

# **Capturing “Trial-to-Trial” Variations in Human Brain Activity: from Laboratory to Real World**

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## **Part One: Variability and Context**

### *Ubiquity of Variations*

Variations in the patterns of human behavior under seemingly identical conditions can be observed across a diverse range of human activities. Glenn Gould's performance of the same Goldberg's Variations at the beginning and near the end of his career differed significantly. Professional basketball players cannot guarantee the success of every long shot in their career. During an uneventful week, one does not rise with the same feeling of freshness and alertness. Children raised in the same family can become distinct individuals displaying little resemblance to their siblings with respect to attitudes and capabilities. The same traumatic event does not result in the development of post-traumatic stress disorder (PTSD) in every individual. Facing the same school challenge, some students rise to the situation while others fall apart. The same food can evoke opposite responses at the beginning or and end of a meal. A first drive along an unfamiliar road can be perceived as amazingly long while the drive seems surprisingly short the second time around. A worker on an assembly line intends to reproduce the same action sequence yet mistakes are made on repetitions. In laboratory experiments, a subject is instructed to respond as fast as possible to the onset of a stimulus, yet the response time is not identical over repeated trials. It is obvious that across what appear to be

repeated “trials” of similar events, the unique context of *each instance* serves as a source of variability creating a wide range of human experiences.

### ***Causal Inference and Removal of Context***

The scientific method as taught in today’s academic institutions has as its explicit goal the establishment of causal relations between two variables, lets call them X and Y (Rosenthal and Rosnow 2008; Rosnow and Rosenthal 2008). The simplest, and also a limited way of evaluating causality, has been to observe Y under an experimental (E) and a control (C) condition, each of which corresponds to one level of X. Students, thus trained, hope to support causality by demonstrating a sufficiently large difference *on average* between the E and C conditions across many units of sampling. Using this framework, variation across sampling units is considered noise to be “overcome” by a sufficiently large effect of X via averaging. Implicit in this approach to causality is the assumption that the ***only*** worthy finding is in the form of a *general* law that X causes Y regardless of the context.

A more sophisticated way of establishing causality while considering context in a limited number of dimensions is via the method of n-way analysis of variance (n-way ANOVA) (Fisher 1962). Using this framework, the causal relation between X1 (factor 1) and Y is context-dependent upon particular levels of multiple variables X2, X3, ..., Xm (factors 2, 3, ..., m). If the causal relation between X1 and Y is dependent upon particular

configurations of  $X_1$ ,  $X_2$ , and  $X_m$  levels, then the  $n$ -way *interaction effects* should be sufficiently large in comparison to the variation of sampling units within each of the conditions. Thus, variability across the sampling units within each of the conditions is once again treated as noise to be removed via averaging. The specific context under which the observation of each sampling unit is made is once again not only ignored but removed.

In both cases, in pursuit of causality from  $X$  to  $Y$ , one would forgo the opportunity to characterize the remaining variation across the sampling units along unspecified dimensions and forgo the attempt to understand their possible functional significance. Side effects of this intense focus on establishing causality between known variables may be: (1) a false sense of generalizability of the causal relation; (2) a lack of sensitivity to the possibility of context-dependency outside of the manipulated dimensions; and (3) a strongly held misconception that all interaction effects between multiple variables  $X_1$ ,  $X_2$ , ...  $X_m$  are trivial extensions of the effects due to  $X_1$ ,  $X_2$ , ... or  $X_m$  *alone*, i.e., interaction effects can be inferred from experiments where only a *single* variable  $X_i$  is manipulated.

The significance of such unintended side effects is a prevailing tendency, that often goes undetected, to over generalize: generalizing a causal relation, initially found within a very narrow range of circumstances, to situations involving different contexts (Kagan 1996).

### ***Return of Context and Alternative Forms of Inquiry***

Against the background of this mainstream approach to scientific inquiry, the significance of context, within which causal relations should be investigated, has been slowly receiving attention. When the skin of the sea slug *aplysia*, is stimulated by a constant force, the populations of single neurons within the abdominal ganglion show highly variable patterns of responses from one touch to another such that a given single neuron may or may not participate in responding on a particular trial of stimulation (Wu et al. 1994). When *aplysia* displays a decrease in the gill withdrawal response, not all of the neurons decrease their firing rate---some show increased, while others show decreased firing rates (Falk et al. 1993). A simple averaging across neurons showing opposite response patterns would lead to the false conclusion that no change in firing rates during a habituated gill withdrawal response was present.

When a rodent neocortical neuron, maintained in isolation, is stimulated by a fixed stimulus of fluctuating current injection, the temporal pattern of the resulting spike train appears to be rather stable. Yet trial-to-trial variations in spike-timing of neocortical neurons can be up to 20 ms (Mainen and Sejnowski 1995) and under the influence of major neuromodulators, such trial-to-trial variations may further increase (Tang, Bartels, and Sejnowski 1997). As it turns out, a spike timing difference of

a few milliseconds can result in qualitative differences in how synapses adjust their strength according to experience. If the pre-synaptic neuron's firing precedes that of the post-synaptic neuron, the synapse is strengthened and if the order reverses, the synapse is weakened (Markram et al. 1997). This appears to be the case not only *in vitro* but also *in vivo* (Fu et al. 2002). The criticality of relative timing of events indicates that the impact of one event cannot be determined by that event alone and that the context plays a critical role.

At the level of large ensemble network activity, an electroencephalography (EEG) study showed that behavioral reaction times are correlated with trial-to-trial variations in the phase relation between the presentation of a visual stimulus and on-going EEG oscillations (Makeig et al. 2002). This finding suggests that the precise phase context is important for subsequent sensory-motor integration. Such a finding is considered “suggestive” because, the phase relation was not manipulated as an independent variable, instead, merely co-varied with the dependent variable, reaction time. Findings of similar sorts are often criticized for “being merely correlational” and hence dismissed by some investigators. In a memory study, variations in the on-going EEG immediately before the presentation of an item to be remembered have been shown to affect how well the item will be recalled later (Otten et al. 2006). Once again, trial-to-trial variations in the on-going EEG offered the critical context

within which variations in memory formation could be explained.

Together, these two studies demonstrate that on-going EEG context can not only affect the immediate sensory processing but also influence subsequent memory formation. Although the origin of these trial-to-trial variations cannot be ascertained within these experiments themselves and the causal relation between the context and the processing outcomes are suggested via “correlational” instead of “experimental” data, the findings nevertheless offer significant value as they serve to characterize cognitive processes in relation to their rich context.

## **Part Two: Capturing the Context of Brain State**

### ***The Context of Cognition***

Perception, action, emotion, and thoughts occur within the rich context of our immediate environment and our past history. Such a rich context lies within a world of unlimited dimensions, in which individual human lives differ in their infinite subtleness. One way to understand the effect of such a rich context is to isolate one dimension or a few dimensions at a time and investigate their specific impact using the “experimental” methods that afford strong causal inferences. An alternative approach is to consider first that the brain is the center of information processing, thus its state at or near the time of such processing must provide highly relevant contextual

information for predicting outcomes, as was illustrated in the two previously described EEG studies. Therefore, an alternative form of inquiry may be to begin with identifying reliable associations between the outcomes of information processing and the moment-to-moment measure of brain states in dimensions higher than those manageable by typical factorial designs used in experimental approaches.

### ***Measuring Brain State with High-Density EEG***

EEG is a mature technique for measuring electrical brain activity non-invasively from sensors directly attached to the scalp (Niedermeyer and Lopes da Silva 2004). The development of high-density electrode arrays in the form of a cap brought this old technology into the arena of brain imaging (Holmes, Brown, and Tucker 2005). With its millisecond temporal resolution, EEG outranks functional magnetic resonance imaging in its capability of discriminating neural events that differ by a few milliseconds. The introduction of two blind source separation (BSS) methods to the analysis of high-density EEG data (Makeig et al. 1997; Tang, Sutherland, and McKinney 2005b) makes the intractable problem of source localization with EEG tractable. For example, using the well-characterized human primary somatosensory cortex (SI)'s response to median nerve electrical stimulation as a “benchmark”, the cross-subject variability of the estimated SI location is within only a few millimeters (Tang, Sutherland,

and McKinney 2005b; Sutherland and Tang 2006). Such tight spatial clustering across different subjects is at least comparable, if not surpassing what is attainable with magnetoencephalography (MEG) (Mauguiere et al. 1997)

### ***From a Sensor-Based to a Source-Based Language for Brain-State Characterization***

Prior to the introduction of BSS methods, the language available for describing brain states was based on the readings from EEG sensors. An EEG researcher may describe a pathological pattern of brain activity in terms of the left frontal (F5) *electrode* for example (Rugg and Coles 1995). A potential problem with this language is that the activity recorded at that frontal electrode is by no means a reflection of only frontal lobe neural activity. The same electrode may be influenced by electrical activity originating from posterior parietal lobe as well as activity associated with eye movement and eye blinks. Thus, it could be argued that without an effective method to translate the sensor-based description to a functional-neural-source-based description, one simply does not have an adequate language for characterizing the functionally relevant context of brain states.

A second problem with this sensor-based language is that over repeated recording sessions and across different subjects, the precise location of the

sensors relative to the underlying neural structures would be highly variable. Because the neocortical tissues are folded, a small change in electrode location can cause a large change in what signal sources are being recorded at a given electrode. Using such a sensor-based language, it is possible that the F5 sensor could end up measuring activity from different brain regions across different recording sessions with the same individual or between two different individuals.

With the aid of BSS methods, now it appears possible to overcome these problems by the arrival of a new language that describes the brain state in terms of millisecond-to-millisecond variations in brain electrical activity originating from *functionally distinct* and *anatomically specific* brain regions.

### **Part Three: Recovering Neuronal Sources Using SOBI---Validations and Proper Usage**

If new technical advances are available, why is it the case that the evolution from a sensor-based to a source-based language has been so incredibly slow since its initial introduction? While there are many barriers to the rapid adoption of any new language, one key barrier here may be a relative lack of validation that would convince the long-time users of the old language that this new language: (1) does offer something different from other previously

described methods, such as principle component analysis (PCA); (2) does provide signals from functionally distinct and anatomically specific brain regions; (3) has a clear internal logic that can be communicated to its users; and (4) comes with a “instructional booklet” that provides streamlined processing and a declaration of all key parameters critical for its proper usage.

Because the algorithm developers tend to focus on the mathematics of the algorithms and speak a language that is unfamiliar to the typical EEG user, and because each data domain has its own unique issues critical for the algorithms’ proper usage, there has been an unfulfilled need for methodological papers that connect the world of algorithms to the world of neuroscience and clinical science application. Below, we will summarize how we have attempted to deal with these issues through our own experience with one particular BSS algorithm, the second-order blind identification (SOBI) algorithm (Belouchrani et al. 1993; Belouchrani et al. 1997).

### ***Validating Using a Common Noise Source***

The word “validation” in the world of source modeling typically means validation using simulated source data that are generated using a known source model with various assumptions made about characteristics of the true neuronal sources. A source separation algorithm is often considered

validated if the simulated sources are properly recovered. This approach wins with the merit of knowing the signal generators but loses on the drawback that the model sources may not adequately represent the real neuronal sources; therefore the validity of the algorithm for separating real neuronal sources cannot be inferred necessarily from the successful separation of sources contained in the simulated data.

We attempted to overcome this drawback by taking advantage of a known source from a typical EEG experiment. That is, the so-called noisy-or bad-sensor. It is considered known because the location of the noisy-sensor can be verified independently from the source separation algorithm by visual inspection of the raw data channel by channel. This is how EEG researchers identify the “bad” sensors independent of any source separation algorithms. For example, in Fig. 1 (Tang, Sutherland, and McKinney 2005b), we know the spatial location of the noisy-source because visual inspection of a brief 200 ms window of continuous EEG waveforms indicates that one particular sensor (boxed) contains an unusually high amount of 60 Hz noise. This known bad-sensor location matches the location of a SOBI-recovered source (Fig. 1B) that contains predominately 60 Hz waveforms (Fig. 1C, blue waveform). Notice the contrast between the recovered source waveforms and those from the raw sensor (Fig. 1C, red), which is a mixture of 60 Hz activity and other brain-related signals as well as signals from other possible noise sources. These observations

serve to confirm that SOBI is indeed able to separate out signals associated with at least one bad sensor correctly.

Now one may ask, what about more than one simultaneously present bad sensor, and what if some noise sources are shared among multiple electrodes as a result of unintended bridging among neighboring electrodes due to excessive gelling. To simulate this situation, we artificially created noisy-sources across multiple electrodes by simultaneously touching the interior of the electrodes with a blunt needle. Fig. 2 shows that the recovered source locations match the known locations where the noise was intentionally “injected” and the time courses from the recovered sources also matched those directly recorded at the touched sensors (Tang, Sutherland, and McKinney 2005b). Therefore, SOBI is able to simultaneously recover multiple overlapping noise sources.

### ***Distinct SOBI Results in Comparison to PCA***

PCA is an algorithm most commonly used for dimension reduction when working with high-dimensional data. Applications of BSS algorithms and PCA to EEG data both involve the use of linear transformations of signals from the original *sensor space* to a space defined by a new set of axes. We investigated whether the axes identified by SOBI differ from those identified by PCA. Once again we take advantage of the known 60 Hz noise-source (Fig. 3AB, Tang, Sutherland, and McKinney 2005b). PCA is

often available as a built-in option within commercially available EEG data analysis software and easily generates components containing 60 Hz signals but the “purity” of the PCA-recovered 60 Hz source is questionable as the power spectra of a PCA-recovered source indicated the presence of non-60 Hz signals within this recovered source) (Fig. 3C). In contrast, the power spectra of the SOBI-recovered noisy-source showed a clear narrow peak centered at 60 Hz (Fig. 3D). Therefore, while SOBI does an excellent job at isolating this type of noise source, PCA is not able to isolate it well.

It should be noted that the recovery of such noise sources does not need *any* manual page-by-page pre-processing prior to SOBI application if the EEG data are collected using normally functioning amplifiers. In contrast to InfoMax ICA which requires pre-cleaning of data (Delorme and Makeig 2004), all SOBI separation results presented in this chapter are a result of direct application of SOBI to raw unfiltered, non-epoched, non-baseline corrected continuous EEG data.

### ***Validating SOBI-Recovered Neuronal Sources***

The most common concern that EEG users have about sources recovered by BSS methods has to do with whether the *recovered*-sources do in fact capture neuronal activity associated with specific physiologically meaningful and neuroanatomically relevant brain regions and whether such recovered source signals are contaminated by signals originating from

elsewhere. A related concern has to do with the use of the phrase “independent component (IC)” derived from the ICA literature. Brain researchers have trouble believing that neural activity from different brain regions is truly independent. Thus, it is easy to dismiss the entire BSS approach on this ground.

Particularly relevant to this concern, is the fact that SOBI differs from other ICA methods in at least one aspect---it is designed for recovering *correlated* sources (Belouchrani et al. 1997) and it does not call itself an ICA algorithm nor does it refer to its recovered sources as “independent components”. To examine whether SOBI does recover correlated neuronal sources, we use data from an experiment involving somatosensory stimulation to provide both correlated (paired left and right) and un-correlated (left or right alone) sensory inputs to the left and right primary somatosensory cortices (Left and Right SI). The correlated sensory stimulation, coupled with the effective inter-hemispherical influence between the two homologous brain regions, guarantees that the to-be-recovered neuronal signals originating from the left and right SI are correlated, thus offering a challenging benchmark for SOBI’s ability to recover neuronal sources that have correlated activities. Similar points can be made with experiments involving a mixture of unilateral and bilateral visual stimulation (McKinney, Sutherland, and Tang 2003).

From EEG data collected from correlated neuronal sources using

mixed left, right, and bilateral median nerve stimulation, SOBI decomposition resulted in the recovery of two SOBI-components that corresponded to the left and right SI (Fig. 4 & 5, Tang, Sutherland, and McKinney 2005b). This correspondence was established via both principled spatial and temporal criteria as discussed in detail elsewhere (Tang, Sutherland, and McKinney 2005b; Sutherland and Tang 2006). Briefly, the SOBI-recovered SI components showed, in the temporal domain, characteristic SI response to median nerve stimulation (Fig. 4) and in the spatial domain, a corresponding single dipole solution that accounted for > 95% of the variance in the component's spatial projections across the sensors (Fig. 5). The benefit in the temporal domain is a clearly improved signal to noise ratio (SNR) (Fig. 6A) and, in the spatial domain, is the ability to conclude that the waveform in the time domain originates from a specific region within the brain as opposed to concluding that the waveform is merely a signal recorded at a particular sensor (Fig. 5). The latter does not address the question of how a specific brain structure corresponds with a specific function.

As both the left and right SI can influence each other via inter-hemispheric connections and share common input during bilateral stimulation, some degrees of correlation between their activation time courses should be expected. Had SOBI incorrectly imposed independence, then one might expect to find the activity of the SOBI-recovered left and

right SI sources to show *a lack* of expected correlation. To check for this possibility, we examined the coherence plots (Delorme and Makeig 2004) between the two recovered left and right SI components (Fig. 7 left). Increased correlations between the two SIs does occur for a brief period shortly after the stimulus onset and within specific frequency bands, as one would expect to happen between two brain regions sharing both inputs and interconnections. As a control, similarly generated coherence plots for a SOBI-recovered SI and a noise-source showed no such frequency- and time-dependent increase in correlation (Fig. 7 right).

### ***Benefit of Using SOBI-Recovered Sources:***

#### ***Capturing Trial-to-Trial Variability in Neural Response***

A major challenge in investigating contextual effects, particularly trial-to-trial variations, is the presumed poor SNR in single-trial EEG data. This assumption is not unreasonable and can be confirmed by every experienced EEG researcher who has viewed large amounts of raw sensor-based data. This assumption is also reflected in the common practice of signal averaging across trials and sometimes across nearby electrodes showing similar response patterns in order to improve SNR. If SOBI can indeed parse the mixture of signals contained in the EEG sensors into their separate sources of origin, then the SNR of each *recovered source* may be sufficiently increased to allow classification of single-trial SEPs,

specifically to determine whether a given trial involved left, right, or bilateral stimulation.

Using a neural network classifier, we compared classification success rates between two types of inputs: small segments (20 ms) of SOBI recovered SEPs from the left and right SIs and the same length of data from the raw waveforms recorded at the so-called “best-sensor” location. Classification success rate for SOBI components was significantly higher in comparison to that from the sensor-based measures (Fig. 6B). Furthermore, the cross-subject *variability* in classification performance was significantly reduced when source-based measures were used (Fig. 6B) (Tang, Sutherland, and Wang 2006), thus potentially reducing the sample size needed and cost of a given study. This benefit should have significant clinical implications in the context of drug testing. Therefore, SOBI recovered neuronal source signals provide a clear advantage over those of the sensors in characterizing trial-to-trial variations in brain responses.

### ***A Short SOBI Primer***

What does using SOBI for analyzing high-density EEG data involve? If we can assume that the data are collected with properly calibrated amplifiers<sup>1</sup>, then the steps are rather simple. First, make sure that the number and range of temporal delays are properly set (Tang, Liu, and

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<sup>1</sup> Inappropriately calibrated amplifiers may generate waveforms containing “steps” due to amplifier saturation.

Sutherland 2005a). Typically, a set of commonly used default values can be adopted without modification. The effects of varying these parameters on recovering benchmark neuronal sources have been documented (Tang, Liu, and Sutherland 2005a). Second, make sure that the input to SOBI is continuous, as opposed *epoched*, EEG data. When concatenated, *epoched EEG* “trials” would *create* abrupt changes in voltage at the boundary of the epochs that did not exist in the original continuous data. Third, make sure that input to SOBI is not filtered or manually “cleaned” by “chopping out” windows of EEG data. Cutting out a window of data would create artificial boundaries similar in effect as that of concatenated epochs of data and filtering would remove useful information that could be otherwise used by SOBI to properly distribute signal variations to its proper sources, including both neuronal and noise sources. Use of a single instead of a wide-range of temporal delays, concatenation of epoched EEG data, and unnecessary pre-cleaning, are erroneous practices likely committed by novice users of SOBI in preparation for source separation.

Internally what SOBI does is conceptually very simple. To recombine signals from different EEG sensors into signals originating from a source is mathematically equivalent to changing the axes within which the high-dimensional EEG data are described. The original axes are the sensors and resulting axes are sources. SOBI makes the transition from the sensor (electrode) based axes to the source-based axes via an iterative process that

minimizes the *sum* of squared correlations between every pair of new axes at all temporal delays. Because it is the *sum* of many squared correlations across different temporal delays that is being minimized, as opposed to having every squared correlation minimized, it is possible for SOBI to find the final set of axes that “tolerate” some degree of correlation at a few temporal delays.

In comparison to other BSS algorithm, SOBI uses a relatively small number of parameters, which are the temporal delays described above. The setting of these temporal delays are not random and can be selected based on the expected temporal delays among the neuronal sources to be separated (Tang, Liu, and Sutherland 2005a). Once these delays are set, there is no randomness in the SOBI process in the sense that only one set of source solutions will be found once the delay parameters are set. This contrasts with InfoMax ICA, whose final set of source solutions are averaged across  $N$  neural networks, each of which starts with a set of randomly selected weights. Each network has to be trained and this training requires the setting of additional parameters, e.g. learning rate and other parameters describing the function of “neurons” in these neural networks. This lack of randomness in the SOBI process, not only makes the interpretation of the final solution clear and straightforward but empirically offers efficiency in finding the final solution. In the case of recovering the left and right SI components using SOBI, as few as 20 iterations were

sufficient to recover the components corresponding to the SI sources described in Fig. 4 & 5. Additional iterations do not lead to further improvement in the resulting source localizations, at least in the case of recovering SI (Fig. 8).

SOBI outputs a square matrix  $W$ , the unmixing matrix. Using this matrix, the time course of the recovered signals can be computed by matrix multiplication (Fig. 9, Step 2) (Sutherland and Tang 2006) and the spatial projection of each recovered source can be obtained from the inverse of  $W$  (Fig. 9, Step 3). From the time course, single-trial as well as averaged event-related potentials (ERPs) can be computed. From the spatial projection, dipole-based or distributed source modeling can be applied to localize the sources to specific brain regions (Scherg 1990; Hamalainen et al. 1993; Sarvas 1987; Ioannides, Bolton, and Clarke 1990). The benefit in the temporal domain is an improved SNR in the averaged ERPs and clearly discernable single-trial ERPs; the benefit in the spatial domain is the circumvention of the intractable inverse problem by reducing the number of possible solutions for each given recovered source.

## ***Part Four: From the Laboratory to the Context of Real World***

### ***External Validity of a Scientific Finding***

Brain imaging studies are often conducted in laboratory settings under

restricted conditions. In most cases, it is not clear to what extent these findings can generalize to real world situations. As the peer review process focuses nearly exclusively on the internal validity of a study, issues of generalization, i.e. external validity, are simply assumed or left to the hands of newspaper reporters. The meaning and relevance of a laboratory finding in the real world can only be established, not merely speculated upon, via a new type of experiment that relaxes most, if not all, major laboratory constraints and removes major laboratory related artifacts. In this section, we will present results from several studies that attempt to extract high-temporal resolution electrical signals from specific brain regions under conditions of free and continuous eye movement without the requirement of repetitive stimulus presentation and without the requirement of a task that entails specific responses.

### ***Separating Sensor Noise, Eye-Movement, and Neuronal Sources under Natural Context***

In human experiments involving the use of scalp recorded EEG, one common characteristic of laboratory experiments is the presentation of a target stimulus against a relatively impoverished background. This is for the purpose of maximizing the chance of detecting neural responses to the specific stimulus against background brain activity. This impoverished background produces minimal variation; therefore the context thus-provided

is bound to differ from those occurring in real world situations, where sensory stimulation is continuously streaming instead of discretely presented and originating from multiple unknown sources instead of a few known ones.

The second common characteristic is the requirement for minimal eye movements during EEG recording due to the large ocular artifact produced by such eye movement that affect signals recorded across many sensors. Participants are often instructed to fixate and withhold blinks. This requirement entails additional mental effort and diverts attention to something other than the processing intended in its natural context.

Aside from these deviations from the natural context, in order to remove remaining ocular artifacts, a large amount of data is often discarded. This is the case even when using some BSS algorithms. For example, it has been recommended that before using InfoMax ICA, manual cleaning of the raw EEG data be performed (Delorme and Makeig 2004). Such manual artifact removal would fail if EEG data are collected during continuous eye movement because there would be no clear on- and off-set of eye movement related signal, thus it would be impossible to remove this source of “noise” by removing particular time windows.

We applied SOBI to data collected under the challenging conditions of free-viewing continuously varying visual scenes involving sustained eye movement and natural blinks. In a simulated warship commander task, the

operator is to monitor, track, and discriminate a wave of incoming airplanes and text-display panels, and make decisions about whether to treat the airplanes as friends or shot them down as enemies. There is no pre-planned operator action and every operator will perform this game freely and differently with the only shared instruction of shooting down enemy planes and avoiding firing upon friends. There is no repetition of visual scenes and, consequently, no repetition of context from one moment to the next during the task.

Under these challenging conditions, SOBI was able to separate not only noise signals associated with “bad sensors” (Fig. 10) but also signals associated with eye movement (Fig. 11), visual processing (Fig. 12), and frontal-lobe activity (Fig. 13) (Tang et al. 2006). It is worthwhile to point out that these data were collected with a 64-channel EEG system in an electrically noisy office environment without any shielding. The “events” used to generate the ERPs were button-presses proceeding either a waiting period or proceeding a display of English text that entails visually-based language processing. It is remarkable that visual evoked potentials (VEPs) originating from posterior visual cortex (Fig. 12) can be cleanly isolated from signals associated with continuous eye movements (Fig. 11) even though the VEP waveforms and lateral eye-movements (towards the text panel) overlapped in time. Furthermore, the SNR is sufficiently high that the VEPs can be discerned even at the single-trial level.

### ***Separating Distinct Neuronal Sources without the Requirement of Task Performance***

The third common characteristic of laboratory-based EEG research is the need for participants to perform some form of a perceptual, motor, or cognitive task<sup>2</sup>. The requirement of task performance sets limitations on the population of research participants whose brain activity can be studied, thus reducing the external validity of the intended research findings. For example, individuals suffering from autism, Parkinson disease, or being in a coma, either have difficulties or are completely incapable of acquiring and performing laboratory tasks. Infants and young children are more than likely to share the same problem due to limitations associated with physical and mental maturation. Therefore, the capacity to isolate neural source signals from functionally distinct brain regions in a *task-free* manner would be critical for studying information processing within these special populations. Such a capacity would also enable sleep researchers to characterize brain states in terms of sources instead of sensor signals.

Applying SOBI to approximately 10 minutes of continuous EEG data collected while a participant was at “rest”, we were able to identify a set of SOBI components that localized to brain regions along both the dorsal and ventral visual pathways (Fig. 14, Sutherland and Tang 2006). This

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<sup>2</sup> With the exception of sleep research.

demonstrates that it is possible to separate sources using SOBI without the requirement of an explicit task. In a study where a larger sample of participants were asked to rest with eyes closed, rest with eyes open, or passively view a video, SOBI was able to isolate neuronal sources: (1) in the absence of any explicit task performance; (2) in the absence of any discrete “trials” of stimulation; and (3) in the presence of free eye movement (Fig. 15, shown only frontal and posterior sources). These findings demonstrate that with the aid of SOBI, a task-free approach to EEG data assessment is viable for the monitoring of developmental, aging, and disease conditions as well as treatment progressions.

### ***Matching Neuronal Sources from One Session to Another—Within Subject Reliability Across Time***

In order to use SOBI-recovered sources to characterize brain state change as a result of development, disease progression, and treatment effects, one needs to be able to match neuronal *sources* recovered from one session to those recovered from another. In other words, one needs to establish within-subject, cross-session reliability in finding the neural sources that correspond to the same neuroanatomical structures. We evaluated SOBI’s ability to repeatedly identify the same neural sources within each subject across a time window of up to one month.

In a longitudinal study involving three testing sessions taking place one

week and 4 weeks from the initial testing session, participants experienced a few minutes of resting with eyes closed, resting with eyes open, watching a silent video, and thinking about the video. No explicit task performance or behavioral responses were required. Subjects were once again free to move their eyes or blink. We applied SOBI to continuous EEG data collected within each session. Neural sources were recovered from posterior visual cortex and frontal cortex within each session and across sessions these sources could be matched (Fig. 15) (Tang et al. 2007).

To researchers of child development, aging, diseases, and treatment, this ability will help to reduce the variations and uncertainties associated with differences in electrodes placement across time and consequently allow better characterization of changes in brain function in health and in disease.

## **Part Five: Understanding Cognition and Emotion in the Real World: SOBI As an Enabling Technology for Investigating Neuronal Variability**

In this chapter, we have argued that to understand cognition and emotion in the real world, it is critical to investigate the phenomena of interest within the rich moment-to-moment context of the real world, that richness of the context as a result of individual history and immediate stimulus environment is encoded in the high-dimensional state of the brain, and that

with appropriate signal processing using SOBI, such high dimensional brain states can be observed and characterized with surprisingly high SNR even in moment-to-moment measures.

In contrast to other chapters in this volume that focus on variations at the level of single neurons or at the level of small networks, our analysis is focused on the level of systems. While at the single-neuron level, one speaks of how the firing rate or timing of a single-neuron may vary from one trial to another, at the systems level, we speak of how the final perceptual, cognitive, or emotional outcomes vary from one instance to another and we speak of how the state of the entire brain as represented in a high dimensional space vary in parallel. Analogous to understanding trial-to-trial variations in single-neuron or small network firing patterns, we seek to understand moment-to-moment variations in psychological outcomes at the systems level in terms of moment-to-moment variations across a set of localizable neuronal sources that characterize the individual's brain state.

Towards this goal, we presented a brief summary of recent advance in high-density EEG signal processing that enables a transition from a sensor-based to source-based language for a dynamic characterization of brain state. We argued for why such a transition is critical for addressing a fundamental question in neuroscience---relating specific brain functions to specific brain structures and their dynamic interactions. It is important to

accompany these statements with the disclaimer that a relative advantage of a source-based language over a sensor-based language in the context of relating *function to structure* does *not* imply that no valuable information can be gained using a sensor-based language.

It is also important to point out that although SOBI is the algorithm for which we have chosen to provide extensive empirical studies, the use of time correlation (as in the case of SOBI) is only one way of separating sources from mixture of signals (Cardoso 2001). SOYA (Gorodnitsky and Belouchrani 2001) and M-COMBI (Tichavsky et al. 2008) are two newer algorithms that improved upon SOBI. These newer algorithms have desirable properties based on theoretical grounds and simulated data and their success in separating large numbers of neuronal sources from high density EEG data within a wide range of contexts remains to be demonstrated.

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## Figures

**Figure 9-1.** SOBI isolation of a noisy sensor. (AB) Comparison of the known location of the noisy sensor (A) and the spatial location of a SOBI component (B) also referred to as a SOBI-recovered source, in sensor space projection maps (indicated by boxed locations). (C) Comparison of the time courses of the known noisy sensor (red) and the SOBI-recovered noise source (blue) across three arbitrarily chosen epochs.

**Figure 9-2.** SOBI isolation of multiple artificially created noise sources. (Top) Location and time course of three temporally overlapping noise sources. Colored boxes indicate the sensor locations where noise was injected. (Bottom) Location and time course of the SOBI-recovered noise components. Colored boxes indicate the center of activation on the current source density (CSD) maps from each of the SOBI components. The numbers on the left give the corresponding sensor and component IDs. Notice the similarity, both spatially and temporally between the known and SOBI-recovered artificial noise sources.

**Figure 9-3.** Comparing SOBI with PCA: The case of isolating 60 Hz noise. (A) Ten randomly selected epochs of unprocessed EEG sensor data from the known 60 Hz noisy-sensor. (B) Power spectra of the ten epochs in A. (CD) Power spectra of the PCA-(C) versus SOBI-recovered (D) 60 Hz noise source (projected at the same sensor as in A). Note that D contains only a single peak around 60 Hz while C contains signals in other frequency ranges.

**Figure 9-4.** SOBI isolation of neuronal sources: Temporal characteristics. (AC) SOBI-recovered left (C-012) and right (C-016) SI showed characteristic SI response to median nerve stimulation (MNS). Boxes indicate the sensor location where the largest responses were observed (SEPs displayed in the inserts). (BD) Sensor space projections of the SEPs from the unprocessed EEG sensor data. Note the more diffused activation in the unprocessed sensor data by contralateral stimulation and the “noisier” SEPs ( $n = 400$  trials).

**Figure 9-5.** SOBI isolation of neuronal sources: Localization. (AB) CSD maps of the SOBI-recovered left (C-012) and right (C-016) SIs. (CD) CSD maps generated from an equivalent current dipole (ECD) model with the best least-squares fit to the data. (EF) CSD maps of the model residuals. (GH) ECD locations for the SOBI-recovered left and right SI, respectively, shown against the structural MRI of a standard brain (left is shown on the right).

**Figure 9-6.** Benefits of using SOBI. SEPs computed from the SOBI recovered SIs showed greater SNR (A) and lower cross-subject variability (B) than those from the raw sensor data measured at the “best sensor”.

**Figure 9-7.** SOBI isolation of correlated neuronal sources: SOBI-recovered SIs preserved the expected correlations. (AB) CSD maps of SOBI-recovered sources.

(Left) The coherence plots between the two recovered left and right SI components.  
(Right) The coherence plots between one SOBI-recovered SI and a noise source, where no correlations were expected. Coherence plots are shown for (CD) bilateral stimulation, (EF) left stimulation, and (GH) right stimulation.

**Figure 9-8.** SOBI source separation is deterministic and fast. The recovery of the SIs in four subjects shown in Fig. 9-6 took only a few tens of iterations. The numbers above the arrows indicate the number of iterations needed to reach asymptote. Further iterations did not produce significantly different source locations or waveforms.

**Figure 9-9.** A schematic illustration of recovering neuronal sources using SOBI. (1) The continuous EEG sensor data,  $x(t)$ , was supplied as input to the SOBI algorithm. The output of SOBI is an unmixing matrix,  $W$ . (2) Identifying the candidate SI components using temporal information: The continuous time course of the  $i^{\text{th}}$  component,  $\hat{s}_i(t)$ , is given by the  $i^{\text{th}}$  row of  $W*x(t)$ . From  $\hat{s}_i(t)$ , left and right stimulation-triggered averages, can be computed for each SOBI component. Components that correspond to left- and right-SI,  $\hat{s}_{\text{Left-SI}(t)}$  and  $\hat{s}_{\text{Right-SI}(t)}$ , can be easily identified by characteristic waveforms in the SEPs following contralateral stimulation. (3) Identifying the candidate SI components using spatial information: The sensor-weight map of the  $i^{\text{th}}$  component is determined by  $\hat{a}^{(i)}$ , the  $i^{\text{th}}$  column of  $W^{-1}$ ;  $\hat{a}_{(\text{Left-SI})}$  and  $\hat{a}_{(\text{Right-SI})}$  are two easily identifiable weight maps that correspond to the

estimated left- and right-SI sources. (4) The sensor space projection of a candidate SI component's average SEP is computed from  $\hat{x}^{(i)}(t) = \hat{s}_i(t) * \hat{a}^{(i)}$ ; (5) Location and strength of the candidate left- and right-SI components can be determined with BESA using the sensor space projection of contra- and ipsilateral SEPs as inputs.

**Figure 9-10.** SOBI isolation of sensor related noise sources in a “real world” task situation where the subject was playing a video game in an electrically noisy office environment and with minor head and body movement. Three examples of SOBI noise-components. ECDs are superimposed on a standard structural MRI showing the origins of the signals are the EEG sensors.

**Figure 9-11.** SOBI isolation of an ocular “artifact” associated with continuous free eye movement in the same “real world” task situation as in Fig. 9-10. (A) CSD scalp map. (B) ECD model. (CD-left) single-trial ERP display. (CD-right) averaged ERPs generated with two contrasting events (COMM, WARN) that differ in the patterns of eye movement as well as in the type and amount of cognitive process. Notice that the ERPs of this SOBI component captures the expected differences in eye movement patterns (C) COMM event: the pressing of one of the many numbered communication buttons, which is preceded by holding a number in working memory, moving the eye from a moving target anywhere on the screen to the array of buttons, and identifying the button whose number matches the one in working memory and is followed by horizontal eye movement to text display box and reading of the text; D)

WARN event: the pressing of the WARN button, which is preceded by an eye movement to the WARN button at a fixed location and followed by a 3 sec waiting period.

**Figure 9-12.** SOBI isolation of a visual source in the same “real world” task situation as in Fig. 9-10. Despite the presence of continuous, free eye movement and the large eye-movement related signals shown in Fig. 9-11, this component has a sensor space projection well accounted for by a pair of dipoles located in the posterior parietal cortex (AB) and has an ERP waveform characteristic of a VEP (CD). All parts arranged as in Figure 9-11.

**Figure 9-13.** SOBI isolation of a distributed and synchronized anterior- posterior (SAP) network in the same “real world” task situation as in Fig. 9-10. Despite the presence of continuous, free eye movement and the large eye-movement related signals shown in Fig. 9-11, this component has a sensor space projection well accounted for by two pairs of dipoles located in both the frontal (anterior) cortex and the posterior parietal cortex (AB). All parts arranged as in Figure 9-11.

**Figure 9-14.** SOBI isolation of a family of neuronal sources from a single subject using ~ 10 min EEG recorded while the subject was at “rest”. Scalp maps (left) and ECD locations (right).

**Figure 9-15.** Cross-subject reliability: SOBI recovered the same neuronal sources across multiple subjects from EEG data collected in the absence of an explicit task. Scalp maps (Row 1), CSD (Row 2), and ECD locations (Row 3) of anterior components (top) and posterior components (bottom).

**Figure 9-16.** Within-subject reliability: SOBI recovered the same neuronal sources across different recording sessions for multiple subjects. ECD locations for the SOBI recovered Anterior component (Left) and Posterior component (Right). Session 1: week 0; Session 2: week 1; Session 3: week 4+. Each ECD location is for one subject.