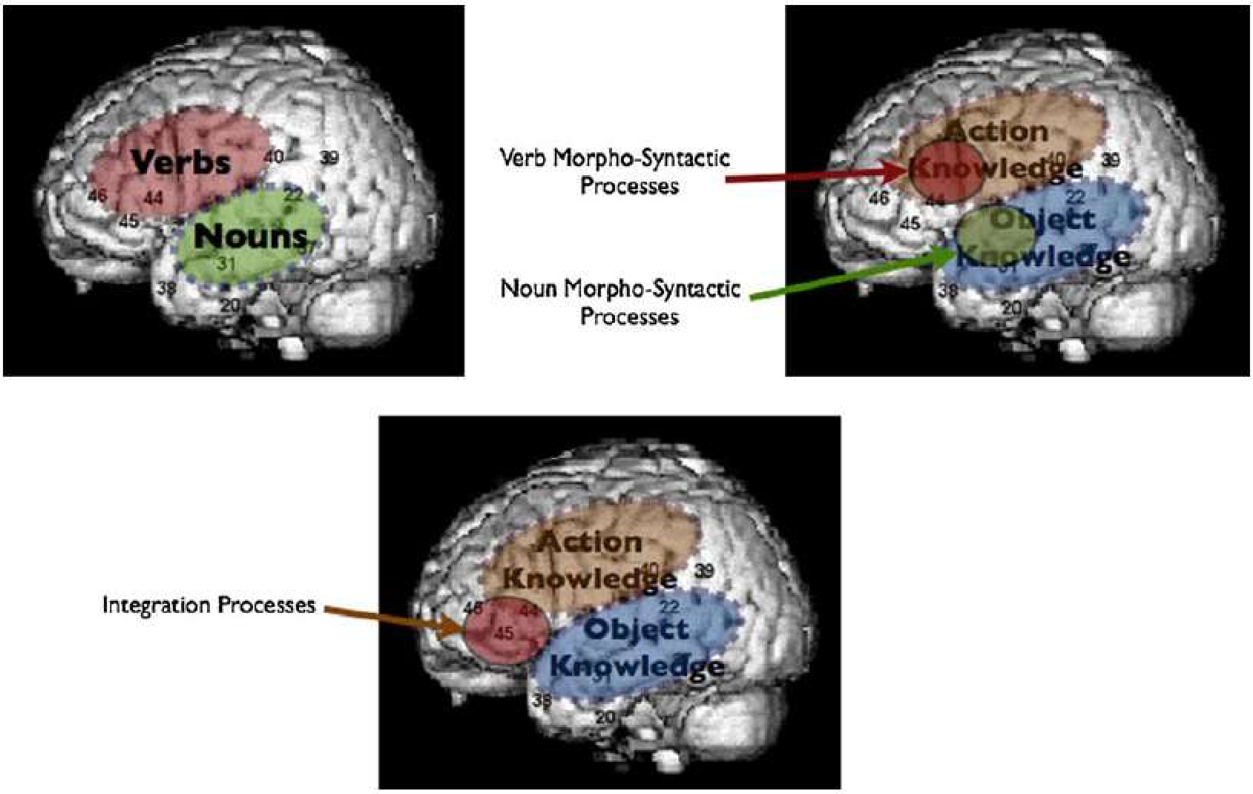
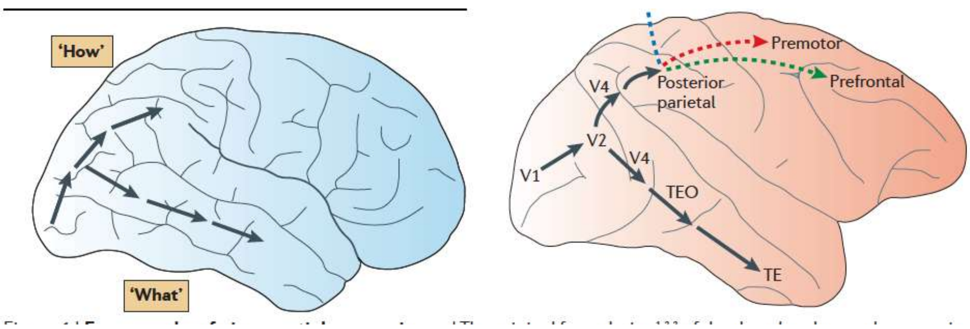
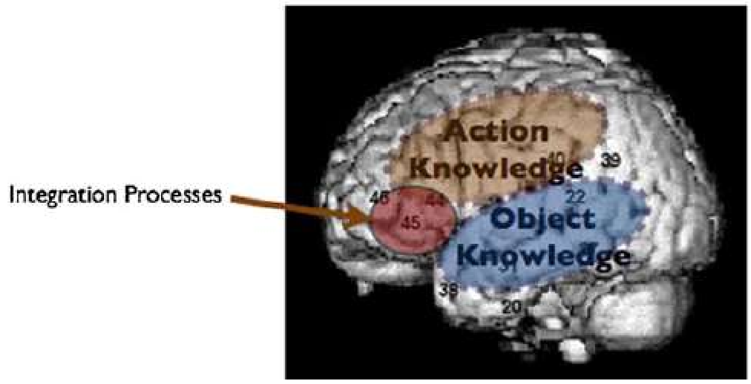


Fig. 2. Schematic overview of different neural models concerning the processing of nouns and verbs.



Kravitz., 2011



Nouns/verbs
Living/nonliving

Fig. 2. Schematic overview of different neural models concerning the processing of nouns and verbs.

Conceptual Knowledge, Lexical-Semantic Networks, Sensorimotor Experience, Embodied Cognition

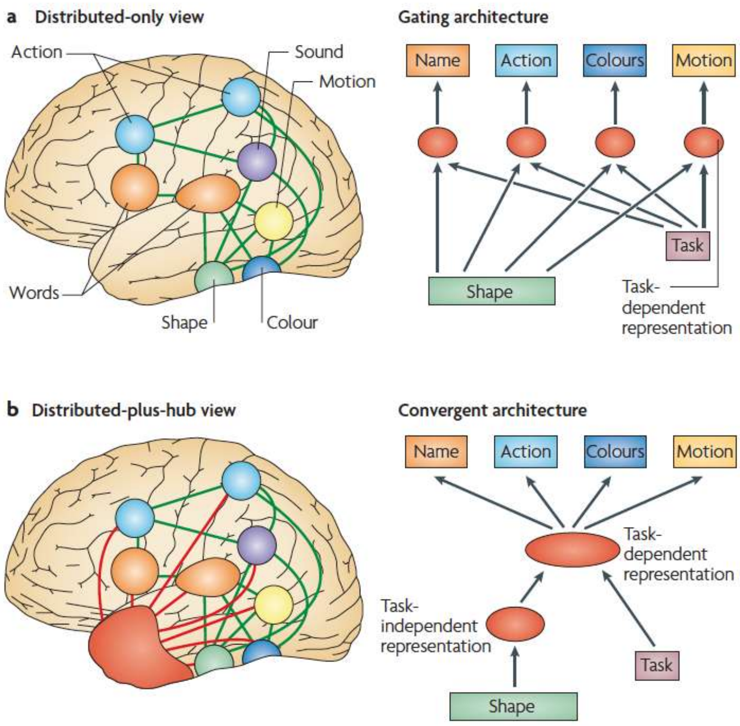


Figure 1 | **Two theoretical positions regarding the neuroanatomical distribution of the cortical semantic network and schematic models based on these views.**

Patterson, 2007

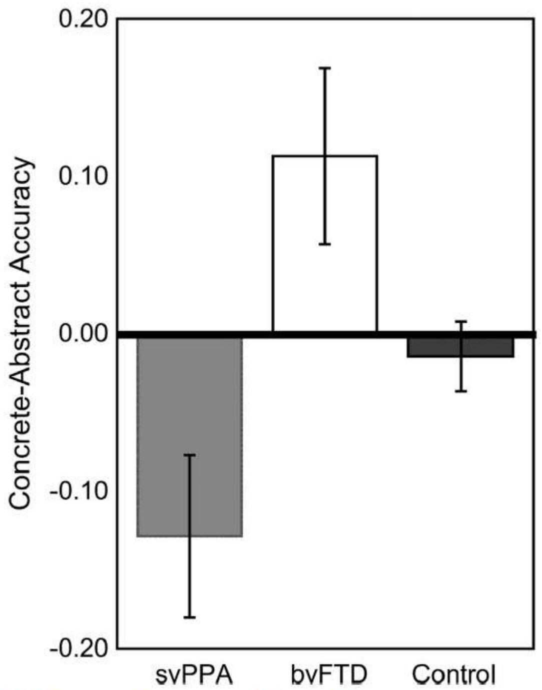


Fig. 2. Magnitude of the Concreteness Effect (CE). The normed accuracy for concrete words minus abstract words, or the magnitude of CE. Negative values indicate a reversal of the CE. svPPA patients are plotted in grey, bvFTD in white, and control in black. Error bars represent standard error of the mean.

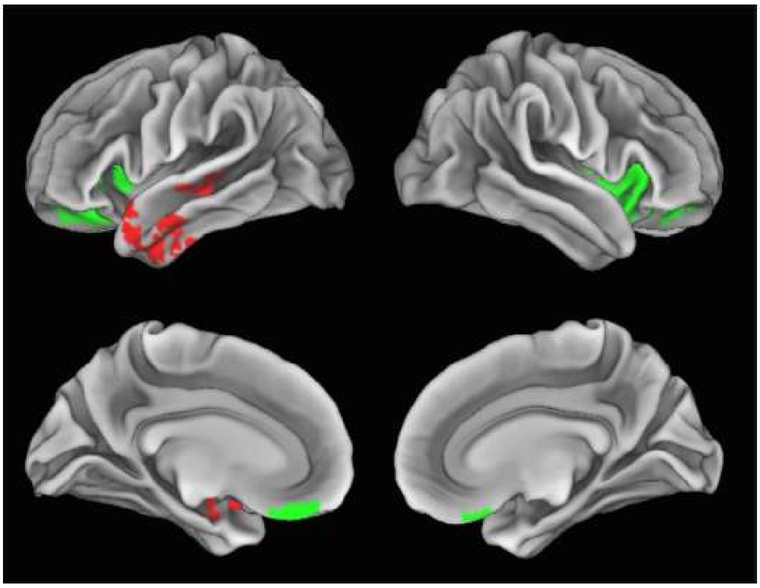


Fig. 4. Regression of grey matter probability with reversal of the CE for svPPA and CE bvFTD. Red indicates areas of atrophy that significantly correlate with the Reversal of Concreteness Effect-better knowledge for abstract words-in svPPA patients. Green indicates areas of atrophy that significantly correlate with the Concreteness Effect-better knowledge for concrete words-in bvFTD patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Cousins et al., 2016