NeuroRehab Lab

Neuropsychological Rehabilitation Laboratory

NRL

Est. 2008

fMRI Applied to Clinical Populations

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MADCC

MICHIGAN ALZHEIMER'S DISEASE CORE CENTER

No Disclosures or Conflicts

Caveats

- Cannot cover all populations or methods in 1 hour
- This lecture is meant to be an **overview** of how fMRI can be applied in clinical populations
- Most of you are interested in aging/dementia and mood/anxiety disorders
  - Lecture designed to highlight basic fMRI design and application to these populations
  - Can easily extrapolate to your population of interest
- Requires understanding / experience with clinical presentation and underlying disease mechanisms (i.e., neuroanatomically informed approach)
  - Don’t be afraid of teamwork! You CANNOT do everything!

Overview

First (mandatory) hour:

1. Discuss task-based fMRI
    - Traditional contrast approaches
        - Block vs. event related
    - Examples of connectivity
    - Examples of meta-analyses (MDD & Anxiety)

2. Discuss resting-state fMRI
    - ICA & seed-based approaches
    - Graph theory methods
    - Dynamic connectivity

Second (optional) hour: open discussion

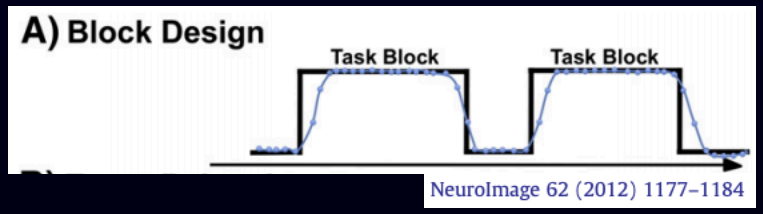
Task-Based fMRI – Block Design

- ”Original” approach to fMRI analysis
  - Compare BOLD signal during one well-defined and time-locked state to that of another

Relevant article: The mixed block/event-related design

Steven E. Petersen [a,b,c,d], Joseph W. Dubis [a,*]

NeuroImage 62 (2012) 1177–1184



- Identical trial types within a given block (e.g., novel stimuli)
- Separated by “rest periods” (allow HRF to return to baseline)
- Could have multiple types of blocks

(Some) Pros

- Robust signal given relatively large amount of data
- Ideal for more lengthy or continuous tasks (e.g., reading, spatial navigation)
- Ideal for examination/activation of specific regions of interest (e.g., surgery planning)

(Some) Cons

- Poor temporal resolution for rapid events
- Cannot distinguish between trial types (e.g., correct vs. incorrect)
- Cannot distinguish positive vs. negative phases

Task-Based fMRI- Event Related

- ”Original” approach to fMRI analysis
  - Compare BOLD signal during one well-defined and time-locked state to that of another

Relevant article: The mixed block/event-related design

Steven E. Petersen [a,b,c,d], Joseph W. Dubis [a,*]

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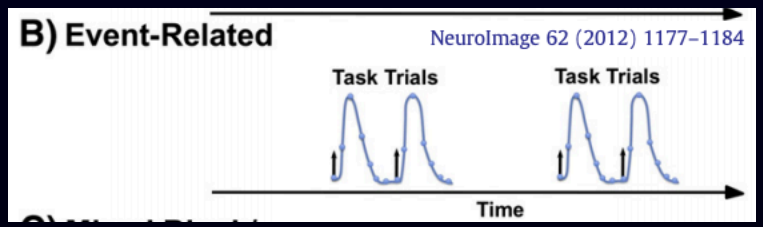


- Identical OR distinct trial types
- Separated by “rest” periods
  - Slow event related (e.g., 8s ISI)
  - Jittered – vary ISI to capture different phases of HRF

(Some) Pros

- Allows for examination of specific trial types (e.g., correct vs. incorrect)
- Greater flexibility vs. block design
- May be more appropriate for connectivity analyses

(Some) Cons

- Reduced SNR vs. block design = less power = more trials
- May increase time

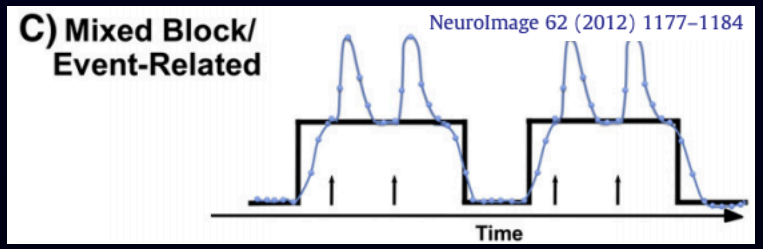
Task-Based fMRI – Mixed Block/Event

- ”Original” approach to fMRI analysis
  - Compare BOLD signal during one well-defined and time-locked state to that of another

Relevant article: The mixed block/event-related design

Steven E. Petersen [a,b,c,d], Joseph W. Dubis [a,*]

NeuroImage 62 (2012) 1177–1184



- Multiple (typically related) trials within a given block
- Separated by jittered ISIs (“rest” periods)

(Some) Pros

- Provides power associated with block design
- Allows for examination of specific trial types (e.g., correct vs. incorrect)
- Sensitive to transient activity (see article)

(Some) Cons

- “The mixed design is a very finicky beast…” that can cause reduced power and signal misattribution
- Different type of power calculations

Two Primary Types of Pathology in Alzheimer's Disease

Frequency of Stages of Alzheimer-Related Lesions in Different Age Categories

H. BRAAK[1] AND E. BRAAK

Neurobiology of Aging, Vol. 18, No. 4, pp 351–357, 1997

0197-4580/97 $17.00 + .00

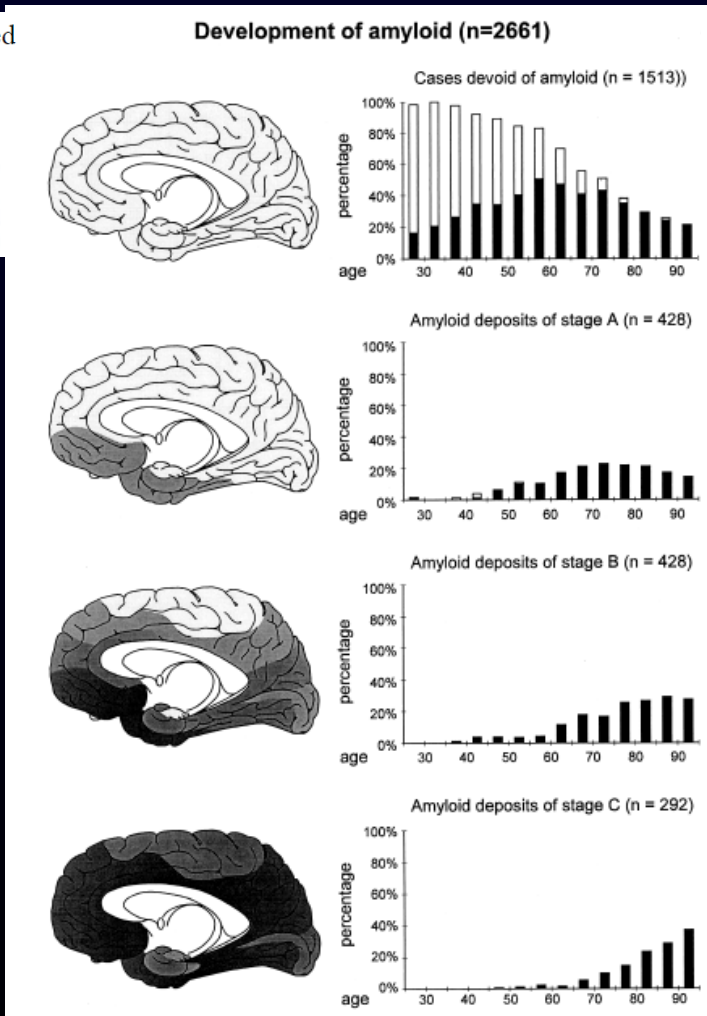


FIG. 2. Development of amyloid deposits in 2,661 nonselected autopsy cases. The first line displays th frequency of cases devoid of changes in relation to the total number of cases in the various age categories. Th second, third, and fourth lines are similarly designed, and show the evolution of the AD-related changes. Th dark areas of the columns refer to subgroups showing the presence of neurofibrillary changes.

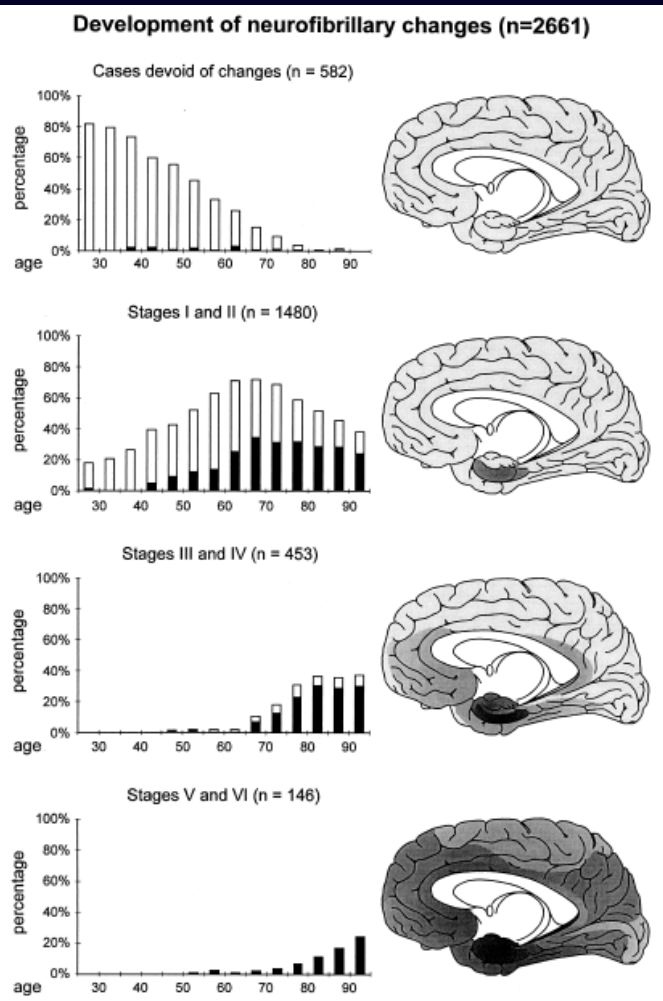
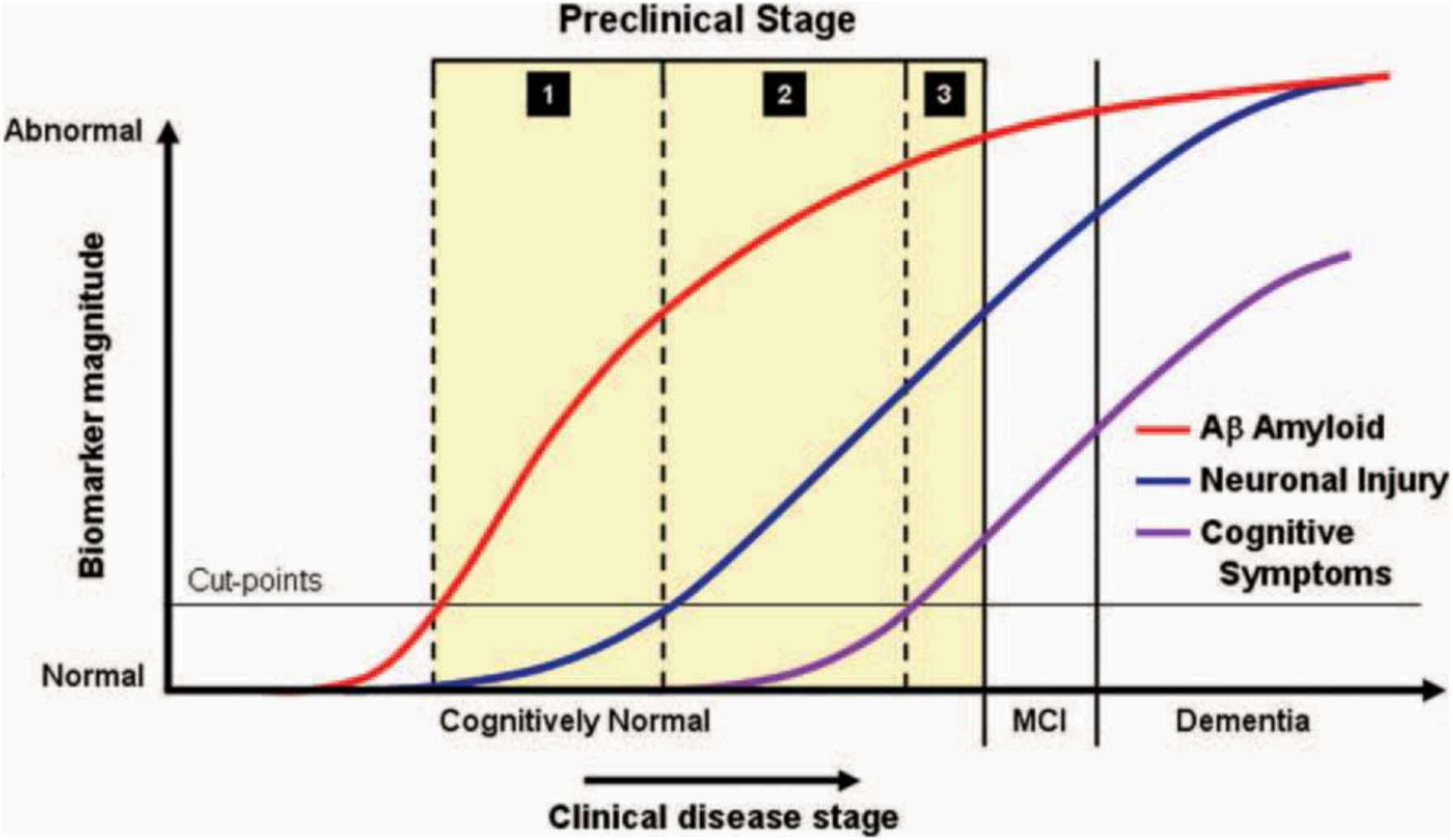


FIG. 3. Development of neurofibrillary changes in 2,661 nonselected autopsy cases. The first line displays the frequency of cases devoid of changes in relation to the total number of cases in the various age categories. The second, third, and fourth lines are similarly designed, and show the evolution of the AD-related changes. The dark areas of the columns represent the subgroups displaying amyloid deposits

Disease Begins Decades Before Symptoms

ANN NEUROL 2012;71:765–775



Ecologically Relevant Memory Test

Neurorehabilitation and Neural Repair 25(3)

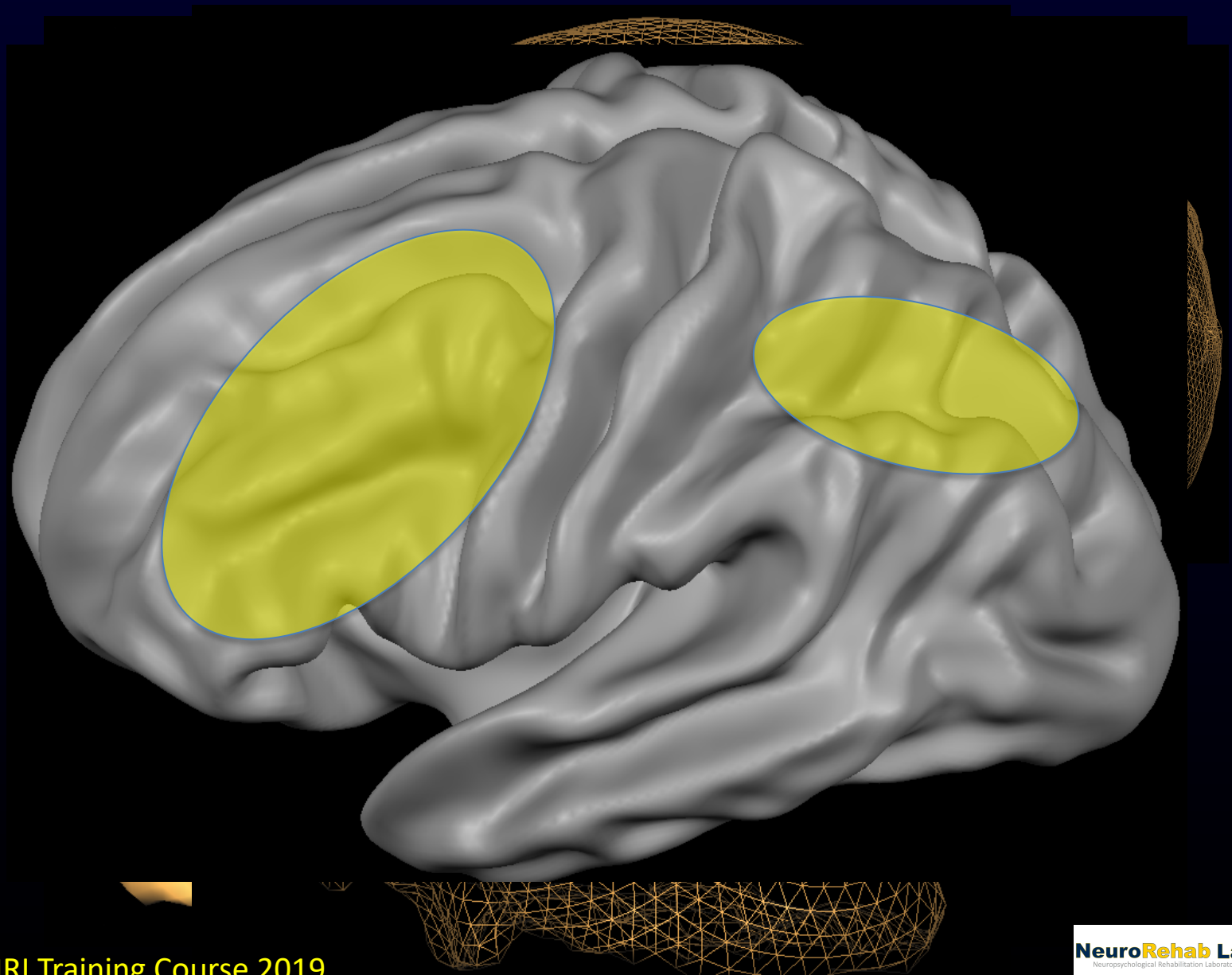
Shawn

All are common complaints

B.M. Hampstead et al. / Neuropsychologia 49 (2011) 2349–2361

B.M. Hampstead et al. / Brain Stimulation 7 (2014) 314–324

Common Memory-Related Neuroanatomy



Disease Begins Decades Before Symptoms

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

C.R. Jack Jr. et al. / Alzheimer's & Dementia 14 (2018) 535-562

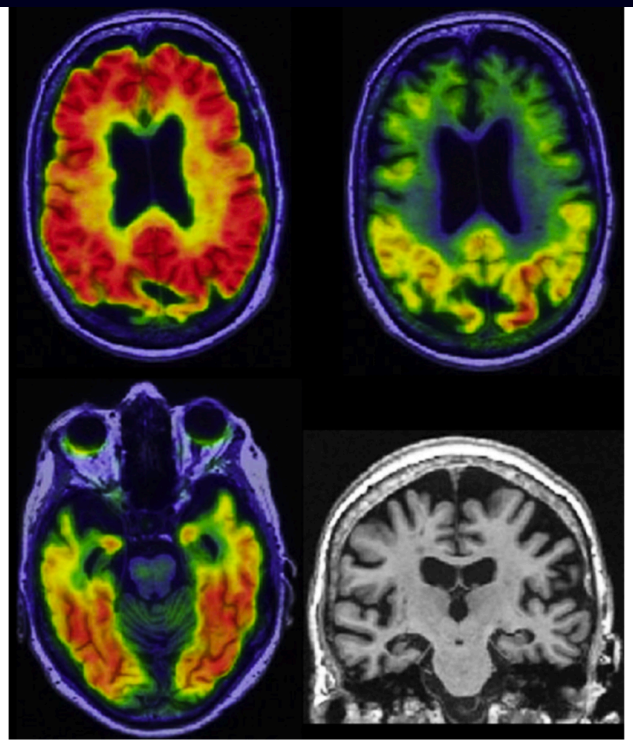


Fig. 1. Alzheimer's disease with dementia. A 75-year-old woman with amnestic multidomain dementia. Participant in the Mayo Alzheimer's Disease Research Center. Abnormal amyloid PET with Pittsburgh compound B (top left), tau PET with flortaucipir (top right and bottom left), and atrophy on MRI (bottom right). Biomarker profile A+T+(N)+.

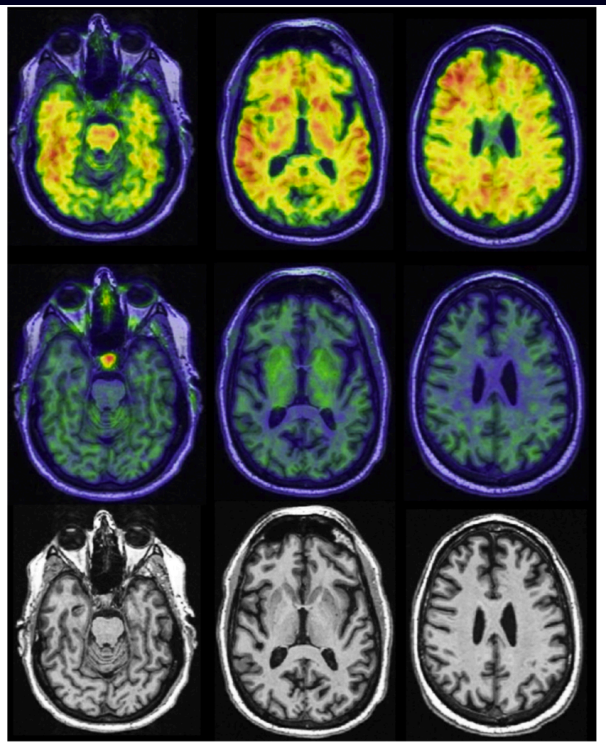


Fig. 2. Preclinical Alzheimer's pathologic change. A cognitively unimpaired 67-year-old man. Participant in the Mayo Clinic Study of Aging. Abnormal amyloid PET (Pittsburgh compound B, top row), no uptake on tau PET (with flortaucipir, middle row), no atrophy on MRI (bottom row). Biomarker profile A+T−(N)−.

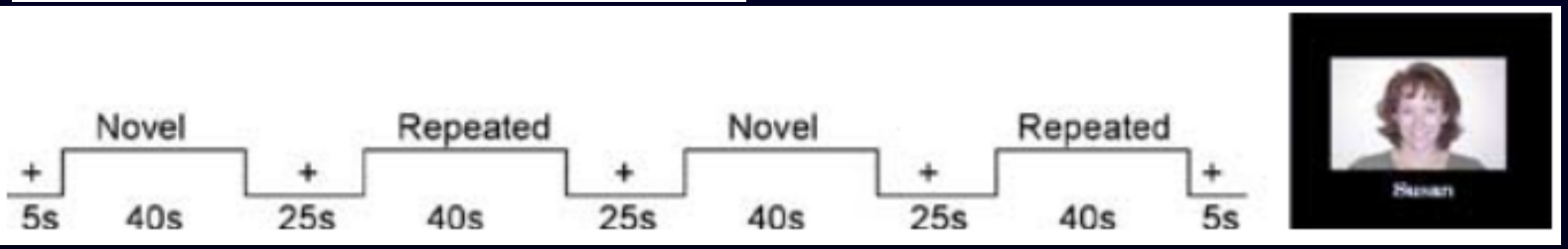
Early Task-Related Findings in Aging/Dementia

Functional MRI Studies of Associative Encoding in Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease

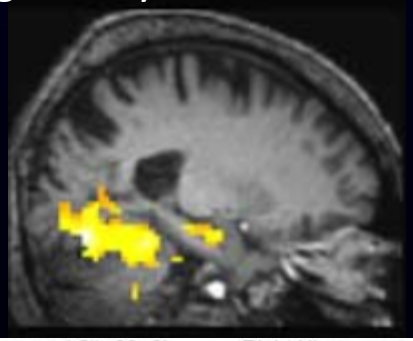
ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

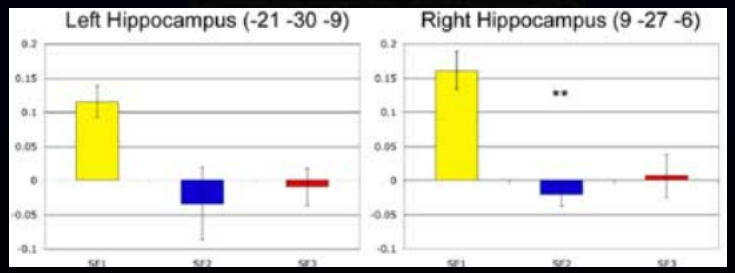
REISA SPERLING

Possible early "hyperactive" period followed by hypoactivation



Cognitively intact older adults





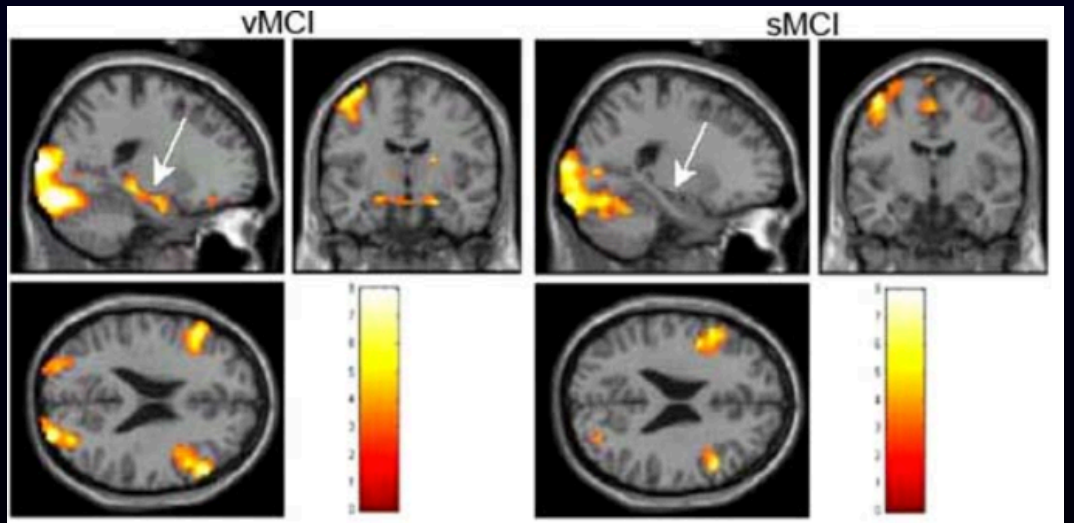
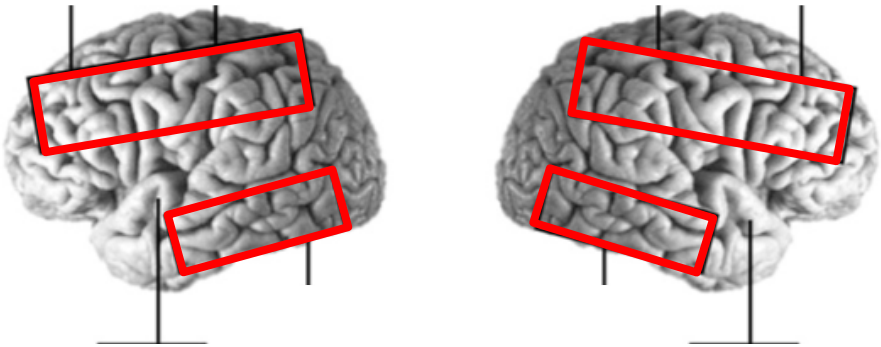


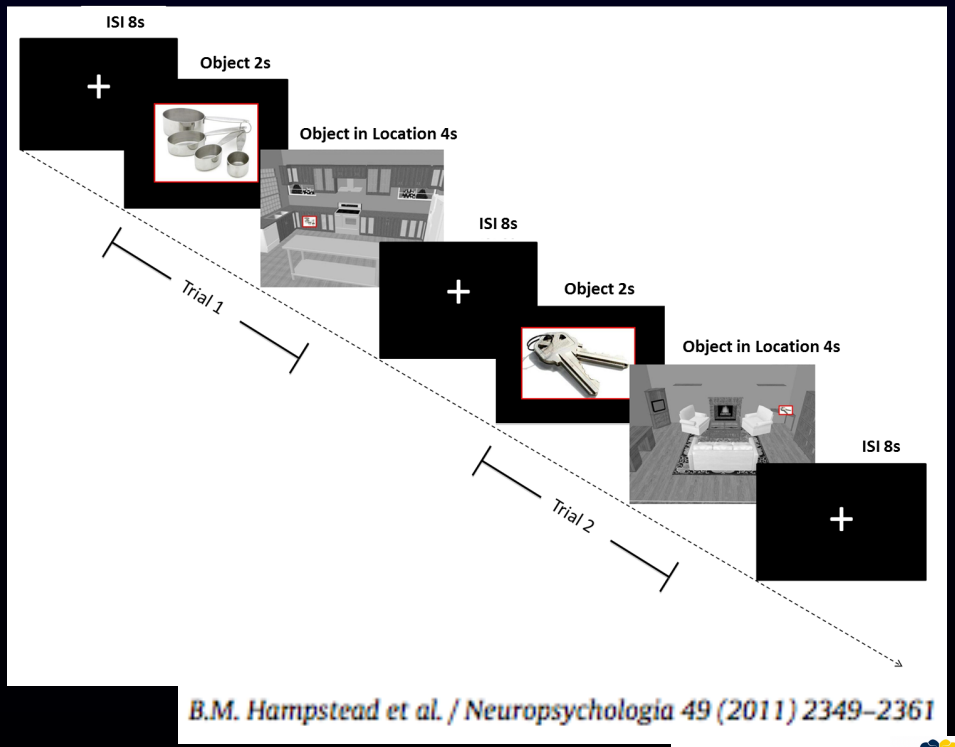
FIGURE 3. Group fMRI data in two groups of MCI subjects, based on the CDR Sum of Box score, was analyzed with ICA. Very mild impaired MCI (vMCI) subjects show significant hippocampal activation that is strongly linked to the timing of the fMRI paradigm ($P < 0.001$). More significantly impaired MCI (sMCI) subjects demonstrated very little hippocampal activation, despite similar or increased neocortical activation.

Functional MRI: Task-based (slow ER)

Ecologically Relevant: Object-location paradigm



A. Postma et al./Neuroscience and Biobehavioral Reviews 32 (2008) 1339–1345



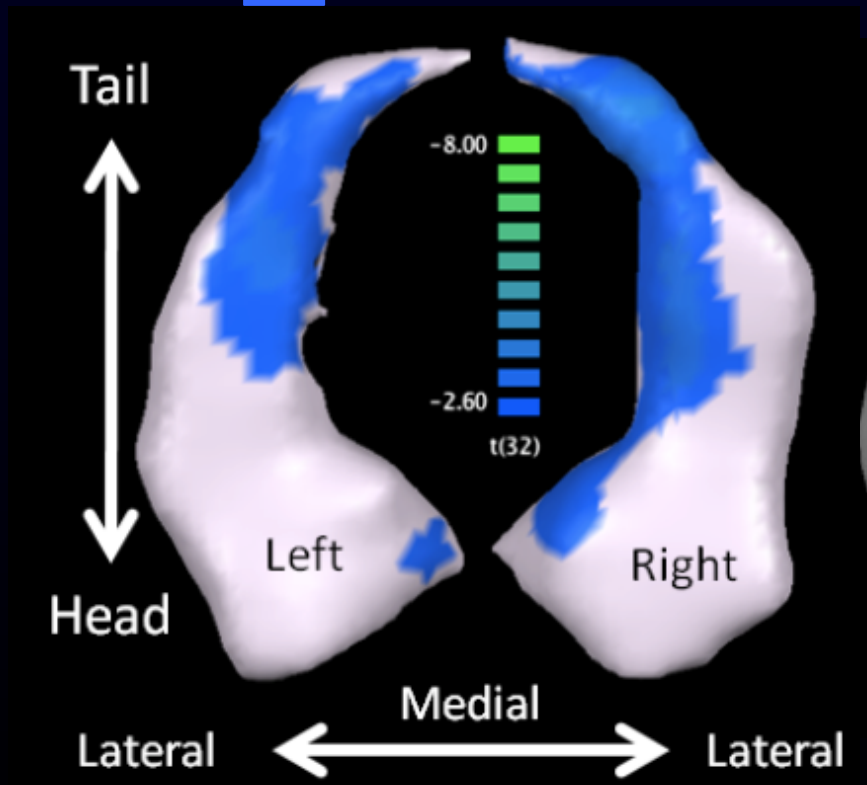
B.M. Hampstead et al. / Neuropsychologia 49 (2011) 2349–2361

What Happens in MCI Patients?

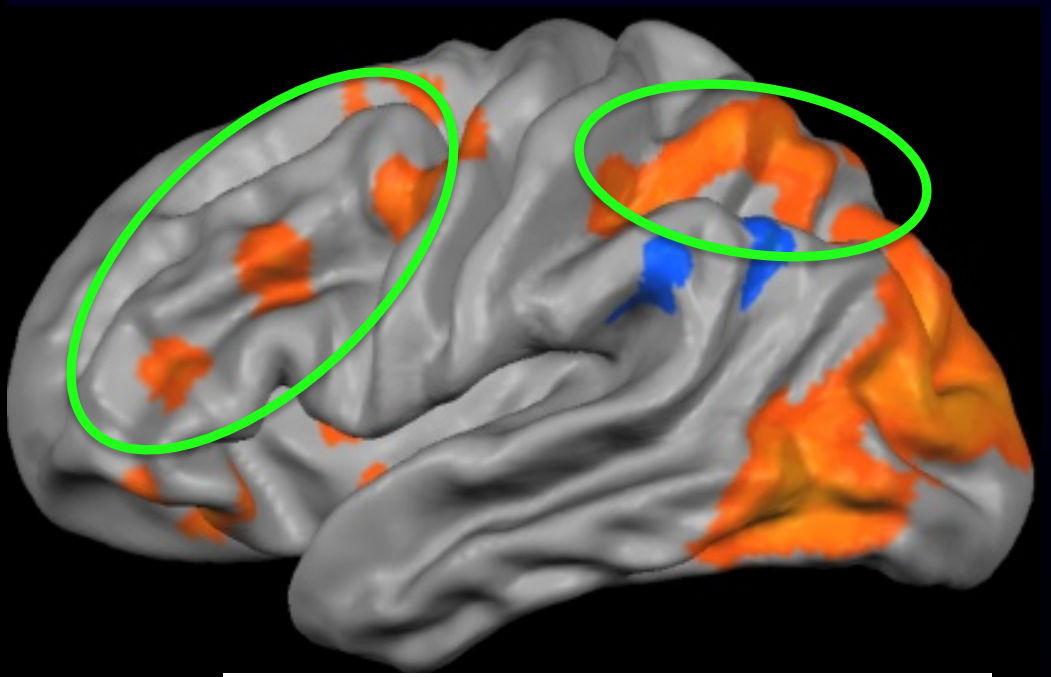
Healthy Controls Show Greater Activation During Encoding

Novel (correct) > Repeated

HEC > MCI

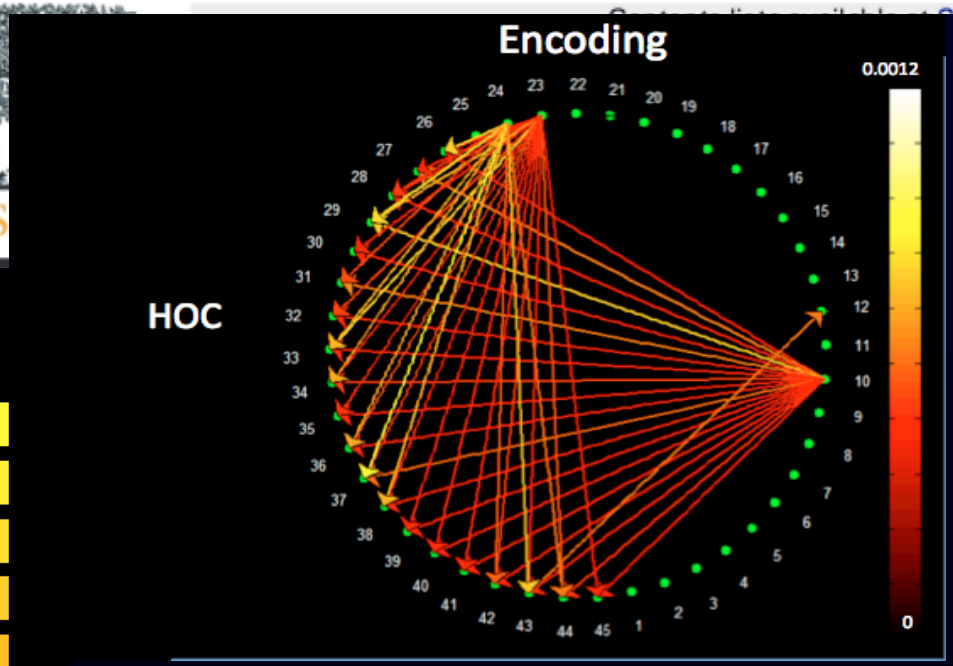


HEC > MCI



B.M. Hampstead et al. / Neuropsychologia 49 (2011) 2349–2361

MCI Patients Process Information Shallowly



HOC – left hemisphere – frontoparietal control network critical for encoding (IFJ, aIPS, PCC)

MCI – right FEF – basic attentional saccades

So how can we increase cognitive control?

Hampstead fMRI Training Course 2019

Mnemonic Strategy Training

	Mnemonic Strategy Training (MST)	Spaced Retrieval Training (SRT)
MCI	29 (21 fMRI)	29 (18 fMRI)

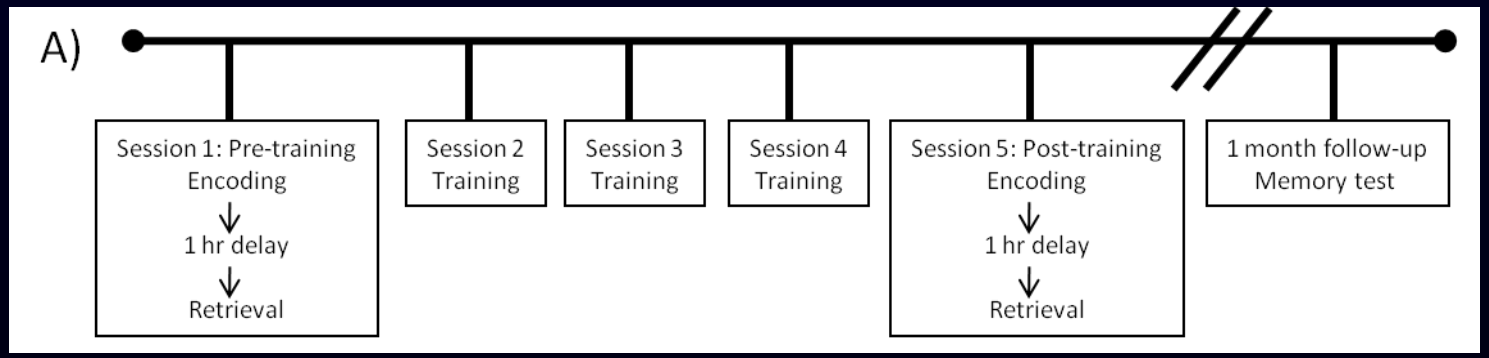
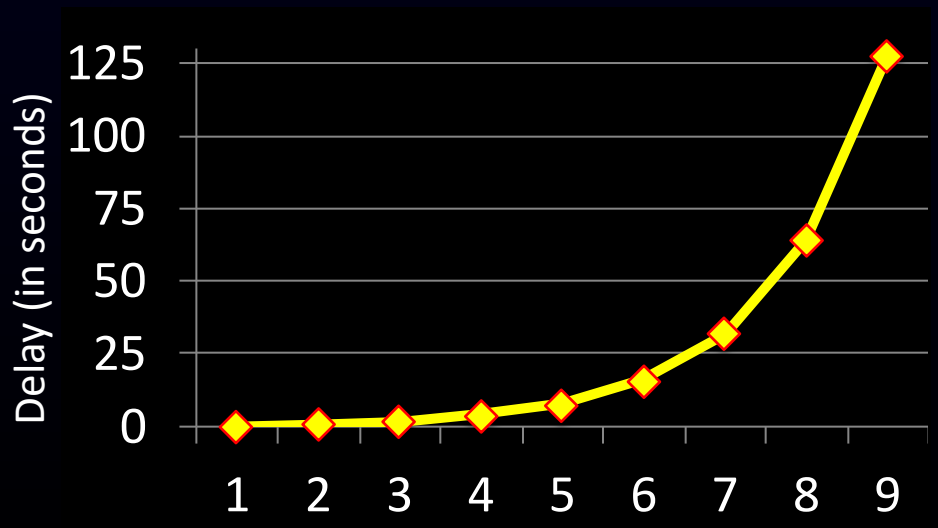
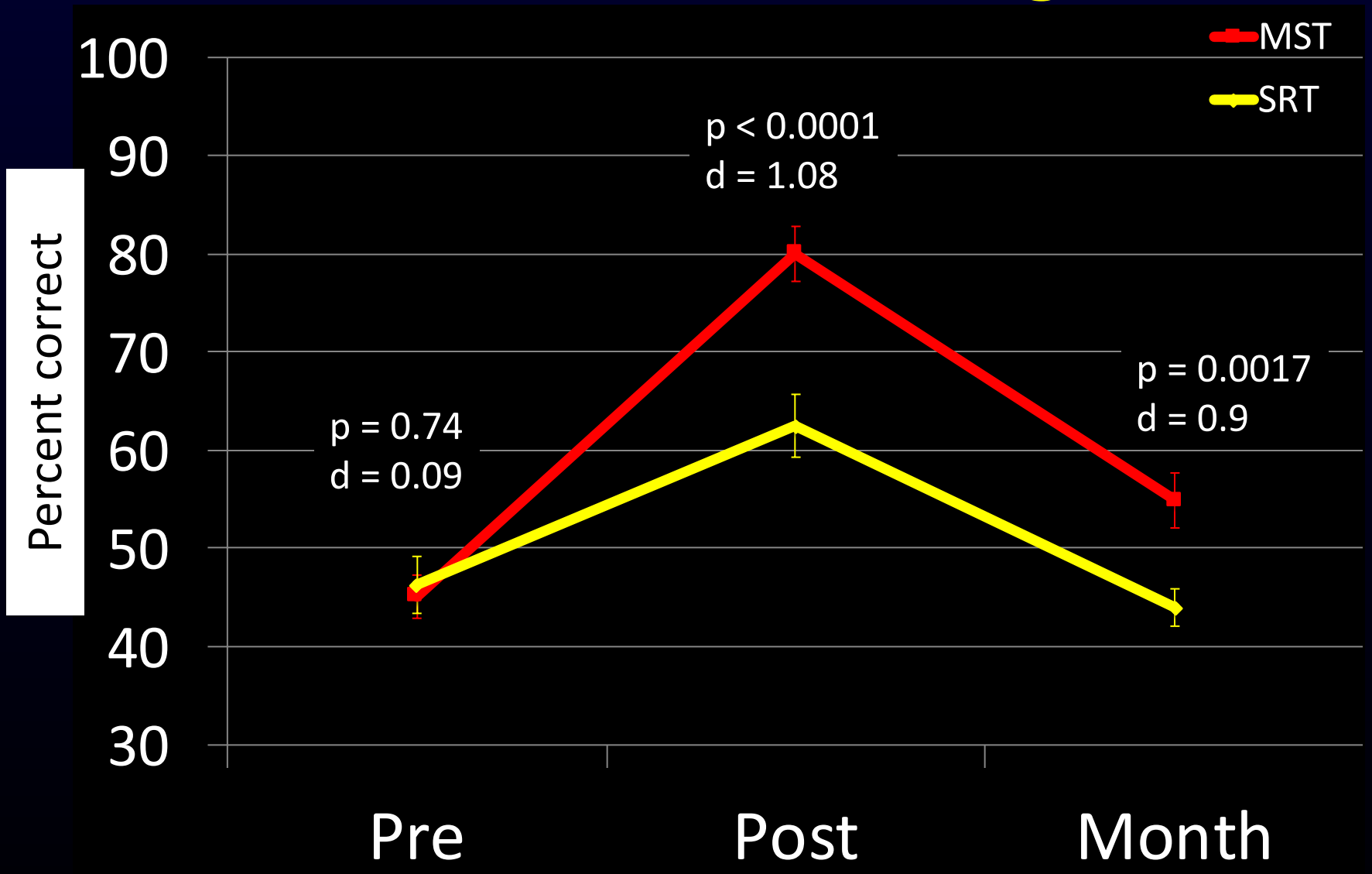


Fig. 2. Examples of stimuli and the mnemonic cues used in the faces & names (left) and objects & locations (right) paradigms. Patients are instructed to close their eyes and develop a mental image after completing the feature and reason steps.



Hampstead et al., *in progress; DO NOT REPLICATE*

MST is Better in the Long-Term



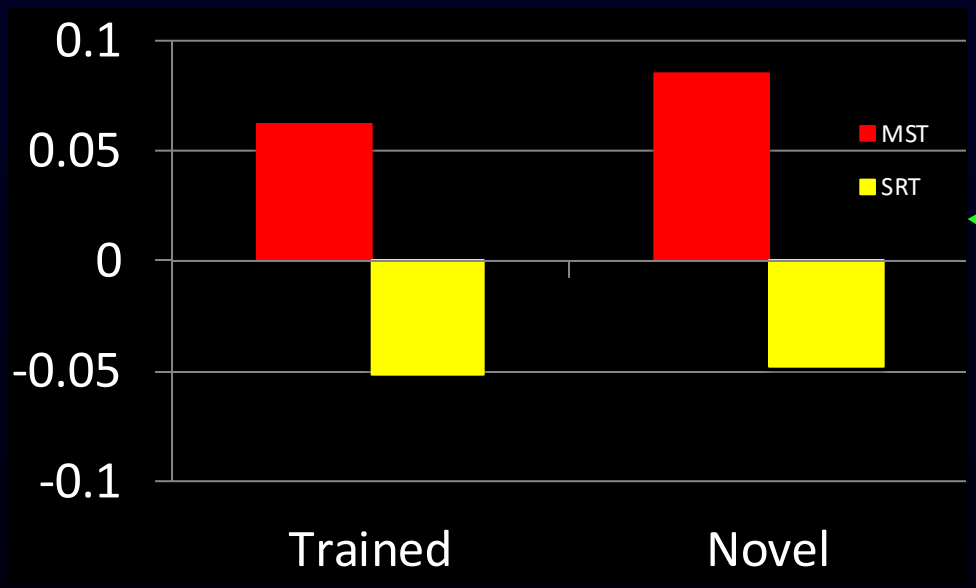
Group x time: p = 0.046

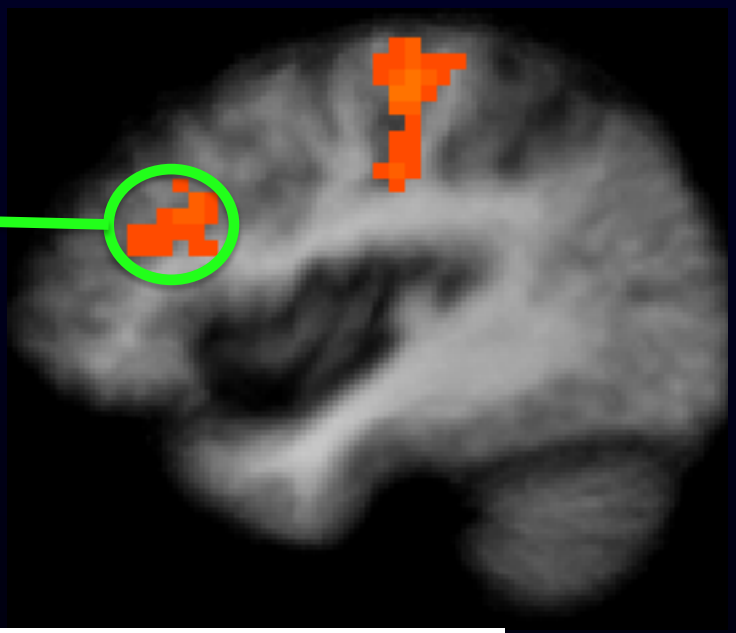
Hampstead et al., *in progress; DO NOT REPLICATE*

Intervention Specific Changes in Activation

Novel Stimuli

Post training > Pre training





Mnemonic strategies

1. Engage “top-down” cognitive control mechanisms
   -- Rostral and lateral prefrontal regions
2. Enhance self-referential processing
   -- Medial frontoparietal / posterior cortices

Hampstead et al., *in progress; DO NOT REPLICATE*

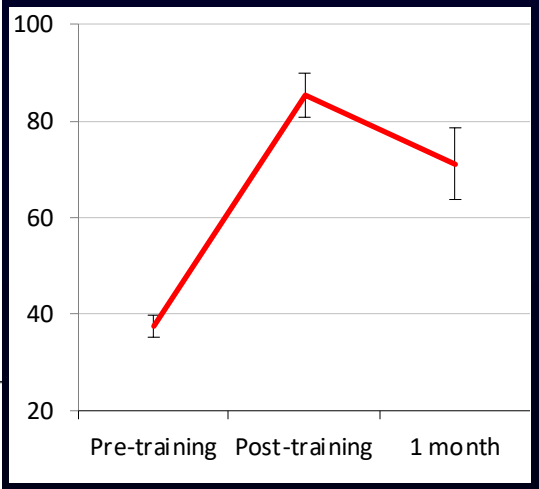
Findings Replicate Earlier Work

Hampstead et al. (2008) *JINS*

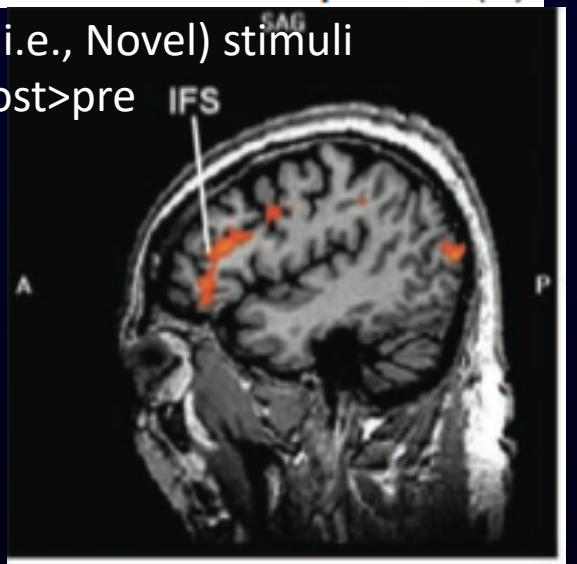
Neurorehabilitation and Neural Repair 25(3)

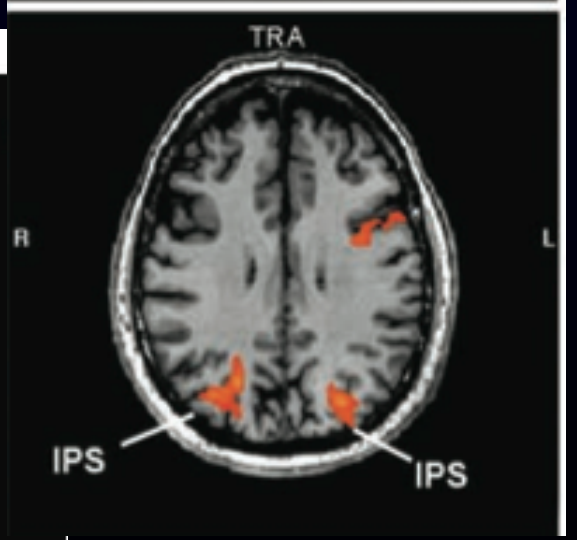
Shawn

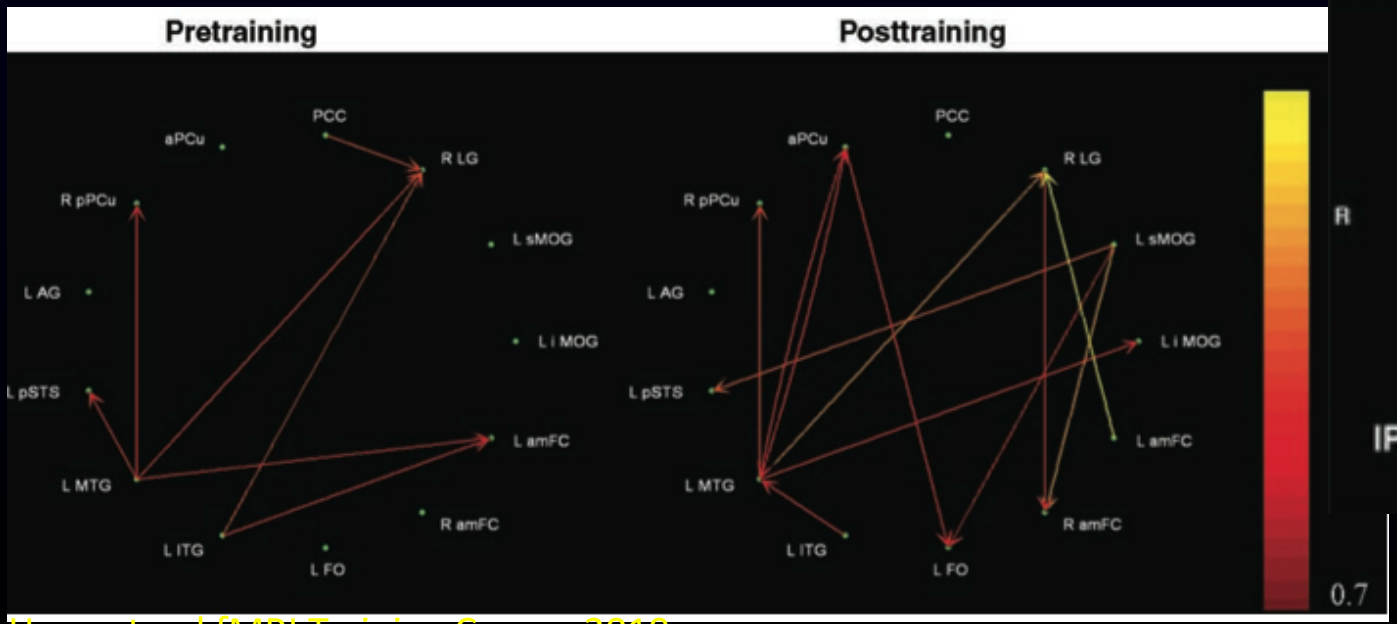
Feature: Mouth
Reason: Large mouth that opens wide to yawn, so we could call him "Yawn– Shawn"



"untrained" (i.e., Novel) stimuli
Post>pre



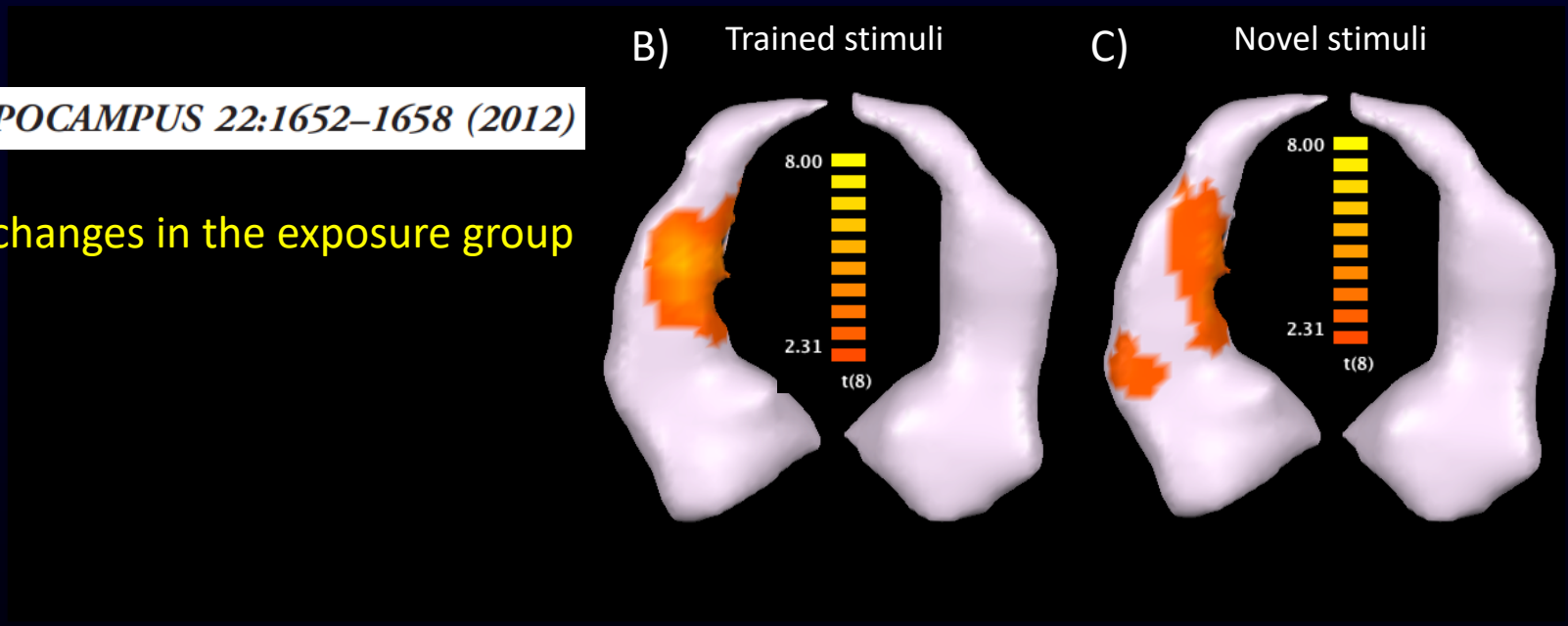




MST Facilitates Hippocampal Activation in MCI

HIPPOCAMPUS 22:1652–1658 (2012)

No changes in the exposure group



Hampstead et al., *in progress*

Application of Task-Based fMRI in MDD

DSM -5

- 5+ (including at least 1 of depressed mood & loss of interest in past 2 weeks) – that represent change & are present nearly every day
  - Depressed mood
  - Loss of interest/pleasure
  - Change in weight/appetite
  - Insomnia or hypersomnia
  - Psychomotor agitation or retardation
  - Loss of energy or fatigue
  - Worthlessness or guilt
  - Impaired concentration/indecisiveness
  - Recurrent thoughts of death or suicidal ideation/attempt
- Symptoms cause significant distress or impairment
- (various rule-outs)

- Can lead to heterogeneous groups
- Same problem for anxiety (e.g., specific phobia, generalized, PTSD, etc)

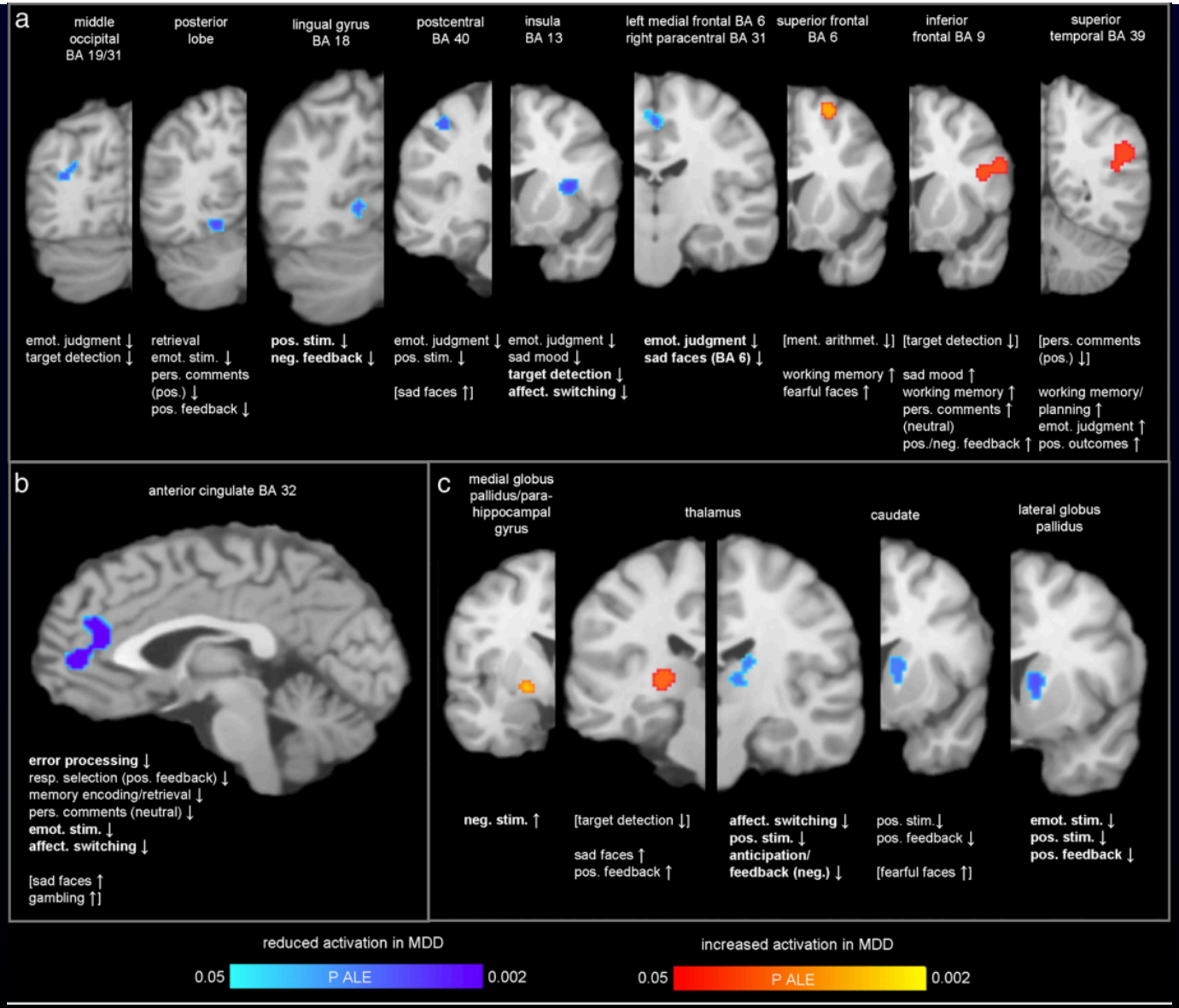
A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression

NeuroImage 61 (2012) 677–685

Carsten Diener [a,*], Christine Kuehner [b], Wencke Brusniak [a], Bettina Ubl [a], Michèle Wessa [c], Herta Flor [a]

- 40 studies from 1998-2010
- MDD & Controls
- Activation Likelihood Estimation (ALE) of between-group differences

- Hypoactive anterior insula & rACC = biased information and poor cognitive control
- MFG hyperactive during cognitive/emotional control



A meta-analytic review of neuroimaging studies of specific phobia to small animals

W. Peñate[a,b,*], A. Fumero[a], C. Viña[a], M. Herrero[a], R.J. Marrero[a,b], F. Rivero[a]
Eur. J. Psychiat. 2017;31(1):23–36

- 20 studies with participants who had specific phobia for small animals
- Greatest effects in left amygdala and insular cortex ("Rapid processing pathway")
- Less common but additional differences in fusiform, DLPFC, left cingulate cortex ("Slow processing pathway")

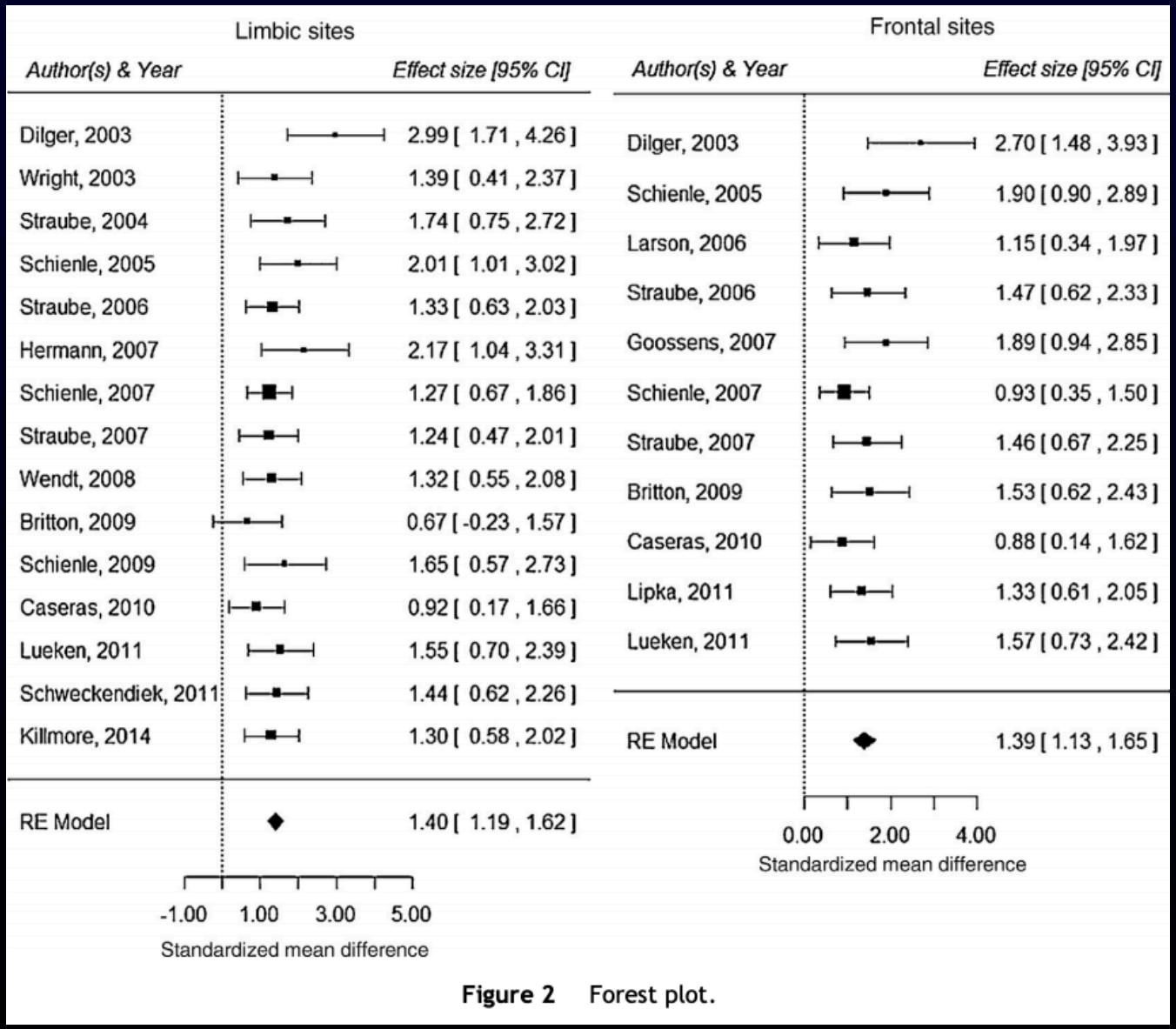


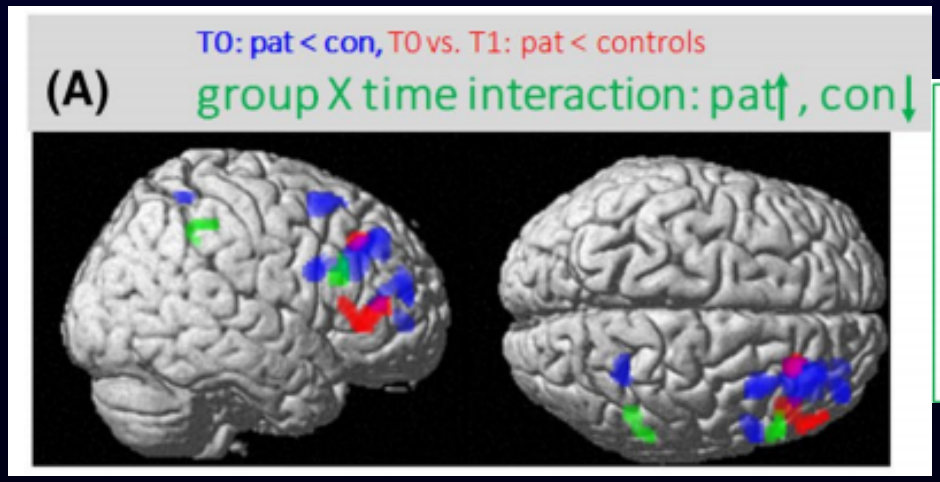
Figure 2 Forest plot.

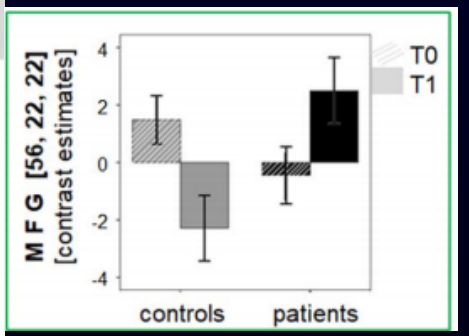
Cognitive-behavioral therapy effects on alerting network activity and effective connectivity in panic disorder

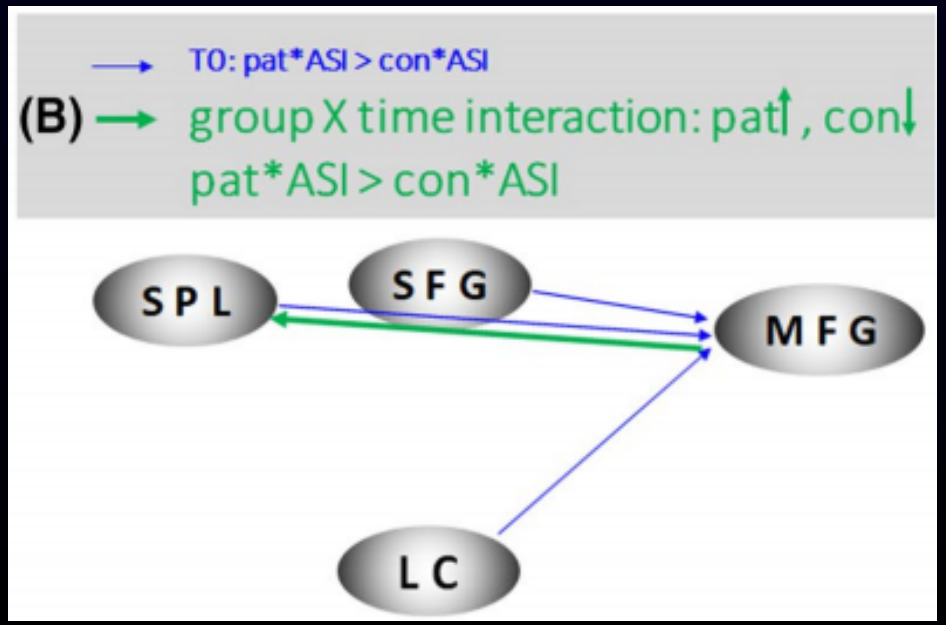
European Archives of Psychiatry and Clinical Neuroscience (2019) 269:587–598

Susanne Neufang[1,2] · Maximilian J. Geiger[3,4] · György A. Homola[5] · Marina Mahr[3] · Miriam A. Schiele[3,6] · Andrea Gehrmann[3] · Brigitte Schmidt[3] · Agnieszka Gajewska[3] · Johannes Nowak[7] · Eva Meisenzahl-Lechner[2] · Mirko Pham[5] · Marcel Romanos[1] · Atae Akhrif[1] · Katharina Domschke[3,6]

- 45 patients and 51 matched controls
- fMRI pre- and post 6 weeks
- Patients underwent cognitive-behavioral therapy; controls had no intervention
- Used dynamic causal modeling on attention network task







- Additional evidence of neurophysiologic change after a non-pharmacologic intervention
- Enhanced top-down control (?)

Watch for This Manuscript (presumably underway)

F124. Mapping the Neural Correlates of Mood and Anxiety Disorders Onto Research Domain Criteria: A Meta-Analysis of 226 Task-Related Functional Imaging Studies

Delfina Janiri[1], Dominik Moser[1], **Gaelle Doucet**[1], Maxwell Luber[1], Alexander Rasgon[1], Won-Hee Lee[1], James Murrough[1], Gabriele Sani[2], Simon Eickhoff[3], and Sophia Frangou[1]

[1]Icahn School of Medicine at Mount Sinai, [2]School of Medicine and Psychology, Sapienza University, Sant'Andrea Hospital, [3]Institute of Neuroscience and Medicine (INM-7, Brain & Behavior), Research Center Jülich

Background: Mood and anxiety disorders are highly comorbid and characterized by persistent negative states. This study sought to identify shared abnormalities in brain activity across mood and anxiety disorders that might underpin their clinical overlap.

Methods: Systematic literature review of functional magnetic resonance imaging literature over the last decade identified 226 studies that compared task-related brain activity between healthy individuals (n = 4755) and patients with mood, post-traumatic stress and anxiety disorders (n = 4507). The Research Domain Criteria framework was used to code task contrasts according to their corresponding domain and construct. Quantitative meta-analyses were conducted to identify clusters of convergence of the peak coordinates of whole-brain case-control differences. Statistical inference was based cluster-forming voxel-level threshold of $p < 0.001$, with family-wise error correction.

Results: Three right-sided transdiagnostic clusters of hypoactivation, mainly associated with dysfunction in tasks of cognitive control, were identified in the inferior prefrontal cortex/insula, the inferior parietal lobule and the putamen. At a lower level, transdiagnostic clusters of hyperactivation, primarily associated with dysfunction in tasks corresponding to the negative valence system, were detected in the perigenual/dorsal anterior cingulate cortex, the left amygdala/parahippocampal gyrus, and the left thalamus.

Conclusions: These results demonstrate that the overlap between mood, post-traumatic stress and anxiety disorders involves shared dysfunction in brain regions associated with cognitive and negative valence system that could serve as a foundation for developing neuroscience informed interventions for prevention and treatment.

Supported By: R01

Keywords: Meta-Analysis, Research Domain Criteria (RDoC), Mood Disorders, Task fMRI

Task-Based fMRI

- Has multiple strengths and increases confidence that "activation" is functionally meaningful
- **But…**
  - **Difficult to develop, implement, and standardize, especially across sites**
- Enter Resting-State fMRI

Resting-State fMRI

- Acquire continuous data for “X” minutes
- Typically with eyes open and instructed to stare at “+”

- Easy to acquire, flexible, can be standardized across sites
- Inherently correlational in nature (i.e., all analyses rely on relationships with cognition/behavior rather than on direct engagement)

Aging, Dementia, and Resting-State fMRI

The Brain's Default Network

Anatomy, Function, and Relevance to Disease

RANDY L. BUCKNER,[a,b,c,d,e] JESSICA R. ANDREWS-HANNA,[a,b,c] AND DANIEL L. SCHACTER[a]

Ann. N.Y. Acad. Sci. 1124: 1–38 (2008).
doi: 10.1196/annals.1440.011

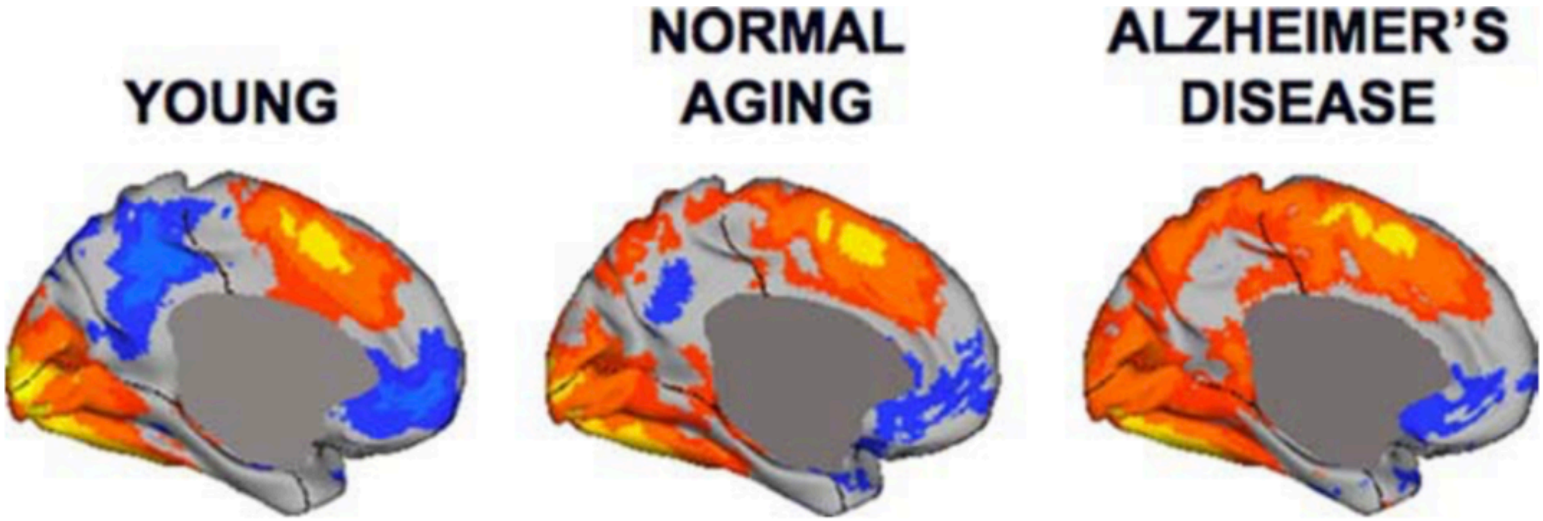
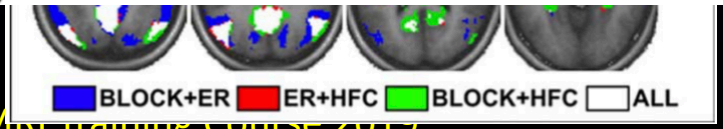
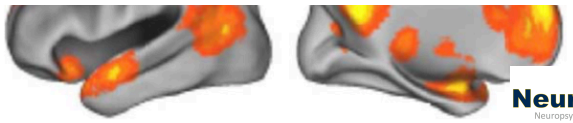


FIGURE 18. Activity within the default network is disrupted in Alzheimer's disease. Task increases (red) and decreases (blue) from a simple word classification task referenced to a passive baseline task are plotted for young adults (left panel), normal older adults (middle panel), and demented older adults with AD (right panel). The young adults show the classic pattern of task-induced deactivation within PCC/Rsp and MPFC. The effect attenuates significantly in AD. Adapted from Lustig et al. (2003, see also Greicius et al. 2004).





Cerebral Cortex October 2011;21:2399-2407
doi:10.1093/cercor/bhr025
Advance Access publication March 7, 2011

Relationships between Beta-Amyloid and Functional Connectivity in Different Components of the Default Mode Network in Aging

Elizabeth C. Mormino[1], Andre Smiljic[1], Amynta O. Hayenga[1], Susan H. Onami[1], Michael D. Greicius[2], Gil D. Rabinovici[1,3,4,5], Mustafa Janabi[3], Suzanne L. Baker[3], Irene V. Yen[3], Cindee M. Madison[1], Bruce L. Miller[4,5] and William J. Jagust[1,3,4,5]

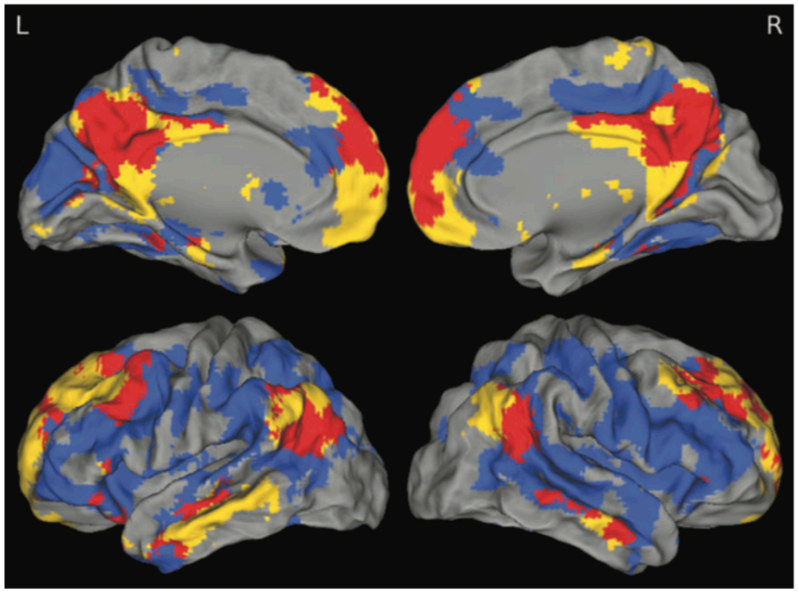


Figure 1. DMN FC and global PIB uptake overlap. One sample *t*-test of DMN best-fit components (yellow), 2-sample *t*-test between high and low PIB subjects (blue), and overlap (red) are displayed. These maps highlight congruence and incongruence between the DMN and the brain regions showing high levels of Aβ deposition. The greatest amount of overlap is in precuneus/posterior cingulate, medial prefrontal, and angular gyri. Although PIB uptake is more diffuse than DMN, there is minimal overlap in retrosplenial and medial temporal portions of the DMN.

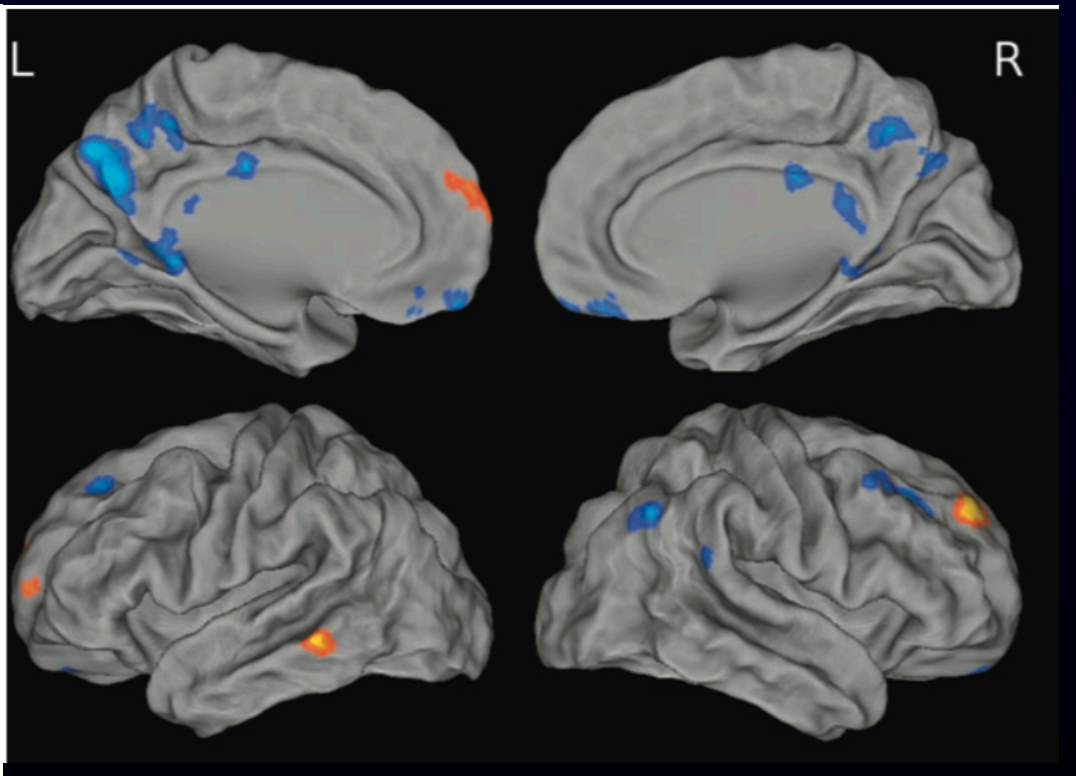
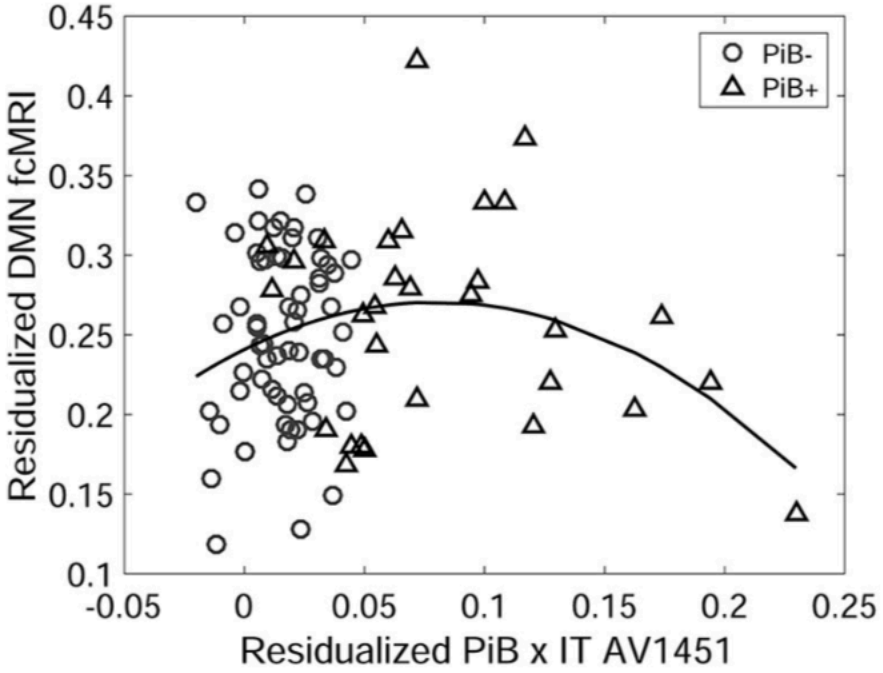


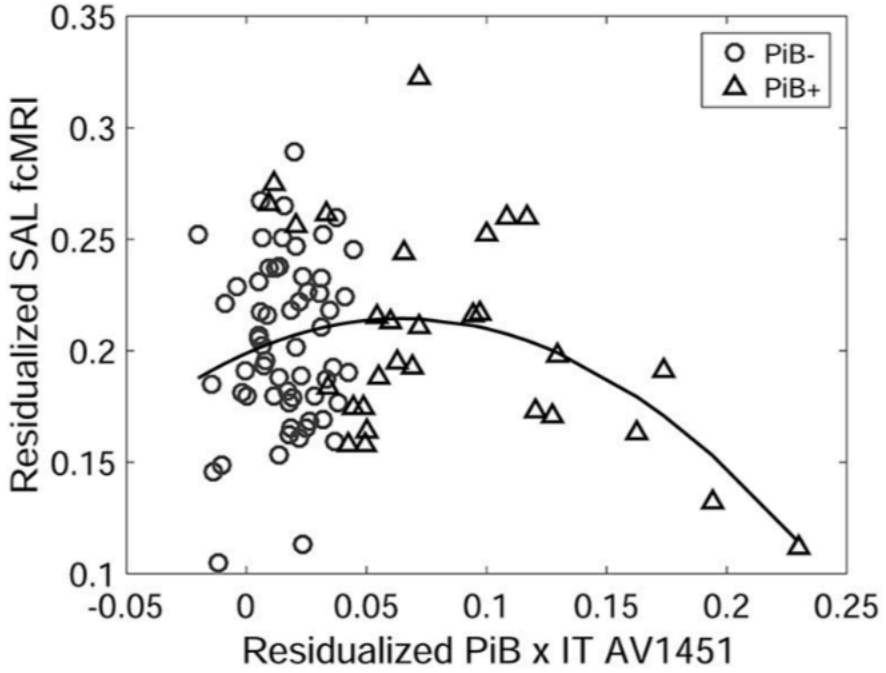
Figure 2. *t*-Maps from voxelwise analysis correlating global PIB with DMN FC.

Phases of Hyperconnectivity and Hypoconnectivity in the Default Mode and Salience Networks Track with Amyloid and Tau in Clinically Normal Individuals

The Journal of Neuroscience, April 19, 2017 · 37(16):4323–4331 · **4323**

Aaron P. Schultz,[1,5] Jasmeer P. Chhatwal,[1,5] Trey Hedden,[2,5] Elizabeth C. Mormino,[1,5] Bernard J. Hanseeuw,[1,2] Jorge Sepulcre,[2] Willem Huijbers,[1,8] Molly LaPoint,[1] Rachel F. Buckley,[1,6,7] Keith A. Johnson,[2,3] and Reisa A. Sperling[1,4]

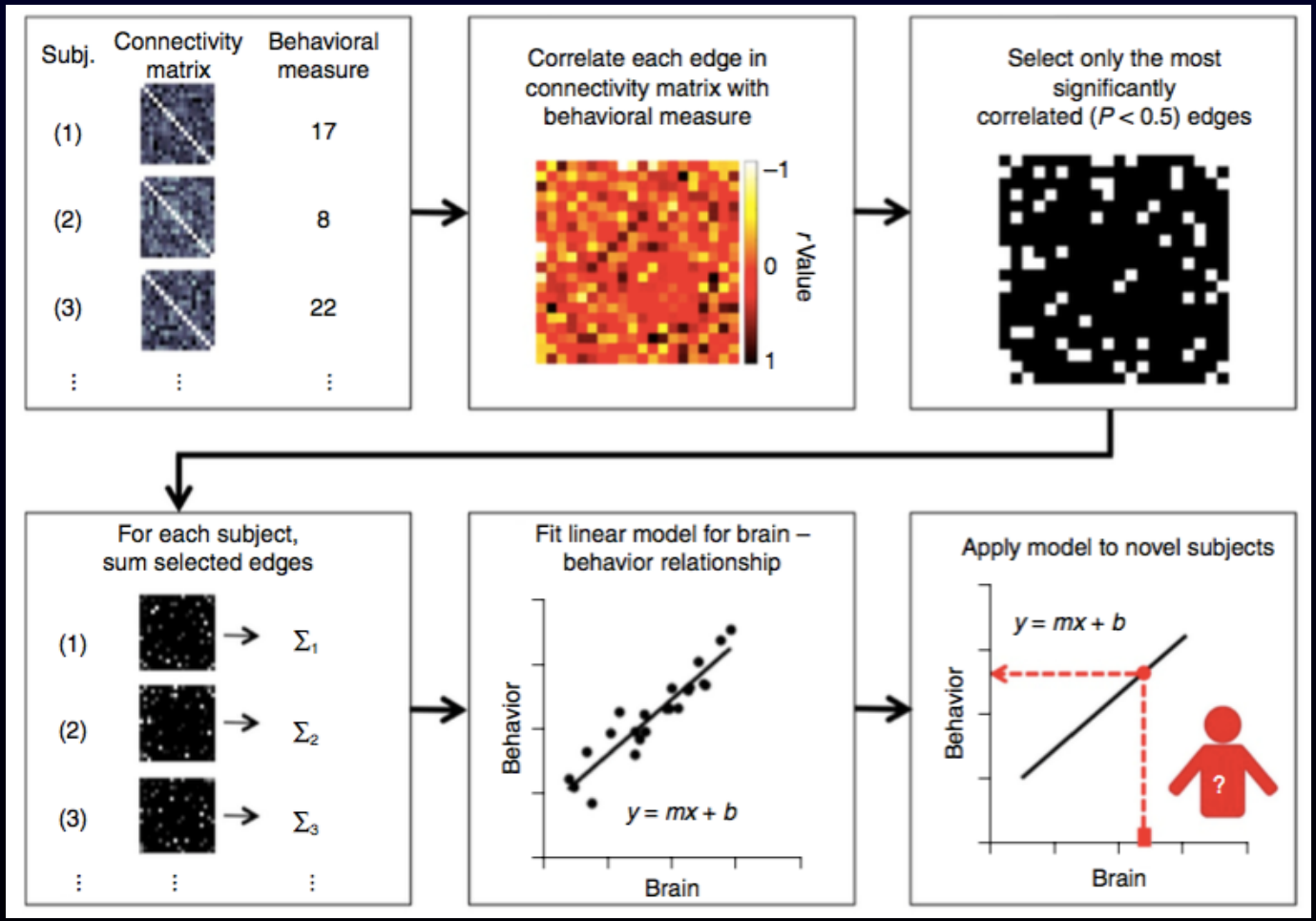




Important to establish biomarkers (what is "normal" aging?)

Connectome Predictive Modeling

(Rosenberg et al., 2016, Nature Neuro)



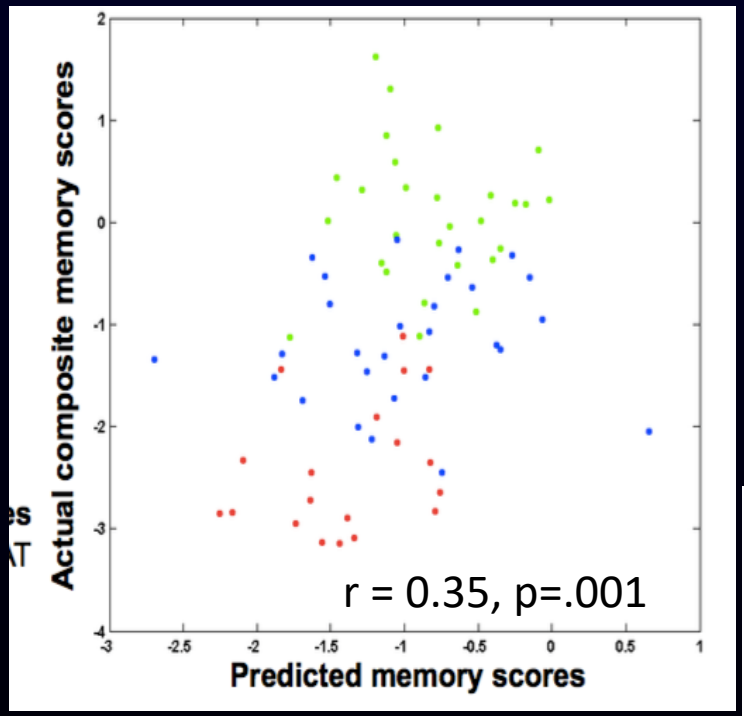
We applied it:

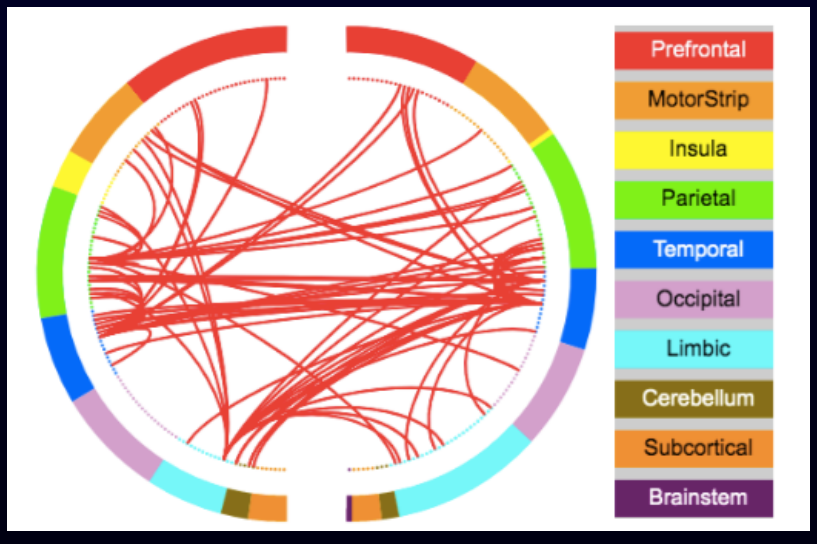
- Leave one out framework
- Connectivity threshold (p<0.01)
- Positive and negative summed separately
- Linear model fit
- Goodness of fit was correlation between predicted and actual memory test scores
- Permutation for significance (1000 iterations)

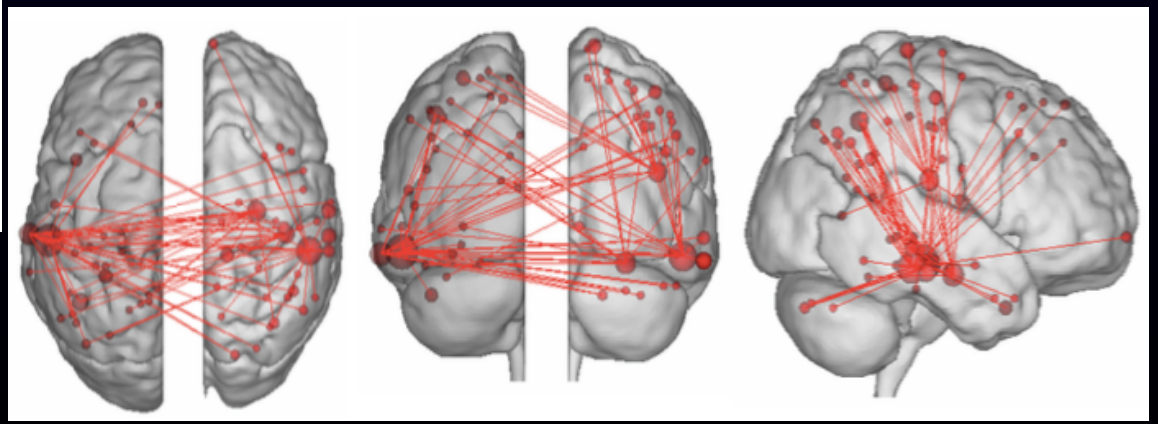
Connectome Predictive Modeling (CPM)

Peltier et al (in preparation) DO NOT REPRODUCE

- 75 participants from P30 funded MADRC (n=28 controls; 28 MCI; 19 DAT)
- Created composite memory score (average delayed recall for story, list, and figure recall)
- Applied CPM to resting-state data



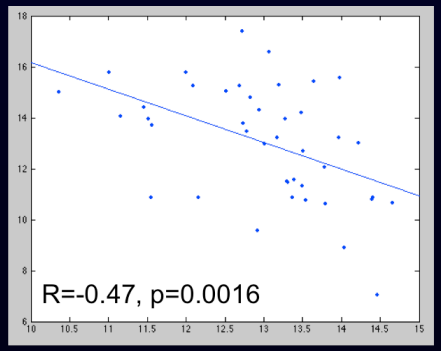


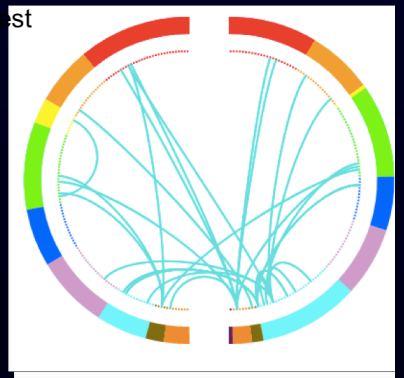


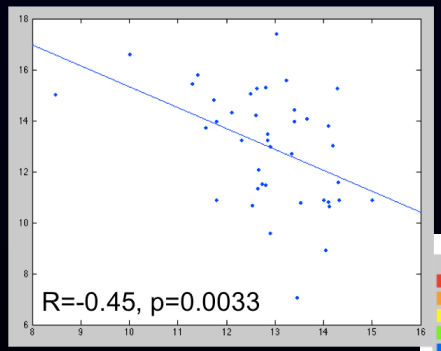
Connectome Predictive Modeling (CPM)

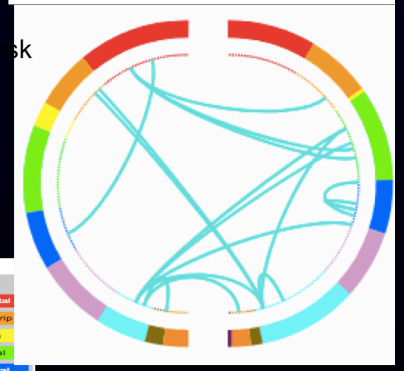
Hampstead et al (in preparation) DO NOT REPRODUCE

- 41 participants with MCI
- Applied CPM to Task & resting-state data

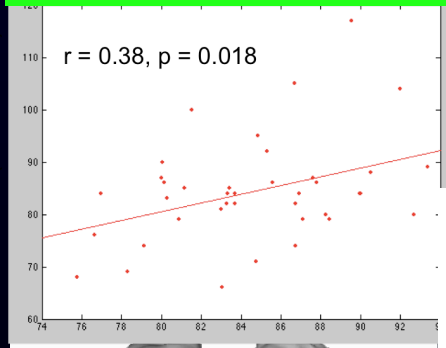


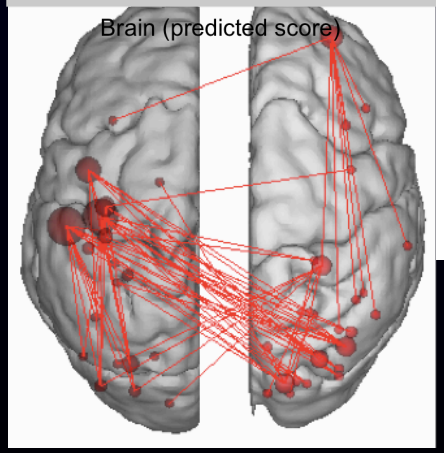


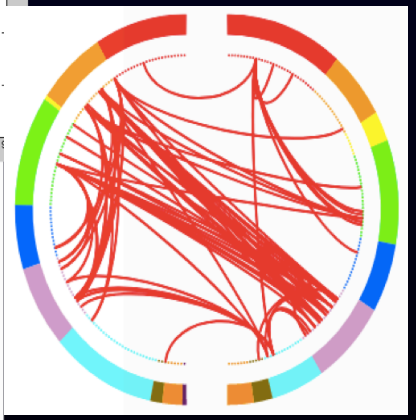




ONLY task predicted independent memory scores (RBANS DMI)







Both task & resting predicted object-location performance (task more efficiently?)

Toward literature-based feature selection for diagnostic classification: a meta-analysis of resting-state fMRI in depression

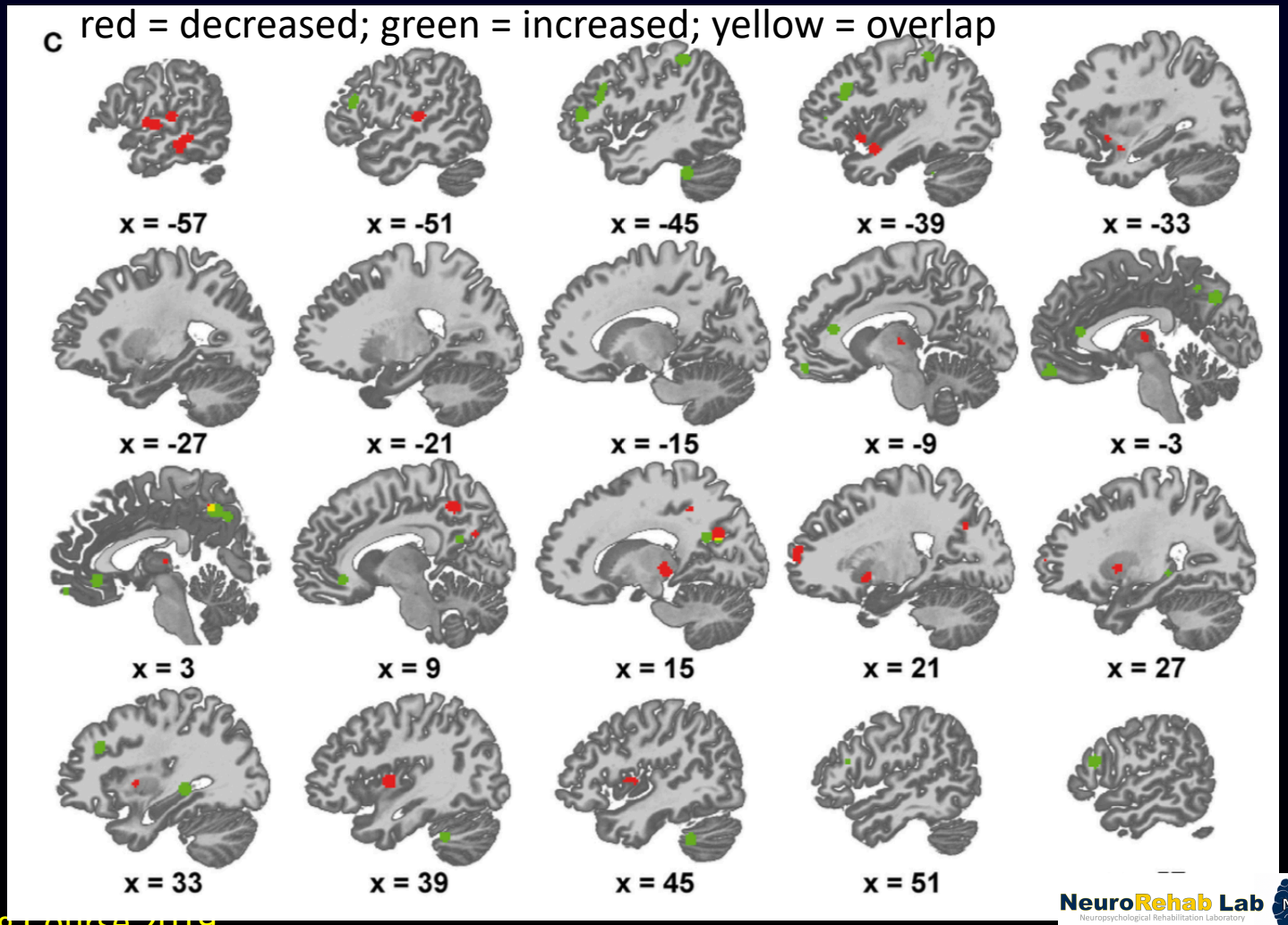
ORIGINAL RESEARCH ARTICLE
published: 10 September 2014
doi: 10.3389/fnhum.2014.00692

Benedikt Sundermann*, Mona Olde lütke Beverborg and Bettina Pfleiderer

Some DMN areas decrease

Some FPN/salience increase

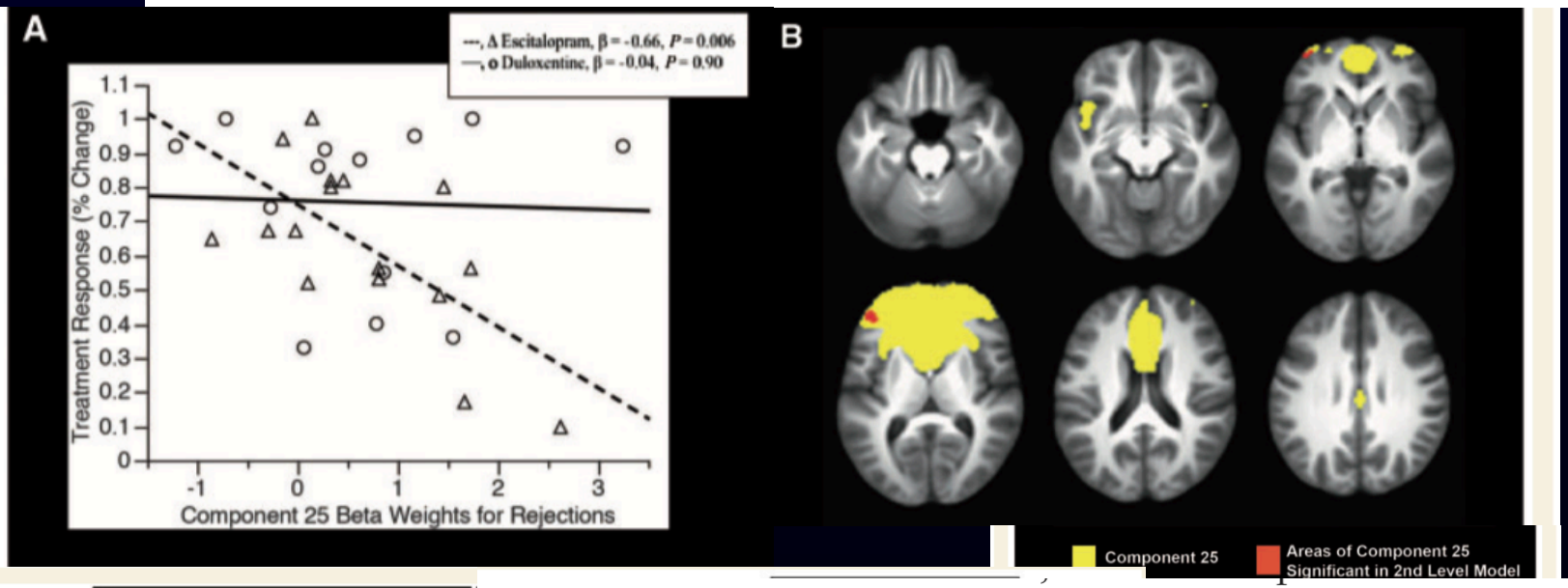
How to interpret?

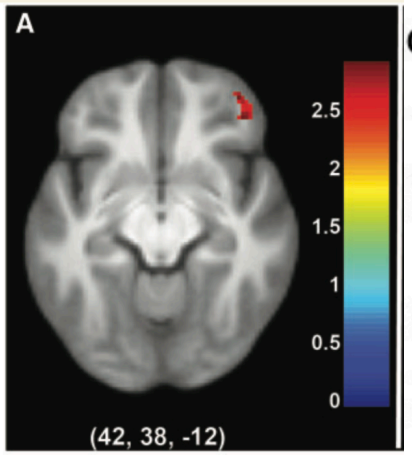


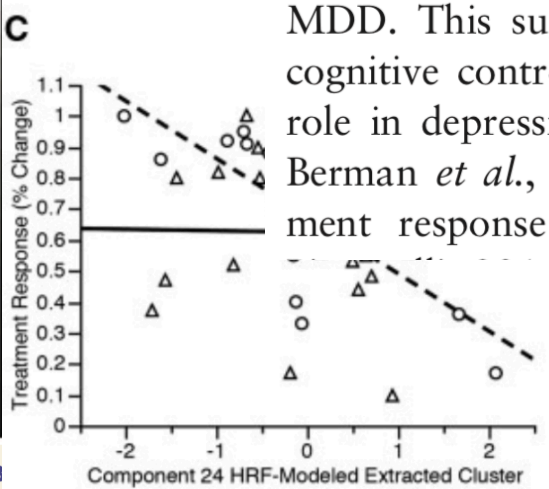
Multidimensional prediction of treatment response to antidepressants with cognitive control and functional MRI

BRAIN 2017: 140; 472–486

Natania A. Crane,[1] Lisanne M. Jenkins,[1] Runa Bhaumik,[1] Catherine Dion,[1] Jennifer R. Gowins,[1] Brian J. Mickey,[2] Jon-Kar Zubieta[2] and Scott A. Langenecker[1,2]



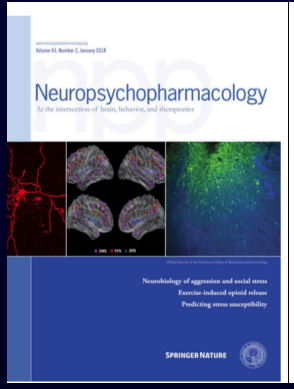




MDD. This suggests that areas involved in attention and cognitive control (Component 25) may play an important role in depression severity (Mitterschiffthaler *et al.*, 2008; Berman *et al.*, 2011; Dillon *et al.*, 2015) as well as treatment response and executive function (Component 24;

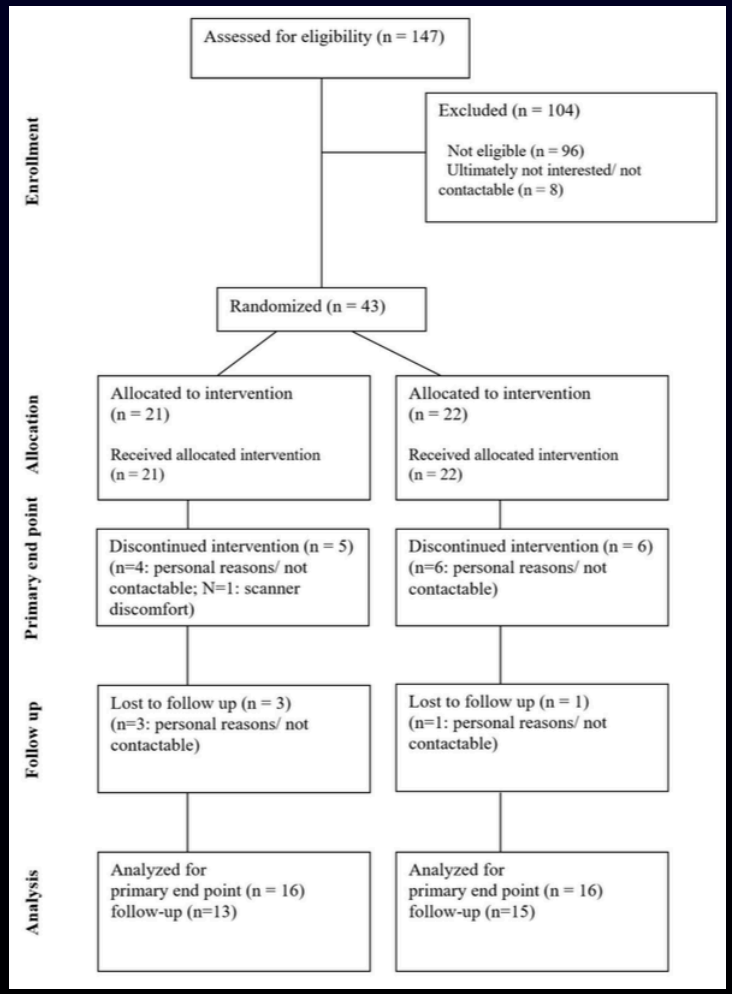
Figure 4 Areas of Components 11 (A), 24 (B

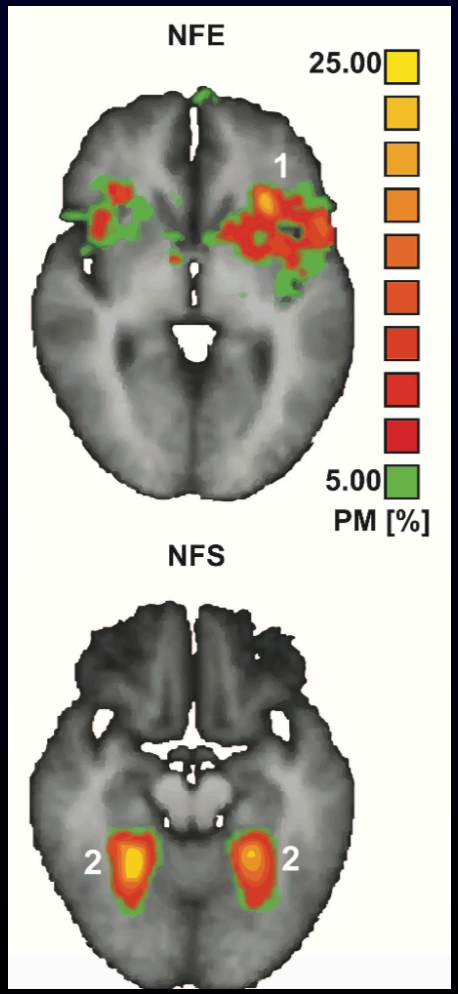
NeuroRehab Lab
Neuropsychological Rehabilitation Laboratory
NRL
Est. 2008



Targeting the affective brain - A Randomized Controlled Trial of real-time fMRI neurofeedback in patients with depression

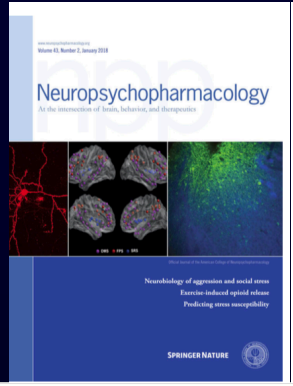
David M. A. Mehler, Moses O. Sokunbi, Isabelle Habes, Kali Barawi, Leena Subramanian, Maxence Range, John Evans, Kerenza Hood, Michael Lührs, Paul Keedwell, Rainer Goebel, David E. J. Linden





”Training” sessions

- Use mental imagery
- Suggested approach but no efforts to ensure use
- Similar sized ROIs used to monitor BOLD change
- Unclear if ruled out changes in other group’s ROI



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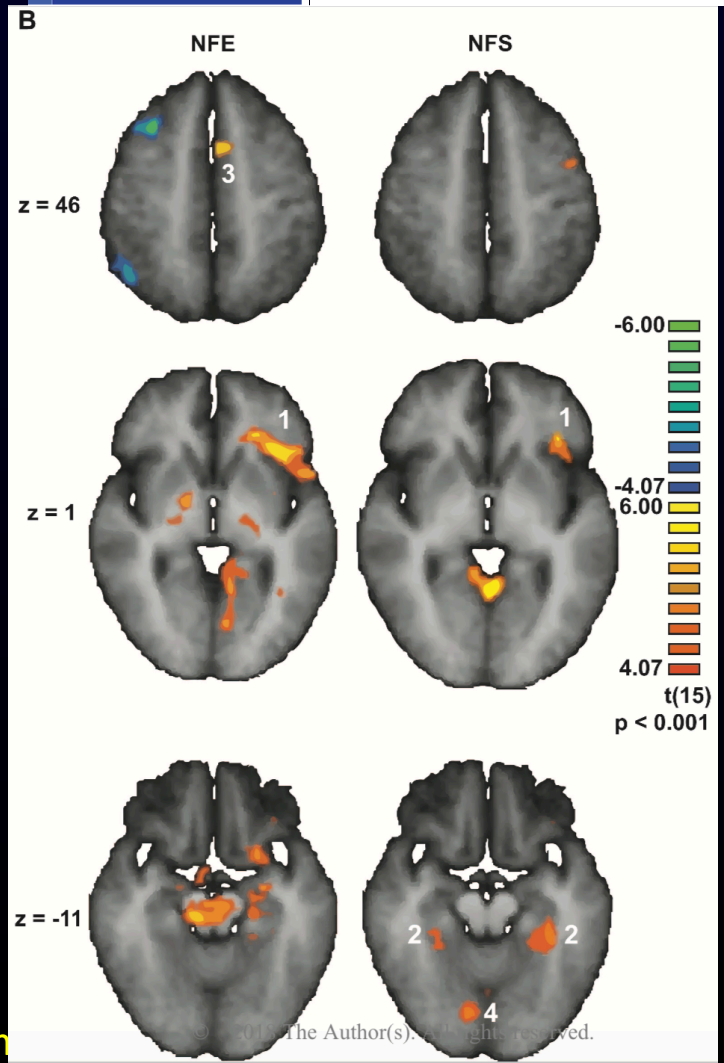
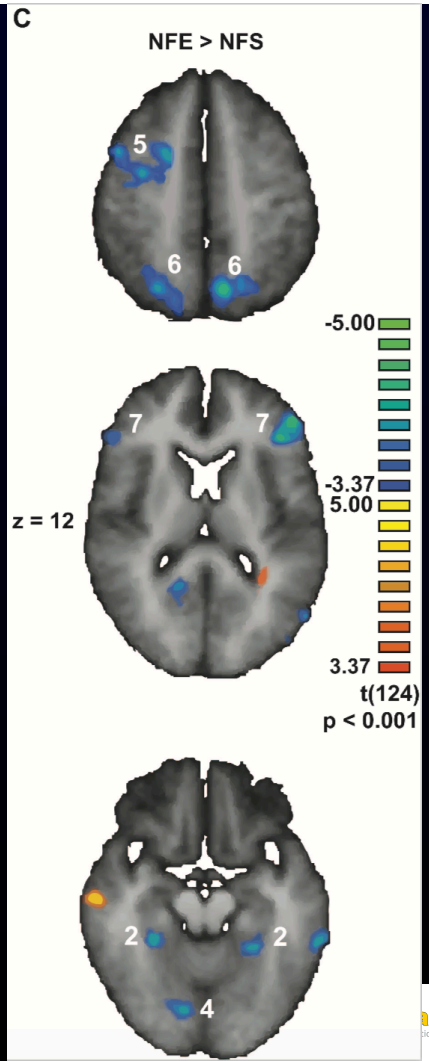


”Training” sessions

- Some overlap in recruited regions
- Insula, MTL

More activation change in scene group

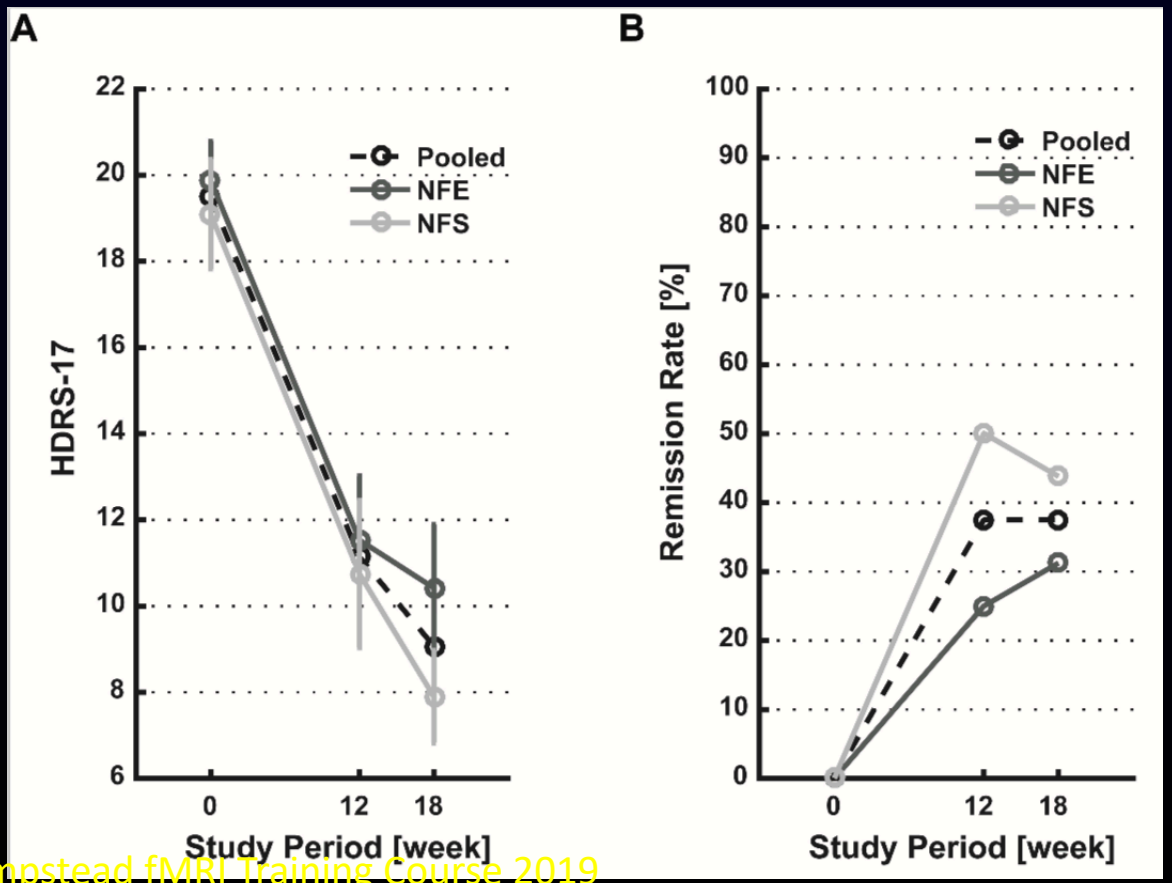


Ham

Targeting the affective brain - A Randomized Controlled Trial of real-time fMRI neurofeedback in patients with depression

David M. A. Mehler, Moses O. Sokunbi, Isabelle Habes, Kali Barawi, Leena Subramanian, Maxence Range, John Evans, Kerenza Hood, Michael Lührs, Paul Keedwell, Rainer Goebel, David E. J. Linden

No differences in outcome but…



Both groups improved

- ~37% remission
- Results persisted at follow up

Summary

- MANY different uses for fMRI in clinical context
- Select the most appropriate approach for your question/purpose
- Pay attention to future efforts with dynamic connectivity

Now…Q&A Time…

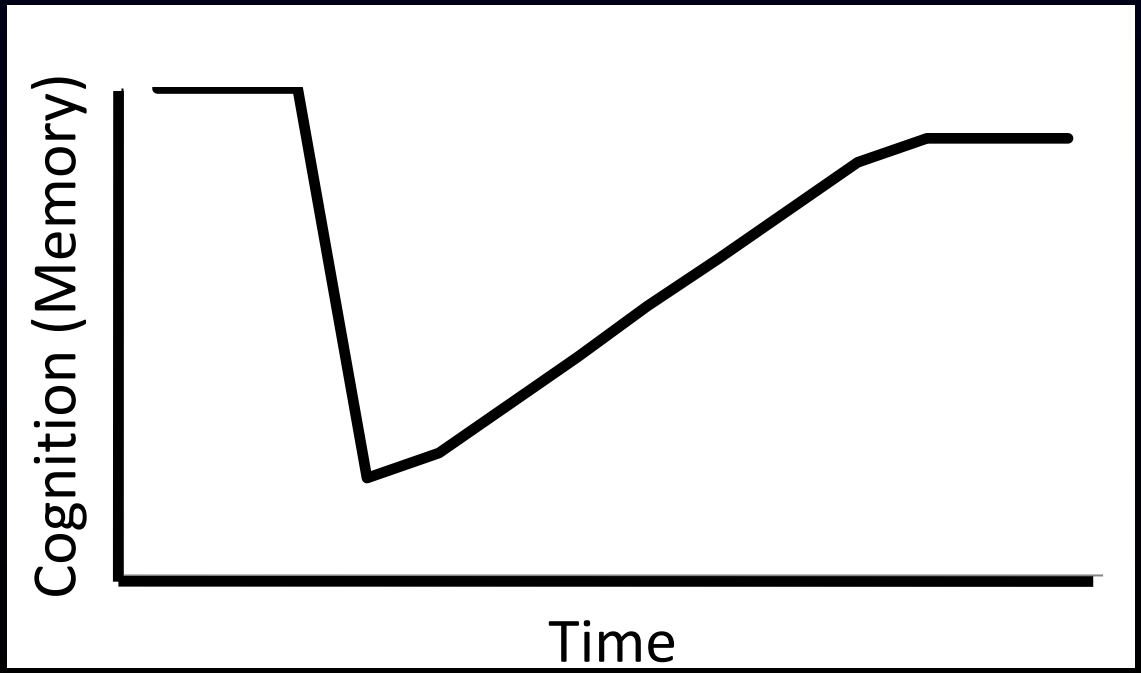
Overview

1. Aging & Dementia
   - Network level changes due to disease
   - Understanding memory deficits
   - Evaluating & targeting treatment
2. Depression
3. Stroke

Cerebrovascular Accident (Stroke)

Damage to the brain tissue that results from disruption of blood flow

- Hemorrhagic
- Ischemic
- Motor and/or cognitive deficits (e.g., aphasia, neglect)
- Typically expect some degree of spontaneous recovery
- Most rapid improvements over first 9-12 months



fMRI & Recovery of Function

CORTEX 101 (2018) 44–59

Re-emergence of modular brain networks in stroke recovery

Joshua S. Siegel [a,], Benjamin A. Seitzman [a], Lenny E. Ramsey [a], Mario Ortega [a], Evan M. Gordon [f], Nico U.F. Dosenbach [a], Steven E. Petersen [a,b,c,d], Gordon L. Shulman [a] and Maurizio Corbetta [a,b,c,e,g]*

Used graph theory measures to examine change over first year after stroke in 107 patients vs. controls

Graph theory:

- Modularity – Global network measure that compares density of connections within vs. between networks (or "communities")

Table 1 – Sample sizes and imaging quality metrics for controls, patients, and case study P108.

Table 1A		Timepoint 1	Timepoint 2
Controls	N	30	30
	N (incl.)	26	25
	Frames	571.4(210.0)	525.4(216.6)
	FD	.234(.062)	.246(.053)
	Lag	.191(.046)	.239(.136)

Table 1B		2 weeks	3 months	1 year
Patients	N	132	103	88
	N (incl.)	107	85	67
	Frames	596.0(209.6)	649.4(177.8)	632.9(177.8)
	FD	.231(.063)	.224(.057)	.223(.057)
	Lag	.182(.156)	.291(.156)	.276(.119)
P 108	Frames	737/896	644/896	637/896
	FD	.2392	.2495	.2408
	Lag	.1428	.1448	.1514

CORTEX 101 (2018) 44–59

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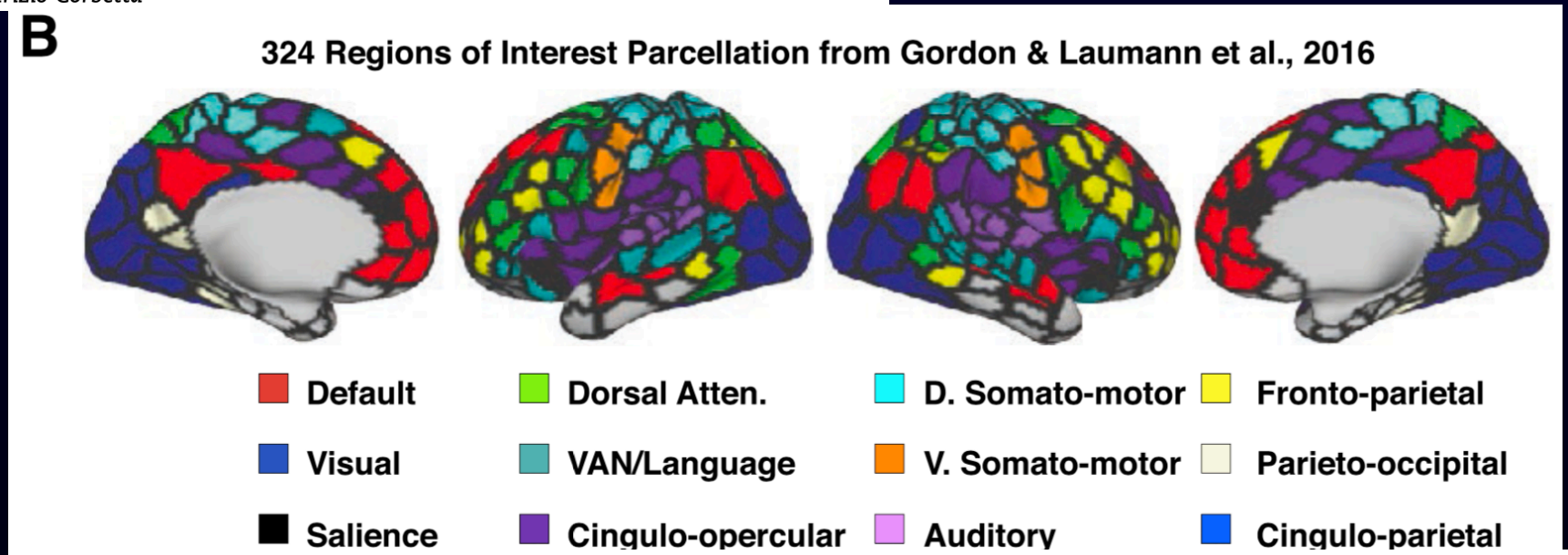

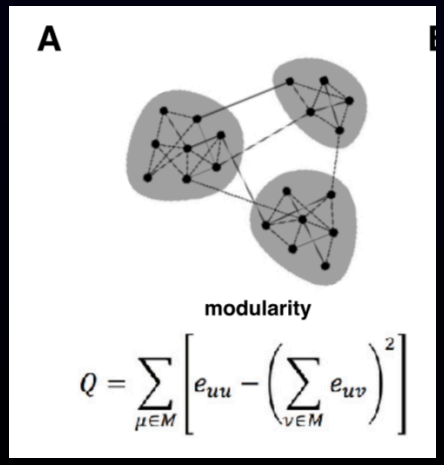

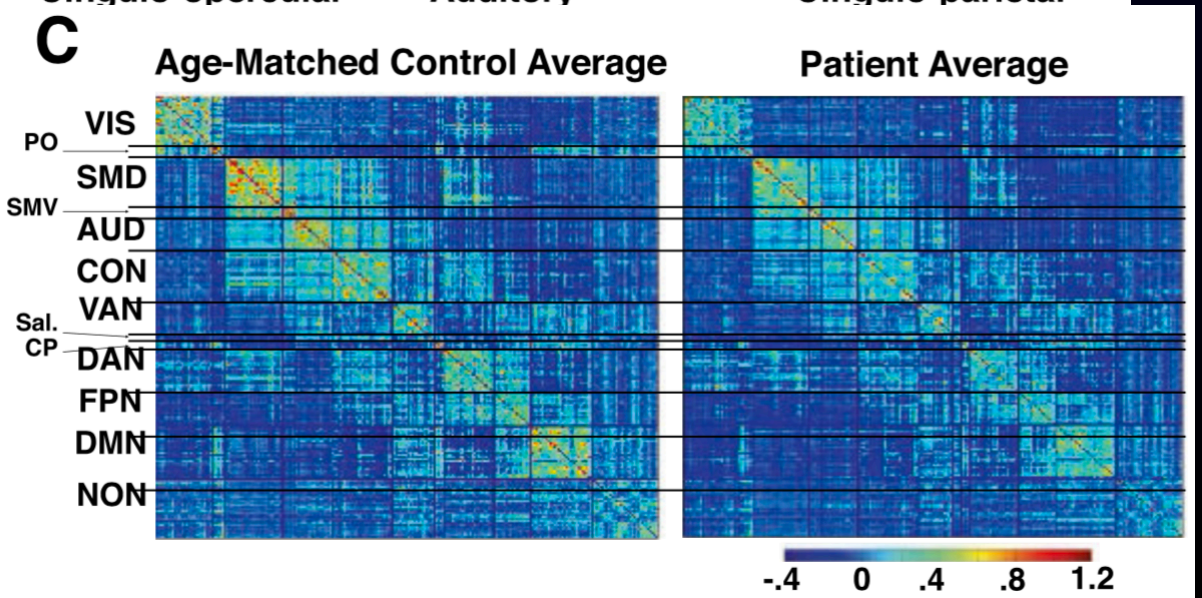

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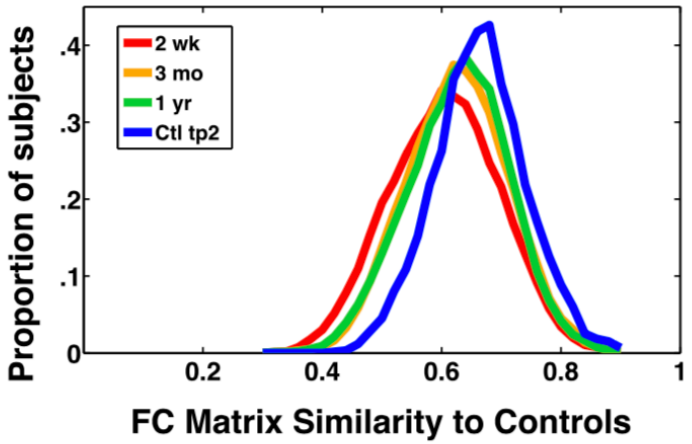

Fig. 2 – Group FC Similarity to controls. Pearson correlation between all members of a given group and control at timepoint 1. The X-axis is a simple measure of FC similarity. This measure is computed by turning the 324-by-324 FC matrix into a 52,326 vector for each subject. For a given group (i.e. patients at 2 weeks), a spatial correlation was computed between the FC vector of every subject and the FC vector of every subject in the control group. Each curve is a histogram of similarity values for one group. Similarity to controls increases between 2 weeks and 1 year post-stroke (paired t-test: $t = 3.9$, $p < .0001$).

CORTEX 101 (2018) 44–59

Re-emergence of modular brain networks in stroke recovery

Joshua S. Siegel [a,*], Benjamin A. Seitzman [a], Lenny E. Ramsey [a], Mario Ortega [a], Evan M. Gordon [f], Nico U.F. Dosenbach [a], Steven E. Petersen [a,b,c,d], Gordon L. Shulman [a] and Maurizio Corbetta [a,b,c,e,g]

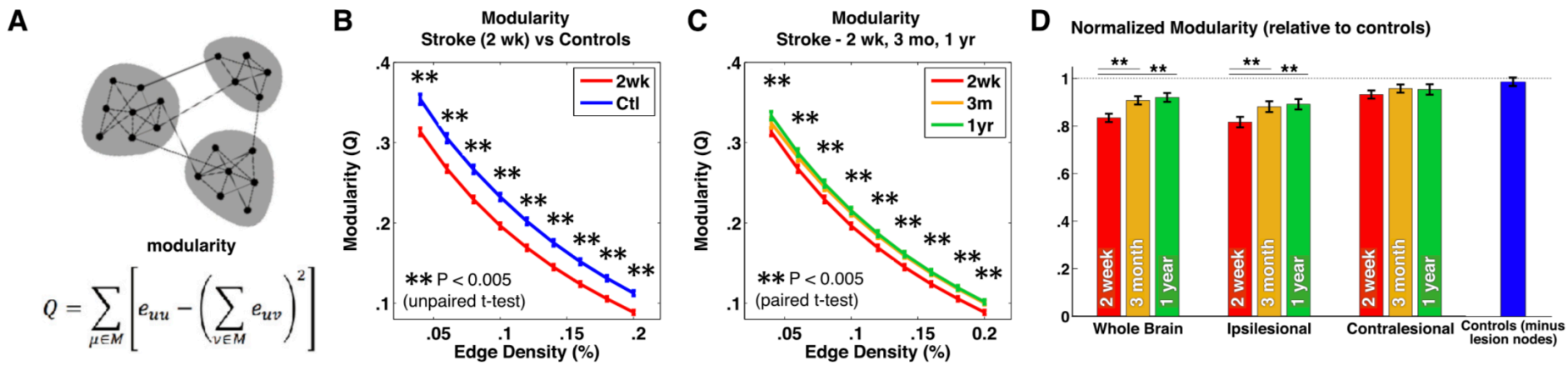

Fig. 3 – Behavior recovery following stroke is predicted by recovery of brain network modularity. A: Modularity measures the density of links inside communities compared to links between communities. Modularity is decreased in acute stroke patients (B), but returns to near control levels at 3 month and 1 year timepoints (C). D: Modularity, normalized to controls and averaged across densities (2–20%) is shown for the whole brain, ipsi-lesional, and contra-lesional hemisphere (compared to single hemisphere modularity in controls). ** indicates $p < .005$ (uncorrected) for an unpaired t-test between patients and controls in B and for a paired t-test between 2 weeks and 1 year for patients in C/D.

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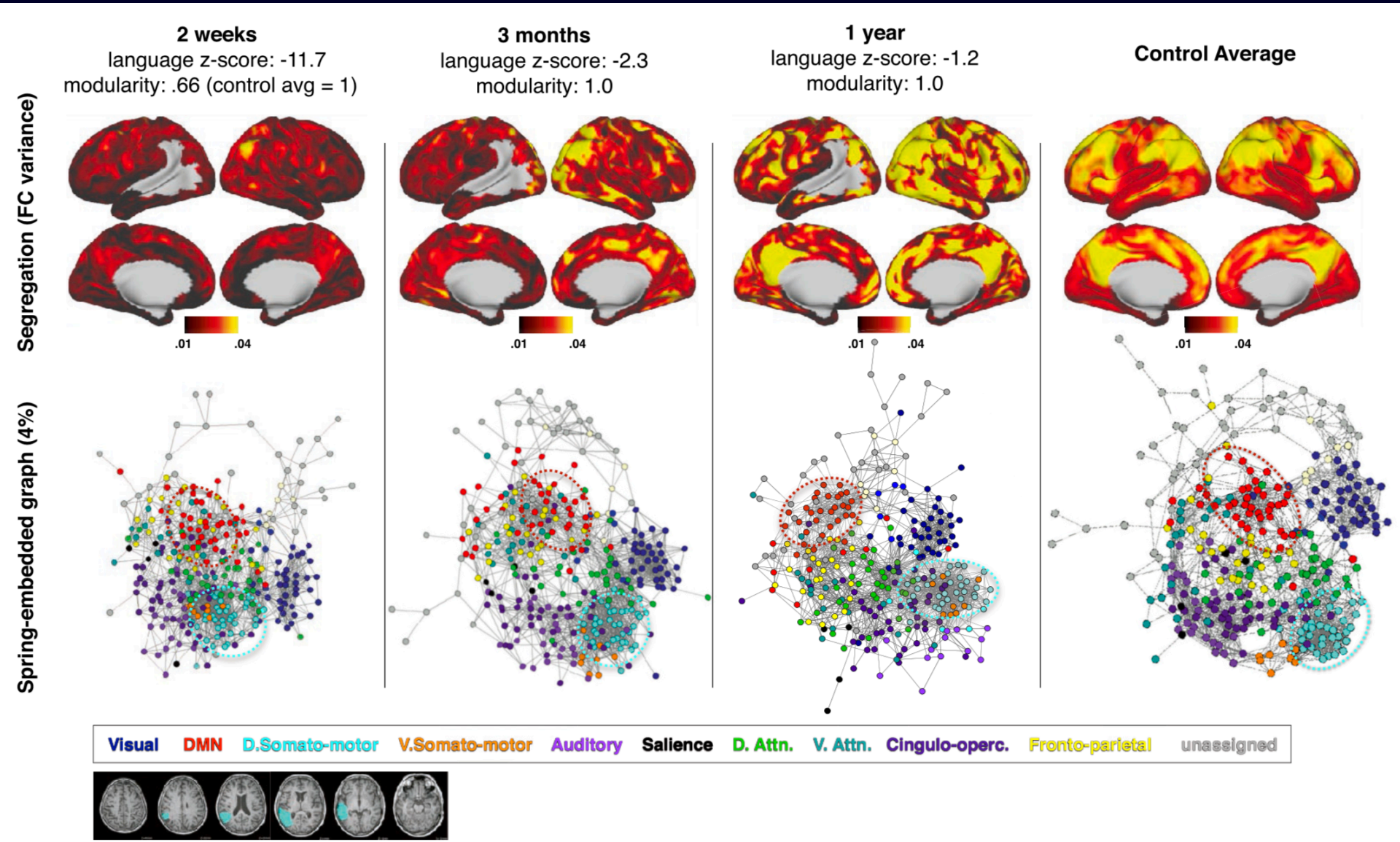

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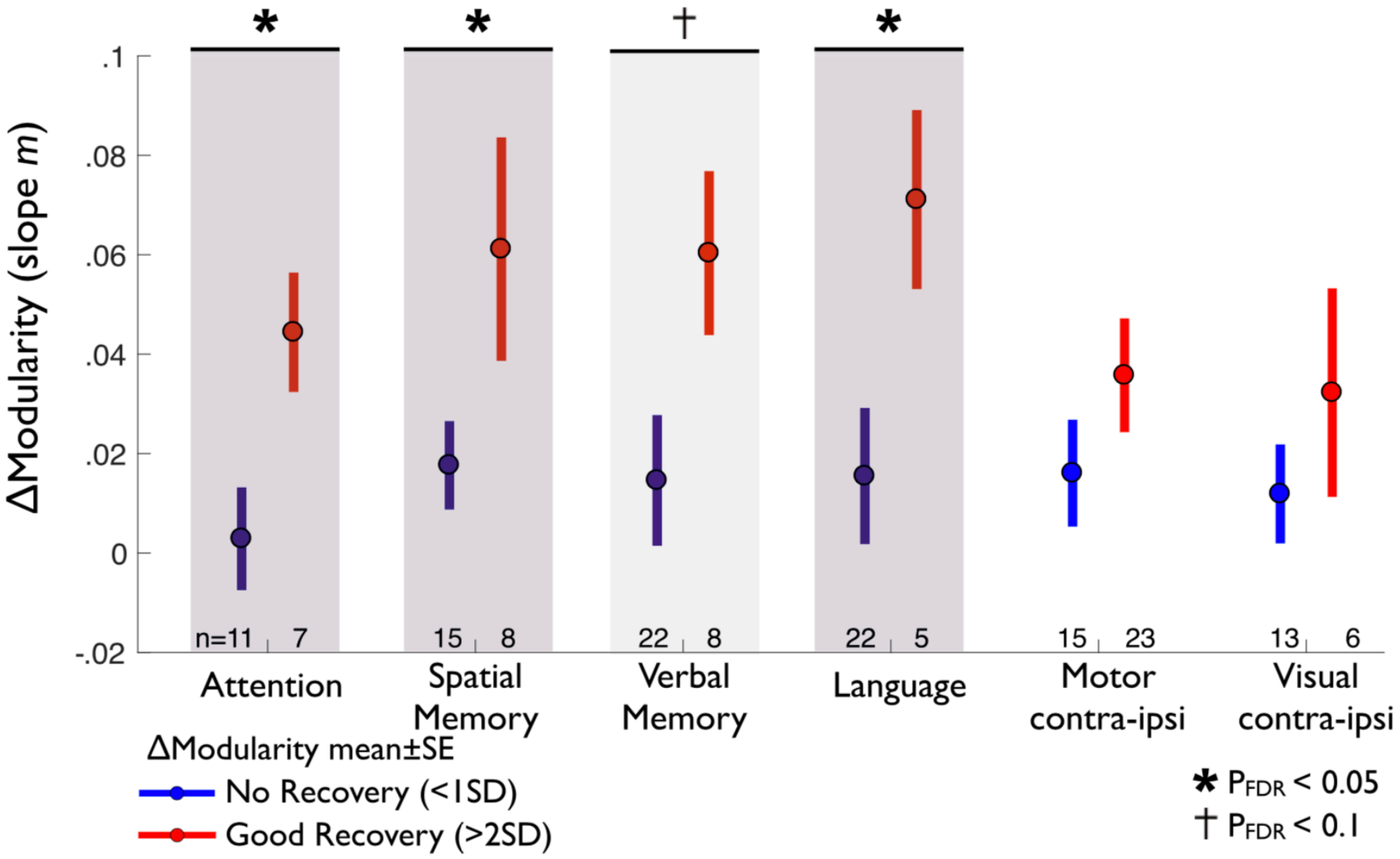


Overview

1. Aging & Dementia
   - Network level changes due to disease
   - Understanding memory deficits
   - Evaluating & targeting treatment
2. Depression
3. Stroke
4. Epilepsy
   - Presurgical evaluation

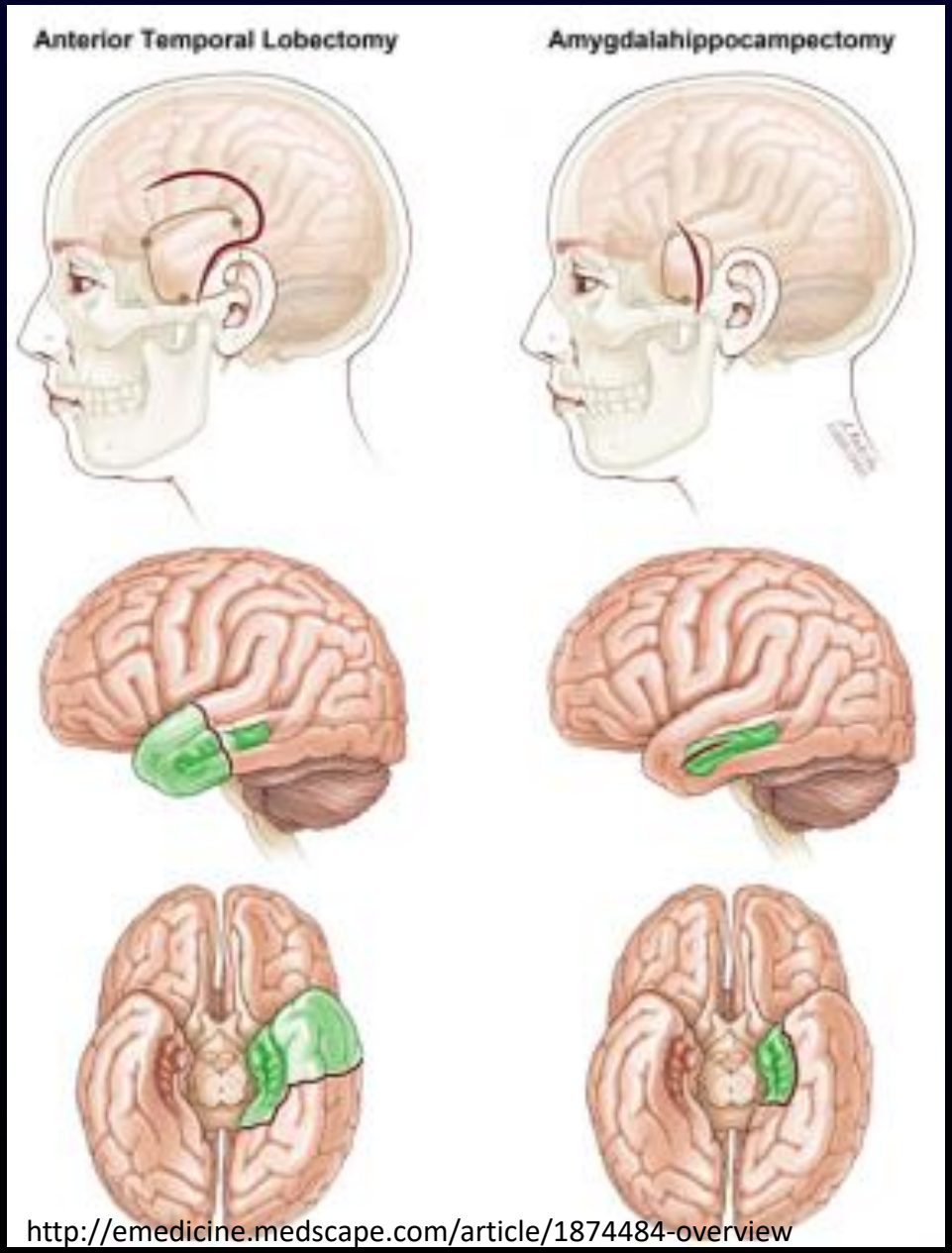
Epilepsy

- Chronic disorder – characterized by recurrent and unprovoked seizures
- Seizure = sudden surge of electrical activity
- ~50% of those who have 1 seizure have 2
- ~80% of those who have 2 have more
- Severely disabling
- Surgical resection is common
  - Typically fail 2+ single medications & combination of 2+ medications

Source: http://www.epilepsy.com

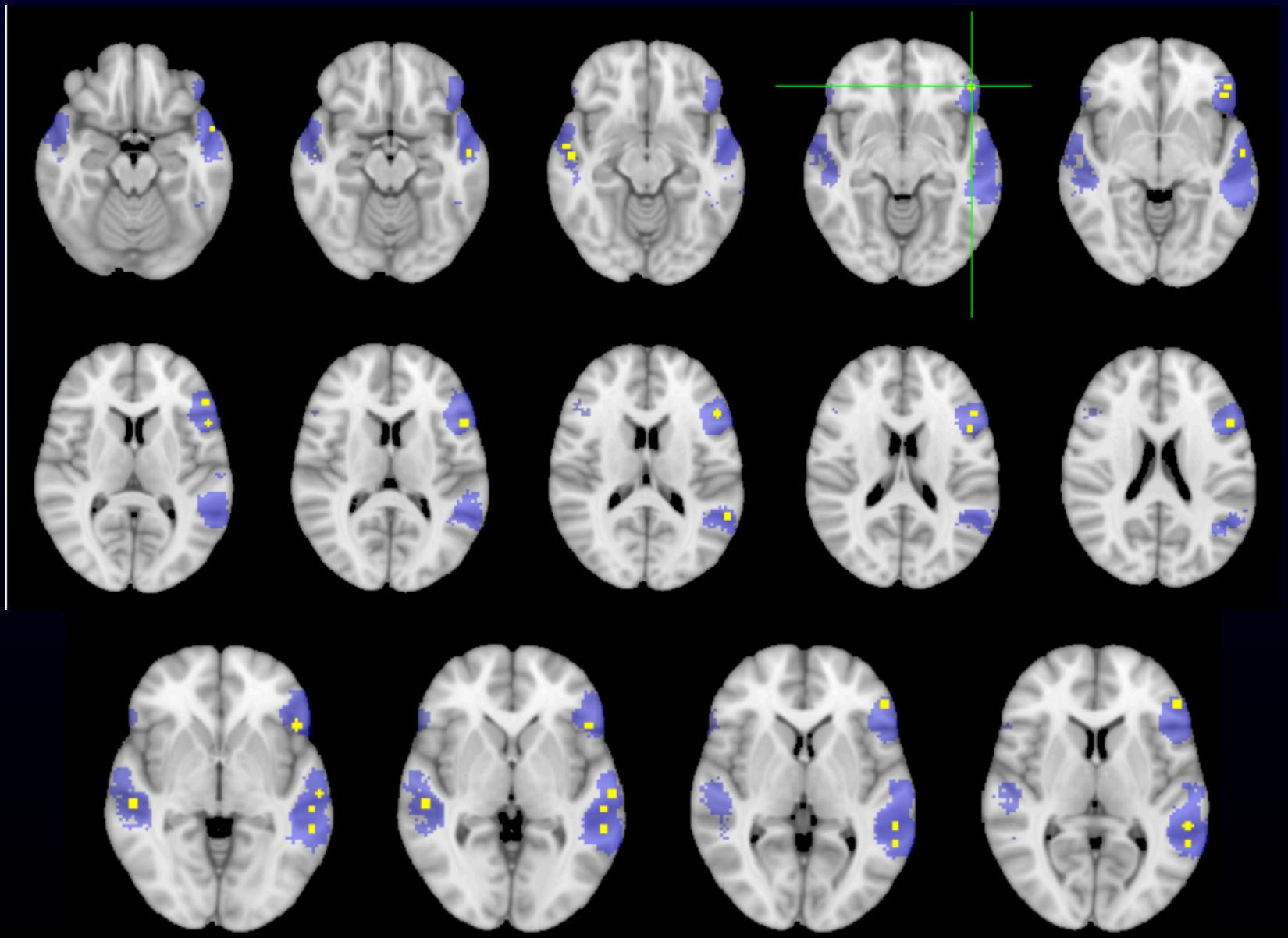
Types of Surgery for Epilepsy

- Removing brain tissue may cause cognitive impairment
- Wada test is “gold standard” for evaluating functioning
- Language & memory



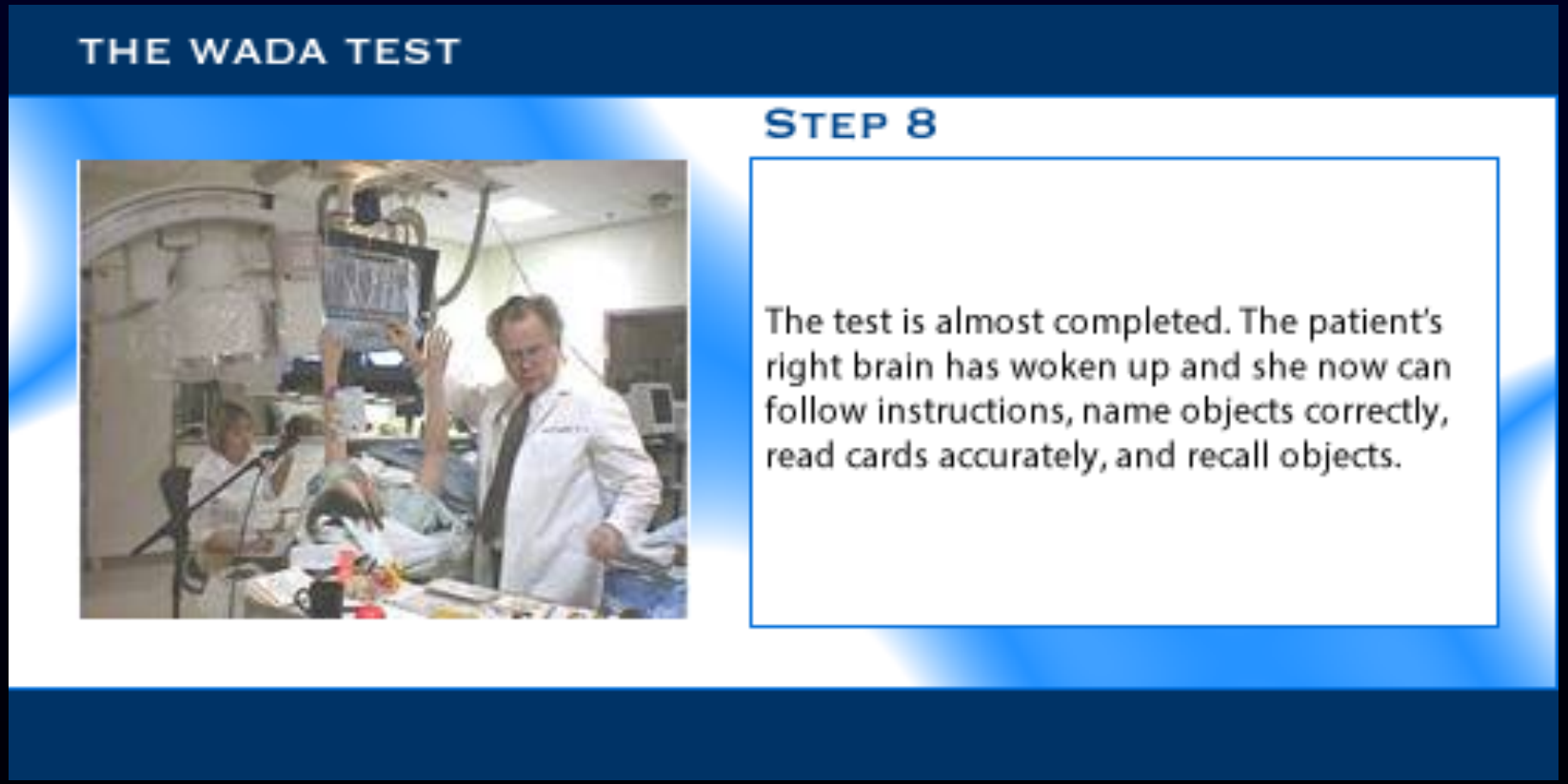
http://emedicine.medscape.com/article/1874484-overview

Language Regions (NeuroSynth)



Wada Test in Epilepsy

- Intracarotid amobarbital testing (IAT)
- http://pcs.hmc.washington.edu/Epilepsy/wadas.htm



Wada Test in Epilepsy

Risks include:

- **Sensitivity to contrast dye.** Reactions may include nausea, hives, and itching. Patients rarely experience difficulty breathing.
- **Bleeding.** Insertion of the catheter requires the puncture of a blood vessel. If blood should leak around the catheter into the tissue, a hematoma (a swollen area filled with blood) may result. It will become black and blue but will get better in time as the blood is absorbed by the body.
- **Sensitivity to sodium amytal,** which is a strong sedative. Rarely it can cause difficulty breathing or low blood pressure.
- **A blood clot** in the leg or brain, which may cause a stroke. This only happens in about one in a thousand cases.

Direct source: http://www.dartmouth-hitchcock.org/epilepsy/wada_test.html#risks

- Dissection?
- Costs (financial, personnel, emotional)

fMRI uses in Epilepsy

- Relatively low cost
- Non-invasive
- Widely available
- Uses include:
  - Language lateralization
  - Memory functioning

- Acquisition and analyses are not (traditionally) standardized

fMRI uses in Epilepsy

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Neurology® 2017;88:395-402

Practice guideline summary: Use of fMRI in the presurgical evaluation of patients with epilepsy

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

- 11 Member Panel reviewed 172 published manuscripts; 37 selected for review based on quality/nature of the study
- Assigned levels of evidence around several key questions:

1. Is fMRI comparable with the current standard (IAP) for measuring language lateralization?
2. Can fMRI predict postsurgical language outcomes in patients with epilepsy undergoing brain surgery?
3. Is fMRI comparable with the current standard (IAP) for measuring memory lateralization?
4. Can fMRI predict postsurgical verbal memory outcomes in patients with epilepsy undergoing temporal lobectomy?
5. Can fMRI predict postsurgical nonverbal (visuo-spatial) memory outcomes in patients with epilepsy undergoing temporal lobectomy?
6. Is there sufficient evidence in terms of diagnostic accuracy and outcome prediction for fMRI to replace the IAP (Wada test) in presurgical evaluation for epilepsy surgery?

1. Does fMRI = Wada for language lateralization?

- Meta-analysis found
  - 87% (201/232) concordance for medial temporal lobe epilepsy (MTLE)
  - 100% (7/7) for MT lesions
  - 81% (48/59) for extratemporal foci
- Recommendations: “fMRI may be considered as an option in lateralizing language functions in place of IAP in patients with MTLE, temporal epilepsy, or extratemporal epilepsy…”
  - Unclear evidence for temporal neocortical epilepsy or temporal tumors

2. Can fMRI predict postsurgical language outcome?

- Strong left frontal activation predicted postresection decline (100% sensitivity; 33% specificity)
- Strong left-lateralized temporal activation during semantic decision task predicted naming decline (100% sens; 73% spec).
  - Wada lower prediction than fMRI
- Recommendation: “fMRI may be considered for predicting postsurgical language outcomes after anterior temporal lobe (ATL) resection for the control of TLE”

3. Is fMRI comparable for memory lateralization?

- Visuospatial task (scenes vs. noise) laterality index (LI) significantly related to IAP (r=.31, p=.007)
  - No relationship in a second study (amytal dose?)
- Novel vs. repeated pictures & number of activated voxels were related to IAP LI in other studies

- Recommendation: “fMRI may be considered as an option to lateralize memory functions in place of IAP in patients with MTLE”

4. Can fMRI predict verbal memory outcome?

- fMRI leftward LI during verbal encoding "probably predicts" verbal memory decline
  - Presurgical Neuropsych testing accounted for 50% of variance; fMRI explained 10%

- Recommendation: "Presurgical fMRI of verbal memory or of language encoding should be considered as an option to predict verbal memory outcome in patients…undergoing evaluation for left MTL surgery"

5. Can fMRI predict visuospatial memory outcome?

- fMRI rightward LI during scene or facial encoding appears predictive of decline

- Recommendation: "Presurgical fMRI using nonverbal memory encoding may be considered as a means to predict visuospatial memory outcomes…"

6. Is there sufficient evidence for diagnostic accuracy to replace IAP?

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Practice guideline summary: Use of fMRI in the presurgical evaluation of patients with epilepsy

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Conclusions. Based on data from 1 Class II study and 1 Class III study, fMRI is possibly an effective method of lateralizing language functions in patients undergoing presurgical evaluation and may be a suitable replacement for the IAP for this purpose. Data on the ability of fMRI to predict language outcomes are limited.

Recommendation. Presurgical fMRI may be used instead of the IAP for language lateralization in patients with epilepsy who are undergoing evaluation for brain surgery (Level C). However, when fMRI is used for this purpose, task design, data analysis methods, and epilepsy type (temporal vs extratemporal, lesional vs nonlesional) need to be considered. Of particular importance for patients with lesional epilepsy is the fact that only small numbers of participants with variable lesion size/location were included in previous studies.

Conclusion. The correlations between fMRI and IAP memory asymmetry measures are modest, and the ability of the memory IAP to predict material-specific verbal memory change is relatively weak. Based on 9 Class II studies, including one study that showed that fMRI of language LI is possibly more accurate in predicting material-specific verbal memory change than was the memory IAP in patients undergoing left ATL resection, fMRI may be an alternative to IAP memory testing. The ability of fMRI to predict global amnesia has not been assessed.

Recommendation. fMRI of language and verbal memory lateralization may be an alternative to IAP memory testing for prediction of verbal memory outcome in MTLE (Level C). fMRI is not yet established as an alternative to the IAP for prediction of global amnesia in patients who have undergone ATL surgery.

Questions / Discussion