A Robust Spelling Device for Locked-In Patients based on Real-Time fMRI

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Overview

- **Real-Time fMRI**
  - Data analysis during ongoing experiment
- **fMRI Neurofeedback**
  - Seeing and influencing own brain activity
  - Novel (clinical) applications of fMRI neurofeedback
- **Application I: “BOLD Brain Pong”**
  - Real-time hyperscanning, brain-brain interactions
- **Application II: “Brain Writing”**
  - Single trial letter encoding for efficient communication

Real-Time fMRI

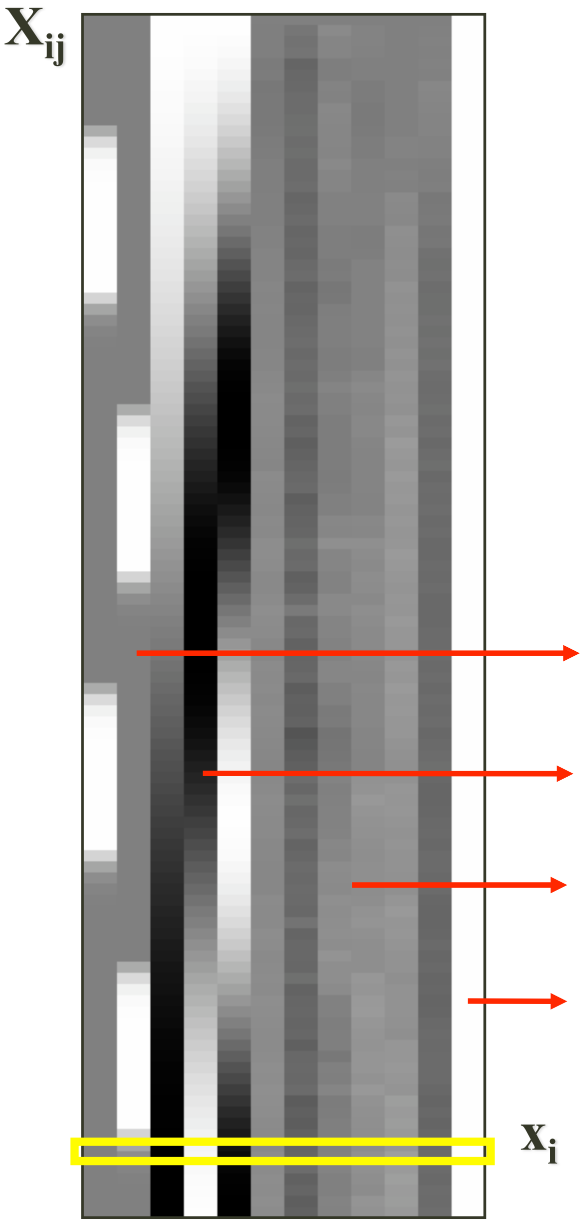
- Can be used to analyze fMRI data directly ***during image acquisition***, allowing “online” observation of the working brain
- Allows for ***quality assurance***: How much head motion? Are statistical maps and time courses o.k.? Stop scanning if enough data or repeat runs if data does not (yet) fulfill statistical criteria
- Allows “**adaptive**” fMRI experiments: The decision when to start the next level of a subject-specific experiment can be based on observed levels of activity in brain areas (reflecting e.g. learning).
- Prerequisite for advanced applications such as ***neurofeedback*** and neurosurgical monitoring

Real-Time fMRI

During functional runs, the following computations are repeatedly performed in real-time fMRI within the time window of ***one time point*** (brain volume):

- Reading of EPI slices into working memory
- 3D motion correction, 3D spatial smoothing
- Incremental statistical analysis (RLS GLM)
- Drift removal via design matrix
- Incremental event-related averaging
- Thresholding, clustering and color-coding of the resulting statistical maps
- Visualization of the maps on EPI images, intra- or extra-session 3D data and rendered cortical surfaces
- Real-time ICA (Esposito et al 2003, *Neuroimage*, **20**, 2209)

Real-time Statistics – Design Matrix



Design matrix is incrementally build and can incorporate real-time data, e.g. separating error trials or adding just calculated 3D motion parameters.

In order to remove low-frequency drifts, Discrete Cosine Transform (DCT) confound predictors may be added to the design matrix.

predictors of interest

DCT confound predictors

motion confound predictors

constant

Standard GLM Analysis

$$\begin{bmatrix} y_1 \\ \vdots \\ \vdots \\ \vdots \\ y_n \end{bmatrix} = \begin{bmatrix} 1 & X_{11} & \cdots & \cdots & \cdots & X_{1p} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & X_{n1} & \cdots & \cdots & \cdots & X_{np} \end{bmatrix} \begin{bmatrix} b_0 \\ \vdots \\ \vdots \\ b_p \end{bmatrix} + \begin{bmatrix} e_1 \\ \vdots \\ \vdots \\ \vdots \\ e_n \end{bmatrix}$$

$$\mathbf{y} = \mathbf{X}\mathbf{b} + \mathbf{e}$$

Fitting a GLM = Finding estimates of the beta values minimizing the sum of squared error values:

$$\mathbf{e}'\mathbf{e} = \sum_{t=1}^{N} e_t^2 = (\mathbf{y} - \mathbf{X}\mathbf{b})'(\mathbf{y} - \mathbf{X}\mathbf{b}) \text{ ® } \min$$

The solution can be directly calculated as: $\mathbf{b} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{y}$

Recursive Least Squares

The beta values and inverted **X'X** matrix can be updated *incrementally* using only information of the new time point with the following recursive equations:

$$\mathbf{b}_{t+1} = \mathbf{b}_t + (\mathbf{X}_t'\mathbf{X}_t)^{-1}\mathbf{x}_{t+1}\frac{(y_{t+1} - \mathbf{x}_{t+1}\mathbf{b}_t)}{1 + \mathbf{x}_{t+1}'(\mathbf{X}_t'\mathbf{X}_t)^{-1}\mathbf{x}_{t+1}}$$

$$(\mathbf{X}_{t+1}'\mathbf{X}_{t+1})^{-1} = (\mathbf{X}_t'\mathbf{X}_t)^{-1} - \frac{(\mathbf{X}_t'\mathbf{X}_t)^{-1}\,\mathbf{x}_{t+1}\mathbf{x}_{t+1}'\,(\mathbf{X}_t'\mathbf{X}_t)^{-1}}{1 + \mathbf{x}_{t+1}'(\mathbf{X}_t'\mathbf{X}_t)^{-1}\mathbf{x}_{t+1}}$$

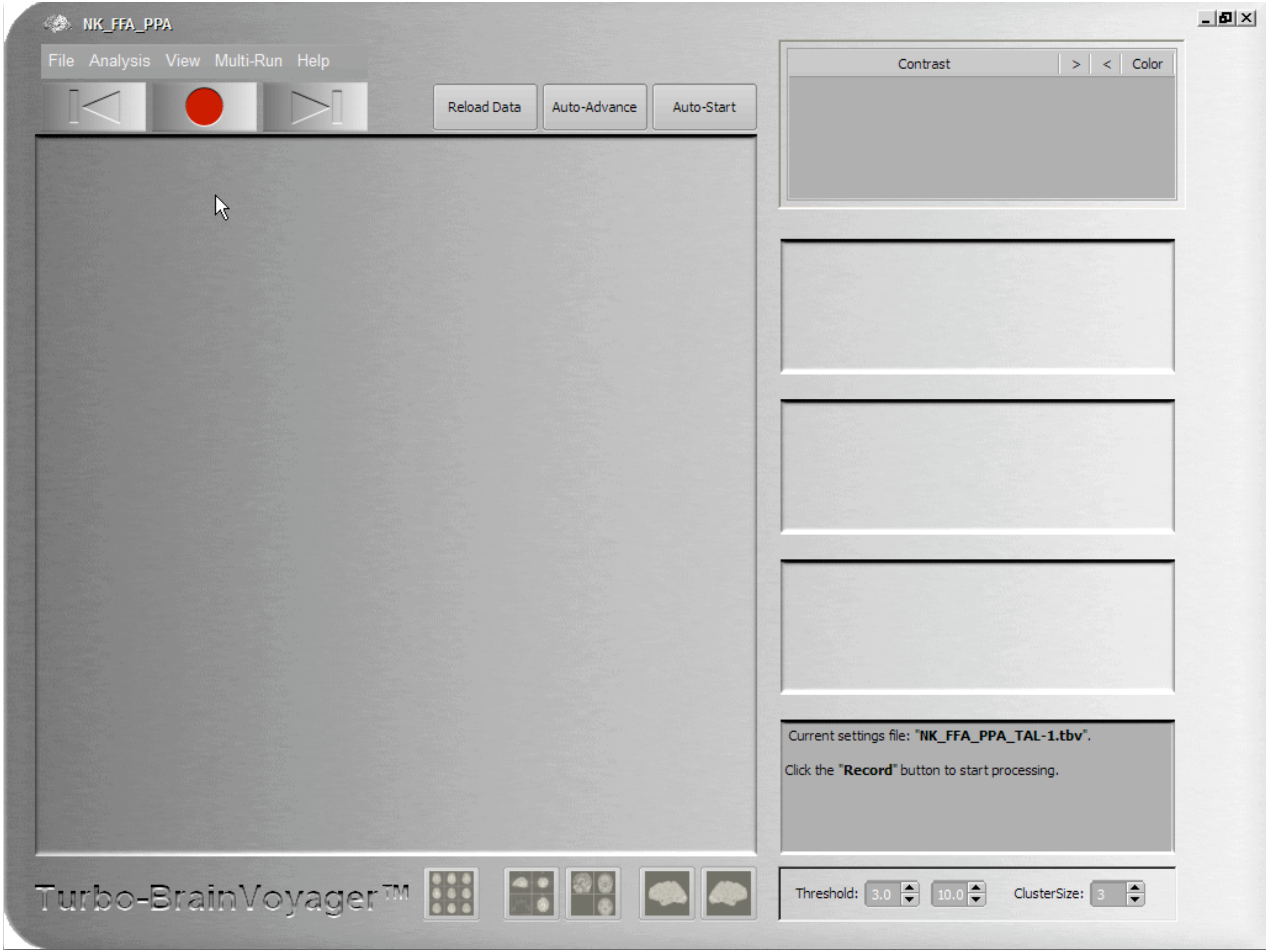
Note: Since the $\mathbf{X'X}^{-1}$ term is the same for all voxels, it can be precomputed before calculating **b** for individual voxels

In its standard formulation, RLS GLMs result in the same beta estimates as a standard GLM using the full time course up to the current time point.

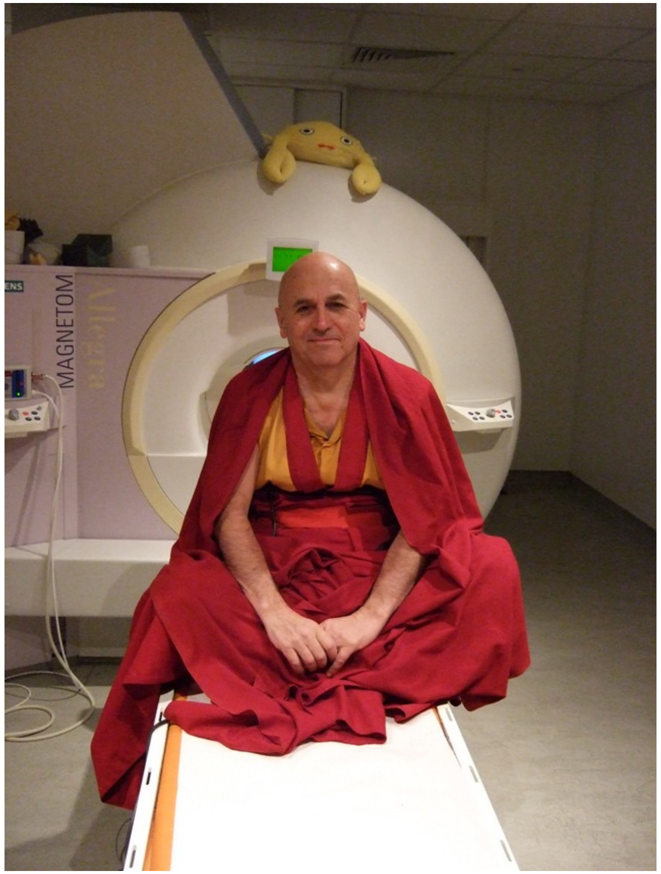
With a slight modification, RLS can be used to weight past values exponentially or to run windowed GLMs (Pollock, 1999).

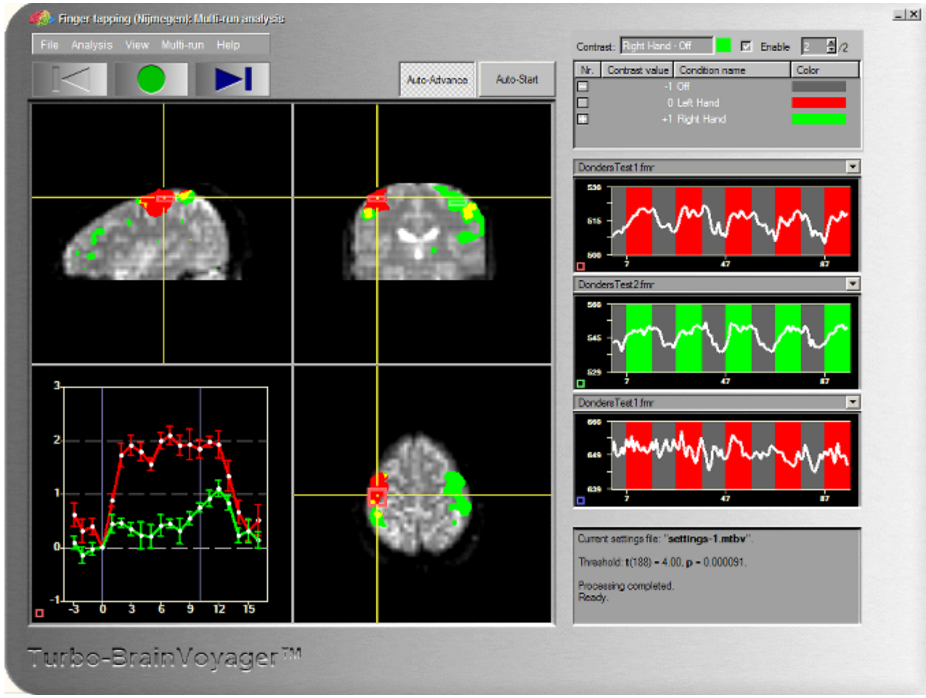
Real-Time fMRI

A demonstration


NK_FFA_PPA
File Analysis View Multi-Run Help
Reload Data
Auto-Advance
Auto-Start
Contrast
>
<
Color
Current settings file: "NK_FFA_PPA_TAL-1.tbv".
Click the "Record" button to start processing.
Turbo-BrainVoyager™
Threshold:
3.0
10.0
ClusterSize:
3

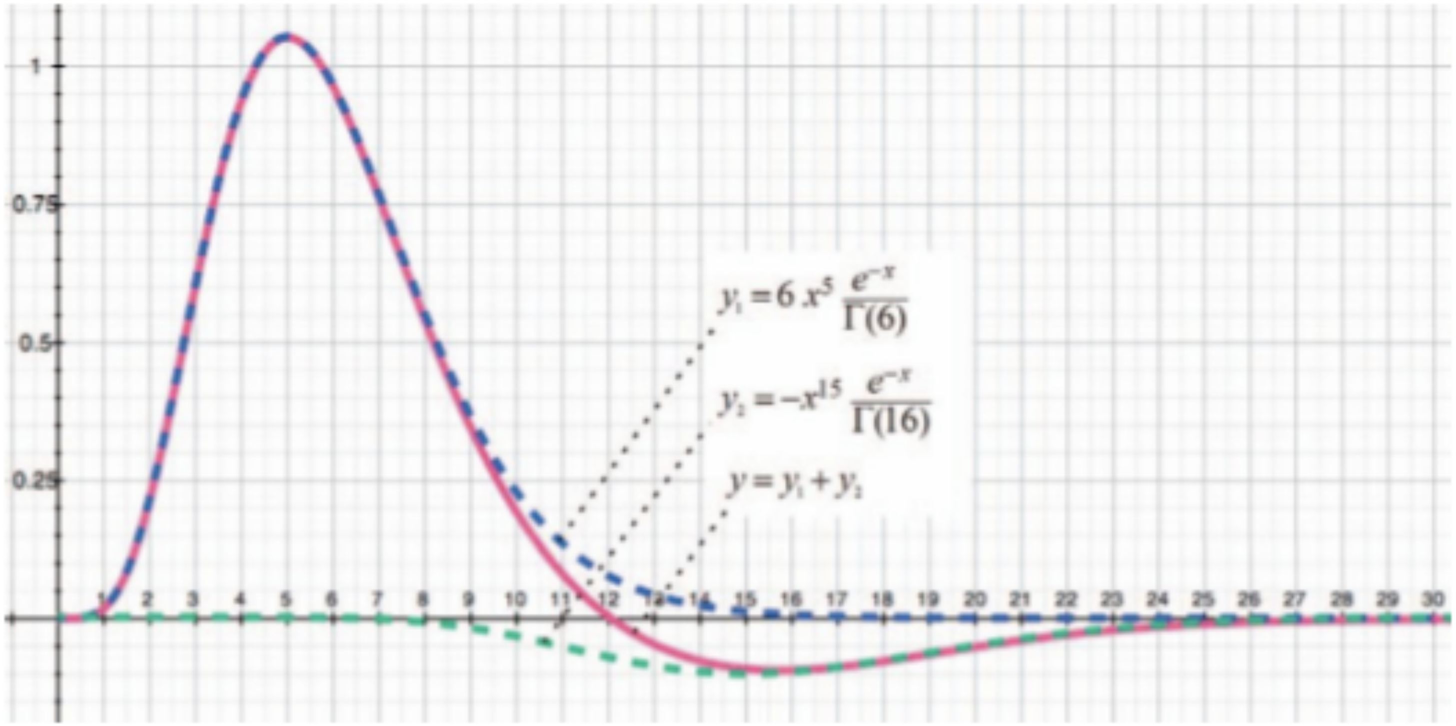
Real-Time fMRI Neurofeedback





- Real-time fMRI enables monitoring changes in the BOLD response ***online***.
- The high spatial resolution of fMRI offers the possibility to investigate the control over ***localized*** brain regions -> ***Feedback is content-specific***.
- Subjects can learn to influence own brain activity from ***one*** or ***multiple*** circumscribed brain regions.

Neurofeedback and the Hemodynamic Delay



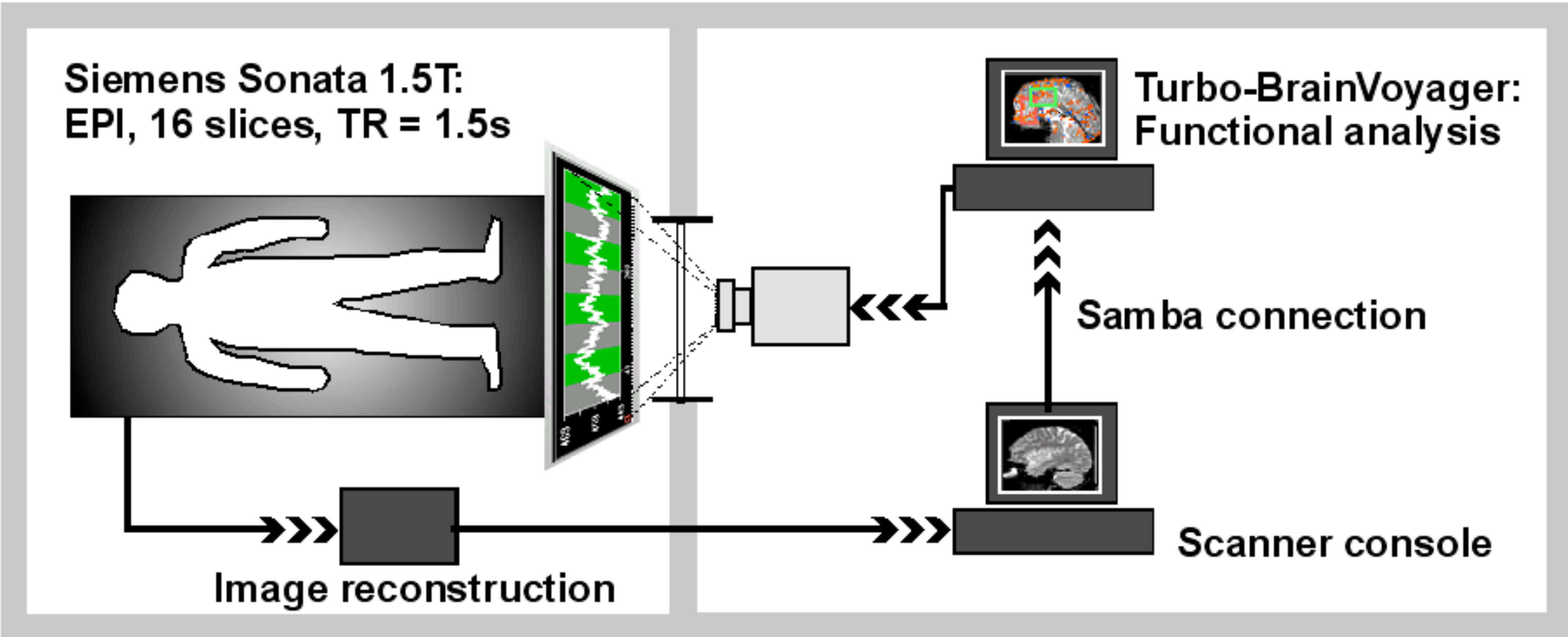
Two-gamma function often used to model typical BOLD response

-> Subjects need to learn to take into account 3-6 seconds delay

FMRI Neurofeedback

First experiment

Experimental Setup and Data Flow

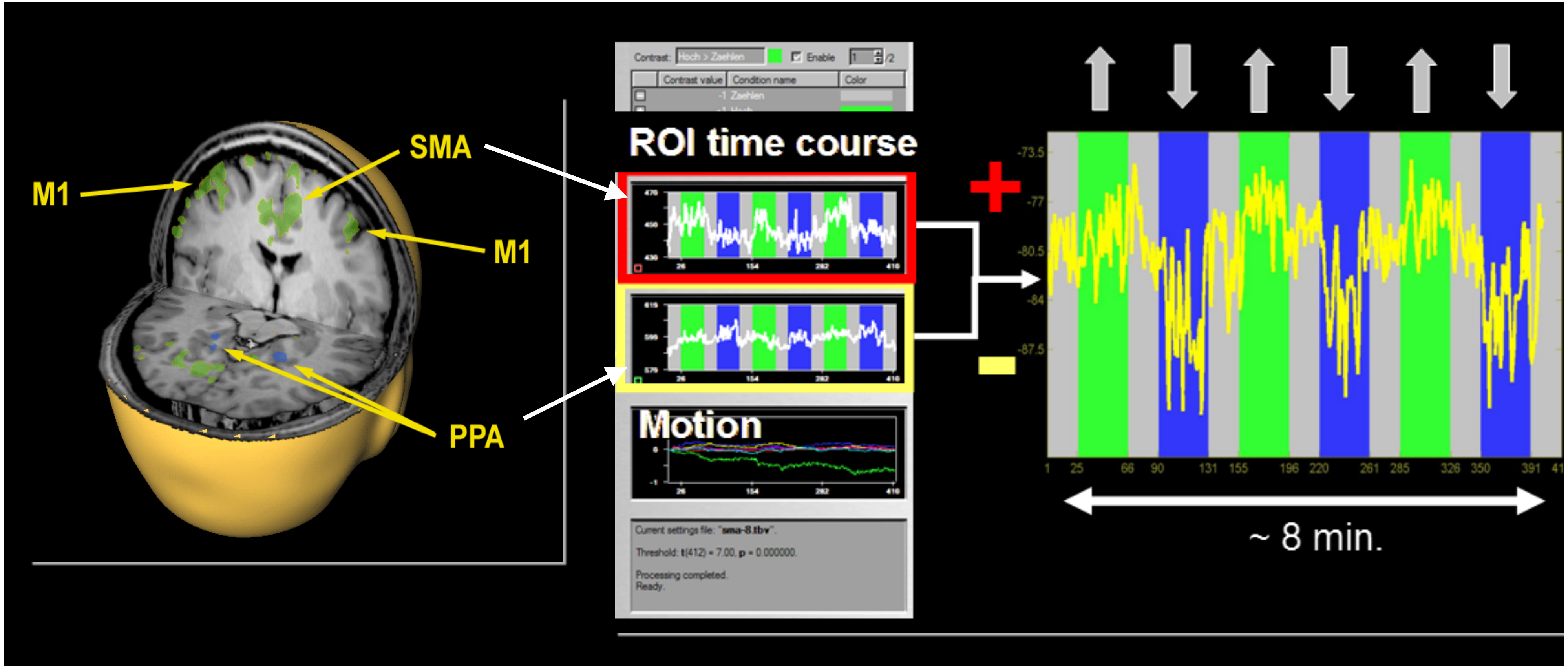


Processing time from acquisition to feedback < 2 s

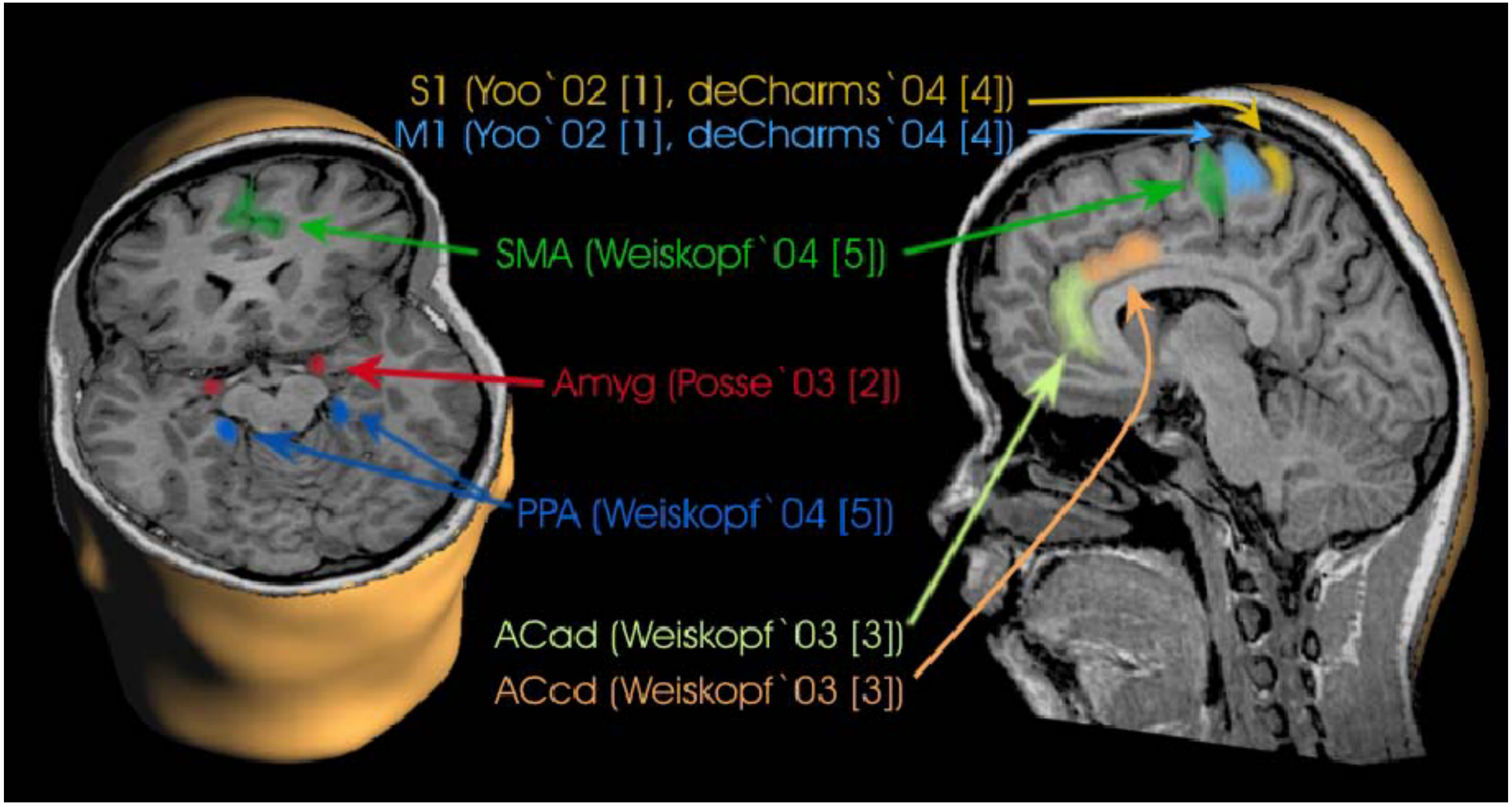
Weiskopf et al., Neuroimage 2003

FMRI neurofeedback

Differential modulation of two brain regions



Overview of fMRI Neurofeedback Studies



Recent fMRI neurofeedback studies have shown that subjects are indeed able to modulate different brain areas using various mental strategies, such as visual or auditory mental imagery. For reviews, see Weiskopf et al. (2004), *J Physiol Paris*, De Charms, *Nat Rev Neurocsci* (2008)

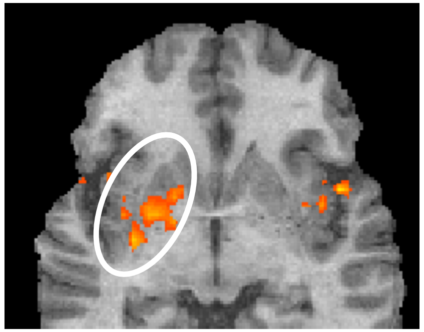
Potential Clinical Implications

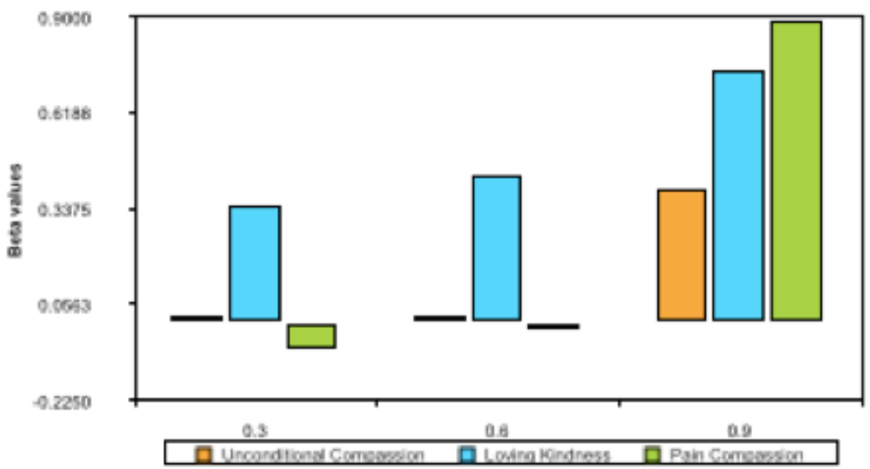
- FMRT Neurofeedback might be an important tool for clinical applications. It has been, for example, successfully applied to reduce pain perception (DeCharms et al., 2005).

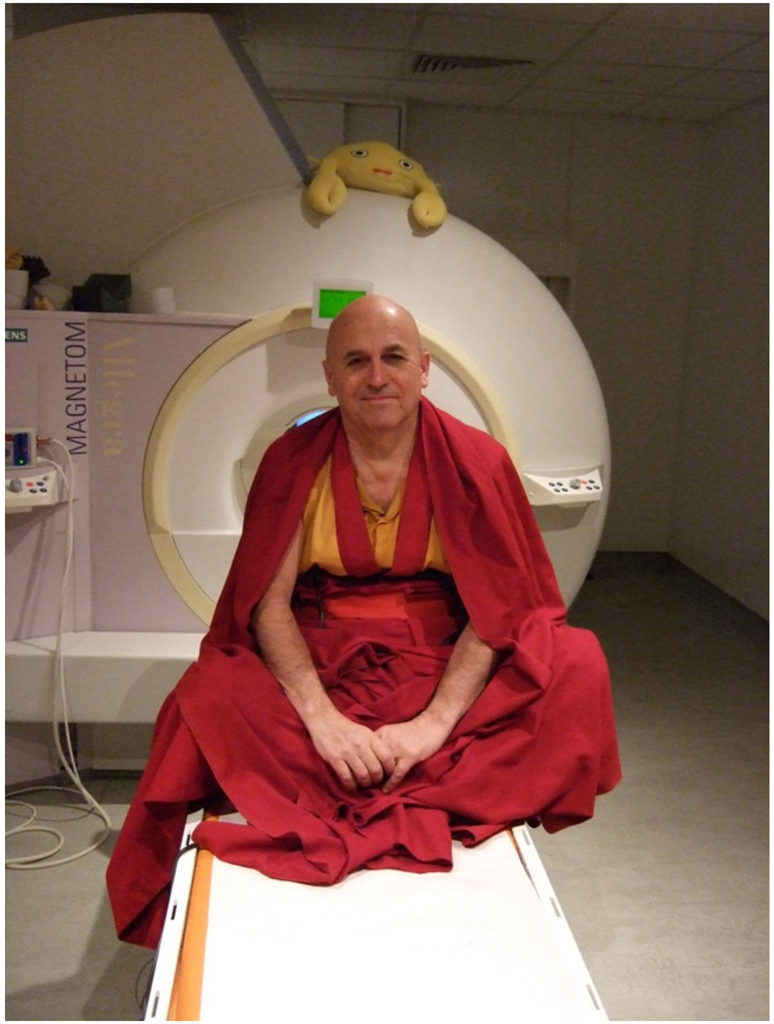
- Other clinical applications might be the reduction of auditory hallucinations, the modulation of mood states/depression (project with David Linden, UK) and phobia (project with Arnoud Arndtz, Maastricht), increasing empathy in children and adults (project with Tania Singer)
  (→ investigated in „BrainGain“ smartmix grant 2008-2013).

Learning from a Meditation Expert

Subject: Matthieu Ricard
Ventral striatum activation is modulated by intensity of positive mental states.

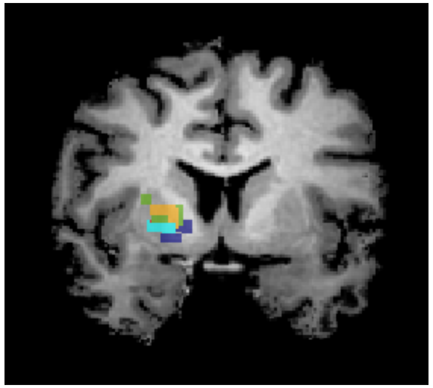


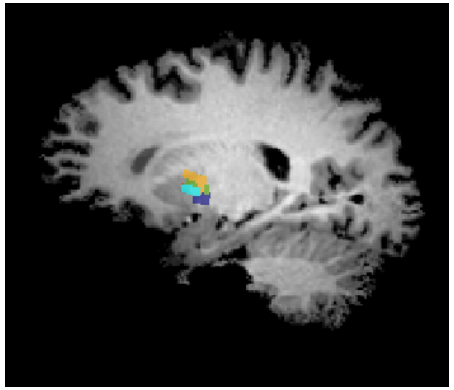




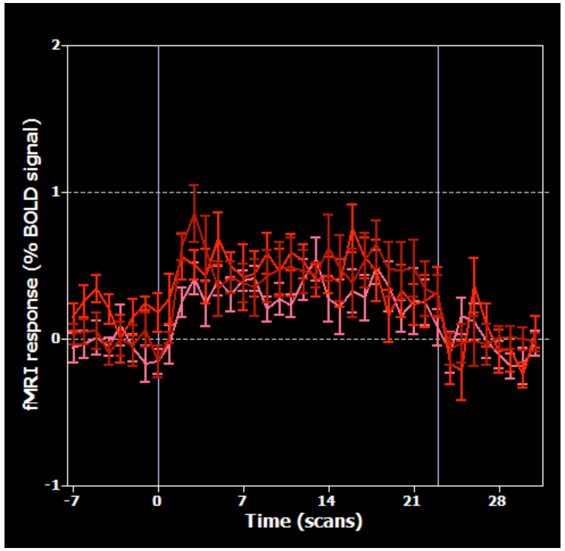
Training Effects in Beginners

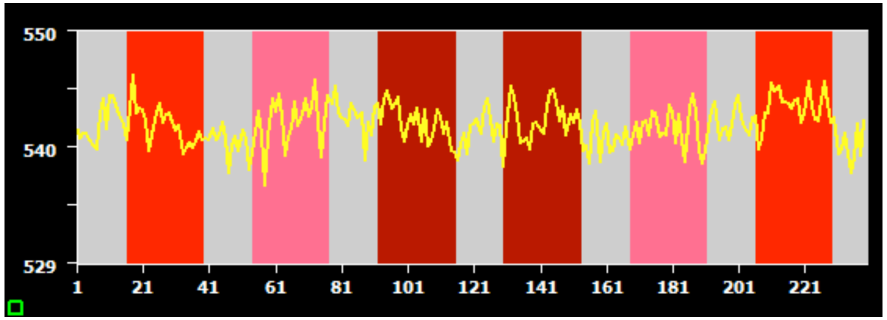
ROI



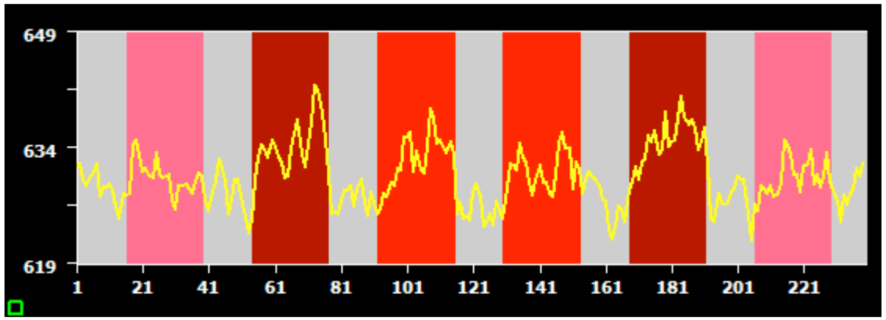


Event-Related Average Plots

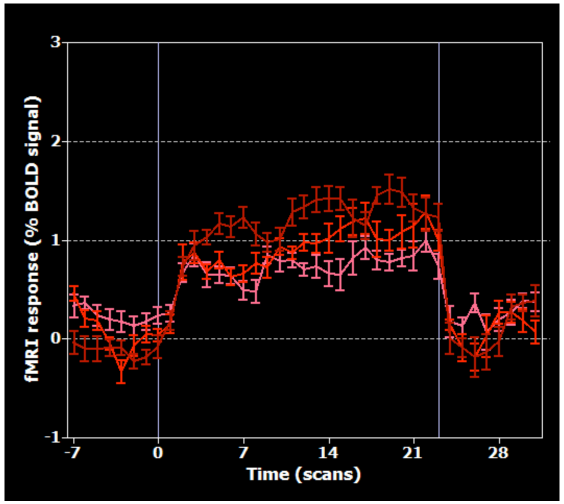




Feedback Session 1



Feedback Session 2

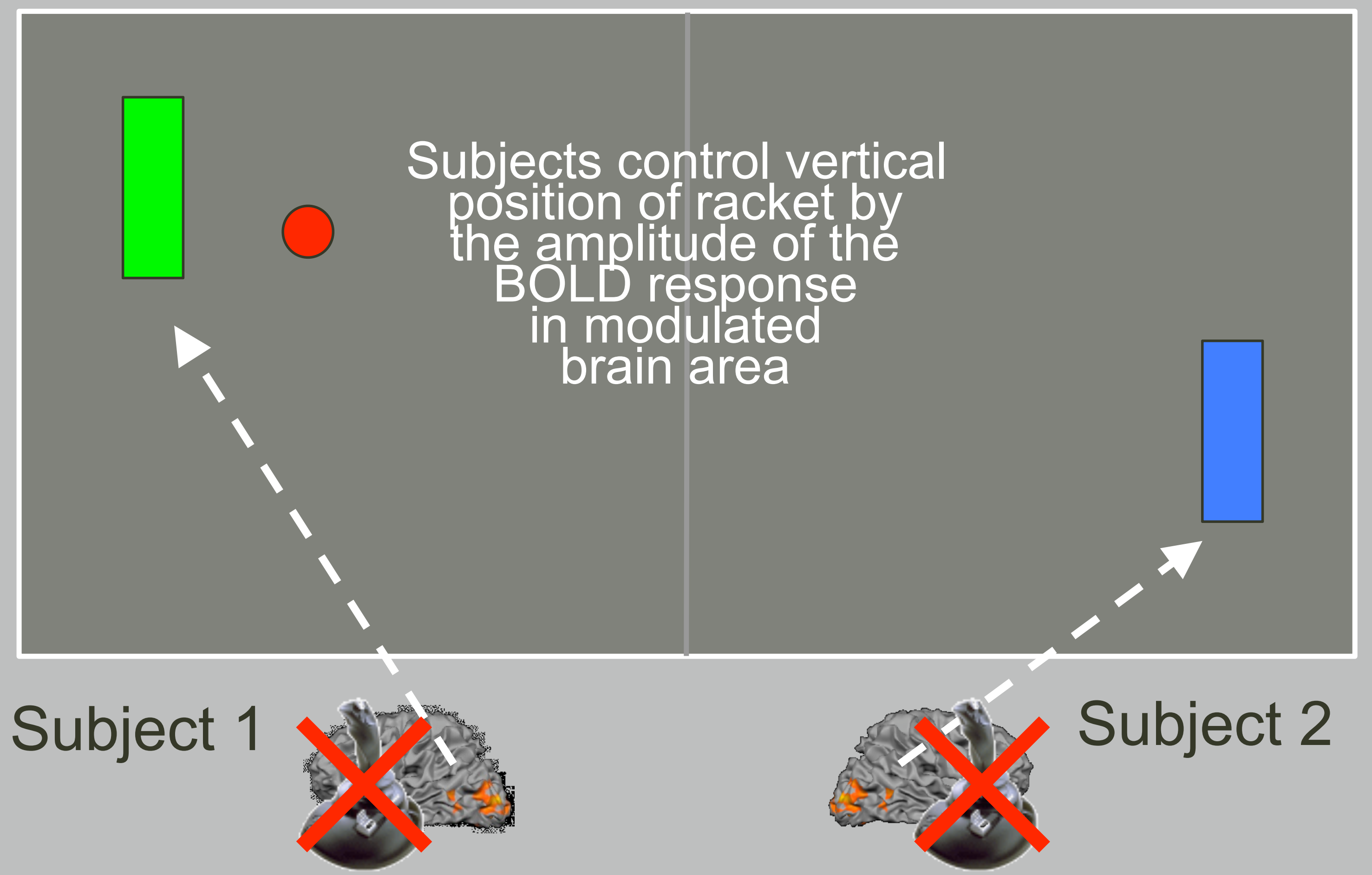


Synchro-Scanning and Neurofeedback

- Is it possible to couple **two** brains ?
- Can two subjects exchange information based on ongoing fMRI measurements?
- How difficult is it to learn to handle the hemodynamic delay? To what extent does this delay limit brain-brain interactions?
- Proof of concept -> **BOLD Brain Pong**

BOLD Brain Pong

Experimental Logic

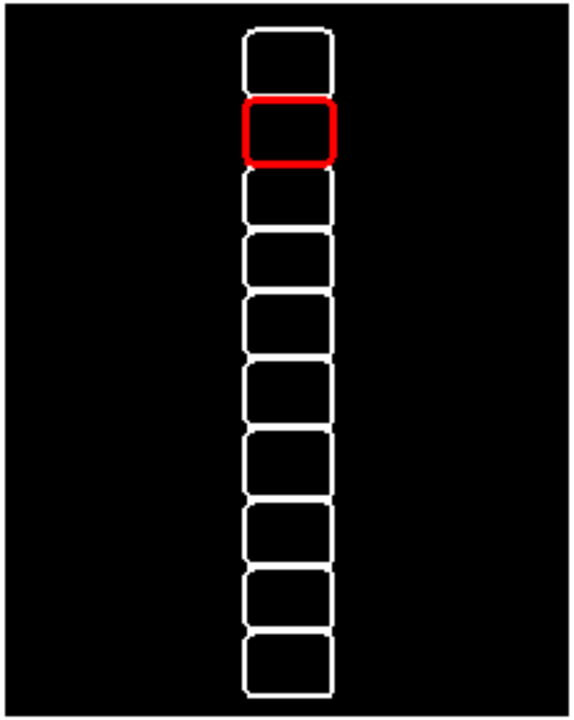


Up-and-down movement of racket requires ***graded control*** !

Subject Pretraining of Graded Control

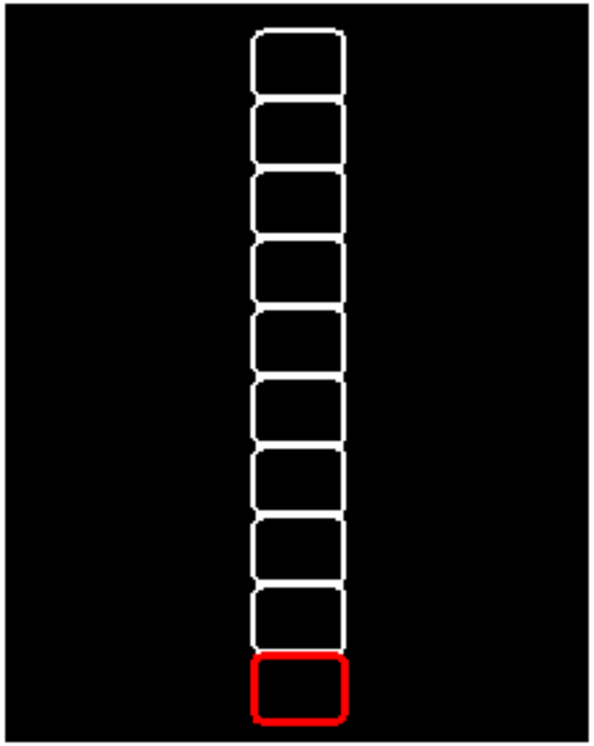
Neurofeedback display

- “Thermometer” visualization of target level and ROI activity
- Easy to interpret by subjects
- Continously updated gradual feedback
- Immediate feedback max. 1 second after data acquisition

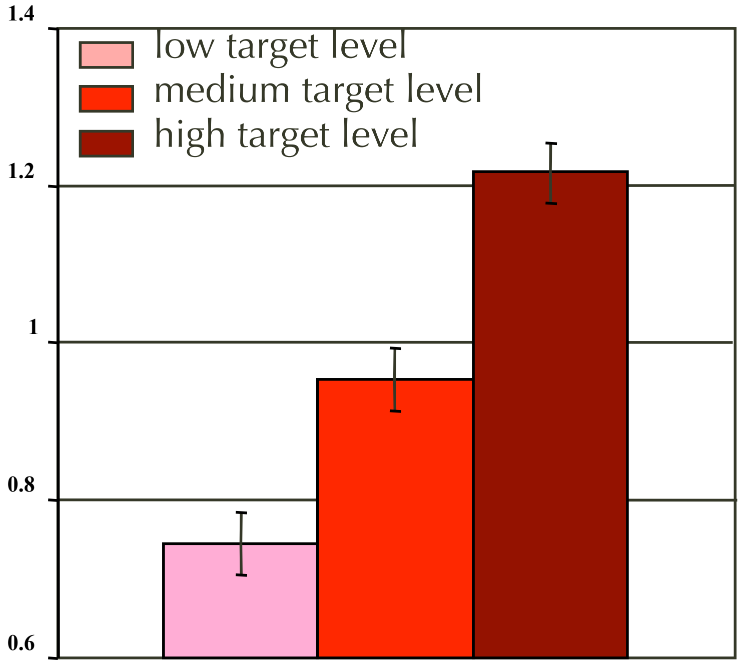


Pretraining of Graded Control

Results



Single episode



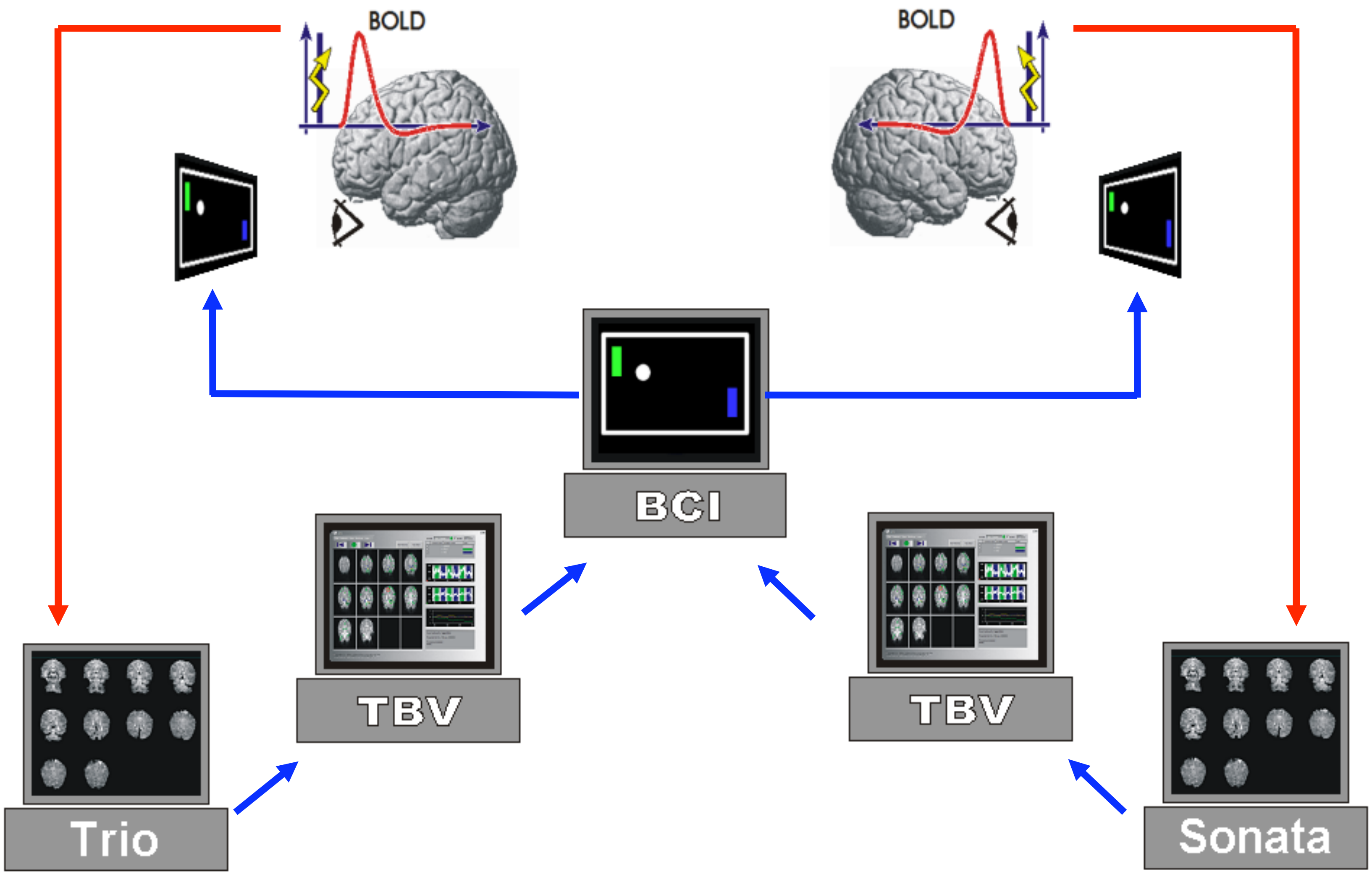
Group analysis (n = 5): Beta weights

All subjects were able to learn to activate spatially localized brain regions to different target levels

Scanning Two Brains Simultaneously

Interactive Neurofeedback

Experimental Setup



Graded Control and Brain Pong

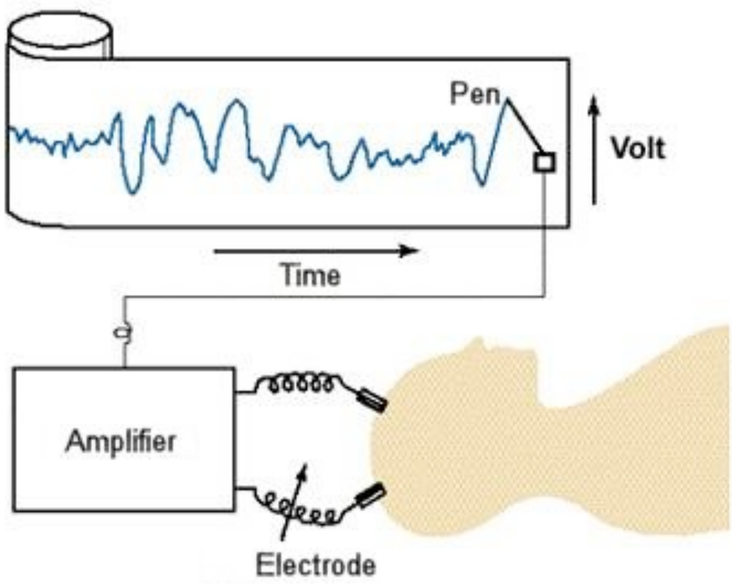
Results – Example game (real-time movie)

BOLD Brain Pong
Results

- In 4 conducted BOLD Brain Pong games, subjects reached a hit rate of 40% – 80% depending on subject-specific performance and training experience.
- Achieved effects were task-specific and can not be explained by task-related motion or cardiorespiratory effects

Brain Computer Interfaces (BCIs)

Previous research: electronic spelling device
based on electroencephalogram (EEG)



Lieber Herr Birbaumer

Hoffentlich kommen Sie mich besuchen, wenn dieser Brief Sie erreicht hat. Ich danke Ihnen und Ihrem Team und besonders Frau Kübler sehr herzlich, denn Sie alle haben mich zum ABC-Schützen gemacht, der oft die richtigen Buchstaben trifft. Frau Kübler ist eine Motivationskünstlerin. Ohne sie wäre dieser Brief nicht zustande gekommen. Er muss gefeiert werden. Dazu möchte ich Sie und Ihr Team herzlich einladen. Eine Gelegenheit findet sich hoffentlich bald.

Mit besten Grüssen
Ihr Hans-Peter Salzmann

Birbaumer et al., 1999

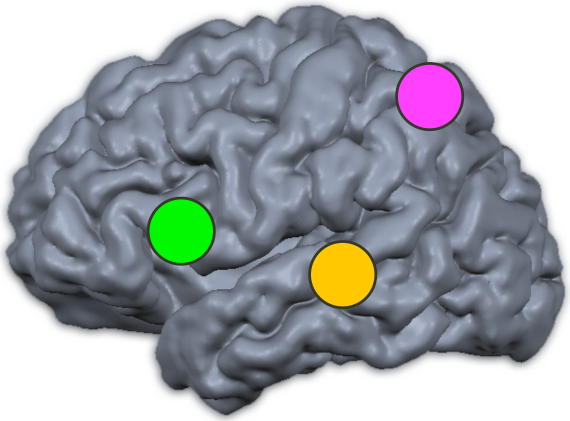
“Brain Writing” Brain Computer Interface

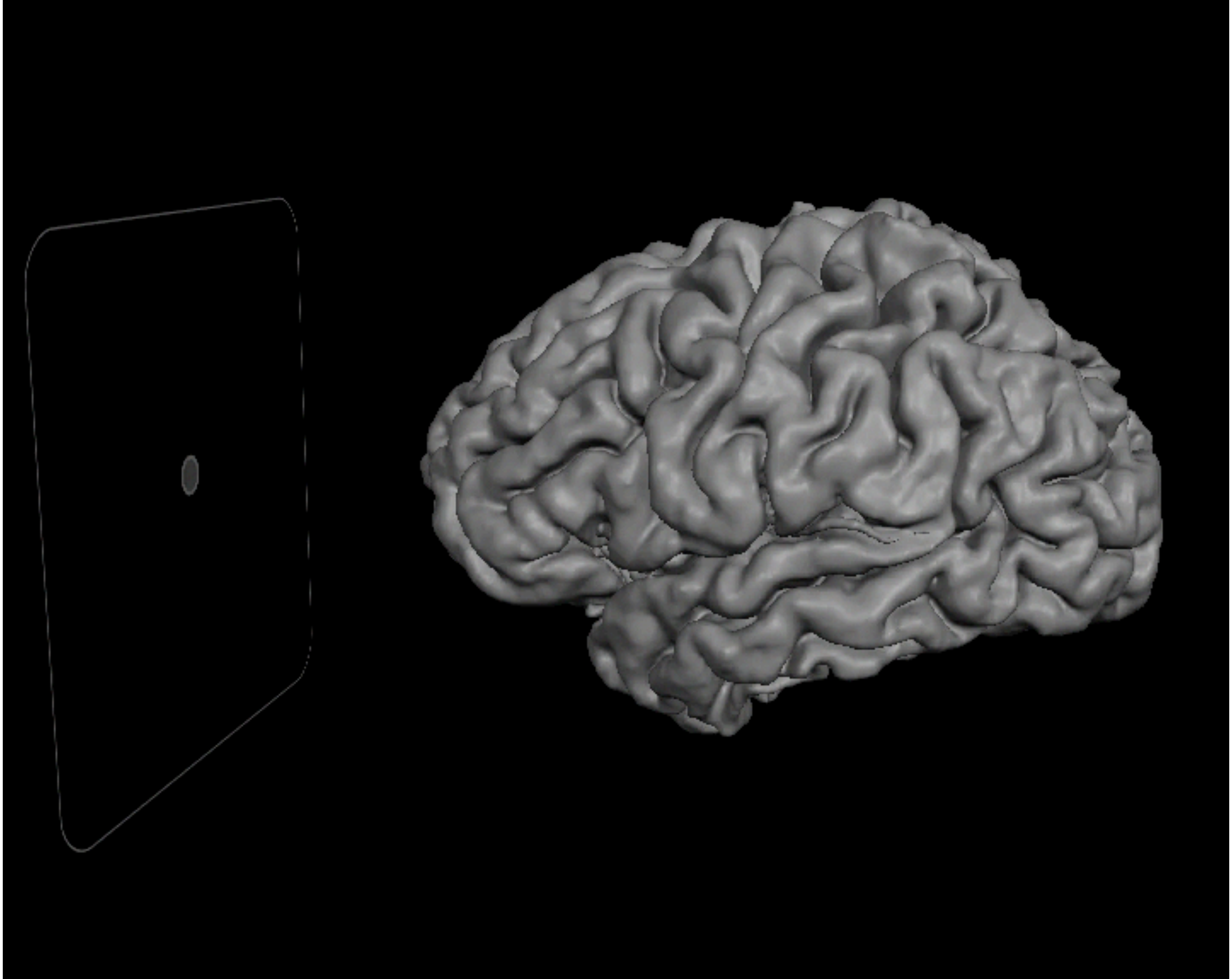
Sorger et al (submitted)

A novel multi-dimensional coding technique

Variation of:

a) 3 (simple) mental paradigms
(e.g. **inner speech**, **mental calculation**, **mental music**)





"Brain Writing" Brain Computer Interface

Sorger et al (submitted)

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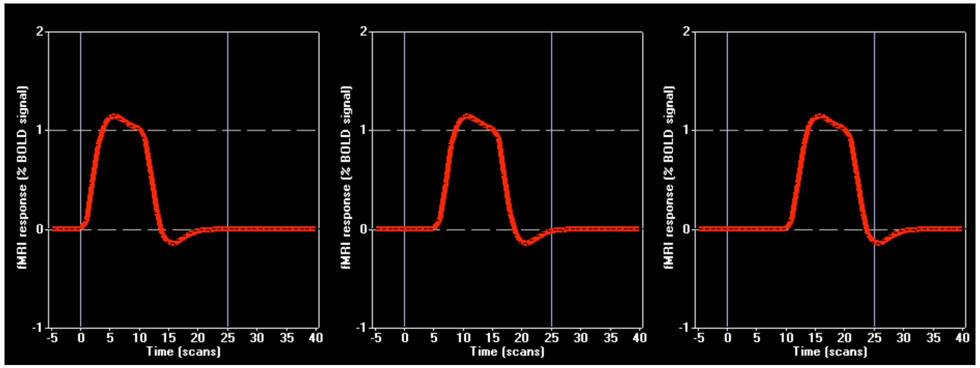


"Brain Writing" Brain Computer Interface

Sorger et al (submitted)

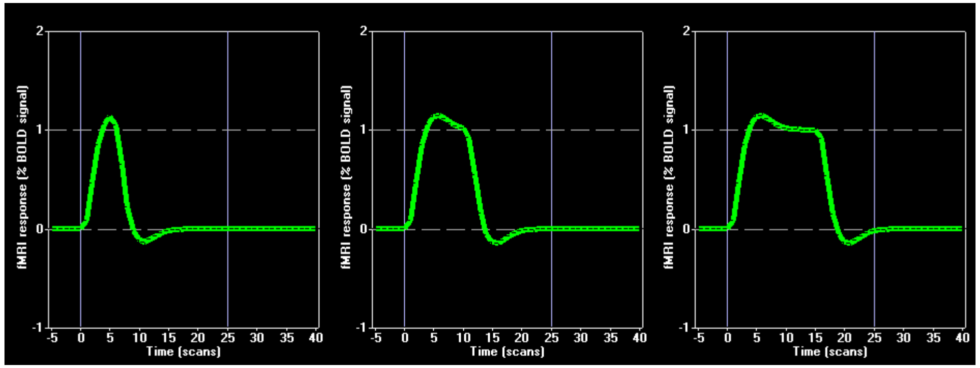
A novel multi-dimensional coding technique

Variation of:

a) 3 (simple) mental paradigms
(e.g. **inner speech**, **mental calculation**, **mental music**)

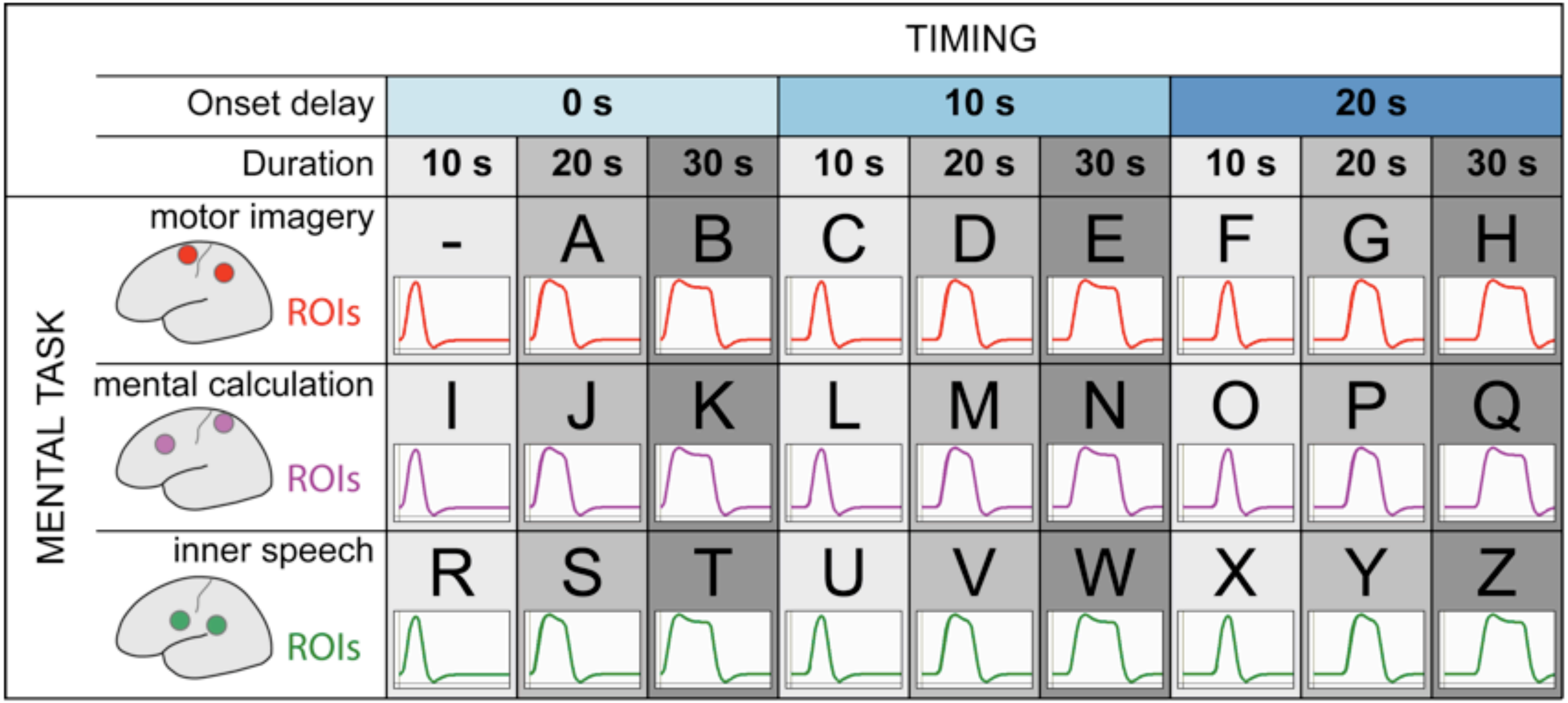
b) performance offset (0s, 10s, 20s)

c) performance duration (10s, 20s, 30s)



“Brain Writing” Brain Computer Interface

Sorger et al (submitted)



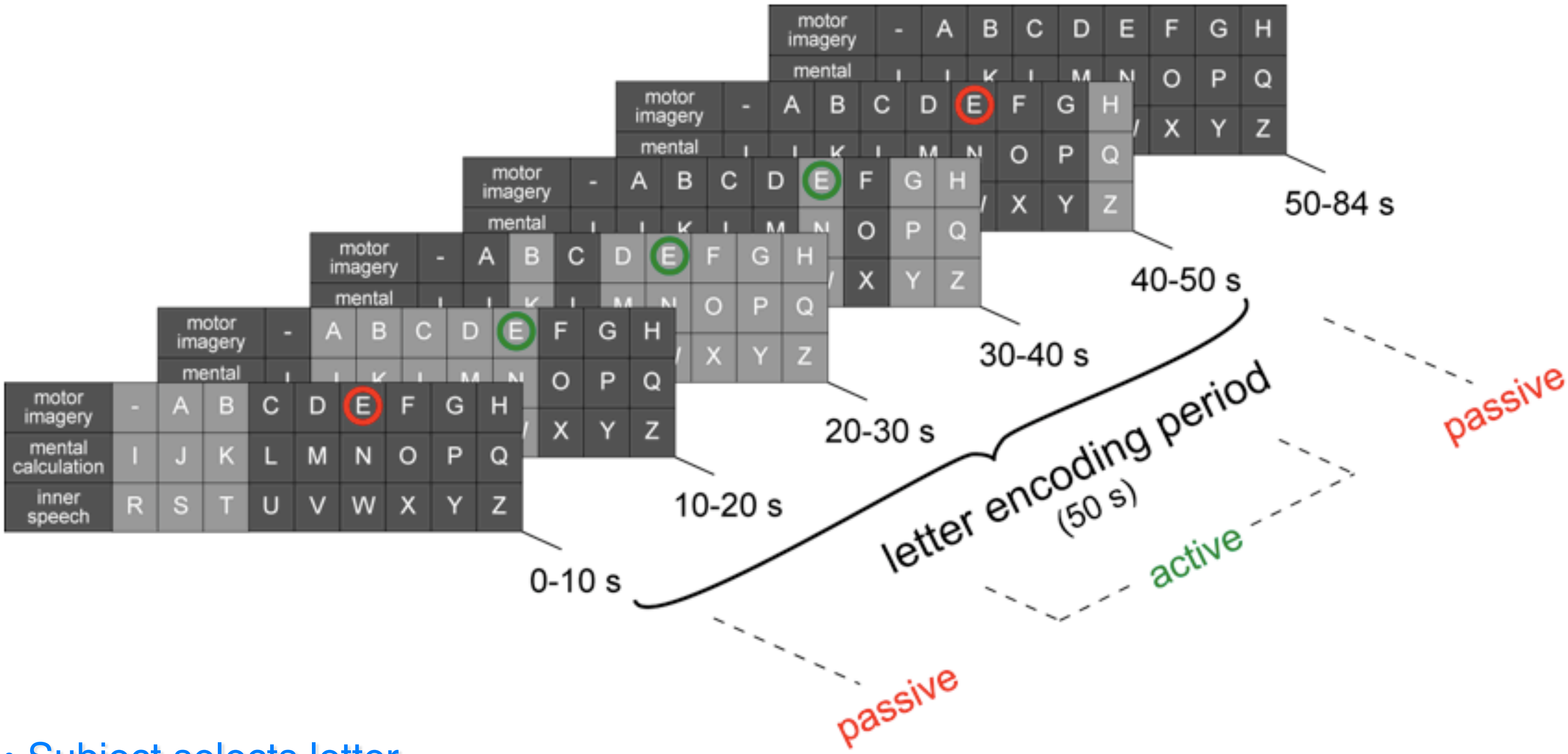
"Brain Writing" Brain Computer Interface

Sorger et al (2007)

- *Guided letter encoding.* In order to verify whether a distinct letter can be represented by a single cognitive event, a *guided letter encoding* task was performed. Subjects (n = 3, S1-3) received visual cues indicating on- and offset of each active encoding phase. All letters of the alphabet and the blank space were encoded pseudo-randomly twice across two functional runs resulting in 54 single trials.

- *Sentence encoding.* To test whether any given thought can be encoded during scanning and detected via the BOLD signal subjects encoded a meaningful and freely chosen phrase unknown to the experimenter.

Easy-to-use instructive display



- Subject selects letter
- Row of letter determines task
- Task performed when letter is highlighted
  → BOLD shape

“Brain Writing” – Guided Display

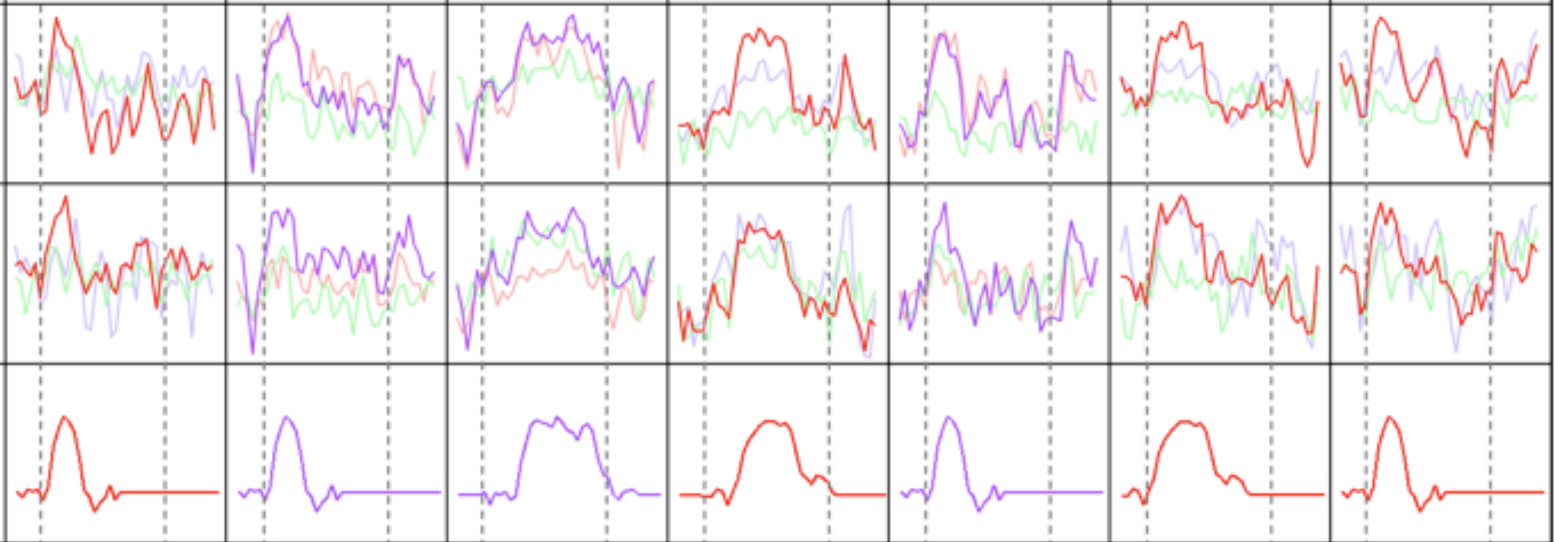
Sorger et al (submitted)

motor imagery	-	A	B	C	D	E	F	G	H
mental calculation	I	J	K	L	M	N	O	P	Q
inner speech	R	S	T	U	V	W	X	Y	Z

“Brain Writing” Brain Computer Interface

Sorger et al (submitted)

encoded answer	-	I	N	D	I	A	-
BOLD signals ('shape/pattern' ROIs)							
BOLD signals (‘pattern only’ ROIs)							
indRTC							
automated decoding (1st letter choice)	-	I	N	D	I	A	-



“Brain Writing” fMRI Brain Computer Interface

Sorger et al (submitted)

Classification results (3 human raters):

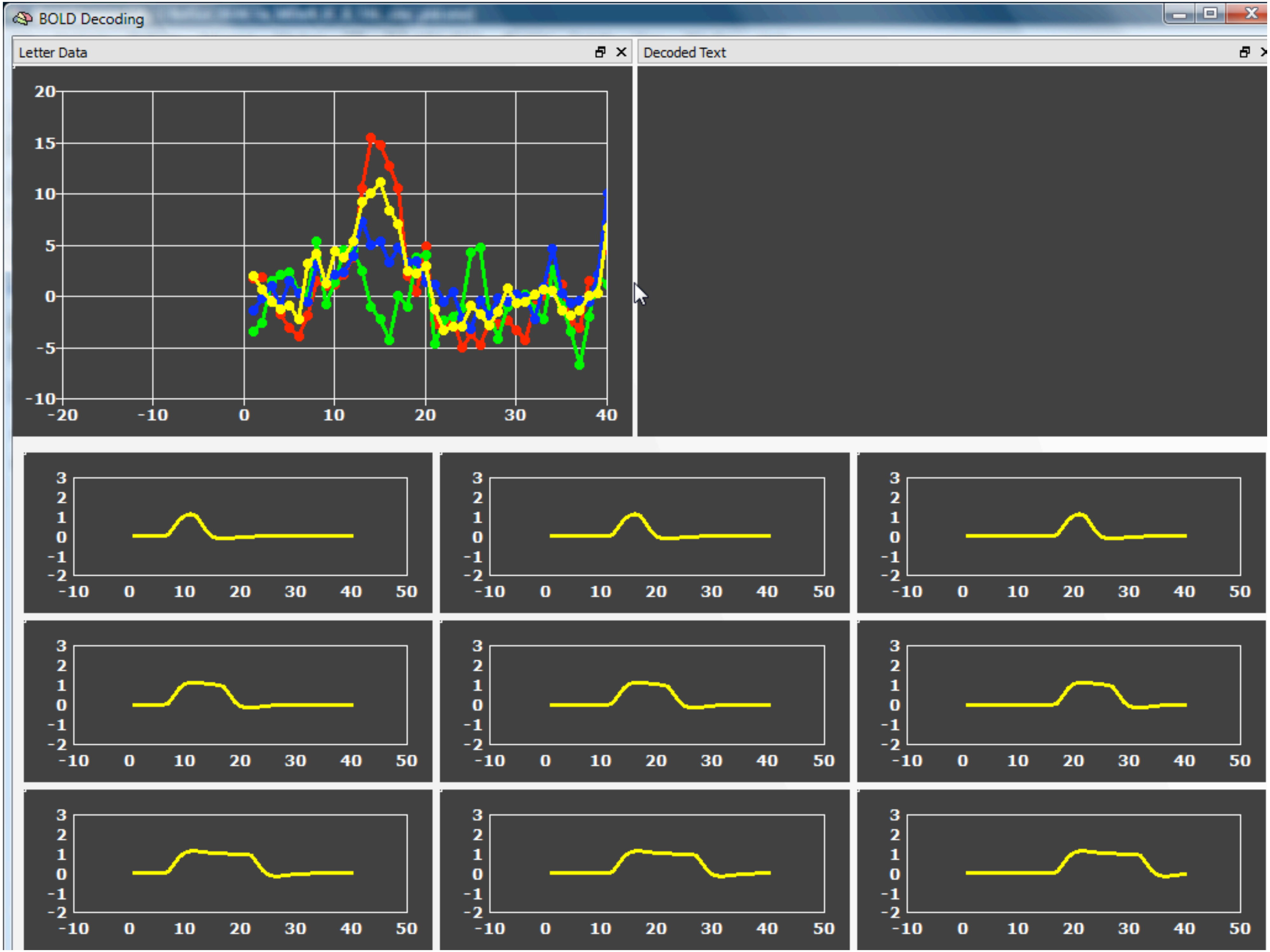
- guided letter encoding data
- exact classification of

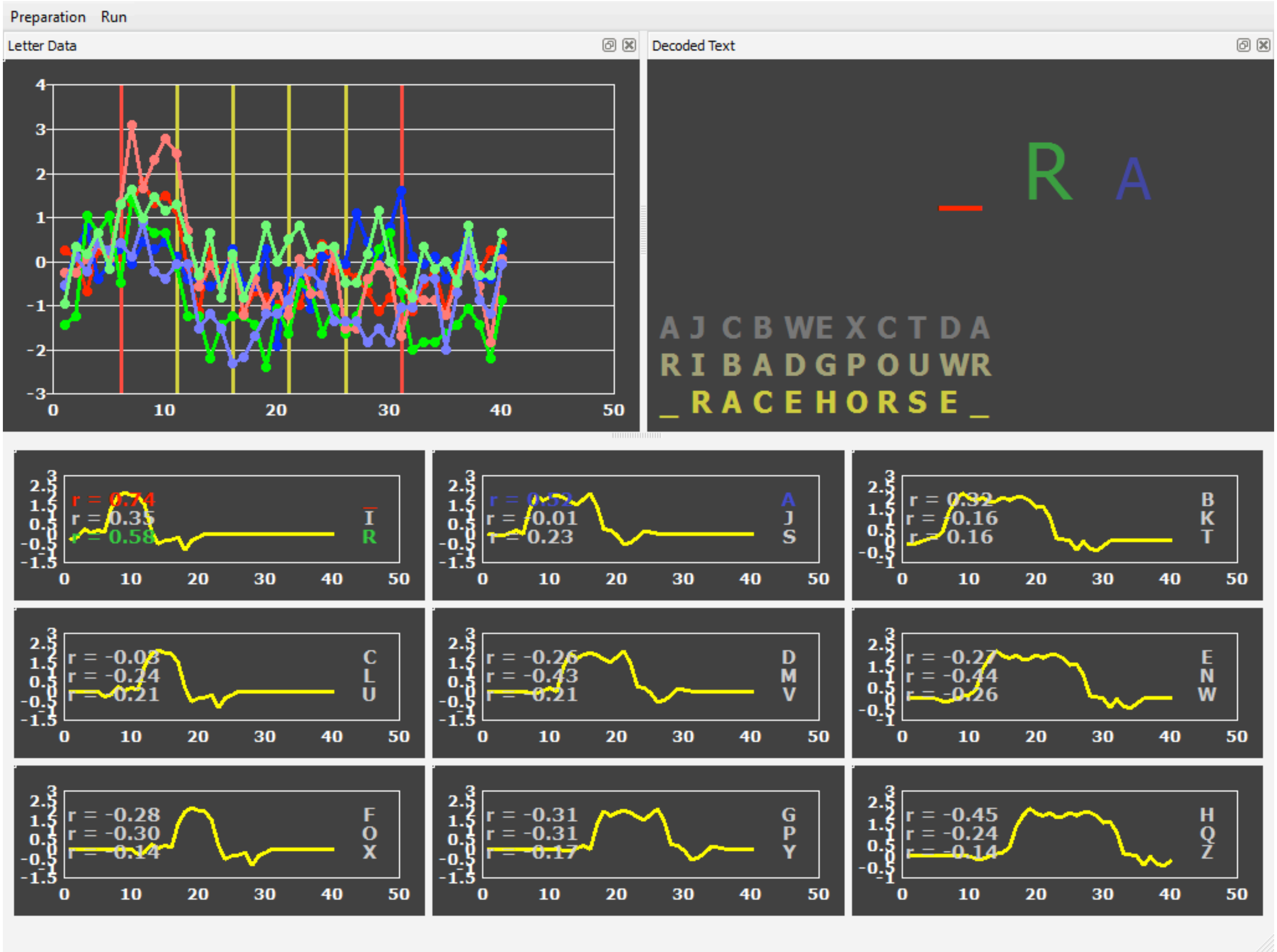
a) the different mental paradigms in 96%

b) the performance offset variations in 96%

c) the varied performance durations in 90% of the cases

- overall correct letter identification: 87% (chance level: 3.7%)
- overall correct phrase identification: 95%
- high inter-rater reliability


BOLD Decoding
Letter Data
Decoded Text
20
15
10
5
0
-5
-10
-20
-10
0
10
20
30
40
3
2
1
0
-1
-2
-10
0
10
20
30
40
50


Preparation
Run
Letter Data
Decoded Text
_ R A
A J C B WE X C T D A
R I B A D G P O U WR
_ R A C E H O R S E _
r = 0.74
r = 0.35
r = 0.58
_
I
R
r = 0.52
r = -0.01
r = 0.23
A
J
S
r = 0.32
r = 0.16
r = 0.16
B
K
T
r = -0.08
r = -0.24
r = 0.21
C
L
U
r = -0.26
r = -0.43
r = -0.21
D
M
V
r = -0.27
r = -0.44
r = -0.26
E
N
W
r = -0.28
r = -0.30
r = -0.14
F
O
X
r = -0.31
r = -0.31
r = -0.17
G
P
Y
r = -0.45
r = -0.24
r = -0.14
H
Q
Z

Word encoding and automated letter decoding

"BOLD" Conversations

Sorger et al (submitted)

participant	'initial' question		'follow-up' question	
	stated question	decoding output/ human interpreter's decision	stated question	decoding output/ human interpreter's decision
1	"What is your hobby?"	- P H O T O G R A P H Y - Q G M X X E I C N G W R R N E P S V H S - Y Z X I I - P H O T O G R A P H Y -	"What did you PHOTOGRAPH last?"	- O Y - H O M E - R M W R Z M O G R A T Z S G V T W A - M Y - H O M E -
2	"Where did you spend your most recent vacation?"	- I N D C N E R C A - A F Q F M M G S I - A I R O B O D F J D C B - I N D O N E S I A -	"What did you like most in INDONESIA?"	- T E K P L E S - I R G M X U D J I A S D L Q M G R A - T E M P L E S -
3	"Where did you spend your most recent vacation?"	- I N D I A - S - E B - C A U A M E A B B - I N D I A -	"What do you consider most typical for INDIA?"	- C L O S H I N G - A A J X T G R M E A R O U P R E A V D R - C L O T H I N G -
4	"What is your hobby?"	- D R S C U S R R N G - R C I T U S U S I P E R A B - R S T R U F M F I - D I S C U S S I N G -	"What is your favorite DISCUSSION topic?"	- A W Y T H I N G - A - N Z S G R P E I B K P W V Z J W H A - A N Y T H I N G -
5	"What are you interested in?"	- X O V I D R A V M U R E S I M X W - N J - M O V I E S	"Which MOVIE did you watch last?"	T O P F U N - V X N N L M I U Y O G J P A T O P G U N -
6	spend your most recent	[illegible]	like most in	[illegible]

Discussion

- Integration of real-time fMRI, neurofeedback and "brain reading"
- Different cognitive strategies ("imagery") are used to exert control over regional, spatiotemporal characteristics of the BOLD response
- Effects (peak responses) are localized, clearly matching cognitive task due to spatial resolution ("spatial filters")
- Allows transmission of distinct information units, i.e. letters
  - at a *single trial level*
  - *without extensive/exhausting pre-training*
- Possibility to encode not only 27 characters but a million words
- Robust results with naïve subjects
- No pre-training, immediate success highly motivating
- Ready for clinical application
- Translation to fNIRS possible

Discussion and Future Work

Comparison with best EEG-based systems

Neuroscience Letters xxx (2009) xxx–xxx

How many people are able to control a P300-based brain–computer interface (BCI)?

Christoph Guger[a,*], Shahab Daban[a,b], Eric Sellers[d], Clemens Holzner[a], Gunther Krausz[a], Roberta Carabalona[c], Furio Gramatica[c], Guenter Edlinger[a]

Table 1
Percentage of sessions which were classified with certain accuracy. *n* specifies the number of subjects participating.

Classification accuracy in %	Row-column speller: percentage of sessions ($N = 81$)	Single character speller: percentage in sessions ($N = 38$)
100	72.8	55.3
80–100	88.9	76.3
60–79	6.2	10.6
40–59	3.7	7.9
20–39	0.0	2.6
0–19	1.2	2.6
Mean accuracy of all subjects	91.0	82.0
Spelling time [s]	28.8	54
Mean accuracy of subjects who participated in RC and SC ($N = 19$)	85.3	77.9

Discussion and Future Work

Why not using more “direct” task, e.g. letter imagery, and MVPA?

The Journal of Neuroscience, February 4, 2009 • 29(5):1565–1572 • 1565

Behavioral/Systems/Cognitive

Top-Down Activation of Shape-Specific Population Codes in Visual Cortex during Mental Imagery

Mark Stokes,[1,2] Russell Thompson,[2] Rhodri Cusack,[2] and John Duncan[2]

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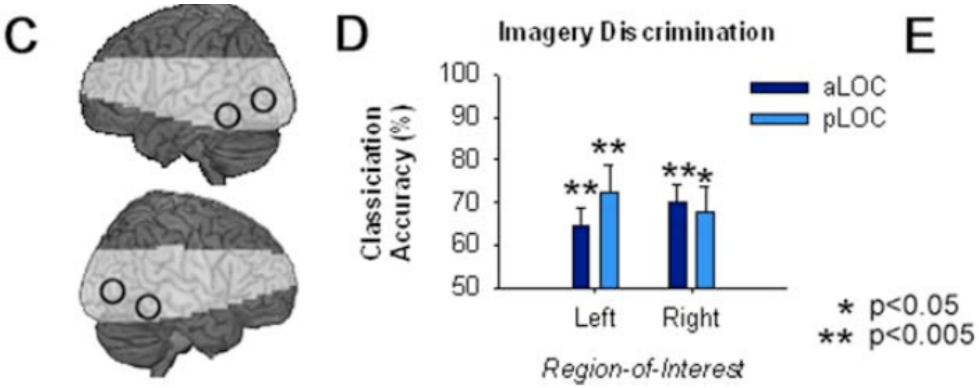
Using functional magnetic resonance imaging (fMRI), we measured changes in brain activity while participants imagined or viewed the letter “X” or “O” (see Fig. 1), and then applied multivoxel pattern analysis (MVPA) (for review, see Haynes and Rees, 2006; Norman et al., 2006) to determine whether observed activation patterns could reliably discriminate between different states of visual imagery, and/or stimulus-driven perception. Fur-

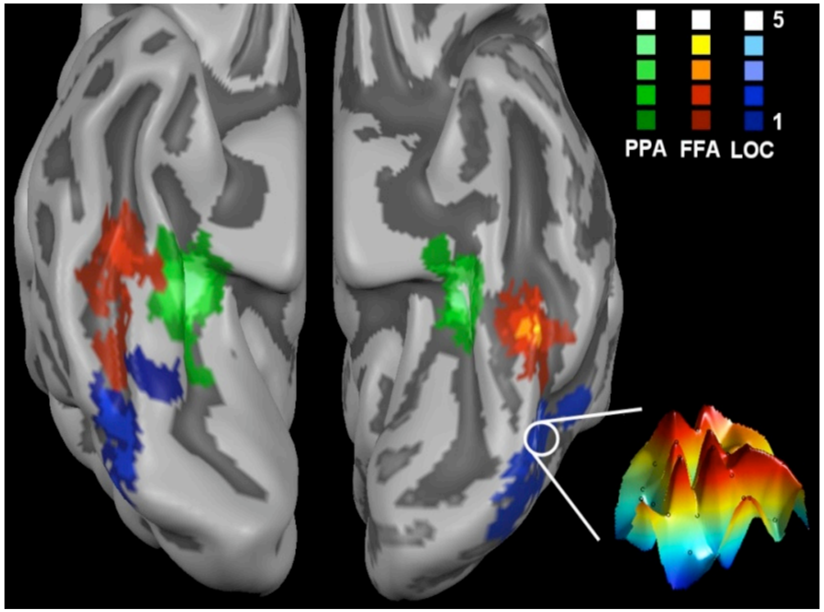


Discussion and Future Work

Why not using more "direct" task, e.g. letter imagery, and MVPA?

Machine learning is very promising, but problems wrt real-time fMRI applications (neurofeedback, communication):

- Requires learning phase, which requires time (many training exemplars for 27 choices...)
- Alignment across sessions at voxel level difficult (not for ROIs)
- Testing (classification of new input patterns) is, however, fast



"Who" Is Saying "What"? Brain-Based Decoding of Human Voice and Speech

Elia Formisano,* Federico De Martino, Milene Bonte, Rainer Goebel

Can we decipher speech content ("what" is being said) and speaker identity ("who" is saying it) from observations of brain activity of a listener? Here, we combine functional magnetic resonance imaging with a data-mining algorithm and retrieve what and whom a person is listening to from the neural fingerprints that speech and voice signals elicit in the listener's auditory cortex. These cortical fingerprints are spatially distributed and insensitive to acoustic variations of the input so as to permit the brain-based recognition of learned speech from unknown speakers and of learned voices from previously unheard utterances. Our findings unravel the detailed cortical layout and computational properties of the neural populations at the basis of human speech recognition and speaker identification.

In everyday life, we automatically and effortlessly decode speech into language independently of who speaks. Similarly, we recognize a speaker's voice independently of what she or he says. Cognitive and connectionist models postulate that this efficiency depends on the ability of our speech perception and speaker identification systems to extract relevant features from the sen-

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Discussion and Future Work

Intact visual attention/fixation not required

Instruction/Guidance

Visual

motor imagery	-	A	B	C	D	E	F	G	H
mental calculation	I	J	K	L	M	N	O	P	Q
inner speech	R	S	T	U	V	W	X	Y	Z

Auditory

Tactile

:

Mental Task Set