Spatiotemporal Analysis Of Neuronal Activity During The First Second Of Visual Conscious Perception

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SPATIOTEMPORAL ANALYSIS OF NEURONAL ACTIVITY DURING THE FIRST SECOND OF VISUAL CONSCIOUS PERCEPTION

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

By
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2019
Abstract
Visual conscious perception occurs in less than one second. Using cerebral cortex electrical readings from human subjects during a behavioral visual task, we studied the spatiotemporal sequence of these events. Nine subjects, implanted with 100-300 subdural and depth electrodes in both hemispheres, were enrolled to complete the threshold perception task. The analysis investigated the role of broadband gamma power changes in electric potential in the range of 40-115 Hertz (Hz). In addition to implementing the behavioral task with the research subjects, my contribution focused on using clustering algorithms to analyze the broadband gamma power time-series to visualize the “switch and wave” model during conscious perception using surface maps. I applied K-means clustering to individual data and group data for Perceived trials, Not Perceived trials, and Combined baselines trials. Based on this analysis, we were able to ascertain vertices on the brain surface with comparable time-courses and classify them into anatomical clusters. Four regions emerged from k-means clustering within the cerebral cortex with comparable within-cluster gamma power z-score time-courses for Perceived stimuli. Cluster 1, localized in the visual and higher association cortices, showed initial increases, then decreases, and late secondary decrease. Cluster 2 showed sustained deactivation in the default mode network, indicating switching off during conscious stimulus processing. Cluster 3 and 4, localized in the visual association cortex, medial temporal lobes, and fronto-parietal association areas, showed intermediate and late increases. For Non-Perceived stimuli, only Cluster 1, localized at the visual cortex, showed significance. Only Perceived stimuli displayed a wave of activity that traveled forward and throughout the cerebral cortex with large-scale network switching. I conducted novel k-means clustering analysis with combined baseline trials. These conclusions are crucial for comprehending the basis of normal conscious visual perception, which ultimately may have implications for tackling brain disorders.
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Statement of Purpose

This study examines the neuronal activity of conscious and non-conscious visual perception and processing using a behavioral paradigm and neuroimaging modalities. We hypothesized a “switch and wave” phenomenon occurring in the first second of consciousness. To tackle this hypothesis, intracranial electrodes implanted in the human subjects captured the cortical electrical signaling during the threshold visual perception task. One of the main aims was to analyze the broadband gamma power changes in electric potential to track population neuronal activity. To complete this aim, I directly contributed to the data collection. Then, I employed k-means clustering for individual and group data for Perceived and Not-Perceived trials, and Combined baseline trials, a novel contribution. These clusters of data were then spatiotemporally mapped on a cortical surface to visualize the brain activity during the first second of visual consciousness. This mapping offers insight into the cortical function, which can be applied to other disease states.
Introduction

In cognitive neuroscience, understanding the differences in brain activity of conscious and non-conscious perception of a visual stimulus is a significant question. Neural correlates of consciousness (NCC) is a particular pattern of brain activity that relates to a specific conscious phenomenon. How a physical process like neural activity can cause subjective awareness is still unclear.

Yet, the field continues to examine, test, and characterize NCC, particularly consciousness in vision. Providing an abundance of anatomical and physiological data, the human visual system has been well-studied. A theory-driven approach for studying NCC for visual consciousness is the global neuronal workspace (GNW) model of consciousness (Gaillard et al., 2009). In the workspace model, for visual information to reach consciousness, the interconnection between the workspace neurons allows for greater spread of information to the other brain processors. This global accessibility of information produces each individual's intrinsic experience of the conscious state. Another model features “ignition” of extensive cortical activity, both gamma power and evoked response amplitude, associated with successful recognition and conscious perception processing, which is not seen in unobserved trials (Fisch et al., 2009).

Even with this model, at present, a cohesive comprehension of conscious perception has not been determined. To develop the cohesive understanding, we aimed to investigate the spread of brain activity across all cortical networks with particular attention to the temporal sequence of events.
In our research, we focused on evaluating the “switch and wave” theory (Herman et al., 2017). We hypothesized the neuronal activity in the first second of consciousness. In the presence of stimulus, the primary visual cortex is activated within 0-200 ms; if the stimuli are perceived, higher order association cortices are also triggered. These polysynaptic connections activate a “switch,” stopping the primary visual and higher order association cortices and instead, triggering a “wave” through hierarchical processing cortices in the next 200-600 ms. Facilitating memory formation during the processing phase, the wave travels through higher association cortices such as the frontoparietal region and temporal medial lobe. The default mode network activity in the primary visual cortex and higher cortex continues to be deactivated to deter internal stimuli from inserting into the processing activity. In the post-processing period at +600 ms, the primary and higher cortex reactivates to allow the individual to present his or her perception while the default mode network remains deactivated.

To investigate this hypothesis, we will be employing various methods such as behavioral studies and cognitive neuroimaging. Behavioral studies have been a mainstay to understand NCC. Recent studies have aimed to reduce methodological confounds. Additionally, cognitive neuroimaging like functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) have proven to boost progress in consciousness research. Given there is no direct visualization of an individual’s subjective perception of a stimulus, correlations between behavior (ie: pressing a button) during visual experience and monitoring of brain states (ie: MEG, fMRI, EEG) are
used to investigate NCC. The following studies will serve as a review of how all three modalities have been used to examine visual consciousness in the recent past.

Li, Hill, and He examined subjective awareness using behavioral measures such as objective performance, subjective awareness, and confidence level using a stimulus-task paradigm (Li, Hill, & He, 2014). Subjects were shown, among blank patches, a Gabor patch with two different orientations. After which, subjects were asked perception questions, orientation discrimination, and confidence level. Combining the behavioral measures with MEG recording, the authors tracked the brain activities underlying conscious perception.

Also investigated was the slow cortical potential (SCP) hypothesis of conscious awareness, which suggests that these low-frequency (<4 Hz) components of the brain field potentials, may be correlated with conscious perception (Li, Hill, & He, 2014). Results showed significant widespread dissemination of SCPs in correlation with subjective awareness after effects of objective performance and confidence were removed. This activity continued for up to 2 seconds after stimulus onset in the fronto-parietal and temporal cortical areas. Juxtaposing this lasting effect of conscious processing, transient brain activity supplied objective performance and confidence.

These results were consistent with the GNW model with regards to late (>200 ms) activity and participation from various brain regions. In contrast to the GNW model, the study included very slow activity, allowing persistence of brain activity for ~2 s as opposed to 200-600 ms from the GNW model. Instead of “global
ignition” found in the GNW model, the authors theorized “global inhibition” as supported by the slow potential and P3b potential, a subcomponent of event-related potential (ERP) that plays a key role in information processing, in the late EEG activity (Li et al., 2014). This activity implies decreased cortical excitability is as a way of updating working memory and preventing unrelated information from reaching consciousness.

With the aim of teasing apart cortical excitability and differentiating true NCCs from “pre-conscious” and “post-perceptual” processing, new paradigms have utilized the modified inattentional blindness paradigm. First tested by Mack and Rock (1998) in behavioral studies, this paradigm tests a backward masking experiment using a 2x2 crossed design to examine task relevance and visual perception (Pitts, Metzler, & Hillyard, 2014). In that study, subjects who perceive a task-irrelevant condition with a preceding distractor phase produced a visual awareness negativity (VAN) component, a mid-latency occipital-parietal ERP negativity around 200-240 ms (Pitts et al., 2014). The masking stimuli may have interfered with pre-conscious processing, resulting in the absence of neural components preceding the VAN. However, subjects who perceive a task-relevant condition without preceding distractor phase generated P3b potential around 380-480 ms after the VAN (Pitts et al., 2014). These results imply that some NCCs may be associated with the retention of visual perceptual information for recall rather than true conscious perception.

Functional neuroimaging allows visualization of brain activity during true conscious perception. Capturing with high temporal resolution, MEG and scalp
EEG have the ability to track sequence of conscious processing on the order of milliseconds. MEG studies, for example, have examined the neural relationship between visual awareness and spatial attention (Li et al., 2014; Wyart & Tallon-Baudry, 2008). Wyart and Tallon-Baudry enrolled subjects to complete a spatial cueing task while recording MEG signals to test awareness and spatial attention as separate experimental variables. With stimuli-presentation, the authors found a neural disassociation between visual awareness and spatial attention within various frequencies in the gamma range (Wyart & Tallon-Baudry, 2008). Though both caused oscillations within the gamma-band range, awareness and attention proceeded in different time-courses with the aware-unaware effect preceding that of attention by >100 ms. Moreover, consciously seen trials induced increased mid-frequency gamma-band activity over the contralateral visual cortex, whereas spatial attention changed high-frequency gamma-band activity in response to both consciously seen and unseen stimuli. The topographies were distinct for both awareness and attention indicative of varying neural sources (Wyart & Tallon-Baudry, 2008).

Through electrocorticography recordings or local field potential (LFP) electrodes implanted in human brain tissue, studies have enabled accumulation of functional mapping in relation to cognitive activity such as error detection, language, and memory with good temporal resolution (Bechtereva & Abdullaev, 2000). Scalp EEGs can also distinguish late ERP differences between contact points in various cortical regions for perceived and non-perceived stimuli (Del Cul, Baillet, & Dehaene, 2007). Comparing local field potentials and fMRI signals from
auditory cortex, there is significant correlation, indicating LFP and fMRI signals are a good surrogate for neuronal firing during stimulus (Mukamel et al., 2005). Moreover, the measurement and examination of the broadband power changes in electric potential, particularly the gamma frequency ranges (30-150Hz), can function as proxy for local neuronal activity and firing rate across individuals and brain sites (Manning, Jacobs, Fried, & Kahana, 2009). Broadband spectral change is a marker of local neuronal activity, likely correlating with mean, asynchronous neuronal population activity, during task engagement (Manning et al., 2009; Miller et al., 2014).

Scalp EEG and MEG do come with some limitations. ERPs do not indicate increases or decreases in neuronal activation, merely changes. Scalp EEG and MEG also are impacted by movement artifacts, which can contaminate gamma band power during cognitive activities (Muthukumaraswamy, 2013). Scalp EEG and MEG are also not able to access structures directly below the scalp that may play a crucial role in cognition (Lovstad et al., 2012). Yet, the progression of ERPs using scalp EEGs have shown that early events in the occipital regions do not change with perception (Del Cul et al., 2007). There is similar activation of the visual cortex post-stimulus regardless of perception. Differences emerge around 300 ms for perceived stimuli (Dehaene et al 1998).

Using techniques like electrophysiology, psychophysiology, functional neuroimaging, the field continues to examine neural changes with consciously perceived and non-perceived stimuli. Recent neuroimaging studies indicate associations between NCC for visual consciousness and the ventral region of the
visual cortex connecting with particular areas of dorsal prefrontal and parietal cortex (Hesselmann, 2013; Rees, Kreiman, & Koch, 2002). But the neural activity related to visual consciousness is jumbled with response and other neuronal signaling, which requires disentanglement.

This study aims to investigate the neuronal activity involved in visual perception. The “switch and wave” model serves as a foundation for our hypothesis for examining the neuronal activity throughout the cortices with attention to the time sequence of events (Herman et al., 2017). Subjects implanted with 100-300 subdural and depth electrodes were enrolled to complete the threshold perception task. After task completion, the subjects were asked to state if the stimuli were perceived or not perceived. To obtain relevant mapping, we aggregated data from electrodes after a behavioral paradigm. The analysis investigated the role of broadband gamma power changes in electric potential in the range of 30-115 Hz. Gamma power changes have been shown to function as a surrogate for local neuronal activation (Manning et al., 2009). Broadband spectral change also serves as a marker for a neighborhood of neuronal activity (Miller et al., 2014).

I directly contributed to the data collection by implementing the behavioral task with the research subjects. Additionally, I conducted k-means clustering analysis on the broadband gamma power time-series to visualize the “switch and wave” theory in action during conscious perception, which resulted in the co-authorship of a paper, as well as co-authorship of several abstracts (Herman et al., 2017; Xiao et al., 2016; Kronemer et al., Abstract 646.04, 2016; Xiao et al., Abstract 646.12, 2016; Kronemer et al., 2016). Additionally, I conducted novel k-
means clustering analysis with combined baseline trials, which produced interesting results that require further investigation. Overall, these analyses provide insight into the spatiotemporal progression of electrical activity during the first second of consciousness. These conclusions may serve as a foundation for understanding various neurological disease states.
**Experimental Paradigm:**

From the Yale Comprehensive Epilepsy Program, twelve adult patients with craniotomy were enrolled for the study. Ultimately, nine subjects, who had between 114 and 286 implanted subdural and depth electrodes, were included in the data analysis. Three subjects were excluded because of insufficient data collection.

A threshold perception task served as the behavioral paradigm (Ress & Heeger, 2003; Wyart & Tallon-Baudry, 2008). At least two days after implantation, I helped test the subject daily as tolerated. An initial calibration run is conducted to determine perceptual thresholds of the visual stimulus, a black and white picture of a face. In all subsequent trials, this stimulus is titrated per subject to allow for 50% detection threshold.

![Figure 1: Behavioral task for report of perception.](image)

(a) For a single trial, a 10s of fixation is followed by a 6-10s jittered pre-stimulus interval. A 50ms face stimulus is shown in 1 of 4 quadrants for 50ms for 50% of the time. The face appeared over one of two backgrounds, which appeared 50% of the time: one with static white noise with no audio (seen here) and another with both audio and video featuring a movie about underwater sea life. After a 1s or 15s post-stimulus delay, the subject must report his or her perception and the location of the stimulus. (b) In a blank trial, when a face was shown, the subject’s perception was on average at 52% (± 3% SEM) versus when a face was not shown, it was at 9.7% (± 3% SEM). There was no significant different for the 1s versus 15s delay. (c) When a face was shown and detected, the exactness of locating the face was 89% (± 3% SEM); but if the face was shown and not detected, the accuracy of the location decreased to 28% (± 2% SEM).

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Each testing run lasted between eight to fifteen minutes and consisted of 28 to 32 face trials. The run would begin with the subjects fixating for 10s on a white cross upon a solid gray background. Next, there would be a randomly jittered prestimulus interval lasting 6-10s. Jittering is a common practice in tasks to make the onset of a stimulus unpredictable. It also can be advantageous for analyzing neuroimaging data collected concurrently.

Then, the visual stimulus appeared for 50 ms in 1 of 4 visual field quadrants on the screen in a random order (Figure 1). The identical face stimulus avoided confounds to conscious perception between trials. The face appeared over one of two backgrounds, which each appeared 50% of the time: one with white-black static video with no audio and another with both audio and video featuring a movie about underwater sea life. The movie served to mimic events in real life; the static video was added lest the movie interfered with the brain activity. The subject was also made aware that some of the trials had blanks with no face stimuli without stating that the blank rate was 12.5%.

After either a 1s or 15s post-stimulus delay, the subject was forced to report his or her perception and the location of the stimulus. The 15s delays served to ensure that the report response was not just automatic but was due to conscious perception. The 1s delays were tested to make sure that the “not perceived” trials in the 15s delay trials were not just due to forgetting. The 1s and 15s delays helped to distinguish between events related to early conscious perception of the stimuli and later events due to questions or motor response. Only data before report was used for analysis.
Using NATUS/ Neuroworks, a platform used to collect, monitor, and manage data from EEG testing, each trial session’s EEG was documented at 1024 Hz with a high-pass filter of 0.1 Hz and low-pass filter of 400 Hz. To reduce the impact of observable noise artifact, signals were compared and recorded relative to a reference electrode selected by the research team. The relevant EEG was trimmed from the entire session’s recording in NATUS/ Neuroworks. Since all the transistor-transistor logic (TTL) pulses differed in time lengths, the TTL synchronization pulses were fitted to the template pulses for significant events like face identification, question presentation, answers, and trial beginnings. An epoch of 2s (2048 samples) was isolated, aligned around the face-stimulus onset. These epochs were then segregated based on “Perceived” or “Not Perceived” trials for each session. Each epoch experienced mild artifact removal.

The remaining, non-rejected epochs underwent time-frequency analysis using a short-time Fourier transformation in MATLAB. For improved statistical data analysis, each epoch was smoothed with a 256-sample (250ms) time window with a shift of 32 samples (31.25ms). For each subjects using all electrodes, we averaged the time-frequency results across both Perceived and Not Perceived trials. We also averaged across all nine subjects to create a total average time-frequency graph. Given that gamma power changes have been correlated with behavioral activity, the 40-115 Hz frequency band was used to examine broadband spectral changes (Miller et al., 2014; Mukamel et al., 2005).
For all trials for each subject, we determined the mean and standard deviation of all average gamma power values (30-115 Hz) for every electrode. Values over 20 standard deviations from the mean of all trials were excluded. For each subject, the remainder of the trials were averaged, and I modified them to z-score values at each time period based on the mean and standard deviation of the 28 baseline values for each electrode.

In order to depict all subjects’ electrodes on one brain image, each subject’s pre-op MRI was converted onto the Montreal Neurological Institute (MNI) standard space brain MRI using BioImage Suite, a tool for neuro image analysis and visualization. Electrodes were co-registered to the pre-op MRI, added and altered in the MNI space. These electrodes underwent a series of co-registrations with the pre-op MRI using post-op CT scans, post-op CT to post-op MRI, and ultimately post-op MRI to the pre-op MRI.

To graph gamma power z-scores on the standard MNI brain surface for each time period, z-score values were designated in spherical territories spanning 15 mm radius around every electrode contact for each subject. The radius was based on previous work (Menon et al., 1996), which identified intracranial-EEG recordings to have spatial resolution of 14-20 mm. If within 1 mm of electrode center, the complete z-score value was credited. If vertices were spaced between 1 to 15 mm, the z-score reduced linearly from the total value at 1 mm to 0 value at 15 mm. Then, a weighted average of these values for all subjects was calculated. A vertex between 15 mm of multiple electrodes was assigned a value equaling the sum of the distance-scaled z-score values from the electrode contacts.
To prevent a false decrease of z-score values of an active electrode contact due to the presence of a nearby electrode contact with poor signals, we utilized sum or “aggregate z-score” instead of the average. For the collective data of each subject, every vertex with z-scores was ascribed the mean of all z-score values at that vertex. To improve the signal/noise ratio (which increases by square root of sample size) and weight the data, the value was multiplied by the square root of the number of subjects influencing data at the vertex.

**Statistical Analysis**

The clustering and statistical analyses were conducted using MATLAB. Primarily, my research focused on analyzing the electrophysiology data. In particular, I used K-means correlational clustering using the MATLAB Toolbox function

\[ idx = kmeans(X,k). \]

\( X \) denotes the matrix including observations and \( k \) specifies number of clusters to divide. The result \( idx \) generates cluster numbers ascribed to each observation in \( X \). In the study, \( X \) holds the post-stimulus gamma power z-score time-series at each vertex and \( idx \) plots clusters across the brain surface and computes the mean time-series within clusters. To investigate the connection between the time-courses from an earlier level of clustering to the time-courses in the next level of clustering, the Pearson’s correlation was used. For example, all time-courses with 5 clusters were compared to those of 6 clusters, each of the times-courses with 6 clusters were then compared to those of 7 clusters, until the
maximum number of clusters. If the Pearson’s correlation coefficient was > 0.95 and p < 0.0001, then correlations were considered significant. Based on this analysis, we were able to ascertain vertices on the brain surface with comparable time-courses and classify them into anatomical clusters.

For all vertices within each cluster, we also computed the average time-courses. For a specific cluster, significant gamma power z-scores time-courses had 1) a mean silhouette value > 0; 2) Wilcoxon rank sum test on the absolute values of all post-stimulus vs pre-stimulus time points with P < 0.05, Bonferroni-correction for the number of clusters. To examine the most significant individual time points of post-stimulus value relative to pre-stimulus baseline, we used a z-test with p < 0.05, Bonferroni-corrected. Additionally, I combined the baselines of the gamma power traces for both the Perceived and Not Perceived to derive the Group Broadband Common Baseline and determined the z-scores time-courses.

**Behavioral Paradigm**

Subjects were appropriately participating in the behavioral testing sequence and not arbitrarily pressing buttons. In a blank trial, when a face was shown, the subject’s perception was on average at 52% (±3% SEM) versus when a face was not shown, it was at 9.7% (±3% SEM) (Figure 1). When a face was shown and detected, the exactness of locating the face was 89% (±3% SEM); but if the face was shown and not detected, the accuracy of the location decreased to 28% (±2% SEM) (Figure 1). In this thesis, location accuracy and inaccuracy served as a confirmatory measure of perception in trials studied. “Perceived” represented trials
in which a face was shown, identified, and correctly located whereas “Not Perceived” represented trials in which a face was not identified and incorrectly located. Regarding the 1s and 15s delays, there was no meaningful difference in identifying the stimuli at 54% versus 49% respectively (Figure 1). With respect to location accuracy, there was also no meaningful difference between 1s and 15s delays for both the perceived and not perceived trials (Figure 1). Regarding the movie and noise backgrounds, there was also no meaningful difference in identifying the stimuli and the neurophysiological events at 50% and 54%, respectively (Xiao et al., 2015). The sample size was enlarged by merging these two trial types for analysis.

**Spatiotemporal Sequence during Conscious Perception**

In the study, due to the significant spatiotemporal resolution and association with local neuronal activity, we honed in on the gamma power signals ranging from 40 to 115Hz. This emphasis was further substantiated by our analysis which showed a broad increase in high frequency (>40 Hz) power in perceived compared to not perceived trials in line with existing literature (Xiao et al., 2016; Kronemer et al., Abstract 646.04, 2016). To chart the temporal sequence of gamma power across the brain surface, I computed the z-scores for changes in comparison to baseline for Perceived and Not Perceived individually in the spherical areas around each electrode and then aggregated the data across subjects with a z-score threshold at 2. I also computed the z-scores for changes in comparison to the
combined broadband gamma power baselines of both Perceived and Not Perceived trials in the spherical areas around each electrode.

Seen in Figure 2, initially at 125 ms post-stimulus, both Perceived and Not Perceived trials displayed similar rises in gamma power in the primary visual cortex. After about 250 ms, the signals decreased in the Not Perceived trials and were negligible in other areas. However, within 250 ms, the Perceived trials showed rises while moving from the occipital area in a broad forward-sweeping surge of neuronal activity. The wave occurred initially to the ventral and lateral occipital and temporal-parietal visual association cortices, which then spread to the lateral frontal cortex, and ultimately reached the medial temporal lobe parahippocampal and entorhinal cortical regions.

Moreover, the Perceived trials showed fluctuations in signaling. By 250 ms post-stimulus, the Perceived trials showed decreases in the visual cortex signal, which was mirrored by decreases in higher-order association cortex like superior parietal lobe, inferior frontal gyrus, and orbital frontal cortex. But around 625 to 750 ms, the visual and higher order association cortices showed a reactivation. This fluctuation of initial decreases followed by increases were repeated in other regions in the higher-order association cortex (Xiao et al., Abstract 646.12, 2016; Kronemer et al., 2016).

Spatial Emergence of Signals in Conscious Perception

My work focused on investigating the anatomical locations displaying similar time-courses after conscious perception of the stimuli. Using Matlab’s k-
means correlational clustering function, I analyzed the time-series of gamma power z-scores values for every point on the brain surface in the group data. The clusters, ranging from 3 to 10, were segmented into four anatomically uniform regions on the cortical surface. These four regions had significant within-cluster temporal correlation with meaningful positive mean silhouette values demonstrating greater within-cluster than inter-cluster reliability. Moreover, these four regions were roughly mirrored between the two hemispheres and exhibited previously identified functional brain networks with discrete temporal courses. However, with regards to results from k-means clustering for Not Perceived trials, only Cluster 1 (green) had meaningful positive mean silhouette values and a significant post-stimulus P value. Moreover, there were no patterns to the emergence of networks.

With regards to Perceived trials, at Time = 0, the stimulus was presented. Cluster 1 (in green) was the first time-course that showed significant change with a small peak of increases localized to the visual and higher association cortices. Following the early increase, there was a pronounced fall and then another rise at 600 ms post-stimulus. Cluster 1 extended from the primary visual cortex to superior parietal lobe to inferior lateral frontal cortex to orbitofrontal cortex and other smaller areas. In Cluster 2 (in dark blue) displayed the next small rise followed by a persistent decline, showing continued deactivation. The areas in play were precuneus, ventral medial frontal, posterior parietal, and lateral temporal cortices.

In Cluster 3 (red), localized to early association cortex, and Cluster 4 (light blue), localized to later association cortex, displayed analogous monophasic
intermediate to late increases found in the visual association cortex, medial temporal lobes, and lateral fronto-parietal association areas. As seen customarily in the default mode network, there was an overlay of Cluster 4 (light blue) particularly clusters in the fronto-parietal cortices and medial temporal lobes and Cluster 2 consisting of task-positive connections (dark blue) (Fox et al., 2005).

Even with changes to the number of clusters, the anatomical regions delineated by k-means clustering were reasonably conserved (Figure 4). When I repeated analysis where cluster number varied from 2 to 10, I found that starting with 4 clusters, the anatomical regions of the clusters continued to be reasonably invariable. The criteria for temporal correlations were Pearson’s correlation
Figure 2: Progression of cortical broadband signaling in first second post conscious perception of stimuli. At 125ms post-stimulus, both Perceived and Not Perceived trials display similar rises in gamma power in the primary visual cortex. At 250ms, the signals decrease in the Not Perceived trials and are negligible in other areas. Within 250ms, the Perceived trials show rises while moving from the occipital area in a broad forward-sweeping surge of neuronal activity. The wave occurs initially to the ventral and lateral occipital and temporal-parietal visual association cortices, which then spreads to the lateral frontal cortex, and reaches the medial temporal lobe parahippocampal and entorhinal cortical regions. The Perceived trials show fluctuations in signaling. By 250ms, the Perceived trials show decreases in the visual cortex signal, which are mirrored by decreases in higher-order association cortex like superior parietal lobe, inferior frontal gyrus, and orbital front cortex. Around 625-750 ms, the visual and higher order association cortices show a reactivation. This fluctuation of initial decreases followed by increases are repeated in other regions in the higher-order association cortex.

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Figure 3: Anatomical and time-course representation of cortical signaling during conscious perception using k-means clustering. (a) The cortical surface was segmented into four anatomically uniform regions with significant within-cluster temporal correlation and approximate mirroring between the two hemispheres. (b) Mean time-courses for each cluster with Perceived stimuli. Colors correspond to same regions as in (a). Time = 0 stands for stimulus onset. Significant clusters are indicated (asterisk). All 4 clusters met these criteria for the Perceived trials. For Perceived trials, Cluster 1 (in green) is the first time-course with significant change given a small peak of increases at the visual and higher association cortices at the superior parietal lobe, inferior lateral frontal cortex, orbitofrontal cortex, and other smaller areas (a). Following the early increase, a pronounced fall occurs and another rise at 600 ms post-stimulus. In Cluster 2 (in dark blue) shows the next small rise with a persistent decline, displaying sustained deactivation. Areas of note are precuneus, ventral medial frontal, posterior parietal, and lateral temporal cortices (a). Cluster 3 (red), localized to early association cortex, and Cluster 4 (light blue), localized to later association cortex, display analogous monophasic intermediate to late increases found in the visual association cortex, medial temporal lobes, and lateral fronto-parietal association areas (a). (c) Mean time-courses during the Not Perceived stimuli for same regions shown in (a).

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coefficient >0.95 and P < 0.0001. When I increased the number of clusters, the four regions became more anatomically specific though the general locations remained.

Since individual subjects have different number of surface electrode contacts, I evaluated the individual subject time-courses for the 4 clusters. For each individual (colored traces) during perceived trials, the gamma power z-score time-courses within the 4 cluster regions resembled the group data (Figure 5). To investigate the correlation between the time-courses from an earlier level of clustering to the time-courses in the next level of clustering, we completed the Pearson’s correlation (Methods). We discovered all four clusters acquired by k-means clustering in Figure 3 were significantly correlated with the time-series for the following clustering with coefficient > 0.95 and P < 0.0001 until 10 clusters (Supplementary Figure 1). Some
cluster series ended since they were not meaningfully associated with the subsequent cluster levels.

The k-means clustering analyses depicted a “wave” of brain activity during visual conscious processing. The 10 clusters of Perceived gamma power z-score data showed activation spread via dorsal and ventral visual processing streams to the higher frontoparietotemporal association cortices (Figure 6; Supplementary Figure 2). Starting in the occipital cortex, intensified signaling could be traced in both lateral frontal lobes as the wave traveled throughout the visual association

Figure 5: Individual subject time-courses for 4 clusters. Given that individuals have varying number of electrode contacts, the individual subject time-courses were evaluated using k-means clustering. The analysis showed that the gamma power z-score time-courses for each of the 4 anatomical clusters for each individual (colored traces) during the perceived trials resembled the group data (see Figure 3b). The cluster regions are the same as Figure 3. The stimuli is presented at time 0. (a) Cluster 1 depicts the visual and higher-order association cortex. (b) Cluster 2 depicts default network mode. (c) Cluster 3 depicts early association cortex. (d) Cluster 4 depicts later association cortex.

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cortex ventrally and laterally. Compared to the pre-stimulus baseline, all post-stimulus time-series were significant (Bonferroni-correct $p < 0.05$, Wilcoxon rank sum test); moreover, for all clusters, the mean silhouette values were positive.

With regards to the extended time-courses due to the 15s delay before first questions, all clusters were meaningful for post-stimulus times versus pre-stimulus baseline (Bonferroni-correct $p < 0.05$, Wilcoxon rank sum test) except for the early association cortex cluster (Cluster 3). By coming back to baseline within 800 ms post-stimulus and staying there, Cluster 3 was not significant. Moreover, like the 1s delay, following stimulus, there was stimulation of primary visual/ higher association cortex cluster (Cluster 1), prolonged decreases of the default-mode network cluster (Cluster 2), and initiation of fronto-parietal cluster (Cluster 4).

Figure 6: Sequence of visual perception processing. Using gamma power z-score data from 10 clusters of Perceived trials, the signaling showed spread via dorsal and ventral visual processing streams to the higher fronto-parietal-temporal association cortices. (a) Cluster 1 is localized in the primary visual cortex/ higher association cortex. Clusters 2-5 are activated subsequently with the activation going back to Cluster 1 as it extends to the higher association cortex (indicated by arrows). (b) The spatiotemporal progression displays this progression with sequential increases in activation in Clusters 1-5 and then reversing to Cluster 1. Clusters 3 and 4 in Figure 3 approximate to clusters 2–3 and clusters 4–5 here, respectively.

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With regards to the Broadband Gamma Power Baselines for both Perceived and Not Perceived trials, we combined the baselines using a weighted average and derived the z-scores that were plotted on the electrodes. The preliminary results revealed mirror images in both the right and left sides of hemispheres though the anatomical distribution did not reveal a generalized pattern. The baseline differences in regional gamma power may signify different brain states due to the stimulus perception presented at threshold. Around 250-375 ms, the visual and higher association cortices showed increases during perception. Starting from 500 ms, the visual association cortex, medial temporal lobes, and fronto-parietal association areas showed activation. In contrast, for non-perceived baselines, the visual and higher association cortices did not play a large role during the same time-courses. But there was similar activation starting around 500 ms near the visual association cortex, medial temporal lobes, and fronto-parietal association areas. Further investigation with additional k-means clustering may shed light on the spatiotemporal overlay (Figure 8).
Discussion:

We investigated and discovered the spatiotemporal neuronal activity during visual conscious perception. We enrolled human subjects with subdural and depth intracranial electrodes to complete a threshold perception task. I directly implemented the behavioral task. In the task, the subjects were presented with localized stimuli and asked about their perception of the target. To chart the neuronal events of perceived stimuli and not perceived stimuli, we used broadband gamma power changes in electrical potential as a measure of local and population-level neuronal activation. Over time, there is an absolute variation in the increase, decrease, and prolonged recurrence in neuronal activity during Perceived trials when assessed against the initial activation of the visual cortex followed by the termination of activity for Not-Perceived trials after the presentation of the stimuli.

Our findings add to the literature that has examined the far-reaching cortical activity during conscious visual perception processing. Prior studies have explored the “ignition” theory of conscious processing (Dehaene, Kerszberg, & Changeux, 1998; Fisch et al., 2009). Our study delves deeper into the spatiotemporal resolution of the neuronal events. Activation of the visual cortex occurred regardless of perceived versus not-perceived trials, whereas there was activation and deactivation throughout the cortical regions only during conscious visual perception. The study suggests a concerted “switch and wave” phenomenon that has not been found in prior literature.

My contribution aimed to analyze the electrophysiology data obtained through intracranial electrodes. For individual data and group data for Perceived
trials and Not Perceived trials, I classified the broadband gamma power changes based on the anatomical and time progression using k-means clustering of cortical areas with similar within-cluster gamma power z-score time-courses. For these analyses, we determined the vertices on the brain surface with similar time-courses and organized them into anatomical clusters.

The surface mapping displayed a “switch and wave” progression of activity during the first second of visual consciousness. For only perceived stimuli, I found four significant clusters organized in symmetric functional networks with significant within-cluster temporal correlation. With changes to the number of clusters ranging from 4 through 10, the anatomical regions were reasonably conserved, implying that strong functional correlations within the analysis existed.

As seen in Figure 3, at time = 0, there was stimulus onset. For Perceived and Not Perceived trials, Cluster 1 represented activations in the visual and higher association cortices at the superior parietal lobe, inferior lateral frontal cortex, orbitofrontal cortex, and other smaller areas. Clusters 2 through 4 were significant only for Perceived trials. Cluster 2 showed sustained deactivation in regions such as precuneus, ventral medial frontal, posterior parietal, and lateral temporal cortices. Cluster 3 was localized to early association cortex, and Cluster 4 was localized to the visual association cortex, medial temporal lobes, and lateral fronto-parietal association areas.

Cluster 1, seen in both Perceived and Not Perceived trials, had a small rise localized to the visual and higher association areas such as the superior parietal lobe, inferior lateral frontal cortex, orbitofrontal cortex, and other smaller areas.
Only in Perceived trials did this early rise before 200 ms lead to a decrease at 350 ms after stimulus, which gave rise to reactivation at around 600 ms. The late and sustained reactivation of the visual cortex and the higher association cortices seen in Cluster 1 around 600 ms after the stimuli may have been connected to post-perception processing. Aiming for recall, the working memory system retrieves crucial information from the visual cortex (Thakral, Slotnick, & Schacter, 2013). Another study has shown short term visual memory is saved in visual regions (Agam et al., 2009). Cluster 1 showed the ability of the brain to maintain attention on the stimuli at hand to allow for successful recall.

Cluster 2, which spanned the default mode network, displayed an initial rise at 250 ms leading to continued deactivation after stimulus presentation. The deactivation of the default mode network allowed for increased bandwidth to assist with further processing of external stimuli. Studies have shown an inverse relationship between the default mode network activity and working memory requirements for an external task (Ossandon et al., 2011; Singh & Fawcett, 2008). For memory encoding and processing of each event, regions found within Cluster 3 and Cluster 4 have shown to be crucial (Burke, Ramayya, & Kahana, 2015). Our results showed monophasic increases at varying latencies with unimodal and heteromodal association cortex. Cluster 3 and Cluster 4 peaked around 400 ms and 600 ms respectively and had sustained activity. The areas found in these clusters have been known for ensuring working memory, processing of the stimulus, and involved in the “task-positive network” (Fox et al., 2005).
I also combined the baselines of the gamma power traces for both the Perceived and Not Perceived to compute the Group Broadband Common Baseline, determined the z-scores time-courses, and plotted them on the cortical surface. Although at the nascent stage of analysis, the symmetric visualization of the electrodes in both hemispheres offered some insight regarding the brain states due to stimulus perception at threshold. The initial activation of the visual and higher association cortex for just the perceived trials suggests that perception of the stimulus acted as a differentiator. However, both perceived and not-perceived trials had similar increases at the visual association cortex, medial temporal lobes, and fronto-parietal association areas starting around 500 ms. These regions are known as stated earlier for working memory formation. In the future, k-means clustering should be applied to the combined baselines dataset.

There were limitations to this study. First, there was a reliance on the subject's recall and report of stimuli perception. It was challenging to unravel perception versus post-perceptual processing. Future studies can use concealed methods of gauging conscious perception to reject needless post-perceptual processing.

In summary, we aimed to chart the spatiotemporal events in the first second of conscious visual perception. Human subjects were asked to perform a threshold perception task while having broadband gamma activity in the human brain monitored using intracranial electrode recordings. Initially there was a rise in visual cortical activity for both Perceived and Not Perceived events. But only consciously perceived events produced widespread cortical network changes featuring the
“switch and wave” progression. We hope to use these results to further study the neuroelectrophysiology of consciousness in the human brain.

**Acknowledgements:**

I would like to thank our subjects and their families, who worked with us to help us achieve our research mission. I would also like to thank Dr. Hal Blumenfeld for his guidance and mentorship during the researching and writing process. Moreover, I would like to extend thanks to Dr. Wendy Herman for her thoughtful insight and support during my first summer in the Blumenfeld lab. This research was made possible with funding support from the National Institutes of Health-NIDDK Medical Student Research Fellowship. Finally, I would not have been able to get through medical school without the support of my family and friends.
Figure 8: Progression of cortical broadband signaling of broadband gamma power baselines post stimuli. The preliminary results reveal mirror images in both the right and left sides of hemispheres in both Perceived and Not Perceived though the anatomical distribution does not reveal a generalized pattern.

Raja et al, 2019 unpublished data.
Supplementary Information

**Supplementary Figure 1:** The four clusters produced from k-means clustering in Figure 3 are significantly correlated with another time-series in the next clustering up to 10 clusters. Arrows specify Pearson correlation >0.95, p<0.0001. Using k-means clustering, Cluster 1 to 4 were identified (same color and numbers as Figure 3) and are indicated in the rectangular box. 2 to 10 clusters are also shown. The rows present cluster groups across columns of cluster levels that surpass the temporal correlation criteria (arrows). Based on temporal correlation, Clusters 1 to 4 are the most significantly conserved with the anatomical regions roughly conserved between levels. Some cluster series end since they are not significantly correlated in the subsequent cluster levels.

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Supplementary Figure 2: 10 k-means clusters for Perceived trials. The 10 clusters are shown (a). These clusters are also seen in Supplementary Figure 1. (b) For the 10 clusters, the time-courses are listed; the colors match the anatomical regions seen in a. At Time=0, there is stimulus presentation. Compared to pre-stimulus baseline, all post-stimulus time-series were significant (Bonferroni-corrected p < 0.05, Wilcoxon rank sum test) with all positive mean silhouette values for all clusters. Significant changes relative to pre-stimulus baseline are seen with asterisks (Bonferroni-corrected p < 0.05, z-test).

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Citations


Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic,


