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Language structure and its deterioration in neurodegenerative diseases affecting cognition

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No conflicts of interests

LANGUAGE

- **A human-specific cognitive capacity**

« What is human in humans is syntactic recursion, (…), that is language »

(*Chomsky, 1975*)

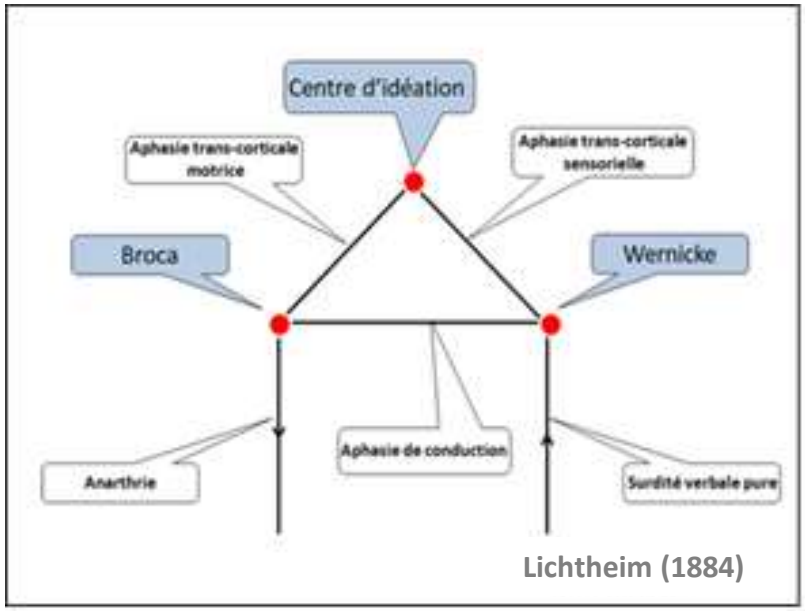
- Language - a cognitive module: **unconscious computations acting on mental representations** (rules and words)

Jerry Fodor (1981; 1983). Representations: Philosophical Essays on the Foundations of Cognitive Science. Cambridge Mass: MIT Press.

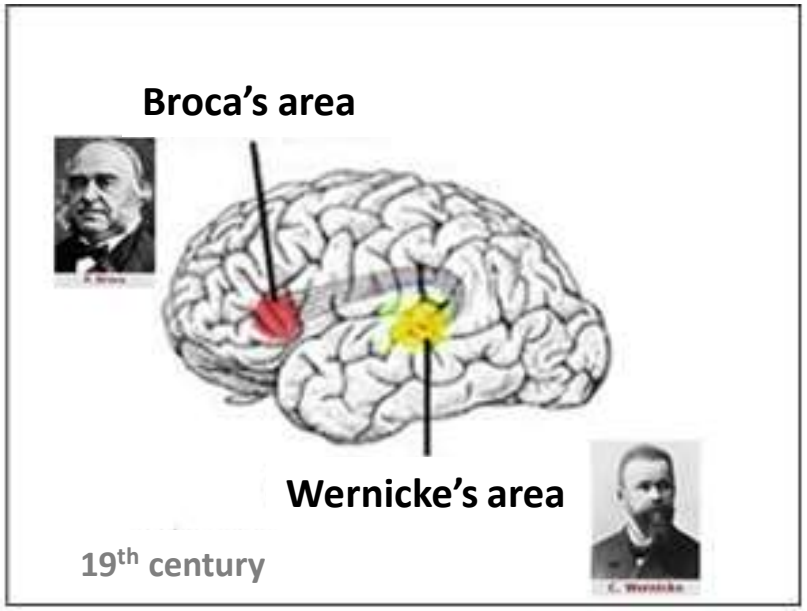
- **An innate capacity**

Poverty of the stimulus argument: children do not only learn language from their environment, but are innately programmed with language-specific processes/computations (*Chomsky, Fodor, ...*)

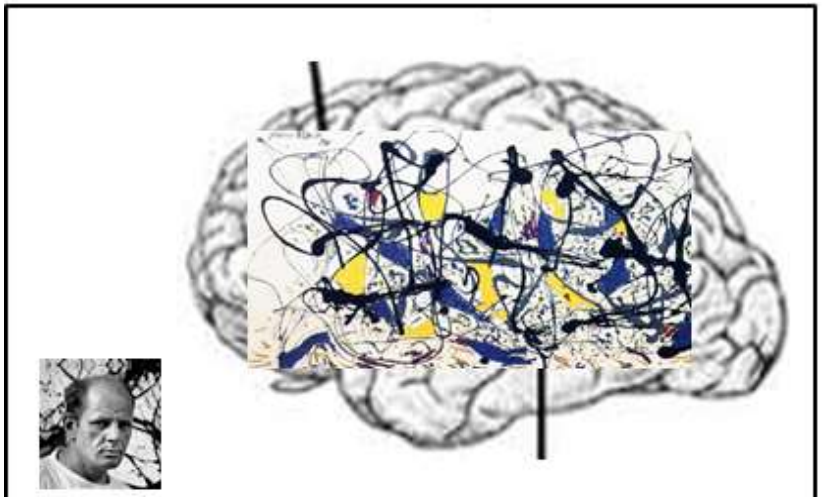
Language - structure and anatomy



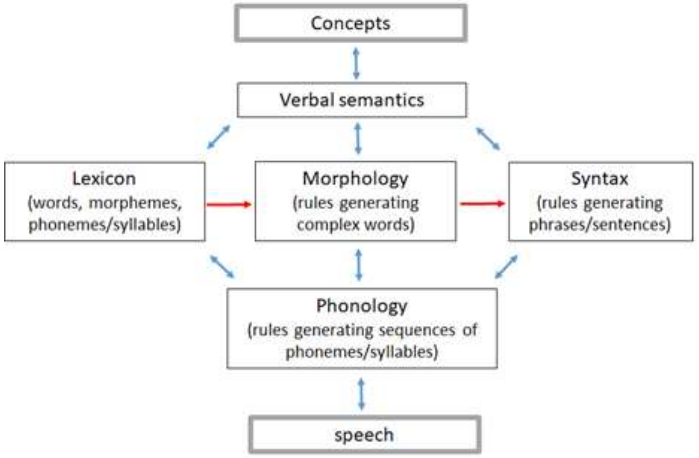
Lichtheim (1884)



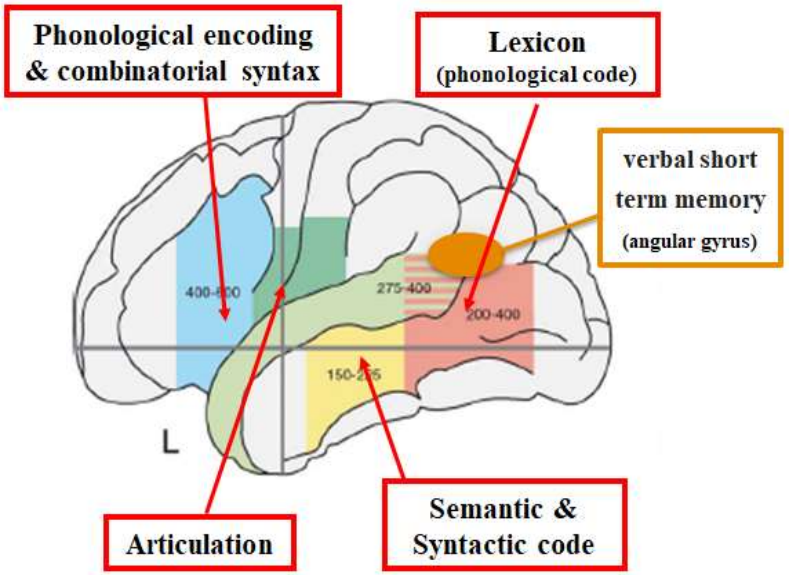
19th century


Polock, 1948

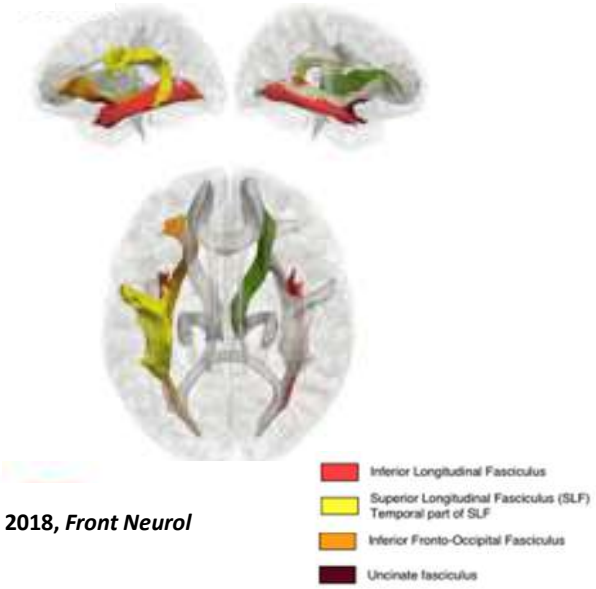
Language - structure and anatomy



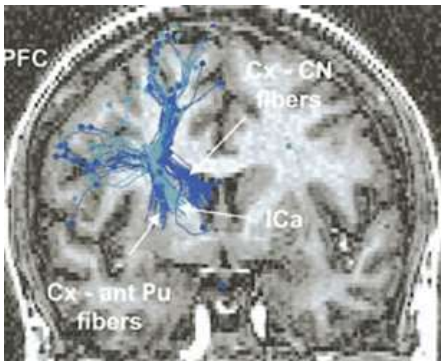
Adapted from Steven Pinker. Words and Rules: The Ingredients of Language; 1999



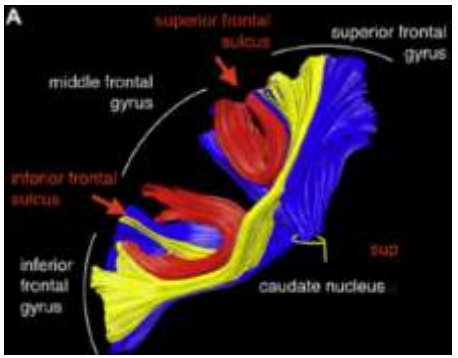
Adapted from Indefrey & Levelt, 2004, *Cognition*



Routier et al., 2018, *Front Neurol*



Lehéricy et al., 2004; *Ann Neurol*



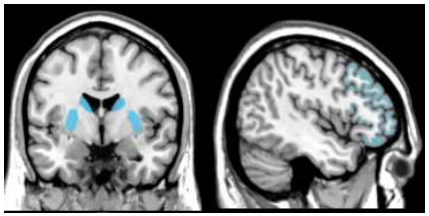
Catani et al., 2012, *Cortex*

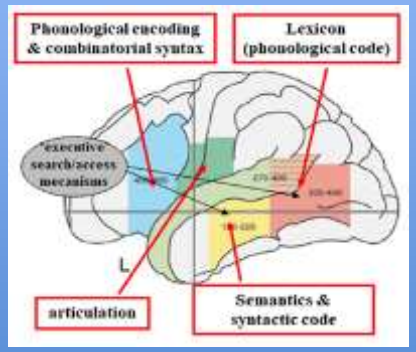
LANGUAGE – 'language performance'

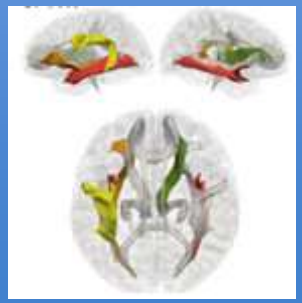
Linguistic Computations

Executive functions

Focalizing attention

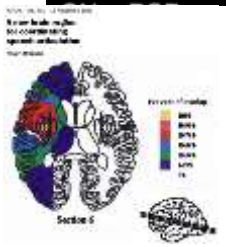






Speech

- **Programming articulation gestures**
- **Articulation**



Motor Systems

(motor cortex -> nerfs/muscles)

Exploring language with patients – using language models to understand patients

'Alzheimer's disease' AND *'language'* ≈ 7200 articles

Frontal-Temporal lobar degenerations (FTLD) ≈ 5000 articles

'Primary Progressive aphasia' AND 'language' *or 'speech'* > 2000 articles

'Frontotemporal dementia' AND 'language' *or 'speech'* > 1700 articles

'Progressive supranuclear palsy' AND 'language' *or 'speech'* > 500 articles

'Corticobasal syndrome' AND 'language' *or 'speech'* > 150 articles

'Huntington's disease AND 'language' *or 'speech'* > 600 articles

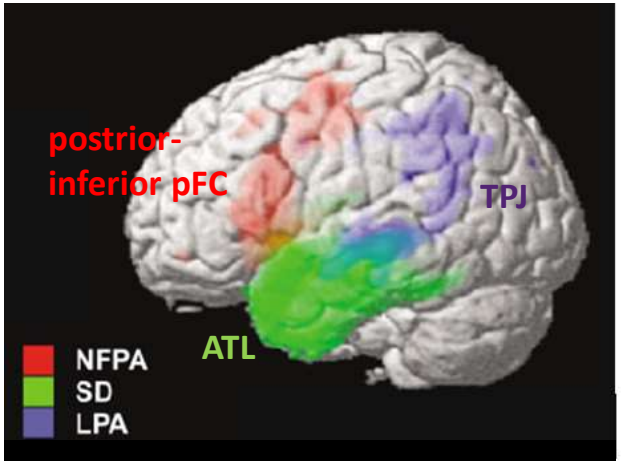
A major lesion model of language structure and anatomy: Primary Progressive Aphasias

First descriptions Arnold Pick (1892)

M. Mesulam (1982; 1987)
'Birth' of Primary Progressive Aphasias

E. Warrington (1975)
Snowden et al. (1989…)
Hodges et al. (1992…)
The concept of 'Semantic Dementia'

('intégré' depuis 2011 dans les APP; Critères internationaux Gorno-Tempini et al., 2011)



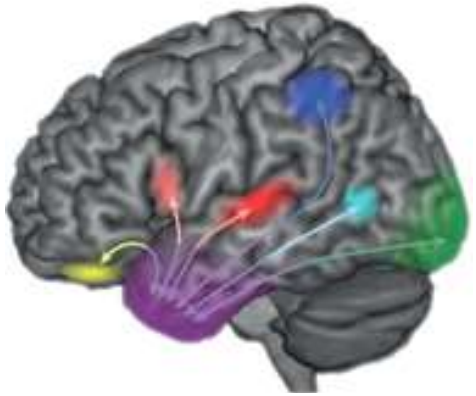
NFPA = APP nonfluente/agrammatique (N=11)
SD = démence sémantique / APP sémantique (N=10)
LPA = APP logopénique (N=10)

Gorno-Tempini et al., 2004

The PPA lesion model is less heterogeneous than vascular/stroke models. It covers the entire brain-language network, including the Anterior Temporal Lobes (ATL)

(usually not affected by stroke, artefacts on fMRI)

Semantic hub



Lambon Ralph et al. , 2017
Nature Reviews Neuroscience

Language Phenomenology of PPA variants

nonfluent/agrammatic variant

hypofluent

Phonemic paraphasias

Agrammatism

↓ Comprehension of complex sentences

Apraxia of speech

Weintraub et al, 1990 ; Grossman et al., 1996 ; Kertesz et al., 2003; Thompson et al., 1997

Breakdown of combinatory computations (phonology/syntax)
Impaired programming of articulation gestures

Logopenic variant

fluent with pauses

↓ word-finding

Verbal Paraphasias

↓ Comprehension/repetition of long sentences

Gorno-Tempini et al., 2004; 2008; 2011

- Lexical breakdown
- breakdown of verbal short-term memory

Semantic variant / Semantic Dementia

fluent

Semantic paraph asias

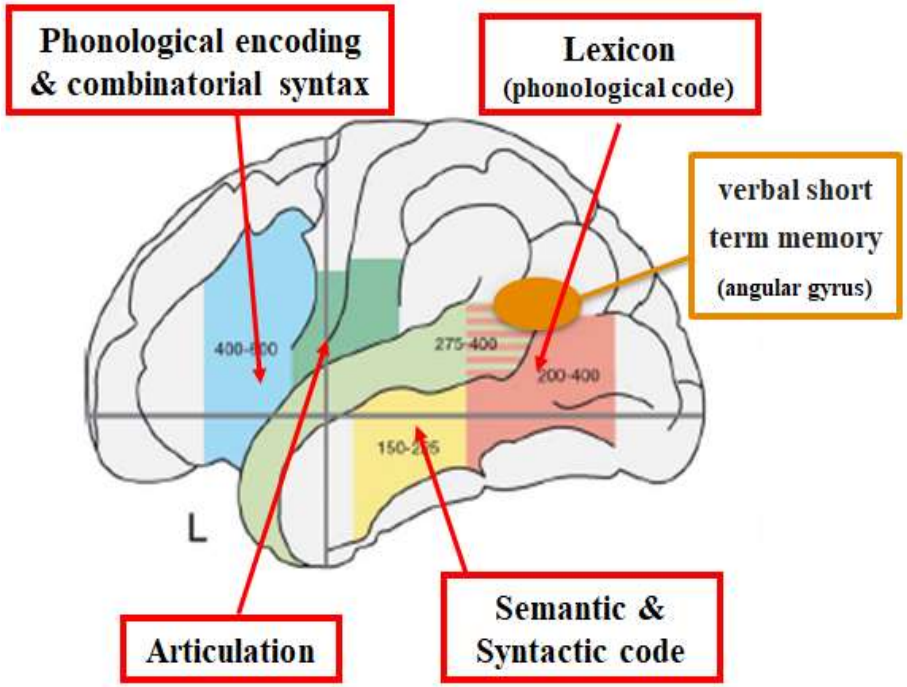
↓ word-finding

↓ Single-word comprehension

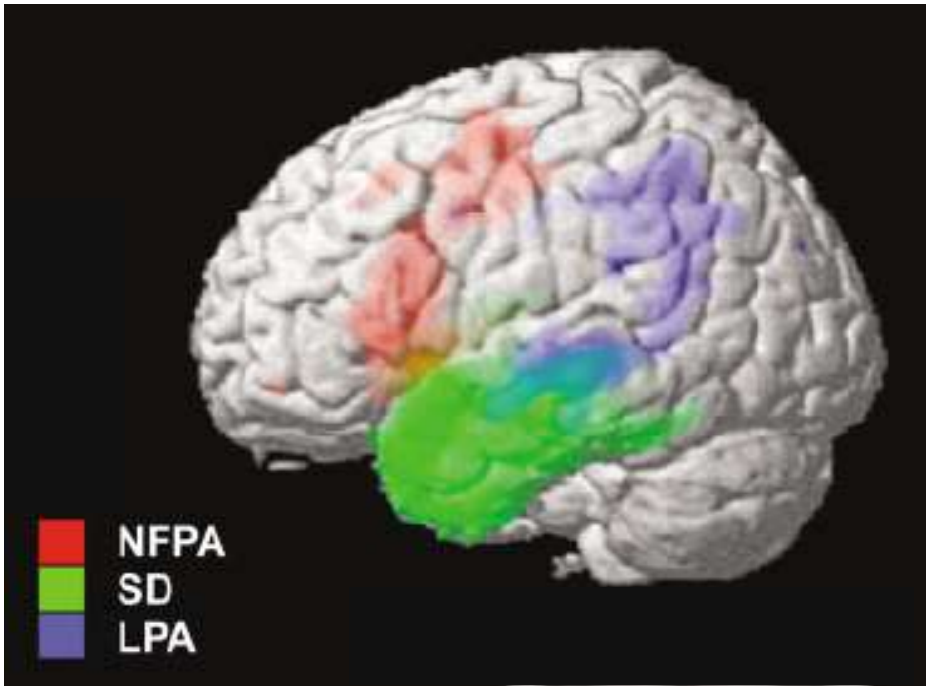
Grossman et al., 1996 ; Woollams et al., 2008; Hodges & Patterson, 2007

Breakdown of the semantic hub

PPA - anatomy



Indefrey & Levelt, 2004



NFPA = APP nonfluent/agrammatic (N=11)

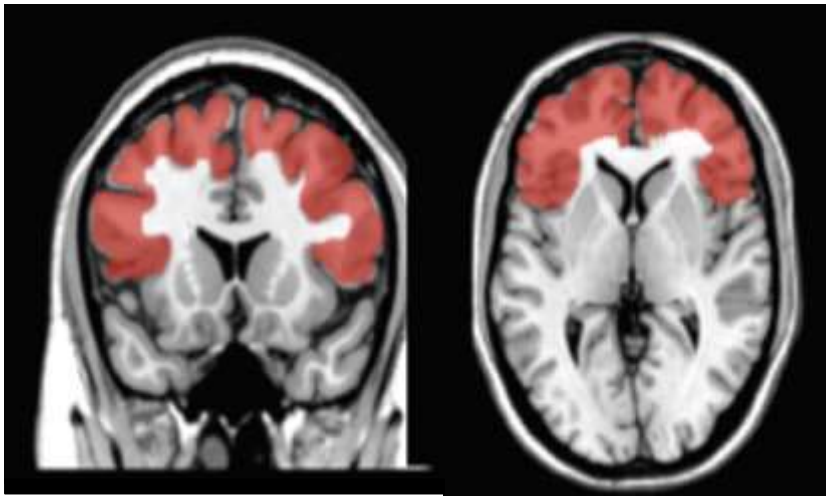
SD = semantic dementia / semantic PPA (N=10)

LPA = logopenic PPA (N=10)

Gorno-Tempini et al., 2004

Fronto-temporal Dementia

(behavioural variant FTLD)



Breakdown of executive functioning
(behavioural and cognitive)

- Inertia (behaviour/language)
- Breakdown of excutive-controlled research mechanisms in the lexical/semantic systems

Adynamic aphasia

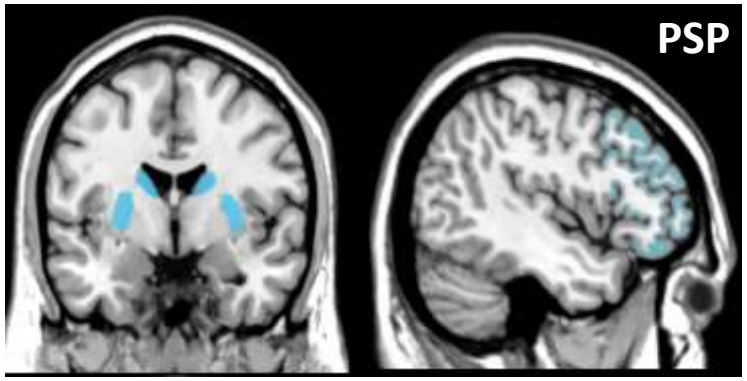
NEUROLOGY

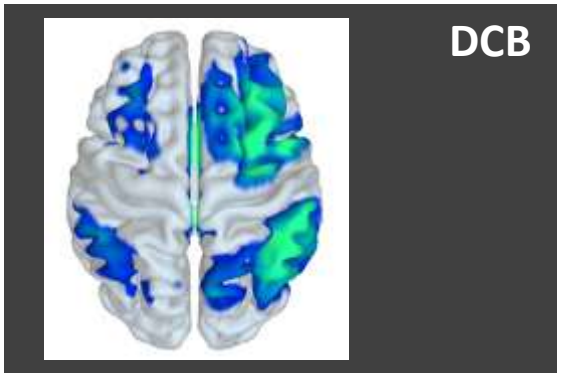
Neary et al., 1998

List 1 *The clinical diagnostic features of FTD: Clinical profile*
Character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental functions of perception, spatial skills, praxis, and memory are intact or relatively well preserved.

I. Core diagnostic features
  A. Insidious onset and gradual progression
  B. Early decline in social interpersonal conduct
  C. Early impairment in regulation of personal conduct
  D. Early emotional blunting
  E. Early loss of insight
II. Supportive diagnostic features
  A. Behavioral disorder
    1. Decline in personal hygiene and grooming
    2. Mental rigidity and inflexibility
    3. Distractibility and impersistence
    4. Hyperorality and dietary changes
    5. Perseverative and stereotyped behavior
    6. Utilization behavior
  B. Speech and language
    1. Altered speech output
      a. Aspontaneity and economy of speech
      b. Press of speech
    2. Stereotypy of speech
    3. Echolalia
    4. Perseveration
    5. Mutism

Progressive supranuclear palsy (PSP) and Cortico-basal Degeneration (CBD)





Breakdown of executive functionning

Adynamic aphasia

+ genuine language disorders

phonological and/or syntactic disorders, apraxia of speech (≈ nonfluent/agrammatic PPA)

Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges Lancet Neurol 2005; 8: 270-79

	Richardson's syndrome	PSP-P	PSP-PAGF	PSP-CBS	PSP-PNFA	Parkinson's disease
Rigidity	Axial much more than limb	Axial less than or the same as limb	Axial	Yes	Sometimes	Limb much more than axial
Bradykinesia	Mild	Moderate	Moderate	Yes	Mild	Moderate
Tremor	No	Yes/no (rest or jerky postural)	No	No	No	Yes (at rest)
Early falls	Yes	No	No	Sometimes	Sometimes	No
Early postural instability	Yes	No	Yes	–	–	No
Early cognitive decline	Often	No	No	No	Yes	No
Early abnormalities of eye movement	Yes	No	No	No	Sometimes	No
Response to levodopa	No	Often	No	No	No	Usually
Hyposmia	No	No	–	–	–	Yes
Cardiac MIBG	Normal	Normal*	Normal*	–	–	Abnormal

PSP=progressive supranuclear palsy. CBS=corticobasal syndrome. PAGF=pure akinesia with gait freezing. PNFA=progressive non-fluent aphasia. MIBG=^{123}I-labelled meta-iodobenzylguanidine. –=unknown. *Author's unpublished data.

Table 1: Clinical features of Richardson's syndrome, PSP-PAGF, PSP-CBS, PSP-PNFA, and Parkinson's disease

AMERICAN ACADEMY OF NEUROLOGY

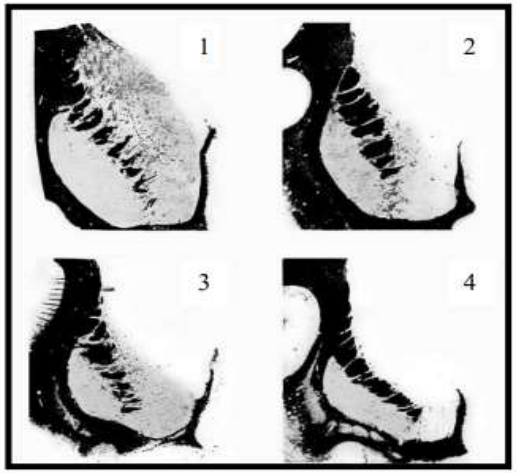
Armstrong et al., 2013

Criteria for the diagnosis of corticobasal degeneration

Table 4 Proposed clinical phenotypes (syndromes) associated with the pathology of corticobasal degeneration*

Syndrome	Features
Probable corticobasal syndrome	Asymmetric presentation of 2 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 2 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Possible corticobasal syndrome	May be symmetric 1 of: a) limb rigidity or akinesia, b) limb dystonia, c) limb myoclonus plus 1 of: d) orobuccal or limb apraxia, e) cortical sensory deficit, f) alien limb phenomena (more than simple levitation)
Frontal behavioral-spatial syndrome	Two of: a) executive dysfunction, b) behavioral or personality changes, c) visuospatial deficits
Nonfluent/agrammatic variant of primary progressive aphasia	Effortful, agrammatic speech plus at least one of: a) impaired grammar/sentence comprehension with relatively preserved single word comprehension, or b) groping, distorted speech production (apraxia of speech)
Progressive supranuclear palsy syndrome	Three of: a) axial or symmetric limb rigidity or akinesia, b) postural instability or falls, c) urinary incontinence, d) behavioral changes, e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

Huntington's Disease:
Basal ganglia / striatum AND Language

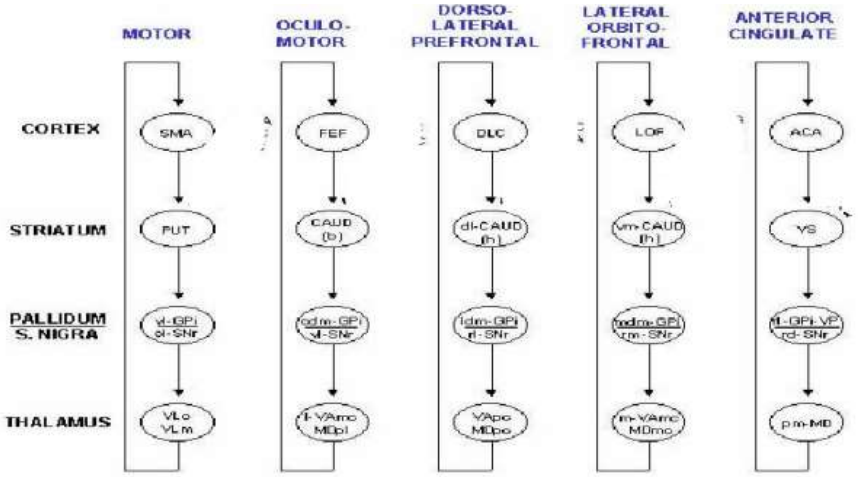


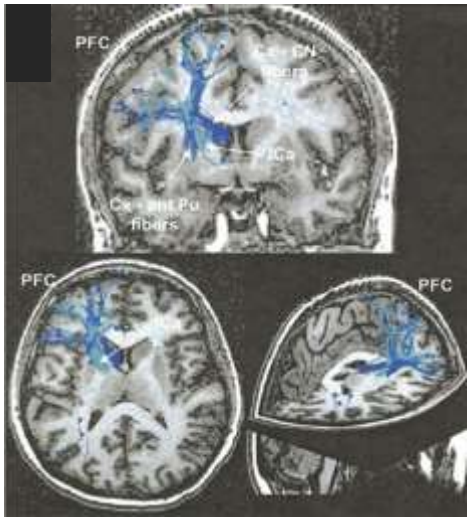
Huntington – Lesion Model of the striatum

Bird & Coyle, 1986

Parallel and segregated organisation frontal-striatal circuits

(Alexander et al., 1968)





Lehéricy et al., 2004

Impaired language processing

A NEUROCOGNITIVE PERSPECTIVE ON LANGUAGE: THE DECLARATIVE/ PROCEDURAL MODEL

Michael T. Ullman

What are the psychological, computational and neural underpinnings of language? Are these neurocognitive correlates dedicated to language? Do different parts of language depend on distinct neurocognitive systems? Here I address these and other issues that are crucial for our understanding of two fundamental language capacities: the memorization of words in the mental lexicon, and the rule-governed combination of words by the mental grammar. According to the declarative/procedural model, the mental lexicon depends on declarative memory and is rooted in the temporal lobe, whereas the mental grammar involves procedural memory and is rooted in the frontal cortex and basal ganglia. I argue that the declarative/procedural model provides a new framework for the study of lexicon and grammar.

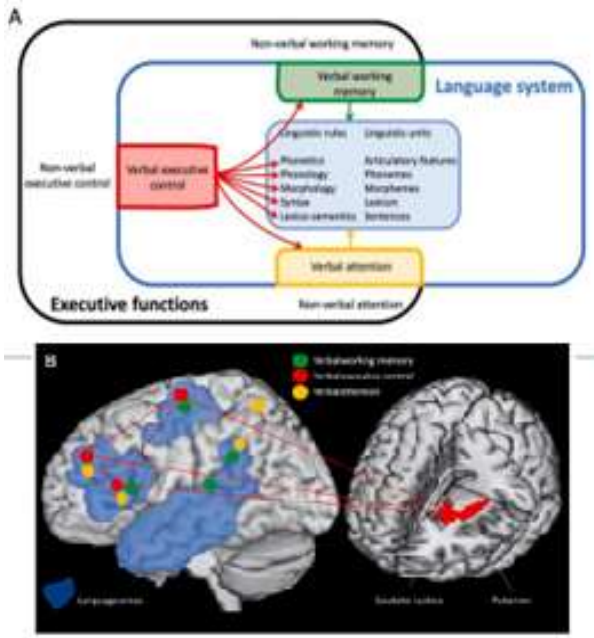
NATURE REVIEWS | NEUROSCIENCE VOLUME 2 | OCTOBER 2001 | 717

Temporal cortex → **Lexicon**

Frontal-striatal circuitry → **Rule computation (syntax)**

Ullman, 2001

Impaired executive capacities impacting on language



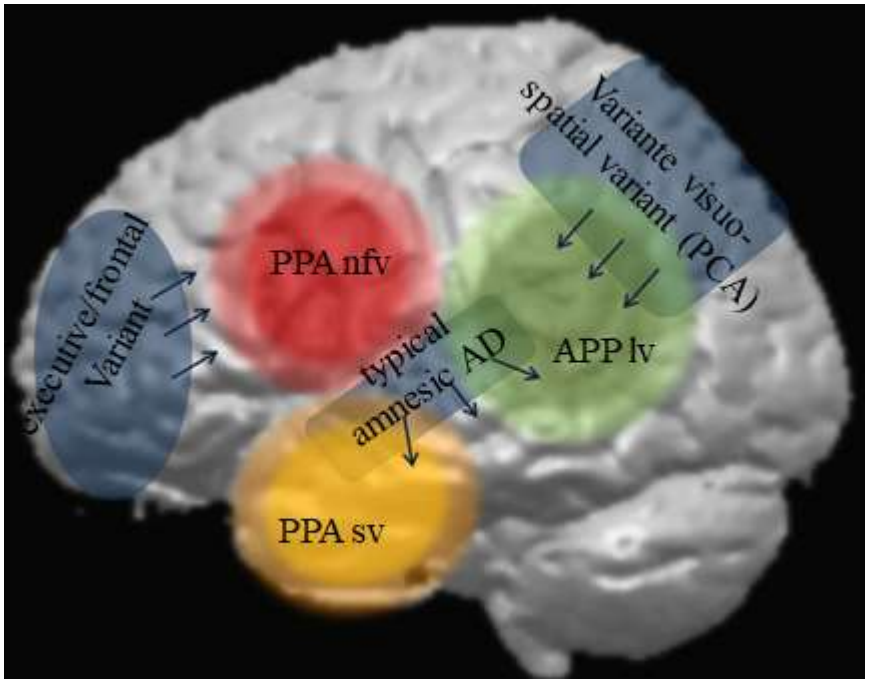
Jacquemot & Bachoud-Lévi, 2021

Language disorders are present in various neurodegenerative diseases

They represent major diagnostic and follow-up markers, and endpoints in therapy trials, and they should be therapy targets in such trials

Primary aphasia syndroms with possible underlying AD

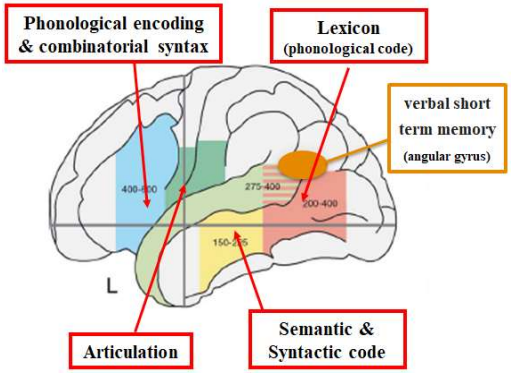
Secondary aphasia syndroms with underlying AD

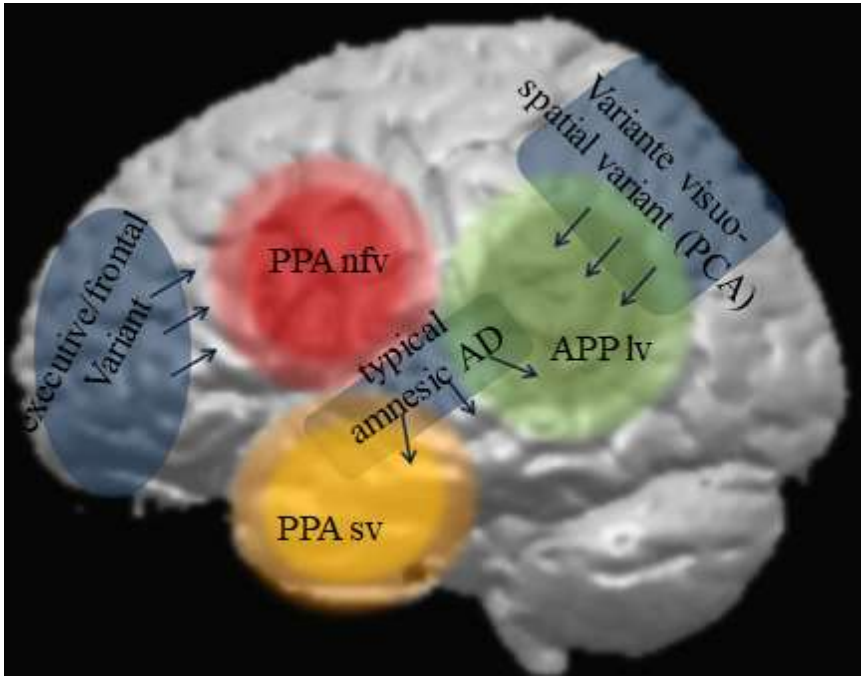


Alzheimer's Disease and its variants

Primary aphasias (‘language variants of AD’)

Secondary aphasias in AD





Typical amnestic AD: lexical + semantic disorders
(Schnyder et al., 1999; Perri et al., 2011)

Visual Variant / PCA: logopenic profile
(Crutch et al., 2013)

Frontal variant: adynamic aphasia

Therapy using non-invasive brain stimulation (NIBS) ?

TMS / tDCS studies targeting language in neurodegenerative diseases

Stim method	Nº of studies	Single / Cumul	Mean N	Brain targets
Alzheimer's disease				
TMS	17	Both	30	DLPFC; Broca and Wernicke; somatosensory cortex; parietal cortex; IFG; STG; precuneus
tDCS	16	Both	19	DLPFC; temporal cortex; TPC
Primary Progressive Aphasia				
TMS	3	Both	4	DLPFC; prefrontal cortex
tDCS	17	Both	15	DLPFC; IFG; frontotemporal; TPC; ATL; posterior perisylvian
Behavioral Frontotemporal Dementia				
TMS	1	Cumulative	9	DLPFC
tDCS	3	Both	12	DLPFC; prefrontal cortex
Parkinson's disease				
TMS	1	Cumulative	10	Ve
tDCS	7	Both	23	DLPFC; moto
Dementia with Lewy Bodies				
tDCS	1	Single	13	DLF
Corticobasal Syndrome				
tDCS	1	Single	17	Parieta
Progressive Supranuclear Palsy				
tDCS	3	Both	7	DLPFC; m
Posterior Cortical Atrophy				
tDCS	1	Cumulative	1	DLF

heterogenous results

~10 % without effects

~40 % improvement maintained for > 1 month

Limits of NIBS interventions

- **Small cohorts**
- **No sham**
- **No double blind**
- **Brain targets**

tDCS in the semantic variant of PPA

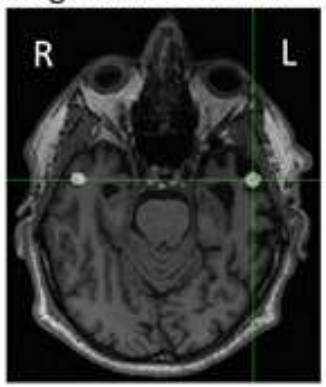
- double-blind, sham-controlled design

- single-shots (single sessions) tDCS - crossover procedure

(left excitatory-anodal, right inhibitory-cathodal, sham)

sv-PPA

Neuro-navigation: 3D T1 RMI

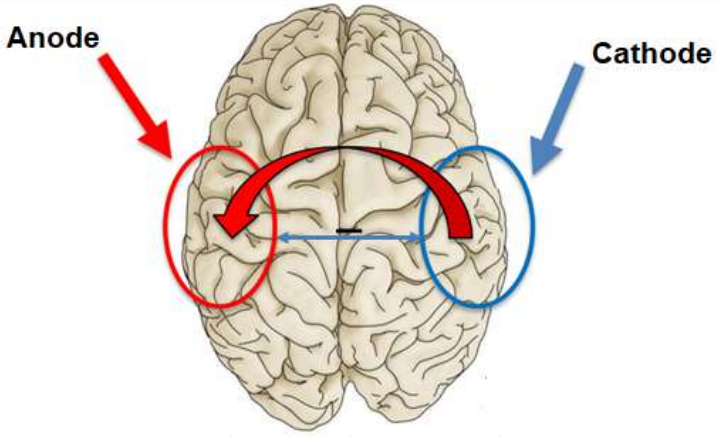


Anterior temporal lobes

MNI coordinates

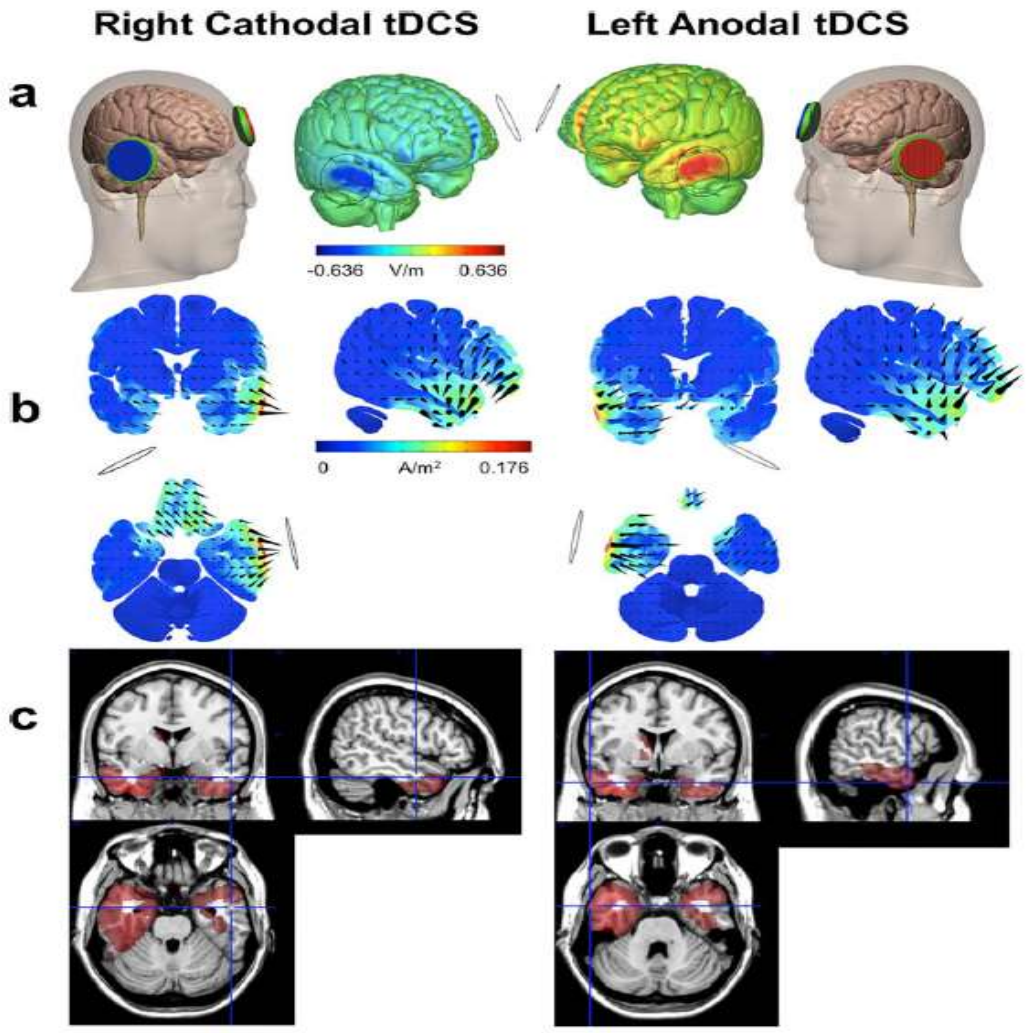
Left (x=-52, y=2, z=-28)

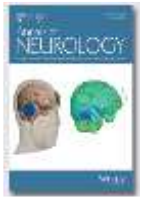
Right (x=53, y=4, y=-32)



inter-hemispheric rivalry

Semantic Dementia study (N=12)





Direct Current Stimulation Over the Anterior Temporal Areas Boosts Semantic Processing in Primary Progressive Aphasia

Marc Tetchmann, MD, PhD,[1,2] Constance Lesoil, MD,[1,2] Juliette Godard, MSc,[2,3,4] Marine Vernet, PhD,[2,3] Anne Bertrand, MD, PhD,[5] Richard Levy, MD, PhD,[2,6] Bruno Dubois, MD,[1,2] Laurie Lemoine, MSc,[7] Dennis Q. Truong, MSc,[8] Marom Bikson, PhD,[8] Aurélie Kas, MD, PhD,[9] and Antoni Valero-Cabré, MD, PhD[2,3,4,10]

a) radial electric field

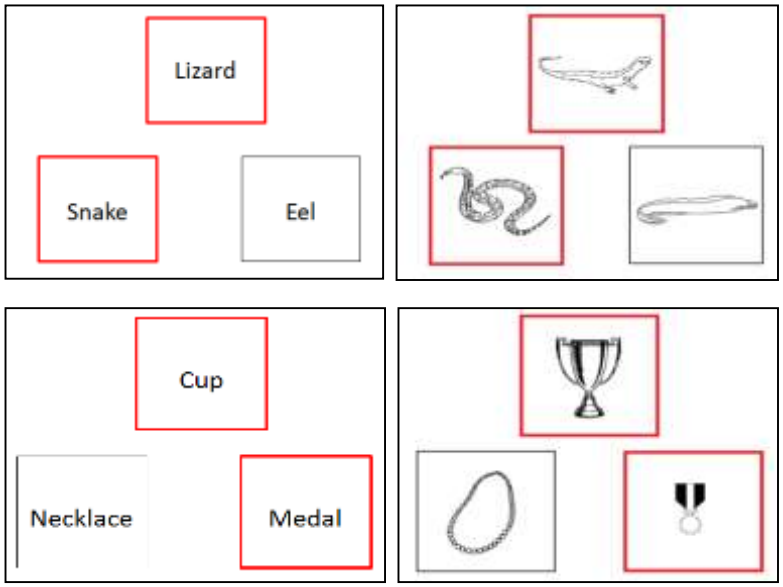
b) current density magnitude

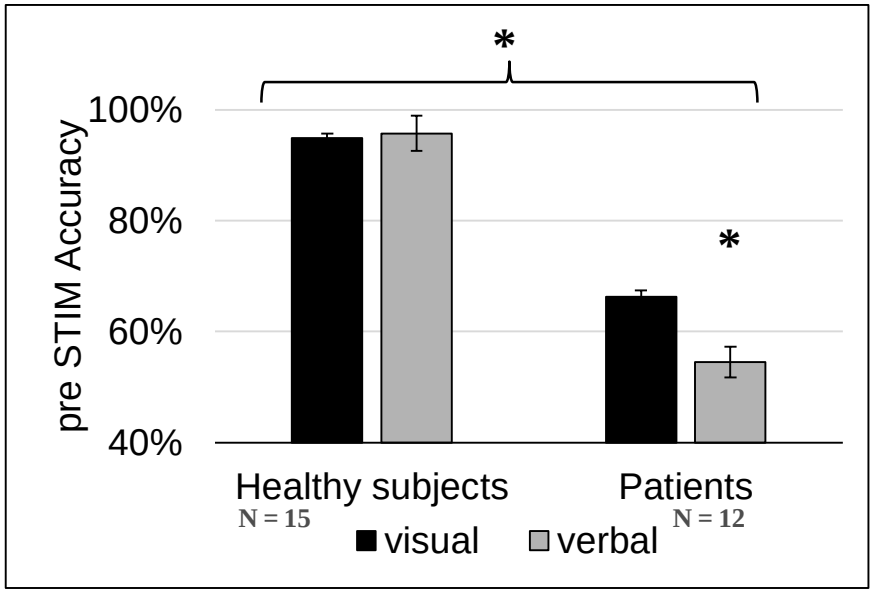
c) hypometabolic regions in the 12 semantic PPA patients

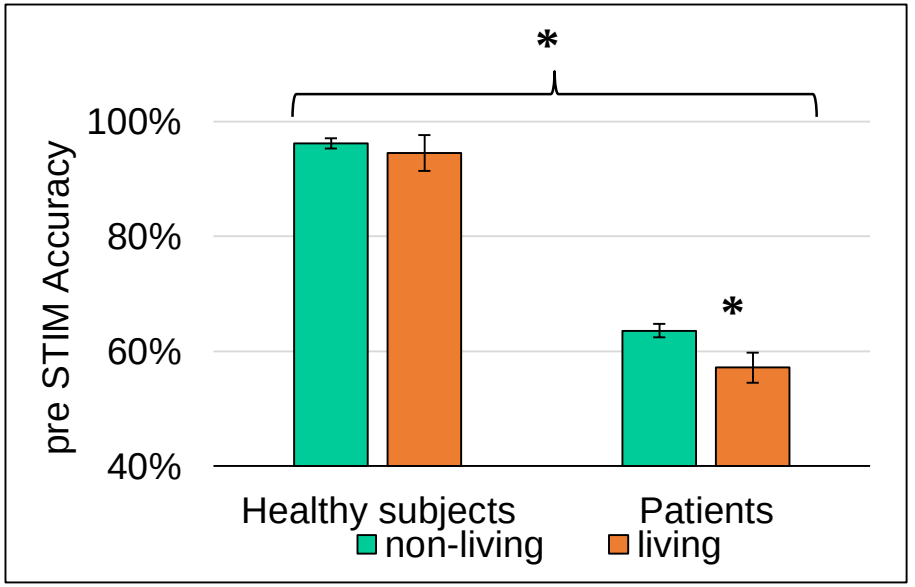
Semantic matching task

Dimensions

verbal / non-verbal [pictures]
'living' / 'non-living'

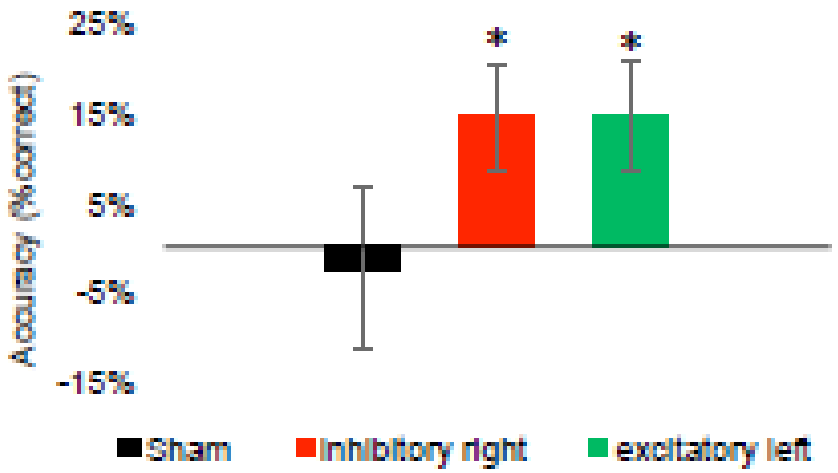




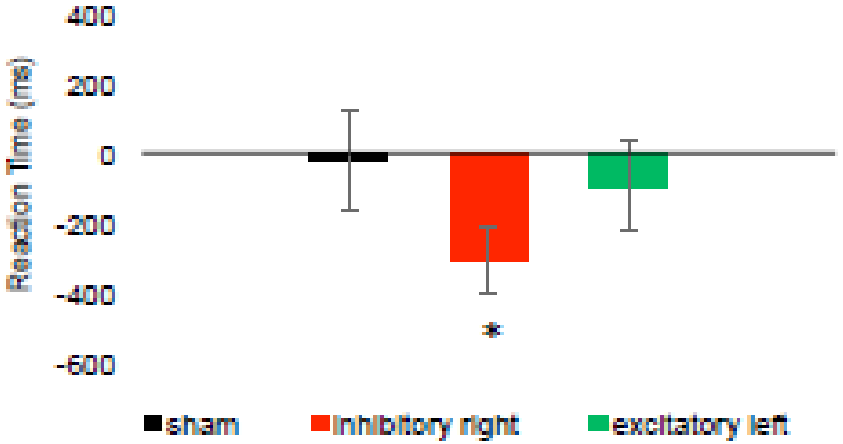


t-DCS effects - gain of function

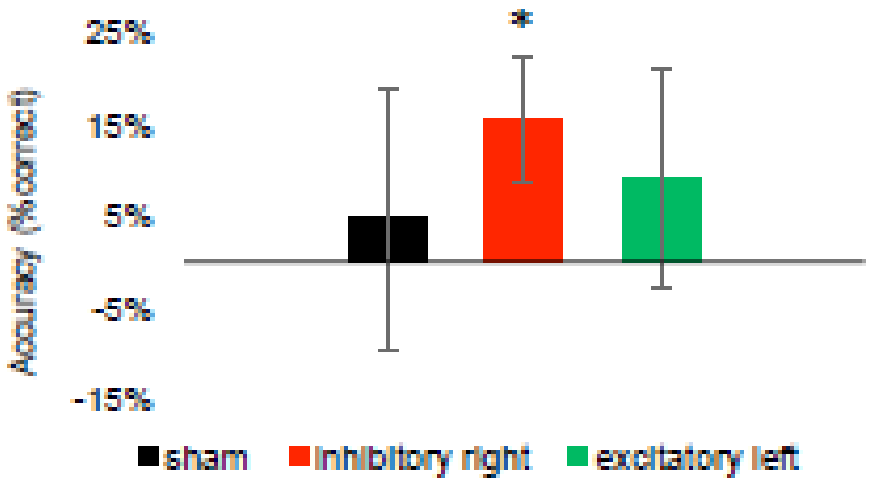
verbal modality

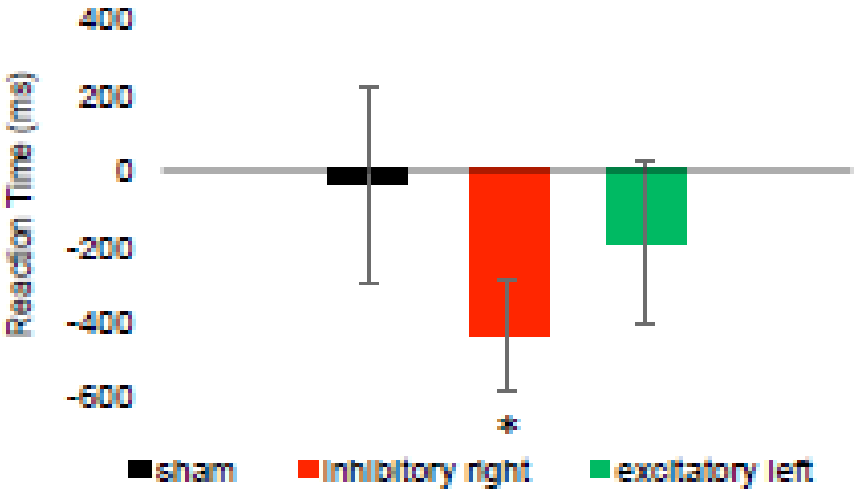


'living' category



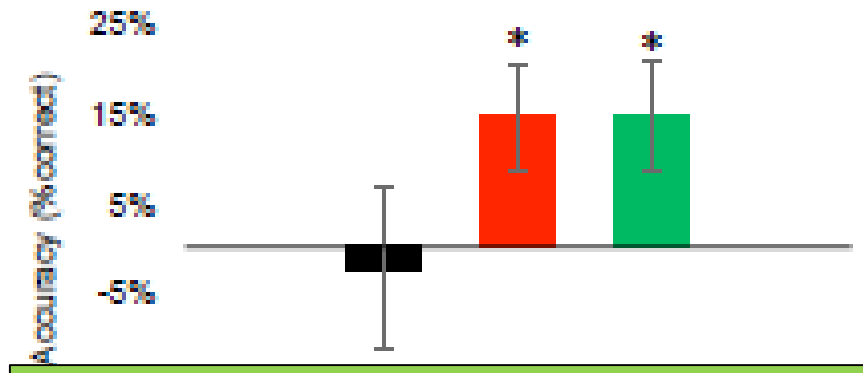
'verbal' x 'living'





t-DCS effects - gain of function

verbal modality



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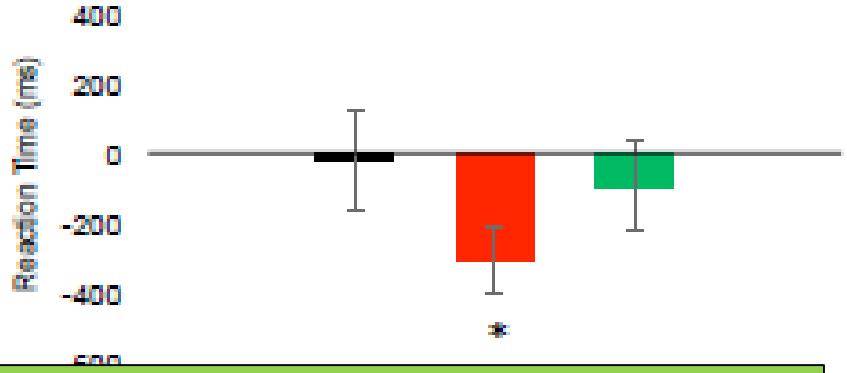

→ **intra-semantic effects**

→ **validation studies needed with larger patient cohorts using multi-day tDCS regimes (➪ brain plasticity – therapy effects)**