FINAL REPORT FOR THE CONTRACT BETWEEN POC AND UCSD

IMPACT OF INTERMITTENT LIGHT ON NORMAL BRAIN FUNCTION

Irina Gorodnitsky

ADDRESS:
Department of Cognitive Science
University of California, San Diego
La Jolla, CA, USA 92093-0515

igorodni@cogsci.ucsd.edu

Phone: 858-822-3221
1. INTRODUCTION

This report describes the findings from a study performed under the contract funded by the Physical Optics Corporation. This was a short term exploratory study to investigate whether we can determine the effect of intermittent (blinking) photic stimulation (IPS) on the brain’s intrinsic activity.

It is well known that the brain produces an evoked rhythmic response in the same frequency band as an externally applied intermittent light, the so called the steady-state evoked potential (SSEP) or “photic-following” response. It is also known that spontaneous rhythmic excitations occur naturally in the brain and are integrally tied to all brain functions. The etiology and exact role of these rhythms in brain function is largely unknown. Even less is known about the possible interaction of the external IPS with spontaneous brain activity, aside from isolated studies showing enhanced/suppressed or locked responses occurring in various frequency channels in response to IPS.

Certain subpopulations are known to be photosensitive, which can be manifested in a spectrum of neurological symptoms from a headache to an induced seizure but the effect of rhythmic stimuli on individuals who do not exhibit strong neurological symptoms is unknown. The effects of IPS, if they exist, are expected to be manifested in the interaction of externally generated rhythms with the brain’s default dynamics.

The best method available to evaluate brain activity is to observe brain waves recorded magnetically outside the head via a magnetoencephalogram (MEG). MEG is the magnetic correlate of the electroencephalogram (EEG). EEG is a mainstay of clinical diagnoses related to abnormalities in brain activity, including epilepsy, suspected seizures, or impaired consciousness. EEG and MEG are the only modalities with sufficient temporal resolution to study changes in the dynamics of brain processes. MEG was used as the experimental modality in this study because it provides a number of advantages over EEG, key ones here being superior signal-to-noise ratio (SNR) and high density spatial sampling of the data.

The overall goal of this project was to uncover the effect of photic stimulation on intrinsic brain rhythms. The specific aims were, first, to identify whether MEG can be used to detect any changes to normal brain rhythms during photic stimulation, second, to determine whether we can correlate any detected changes to the neural system in the brain responsible for producing the observed dynamics, and, third, to characterize any observed changes to the best of our ability in terms of brain processes and what the their implication for changes in brain function may be.

The specific findings related to the third goal are presented in the Results section and summarized in the Conclusions section. However, the most significant finding by far of this study is that we could explore noninvasively, by means of MEG, brain dynamics at the system level and are able to separate the rhythms generated by specific neuronal networks and structures of the brain, including subcortical brain structures, and observe how the rhythms from the different networks interact and influence each other.

Note: The directories containing figures that accompany the analysis in the Results section are very large. Therefore, they are not bundled with the report. Instead, zip files of the directories containing the figures are made available for download from the publically accessible website: http://cogsci.ucsd.edu/igorodni/POC/. The files contained on the website are described in more detail in the Results section. These figures from the website need to accompany copies of this report.
2. BACKGROUND

2.1. Quantatization of brain responses

The point of the current study is to investigate how external rhythmic stimuli may affect the natural activity of the brain and thus affect user’s sensory, associative, or cognitive processes. Several major limitations to this endeavor should be stated from the start. First, we lack understanding of the role of specific spontaneous brain rhythms, except that brain rhythms appear to be integrally tied to all brain functions. Second, we lack of understanding of the etiology of brain dynamics: which rhythms are generated by which brain system and which specific neuronal network within that system; how neuronal networks may be linked and how the activity of one network influences the activity of others. Third, we know very little about the link between brain dynamics and brain function, be it the behavior or cognitive processing.

What is known is that IPS produces a pathophysiologic response even in some nonepileptic individuals, albeit at a rate estimated to range anywhere from 0.5 to 8.9% of the population. This response is defined by paroxysmal epileptiform EEG discharges elicited by IPS. Other neurological symptoms known to be linked to intermittent light stimui include headaches, visual disturbances, giddiness, restlessness, fainting, and sleeplessness. What is unknown is the effect of IPS on normal brain function.

Nevertheless, in recent years a sophisticated appreciation of the role of neural rhythmicity and temporal synchronization in brain function has emerged and led to a surge of studies in this area. These studies have yielded some basic facts and results which I review here as they provide the foundation for the analysis performed for this project.

Brain rhythms are defined as regularly recurring waves of similar shape and frequency. When networks of neurons interact, the result is often rhythmic activity within defined frequency bands that can engage in temporal synchronization and de-synchronization. Historically, five major frequency bands are recognized in continuous awake EEG and MEG recordings: delta (1-4Hz), theta (4-8Hz), alpha (8-13Hz), beta (13-30Hz), and gamma (30-80Hz). There is no precise agreement on the frequency ranges for each band. Different frequency bands within the same neuronal network are typically associated with different brain states and compete with each other. However, we don’t know specifically which frequency bands in a given neuronal network are associated with which brain state.

The best studied neuronal properties and network synchronization is that of spindle oscillation (7-14 Hz), which is generated in the thalamus and characterizes the state of light sleep. Slow sleep oscillation (0.5-1 Hz) in the neocortex have also been reasonably well described on the level of their the cellular generating mechanisms. The spindles and slow sleep oscillations are associated with prolonged inhibitory processes in thalamic and cortical neurons, thus preventing processing of information from the outside world.

We also have some knowledge of various brain structures and neuronal types generating beta and gamma waves. There is, however, a continuous debate about the significance of these fast rhythms, some claiming some role in higher cognitive processes and consciousness during waking and sleep during rapid-eye-movements (REMs), others challenging this hypothesis on the basis that the same rhythms also appear, discontinuously, during slow-wave sleep or deep anesthesia when consciousness is suspended. The theta rhythm (4-8 Hz), produced in the hippocampus and occurring during different forms of arousal, have been the focus of many recent studies at the cellular level using rodent models, but its precise mechanisms are still subject to controversy. Even though alpha waves, whose frequencies overlap those of spindle waves, were described almost 80 years ago, we know virtually nothing about their underlying neuronal mechanisms.

A theory has been proposed that by locking into an oscillation frequency, the brain uses rhythms to coordinate
the workings between the various brain systems and regions. This coordination is needed to integrate information in the brain. Thus, a brain state is not defined merely though a set of measured brain rhythms arising in various brain regions, but through a coordinated interplay between brain systems organized into both local and diffused networks locked together by oscillatory dynamics.

Two major networks which have been recognized in the brain are the Corticothalamic network and the Hippocampus-neocortical network.

**Corticothalamic network**

The largest amplitude and slowest waves reflect strongly synchronized, cooperative patterns in large aggregates of cortical and thalamic neurons. The rhythms which have been observed during sleep in these large assemblies are slow oscillation (0.5 to 1 Hz), delta waves (1 to 4 Hz), and sleep spindles (7 to 15 Hz). In an awake brain, faster and much lower amplitude beta and gamma (20 to 80 Hz) oscillations emerge. The fast oscillations, spatially localized and temporally short-lived, are believed to tie together active neuronal assemblies.

Cortical gamma oscillations are hypothesized to be the mechanism by which information processing in the separate neuronal assemblies is linked across widespread cortical regions. Rhythmic cortical feedback to the thalamus is a major factor in amplification of thalamocortical oscillations. But, as cortical neurons increase their commitment to an oscillatory network, their responsiveness to external inputs progressively decreases. This implies that a rise of strong thalamocortical oscillations reduces the receptiveness of the brain to environmental inputs and thus impairs the integration of various attributes of visual input processed in separate neuronal assemblies. Hence, perception appears to be a function of the cyclic changes in the network, and is negatively affected by recruitment of cortical areas into strong thalamocortical oscillations.

**Hippocampus-neocortical network**

Another well-studied brain rhythm is the so-called hippocampal theta rhythm, between 4 and 12 Hz, which is different from the frequency band convention used to classify EEG signals. This theta rhythm derives from the synchronous firing of neurons located within the various cell layers of the dentate gyrus and hippocampus. Synchronization is maintained by the action of inhibitory interneurons that initially suppress the firing of principle neurons. The neuronal circuitry is set up so that the initial wave of inhibition results in a subsequent disinhibition as the firing rates of interneurons decline.

Because the brain is largely a prediction mechanism that relies on its past experiences, we expect an almost continuous dialog between the memory-centered hippocampus and parts of neocortex. In fact, hippocampal theta rhythms are among the rare sustained rhythms of the brain.

Most of the hippocampal theta rhythm studies have been performed on rodent and cat brains. The theta rhythm is seen prominently when animals are engaged in voluntary movement, while immobile yet alert, and during periods of REM sleep. Among the more intriguing findings is a link between the theta rhythm and behaviors, some of which are fairly complex and tap into memory and/or decision-making, such as rats exploring a maze or humans navigating, planning or recalling events.

Recent studies (e.g. M. Wilson and M. W. Jones, 2005) have shown theta frequency correlations to exist between the hippocampus and the decision-making prefrontal cortex. For example, a rat running a maze must integrate spatial information, memory of where the reward is located, route information, and rules about how to navigate the space. When its relevant brain structures are all working, its theta rhythms are locked in sync. When these rhythms are not synchronized prior to decision-making, the animals make errors.

Thus, the Hippocampus-neocortical network seems to work as a mediation system within which different brain areas can work alone and "tune in" to information from other areas when necessary. It can be concluded that a disruption
in the communication between the two structures will impair performance.

However, simply interpreting the interaction between two or more brain structures as that of a giant harmonic oscillator is too simplistic because it neglects the role of the dynamics of the individual components and the nature of their coupling. For example, Ros Adey et al. (1960), studied the relationship between hippocampal and entorhinal cortex theta rhythms in cats that learned a visual discrimination task in a T-maze. In early training, hippocampal theta had a phase lead over that in the cortex, but by the end of the training the phase relationship reversed. Most importantly, this phase reversal between the two structures occurred in the correct vs. incorrect trials in the trained animals. In incorrect trials, the hippocampus was leading the oscillations as in the early stages of learning. Also, the frequency of theta rhythm was slower in incorrect trials than in correct trials.

The last example implies that, as in the case of the Corticothalamic network, a rise of strong hippocampus dominated oscillations will be disruptive to the person’s ability to quickly tune information in and out that is critical for informed decision-making and will lead to performance impairments.

The current study examined changes in temporal dynamics in response to different experimental conditions. An advanced signal processing technique was used to extract components of data which I believe reflect, with sufficient for our purposes fidelity, the temporal dynamics of the large oscillatory networks, i.e. the Corticothalamic and the Hippocampal-neocortical networks. These global oscillators were found to be the largest contributors to the measured data. Thus the current study, constrained by limited scope, focused primarily on changes in these global oscillator behaviors. The signal processing method which was used to decompose data into the components which captured the behavior of the global oscillatory networks is discussed next.

2.2. Advanced Data Analysis Methodology

Blind source separation (BSS) has been used in analysis of EEG and MEG data for the last 10 years. The initial attraction of BSS for these applications was that it could circumvent the problems associated with classical source localization analysis. Instead of solving the underdetermined source localization problem, BSS separates the total field into individual activities occurring in some small regions in the brain and jointly giving rise to the measured field. This interpretation of the methodology is, clearly, an idealization. As with source localization, a BSS decomposition is highly dependent on the assumptions one incorporates into the technique to find the solution. In fact, there are many different BSS assumptions which can be applied to the same data to decompose them into projections that don’t agree in either their spatial distribution or the temporal dynamics. In general, a single BSS component can even describe an amalgam of activities coming from disjoint or extended cortical areas. Hence, the traditional term “source” in the field of blind source separation, should not as a rule be interpreted literally as referring to neuronal circuits generating electric current.

A quickly recognized utility of BSS was its capability to separate out and remove noise and artifacts from multi-channel data. Hence, it enabled researchers to move away from traditional EEG analysis methods such as trial-averaging and into a new territory where individual trials could be analyzed. The other use of BSS components is in modeling activity of localized cortical neuronal assemblies. Unfortunately, there are no direct means by which one can validate how closely a found BSS component describes any particular neuronal source of electric activity inside the head.

Nevertheless, a few modern developments give this approach further credence. Methods have been developed, one of them used in this project, which separate sources by incorporating more than one independence assumption. The analysis in this project uses a promising novel BSS algorithm, called COMBI [?], which efficiently combines statistical (marginal) distributions and differences in temporal behavior.
Merging of information appears to improve the spatial stability of the found components across many different experimental paradigms and subjects, giving rise to the hypothesis that some BSS methods are capable of finding components of data which model fairly closely the actual neuronal systems in the brain.

Specifically, the COMBI algorithm used in this project was found to separate measured fields into components which were spatially invariant for all experimental conditions and subjects. The separated components were further analyzed by projecting their activities to the surface montage (sensors) to examine each component’s scalp topography. From those one can extract the approximate location of the corresponding electric activity in the brain. The locations found from the surface maps pointed to neuronal systems in the brain whose known temporal dynamics agreed with the temporal dynamics described by the corresponding components.

More specifically, decomposition of every single baseline and trial dataset produced three components which were persistently dominant in all cases, as gauged by their contribution to the overall surface data, and which were localized to subcortical areas. The frequencies and wave morphologies in these components were consistent with those that have been found to occur in thalamocortical and hippocampal-cortical oscillations. This provides strong support for the working hypothesis used in this study that the subcortical generators identified via the COMBI algorithm capture at least the gross properties of the dynamics of the two global brain oscillator networks and thus can provide an estimate, albeit to within certain error, of thalamic- and hippocampal-cortical signaling. The components corresponding to these three subcortical sources will be referred to as the ‘global components’ throughout the report. The decompositions also revealed a number of physiologically plausible active localized cortical sites, i.e. activations over small patches of cortex.

The temporal dynamics of the sources localized to the same area in the different experimental conditions varied, however. This provided a way of analyzing the activities of the individual neuronal networks in the brain as a function of the experimental parameters. An example of the component decomposition and an explanation of how the components were interpreted will be given in the Methods section.

2.3. The Connection between the Electric Current and Magnetic Field

Neuronal activity localized to a single small area in the brain can typically be approximated by electric current dipoles. An electric dipole is defined as a separation of positive and negative charge. A magnetic dipole is a closed circulation of electric current.

Magnetic field lines used to display magnetic fields (and used in this report to plot scalp maps as discussed later), are a mathematical construction which provides a description of the structure of the projected magnetic field. Field lines converge where the magnetic force is strong, and spread out where it is weak. Current flowing through a wire produces a magnetic field with field lines wrapped around the wire. The field is oriented according to the right-hand rule. This information will be useful in interpreting the scalp maps of the magnetic fields used in this report.

3. METHOD

3.1. Subjects

Two healthy right handed males in the 24-30 years old age bracket were recruited. The subjects were screened according to the following criteria: good general health, the absence of neurological symptoms in response to IPS, not color blind, free of the following: neurological or psychiatric disorders, conditions that may prevent them from committing 1 to 1.5 hours at a time to the experiment, severe trauma to the head, learning disabilities, memory problems, and claustrophobia.
that would prevent them from sitting in the recording chamber. In addition, the chosen subjects were not taking any medications known to affect individual responses, for example cause drowsiness or slow reactions, and they had at least 20/30 vision without correction. The last requirement was used because metal parts in eye glasses interfere with recording the brain’s magnetic field and induce artifacts, while contact lenses can cause dryness of the eyes, which leads to a subject’s frequent blinking, which also generates large artifacts.

These selection criteria were chosen so as to eliminate any putative risk and discomfort for the subjects while fulfilling the objectives of the study. It is important to note that photosensitive epilepsy, characterized by seizures exclusively provoked by a flicker, is typically a disorder of adolescence, with a female predominance, with some studies suggesting it disappears completely around 24 years of age. Thus the use of female subjects and individuals younger than 24 years old was not advisable for this study. The chosen subjects were from the most risk-free demographic group.

Consent was obtained prior to participation in the experiment, as follows. On the day the subjects appeared for the experiment, they were given a written consent form to read and sign prior to participation in the experiment. The consent forms were approved by the University of California Human Subject Protection Office and were presented to the subject by the PI who was available to answer questions. The consent forms were pre-coded in advance by the PI with the code number chosen for the subject. Each form listed a code number for the subject, the date of the experiment, signatures from the subject and a witness, but not the name of the subject. The signed consent forms are being kept in a separate binder in the PI’s office. The name of the subject with her/his corresponding code and the subject’s contact information are being kept by the PI in a separate file.

3.2. IPS delivery system

IPS was produced by light emitting diodes (LEDs) arranged on a disk of 250mm diameter. LEDs were arranged in various patterns of the same color: Green, Blue, and Red. The output of an individual diode bulb was 350lux at 3m. This instrument, ‘the lamp’, was provided by the Physical Optics Corp.

The lamp was connected to the control box which was programmed during each trial to specify the frequency of the light flicker and the shape of the light pulse. Sets of diodes of specific color, Green, Blue, or Red, were selected manually during each trial by selecting one of the switches on the side of the lamp base. This set-up provided four types of Light Intensity and Color combinations: Green High Intensity, Green Low Intensity, Blue Low Intensity, and Red Low Intensity. The Green High Intensity stimuli were generated using 7 diodes (2450 lux). The Green and the Blue Low Intensity stimuli were generated using 4 diodes (1400 lux). The Red Low Intensity stimuli were generated using only 3 diodes (1050 lux).

Two people were operating the hardware during the experiments. One person manned the clock and switches on the lamp and the second person programmed the control box as needed.

3.3. Experimental Paradigm

During the experiment the subjects were seated in a chair in a magnetically shielded chamber and asked to look through a small window of the shielded chamber located 3.6 meters in front of them. The IPS was generated by the system described above. The stimuli were presented through the window and consisted of IPS generated by groups of LEDs of specified color and with preset flicker frequency and light pulse shape. Room lighting was dim.

Experiments were divided into ten 7-8 minute sessions each consisting of 6-8 trials with 20-25 minute breaks between sessions. The individual trials were 12 sec in duration in the first 2 sessions and 10 sec in the last 3 sessions.
Furthermore, the trials were broken up by pauses between them that were 48 sec long (and sometimes longer, depending on the time it took to reprogram the control box). Each subject was assigned half (five) of the total sessions and the experiment took approximately 3.5 hours of lab time (counting the breaks).

The protocol was designed after consulting the stringent European and Japanese IPS guidelines (listed in the Bibliography section) which have been developed to avoid provoking photo-paroxysmal responses in individuals. These guidelines include the guidelines developed for television in Japan in 1999, standardized protocols for screening with photic stimulation, and protocols used by two prominent groups working in photosensitive epilepsy. This was done so as to eliminate the possibility of inducing paroxysmal response in subjects during the experiments. The standardized protocols allow between 4 to 10 sec pauses between pulse trains, which is considered far more than sufficient time for a photo-paroxysmal discharge to resolve if it occurs. The guidelines also recommend subjects sit 2 meters away from the stimulus. The current study used 48 sec pauses instead of 4 to 10 sec pauses and subjects were sitting 3.6 meters from the stimulus. Furthermore, the stimuli blocks have been reduced to not exceed 7 minutes in durations, which is considerably shorter than the pulse trains used in the standardized protocols.

The control parameters in the experiment included light intensity, light color, flicker frequency, and light pulse shapes. Each experimental condition was run exactly ONCE, that is there were no repeated trials, except in the case of 10Hz frequency, for which 3 experimental conditions were run twice as a control.

Experimental Design:

The two proposed experiments were run in a single setting to minimize rental MEG time. The conditions for the two experiments were split among the 10 sessions with 5 sessions assigned to each subject. The conditions which were tested included:

- Color: Green, Blue, Red
- Pulse shapes: Rectangle with 75% duty cycle, Gaussian, and Camelback
- Frequencies: 3, 6, 10, 12, 15, 18, 20, 24, 27, 30 Hz
- Intensity: Green light: High and Low; Blue and Red lights: Low.

The stimuli were grouped by sessions as listed below. Each line represents one session. Subjects were rotated after each session, i.e. Subject 1 = Session 1, Subject 2 = Session 2, etc. Occasional operator errors switched some of the trials and one trial was omitted in the original sequence and was run last. The order listed below indicates the actual order in which the experiments were performed.

Notation:

Stimuli are coded using the first letter of the parameter of each condition in the following order: [frequency pulse color intensity]. Example: 10RGH = 10Hz, Rectangular, Green, High intensity. The intensity was varied by using different numbers of diodes as described above.

- 'baseline’ = a 12 sec recording during which no stimulus was delivered
- 'DC-GH’ = High intensity, steady (non flickering) green light delivered for 12 sec
Session 1: baseline DC-GH 10CGH 10CGL 10RGH 10RGL 10GGH
Session 2: baseline 3RGH 3RGL 10RGH 6RGL 6RGH 6RBL
Session 3: 20RGH 18RGL 18RGH 12RGL 12RGH 12RRL 12RBL
Session 4: 24RGH 24RGL 30RGH 30RGL 27RGH 27RBL 27RRL
Session 5: 3CGH 3CGL 10CGH 6CGL 6CGH 6CBL 6CRL
Session 6: 20CGH 18CGL 18CGH 12CGL 12CGH 12CRL 12CBL
Session 7: 24CGH 24CGL 30CGH 30CGL 27CGH 27CBL 27CRL
Session 8: 3GGH 3GGL 10GGH 6GGL 6GGH 6GBL 6GRL
Session 9: 20GGH 18GGL 18GGH 12GGL 12GGH 12GRL 12GBL
Session 10: 24GGH 24GGL 30GGH 30GGL 27GGH 27GBL 27GRL 6RRL

Notes on baselines: In addition to the specified baselines in Sessions 1 and 2, additional baselines in each session were extracted as explained later in the data analysis subsection.

Notes on trial sequence: High and Low intensities were alternated to avoid overtiring subjects and to minimize any cumulative effects from exposure to High intensity light. Switching between High and Low intensity required only the flip of a switch. Otherwise, the design minimized the programming changes needed to transition from one stimuli to the next within a single session. Hence pulse shapes were changed intra-sessions only. The exception was the first session where pulse shape had to be changed within the session. To minimize the programming time, the first pulse shape was loaded into the control box and the laptop was pre-programmed for the second shape to be loaded during the pause.

Changing color required moving the lamp slightly. The positions of the lamp for the different color conditions were marked with tape on the table before the experiment so that the lamp could be moved quickly to the correct position.

3.4. Data Collection

The magnetoencephalography (MEG) scans were performed at the UCSD Radiology Imaging Laboratory (RIL) located in the General Atomic Building, 3510 Dunhill Street, in Sorrento Valley. The RIL houses a whole-head Elekta-Neuromag MEG system (Helsinki, Finland) and is also equipped with a magnetically shielded room (IMEDCO-AG, Switzerland).

Subjects were seated in a comfortable chair in the magnetically shielded room. Head and neck were padded with foam and legs were supported to make them as comfortable as possible during data collection. Two-way intercom was available. Brain responses during entire sessions, including trials and pauses, were recorded by the Elekta-Neuromag
whole-head MEG system with 306 channels (204 planar gradiometers and 102 magnetometers). Two pairs of EOG electrodes were used to detect eye blinks and eye movements. During the preparation phase, three small coils were attached to each subject’s head. These coils provided specification of the position and orientation of the MEG sensors relative to the head. A Polhemus system was used to digitize the location of the three coils and about 80 points across the surface of the head including anatomical landmarks. Sampling frequency of the data was 1000 Hz.

3.5. Data Analysis

3.5.1. Data Preparation

The data were converted from the Neuromag MEG proprietary format into ascii format and subsampled to 256Hz to reduce the volume of data. Exploratory analyses were run on the data to understand its dynamic range and the effective dimension. The final analysis used a subset of 38 magnetometers and filter settings described below.

The magnetometers were selected over the gradiometers because the magnetometers provided at least twice the signal-to-noise ratio (SNR) of the gradiometers and often more than that. Figure 1 shows locations of all 102 magnetometers around the head. The magnetometers which were selected for the analysis, along with their coordinates, are listed in Table 1.

![Fig. 1. Locations of the 102 magnetometers used for data collection.](image)

Data for each trial were extracted, beginning with 300 msec after the start of the stimulus and ending 300msec after the stop of the stimulus. This was done to eliminate capturing any transient responses to the initial switching of the light and to capture any short-term residual effects after the termination of the stimuli. Additional to the baselines recorded in Sections 1 and 2, baselines were obtained for Sessions 3 to 10 by selecting pre-stimulus intervals at the beginning of each session. These intervals lasted anywhere from 3 to 10 sec duration and they were used to access the
Table 1. The list of magnetometer sensors used in the analysis and their XYZ coordinates in meters. The coordinate convention is that the x-axis points out from the right ear (PA), the y-axis points out from the nose, and the z-axis points up toward the vertex.

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subject’s current “brain state”. The extracted data were high-pass filtered with a 16th order recursive least-squares FIR filter designed using the Matlab routine YULEWALK with a 0.5 Hz frequency cut-off.

3.5.2. Analysis

PHASE I

A standard analysis of magnetic fields around the scalp was performed and included analysis of changes in spectral power distribution in the four main frequency bands in the magnetic signals and in the spatial distribution of the magnetic field in each frequency band, coherency in the temporal structure between the channels in the different parts of the scalp, and a review of spike activity in each experimental condition.

The analysis showed a variety of deviations from the baselines in response to particular experimental conditions. For example, a significant rise in the occurrence of spikes appeared in response to 6Hz frequency and a rise of very large oscillations was seen in response to integer multiples of 10Hz IPS frequencies.

The deviations from the baselines indicated that certain flickering lights were inducing changes in the brain dynamics. However, analyses of the surface magnetic fields per se could not shed sufficient light on the nature of these changes, namely which brain structures and systems were being affected and in which way in the observed responses. To understand how individual neural systems were affected by the particular experimental conditions, a mathematical technique called Blind Source Separation (BSS) described above was applied in the second phase of the analysis to the recorded surface magnetic signals to separate them into distinct temporal components.

PHASE II

The COMBI algorithm was used to separate the total brain activity measured outside the head into individual activities occurring in some small regions in the brain, as was described in Sec. 2. An idealistic and schematic interpretation of a component is that it describes the time courses of a localized electric current which is composed of local field potential signals (LFP) that are generated by the web of input neuron activity, mostly from the neurons’ dendrites. Corresponding to the components are the so called sources of the measured field, which are the localized electric currents.

Components computed for each trial were arranged in decreasing order of the amount of variance of the measured magnetic field that they explain. This order of the components is used in all figures in this report. The analysis described in the report relied on examining the temporal features present in the components, their spectra, and the scalp maps or topomaps, which depict the field generated by a source of unit strength being projected onto the surface montage (sensors). From scalp maps I estimated the approximate locations of the sources in the brain that corresponded to the found components. The activity of each source was then compared across the experimental conditions. It is significant that while temporal dynamics of each source activity varied across the trials, certain waveform features for each source were persistent, further supporting the hypothesis that the found sources were describing, to within some error, activities of specific, physiologically realistic neuronal networks.

Figure 2 shows an example of COMBI components computed for the baseline (pre-stimulus) data recorded from Subject 1 (first session). The field corresponding to the individual component is described by an individual scalp map. Each topographic map is a 2-D projection of a 3-D magnetic field that is being generated by a source with normalized amplitude, projected to the surface montage. The orientation of the electric source is chosen such that the maximum value of the field is positive.
The first three scalp maps shown in Fig. 2 correspond to the three global components already described elsewhere in the report. The order in which the components appear in Fig. 2 is the typical order that is seen in most experimental conditions, for both subjects. However, this was not universally the case. The order changed in the baselines extracted from the later session and in some experimental conditions where a significant shift from the normal brain states occurred. The changes in the order and the morphology of the components seen in the baselines in the later sessions are most likely due to subjects being bored and fatigued.

Note, Sub. 2 had poor blink suppression, so the first component in the COMBI decomposition for that subject always corresponds the blink signals since these signals by far dominate surface recordings. However, even this was reversed in at least one occasion, when induced oscillatory brain activity exceeded the blink signal. The blink component was discarded from the analysis. Therefore, the COMBI decomposition components for Sub. 2 are referenced in the report as if the blink component did not exist.

From the diffuse nature of the fields generated by the three components we can see that these sources are deep,
located centrally in the subcortical structure in the brain. The orientation of the electric dipole modeled by each of the first two sources closely parallels the X-Y plane. The field lines in the scalp map corresponding to the first component run from one ear to the other, across hemispheres. Hence, this component and its corresponding source will be referred to as HC. The field lines in the scalp map corresponding to the first component run anterior-posterior. Therefore, this component will be referred to here as AP. The third component is radially oriented. It is referred to in the report as HC.

The waveforms of each component and their spectra are shown correspondingly in Figs. 3 and 4. An examination of the first component waveforms shows episodic appearance of spindle-shaped, \( \approx 7 - 10 \text{Hz} \), waveforms. These bursts are broken occasionally by slow waves (4-8Hz) overlapped with gamma activity. The morphology of this waveform is related to that of waves recorded from thalamic and cortical neurons in cats (Steriade et al. (1993, 1996) and Steriade (2004)). The spectrum of this component reveals the presence of theta and alpha (spindle) rhythms and gamma rhythms \( > 50 \text{Hz} \). Overall, the component appears to closely describe the known activity of the Corticothalamic network.

Similarly, the morphology of the waveforms seen in the second component is most consistent with those observed in EEG recorded during stage 3 and 4 sleep, that is, the deep sleep when the thalamus takes over control of the brain. The predominance of theta energy makes me hypothesize that this component may be describing Hippocampus-neocortical signaling, but this is impossible to tell unequivocally. The component may just as well describe some combination of Corticothalamic and Hippocampus-neocortical signalings. We can also observe from Fig. 3 that the first two components are partially coherent. An interesting feature in the second component is a peak in power at 31Hz. Similarly, Sub. 2 had two gamma peaks at 29Hz and 38Hz. This suggests the existence of strong gamma rhythms which could potentially be exploited, either amplified or damped, through externally applied oscillations.

The third component contains slow wave formations and sustained gamma bursts \( > 50 \text{Hz} \). The gamma bursts have short durations in this particular example but stronger and longer gamma bursts are consistently seen in this
component in most of the trials. Subject 2 also had considerably more prominent gamma activity in this component.

The three components, which are referred to in this report as the ‘global components’ appear to describe features of Corticothalamic and Hippocampus-Cortical signaling, although it would not be prudent to assign a specific network activity to any one of these components, and, in fact, such assignment is irrelevant for the analysis here. What is relevant is the separation of the activity into cortical and subcortical origins.

The fourth component in the decomposition describes the ocular source, i.e. the eye activity. This can be concluded from the source location (frontal) and the presence of high frequencies with no distinct morphology, e.g. bursts.

Components 5 through 12 model various cortical sources that exhibit theta and alpha oscillations. The source represented by components 8 and 12 will be referred throughout the report as the Cz source because of its central location close to the position of the Cz sensor in the 20-10 EEG cap montage. This source is found in many experimental conditions and I hypothesize that it models ocular motor control activity. It has a very rhythmic pattern of high frequency bursts. Single spikes were found to be generated with great consistency by this source in the 6Hz flicker condition (and some trials that used integer multiples of 6Hz flicker). Another source found consistently in many conditions is represented by component 9. It is referred to as the TP (tempo-parietal) source throughout the report.

4. RESULTS

The majority of the conclusions in this section are based on analysis of the components extracted from the data using the COMBI algorithm. The analysis examined the temporal features present in the components, their spectra, and the scalp maps. This provided very detailed and extensive information on activities of specific, physiologically realistic neuronal networks. The effects of IPS varied with almost every experimental condition and covered the gamut of severity from subtle to dominant. Due to the limited scope of the current study, it was not possible to fully analyze all the information obtained. Therefore, the report on results in this section and in the conclusions in the next section focus solely on the most extreme deviations from the baselines.

As was explained above, the directories containing figures depicting the components, their spectra, and the scalp maps for all the trials and the baselines are available from http://cogsci.ucsd.edu/igorodni/POC/-. There are three zip files on the site: ica-components.zip, ica-spectra.zip, and ica-topomaps.zip. The files can be downloaded by clicking on individual files. The files need to be unzipped on the recipient’s computer. The figures contained in these directories should accompany copies of this report.

Each file name and its corresponding figure label reflect the experimental conditions they pertain to. The first number in the label corresponds to the frequency; the letter that follows it indicates the pulse shape (G= Gaussian, R= rectangle, and C= camel back), the 2nd letter indicates the color (G=green, R= red, B= blue), and the 3rd letter indicates the light intensity (H= high, L= low). Thus, the label 03GGH stands for the 3Hz, Gaussian Pulse, Green light, High intensity experimental condition. Additional characters in the labels may be present and have the following meanings. The letter ‘J’ or ‘C’ indicates the 1st or 2nd subject, respectively. The last set of numbers, (#session/#trial), indicate respectively the session and the trial number within that session.

A pre-stimulus baseline was extracted from each of the 10 sessions, as was explained in the Methods section. The names of the figures depicting the relevant information for the baselines all begin with either ‘JBAS’ or ‘CBAS’. ‘J’ indicates 1st subject and ‘C’ indicates 2nd subject. The number at the end indicates the session from which the baseline was extracted. For example, CBAS1.eps is the baseline for the 2nd subject (‘C’) for the 1st session. Similarly, JBAS2.eps is the baseline for Sub. 1 (‘J’), second session The baselines are also referred to throughout this report as BAS# where # corresponds to the session number.
4.1. Discussion of subjects and baselines

The two subjects present very different baseline dynamics. Hence comparison between the trials that were assigned to different subjects has to account for the individual’s differences. Moreover, the baselines change significantly throughout the duration of the experiment. The changes which are detailed below could be due to boredom, relaxation, fatigue, and cumulative effects of the experiments. Following is an overview of the baseline activity for both subjects.

SUBJECT 1:

General observations: Subject is alert and has good attention. This subject had excellent suppression of blinks.

Baselines (in order of the sessions):

1) HM power is moderate at 5Hz, and large at 10 -12 Hz, AP: Large peaks at 5Hz and 30Hz; HC: Energy distributed in the 4-11Hz range. A single large spike generated by the Cz source.

2) Large synchronization across frequencies. Large synchronized 9-11 Hz burst activity and suppression of 12 Hz rhythms primarily in HM and HC. Significant cortical activity in the left and right OC areas that is 7dB larger than that in the BAS1. AP: a slight suppression of 5Hz activity but it is still significant. 4dB suppression in 30Hz activity, appearance of 35Hz oscillations.

3) A large artifact made this section of data unusable.

4) No synchronization except at 11Hz. HM: Increased burst activity, sharply defined at 11 Hz and the appearance of slightly weaker 12 Hz oscillations not seen until then. AP still has oscillations at 5Hz, slightly weaker but nevertheless dominant 10.5Hz activity, and suppression to baseline of 30Hz. HC: distinct accentuation at 8 and 10 Hz.

5) Asynchronous, except at 5Hz. Decrease in AP, possibly split into two components in the decomposition, occipital source with power at 4.5 Hz and anterior at 9 -10Hz. HM: Significant increase of 5Hz rhythm and significant power at 11Hz oscillation.

SUBJECT 2:

Subject’s responds to questions slightly slower and more deliberately than Sub. 1, but the subject is clearly alert. Subject had poor blink suppression.

Global components are initially synchronized at < 13Hz and 30Hz, otherwise desynchronized at > 15Hz.

Baselines (in order of the sessions):

1) The HM and AP components have more power in the theta range than in the alpha range as compared to Sub. 1. AP does not have a distinct oscillatory alpha frequency and its alpha power is negligible compared to the theta power. It has characteristic small spike formations and no bursting. HM and AP spectra have distinct peaks at 29 and 38Hz. 29Hz peak is lower than the AP gamma peak in Sub 1. 38Hz peak is not evident at all in Sub. 1 BAS1. HC shows a typical pattern of widespread power distribution in theta-alpha range. HC also has very high level of beta-gamma activity, which is not present in Sub. 1 BAS1. HC in Sub. 2 exhibits significantly higher level of high frequency bursts than the HC in Sub. 1. Two to three noteworthy posterior cortical sources with peak energy at 4.9 and 8 or 12 Hz are also present.

2) Synchronized behavior is similar to Session 1 but the energy in AP is shifted to the 2-4Hz, dominating the overall activity. Also 10 and 38-39Hz are present in AP. HM: large 12 Hz and medium 29 and 38Hz peaks.
The dynamics of the global components appears to be very similar to the BAS1 case and there is no evidence of synchronizations between the global component. There is a small spike at the beginning of the recording which is seen in all three components. HM has very short periods of low amplitude bursting. It has a distinct peak of equal power in the theta and alpha ranges. AP is spiky and is dominated by low frequencies with main power now shifted into delta range (2-4Hz). A small but distinct peak is present at 10Hz in AP. The peaks at 29 and 38-39Hz are present in HM and AP, as in BAS1. HC shows relative rise in delta power at approximately 3Hz as compared to BAS1, and distinct peaks in the theta and alpha ranges, instead of the uniform spread of power across all frequencies. The distinct alpha peaks in AP and HC indicates sustained oscillatory activity at the specific alpha frequencies.

3) Global components appear similar to the previous 2 baselines and show no synchronization. The two exceptions are a short theta wave burst with increased amplitude in HM and absence of high frequency bursts in HC. HM’s power spectrum is dominated by a 5Hz peak and the level of alpha power is not significant. AP is completely dominated by delta and theta activity as in BAS2 and no longer has a peak in the alpha range. HC no longer has significant power in the delta-theta range. It is dominated by the alpha activity with peaks at 8, 9 and 12.5Hz. It still has significant beta power as in the BAS1 and BAS2 cases.

4) There are two bursts of slightly increased amplitude in HM. AP remains unsynchronized and is dominated by four fairly equally spaced large spikes. HC does not show high frequency bursting seen in the first two baselines. The power spectra of the global components look similar to the BAS1 case, except the peaks at 29 and 38Hz are no longer significant. A large posterior-central mu-wave cortical source is present, which is possibly indicative of subject wanting to move or trying to control movement.

5) HM exhibits no bursting and the global components remain desynchronized. AP is dominated by four moderate size spikes and a few smaller spikes. HC contains high frequencies as in the first two baselines, but bursting periods, if present, are very short. The spectra for the global components are similar to the BAS1 case except for the presence of a strong delta peak in AP, slight dominance of theta power in HM, and power in the beta range in HM and AP is now widely spread across frequencies instead of being concentrated at 29 and 38Hz. There is a strong central cortical source producing mu-wave bursts which is possibly due to subject being restless and wanting to move.

Discussion of baselines:

Immediately upon the start of stimuli presentations (10CGH/L), synchronization between AP and HM occurred and bursting appeared in these components. Hence, it is possible that synchronization between AP and HM seen in the later Sessions was triggered by the stimuli.

AP in particular appears to weaken overall in later sessions. In Sub. 1 AP shows polymorphic topology in Session 4 and no clear AP is found in Session 5. Sub. 2 shows diffused presentation of AP in Session 3 and either diffused or non-existent AP in Sessions 4 and 5. The energy in this AP-like component in the last 2 sessions is dominated by delta (dominant in Session 5) and theta waves. Its rank is superceded by a parietal source in Session 4. HM also shows a predominance of 4Hz delta energy in the later Sessions (4th and 5th) that is not evident in the 1st and only slight in 2nd sessions.

Reduction of alpha and higher rhythms in AP in the later Sessions may be due to boredom, fatigue, or even relaxation, and it may be compounded by the cumulative effect from the stimuli or other environmental conditions experienced by the subjects.

Spikes:
Traditionally, EEG spike formations have been thought to be associated with epilepsy or other neurological conditions. Currently, spikes observed in otherwise healthy individuals are starting to be recognized as normal variants of no clinical significance. Their recognition in the baselines is important to avoid overinterpretation with regard to their significance in experimental trials.

Sub. 1 exhibited isolated spontaneous large spikes in all the baselines. Morphology of those spikes was typically dysphasic and seizure like, i.e. sharply contoured theta. Some were focused and centrally located, i.e. top of the head midline. Others were widespread or bilateral.

Spontaneous high energy bursts, possibly Wicket spikes, were also evident in the alpha range (8, 11Hz) in HM and in parietal and mid occipital sources. In the later sessions this alpha-burst activity moves posterior to low OC (4th Session). In 5th Session no posterior spiking was present but high energy alpha burst activity appeared in HC in a widespread alpha frequency range.

Sub. 2 exhibited high energy bursts occurring in short runs, possibly Wicket spikes, in HM and in midline and posterior cortical generators in the first Session. At least one large steep contoured spike that was either dysphasic, with sharp decline after the first positive peak or had a sharp positive peak alternating with a rounded negative component was present in AP in the first Session. In subsequent sessions large dysphasic spikes occurred with increasing frequency in AP and were also present in low-OC generators in Session 5. Wicket-like spikes were not evident in HM in the later sessions but were present in some cortical sources.

### 4.2. Detailed description of findings for each experimental condition

The trials in this section are organized in the increasing order of frequency, and divided by subject within each frequency bin.

#### 3HZ

**Sub. 1:**

3CGH (3/1) and 3CGL (3/2):

Note: What appears as a large spike in the 3CGH condition is most likely an artifact. The same type of artifact is seen in the session baseline.

No notable deviations from the baseline are found except that low frequencies (4 and 7 Hz peaks) are dominant in AP in the 3CGH condition which, I believe, is due to 3 Hz camelback pulse being responded to by at least some brain process as a 6Hz stimulus.

**Sub. 2:**

3RG : (1/1), (1/2) : The responses look fairly standard for this condition with exception of small low frequency spikes in AP. Significance of these is unknown.

3GG: (4/1), (4/2): Reduced alpha in AP and overall lower level of AP activity is consistent with the resting baseline. There appears some kind of coupling present between AP, HM and HC signaling. HC shows distinct high frequency bursts which have slightly higher power in the H condition. The start of the HC bursts coincides with low frequency spike-like formations in AP and HM. These particular bursts are not obvious in other conditions and may indicate driving of HC excitation by the 3GG stimuli.
Short Summary:
The reduction in the alpha energy in AP that is seen in the 3GG condition and which appears to be in-line with the resting baseline may be significant. It is assumed that suppression of AP alpha in the baseline is due to boredom or fatigue, other words it is correlated with reduced cognitive activity. Alpha energy typically raises in AP during the experimental presentations. This is not observed for the 3GG stimuli, however, which instead produces oscillations in AP primarily at 4Hz. This may correspond to an enhanced relaxation state or it can indicate failure to recruit sufficient AP activity needed for cognitive tasks. It is impossible to tell more from the given data. Likewise, significance of the described coupling between the AP, HM and HC components is not known.

3GG condition generated what may be labeled as mild deviations from the baseline compared to those seen in other conditions. Since the effect of the described deviations on cognitive performance is unknown, 3Hz stimuli does not appear to be a likely candidate for future investigations.

6Hz

Sub. 1:
6CGH (3/5) and 6CGL (3/4): Somewhat subdued bursting in HM with no recruitment of AP or HC. HC does not have high frequencies. The peak in HM is shifted to 12Hz. The beta peaks which are present in the baseline HM and AP are gone. SSVEP is at 5, 12 and 17Hz, with smaller peaks at 23, 35, and 48Hz. The responses in the H and L conditions are analogous except that the L condition shows large 4Hz activity that is absent in H. A large spike at Cz occurred in the L condition. H shows higher cortical activity in OC.

6CBL (3/6) and 6CRL (3/7): The Blue light condition produces clear oscillations in HM with two dominant frequencies, 5 and 11Hz. The activity is clearly stimulus driven. There is limited bursting in HM which is synchronized with AP. SSVEP is present with single 5Hz energy peak.

The Red light condition shows suppressed delta at 4Hz and two alpha peaks at 11 and 12Hz in HM. The suppression of delta is similar to the 6CGH response. AP shows a suppression of alpha that is not seen in other 6C conditions. A sharp spike occurred at Cz 8 sec into trial and it coincided with a start of bursting in HM which is was not seen in other 6C conditions. The spike and the bursting are clearly linked. There is significant cortical activity with posterior dominance. An SSVEP-like source shows large amount of activity at 5, 11, 17, and 23 Hz.

Short Summary:
There are few deviations from the baseline, most notably in the delta energy in HM and the alpha energy in AP.

A suppression of these energies occurs in the R condition. Suppressed delta and alpha are consistent with a subject being in a less relaxed state. The suppression of delta seen in HM in the R condition is analogous to that observed in the 6CGH, but the 6CGH condition produces significant alpha energy in the AP, while the R condition shows suppressed alpha in AP. Thus the R condition appears to produce most deviation from what we know to be a state of relaxation and impact more than other conditions the critical frequencies of the brain. One the other hand, the Blue light produces most enhanced synchronized responses that most closely represent what we would expect to be the rest state.

A spike originating in Cz occurred in 2 out of 4 6Hz trials for this subject.

Sub. 2:
6RGH (1/5) and 6RGL (1/4): HM shows limited bursting with some recruitment of AP in H but not in the L condition. This bursting begins slow, 10sec into the trail. The three global components appear to have similar frequency content in
The exception being a .5 sec train of 4Hz spikes in AP in the middle of the trial. This means very slow global brain waves which would be considered clinically significant. In the L condition, HC has more power in the high frequencies than the HM or AP. The component spectra agree overall with the baseline. AP in L has less significant alpha than HM, showing it is less driven by the stimulus. H generates significant SSVEP type activity in OC with frequency peaks centered at 5, 11, 17, 23, 29, 35, 42, 48Hz.

6RBL (1/6): There is no evidence of bursting or synchrony in the global components, which is highly unusual for the Blue light condition, but spectral features are otherwise consistent with the baseline. Sharp spike is generated at Cz. The TP source is prominent primarily because of excessive spike activity immediately preceding the Cz spike.

6RRL (5/8): Note: this condition was omitted from the first session and was ran instead at the end of the 5th session. Because of an additional mix-up in the 5th session, there is some possibility that mislabeling occurred.

HM component shows large scale oscillations with recruitment of AP that swamp out the rest of the activity. The oscillations have clean 11Hz wave morphology. Correspondingly, AP and HM spectra show dominance of alpha energy centered at 11 Hz. The magnitude of the 11Hz activity in both components is the same as the blink energy, which is significant. HC shows unusual spectrum with peaks at 5 and 11 Hz which indicates its recruitment by the other two global components. HC also contains high frequencies. At the same time there is a high level of posterior cortical activity with the 5, 10, 11, 17, 24, 29, 35, 42, and 48Hz peaks. A sharp spike is generated at Cz 9sec into trial.

6GGH (4/5) and 6GGL (4/4):

L: Small amount of bursting occurs in HM but no recruitment of AP is evident. AP has only low-to-moderate level of alpha energy. Significant central and parietal cortical activity supercedes HC in component order. Some of the cortical sources have dominant theta energy. Also, a central cortical source is present (No. 5) which shows very unusual steady rising energy in all frequencies up to 24Hz. A sharp spike is generated at Cz 9 sec into the trial.

H: The three global components are prominent but no evidence of bursting or synchronization. Alpha is well represented in all components and is dominant in HC which indicates some excitation in the global components due to the stimulus. Nothing else is notable except that there is no clear SSVEP.

6GBL (4/6): No bursting and no synchronization is evident, but three global components remain prominent. HC has reduced high frequency content. There are no notable other deviations form the baseline.

6GRL (4/7): No bursting and no synchronization is evident and OC cortical activity is higher than AP. The energy distribution in the OC component is the same as for the 6RRL condition above. No notable deviations in the global component spectral features. A sharp spike is generated at Cz 8sec into trial.

Short Summary:

Of the 3 types of pulses in this experiment, the rectangular pulse seems to generate most notable deviations from the baseline. Large scale oscillations with global recruitment occurred in the 6RRL condition. The oscillations were not as large as those that occurred in the similar responses to 10, 20, and 30Hz stimuli. The effect of the stimuli preceding the 6RRL trial cannot be discounted either thus it is not clear if the same response would have been produced if 6RRL trial occurred in the first session.

Nevertheless, even discounting the large scale oscillatory response, the 6Hz stimuli produced a number of responses that appear to be outside the norm. There was a clear absence of rhythmic activity and synchronization in most conditions, including all three colors of light for the Gaussian pulse.
Red light does not promote rhythmic activity in the global components, but the absence of clear bursts in responses for other colors is odd. Red light appears most disruptive overall due to lack of synchronization and pure wave oscillations. A spike with Cz origin occurred in every Red light 6Hz trial. The combination of the Red light and rectangular pulse produced the most extreme oscillatory response for the 6Hz condition.

The rate of spikes with Cz origin was by far the largest for 6Hz among all frequencies. The rate was 50 (for Sub. 2). 3 spikes occurred during Red light trials, 1 spike occurred during Blue light trial, and 2 spikes occurred during the Green, low intensity trials.

As the whole there was enough anomalous activity observed for the 6Hz conditions to warrant further investigation.

10 Hz

Three trials were run twice at this frequency as a control. 10GGH condition was presented to Subs. 1 and 2; 10RGH was also presented to Subs. 1 and 2; and 10CGH was run twice with Sub. 1. The results for the 10RGH condition were in agreement for the two subjects and the results for the 10CGH condition were consistent between both trials. On the other hand, the 10GGH produced what appears to be a transition into a different dynamic regime in Sub. 1 but not in Sub. 2, possible reasons for which are discussed in the Summary below.

10RGH: Sub. 1 (1/4) and Sub. 2 (1/3). The responses for the two subjects were consistent as described below.

Sub. 1: An increase in energy at 4Hz and a shift to 12Hz from 11Hz in HM; Alpha dominance is seen in AP, predominantly at 7Hz and a shift of peak power to 12Hz. Increased beta is seen in HC. Overall consistency with the baseline. SSVEP moderately weak relative to the high background with peaks at 10, 20, 40Hz. Central parietal cortical source with sustained oscillatory activity is present.

Sub. 2: Increased alpha in AP and also to a lesser extend in HC. Overall consistency with the baseline. The TP source is active with prominent alpha energy. SSVEP is well defined SSVEP.

10RGL: Sub. 1 only (1/5). Overall consistency with the baseline except for the absence of the 30Hz AP component. Furthermore, AP was not as well defined in the decomposition. Background activity is diffused and posterior dominant with energy in theta to mid-alpha range and peaks at 20 and 40 Hz. Significance of this 20 and 40 Hz activity is unknown.

10CG: Sub. 1

10CGH: ran twice: (1/2) and (3/3)

10CGL: (1/3): This was the first experimental trial after the two baselines. The activity reflects recruitment of AP and HC components by the HM component, which is a normal occurrence. Aside from this, no significant deviations from baselines are seen.

10CGL: (3/3): In the 3rd session an increase is seen in posterior diffused theta and low-alpha activities but this is consistent with BASE3. SSVEP is present and strong at 9-9.5Hz in all trials but the rise in the theta-alpha background makes this peak less distinct. Findings overall are within the norm.

10GGH: Sub. 1 (1/6) and Sub. 2 (4/3)

Sub. 1:

Large scale frankly excessive in amplitude AP oscillations at 10Hz - 10.5Hz. The activity may be slightly dichotomous or distributed since it is represented by two components. HM is not evident in the decomposition and possibly was
recruited into AP oscillations. HC is present with dominance at 10-10.5Hz. A central-parietal source is also 10Hz dominant. SSVEP is present but weak relative those observed for other experimental conditions. Moreover, 10Hz is absent in the SSVEP and instead 20Hz is present.

Sub. 2 (4/3):

The trial is in the 4th block which has poorly presented AP in the baseline. However, AP is normalized by the first two 3G stimuli and appears normal and has clear increase in alpha (10-11Hz) activity over the baseline. HM does not appear to be recruited by the AP as in the case of Sub. 1 but it shows some bursting. HC is consistent with the baseline that has enhanced alpha in 9 - 10Hz range. Increased amplitude high frequency bursting is evident in HC but is consistent with the rest of the subject responses in block 4. The same central parietal source as for Sub. 1 is prominent and has 4Hz and 9-11Hz peaks. Widely distributed, sustained occipital and parietal 9 Hz SSVEP with well defined bursts is present.

Short Summary:

The only condition which produced a strong deviation from the baseline in the 10Hz experiments was 10GGH. In Sub. 1 it led to the transition to the large amplitude oscillatory regime with AP dominance and recruitment of all the global components. Sub. 2 did not produce the same response. The L condition, i.e. 10GGL was not part of the in the stimuli, so no comparison could be made. Although no significant deviations from the baseline were found for the 10GGH condition for Sub. 2, HM presents weaker and shorter bursts in this subject, which may indicate some dominance of HM by AP, consistent with the response by Sub. 1.

Analogous oscillatory responses were produced by frequencies which are multiples of 10, i.e. 20Hz and 30Hz stimuli. This supports the conclusion that this response is not an aberration, but that these frequencies can induce what looks like excessively large oscillations in the brain.

Several explanations may be found as to why the two subjects responded so differently. The oscillatory response observed for Sub. 1 is not simply an extreme case of a normal activity as observed in the baselines. What is observed is a qualitative change in the brain dynamics. It is possible that Sub. 1 has the bifurcation point for this transition that is easier to reach or trigger than a similar point for Sub. 2. The pre-stimuli periods for Sub. 1 show a high degree of pure frequency oscillations, often expressed as bursting, and a large degree of coherence between the three global components. Sub. 2 does not show the same degree of pure oscillatory activity and coherence between the global components in the baselines. Therefore, because high level pure waveform oscillations is already present in Sub. 1 global dynamics, it is feasible that Sub. 1 may be more easily moved into the observed high oscillatory mode.

The order in which the experimental conditions were presented and their cumulative effect can also be a factor in the different responses seen in the two subjects. The 10GGH trial for Sub. 1 was preceded by four other trials having 10Hz stimuli. This was the only instance when trials with the same frequency were presented consecutively more than twice. It is feasible that the repeated exposure to the 10Hz pulses made is easier for Sub. 1 to shift into the high oscillatory regime during the 5th 10Hz trial. Sub. 2 was not exposed to any other 10Hz stimuli prior to the 10GGH presentation.

However, the same high oscillatory response occurred for Sub. 2 twice during the experiment - the same number of times as for Sub. 1. One of the trials that elicited this response in Sub. 2 is the 30RGH trial, which has frequency that is a multiple of 10Hz. The second episode of this response was elicited by a 6Hz stimulus after a long series of presentations, 8 trials with high frequencies, including the 30Hz frequency, and, in addition, broken up by several successive on and off switching of the lamp by error. The cumulative effect of the preceding trials could not be discounted in this case.
Sub. 1:

12GGH (5/5) and 12GGL (5/6): The responses appear fairly close to the 1st baseline. Both H and L conditions present synchronized alpha in HM. AP is clearly raised to Baseline 1 level from the non-existent level in Baseline 5 and has synchronized alpha activity. However, the alpha activity has wide 8-11Hz distribution, and synchronization between AP and HM is not well defined. For L: 4Hz power in HM is removed entirely and HC is not well defined; For H: The bursting activity is less well defined in HM and AP as compared to the L condition. Bursting is also weak than in the L condition or not present at all at parietal sites. A TP source is prominent and a slow 4Hz burst is seen at the very end of the trial at this source. SSVEP is present for both conditions with distinct peak activities at 24, 36, and 48 Hz. The location of the activity is low occipital lobe with at least two localized sources. One of the sources with peaks at 24 and 48 Hz frequencies in both L and H condition, has very low occipital position, close to mid-line. There is a possibility that a source appearing so far down the skull originates from the cerebellum.

12RGG (2/5) and 12RGL (2/4): Overall, very large bursting alpha activity in HM and AP with periods of suppression not very well defined. Also significant is the excessive and anterior directed HC activity which is on the order of HM and AP in both. It contains equal power in evenly distributed theta and alpha frequency ranges for L. However, for H, the HC component is predominantly in at 4Hz. In the L condition AP has activity in the 4Hz as well as in the alpha range, but with the superior peak shifted to 12Hz and sub peak at 11Hz and inferior at 39Hz. HM activity remains superior at 11Hz with baseline equivalent activity at 4Hz. In the H condition, the far dominant AP component is at 4Hz with suppression in the alpha range. HM energy in alpha range has a sharp superior peak that is shifted to 12Hz and an equal power in 4Hz.

TP source has a strong presence with sustained and excessive in amplitude low-theta burst activity that is an order of magnitude larger in H than in the L condition and, significantly, is an order of magnitude larger than the HM and AP burst activity. The predominant power of the bursts is 4Hz for the H condition and at 4.5-6Hz for the L condition. A notable feature is that for the H condition, the bursting undergoes complete suppression at 7.5 sec into stimuli. In this condition, bursts begin almost immediately (.5 sec) followed by on-off suppression after 5 sec with complete suppression at 7.5 sec. In the L condition the bursting starts at 5 sec into the stimuli followed by a slight downgrade in amplitude after 3sec and then increase in amplitude again with no suppression.

12RBL (2/8 and follows the 12RRL stimulus): Bursting of equal power is present in HM (peak power at 3.5Hz, 9, 10.5Hz), AP (superior peaks at 4.5Hz and 10Hz, sub peaks at 28 and 33Hz), and HC (with background levels in the theta-alpha bands, peak power at 4Hz and 10, 11Hz, and a sharp drop off after 11Hz). Unlike the Green light condition, alpha is normalized to 10-11Hz that is the resting alpha for this subject. Also, AP and HC have higher power in alpha than the preceding stimulus, that is larger oscillatory activity which is consistent with the other Blue light conditions. AP has large localized peaks at 28 and 31Hz, the same as in the baseline. HC activity is constant, sustained, and is higher than the baseline but the residual effect from 12RG cannot be ruled out. Occipital SSEVP is not well defined (3 sources total), dominated by evenly distributed theta-alpha 4-11Hz and higher than normal beta background up to 40 Hz. Localized peaks above the background are at 24, 36, and 48 Hz. A large spike was generated by the Cz source.

12GBL (5/7 and follows the 12GRL stimulus): Here background shows posterior dominance with low frequency of 4Hz possibly affecting HM. Localized parietal activity at 11Hz and upper occipital at 11.5 Hz are above HC and also show significant energy at 4Hz. HC appears normal but weaker than the localized parietal and upper occipital activity. Occipital SSVEP is dominated by evenly distributed 4-11Hz power plus localized peaks at 24 and 48 Hz.

12RRL (2/7 and followed 12RGH stimulus): There was a short mishap at the beginning of the presentation of this
stimulus where the Red and the Blue lights were both switched on for a short time, then switched off together, and then the 12RRL stimulus was turned on. The power distribution closely resembles 12RGH in HM (identical power in 4 and 12 Hz). The shift to 12Hz in the alpha activity may be significant but it could be due to the residual effect from the preceding 12RGH stimuli. AP has superior peak at 4Hz and equal peak at 28Hz - consistent with the baseline. HC shows rise in 12Hz not present in the preceding 12RGH condition. Note that 12Hz max alpha was also present in the 12RGL condition. The bursting is not apparent in any of the components, but a sustained SSVP central parietal source (11.5 and 24 Hz) is present.

12GRL (5/6): Well defined 11Hz bursting is seen in HM. Absence of bursting in AP, with power distribution analogous to Baseline 1. HC also follows baseline spectral distribution. Rapid eye or ocular muscle movement is evident. Strong occipital SSVEP with 11.5, 23, 35, 48Hz frequency peaks.

**Short Summary:**

The response to the 12GG condition was found to be mixed. It was consistent with the resting conditions, especially the 12GGL stimulus, but there was less synchronization and bursting in parietal sources than in the resting conditions. Strong OC activity is also present significance of which is unknown.

12RG have presented significant deviations from the baseline rhythms. The changes were significantly more pronounced in the H condition but they may also be significant for the L condition. Excessive low-theta bursting at TP may be related to the mu-rhythm and may have ramification on motor related functions. Overall rise in focal as well as global 4Hz activity that is seen in several components, in particularly in H condition would be considered to indicate dysfunction (i.e. encephalopathy) in clinical evaluations.

12RB and 12GB conditions did not produce a TP source that was seen in the Green condition. Instead, a localized strong central parietal source is present with theta-alpha range. The core activity power in the theta-alpha range appears closer to baseline than in the 12RG condition, but more deviant from the baseline than in the Red conditions. However, high beta background is present in 12RB and no clean bursting is presented. These conditions were not observed in 12GB. The presence of localized 28 and 33Hz in AP for 12RB (28Hz was also seen for the 12RR in AP) is consistent with the baseline. These beta peaks were absent in AP in the case of green light. Theta-alpha frequency posterior dominance with no distinct alpha frequency SSVEP in both of the Blue conditions and a high level of beta in 12RB condition may indicate nontrivial interference with normal activity.

12RR: Burst activity is almost completely absent and power distribution similar to 12RGH although the residual effect by the preceding 12RGH stimulus as the cause cannot be ruled out. Therefore, no conclusive decision could be made with respect to 12Hz shift but the overall response is distinct from 12RGH. Analogous to the Blue light, Red light did not produce significant TP source activity that was seen in the Green condition.

Sub. 2

12CGH (3/5) and 12CGL (3/4): The Low intensity trial shows normal levels of bursting in HM, no bursting but spike formations in AP, which also have normal appearance, and high frequency bursts in HC, also a typical response for this subject. The High intensity trial does not show bursting in HM and AP appears to be slightly smaller in amplitude. HC does not contain sustained high frequency bursting activity. The spectra for these components appear to agree with the baseline except for the presence of a 24Hz peak in HC and higher beta energy level around 24Hz in the other components. The elevated energy level around 24Hz provides evidence that the 12Hz Camelback source is being perceived as a 24Hz signal.
A prominent superior parietal source is seen in both intensity conditions and it is also seen in the 4th baseline. At least two TP sources in each of the conditions are seen with bursting activity in alpha range.

12CBL (3/7) : HM and HC components are not clearly separated compared to the separation of these components in other conditions. The two components which may relate to HM and HC, namely components 2 and 4, describe activity split between frontal and posterior region. The power spectra of the two components resemble spectra characteristic to the HM component rather than HC. High beta energy is not evident in either of these two components. Curiously, wide spread high beta energy exists in the AP component. Importantly, there is no bursting or pure periodic oscillations, except for two short instances of $\approx 0.5$ sec in the second component. Also, the global components are not synchronized. This is a highly atypical response to the Blue light. AP in particular, exhibits primarily erratic activity with spiking characteristic of the Red light response. The range of AP activity is almost evenly spread through upper delta to upper alpha (3 to 12.5Hz) and continues on to the beta range. It is suspected that the two conditions were reversed during the experiment, that is the Blue light was presented in place of the Red light and visa versa. Of note, alpha energy has a peak in the high-end of the range, at 12.5Hz, in the HM and AP components.

A strong bilateral TP source is present, expressed in components 6 and 8 in the decomposition. It is showing a strong mu-wave activity. No separate SSVEP source is evident.

12CRL (3/6): A number of short bursts is present in all three global components and the components are highly synchronized. Bifurcation into higher and regular oscillatory regime occurred at $\approx 8$ sec and affected components HM and AP. The spectra for these components is not outstanding. The overall presentation in the MEG is consistent with the Blue light condition, indicating that the Red and Blue light conditions might have been switched during the experiment. Strong mu-wave activity is present at bilateral TP source and a central posterior source, which may be an SSVEP source.

18Hz

Subj. 1: 18GGH (5/3): HM is the only main component that is well defined in the decomposition. The component has dominant energy at mid range theta 6Hz and a weak peak at 11Hz. AP is not well defined, which this is consistent with the baseline. HC is also not well defined, but that is different from the baseline. However, a closer to the skull, HM like source is present with 10.5Hz peak. The most distinct activity that is seen is the TP source activity that at the start of stimulus has very large amplitude which is sustained for 2 sec and followed by a complete shut down of activity at this source.

18GGL (5/2): A dichotomous spike-wave formation occurred approximately 4 sec into stimulus. The spike coincided with a short, approximately .7 sec duration large amplitude oscillations in HM, which span the time of the occurrence of the spike. Presence of these features in the signals may affect the power spectra commuted for the overall time series. Spikes were observed in two baselines but in those cases had different topology and apparently different sources. The spikes occurring in the baselines were not associated with the main components and did not have coincident excessive HM activity spanning the time of the spikes. Also, AP is not present in the 5th block baseline. Overall, it is difficult to tell conclusively whether the spike was induced by the stimulus or was part of this subject’s standard activity.

Spectral content of the two AP sources show very high flat spectrum in delta-theta range and a low alpha (6 and 7 Hz) with sharp drop off beyond 6-7 Hz. A widespread 20Hz peak is present in both. A rise in energy in the 23-38 Hz range
is also present but such a rise is also seen in the Block 1 baseline. HM shows energy at 2Hz, then mid-peak at 4Hz and high peak at 6.5Hz after which there is a sharp drop off in energy until a wide peak at 19Hz and smaller one at 25 Hz. The frequencies in the 13Hz range in both components are too low to be considered clinically normal. A distinct SSVEP source has high delta-theta-alpha background, with high peaks at 6.5, 9-10, and 18, 36Hz. TP source is not present.

18RGL (2/2) and 18RGH (2/3): General observation: These two conditions followed the 20RGH condition which caused massive AP oscillations. AP amplitude remained relatively high in the responses to the 18RG conditions, being similar to the amplitude of the HM oscillations. It is not possible to tell whether this was due to the 18RG condition or to the residual effect from the preceding 20RGH condition.

The H condition: A rise in the theta power is seen: The 4Hz peak in HM is close in power to the 11Hz peak. Also a peak at 23Hz is present but no significant activity at 28 and 32Hz. AP shows shift to higher alpha with peaks at 11 and 12.5Hz. Also very large peaks at 24 and 28Hz, widespread distribution of power at 37-39Hz range, and a mid-level activity at 45-50Hz. HC consistent with the baseline for 1-11Hz, except the high power range extends to 12Hz here; higher background beta activity with mid-range peaks at 23-24, 28, and wide distribution at 37-39Hz range. No TP source but upper parietal slightly right source with evenly distributed theta-alpha energy and a large peak at 23.5Hz is present. SSVEP is present but is relatively weak with large delta-theta-alpha background that is close in power to the 18Hz peak. 36Hz SSVEP is also present.

The L condition: Follows directly after 20RGH and produces large 11Hz bursts in HM, AP, and HC. HM and AP are synchronized but HM appears to have overtaken the control, i.e. initiation of bursting in HM precedes associated activity in AP and HC. This is a normal pattern of recruitment for this subject and indicates a return to normal function after the 20RGH response. The general topology in delta-theta-alpha range is consistent with the baseline except that HM has a peak at 11 and 12Hz, beta is suppressed overall with only the 37Hz peak present. SSVEP is well localized and does not have large background activity.

Sub. 2:

18CGH (3/3) and 18CGL (3/2): HM appears normal in the theta-alpha range but is missing the beta peaks although it is consistent with the session baseline. AP presents alpha activity with a broad spectrum but also peaks at 18, 22 (L condition), 24 (H condition), 36, 37 (L condition), 39 (H condition) Hz. HC appears normal. OC and central midline are dominated by high beta with high energy at 18Hz, and even higher at 22-23Hz. 36Hz peak is seen in several OC components, and exists as an isolated peak in a low-OC source. This source also shows high peak at 8Hz for the H condition. The origin of source with such a low position in the scalp could be cerebellum.

Additional notes: 18CGL (3/2): Vertically directed positive spike with rounded negative component occurred in Cz. The morphology and location of the spike is different from the spikes observed in the baseline for this subject. Rather, the spike is consistent with those generated by the Low intensity 6Hz stimuli. 18Hz is a multiple of 6Hz frequency. Furthermore, a Camelback pulse could be perceived as 36Hz Gaussian pulse. The occurrence of the spike for this condition supports the finding that 6Hz (and possibly some multiples of 6Hz) Low intensity light induce spikes.

Short Summary:

The 18Hz conditions did not induce the bifurcation response observed in 20RGH condition. Nevertheless, significant deviations from the baseline activities were found. 18RGH and 18CGH, 18CGL produced large 22-24Hz activity in the main components as well as in the parietal cortical (and additionally in OC for Sub 2) components. The significance
of such high beta cortical activity is not known except that it shows significant recruitment of cortical processes toward some sorts of activity. These beta peaks were absent in the 18RGL condition (Sub 1) but present in both L and H condition in Sub. 2. It should be noted, though, that the 18Hz Camelback pulse may be perceived as a 36Hz pulse. 18Hz conditions also induced higher frequency than normal alpha (12 and 12.5Hz) activity in the main components in Sub 1 which could prove significant for this subject. Finally highly focal in the low OC area 36Hz activity was observed in 18RGH 18CGH, and 18CGL conditions and may have cerebellum origin.

18GG condition (Sub. 1) presented a shift to low alpha (6-7Hz) which is considered abnormally low and appearance of 2Hz in HC is also considered abnormal. The two distinctive responses were the shutdown of TP for the H condition and a deep dichotomous spike-wave discharge with associated excessive burst semi-regular HM burst activity. Sub had high OC activity in the 7-40Hz range for the H condition.

18CGL (Sub. 2) also produced a spike with Cz origin with morphology and topology different from the baseline spikes but consistent with spikes induced by the 6Hz stimuli.

The findings for 18Hz trial, taken as a whole, in my opinion indicate significant alteration in the normal brain activity.

**20Hz**

Sub. 1:

20GGH (5/1): Suppression of alpha in the global components is seen. Alpha is also weak in cortical components. Beta is low. A single SSVEP peak at 20Hz is well defined. Normal amount of bursting and synchronization.

20RGH (2/1): The stimulus produced the same transition into the global oscillatory dynamical regime seen that was also observed at 6, 10, and 30 Hz. The response to the present stimulus was by far the strongest among these responses. The oscillatory activity which as in the other cases is dominated by AP, is 4 orders of magnitude larger than the baseline AP oscillations. Its frequency range is 8-10.5HZ. The generator of the activity is still fairly focal although more diffused than normal since the decomposition produced over 20 of the components with dominant orientation being left-frontal to right-posterior. The two other global components, AP and HM are present but are much weaker than AP. CZ, TP, and low-OC sources are present.

Sub. 2:

20CGH (3/1): Response does not appear to be significantly different from the baseline.

**Short Summary:**

Sub. 1 appears to undergo a transition into a different dynamical regime that presents itself in massive oscillations originating in the hippocampus in response to 10, 20 Hz stimuli. Excessive AP bursting activity also occurred in the 24CGH condition, but in that case it did not overwhelm the other global components to the same degree. The same transformation in dynamics was observed for Sub. 2 in two experimental conditions. Its significance is discussed in the Final Summary.

**24Hz:**

Sub. 1:

24CG: L (4/2): Normal HM except for the shift in peak alpha to 12Hz. AP has flat widespread 4-11Hz theta-alpha spectrum. A couple of cortical sources are present with high alpha activity. HC is normal but has a large 48Hz peak. SSVEP has large theta-alpha activity and 24 and 48Hz peaks. Beta is slightly above the baseline.
H (4/1): Synchronization of global activity with excessive in magnitude alpha bursting is seen. The response is not as large as with the 20RGH case, but is at least 3 times the magnitude of the normal peak activity for AP. The spectra show 10.5Hz peak power for the global components and a couple of cortical sources that are above the background. SSVEP does not have a clear 24Hz above the background and has large theta-alpha spectrum power. Instead a distinct peak at 48Hz is present in SSVEP.

Short Summary:
A flat alpha response in the L condition versus the high 10.5Hz oscillatory activity in AP in the H condition indicates a move toward the bifurcation that was found in responses to the frequencies that are multiple of 10Hz. Based on the responses to other frequencies, the Camelback pulse may be perceived as stimulus with twice the frequency of the presentation. Therefore, it is likely that 24CG was perceived as a 48Hz stimulus which is close to 50Hz. In this case the observed high AP oscillatory response in 24CGH is consistent with responses obtained for the other multiple of 10Hz frequencies.

Sub. 2

24RGH (2/1) and 24RGL (2/2): The two levels produced almost identical components which were also very consistent with the Session 2 baseline. The exception was a less significant AP in the H condition which was likely due to the absence of alpha activity in this component. This is consistent with the observed flat alpha spectrum in AP for the 24CGL condition in Sub. 1. High frequency bursting in HC present in this condition is consistent with the baseline.

24GGH (5/1) and 24GGL (5/2)

H: Produced pure alpha frequency large synchronized bursting between AP and HM. HC may be recruited but is showing well defined alpha activity as well as high frequency bursts.

The rest of activity was consistent with the baseline except for the appearance in CZ of a vertically directed positive spike with rounded negative component identical to that observed in the 18CGL condition for this subject. The morphology and location of the spike is different from the spikes observed in the baseline.

Short Summary:
A few nontrivial observations were seen in the 24Hz case, one of which is the shift in the alpha power to 12Hz in HM in Sub. 1. The absence of alpha in AP for 24RGH or the absence of a dominant alpha frequency in AP for 24CGL may be significant in its affect on cognitive processing but this significance at this point it is unknown. The spike at Cz is consistent with spikes which were produced for several 6Hz conditions and a 18Hz condition which was likely perceived as 36Hz. Multiples of 6Hz were not exclusively the frequencies at which Cz spikes occurred, as discussed below.

The large oscillatory response is AP seen in the 24CGH condition is likely due to the pulses being perceived as having 50Hz frequency and inducing response that is in-line to responses found in the case of 10, 20, and 30Hz stimuli.

27Hz

Sub. 1:

27CGH (4/5): HM appears to be driven by the stimulus although bursting is moderate in amplitude until the end (9.5 sec into the stimulus presentation) at which point a start of a large clear burst is seen. 12Hz peak is present in HM. No recruitment of AP is evident. HC is not present in the decomposition. Delta is present in HM. The 27HZ energy that is
in the baselines is not evident in any of the components. Cortical sources appear somewhat diffused and show elevated delta and beta. A large spike originating at Cz occurred 8 sec into trial.

27CBL (4/6) and 27CRL (4/7):

4 Hz delta is amplified in the global components when color is Blue. With Red color, delta is high but its frequency is shifted up in AP and it is not significant in HC. Higher delta may be due to a residual effect from the preceding Blue color trial. In the Blue color trial, HM shows moderate bursting, but AP is not driven and HC is not recruited. R shows little to no bursting in HM but a synchronization between HM and AP in the first second of the trial occurs. HC is not recruited. Nothing else is remarkable. R shows a well defined SSVEP while B has 10 Hz peak in an occipital component.

Sub. 2:

27RGH (2/5):

HM is driven by the stimuli and shows clean 11.5 Hz burst activity that is moderate in amplitude. HC is synchronized with HM also producing bursts. High frequencies that are typical seen in HM are subdued. Alpha spectrum in AP is flat and low. SSVEP is poorly represented above the background activity. Nothing else notable.

27RBL (2/6) 27RRL (2/5):

The results appear similar to the results for the 27C condition above. The Blue light produces high degree of moderate in amplitude bursting and synchronization between HM and AP. A small degree of synchronization with HC is evident but HC retains its high frequency activity. The Red light shows no bursting or synchronized activity in global components. Blue is the only color of the three tested which produced distinct peaks in alpha spectrum. For the Red light, alpha is somewhat suppressed compared to even the alpha for the Green light. The Red light condition produces a well defined 26 Hz SSVEP while the Blue light produces a detectable SSVEP but the signal is swamped by large delta-theta-alpha-beta background.

27GGH (5/5): Note: There was a mishap with the presentations preceding 27 Hz trials in this session where the lamp was turned on and off several times in rapid succession. There were large gaps between stimuli presentations after this as well. Thus there is a possibility that mix up occurred where trials were not presented in the order that they appear in the schedule.

A synchronized recruitment is seen across HM, AP, and HC, that is moderate in amplitude and centered around 11.5-12 Hz. Alpha peak is present in all three components. HC has suppressed theta and smaller relative to the baseline beta. Typical for this subject high frequency bursts are present in HC. Left parietal and right parietal cortical sources are present and show alpha activity. SSVEP is poorly expressed above the background.

27GBL (5/6) and 27GRL (5/7): Note the order of the two trials appears to be been switched based on the responses.

The results look very similar to the 27C results above if we assume the order of the two trial is switched. 4 Hz delta has the same pattern of activity as in 27C. In the B trial, moderate bursting and synchronization between HM and AP and HC is recruited in the last part of the trial. Recruitment of HC also coincides with decline in high frequencies in HC. R shows no bursting in any of the global components and no synchronization. HC retains high frequency throughout the trial. R shows a well defined SSVEP while B has 4 Hz and 11 Hz peaks in occipital components.

Short Summary:
27Hz does not present as strong of deviations from the baseline as some of the other conditions. The flat alpha spectrum in the G and R conditions indicates failure to synchronize in that frequency range but significance of this with respect to cognitive function is unknown.

30Hz

Sub. 1:
30CG:
The most outstanding feature observed in responses to the 30CG stimuli is the shift in alpha energy to higher frequency. A sub-peak at 12 Hz is actually present in the HM baseline Session 4. But such peak at 12Hz becomes more prominent in both the L and H conditions in HM. The shift of power to 12.5Hz is also present in AP in both conditions, which is not present in the baseline.

In the H condition, the camelback pulse breaks the synchronous bursting in the global components that is characteristic for this subject. However, the bursting in cortical activity remains. All other features are consistent with the baseline and no SSVEP is evident.

Sub. 2:
30RG:
H (2/3): This stimuli produced one of the shifts into the global oscillatory dynamical regime which was observed at 6 Hz for this subject, and 10 and 20 Hz for Sub. 1. The recruitment of all three global components is present. A spike also occurred in HC and AP at the onset of the prolonged burst run that lasted 6 sec. The burst appears to be HM driven and the HM component is excessive (3 times the standard amplitude). The type of response occurring in this subject has an even greater significance because its baselines lack the rhythmic synchronized bursting in the global components that is seen in Sub. 1. Cortical sources are also present and exhibit clean sustained bursting 11Hz waves.

L (2/4): The lower intensity did not produce the shift in the dynamic regime but some synchronization between the global components is evident.

There was a shift in alpha from 12Hz peak in the HM and HC components’ baseline to 11Hz in the H condition. Alpha suppression is present in the AP component in the L condition. Several cortical sources with significant alpha activity are present in both conditions. SSVEP is not clear.

30GGH (5/3):
Recruitment and synchronized bursting is present in the global components but not to the degree that occurred in the 30RGH condition. Alpha activity is present but is flat across the 4-12.5Hz spectrum. Note: Alpha is suppressed in the baseline in the 5th session. HC has high beta activity. Other features are not remarkable and SSVEP is present.

5. CONCLUSIONS

Almost every experimental condition induced changes in the brain dynamics with respect to the baseline and the changes were almost universally different for the different conditions. The effects varied from subtle, such as shifts in the peak frequency of oscillation, to more obvious, such as synchronization of distinct oscillators and emergence of large pure oscillations in the global network. In extreme cases, large oscillations entrained the rest of the brain circuits to a common frequency. This section will summarize what can be characterized as bifurcations or drastic changes in the
intrinsic brain dynamics. However, this should not be taken to imply that other effects from IPS listed in the results section are not significant. More detailed summaries of the effects induced at various IPS frequencies can be found throughout the Results section under the subheadings: ‘Short Summary’. Consideration of the relevance of all the effects was limited by the scope of the contract.

The most obvious deviation from the intrinsic brain dynamics was the rise of very large amplitude oscillations driven by the AP source. The HC and HM activity were synchronized to AP and typically recruited into the same pure oscillatory mode. In extreme cases, the oscillatory mode that emerged was almost the only dynamical feature present in the entire brain. This extreme response occurred twice in Sub. 1, in the 10GGH and 20RGH conditions, and twice in Sub. 2, in the 6RRL and 30RGH conditions. A similar response but with lesser amplitude oscillations occurred in Sub. 1 in the 24CGH condition. As was already observed in the Results section, 24Hz Camelback pulses appear to be perceived as a 48Hz signal, which is close to 50Hz. Since the strong oscillatory responses were triggered primarily by integer multiples of the 10Hz frequency there is a strong possibility that the strong oscillatory response to the 24CGH condition was triggered because the actual input signal was close to 50Hz but the response did not reach the same intensity as, for example, the response to the 20RGH condition, because the stimulus was not exactly 50Hz.

It is further observed that the 20 and 30 Hz Rectangular pulses produced the most unambiguous responses of this type. The 10GGH elicited the response in Sub. 1 but not Sub. 2 and the response in Sub. 1 occurred after 4 other 10HZ frequency trials. This was the only case where the same frequency - color combination was presented more than twice in the row. Therefore, the trigger of the large oscillatory response through a cumulative effect of repetitions of the same frequency trials cannot be ruled out in this case. Similarly, the response in Sub. 2 to 6RRL stimulus (which was run at the very end of the experiment due to operator error) occurred after a long sequence of trials which already elicited strong rhythmic responses in the global oscillators. Therefore, a cumulative effect could be at play in triggering that response as well.

The possibility of a cumulative effect of IPS brings up a question of possible effects which may exist but have not been uncovered in the present study because only short stimuli tra ins were used and because the nature of the stimuli in consecutive trials was changed as much as possible. Longer exposure to IPS than was used in this study may induce similar types of responses for lower intensity IPS, as was the case with the response to 6RRL pulses, or it could induce entirely new responses.

The general conservative conclusion that can be made is that exposure to 20 and 30 Hz stimuli induces a drastic change in brain dynamics. The rise of strong pure oscillations in subcortical generators is likely to have an impact on cognitive processes. As was mentioned in the background section, in the trials where animals made errors in performing tasks they had already learned, the hippocampus always lead the oscillations.

At least two possible models can be offered to explain the mechanism involved in this response. One model is simply the existence of a mechanism that allows coupling of integer multiples of 10Hz external inputs with the global brain oscillators. Another explanation is that the strong gamma rhythms seen in the AP component are enhanced by the external beta and gamma stimuli whose frequencies are close to (or an integer factor of) the intrinsic AP gamma rhythm. One of the gamma peaks in Sub. 2 was at 29Hz, close to the 30HZ signals which produced the dramatic shift in this Subject’s brain dynamics. If the second model is correct, this implies that there may be an individual difference in this response that depends on the frequency of the gamma oscillation characteristic to that individual. Clearly, this question of the mechanism needs to be investigated further if one is interested in eliciting the large oscillatory responses across wide groups of people with a set frequency.
The second consistent effect was the generation of spikes by the Cz source, primarily in the 6Hz conditions, where spikes were generated in 50% of the trials. The Red color 6Hz stimuli produced spikes in every trial. The Green Low intensity 6Hz stimuli produced using Rectangular and Gaussian shaped pulses also induced these spikes, while the Camelback pulses were interpreted as 12Hz signals and did not produce spikes. The same type of spike was produced in 12Hz (RBL), 18Hz, 24Hz, and 27Hz trials. The frequency of the 12RBL trial is a multiple of the frequency of the 6RBL trial, where the analogous spike also occurred. The last 18Hz, 24Hz, and 27Hz trials that also produced spikes all had Camelback pulses. These pulses were likely perceived as 36Hz, 48Hz, and 54Hz signals, all multiples of 6Hz. However, these frequencies are also close to frequencies which are multiples of 7Hz. It is possible that Cz spikes may be generated at an even greater rate for frequencies of IPS that are slightly greater or smaller than 6Hz. Another possible explanation is that IPS in the gamma range (> 30Hz) may produce Cz spikes as well as the IPS around 6Hz. Further investigations would be needed to answer these questions.

The third observation to be discussed here is the flat or suppressed alpha in the global components that is seen for the 24Hz and higher frequencies. Furthermore, there appears to be a reverse correlation between the amplitudes of the global oscillations and the amount of the cortical activity observed during the responses. A rise in the strength of the global oscillations seems to correlate with a decrease in the cortical activity. This is particularly evident with the Blue and the Green light stimuli which were accompanied by large amplitude bursts in the global components. The implication of the extensive excitation in the various cortical areas seen for the 24Hz and higher frequencies is not known. It is possible that the resources which otherwise may be used for cognitive processing are being taxed by these IPS stimuli. If that is the case, prolonged exposure to such stimuli may also lead to fatigue.

Red Rectangular pulses appeared to be the most disruptive condition overall while the Blue Gaussian pulses appeared to induce dynamic patterns which are most closely associated with a relaxed state. The characteristic responses to the Blue light included high delta rhythms in HM and significant alpha rhythms in AP. On the other hand, responses to the Red light were characterized by absence of delta in HM and depressed alpha in AP. There was a distinct absence of coherency among the global components in the Red light trials. Implications of these differences in the dynamics are not known and many scenarios are possible. For example, the less relaxed state could possibly tax the subjects in some way and lead to fatigue. On the other hand, a relaxed brainwave pattern may interfere with the person’s ability to concentrate and attend well under pressure. What is apparent, nevertheless, is that the beta IPS produced consistent shifts in overall brain activity which were greater in impact on the overall dynamics than the effects produced the lower frequency IPS.

Seven to eight seconds into a stimuli presentation appeared to be a critical time during which transitions in brain dynamics were observed under a number of conditions. The spikes at the Cz source occurred most often around 8 sec after the start of the stimulus presentation. Bifurcations into high oscillating modes often occurred around the same time, as in the 12CRL case, for example. Transitions from a high oscillatory mode into a shutdown mode were also observed around the same time, as in the 12RGH case for example.
Fig. 4. Spectra of all 38 COMBI components computed for the first 10 sec of Subject 1, Section 1 baseline.