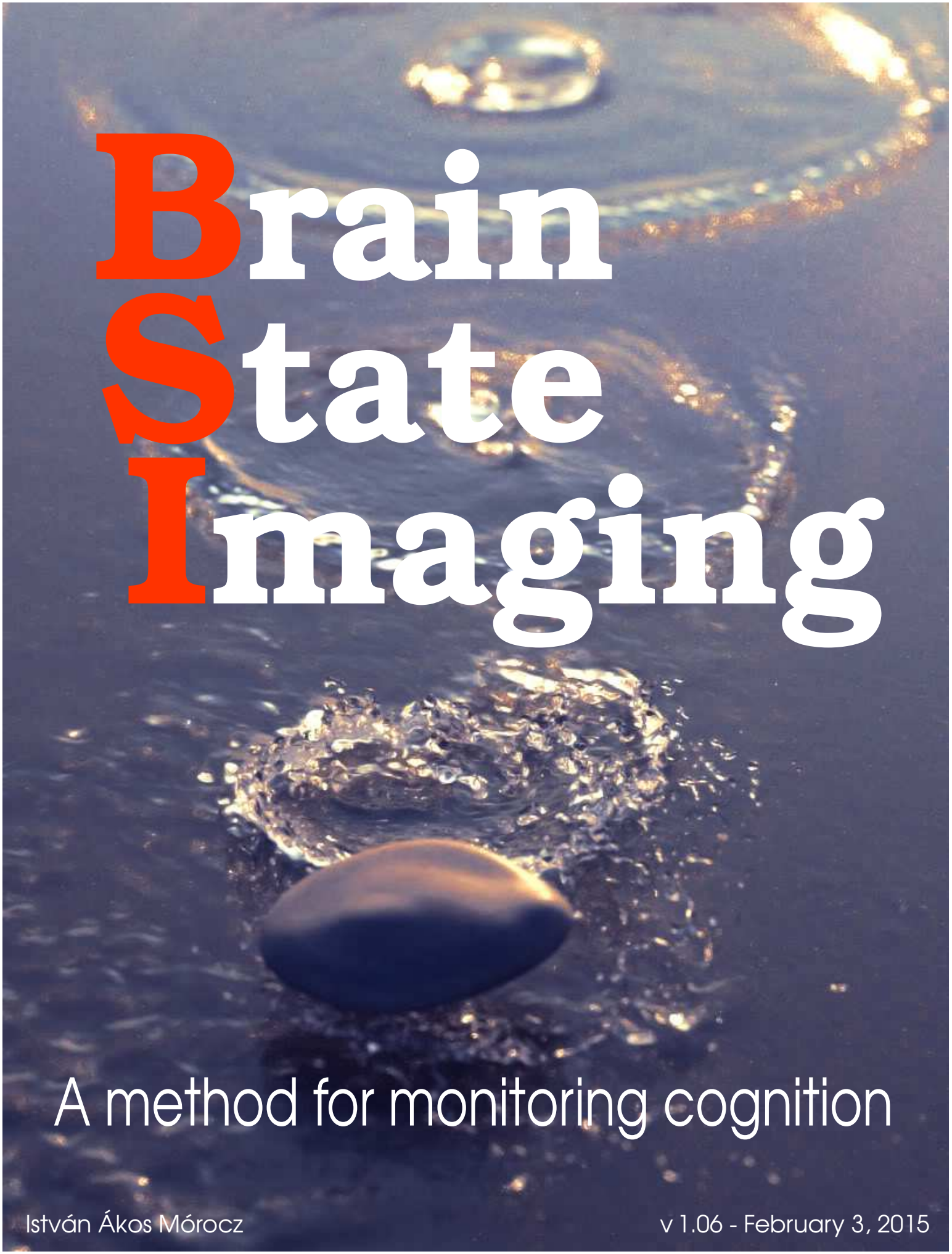

Brain State Imaging

A method for monitoring cognition

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Abstract

The recognition and analysis of metabolic brain activity is non-trivial and remains a daunting and in large part unsolved problem in the discipline of neuroscience. In fact, the lack of certitude in relating brain measures objectively to human behaviour makes a comprehensive neuro-psychiatric reckoning of the population infeasible. This brochure briefly highlights the origins for such failure in the past. Moreover, it advocates novel pattern identifying principles that arose in recent years in the fields of mathematics and computational neuroscience. Finally, we introduce the Brain States Imaging method, or **BSI**, and thereby pave the way for collaborative initiatives with academia and industry to inquire on human cognition and mental health by means of quantitative brain mapping.

1. What is BRAIN STATE IMAGING used for ?

Brain disorders cost the United States and countries in Europe more than any other group of disorders, including cancer, cardiovascular disease and diabetes *combined*, but receive disproportionally little funding.[1] Even the pharmaceutical industry is increasingly shying away from these brain disorders.[2] The problems basic science is faced with are manifold, like unrealistic animal models, difficulties in diagnosing and allocating patients to trials and unpredictable results from early studies.[3,4]

Cognitive wellness and quality of life are increasingly recognized as outcome measures in treatment studies of brain disorders. The clinical implication of a brain mapping technique that comprehensively captures complex cognitive processes in the human brain could be immense.

The central nervous system harbors cognition, the most complex, fugacious and intangible of all neurological functions. We are not aware of robust neurobiological tools that quantitatively monitor patients' mental performance and cognitive integrity over time. Due to this, simple paper/pencil tests often convey more relevance for therapeutic guidance, than conventional brain mapping techniques.

The problems are conceptual as common acquisition and analysis techniques are inaptly designed[4,5] for the complex nature of functional processes. • Uni-dimensional analysis approaches are robust in the statistical sense, but the resulting activity maps relate too vaguely to the true temporo-spatial nature of aberrant trajectories that pathological thought processes consist of.
• Then, traditional structural brain imaging techniques only coarsely detect anatomical changes and inflammation over time.
• Lastly, standard cognitive tests during clinical examination reflect only remotely the subtle deficits in executive functioning which are commonly seen in neurological and psychiatric conditions.

BRAIN STATE IMAGING in contrast relates directly to the active disease state of a brain disorder. Its broad way of valuing neural effects conforms well with the distributed nature of higher cognitive brain functions and the usually diffuse manifestation of pathologies in the central nervous system. Hence, repeated physiological measures serve as sensitive indicators for cognitive integrity and for disease propagation on an individual basis. In other words, **BSI** forms a metabolic effigy for cognition that equates to the clinical course of mental health. We predict **BSI** will help to customize treatment for brain disorders.

2. Reality in the Brain

Brain processes are intensively intermingled and still manifest in space and time as organized hierarchic notations in the neural signal. A response of this system to inner or outer stimuli invokes a cascade[6–9] of electrical, chemical and hemodynamic activity, that last from a few milliseconds to several seconds. These complex effects merge with the ongoing background brain activity. **BSI** as a spatio-temporal analysis technique accounts for the transient and brain-wide nature of neural activations[10] and distinguishes their imprints amongst the total brain signal.

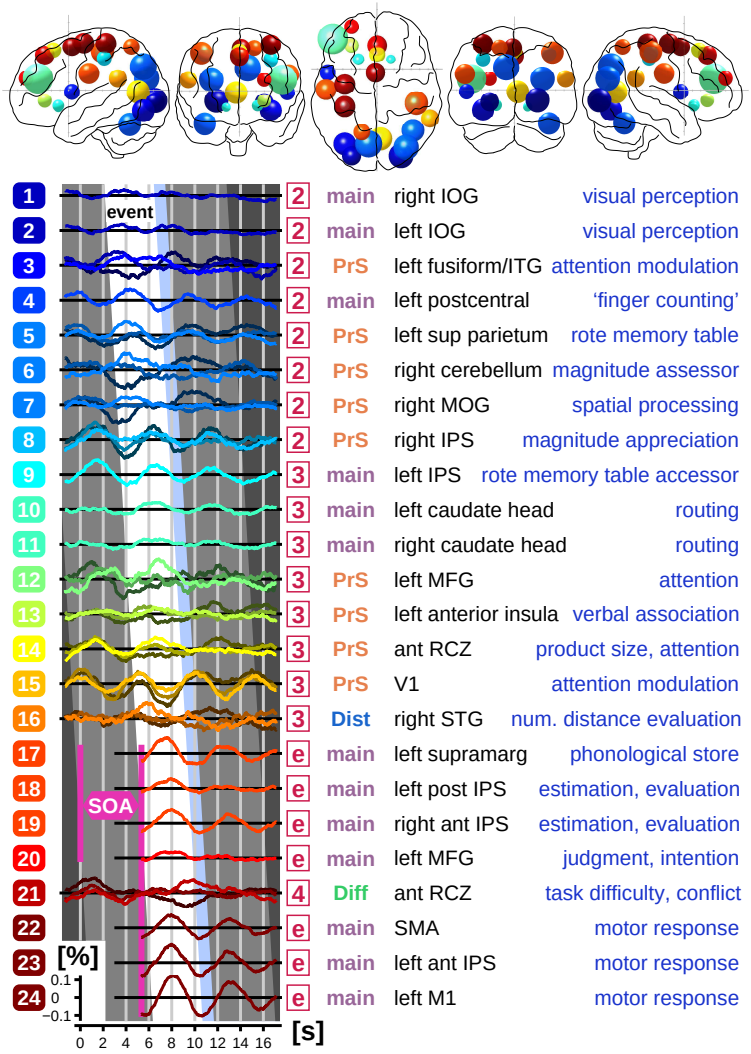


Fig. 1 Complex cognitive tasks like mental arithmetic modulate the brain BOLD signal in form of a cascade-like recruitment. A rich picture emerges in numerous distributed foci in *time* and *space*. Each ROI signal time-course is shown as average from 9,100 time-locked event-related data excerpts. The diagonal white shaded area represents the time window for an event.[6]

Brain responses to stimuli are minute, no matter what types of physiological responses are measured (including fMRI and EEG). • In fact, a stimulus induced effect is so negligible, not to mention the noisiness in the background signal, that sensible analyses can not be computed from small regions of interest. • Furthermore, the more that subjects are enthralled by a real-life-like test exercise the more their concomitant neural responses will appear scattered in time and space. • Lastly, the brain embeds the effect of a cognitive stimulus it responds to, in a vast plethora of ongoing neural processes - *as in the analogy of a skipping stone that hits the unruly surface of water*. This maneuver necessarily re-allocates mental resources like attention and working memory, and, by doing so, it reshapes at once the entire signal landscape in the brain.

A data mining approach that intrinsically discerns large distributed signature spaces is better equipped to capture these natural brain responses.[11] Therefore, only spatio-temporal analysis techniques like the proposed **BSI** method account for the truly multi-dimensional character of the neural signature space that cognitive processes live in.

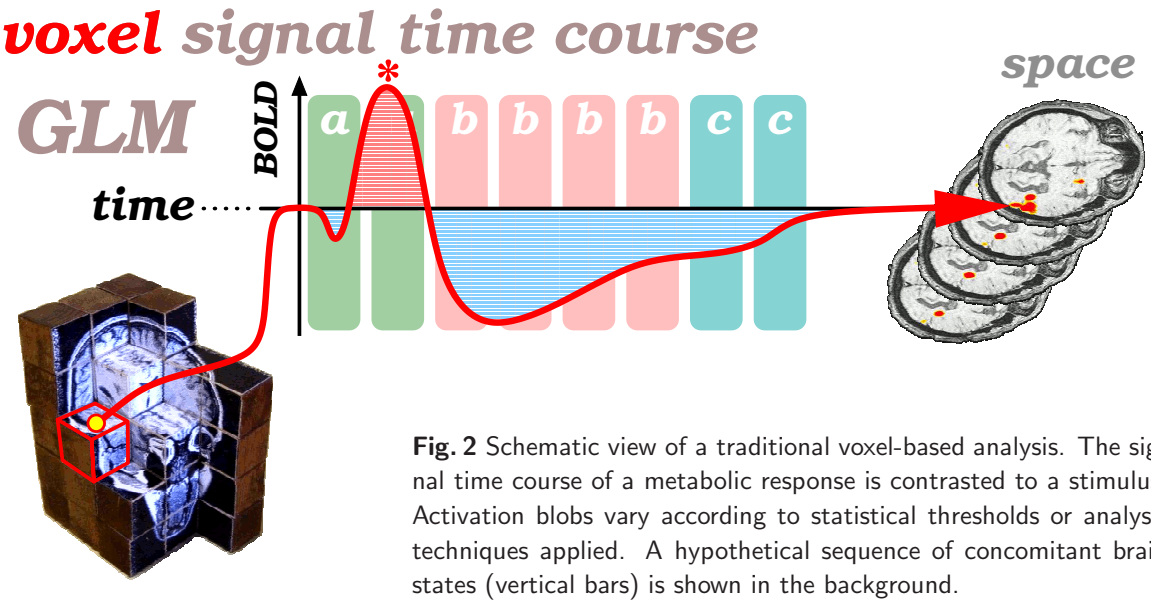


Fig. 2 Schematic view of a traditional voxel-based analysis. The signal time course of a metabolic response is contrasted to a stimulus. Activation blobs vary according to statistical thresholds or analysis techniques applied. A hypothetical sequence of concomitant brain states (vertical bars) is shown in the background.

3. Current Approaches

It is commonly accepted that a specific exercise causes the neural signal in a region of interest to predictably respond. Inversely, it is hypothesized that a focal brain signal matches directly with a stimulus input or an action output. This view suggests a one-to-one automatism of neural recruitment.

Current brain mapping analyses frequently rely on the General Linear Model (GLM), a simple though admittedly powerful unidimensional framework. The highly popular Statistical Parametric Mapping (SPM) uses GLM to identify spatial activation maps that correspond solely to the structure of an experiment. However, this approach ignores the temporal state sequence intrinsic to brain data. As reality may be much more intricate,[5] we are faced with three misleading shortcomings:

1. **The assumption** that a focal observation in the brain can explain a thought process in its entirety.[12]
2. **The premise** that data uniformity in space and time can be achieved through 'spatial normalization'.
3. **The fact** that valuable temporal information is neglected and left undeciphered in the brain signal.

Similarly, the popular Independent Components Analysis (ICA) approach[13] explains the data in terms of temporal basis vectors. However, unlike the **BSI** states, the ICA components do not take into account distinct 'temporal brain regimes' that are quite different in nature.

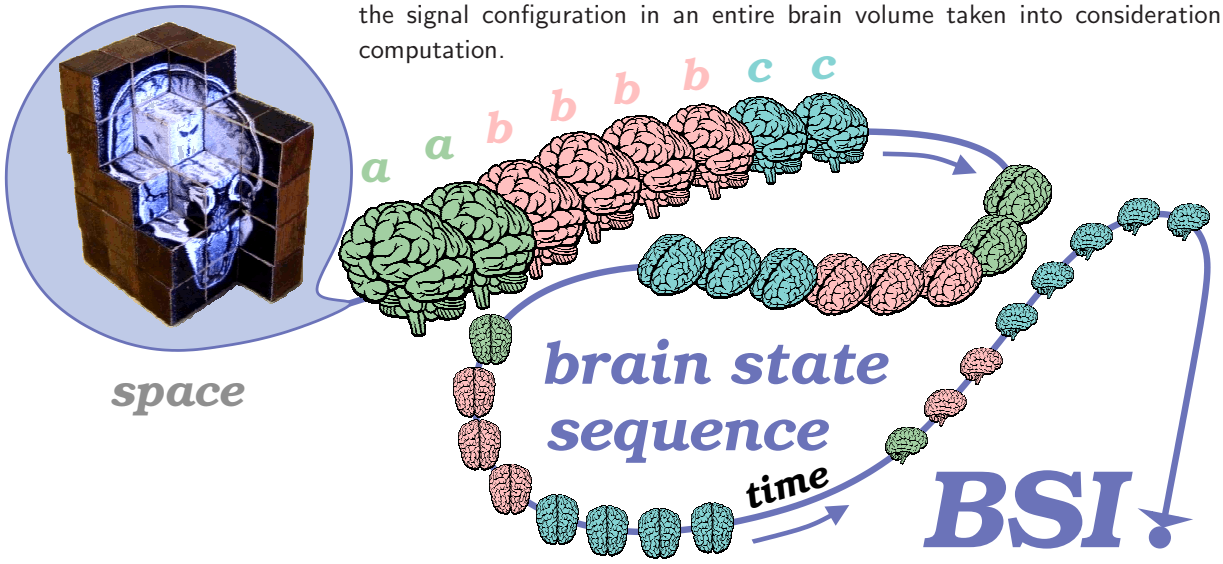


Fig. 3 Schematic view of a **BSI** sequence of 'brain states'. States are labelled according to their assumed state space clusters **[a b c...]**. At each time point is 'holistically' the signal configuration in an entire brain volume taken into consideration during computation.

4. Brain State Imaging

Neuroscientists traditionally compute spatial maps that are used to localize neural processes, and then assess the temporal evolution in selected foci. However, as cognition happens in the entire brain, the physical dimensions of the underlying mental processes are inherently linked as being spatio-temporal in nature. Conventional methods undervalue this *dual*-character of space and time in neural communication. Hence they necessarily compromise on extracting the entire information from the acquired data.[4,5,11]

Over the years there have been many approaches to fMRI analysis that focus on either the temporal structures or the spatial patterns in the signal. We combined former concepts on spatio-temporal clustering[14,15] and developed with an innovative implementation of the State Space Model (SSM) approach the here introduced novel analysis technique **BSI**. Already, the SSM decomposition was successfully applied in finding group differences[8,9] as well as for elucidating the underlying structure of cognition.[6] Its algorithms decompose the data with the Hidden Markov Model (HMM) into a temporal sequence of symbolic 'brain states' each associated with a spatial activation map, that combined reflect the hierarchical dynamics in brain activation.

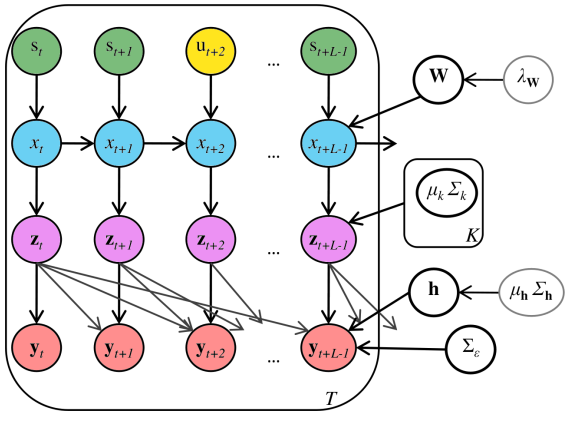


Fig. 4 **BSI** models a functional brain as it transitions - while performing a mental task - through a set of (unobserved) cognitive states x_t=1...K. Experimental parameters are represented by s_t while the resulting neural activation pattern is z_t. Neural activity pattern is translated into the fMRI data y_t after convolution with an unknown hemodynamic response **h**.[8,9,16]

5. BSI Sequence

Neural information is accumulated in excerpts. Each quantum of information is a spatio-temporal signal constellation similar to the transient configuration of a molecule's electron cloud. Neural processes trigger distinct units of information, which amalgamate into a restless brain signal, unique to a subject, a disease or an environment.[17,18] **BSI** uncovers latent yet unique temporal dynamics and inner workings of cognitive processes, that would otherwise go undetected. It computes a sequence of brain states adding statistical attributes to each. It is this sequence that elucidates the structure and organization of the neural signal. It subsequently offers unique insights into the flow of cognitive information as the following points explain :

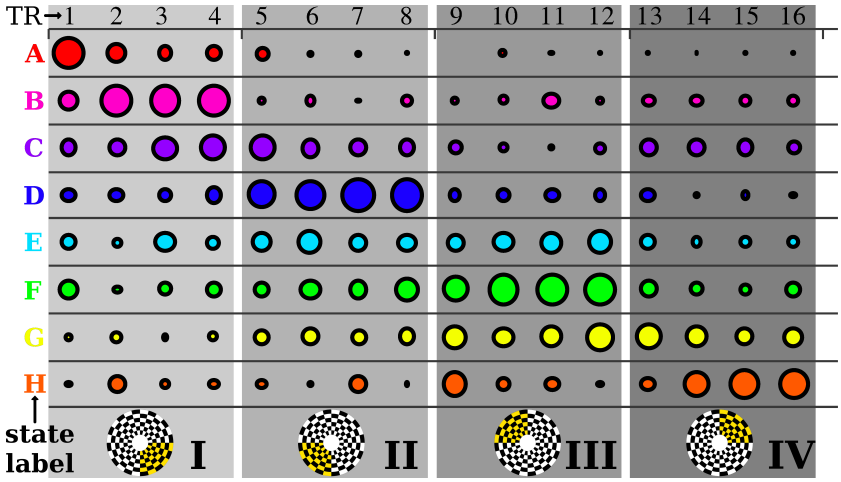


Fig. 5 **BSI** probability for one subject. Circle sizes correspond to the marginal probabilities of the states during the display of the wedge in four quadrants for 4TRs each (phases I–IV). States have been relabeled for expository purposes and transition probabilities have been omitted for clarity.[19]

1. **An optimal number of brain states** is computed from fMRI data and falls empirically between 10 and 20 (in the above example case [A...H] = 8).
   *The number of brain states informs about the kinetics within the **BSI** model as well as the dynamics of cognitive processes and the underlying data.*

2. **A sequence for the brain states** is determined where each time point in the data [1,2,3...] will hold a probability [circle size] of each state at that time [A,B,C...].
   The state sequence says what brain states [D,E] a cognitive process [II] lives in.

3. **A probability for each brain state** is then computed [A,B,C...].
   This statistical value says how unique and robust a given brain state manifests.

4. **A spectrum with all brain states** is determined for a given phase of interest [ABC dominant in phase I ; CD in phase II ; FG in phase III etc].
   The mix of brain states in a given cognitive phase [I] is crucial and specific, as compared to another phase, [II] for example.

5. **An activation map for each brain state** [A,B,C...] is generated.
   This map anatomically depicts all regions a brain state of interest has recruited.

6. **Activation maps for phases of interest** [I, II...] are computed.
   These maps reveal the activation space recruited during a phase of interest. ***BSI*** *derived maps are expected to resemble traditional hypothesis-based activation maps.*

6. BSI Mutual Information

BSI first determines a sequence of manifold states that directly mirrors the data. The enormous significance of the sequence lies in its *inverse* application in that the state space model (SSM) can in principle accurately re-generate the original content of the data. This opens doors never before known. The model of one data may now serve as reference to test other data through **mutual information** in a crisscrossed fashion. The indices in such a **MI** table offer a wealth of unprecedented possibilities to study continuous spectra of biomeasures in cognition.[6,8,9]

Probably the most important clinical application for **BSI** could be in the prediction of cognitive decline. For example it will help with:

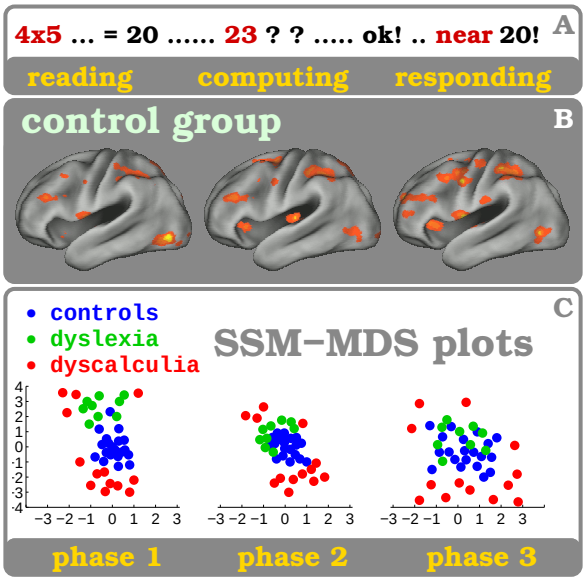


Fig. 6 Activation maps for **mental arithmetic**. Subjects estimated distance of incorrect results to correct multiplication products. **C:** Functional similarity using **MI** is shown for *three* experimental phases for three subject groups: Dyscalculic subjects (red) seclude throughout all phases from controls (blue) while Dyslexic subjects (green) deviate solely during reading - even though digits are shown, and not words or letters. Neuropsychological attributes utilized as covariables facilitate separability between subjects.[6,8,16]

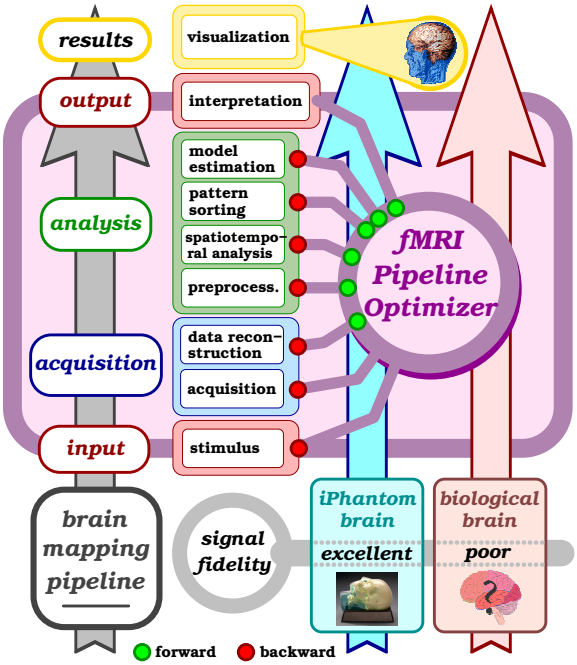
1. **Longitudinal studies** of cognitive performance through serial measures in:
   Alzheimer's disease, schizophrenia, multiple sclerosis, brain development and aging.

2. **Population studies** with medical, genetic or cultural emphasis for:
   effective treatment regimen, drug development, twin research, learning disability.

3. **Research studies** to improve cognitive experiments and design parameters:
   working memory, task severity, conflict resolution, task switching cost.

7. BSI A Pipeline Solution

Innovative as the **BSI** technique is, it is also just part of a complex machinery where technical synergism is essential. The system decisively benefits if the internal links are tuned and optimized throughout the brain mapping pipeline. **BWMRC**, the new MRI Research Center at Brigham and Women's Hospital and Harvard University in Boston is the home for **BSI** where the technique was developed by Firdaus Janoos, Raghu Machiraju (OSU) and István Mórocz. The center houses four research MRI scanners, a robust implementation of **BSI** in software and hardware and expertise in cognitive brain mapping and experimental design.

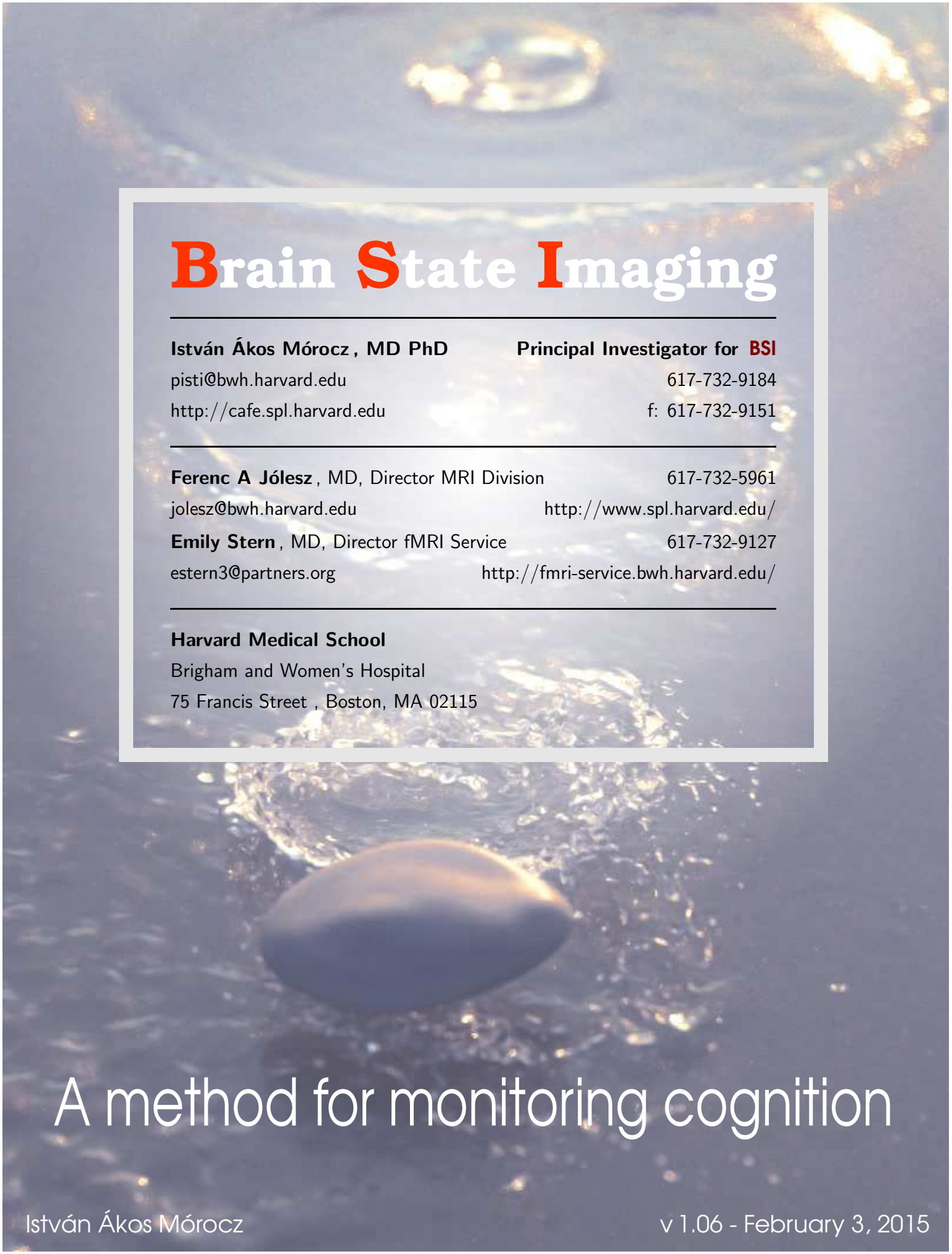


8. Collaboration and Outlook

The **BWMRC** is a hub for *translational* collaboration in large-scale population studies of mental health and research projects in cognitive brain mapping and neuropharmacology. Our partners are in both academy and industry where the prime goal for **BSI** is to provide the neurobiological means for quantitative monitoring of cognitive integrity in humans.[6,8,9]

Bibliography

1. Smith, K. *Nature* **478**, 15 (2011).
2. Schwab, M. E. & Buchli, A. D. *Nature* **483**, 267–268 (2012).
3. Abbott, A. *Nature* **499**, 272–274 (2013).
4. Koch, C. *Consciousness. Confessions of a romantic reductionist* (MIT Press, Cambridge, MA, USA, 2012).
5. Satel, S. & Lilienfeld, S. O. *Brainwashed: The Seductive Appeal of Mindless Neuroscience* (Basic Books, 2013).
6. Mórocz, I. Á. *et al. Int J Imaging Syst Technol* **22**, 81–96 (2012).
7. Janoos, F. *et al. Computer Graphics Forum IEEE-VGTC* **28**, 903–910 (2009).
8. Janoos, F., Machiraju, R., Singh, S. & Mórocz, I. Á. *Neuroimage* **57**, 362–377 (2011).
9. Janoos, F., Wells, W. M., Mórocz, I. Á. & Brown, G. G. *Psychometrika* **78**, 279–307 (2013).
10. Buzsáki, G. *Rhythms of the brain* (Oxford University Press, Inc., New York, NY, U.S.A., 2005).
11. Turk-Browne, N. B. *Science* **342**, 580–584 (2013).
12. Gross, C. G. *Neuroscientist* **8**, 512–518 (2002).
13. Calhoun, V. D., Liu, J. & Adali, T. *Neuroimage* **45**, S163–S172 (2009).
14. Lehmann, D., Strik, W. K., Henggeler, B., Koenig, T. & Koukkou, M. *Int J Psychophysiol* **29**, 1–11 (1998).
15. Lehmann, D., Pascual-Marqui, R. D., Strik, W. K. & Koenig, T. *Neuroimage* **49**, 1073–1079 (2010).
16. Janoos, F., Singh, S., Machiraju, R., Wells, W. M. & Mórocz, I. Á. *Inf Process Med Imaging* **22**, 588–599 (2011).
17. Mitchell, T. M. *et al. Science* **320**, 1191–1195 (2008).
18. Norman, K. A., Polyn, S. M., Detre, G. J. & Haxby, J. V. *Trends Cogn Sci* **10**, 424–430 (2006).
19. Janoos, F., Li, W., Subrahmanya, N., Mórocz, I. Á. & Wells, W. M. In *Advances in Neural Information Processing Systems (NIPS) 25* (eds. Bartlett, P., Pereira, F., Burges, C., Bottou, L. & Weinberger, K.), 683–691 (2012).



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