Real-time fMRI and Neurofeedback

Javier Gonzalez-Castillo, PhD.
Senior Associate Scientist
Section on Functional Imaging Methods
National Institute of Mental Health, NIH, Bethesda, MD

NIMH fMRI Summer Course

July 14, 2026

National Institute of Mental Health

Agenda

- **REALTIME fMRI**
  - What is it?
  - Additional computational infrastructure needed
  - Realtime Pre-processing vs. Offline Pre-processing
  - Best Practices / Available Platforms
  - Potential applications

- **fMRI NEUROFEEDBACK**
  - State-of-the-Art overview
  - Sample studies as models for NF experimentation
  - Open challenges for fMRI-Neurofeedback

What is Realtime fMRI?

	 IMAGE RECONSTRUCTION	 ANALYSIS
SEQUENCE DEVELOPMENT	OFFLINE	OFFLINE

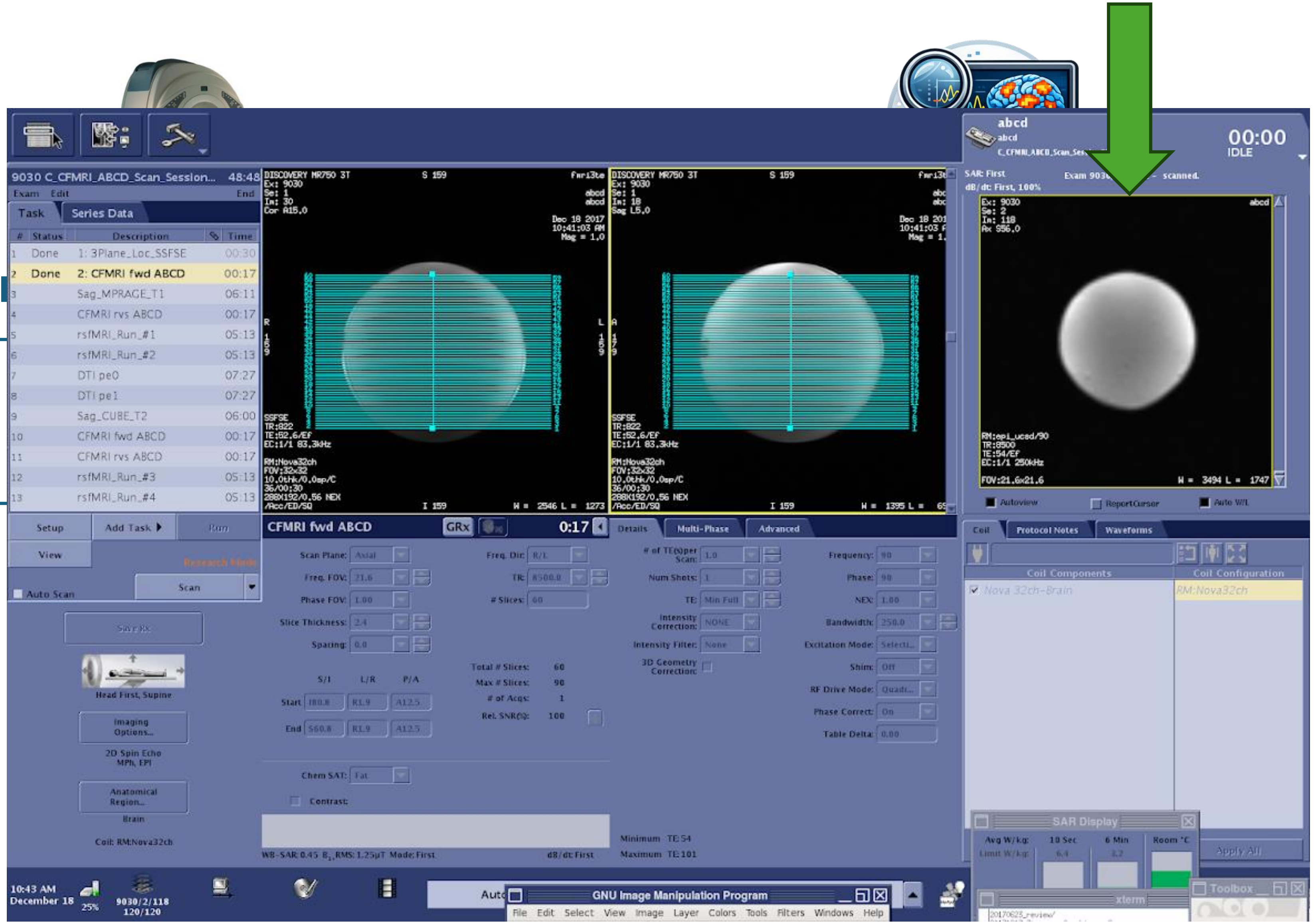
What is Realtime fMRI?

	 IMAGE RECONSTRUCTION	 ANALYSIS
SEQUENCE DEVELOPMENT	OFFLINE	OFFLINE
TRADITIONAL FMRI EXPERIMENTATION	REALTIME	OFFLINE

What is Realtime fMRI?

SEQUENCE DEVELOPMENT

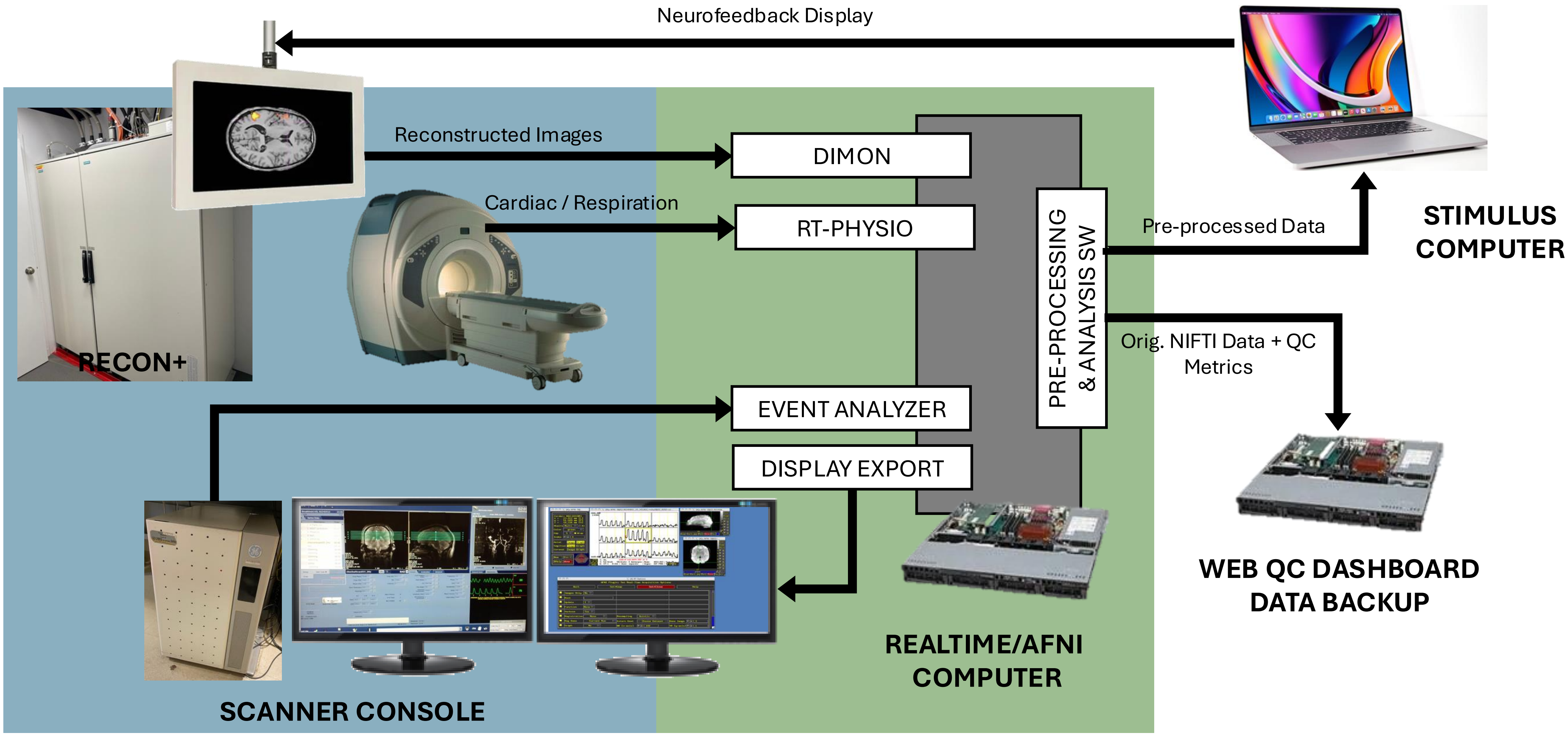
TRADITIONAL FMRI EXPERIMENTATION



What is Realtime fMRI?

	IMAGE RECONSTRUCTION	ANALYSIS
SEQUENCE DEVELOPMENT	OFFLINE	OFFLINE
TRADITIONAL FMRI EXPERIMENTATION	REALTIME	OFFLINE
REALTIME FMRI EXPERIMENTATION	REALTIME	REALTIME

Realtime fMRI | Computational Architecture



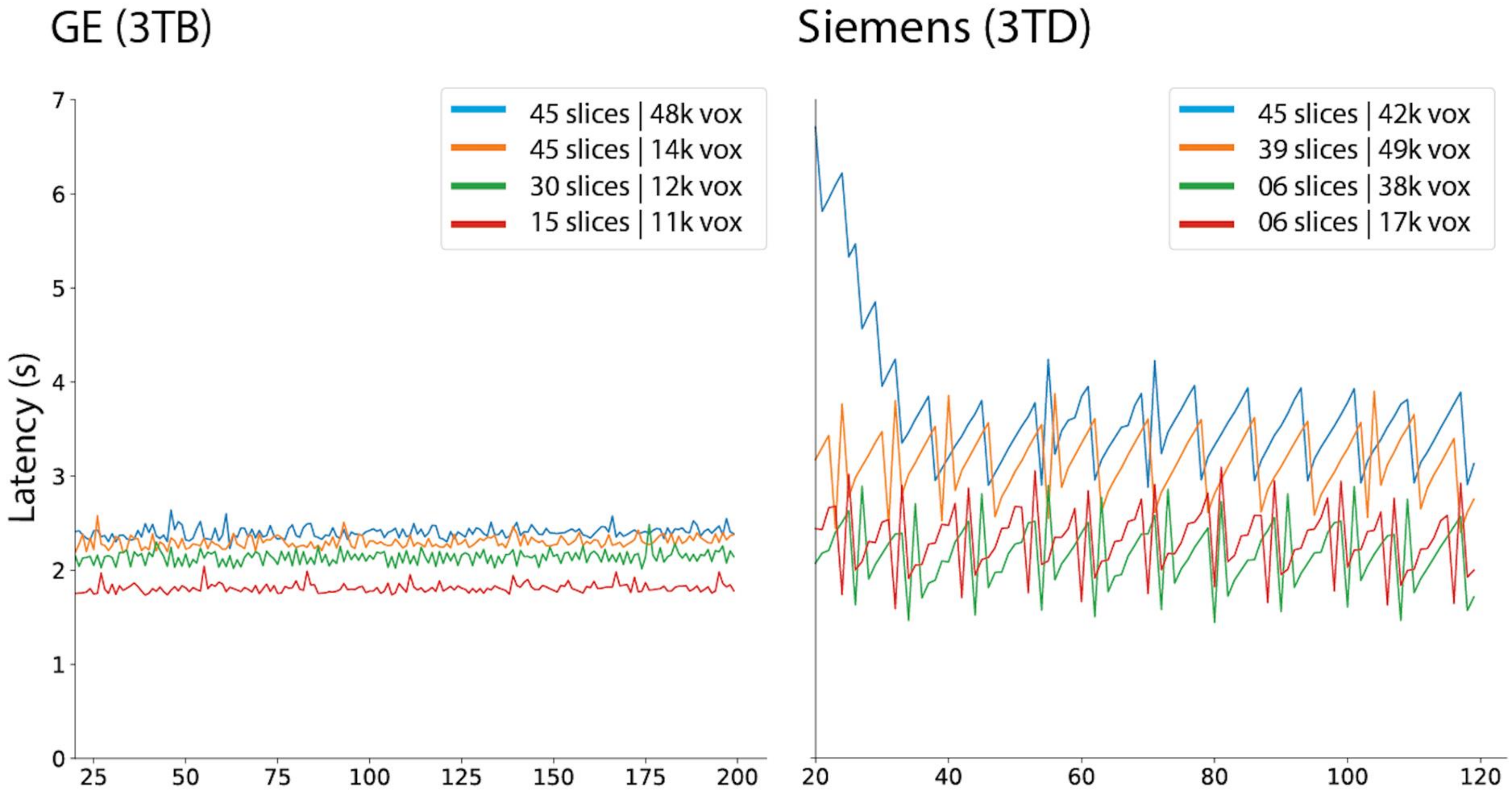
Realtime fMRI | Computational Architecture | Delays

RECON ENGINE
Writes DICOMs to Disk

DICOM
Detects/Organizes DICOMs

REALTIME/AFNI
Pre-Process and Extract Features

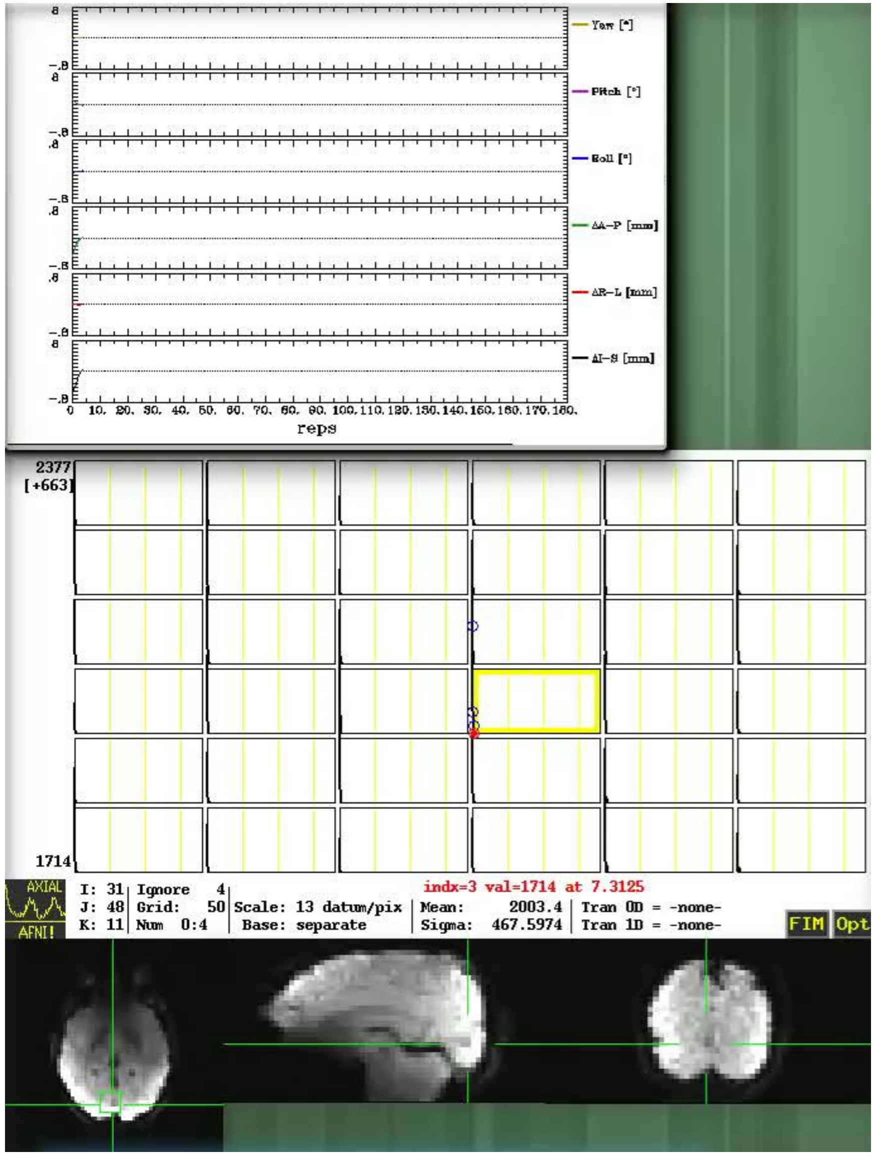
STIMULUS PC
Analysis and Stimulus Generation

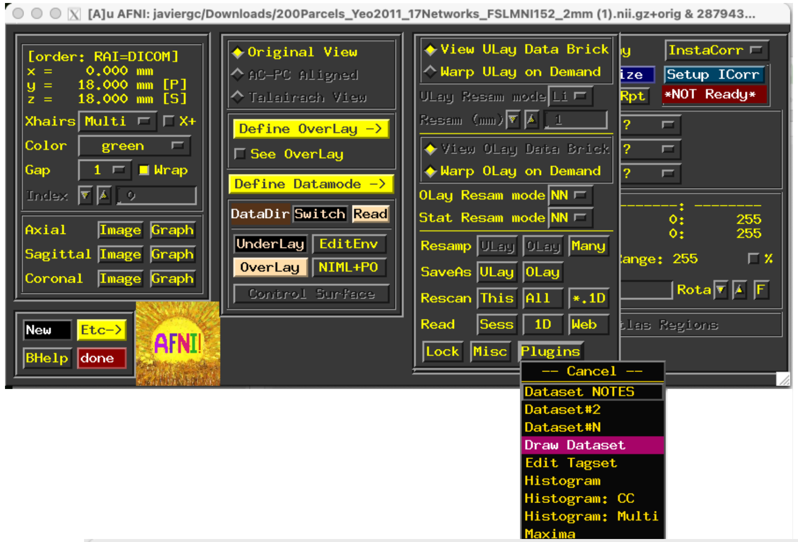


Realtime fMRI vs. Offline fMRI | Pre-processing

	Additional Delays	Robustness / Availability	Effect on Feedback Signal
Slice Time Correction	POSSIBLE / UNCOMMON		
Head Motion Correction	POSSIBLE / COMMON		
Distortion Correction			
Spatial Normalization			
Echo Combination			
Nuisance Regression			
Bandpass Filtering			
Spatial Smoothing			
Quality Assurance			

Realtime fMRI | Motion Correction





Realtime fMRI vs. Offline fMRI | Pre-processing

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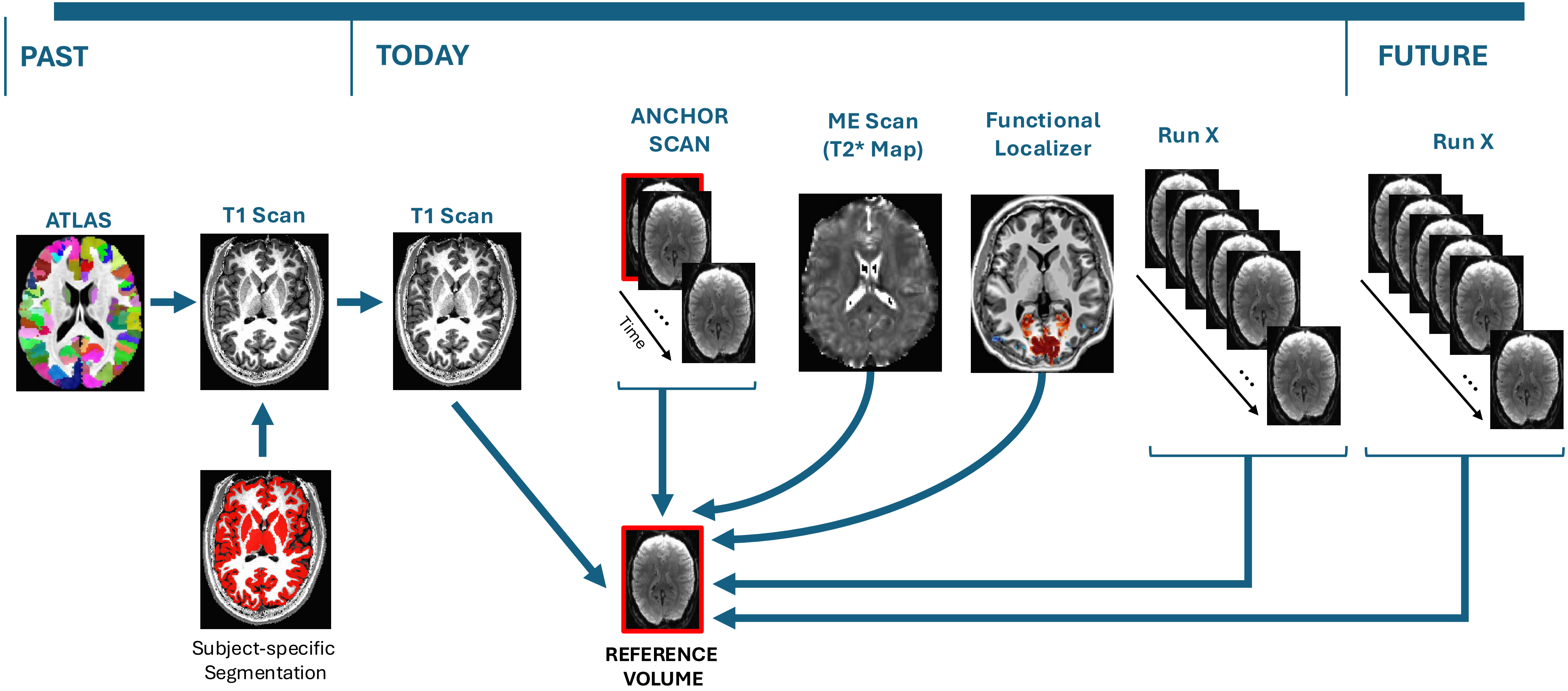
Echo Combination	POSSIBLE / ADDITIONAL SCANS / RECOMMENDED (if working with Multi-Echo Data)	
Nuisance Regression		
Bandpass Filtering		
Spatial Smoothing		
Quality Assurance		

Realtime fMRI | Reference Volume Selection & Spatial Alignment



Realtime fMRI | Scan Plan

1) 3D Localizer

2) Acquire High Resolution Anatomical Scan (6mins)

3) Acquire a 20s Reference Scan

    Set Reference Volume for subsequent alignment

Align anatomical scans and data from prior sessions to reference volume

3) Acquire Rest Scan | ME Scan | Localizer

Create masks, T2* map, trains classifier, etc.

4) Acquire other data of interest

5) Experimental Run 1

6) Experimental Run 2

...

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Bandpass Filtering		
Spatial Smoothing		
Quality Assurance		

Realtime fMRI | Nuisance Regression

COMMON REGRESSORS FOR OFFLINE ANALYSIS

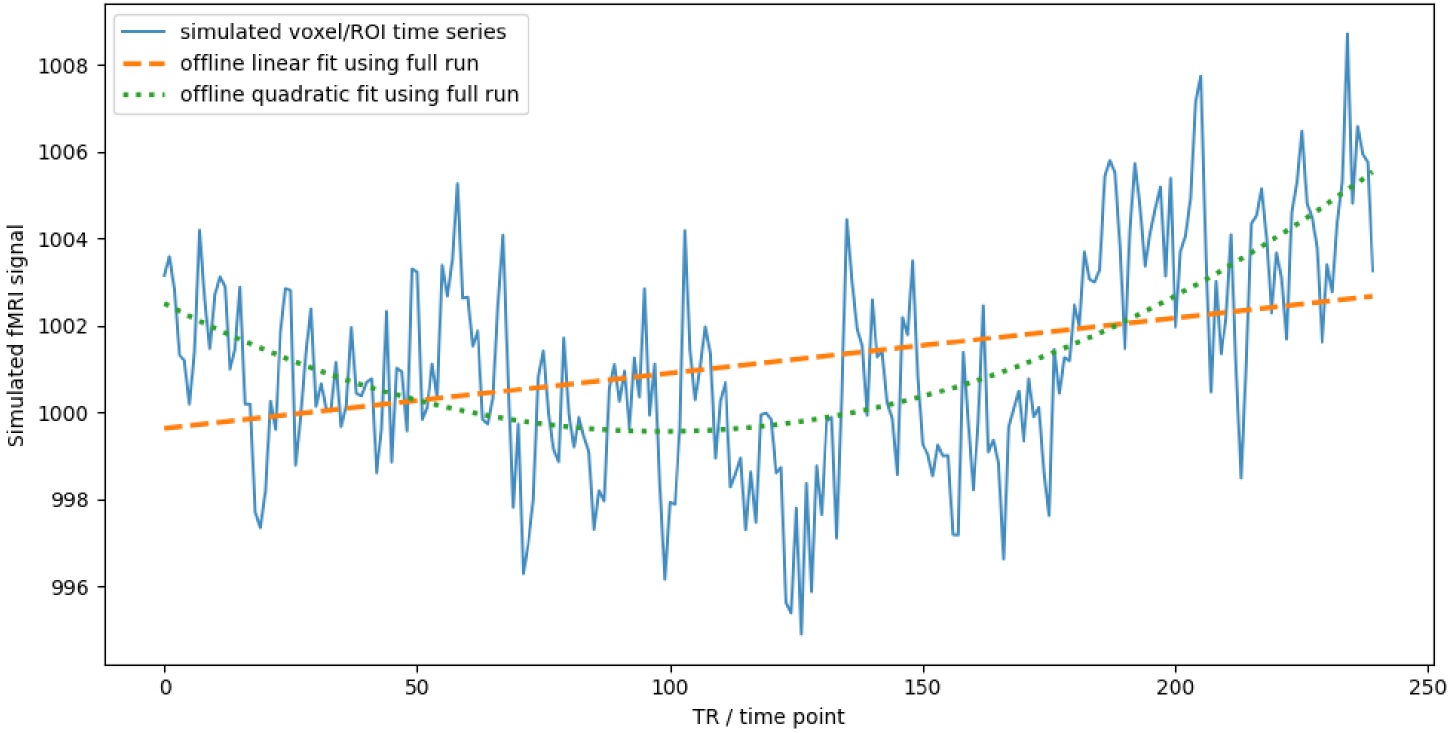
- Motion Estimates
- 1st Derivative of Motion Estimates
- Xth Order Legendre Polynomials
- Physiological Noise Regressors
- Noise ICs
- WM Signal
- Etc…

Main constrain is not running out of degrees of freedom

REGRESSORS FOR REALTIME FMRI

- Constant and Linear Drift
- Motion Estimates?

Stability and Accuracy without waiting too long



Realtime fMRI | Nuisance Regression

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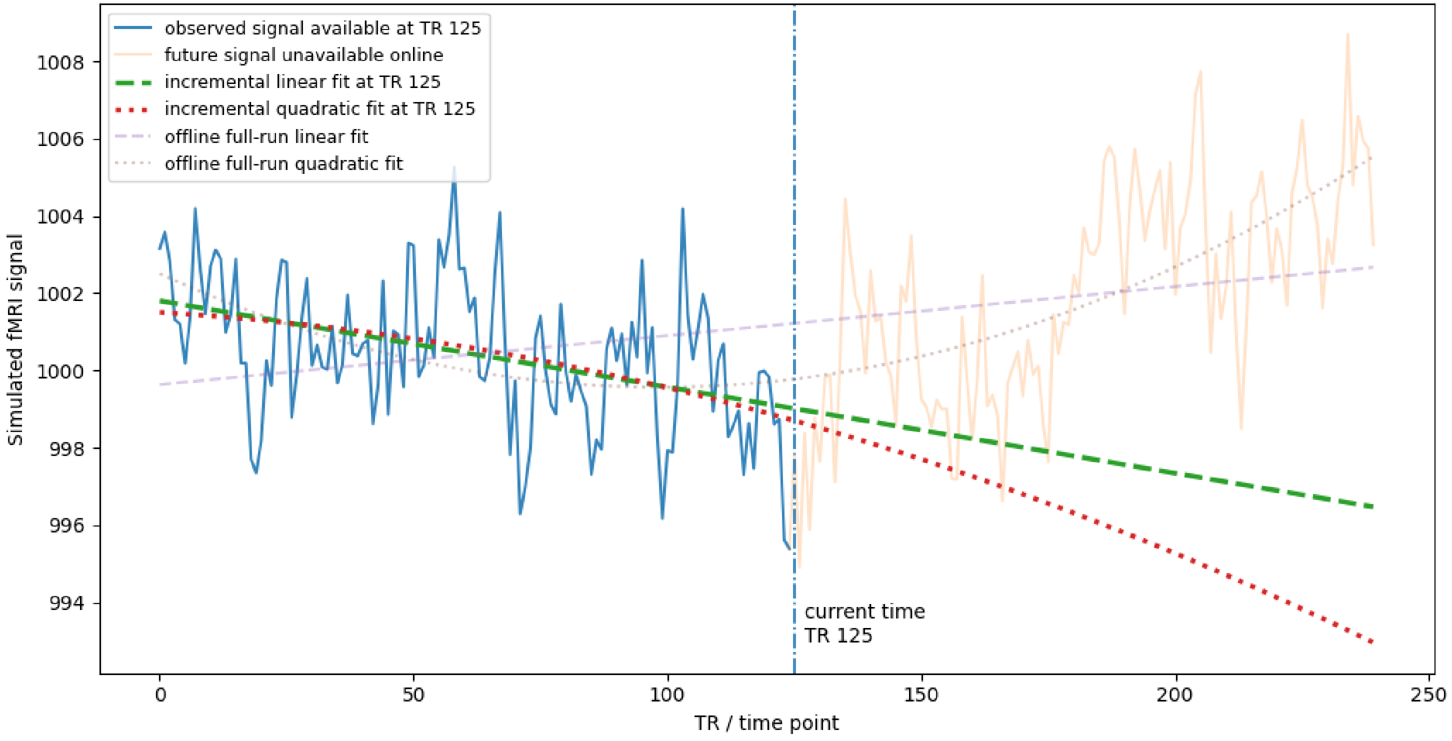

Realtime fMRI | Nuisance Regression

COMMON REGRESSORS FOR OFFLINE ANALYSIS

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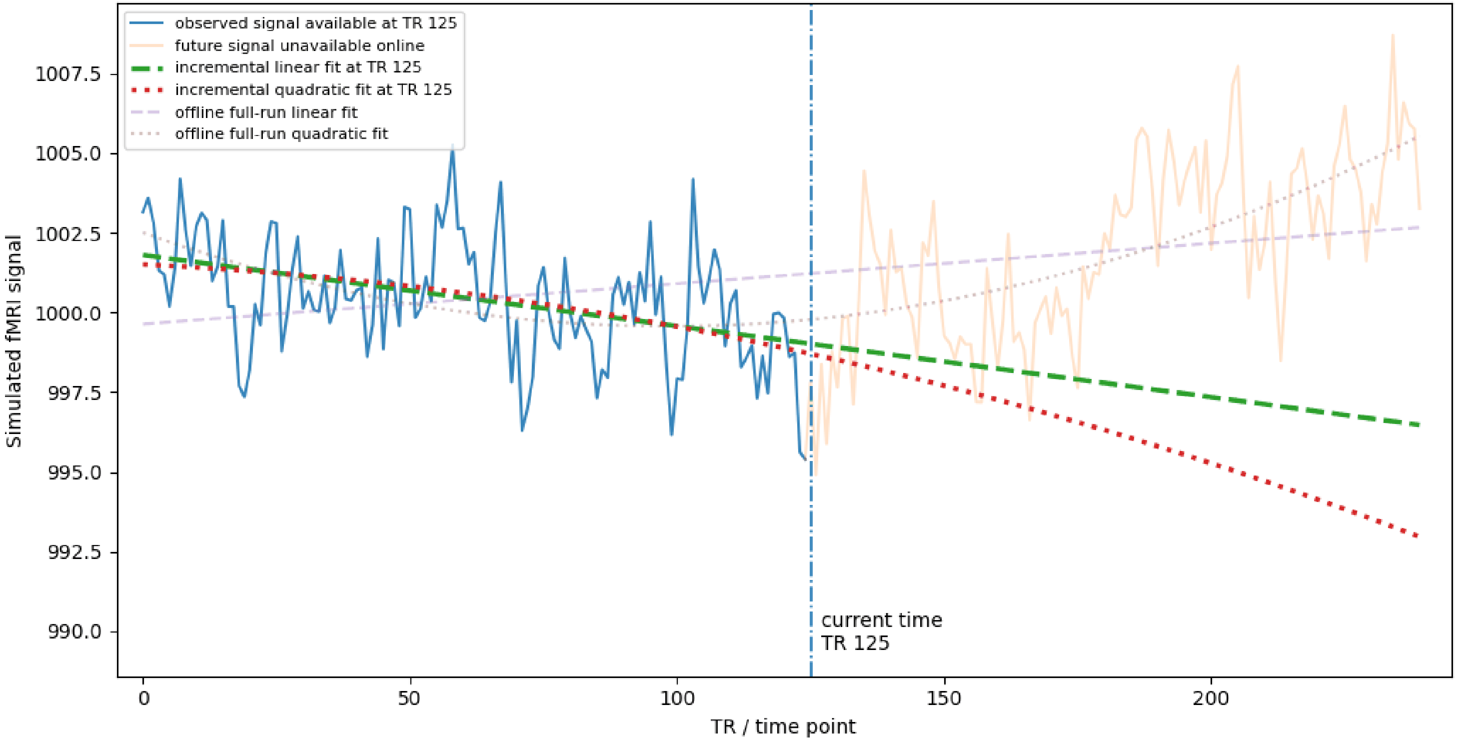
- Physiological Noise Regressors
- Noise ICs
- WM Signal
- Etc…

Main constrain is not running out of degrees of freedom

REGRESSORS FOR REALTIME FMRI (incremental GLM)

- Constant and Linear Drift
- Motion Estimates?

Stability and Accuracy without waiting too long



Realtime fMRI | Nuisance Regression

COMMON REGRESSORS FOR OFFLINE ANALYSIS

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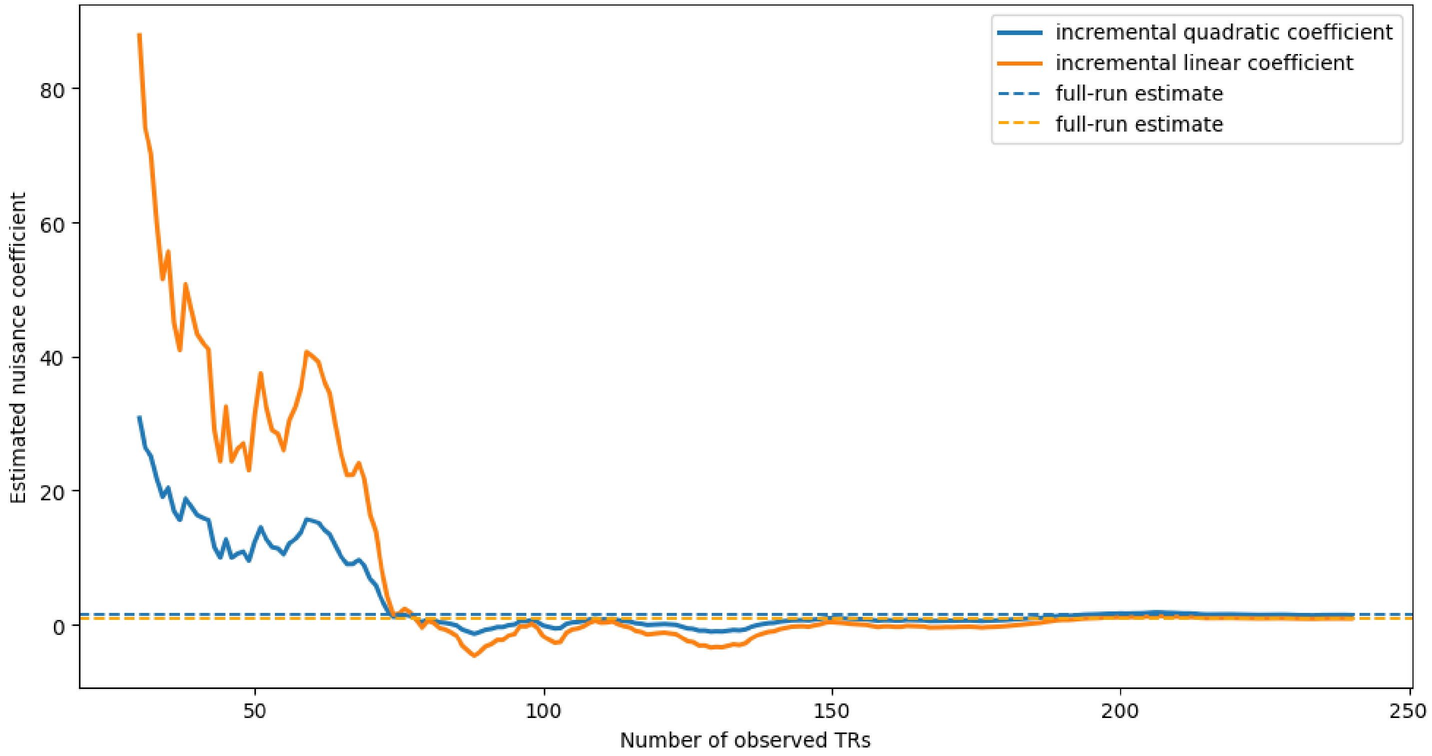
- Motion Estimates?

Stability and Accuracy without waiting too long



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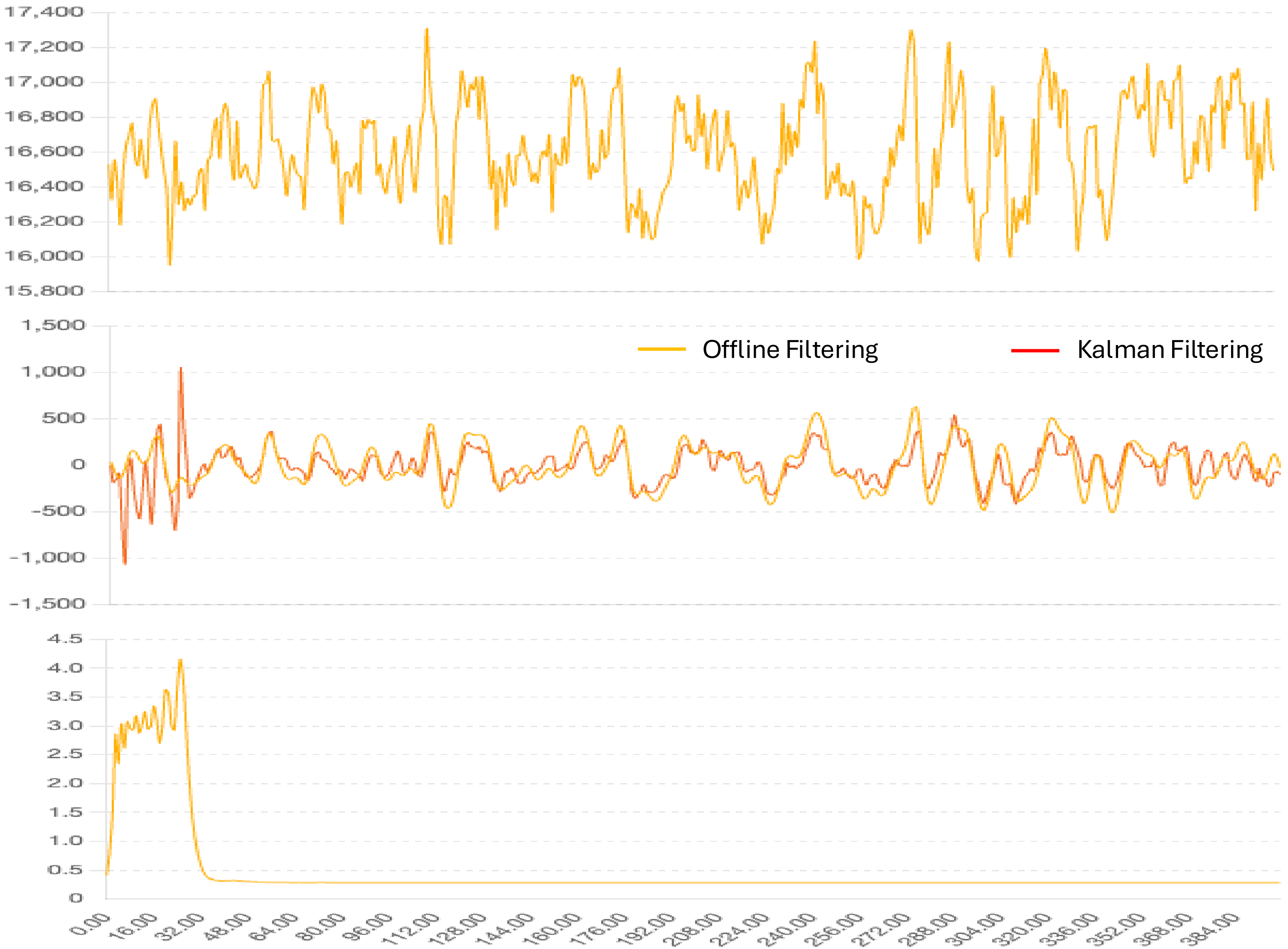
Bandpass Filtering	POSSIBLE / UNCOMMON	
Spatial Smoothing		
Quality Assurance		

Realtime fMRI | Bandpass Filtering (Kalman approach)



Raw ROI Time series

ROI Time series post-filtering (0.01 – 0.1 Hz)

Stability (Kalman Gain)

Realtime fMRI vs. Offline fMRI | Pre-processing

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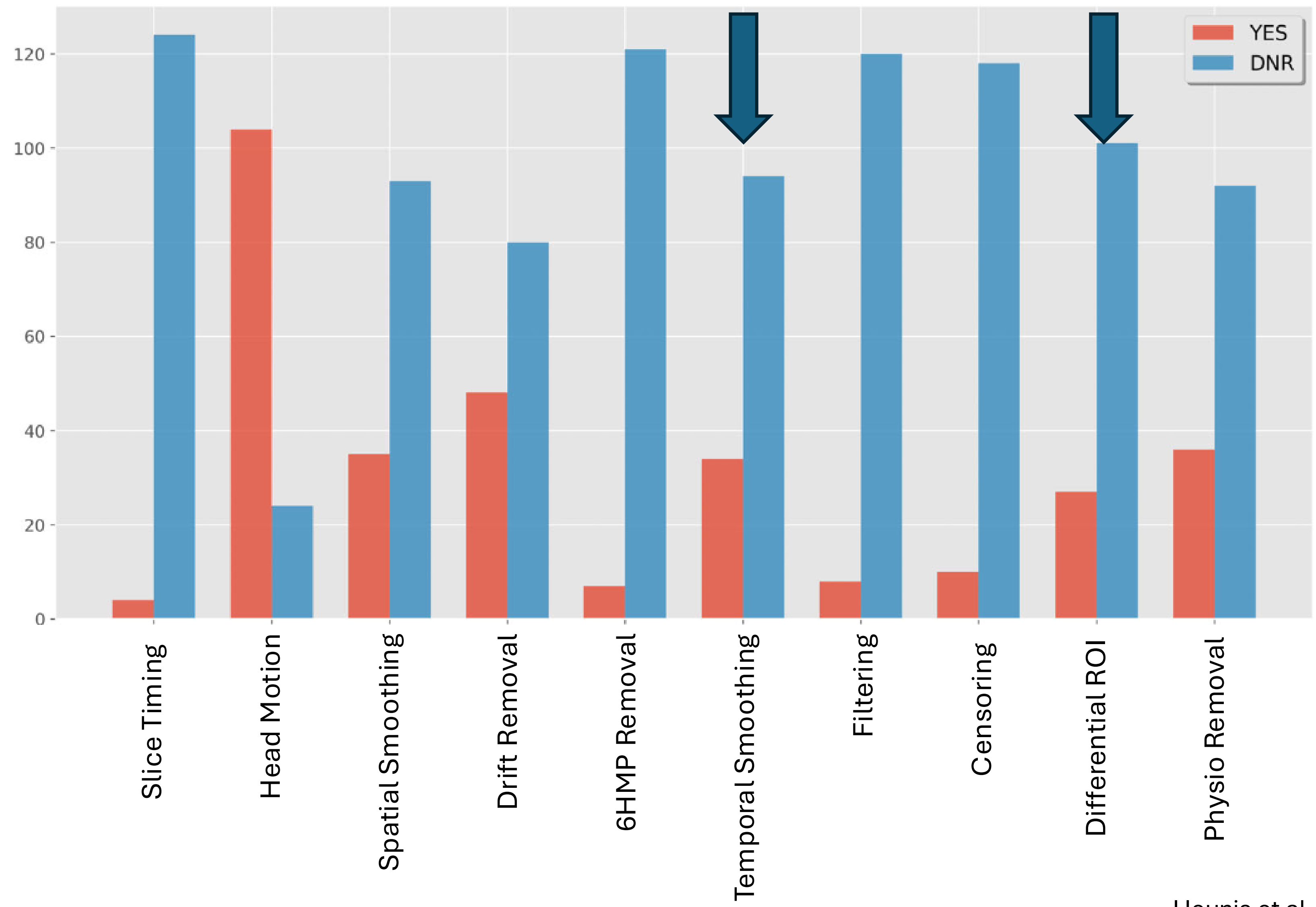
Nuisance Regression	POSSIBLE / MINIMAL REGRESSOR SET / COMMON	
Bandpass Filtering	POSSIBLE / UNCOMMON	
Spatial Smoothing	POSSIBLE / COMMON	
Quality Assurance	POSSIBLE / COMMON / AT THE END OF THE RUN	

Realtime fMRI: Pre-processing in the literature



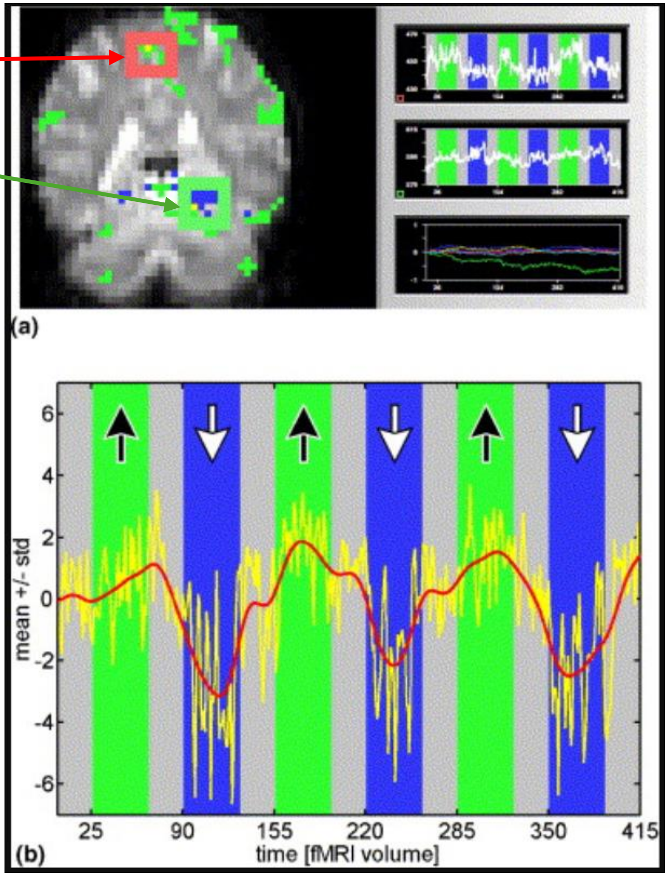
Heunis et al. (2020) Human Brain Mapping

Realtime fMRI: Differential Feedback Approach

- GOAL: remove global effects (e.g., respiration)
- ROI1 = Target Effect + Global Effect
- ROI2 = Global Effect
- FEEDBACK = ROI1 – ROI 2

ROI 1 = SMA

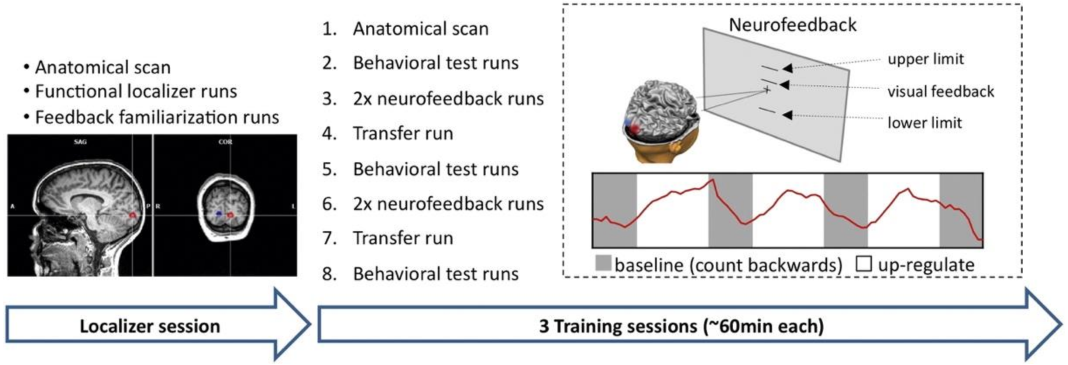
ROI 1 = PPA



Weiskopf et al. (2004) IEEE Transactions Biomed. Eng.

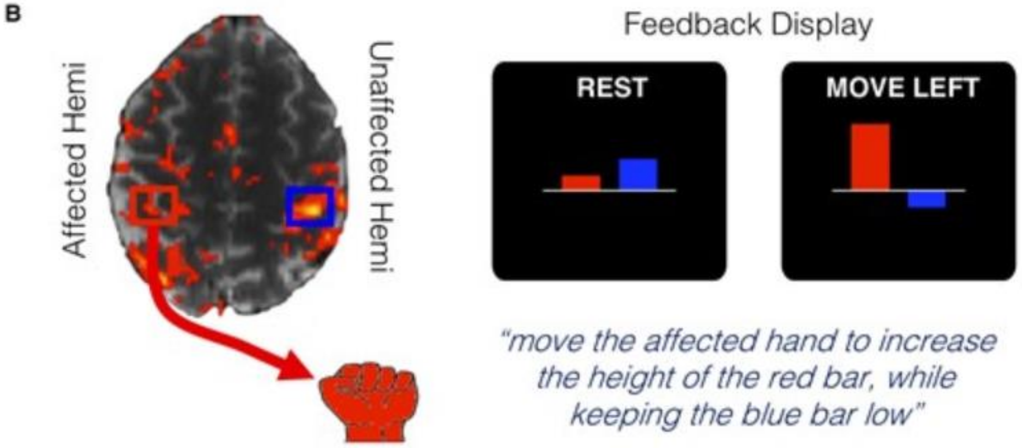
Interhemispheric balance between L & R visual cortices

(proof of concept)



Robineau et al. (2004) NeuroImage

Regaining Motor Laterality after Stroke



Britt-Sanders et al. (2022) Brain

Realtime fMRI | Methods & Best Practices Review

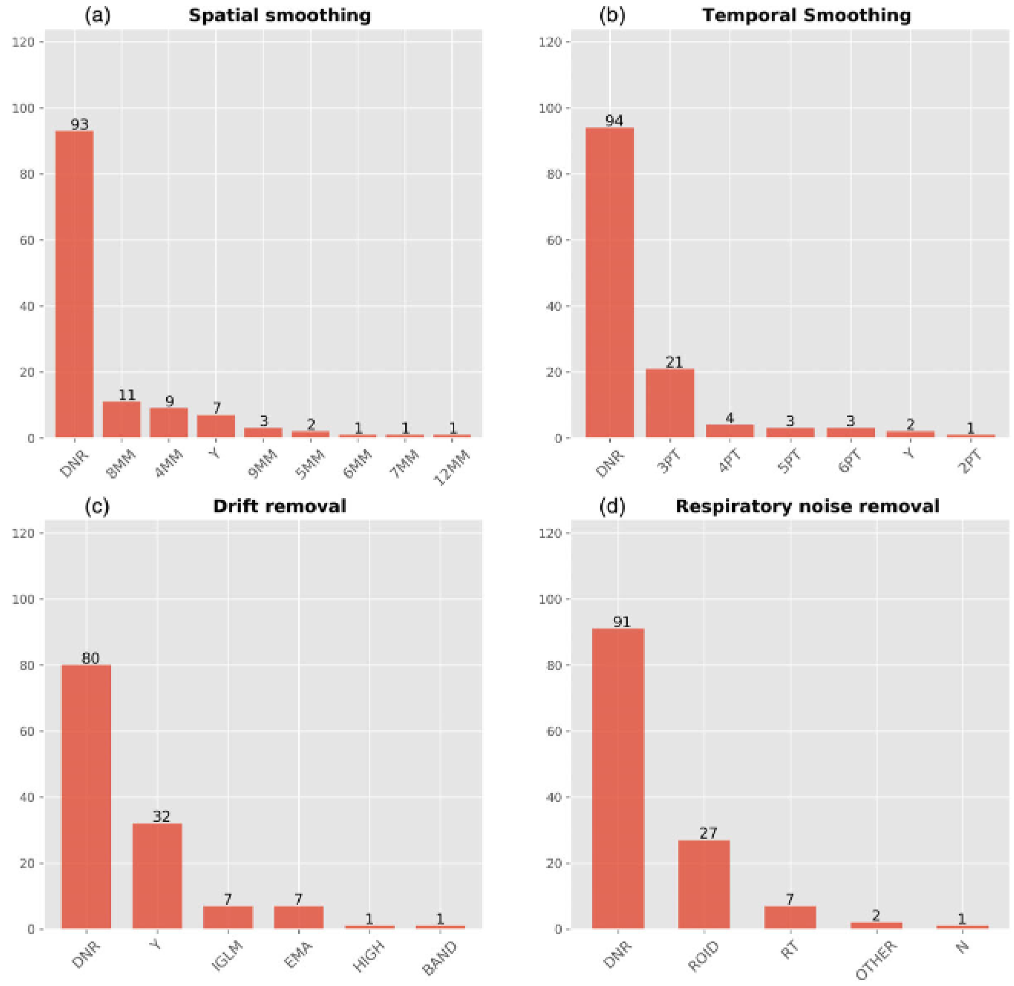
Received: 23 September 2019 | Revised: 13 February 2020 | Accepted: 3 April 2020
DOI: 10.1002/hbm.25010

REVIEW ARTICLE

WILEY

Quality and denoising in real-time functional magnetic resonance imaging neurofeedback: A methods review

Stephan Heunis[1,2] | Rolf Lamerichs[1,2,3] | Svitlana Zinger[1,2] | Cesar Caballero-Gaudes[4] | Jacobus F. A. Jansen[1,5,6] | Bert Aldenkamp[1,2,6,7,8] | Marcel Breeuwer[9,10]



Realtime fMRI | Recommended Reporting Practices

Category	Reporting suggestions
General (items apply to all categories)	• Report the space in which each real-time processing is performed (i.e. native volume, native surface, MNI volume, template surface, native structural, other) • Report whether real-time processing steps are executed on the whole brain, within a region of interest (ROI), or on the calculated neurofeedback signal • Report the order in which real-time pre-processing steps were implemented • Provide reasoning if steps were not implemented • For custom implementations, specify details
Software (items apply to all categories where software use is reported)	• Software used for real-time processing (e.g. Turbo BrainVoyager, AFNI, SPM + Matlab, OpenNFT, BART, FRIEND, BioImage Suite, Other, Custom) • Software used for offline processing (with clear distinction from real-time processing) • Indicate when default settings for the implemented software were used • For each software used, be sure to include version number, revision number, URL and Research Resource Identifier • For custom software/scripts, provide dependencies and link to code if possible

Heunis et al. (2020) Human Brain Mapping

Realtime fMRI | Recommended Reporting Practices

Category	Reporting suggestions
Slice time correction	• YES/NO • Name of software/method • Whether performed after or before motion correction • Reference slice • Interpolation type and order (e.g. third order spline or sinc)
Motion correction	• YES/NO • Name of software/method • Use of non-rigid registration, and if so the type of transformation • Use of real-time motion susceptibility correction (fieldmap based unwarping), as well as the particular software/method • Reference scan (e.g. a template volume from the pre-real-time scans or the first volume of the real-time session) • Image similarity metric (e.g. normalised correlation, mutual information etc.) • Interpolation type (e.g. spline, sinc), and whether image transformations are combined to allow a single interpolation • Use of any slice-to-volume registration methods, or integrated with slice time correction • Explanation of software and hardware used in the case of prospective motion correction
Function–structure (inter-subjective) co-registration	• YES/NO • Name of software/method • Type of transformation (rigid, non-linear); if non-linear, type of transformation • Cost function (e.g. correlation ratio, mutual information, boundary-based registration etc.) • Interpolation method (e.g. spline, linear) • Distinguish between coregistration applied pre-real-time (e.g. to support real-time operations like tissue masking) and coregistration done in real-time
(Gradient) distortion correction	• YES/NO • Specify if implemented as part of real-time acquisition sequence on (as opposed to as a real-time processing step)
Spatial smoothing	• YES/NO • Name of software/method • Size and type of smoothing kernel • Filtering approach, for example, fixed kernel or iterative smoothing until fixed FWHM
Nuisance regression	• YES/NO • Specify software and GLM algorithm type (e.g. cumulative, windowed, incremental) with applicable parameters (e.g. window length) • If head motion parameters are included, report the expansion basis and order (e.g. first temporal derivatives; Volterra kernel expansion) • If tissue signals are included, report the tissue type (e.g. whole brain, grey matter, white matter, ventricles), the tissue definition (e.g. a priori seed, automatic segmentation, spatial regression) and signal definition (e.g. mean of voxels, first singular vector etc.) • Report any other included regressors and how they are calculated

Category	Reporting suggestions
Detrending/drift removal	• YES/NO • Name of software/method (e.g. nuisance regression using a real-time GLM with linear and/or cosine basis set regressors; exponential moving average filter; custom filter) • If nuisance regression is used, specify the order of regressors and/or cutoff frequency • If nuisance regression is used, specify GLM type (cumulative, windowed, incremental) with applicable parameters (e.g. window length)
Physiological noise removal	• YES/NO • Name of software/method • If differential regions of interest are used (e.g. to cancel global effects of respiration) specify ROI definition and how the difference is calculated per time step • If respiratory and heart rate information are included in real-time nuisance regression with a GLM, report the modelling choices (e.g. RETROICOR; cardiac and/or respiratory response functions; partial correlation to compartment signals) and number of computed regressors • If RETROICOR-based nuisance regression is used, specify the software/method for computing the regressors and specify how subject physiology traces are accessed in real-time • Distinguish clearly between real-time physiological noise correction and offline correction and quality checking
High frequency filtering	• YES/NO • Name of software/method (e.g. modified low-pass Kalman filter as implemented in OpenNFT to remove high frequency spikes related to subject physiology)
Volume censoring (a.k.a 'scrubbing' or 'despiking')	• YES/NO • Name of software/method • Criteria for censoring (e.g. real-time framewise displacement threshold, DVARS threshold, percentage BOLD change threshold, or standardised voxel intensity threshold) • Use of censoring (e.g. temporal censoring regressor in real-time GLM) or interpolation; if interpolation, method used (e.g. spline, spectral estimation)
Serial correlations	• YES/NO • Name of software/method (e.g. a first-order autoregressive model AR(1) as implemented in OpenNFT)
Temporal averaging	• YES/NO • Name of software/method (e.g. a 5-point moving windowed average applied to the neurofeedback signal)
Intensity normalisation/scaling	• YES/NO • Name of software/method • Scaling factor description (e.g. z-score normalisation per voxel using the past *n* volumes; whole-brain intensity scaling to a mean image intensity of constant *k*; voxel efficiency scaling to avoid undesired noise weighting in direct averaging of all voxels within the neurofeedback ROI; scaling of the neurofeedback signal to prevent sudden changes in visual feedback display) • Where applicable, provide equations for the scaling of each time step of the volume/ROI/signal
Real-time data quality control	• YES/NO • Name of method (e.g. head motion parameter or physiology trace feedback to subject; real-time display of quality control measures like tSNR to researcher; adaptive acquisition and processing

Heunis et al. (2020) Human Brain Mapping

Realtime fMRI | Software (at NIH)

SCANNER

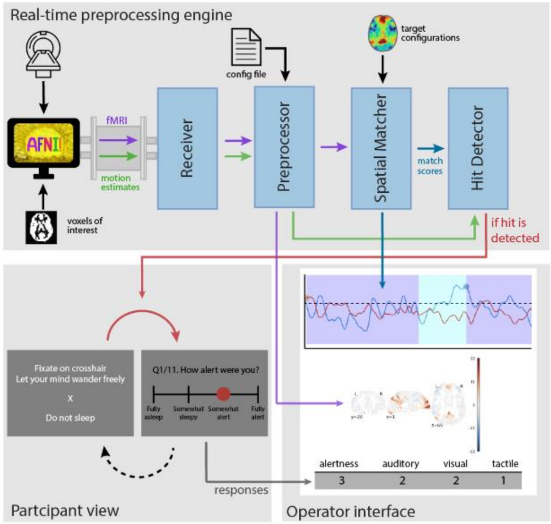
GE : Full integration
Siemens: Semi-manual integration

REALTIME PC

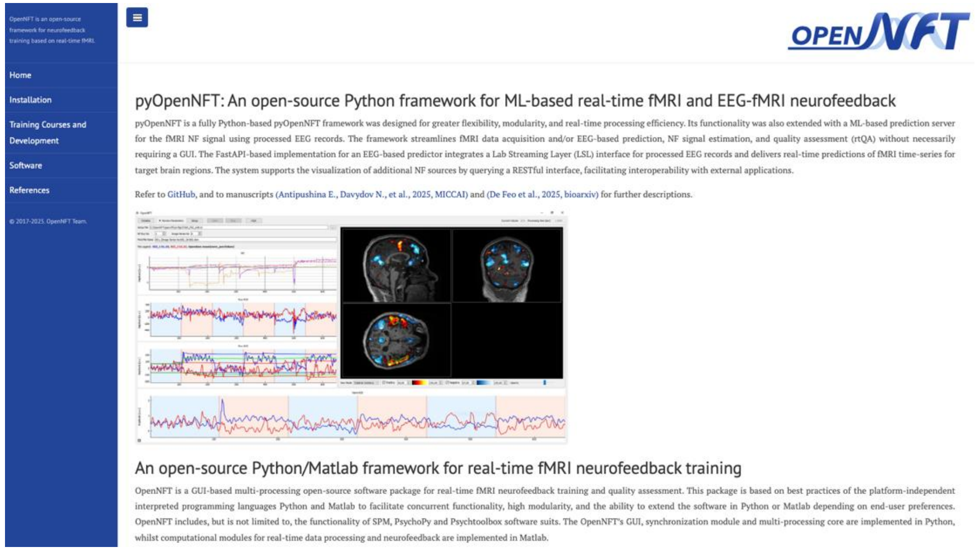
- Motion Correction / Alignment
- ME combination
- Basic detrending
- Motion regression
- Spatial Smoothing
- Serves data from user defined ROIs
  - All voxels
  - ROI mean
- Serves motion estimates
- Support Vector Machine
- TSNR maps per scan

STIMULUS PC

- afni-fmrif-neurofeedback toolbox
  - Feedback based on ROI signal
- rt-cog
  - Advance pre-processing
  - full brain pattern matching
  - Interactive paradigms

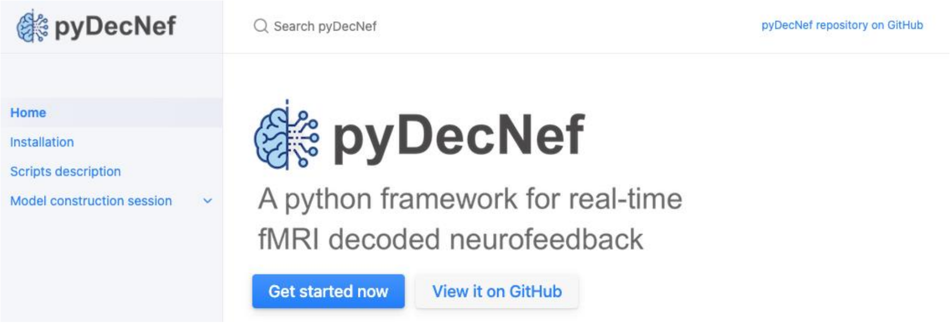


Realtime fMRI | Software (others)

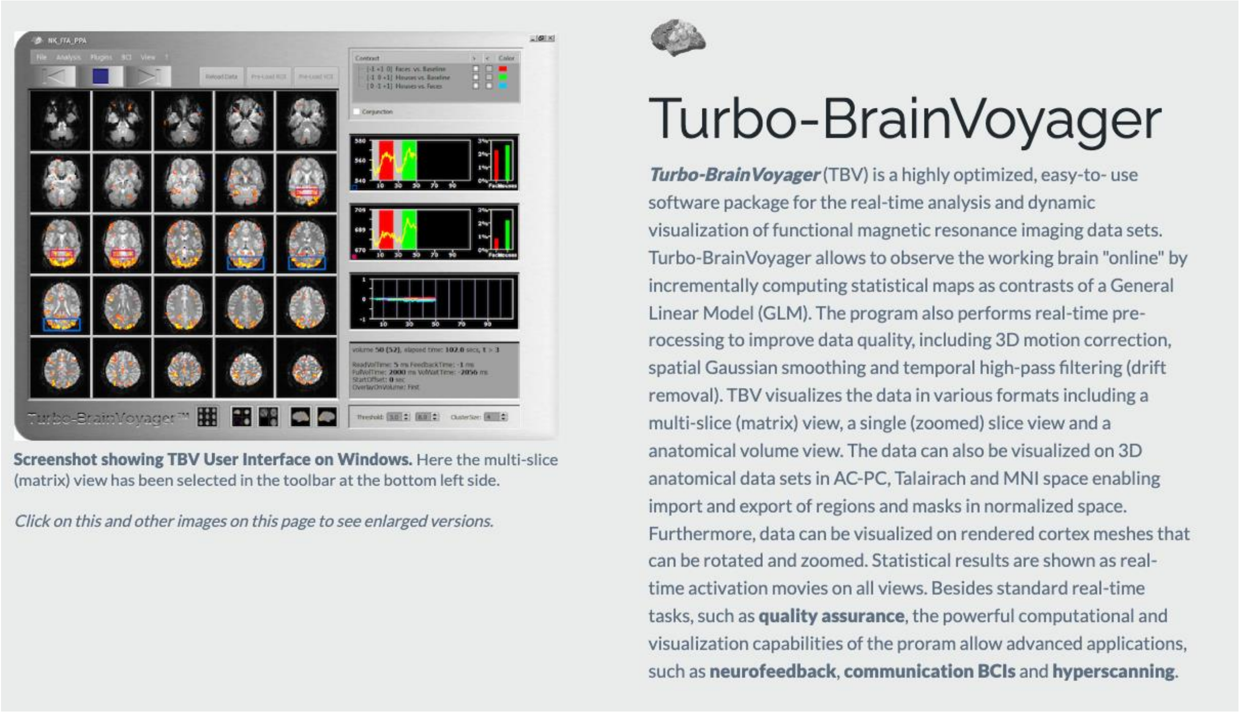


Davydov et al. (2022) NeuroInformatics

Koush et al. (2017) NeuroImage



Margolles et al. (2025) bioRxiv



Realtime fMRI | Common Applications

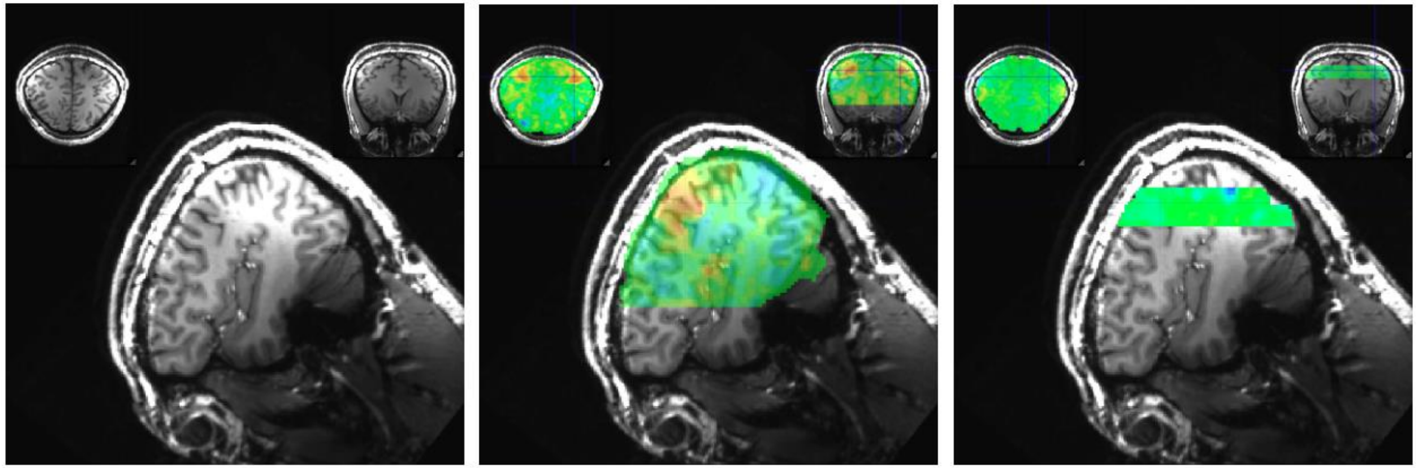
At-the-scanner Quality Control — Head Motion, Good Contrast, Artifacts, Basic QC

Educational Purposes

Functional Localizers

1 Define target regions for main experiment more precisely…

…so that we can scan faster and/or at higher spatial resolution



HIGH RES-ANATOMICAL	EPI FUNCTIONAL LOCALIZER	MAIN EXPERIMENT
1x1x1mm	52 Slices @ 2x2x2mm TR=2000ms	11 Slices @ 2x2x2mm TR=400ms

Realtime fMRI | Common Applications

At-the-scanner Quality Control

Head Motion

Good Contrast

Artifacts

Basic QC

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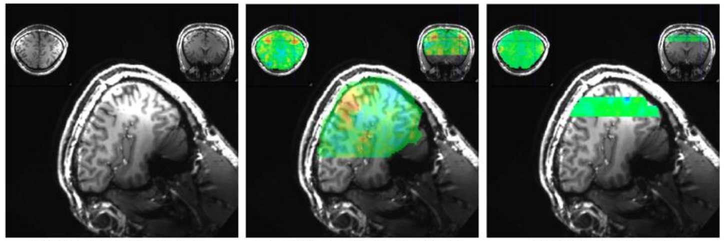

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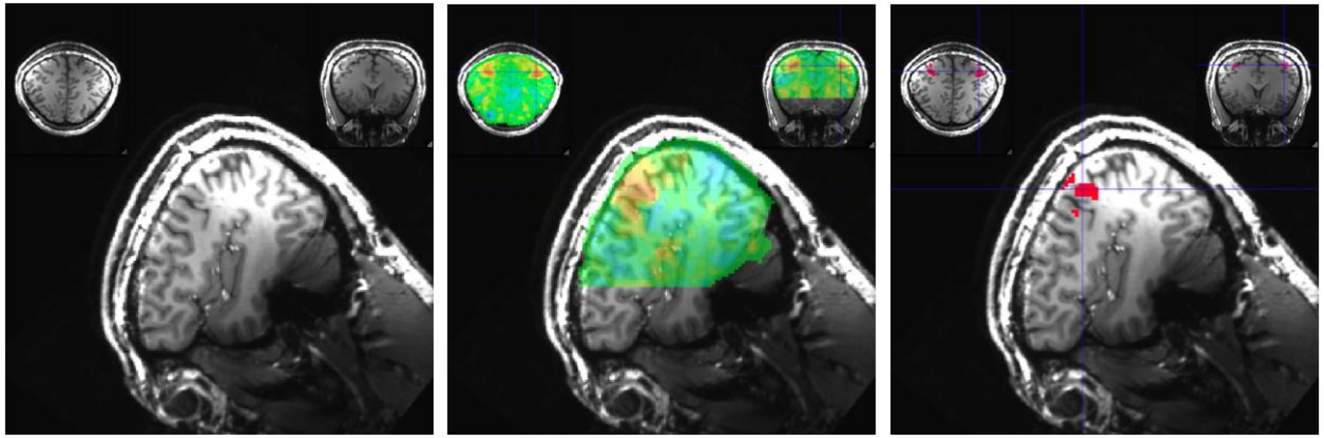
1x1x1mm	52 Slices @ 2x2x2mm TR=2000ms	11 Slices @ 2x2x2mm TR=400ms

2 Define target regions for main experiment more precisely…

… to obtain a Region of Interest (ROI) for a subsequent Neurofeedback scan



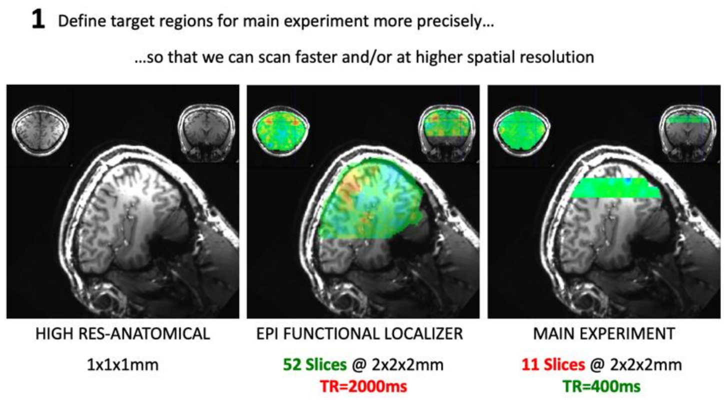
HIGH RES-ANATOMICAL	EPI FUNCTIONAL LOCALIZER	ROI FOR MAIN EXPERIMENT
1x1x1mm	52 Slices @ 2x2x2mm TR=2000ms	NEUROFEEDBACK/BCI

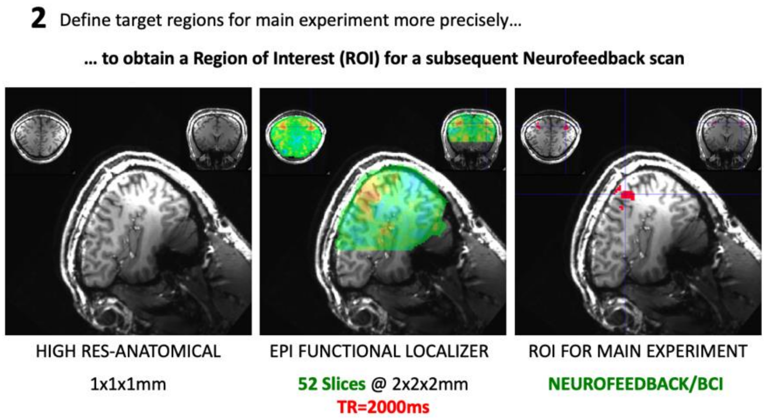
Realtime fMRI | Common Applications

At-the-scanner Quality Control Head Motion Good Contrast Artifacts Basic QC

Educational Purposes

Functional Localizers



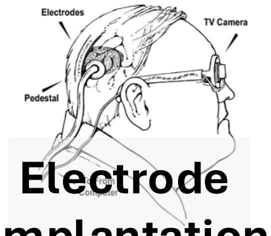


Interactive Paradigms (such as Neurofeedback)

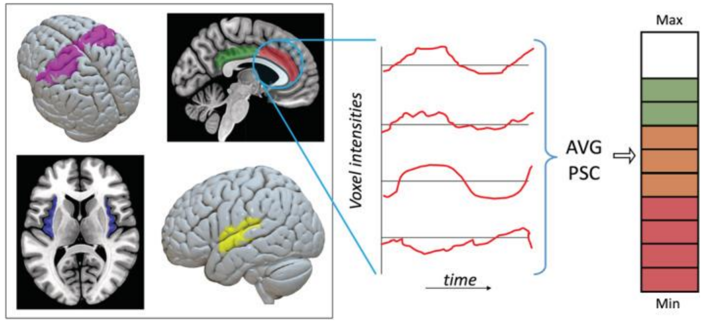
fMRI-based Neurofeedback

“Neurofeedback is a form of biofeedback in which information about neural processes is given to an individual”

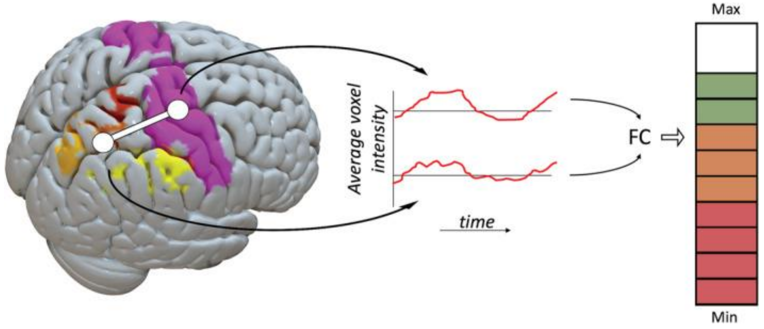
Fede et al. (2020) Frontiers Hum. Neurosci.

	NON-INVASIVE	PORTABLE	INTERFACE	SPAT. SPECIFICITY	DEEP STRUCT.
 Electrode Implantation	✗	✓	Neuronal Activity	VERY HIGH	✓
 EEG-based	✓	✓	Electric Fields	LOW	✗
 fMRI-based	✓	✗	Hemodynamic Response	HIGH	✓

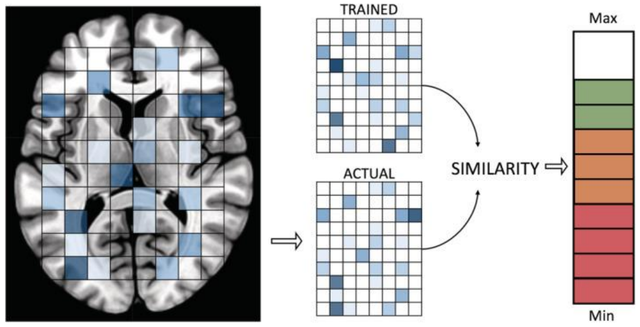
fMRI-based Neurofeedback



Single ROI



FC between ROIs



Multivariate Pattern Match

Images from Heunis et al. (2020) Human Brain Mapping

fMRI Neurofeedback | State-of-the-Art

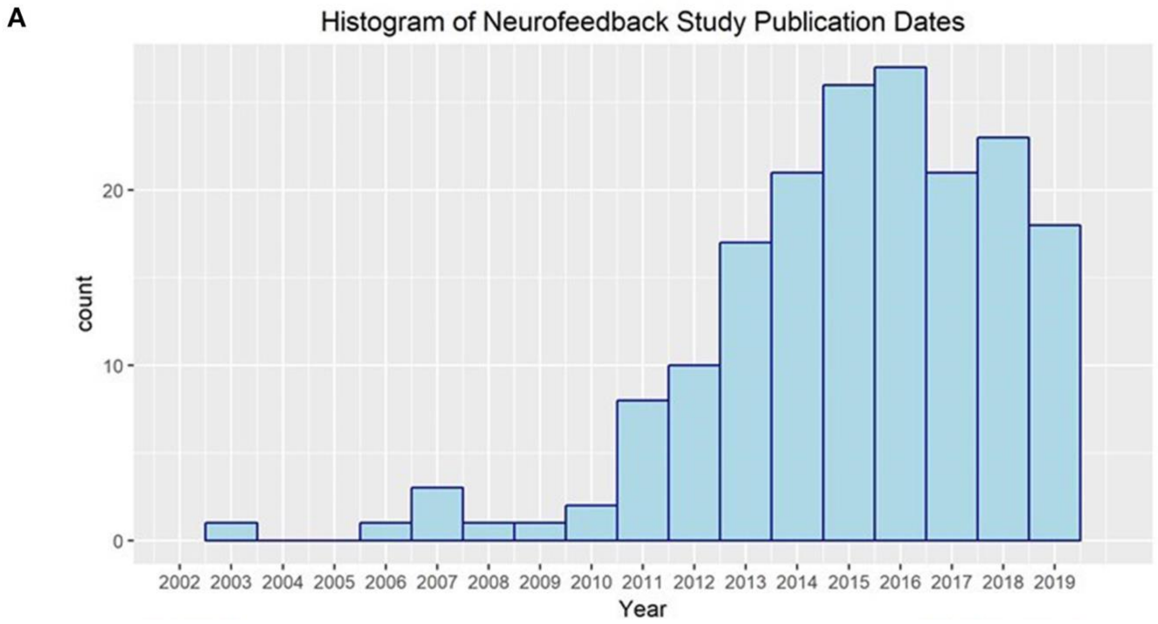
A Guide to Literature Informed Decisions in the Design of Real Time fMRI Neurofeedback Studies: A Systematic Review

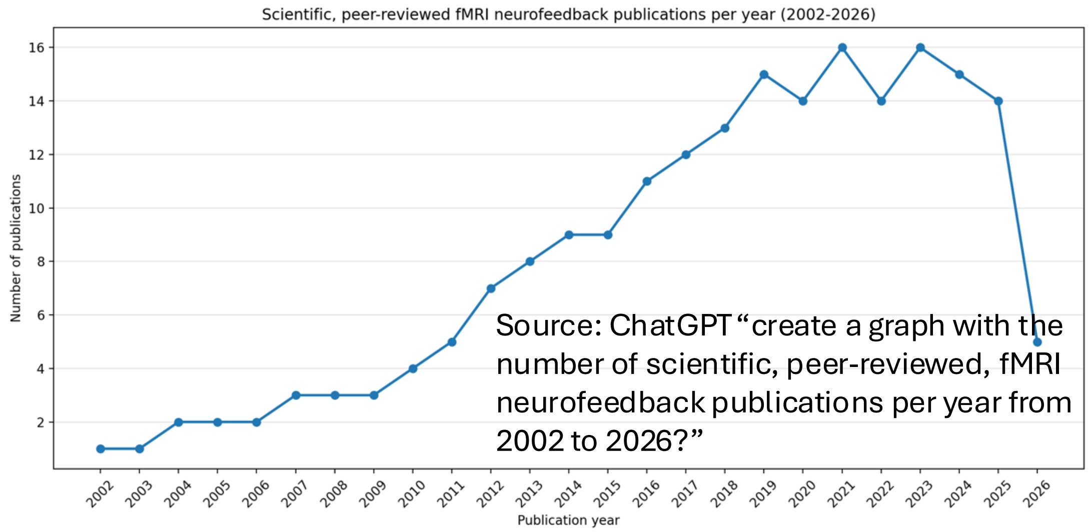
Samantha J. Fede, Sarah F. Dean, Thushini Manuweera and Reza Momenan*

Clinical NeuroImaging Research Core, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, United States

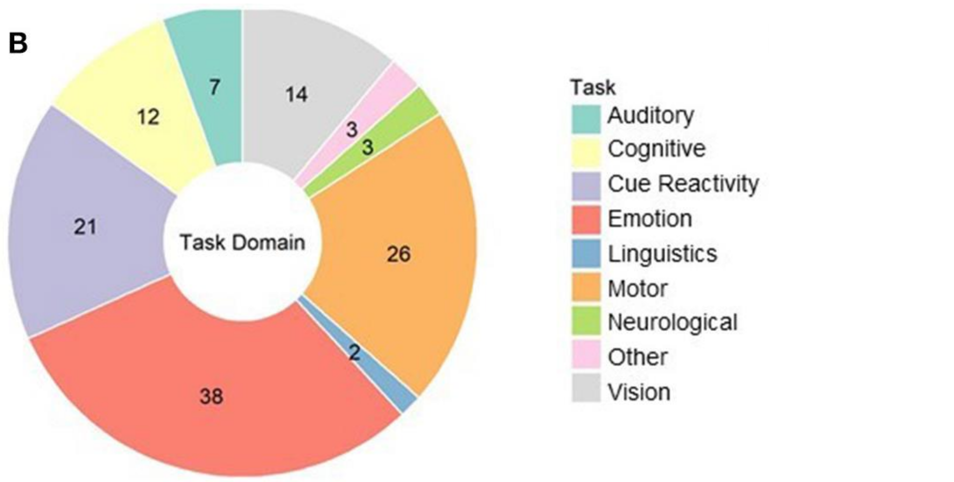
Frontiers in Human Neuroscience (2020)

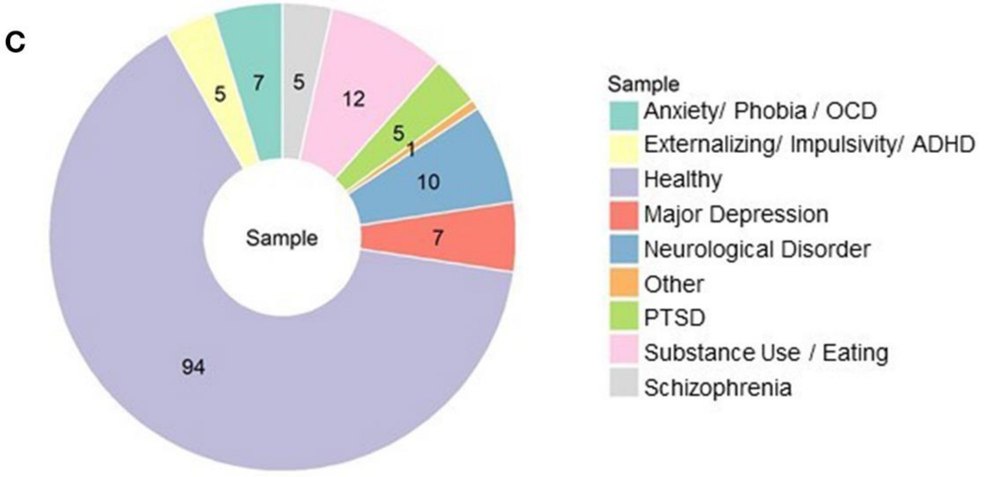
fMRI Neurofeedback | State-of-the-Art





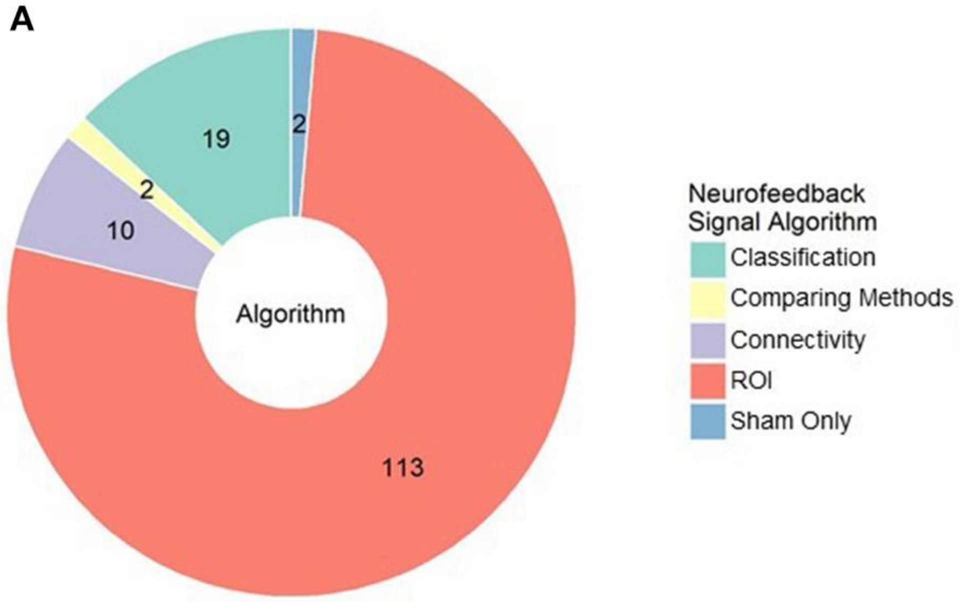
Source: ChatGPT "create a graph with the number of scientific, peer-reviewed, fMRI neurofeedback publications per year from 2002 to 2026?"

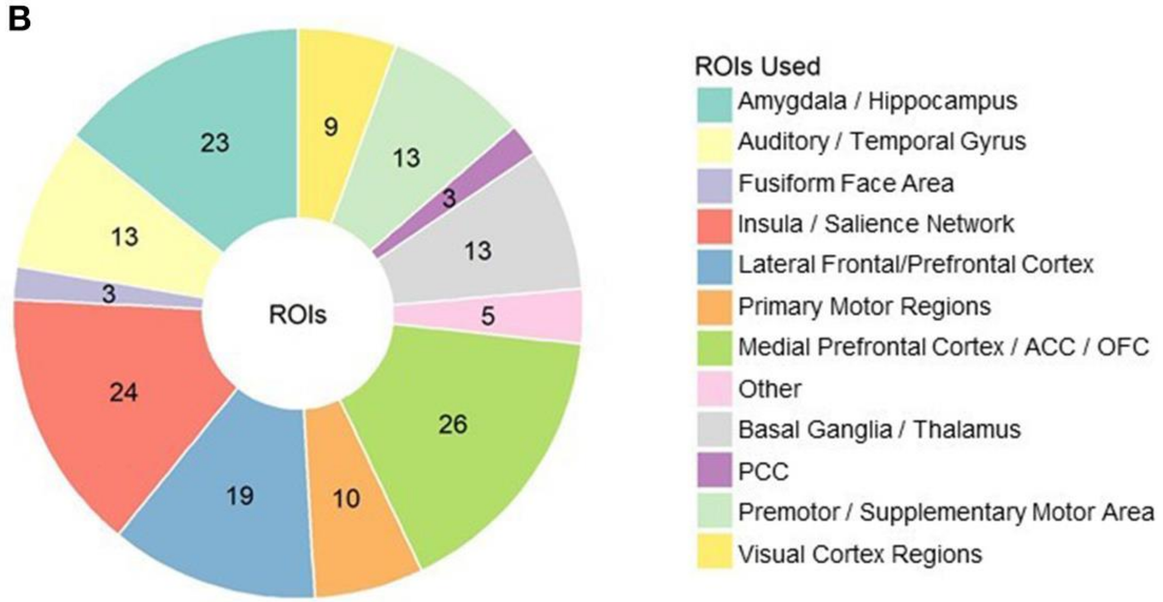




Fede et al. (2020) Frontiers Hum. Neurosci.

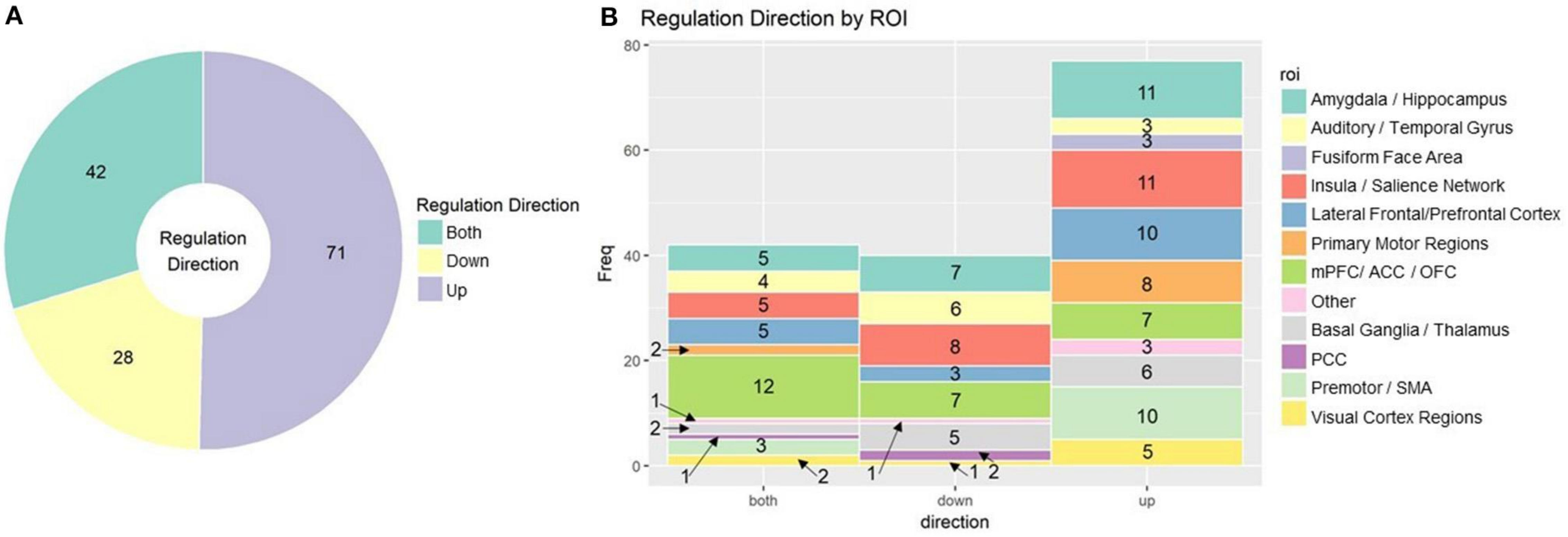
fMRI Neurofeedback | State-of-the-Art





Fede et al. (2020) Frontiers Hum. Neurosci.

fMRI Neurofeedback | State-of-the-Art



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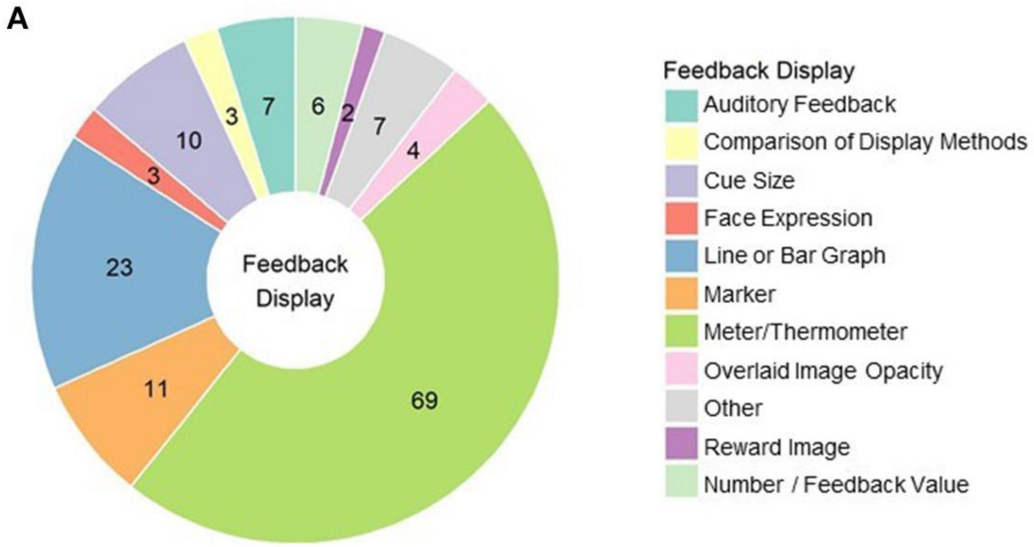
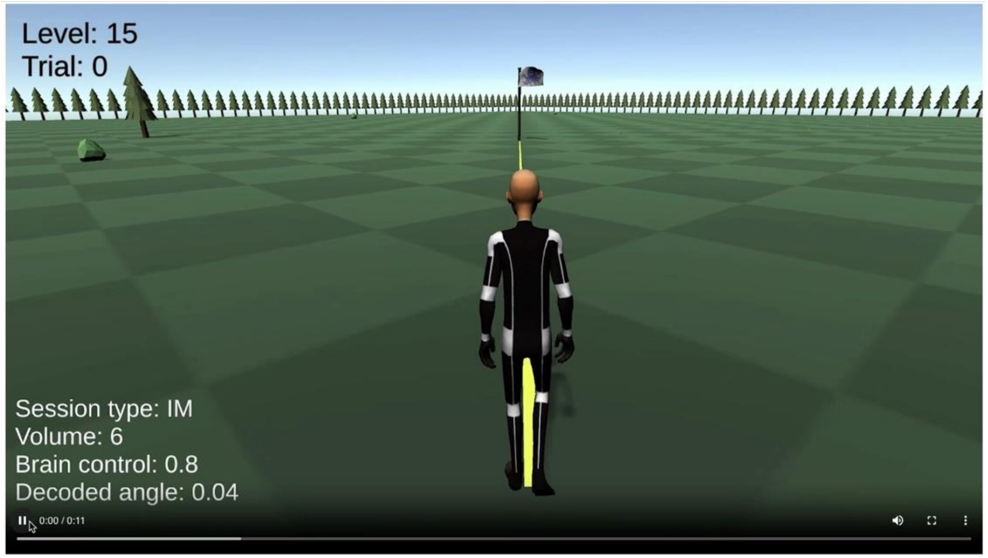
fMRI Neurofeedback | State-of-the-Art

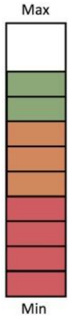


Fede et al. (2020) Frontiers Hum. Neurosci.

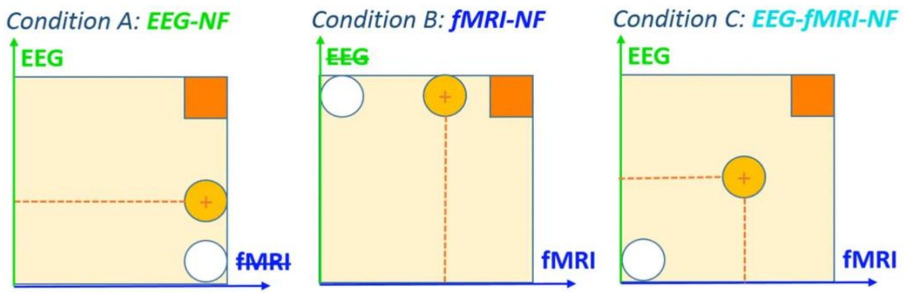


Busch et al. (2026) Nature Neuroscience

3D Game Environment

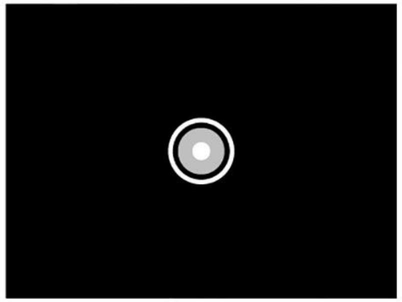


Meter/ Thermometer



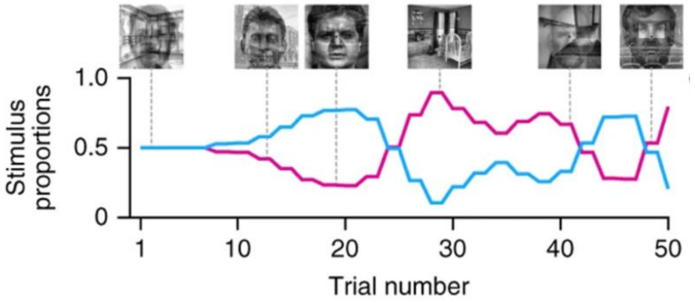
Perronnet et al. (2017) Frontiers Hum. Neurosci.

Moving Target



Amano et al. (2016) Current Biology

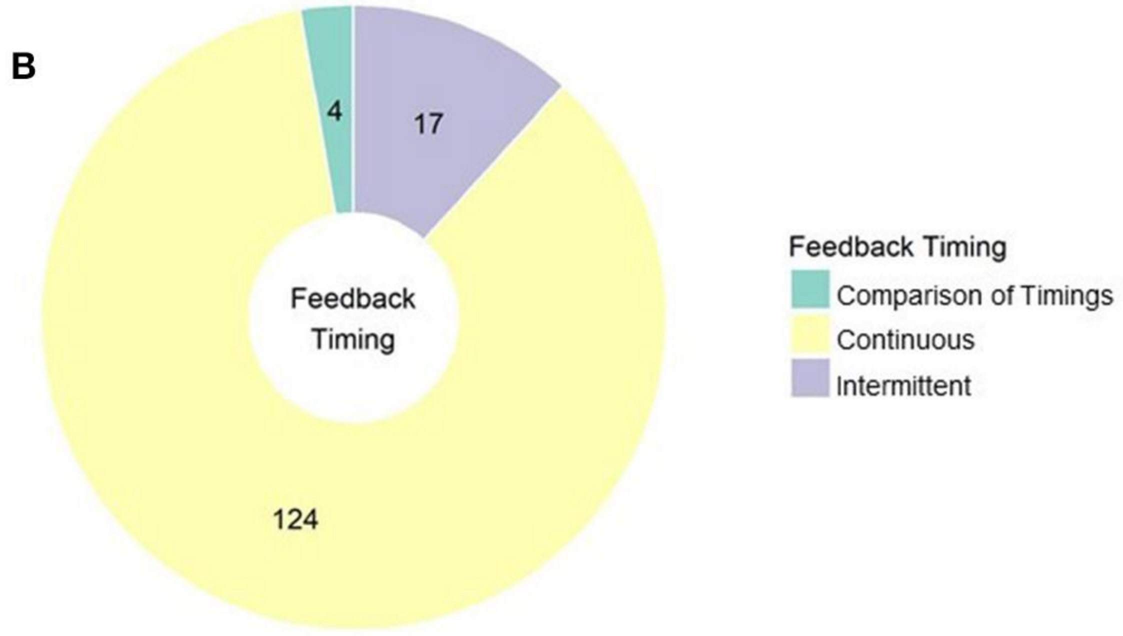
Size-varying Circle

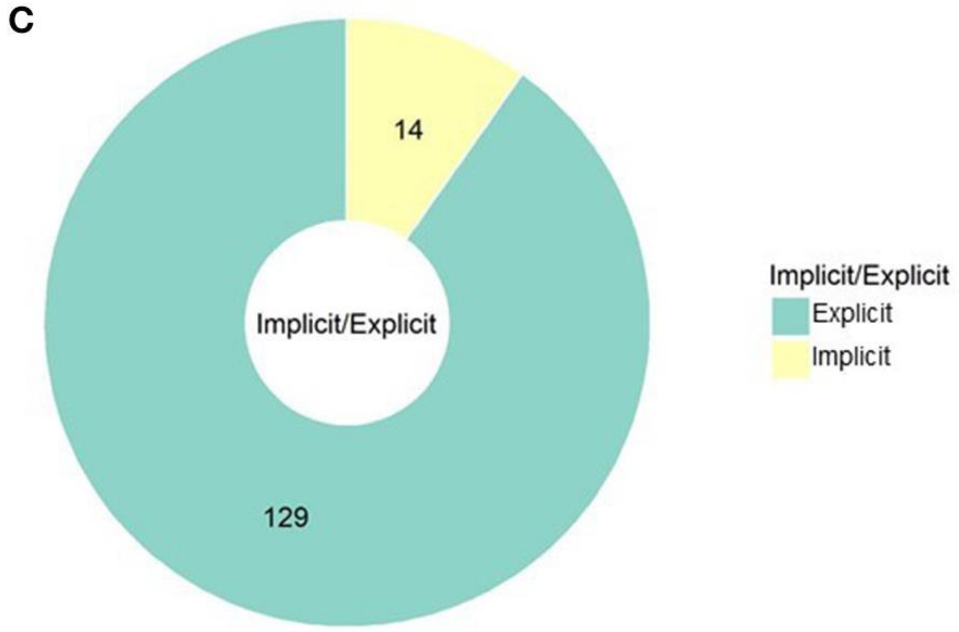


De Bettencourt et al. (2016) Nat. Neuroscience

Changing Opacity

fMRI Neurofeedback | State-of-the-Art

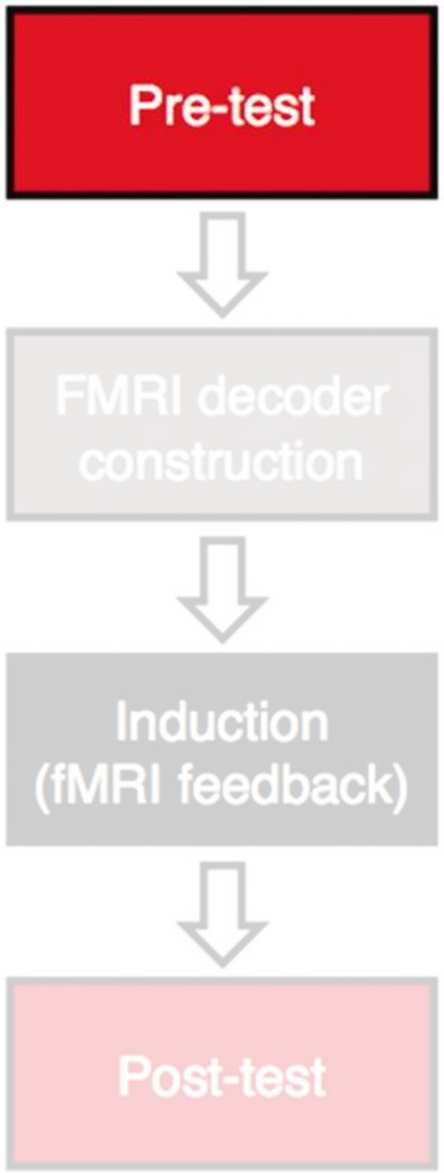


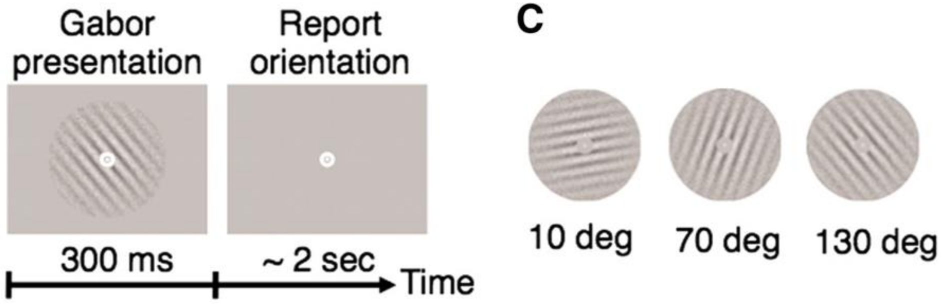


Fede et al. (2020) Frontiers Hum. Neurosci.

Example: Implicit Decoded NF

“whether the adult primate early visual cortex is sufficiently plastic to cause visual perceptual learning (VPL)”





Shibata et al. (2011) Science

Example: Implicit Decoded NF

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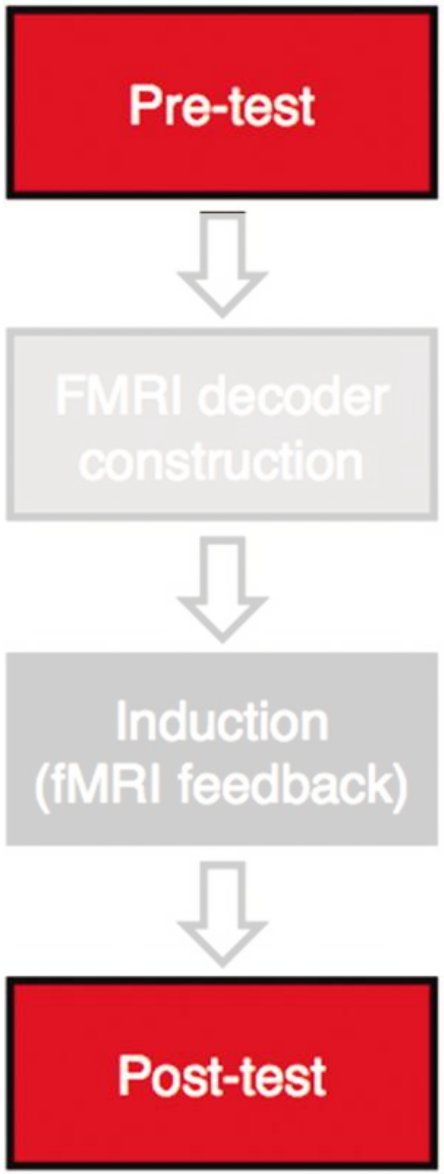

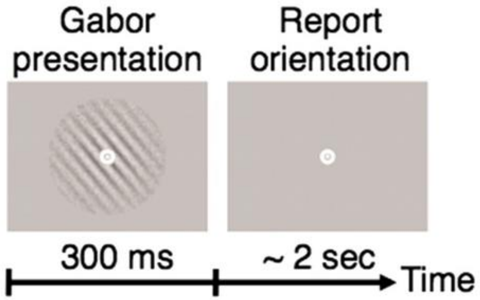

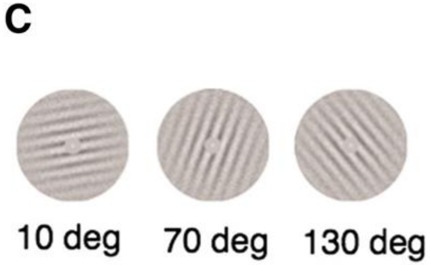

Shibata et al. (2011) Science

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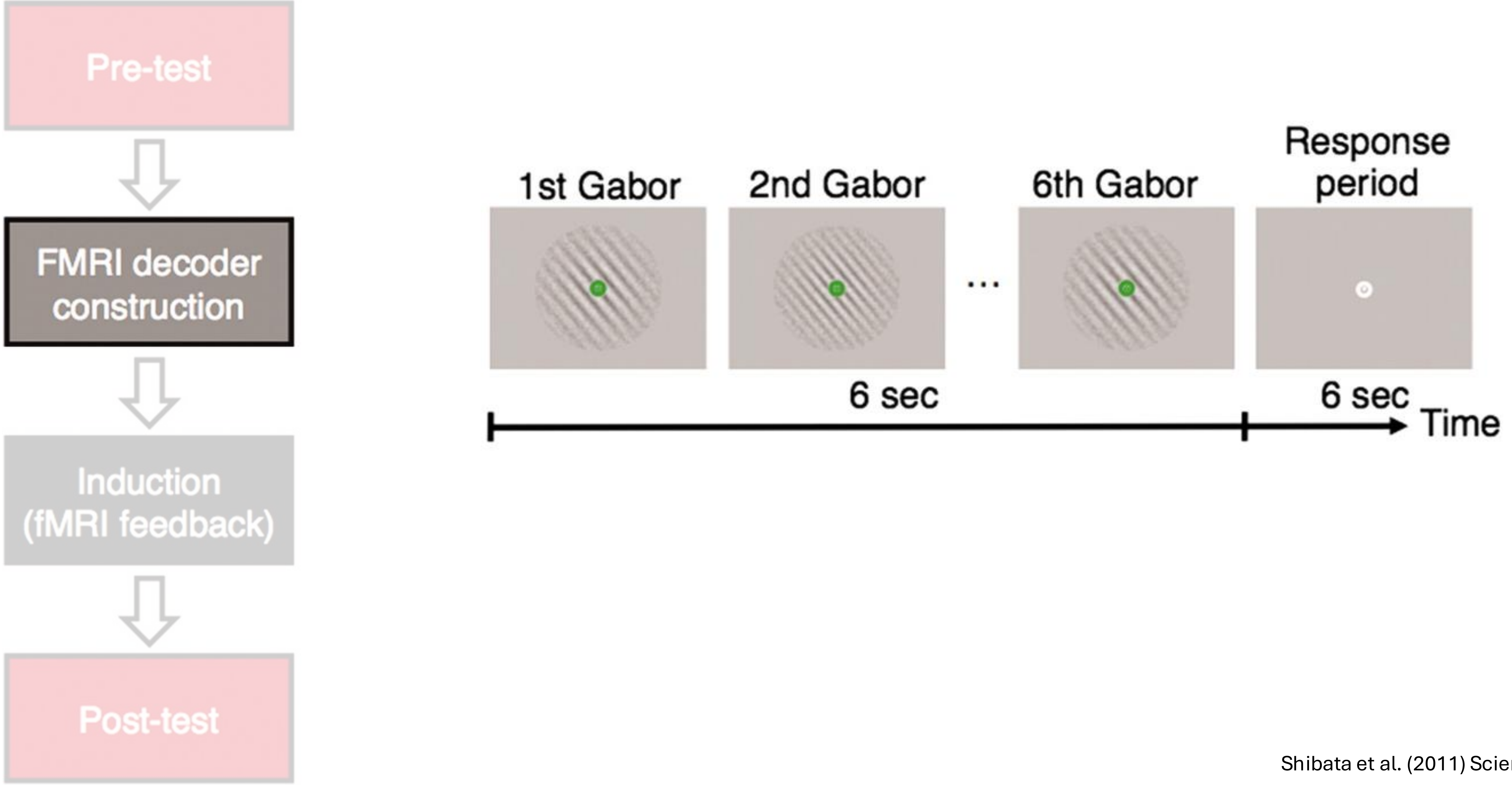

Shibata et al. (2011) Science

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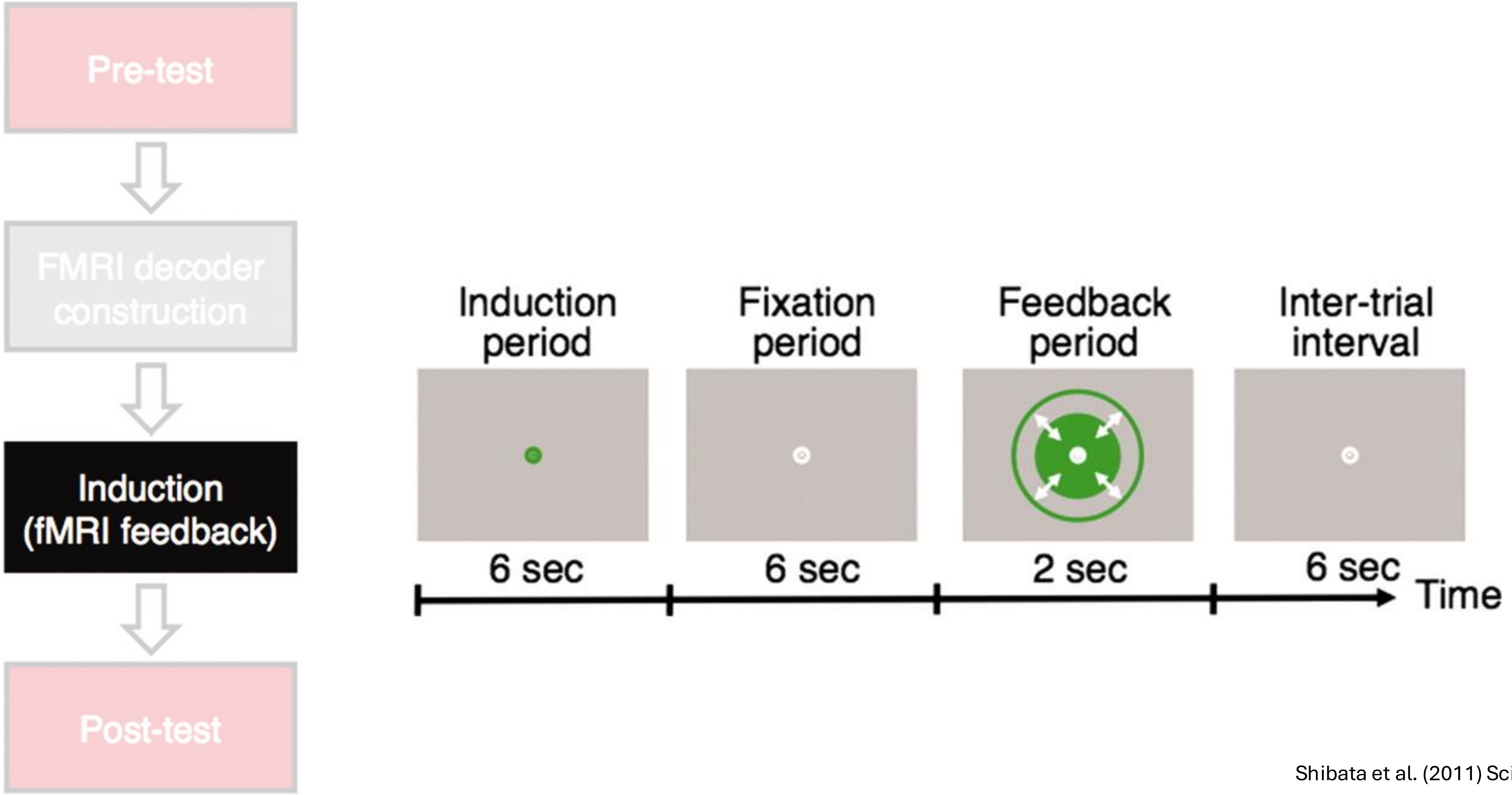

Shibata et al. (2011) Science

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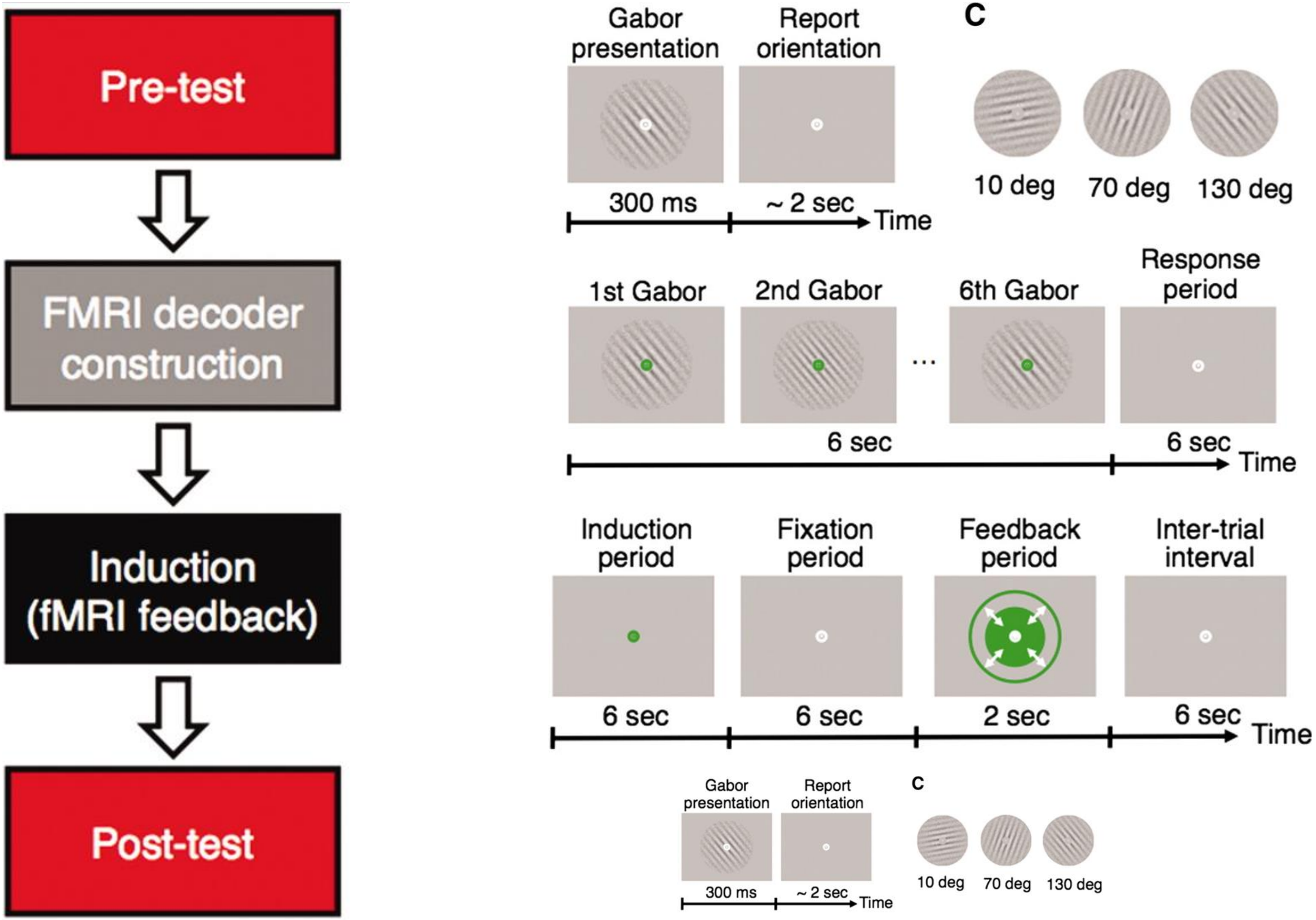

Shibata et al. (2011) Science

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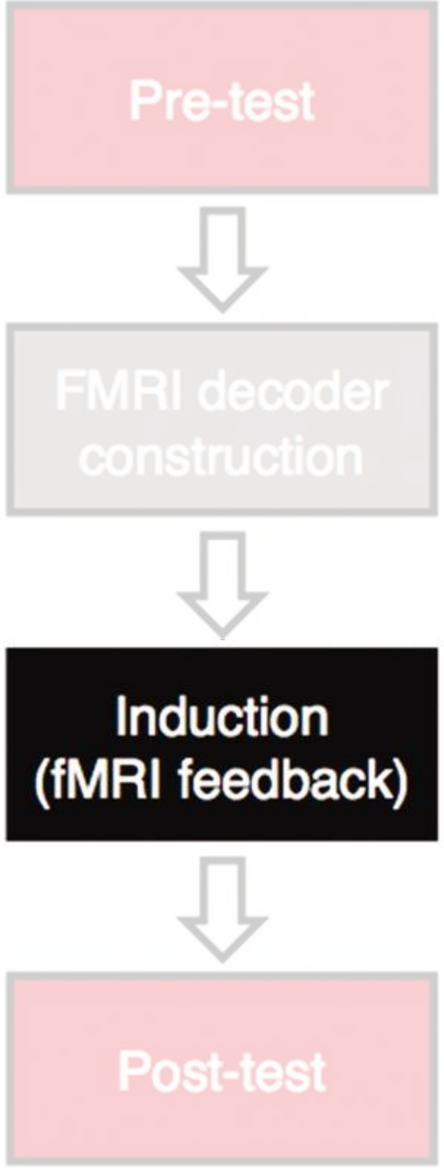
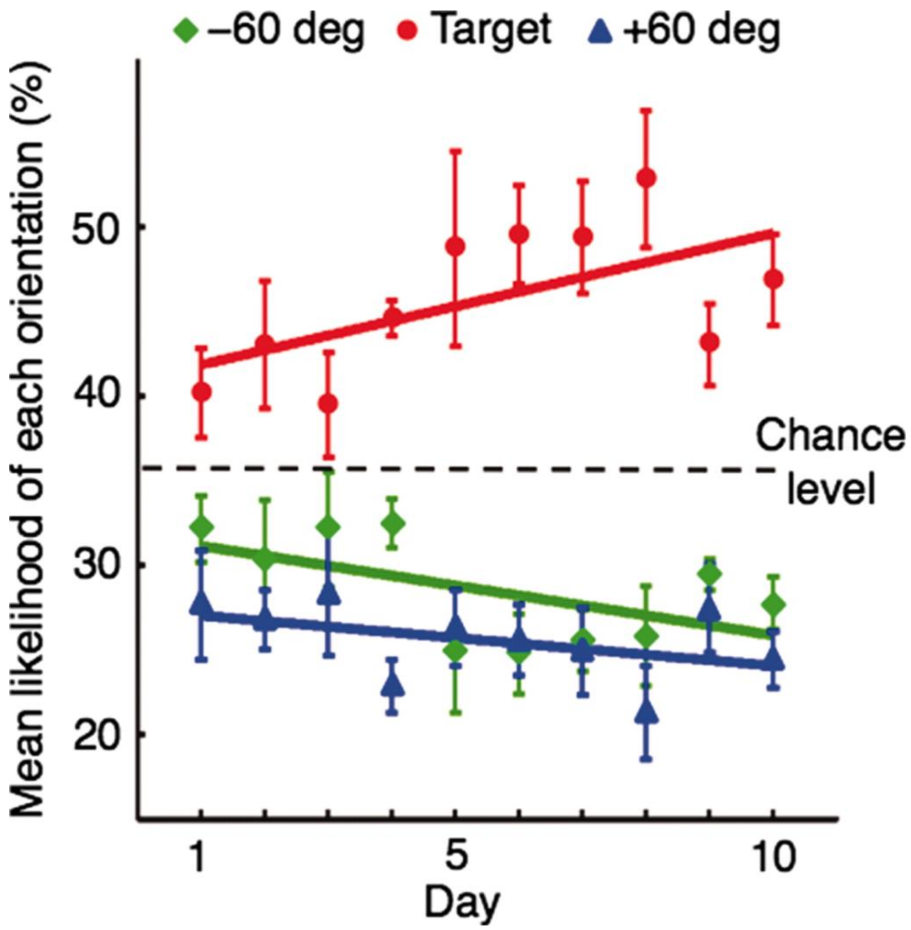




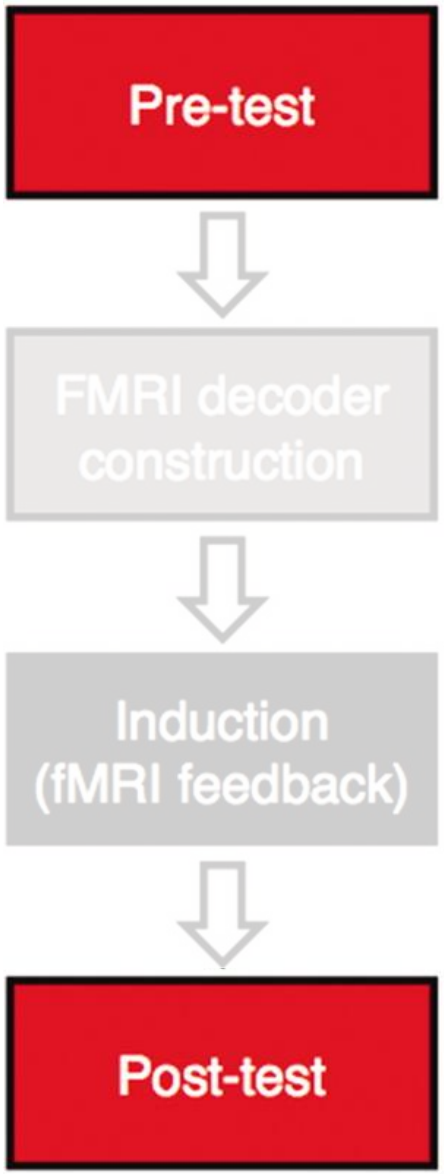
“the overall mean target-orientation likelihood in V1/V2 was significantly higher than chance across the participants, on average, during the induction stage”

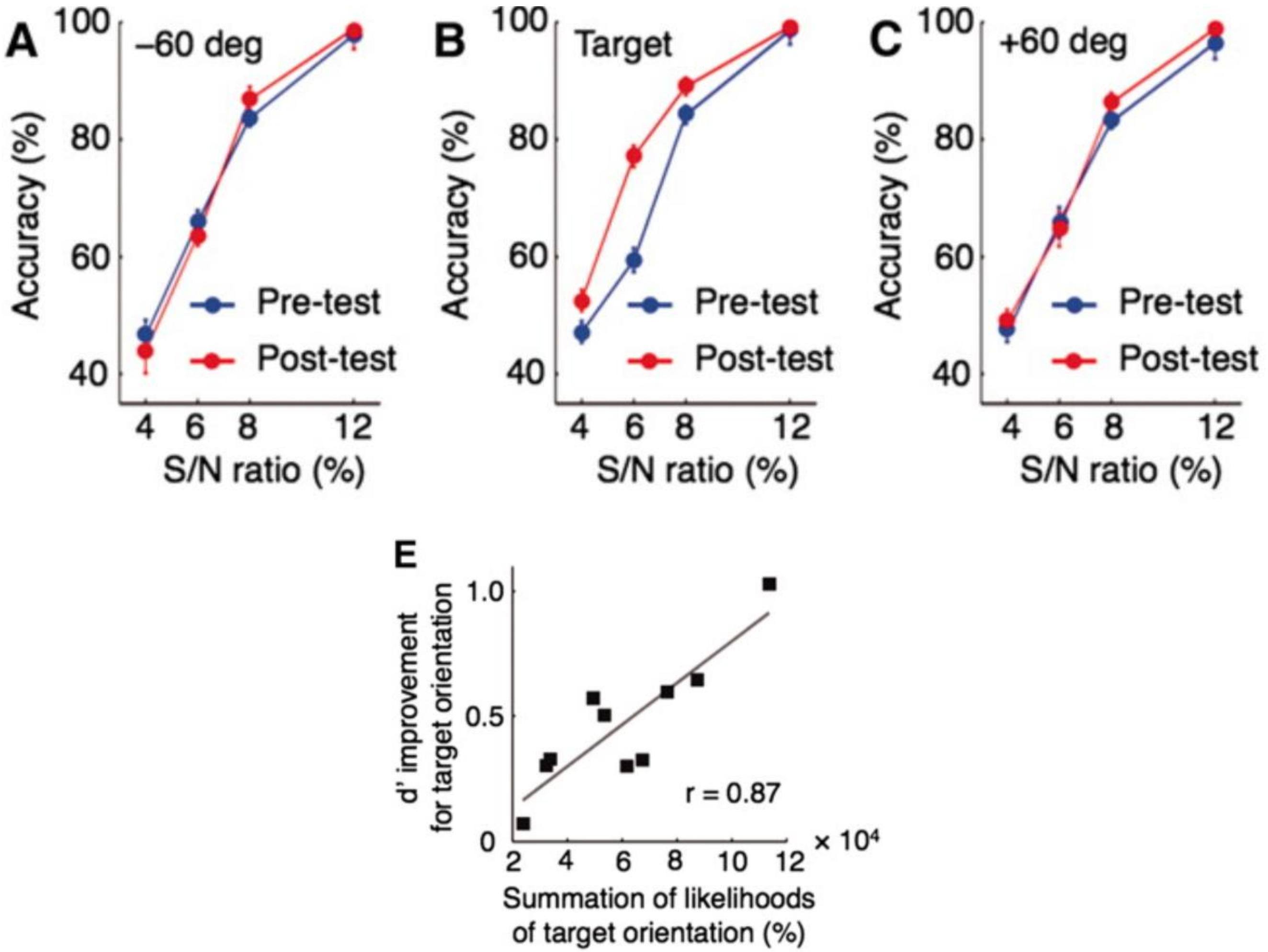
“After the post-test stage, participants were asked about what they thought the size of the feedback disc represented, but none of their responses was even remotely related to the true workings of the experiment”

Shibata et al. (2011) Science

Example: Implicit Decoded NF

“whether the adult primate early visual cortex is sufficiently plastic to cause visual perceptual learning (VPL)”

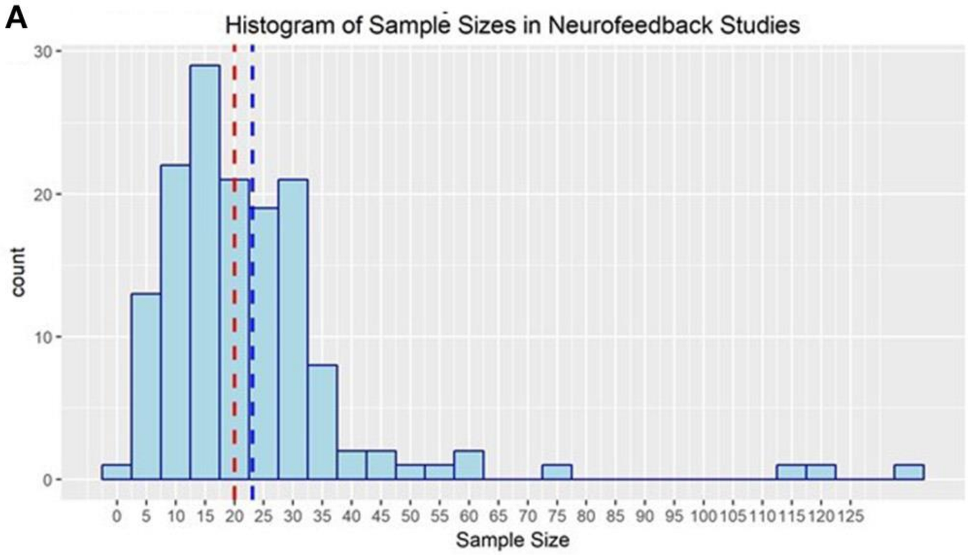




…the mere repetitive induction of specific activation patterns in V1/V2 causes VPL reflected as performance improvement

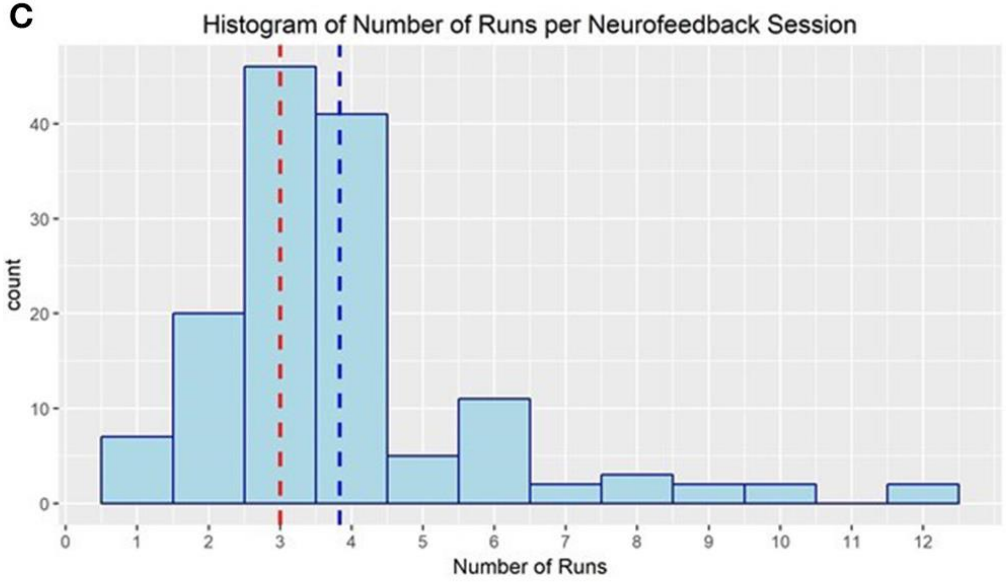
Shibata et al. (2011) Science

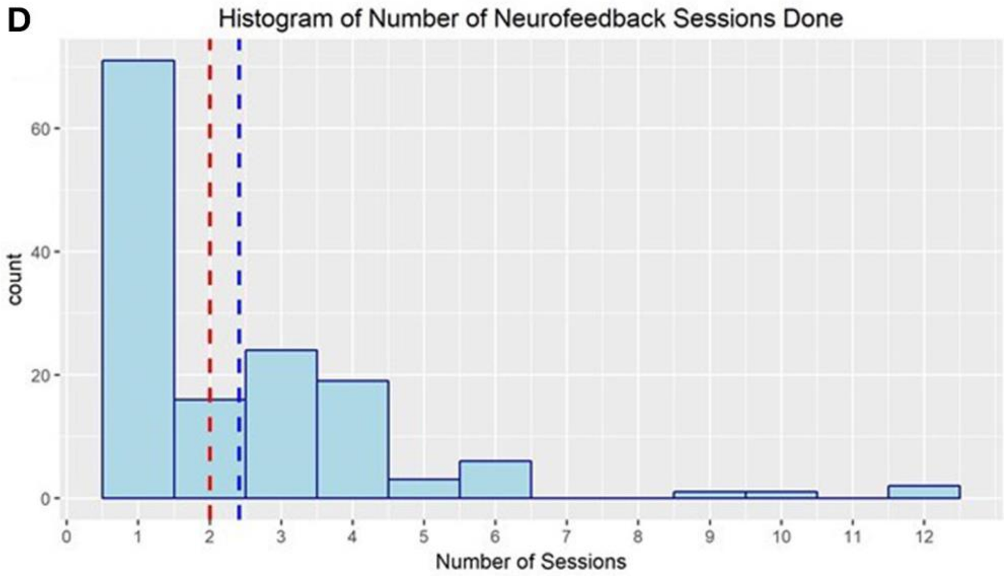
fMRI Neurofeedback | State-of-the-Art



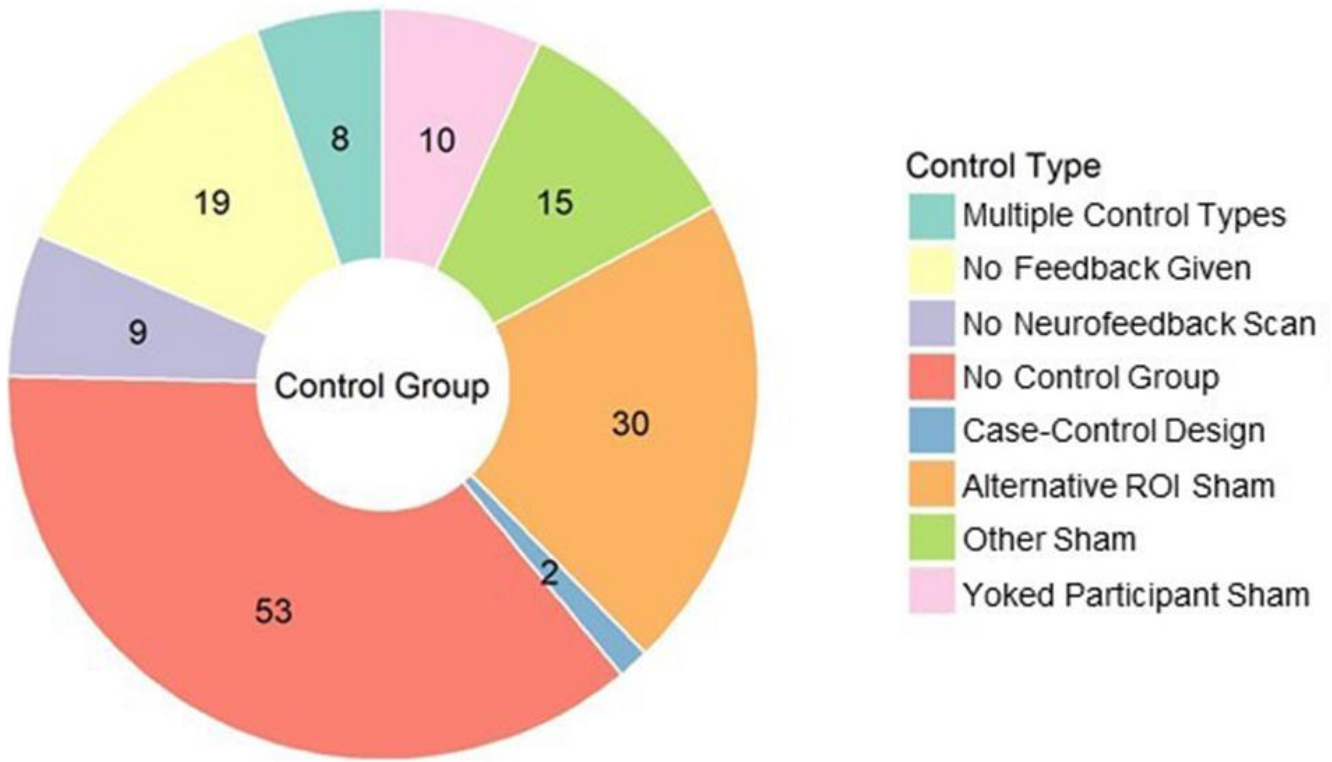
“account for a 25% rate of non-responders in your recruitment goals” Fede et al. (2020) Frontiers Hum. Neurosci.

Scharnowski et al. (2012) J Neuro → 36% Non-responders
Haugg et al. (2020) HBM → 38% Non-responders



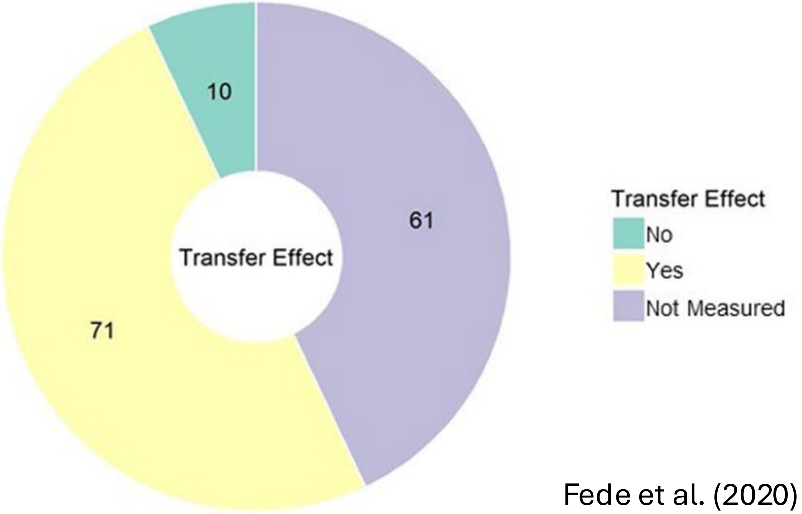


fMRI Neurofeedback | Demonstrate Specificity of Effects

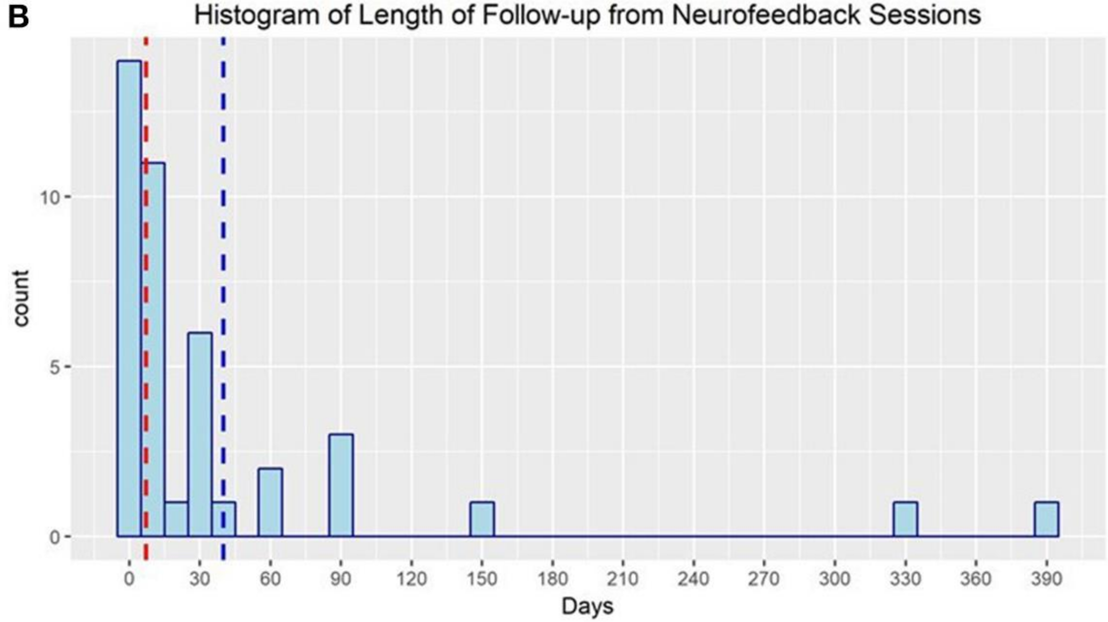


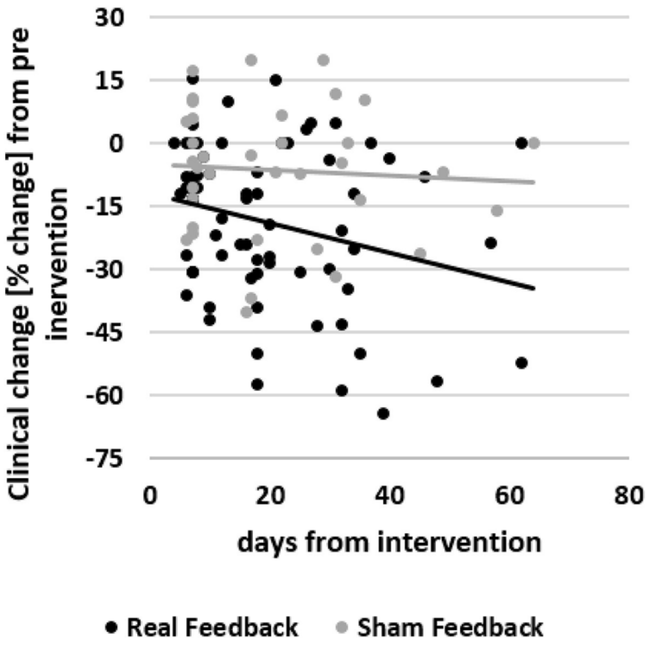
Fede et al. (2020) Frontiers Hum. Neurosci.

fMRI Neurofeedback | Long-term effects



Fede et al. (2020) Frontiers Hum. Neurosci.



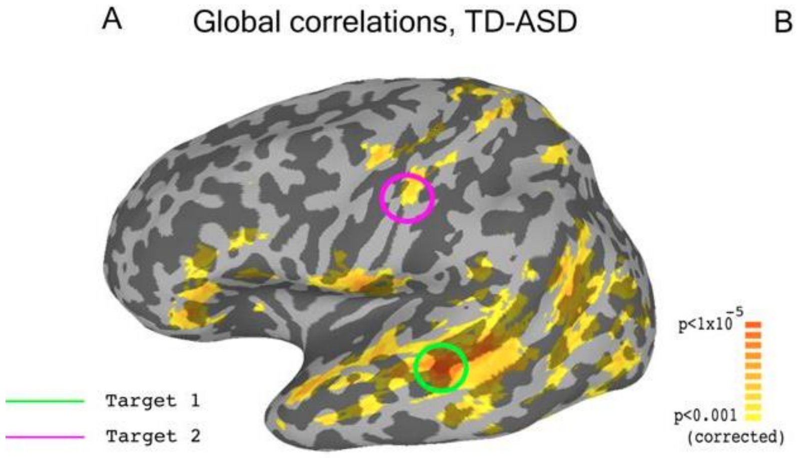


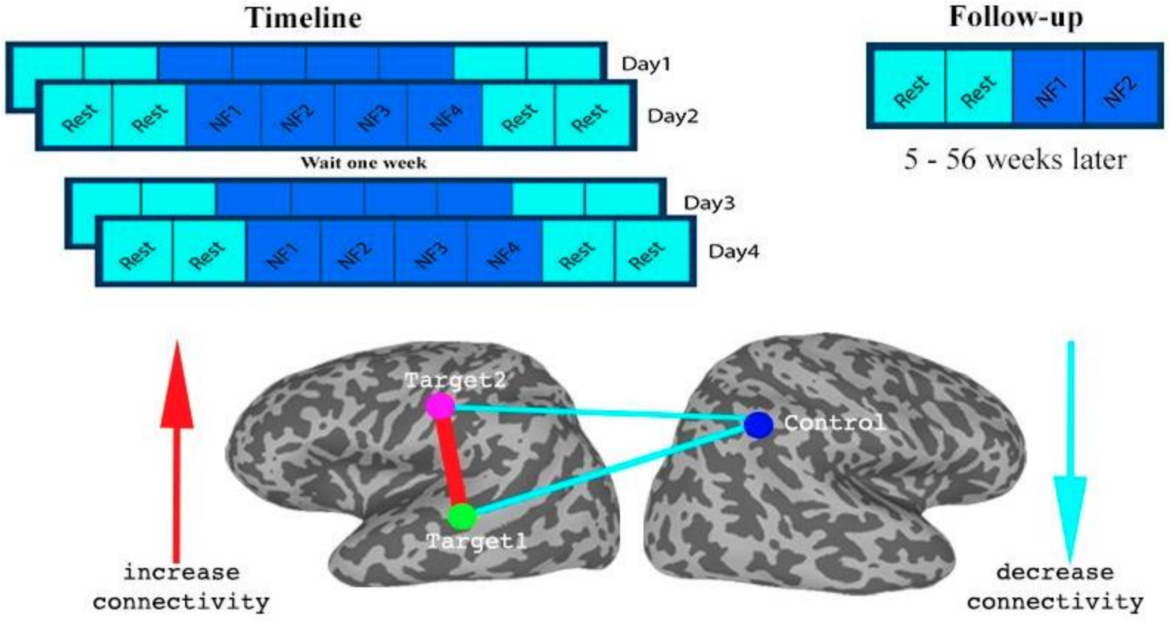
"Symptoms neither regressed to baseline nor remained stable over a follow-up period of many weeks; instead, symptoms continued to improve over time"

Rance et al. (2018) NeuroImage

Example: Implicit Functional Connectivity NF

Increase connectivity between nodes of the "social network" involved in social processing, which has been shown to have low FC in high functioning autism compared to healthy controls.



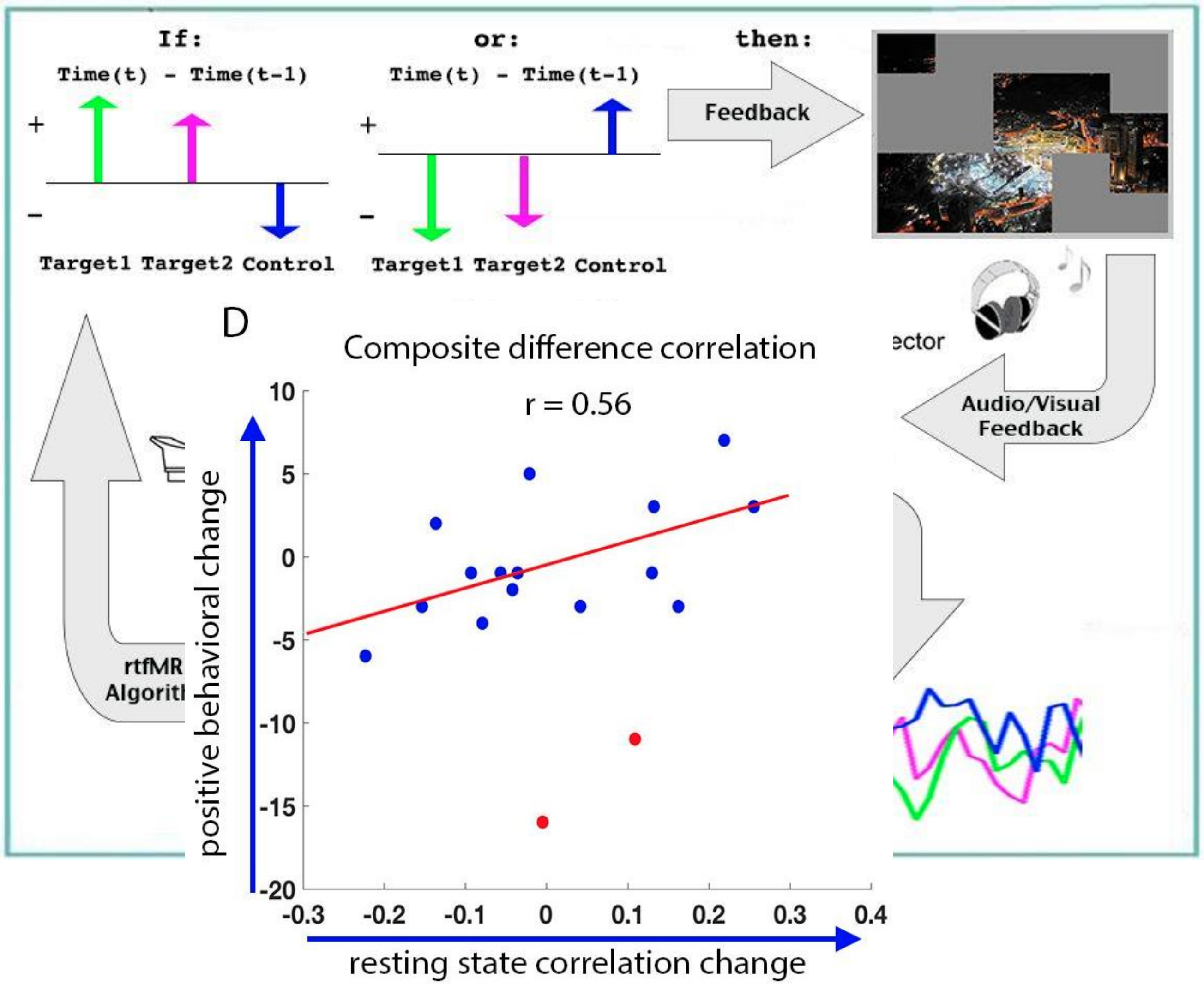


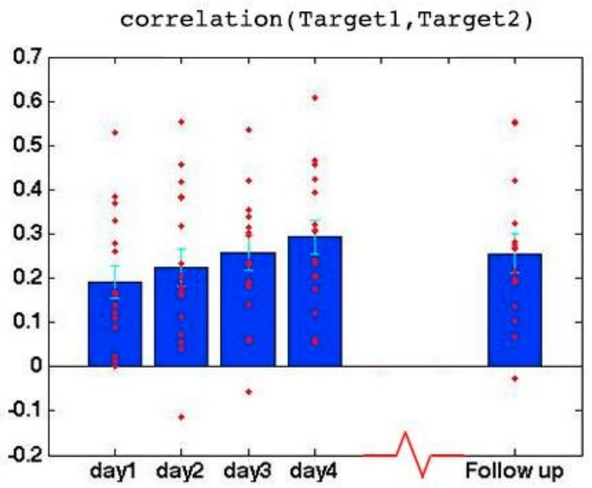
17 ASD Participants
10 TD Participants

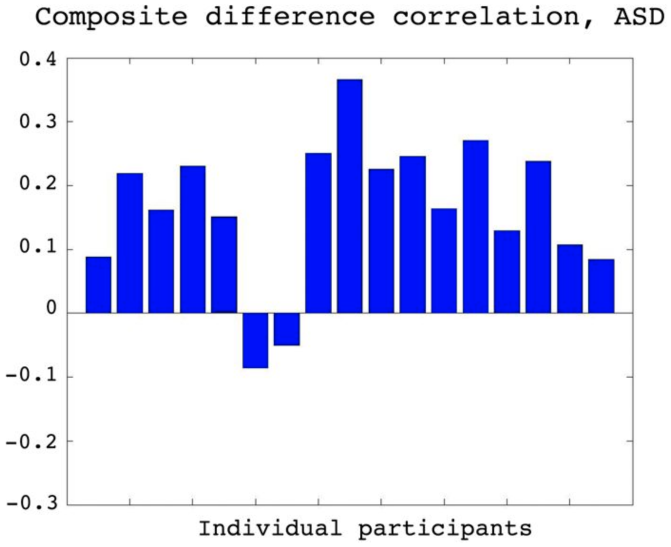
4 training sessions over the course of 8 days
Behavioral surveys before training and 2 weeks after training

Ramot et al. (2017) eLife

Example: Implicit Functional Connectivity NF



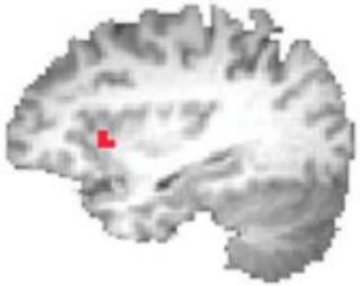


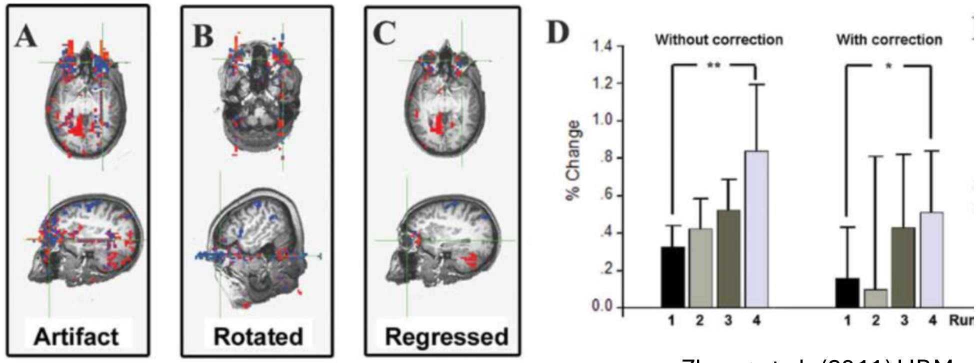


Ramot et al. (2017) eLife

Conclusions

- Real-time fMRI enables new experimental approaches, including neurofeedback interventions and interactive designs that can test causal brain–behavior hypotheses.
- Neurofeedback allows participants to attempt voluntary regulation of targeted brain activity, but learning success varies substantially across individuals.
- Real-time pipelines require methodological choices that may differ from offline fMRI analysis.
- Most current work remains proof-of-concept or preliminary, and robust clinically relevant effects are still challenging to demonstrate.
- The field lacks strong methodological consensus on controls, sham feedback, outcome measures, training dose, and follow-up assessment.
- Participants may use unintended strategies. Rigorous controls are essential to separate genuine neurofeedback learning from nonspecific effects, artifacts, and placebo-like mechanisms.





Zhang et al. (2011) HBM

Where to go next…

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/ynicl

A systematic review of fMRI neurofeedback reporting and effects in clinical populations

Anita Tursic[a,b,*], Judith Eck[a,b], Michael Lührs[a,b], David E.J. Linden[c], Rainer Goebel[a,b,d]

A Guide to Literature Informed Decisions in the Design of Real Time fMRI Neurofeedback Studies: A Systematic Review

*Samantha J. Fede, Sarah F. Dean, Thushini Manuweera and Reza Momenan**

Clinical NeuroImaging Research Core, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, United States

REVIEW ARTICLE

WILEY

Quality and denoising in real-time functional magnetic resonance imaging neurofeedback: A methods review

Stephan Heunis[1,2] | Rolf Lamerichs[1,2,3] | Svitlana Zinger[1,2] | Cesar Caballero-Gaudes[4] | Jacobus F. A. Jansen[1,5,6] | Bert Aldenkamp[1,2,6,7,8] | Marcel Breeuwer[9,10]