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Budapesti Műszaki és Gazdaságtudományi Egyetem
Gazdaság- és Társadalomtudományi Kar
Pszichológia Doktori Iskola

Evidence of Neural Recruitment in functional MRI

PhD thesis

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Abstract

This PhD thesis is about methodologies applied in functional magnetic resonance imaging that have profound implications for cognitive brain mapping studies in humans.

I present four published theses and scrutinize the experimental paradigm chosen and the fMRI techniques applied for image acquisition and analysis. Healthy participants and subjects with neurological conditions participated, the experiments included various cognitive tasks, the paradigm types were of block–design or event–related design, data acquisition relied on 2D multi–slice and 3D imaging techniques, and data analysis comprised of customary correlation of the fMRI signal with model curves in the general linear model framework.

The resulting activation maps comprehended solid foci in numerous brain regions. Nevertheless, the maps appeared in view of the complexity of the associated mental processes as oversimplified and static reflections thereof. Following this logic the slow data acquisition rate in fMRI proved as the single–most inimical limitation to cognitive imaging.

Subsequently I summon principles that shall harmonize the synergistic interplay between paradigm design, scanner technology and analysis method. The approach shall fathom out both spatial and temporal information that is intrinsic to and embedded in the BOLD fMRI signal. The final goal is to gain

knowledge about the multi–focal but hierarchic cascade of neural recruitment in a thought process. An exact description of activation trajectories and time–resolved functional connectivity will then facilitate in distinguishing healthy from irregular patterns of dynamic brain states, and in a more general perspective, in delineating the neural circuitry of human cognition.

Introduction

A device as complex as the human brain will at any given point in time reckon in the vast majority of areas that are available in its computing substrate. These areas interconnect locally, regionally and remotely via axonal pathways in the white matter, but other lesser known or even unknown cellular, physiological, physical and chemical mechanisms likely contribute further to the functioning of this machinery[3]. Common tomographic imaging methods are very inept at capturing the brain's temporal agility at the neurovascular level[27,36,44] with deleterious consequences: interpretations based on current acquisition and analysis methods consider necessarily very few time points in an arguably *rich* neural recruitment tree. Activation blobs resulting from interpolation and averaging at best represent one or two stations in the functional cascade associated with a mental trigger. Subsequent inferences, blinded by such a large but epiphenomenal effect[9], may be *oversimplified* and overlook the underlying source of a neurological condition.

There is a maturing agreement in the community that the signal changes, we are interested in verifying through imaging, correspond to rather long episodes of up to several seconds of coherent oscillatory bursts within neural networks[45,46] which mirror focal brain activations following cognitive enrollment. The fluctuating oxygenation rate in the local capillary bed appears

to reflect with enough fidelity the metabolic demand of the underlying oscillating neural system[27,29,36].

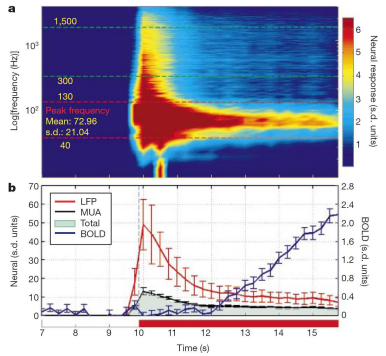

Fig. 1 Correspondence is shown between fMRI BOLD signal and field potential measures in the primate visual cortex. Gamma frequency demonstrates best temporal correlation with BOLD effect.[27]

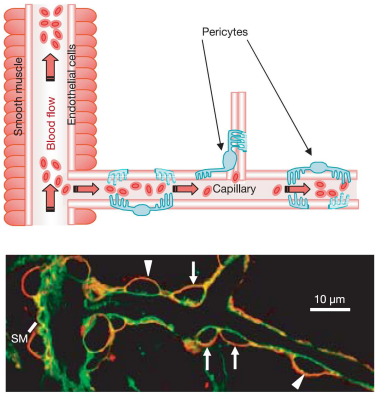

Fig. 2 Capillaries are capable of regulating their vessel diameter rapidly, and therefore are in the position to herald via the BOLD contrast mechanism swiftly neural activity that occur in neighbouring neuronal cells.[39]

Imaging

MRI machines are highly flexible tools and offer a great variety of imaging modalities which permit in a given case to fine-tune not only settings of machine parameters but even the types of pulse sequences used which differ in fundamental physical properties. The principal acquisition technique applied nowadays in functional neuroimaging is T_2^* or BOLD sensitized two–dimensional echo–planar imaging (2D–EPI). An important factor to consider is the order of slice acquisition in a stack of slices, which is usually done in an interleaved fashion. The consequence

for neuroimaging is that with 2D–EPI a significant time discrepancy is introduced between slices that needs to be accounted for during spatial and statistical processing further down the analysis processing pipeline. As data acquisition techniques become faster, the slice timing problem will turn out detrimental if the purpose of the fMRI experiment is the study of temporally resolved hierarchic road–maps of event–related brain recruitment.

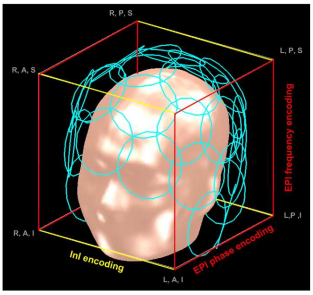

Fig. 3 EVI : The 3D InI spatial encoding scheme implemented using a high–density 32-channel array of coils.[25]

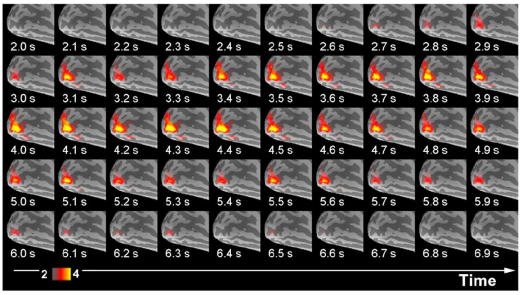

Fig. 4 EVI : Succession of single frames of the InI dSPM t–values in visual cortex averaged across five participants. Temporal interval between frames was kept at 100 ms.[25]

A stack of image slices can be acquired as a true three-dimensional slab (3D–EPI and EVI) where total acquisition time per volume corresponds to number of slices $\times$ the time needed for one slice. These slabs may be acquired in *multi*–shot or in *single*–shot fashion. In order to reduce the 3D–volume scan time and the related accumulation of artefact signal a plethora of speed-up techniques were proposed over the years such as the echo–shifted PRESTO technique[16,35,48], parallel imaging techniques using multi–coil RF arrays[7,16,21], *sub*–sampling techniques that come to play in the image reconstruc-

tion phase [15,16,22,28], and nowadays for ultimate acceleration the *single*–shot techniques that acquire full–brain data sets in a fraction of a second like EVI and INI [25,40] or OVOC (one-voxel-one-coil)[19].

Analysis techniques

The analysis of imaging signal data sets for the study of the inner workings of neural networks will require the development of non–traditional novel statistical tools different from those used nowadays for functional neuroimaging. The conventional, but at the same time perhaps most powerful way to test for simple signal changes - we shall call here 'activations' secondary to stimulus triggers - is the hypothesis-driven correlation analysis where a model curve, convoluted with an input response function, is compared to the measured fMRI signal on a voxel–by–voxel basis. This function, frequently a hemodynamic response function (HRF, composed of two gamma functions)[1], models for a fix period of time the hypothetical signal secondary to a neural response. A fundamental limitation of the HRF method, however, is its weak sensitivity for the relative and absolute temporal engagement of focal contrasts of interest which renders our ambition futile in computing, based on ordering principles, hierarchic and temporally resolved activation maps.

The *F*inite *I*mpulse *R*esponse (FIR) function on the other hand has the advantage of analysing data in time–bins and pre-

senting the resulting activation maps at a finer grained temporal resolution - which evidently depends directly on the acquisition frequency - and still be a hypothesis driven method, while at the same time remain entirely assumption–free regarding the temporal characteristics of the shape of the neural responses.

A fundamentally different approach is to apply assumption-free methods where signal characteristics intrinsic to the data determine outcome of the analysis. A prominent candidate, the *I*ndependent *C*omponent *A*nalysis (ICA) of the voxel BOLD signal time course, produces components with temporal and anatomical distribution maps for maximally independent signal properties that may be shared across voxels or clusters.

Compilation of Theses

The following four theses shape the main scope of this work where various functional MRI techniques were used as the principle measure for characterizing metabolic effects in cognition. The aim is to compile the experiences I gained from these four theses and to present them to the community. The four theses share one common quality : It is the definite temporal rift between the expected swiftness of brain responses and the sampling rate their brain data was acquired at. It is the relative under–sampling thereof that is the common undesired denominator among the four theses. This under–sampling is also the principal point of my discussion that raises by its very existence a flurry of daunting questions about the completeness of commonly computed brain activation maps - questions that evidently are not simple to address.

Thesis I Aurae in Musicogenic Epilepsy.[32]

This fMRI study is about the characterization of epileptic aurae, a neurological condition induced by prolonged exposure to the seizure invoking stimulus, a musical tune the patient is familiar with. During epileptic aurae initiated by the stimulus, signal increases were found in the left anterior temporal lobe, correlating with ictal EEG and SPECT showing a left anterior

temporal focus, and the right gyrus rectus. Because fMRI indicated the onset of a recruitment cascade within the ventral frontal lobes, we think the left anterior temporal lobe activity could be secondary to a right gyrus rectus focus, possibly triggered by emotional processing of the epileptogenic music.

A very simple block paradigm was applied in order to accommodate for the technical restrictions. In fact, each paradigm was repeated ten times and consisted of only two blocks of 39 s length. In this respect it is surprising that equivalents of seizure foci were traceable as well as the biological effects of music exposure. Moreover, the very slow scanner repetition time of 5 s was sufficient to pick up the BOLD contrast based signal changes which may be related to the slow nature of the neurological phenomena studied. In a more ideal scenario a faster scanner combined with a prolonged and multi-cycle paradigm may ultimately reveal a much richer picture about brain areas that get stimulated by musical appreciation[42,43,50].

Thesis II Reading Acceleration in Dyslexia.[20]

The neurobiological basis of reading training and the beneficial effect of accelerated reading was studied in subjects with developmental dyslexia. It was observed in earlier studies that reading 'automatizes' to a certain extent without curtailment in accuracy if reading material are presented at a faster pace than

the normal routine. Corresponding with the theory, *fast* presentation rates for reading *non-words* did not differentiate the two population groups. However, and perhaps contra–intuitively, *slow* presentation rates did, and stimulated in control subjects stronger the visual areas, while in dyslexic subjects a relative signal increase was shown during grapheme–to–phoneme conversion for the left BROCA's area and operculum.

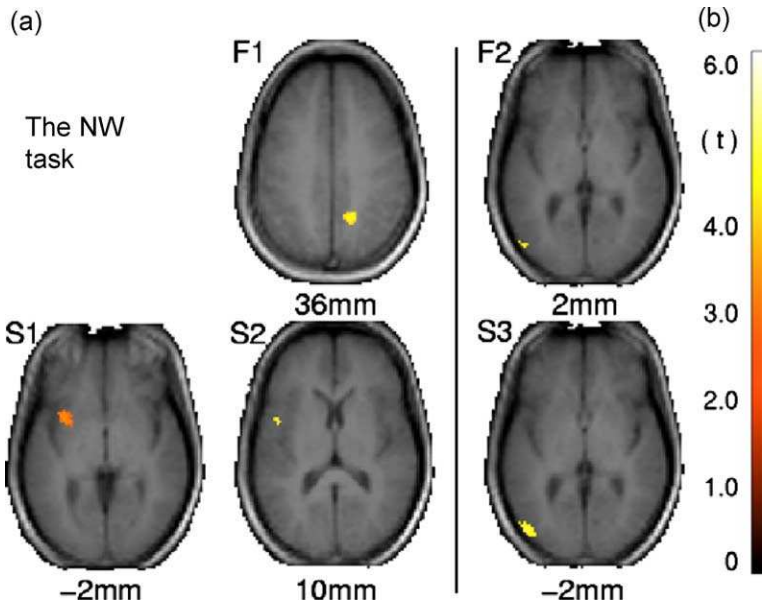

Fig. 5 Brain regions in which differential responses were evoked in the *nonword* task in the two reading groups: (a) dyslexic>control readers; (b) control>dyslexic readers. (F1, F2) fast stimulus presentation rate ('fast' condition); (S1, S2, S3) slow stimulus presentation rate ('slow' condition). Axial slice level is indicated by the z (mm); $z = 0$ is the AC-PC line. The t-score threshold was at $p < 0.05$ corrected for multiple comparisons. The color bar represents the t-score range.

Only two blocks of the same stimulus type were contrasted to three baseline blocks within the very same scan which renders the design inherently susceptible to drifts and oscillatory artefacts. Importantly, the comparison between stimulus types is done *across* fMRI runs. It is not unlikely that also the *fast* condition would reveal differences between the two population groups had we applied cautiously a more elaborate, *mixed* and *event-related* paradigm design with *longer* scan runs. It would help to reduce the aforementioned artefacts. At the same time it could reveal a far richer activation pattern, and with that render a more realistic scenario about brain recruitment during reading even in developmental dyslexia. A detailed map about sequential brain involvement would increase chances to eventually point out faulty trajectories in developmental learning disabilities like dyslexia.

Thesis III Reading an Artificial Script.[2]

In neuroimaging studies of word reading in natural scripts, the effect of alphabeticality is often confounded with the effect of practice. An artificial, *Morse*–like scripting system was studied in order to explore separately the effects of practice and alphabeticality following multi–session training with and without explicit letter instructions : The *explicit* condition involved training with letter decoding instructions, the *implicit* showed

whole words without instructions, while the *arbitrary* condition presented non-sense words. After training fMRI scans were acquired for reading of trained words and novel words. In short, the left posterior inferior frontal gyrus (IFG) showed greater response for *novel* words in the well-trained (*explicit*) condition. This effect was interpreted as evidence that this brain area plays a role in decoding letters, it does the more, the less familiar the stimuli, hence words, are.

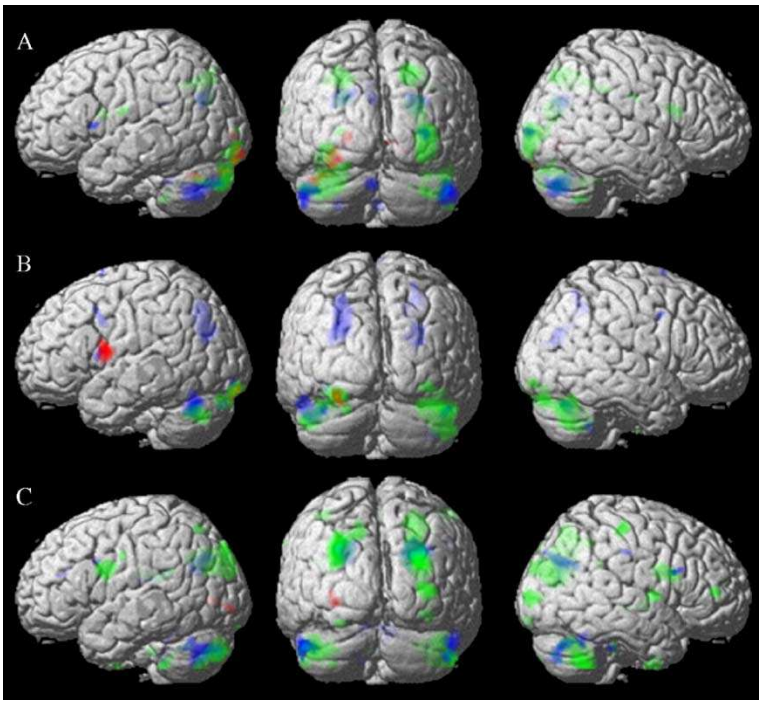

Fig. 6 Brain regions showing activation in the *Explicit*, *Arbitrary* and *Implicit* conditions, in *trained* words (A), word-transfer *novel* (B) and symbol-transfer (C) items.

The stimulus onset asynchrony (SOA) is lavish and hence nu-

merous brain scans (TRs) do capture the time course of each event. In theory more than one haemodynamic response function (HRF) could model for activation foci and the associated cognitive effects but this is still problematic in practice due to the quite long time course of the HRF curve. Alternatively, a FIR-based analysis approach may seclude the SOA time course into small time bins - but then again harms the rather slow TR of 3 s such efforts. In sum, in order to extract interesting maps of sequential neural recruitment - like in this scenario it would be a highly desirable analytic undertaking to reveal neural roadmaps of cognitive involvement while solving this tantalizing task - it will be an absolute necessity to run the data acquisition machinery at a magnitude *faster* pace.

Thesis IV Schizotypal Personality Disorder.[10]

A cardinal feature of schizotypal personality disorder (SPD) is language abnormalities. The focus of this study with neuroleptic-naïve subjects was to determine whether there are processing abnormalities for pure tones differing in pitch and duration in SPD. The fMRI study was originally designed as a *block-design* experiment where the subsequent GLM analysis in traditional block–design fashion *failed* to reveal differential activation for the conditions containing tone deviant *off*-stimuli. A *parametric event-related* analysis approach luckily did disclose the expected

contrasts where pitch deviant tones elicited in people with SPD an overshoot of BOLD response in both auditory cortices.

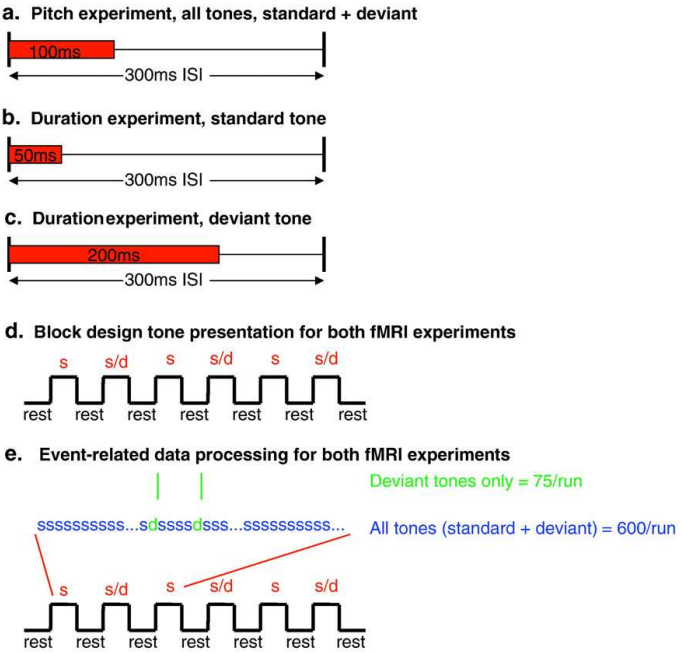

Fig. 7 Stimulus presentation and processing. (a) For the pitch experiment all tones are 100 ms in duration followed by 200 ms of silence. (b) For the duration experiment, the standard tone is 50 ms in duration followed by 250 ms of silence. (c) For the duration experiment the deviant tone is 200 ms in duration followed by 100 ms of silence. This variation decreases the expectancy factor. (d) Tones were presented in block design. (e) Hemodynamic response curves were generated for all tones together (both standard and deviant, all tone condition) and for only the deviant tones (deviant condition). ISI = interstimulus interval; ms = milliseconds; s = standard; s/d = standard and deviant tones intermixed; rest = silence.

On may call this result somewhat fortunate considering the unfavourable ratio between scanner pace and stimulus delivery frequency. Still, had been these two frequencies more in tune, the outcome of this analysis and also those of the three previously discussed theses could have become considerably richer and more multifaceted, or in other words, simply more informative - a feature not to neglect in view of expectedly complex cognitive responses to startling events[5,41] like such pitch-deviant tones.

Discussion

A cardinal goal in this our field of functional brain mapping is to unveil cascades of neural recruitment that underlie cognitive thought processes and which are embedded in signal time–course patterns and are hence in principle deducible from the temporal and spatial spectra of fMRI data.

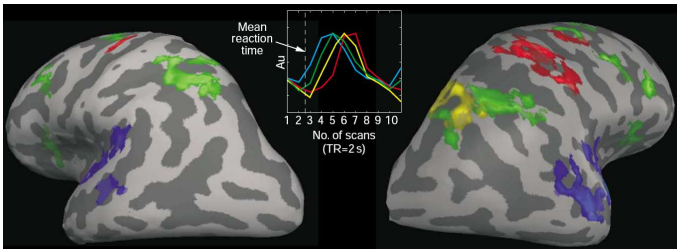

Fig. 8 Example of a complex *serial* task in mental chronometry during a visuo-spatial mental imagery. Analysis is based on ICA of fMRI data. Different colors are derived from different ICA components: (blue) for auditory and language regions, (green) mainly left PPC, (yellow) right PPC in IPS, (red) sensori-motor regions.[12]

Mental processes are short–lived phenomena in the range of tens or hundreds of milliseconds[3]. Common tomographic imaging methods do injustice to time by neglecting the brain's temporal agility[9,49] at the neurovascular level[36,44]. Not surprisingly do interpretations based on current acquisition and analysis methods consider very few time points only: Activation blobs resulting from interpolation and averaging at best represent one or two brain stations in a arguably rich neural cascade. Inferences, blinded by such epiphenomenal effects, may be oversimplified.

A comprehensive cognitive roadmap about neural recruitment requires high enough sampling rates during data acquisition. The effects we are looking for, *i.e.*, BOLD signal changes, are primarily metabolic equivalents of oscillatory electrical phenomena called 'gamma bursts' (Figg. 1,9) that resonate in unison[38,49] at around 40 Hz for about 50 to 5000 ms[4,11,27,49]. The hemodynamic response turns out to be less sluggish than long assumed (see page 4 and Figg. 1–2): capillaries and arterioles change their vessel bed diameter within 50-100 ms following neuronal activity in their neighbourhood[26,27,39,47].

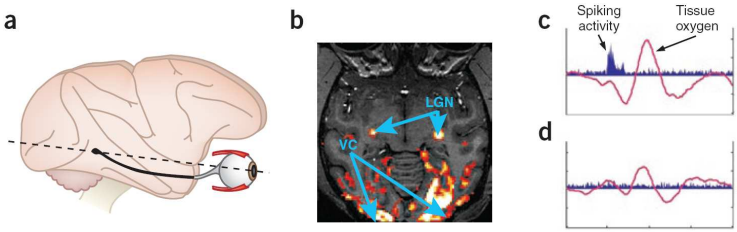

Fig. 9 Evidence is shown that local field potentials are plausible to characterize high frequency perisynaptic spiking activity (c) which correlates best with the observed BOLD signal time course.[26]

Technical advancements of the last few years raise hope that some limitations of fMRI techniques will be addressable soon. For example the slice timing problem between 2D EPI slices, acquired as a 3D stack, is a serious hindrance for accurately comparing the onsets among activation foci (page 5). New super-fast single-shot techniques (page 7) [19,25,40] are a necessity for investigating the internal schedule within activation trees where foci are likely distributed over time and throughout the entire brain.

An impression about the complexity of spatial and temporal evolution among activation foci can be found on page 20 (Fig. 11).

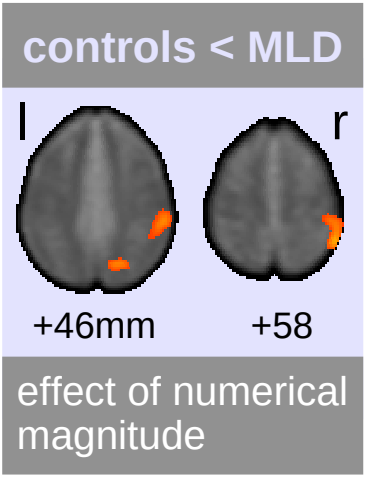

Fig. 10 Standard activation map of mental arithmetic comparing subjects with and without MLD (mathematical learning disability). The **HRF** analysis reveals mainly *one* large confluent activation blob in the **right intraparietal sulcus** in subjects with MLD. A stronger working memory effect for numerical magnitudes is observed in MLD while solving of multiplication and estimation problems.[34]

There exist most distinct approaches for interpreting recorded equivalents of neural responses like nowadays the BOLD signal time course. Not surprisingly do the resulting maps and the associated attempts for their elucidations vary wildly and rather concerningly. For example, the true problem for many subjects with MLD (Mathematical Learning Disability) may not reside solely in the **right intraparietal sulcus**[8] (see Fig. 10 for HRF analysis) but instead perhaps in the **right cerebellum** seconds earlier within the activation cascade (see Fig. 11) where neural networks in healthy subjects may contribute as hyperfast assessors of numerical magnitudes for the successful solving of a mental multiplication task[31,33,34].

Analysis concepts change over time as knowledge accumulates[14]. It is likely that in the future *machine learning* algorithms and *multivariate pattern classifiers*[17,18,30,37] will super-

sede the customary region and voxel–based understanding of the BOLD response and introduce the rather new principle of brain states[23,24] which in their entirety make up the temporo–spatial signature space of task units the brain solves over time.

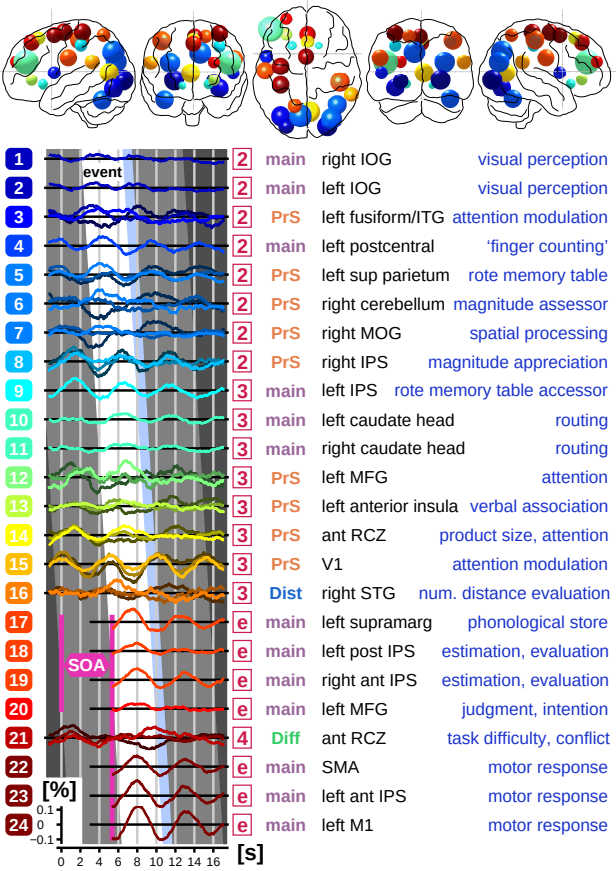

Fig. 11: Hierarchic cascade of brain activations during mental multiplication and estimation in healthy controls. Time courses were computed with an event–related time–shifted signal averaging technique. The white diagonal depicts temporal drift over time of phase for one arithmetic event, where top reflects the event's beginning, and bottom the event's end. Colors of boxes with white digits correspond in time with colors of spheres in the glass brains at figure top.[33]

In such a new feature space, built from fingerprints of brain states, may the physiological presumptions, e.g., about the dynamics of the neuro–vascular coupling in the BOLD signal, loose their traditional meaning while instead descriptors for short–lived holistic brain signal patterns could serve as *abstract labels for neuropsychological microstates*[23,24] that were thought to exist for long time in the literature[4,6]. In this respect becomes apparent the detrimental relevance for taking into sincere consideration the fine–tuned, synergistic and yet fragile interplay between neuro–behavioural paradigm design, image acquisition machinery and the subsequent analysis strategy in order to arrive at meaningful and intelligent, hierarchically organized functional roadmaps of neural recruitment that characterize thought processes. Otherwise the outlook on the temporal aspect of the functioning of the neural circuitry in complex cognitive tasks[4,13,24,33] may never surface, may be *hidden* entirely and consequently neglected simply. The individual links *per se* in the long chain of refined fMRI techniques may play a tune in their own sophisticated scientific framework, but only unison, in the *multidisciplinary* concert with the other methods together, will they lead to the überproportionate breakthrough and quantum leap needed in neuroscience in order to probe for the temporal *orchestration* of active brain areas which are in essence oscillating electrophysiological networks *transiently* interconnected in human cognition.

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