

ABSTRACT

Title of Document: Analysis of Gamma-Band Auditory Responses in Schizophrenia

Benjamin Walsh, Master of Science, 2015

Directed By: Professor Jonathan Simon, Department of Electrical and Computer Engineering, Institute of Systems Research, Department of Biology

Schizophrenia is a debilitating mental illness that affects 1% of the general population. One characteristic symptom is auditory hallucinations, which is experienced by almost all patients sometime in their lifetime. To investigate differences in auditory response in general, 50 schizophrenic patients and 50 age and sex-matched healthy controls were presented with auditory click trains at 40 Hz. Responses are recorded using electroencephalography (EEG). Magnitude and phase of responses at 40 Hz are computed using Gabor filters.

Supporting previous literature, a significant difference in inter-trial phase coherence (ITC) and overall power is found between patients and controls, in particular near stimulus onset. Additionally, this study also investigated inter-subject phase coherence (ISC). This study finds that ISC is in fact higher for patients, in particular near stimulus onset. One possible explanation is that while healthy controls develop a preferred phase for perception, schizophrenic patients exhibit phase that is primarily stimulus-driven.

Analysis of Gamma-Band Auditory Responses in Schizophrenia

By

Benjamin Walsh

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Examining Committee:

Professor Jonathan Z. Simon, Chair
Associate Professor Pamela Abshire
Assistant Professor Behtash Babadi

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1. Introduction

Schizophrenia is a chronic, debilitating mental disorder that affects 1% of the general population. The range of symptoms can include hallucinations, disorganized speech, and catatonic behavior. The severity of these symptoms can greatly affect the livelihood of schizophrenic patients, however the wide range and variety of symptoms make it difficult to diagnose. The standard diagnosis uses the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM). The DSM lists the following six symptoms, of which two must be present most of the time during one month, with some level of disturbance over six months: delusions, hallucinations, disorganized speech, extremely disorganized behavior, catatonic behavior, and negative symptoms (First et al. 2007). The scale is inherently subjective, and ideally there would be a diagnostic measure that is both quantitative and objective.

Auditory hallucinations are exhibited in approximately 60% to 90% of schizophrenic patients (Cummings and Mega 2003). The prevalence of auditory hallucinations in schizophrenia has motivated research of processing abnormalities in schizophrenia for decades. Although the frequency and severity of auditory hallucinations varies widely among patients, one interpretation is that the symptom is a result of reduced local connectivity in the auditory cortex. Local connectivity, or the activity of smaller populations of neurons, may be reflected in gamma band (30 – 50 Hz) activity (Hong et al. 2004). An auditory hallucination could also be the result of an incoherent percept, which has also been associated with gamma band activity in auditory detection tasks (Jokeit and Makeig 1994). These associations suggest that the gamma band is informative in illustrating differences in auditory processing of schizophrenics.

A standard method of investigating auditory processing is to measure the auditory steady-state response (aSSR). Amplitude-modulated (AM) tones and click-trains elicit an aSSR at the stimulating frequency in recordings with electroencephalography (EEG). EEG is an advantageous modality for recording electrophysiological responses, being quiet, non-invasive, having moderate spatial resolution, and having high temporal resolution. The amplitude of the aSSR is largest in the gamma band in humans, and within the gamma band is highest at 40 Hz (Azzena et al. 1995, Galambos et al. 1981). The preference for 40 Hz has been suggested to be the reflection of maximal phase locking of individual trial responses (Artieda et al. 2004). These qualities of gamma band aSSR in healthy humans, and 40 Hz in particular, further motivate gamma band aSSR research to illustrate differences in auditory processing of schizophrenics. Schizophrenic patients exhibit an aSSR with reduced power (Kwon et al. 1999, Schnitzler et al. 2005, Light et al. 2006, Krishnan et al. 2009), delayed phase (Kwon et al. 1999), and reduced inter-trial coherence (ITC) (Schnitzler et al. 2005, Light et al. 2006, Krishnan et al. 2009) to a 40 Hz click train. The deficit in 40 Hz aSSR extends to first-degree relatives of patients, although the aSSR is not as reduced (Hong et al. 2004). While schizophrenia occurs in 1% of the general population, risk is increased as much as 18-fold as a relative of a schizophrenic (Kendler et al. 1985).

Overall, despite the debilitating nature of schizophrenia, diagnosis is challenging and inherently subjective. Gamma band auditory responses are a promising candidate to determine objective differences, with well-documented differences in aSSR. Expanding on these differences may explain the origins of auditory hallucinations in schizophrenia, for instance as a bottom-up problem, e.g. erroneous processing of auditory stimuli, or a

top-down problem, e.g. from attentional deficits that alter perception. This thesis investigates the differences in gamma band auditory responses in schizophrenic patients using EEG, aiming to eventually objectively diagnose schizophrenia and reveal underlying neurobiology that would facilitate treatment development.

2. Experimental Methods

2.1 Data Collection

50 schizophrenic patients were age and sex-matched with 50 healthy controls. Participants were between 16 and 58 years of age. Schizophrenia was diagnosed using the Structured Clinical Interview for DSM-IV (First et al. 2007). All subjects were presented with a stimulus of 15 clicks in a sound-attenuated chamber. The clicks were presented at 40 Hz, and the same stimulus was presented for 75 trials. The inter-stimulus interval pseudorandomly varied among 320, 370, and 420 ms. More information on the stimulus can be found in the Appendix.

Electroencephalography (EEG) is recorded continuously (<5 kOhms) from a 64 electrode Quick-Cap (Neuromedical Supplies, TX) with a Neuroscan SynAmp2. Data are sampled at 1 kHz and hardware band-passed between 0.1 and 200 Hz.

2.2 Data Pre-processing

The raw, full-duration waveforms are first epoched into the 75 individual trials, comprised of a 100 ms pre-stimulus interval, 350 ms of stimulus presentation, and a 300 ms post-stimulus interval. Each trial is ordered by overall power and maximum absolute amplitude. Trials with high (above two standard deviations) power or maximum absolute amplitude were considered a result of an artifact and were rejected. Data is further band-passed between 5 and 55 Hz. EEG analysis of auditory data typically low-passes between

5 and 10 Hz, reducing unrelated noise such as a heartbeat, and high-passes between 50 and 60 Hz, reducing unrelated noise such as 60 Hz power line frequency noise (Light et al. 2006, Krishnan et al. 2009). Data is re-referenced over average of channels, excluding channels with power above or below two standard deviations of the average.

Data is then detrended linearly over time and processed by time-shifted Principal Component Analysis (tsPCA) (de Cheveigné and Simon 2007), which filters out environmental noise based on reference sensors. The reference sensors assumed to be dominated by stimulus-unrelated activity were the ocular, occipital, and mandibular notch electrodes. Data is then taken from the single Cz electrode. EEG analysis of auditory data commonly uses a single midline electrode, typically either Fz (Light et al. 2006) or Cz (Tallon-Baudry et al. 1996, Krishnan et al. 2009). Kwon et al. (1999) found Fz to have the maximal 40 Hz response while Tallon-Baudry et al. (1996) found Cz (or C4) to have the maximal 40 Hz response.

2.3 Data Analysis

2.3.1 Gabor Filter

Temporal (1-D) Gabor filters have been utilized to illustrate response amplitude over time at modulation frequencies, in both EEG (Sinkkonen et al. 1995) and MEG (Ross et al. 2002). Gabor filters $g(t)$ are Gaussian kernels $w(t)$ modulated by a complex exponential $s(t)$ (Movellan 2002).

$$g(t) = ke^{j\theta}w(at)s(t)$$

$$w(t) = e^{-\pi t^2}$$

$$s(t) = e^{j(2\pi f_0 t)}$$

Here θ can tune to a particular phase, a controls the bandwidth, and the maximum amplitude corresponds to f_0 . In this analysis, θ is 0, f_0 is 40 Hz, and a is 10 Hz. Output can be analyzed in terms of its real $r(t)$ and imaginary $i(t)$ components. Energy $e(t)$ at a target frequency f_0 is calculated as the sum of the squares of the real and imaginary components, and phase $\varphi(t)$ is calculated as the four-quadrant inverse tangent of the ratio of the imaginary to real component. Note that while the individual outputs are sensitive to phase, but the energy output is phase insensitive.

$$r(t) = kw(at)\cos(2\pi f_0 t + \theta)$$

$$i(t) = kw(at)\sin(2\pi f_0 t + \theta)$$

$$e(t) = r(t)^2 + i(t)^2$$

$$\varphi(t) = \begin{cases} \tan^{-1} \frac{i(t)}{r(t)}, & r(t) > 0 \\ \tan^{-1} \frac{i(t)}{r(t)} + \pi, & r(t) < 0 \end{cases}$$

2.3.2 Phase Coherence

Phase coherence is generally the average magnitude of a set of phasors constrained to the unit circle. With this constraint, the maximum value is 1, and the minimum value is 0. The maximum occurs if all phasors have the same phase, regardless of the particular phase value. Most commonly, phase coherence is calculated over the set of trials for a subject. Phase coherence over trials as well as subjects is investigated here. For notation, we denote ISC as the inter-subject phase coherence and ITC as the inter-trial phase coherence. ITC is sometimes denoted as phase-locking factor or PLF (Tallon-Baudry et al. 1996).

$T, i = 1, 2 \dots T$	Total number of trials, index
$N, n = 1, 2 \dots N$	Total number of subjects, index
$\mathbf{X}(t) \in \mathbb{C}^{N \times T}$	All response data as unit phasors
$X_{ni}(t) \in \mathbb{C}$	Response data for n^{th} subject, i^{th} trial
$ITC_n(t) = \left \frac{1}{T} \sum_i X_{ni}(t) \right $	Inter-Trial Phase Coherence
$ISC_i(t) = \left \frac{1}{N} \sum_n X_{ni}(t) \right $	Inter-Subject Phase Coherence

3. Experimental Results

3.1 Trial Data For Representative Subject

Trial data for a representative subject is shown in Figure 1. The responses for individual trials are shown in cyan (only 20 shown for visualization) and the average is shown in dark blue. The average is scaled for visualization. The stimulus is presented between 0 and 350 ms, depicted in the figure with the gray bar. Visually, it is clear that the average response exhibits a dominant frequency (40 Hz), with a short latency with respect to stimulus presentation. The energy at 40 Hz is quantified using a Gabor filter and displayed in the figure that follows. Additionally, the trial data shows that while the average data exhibits a dominant frequency, there is phase variation across trials. The coherence of the phase over trials, namely the ITC, is calculated at each point in time and is displayed later. Outside of stimulus presentation, responses exhibit large variations across trials and 40 Hz components are not salient.

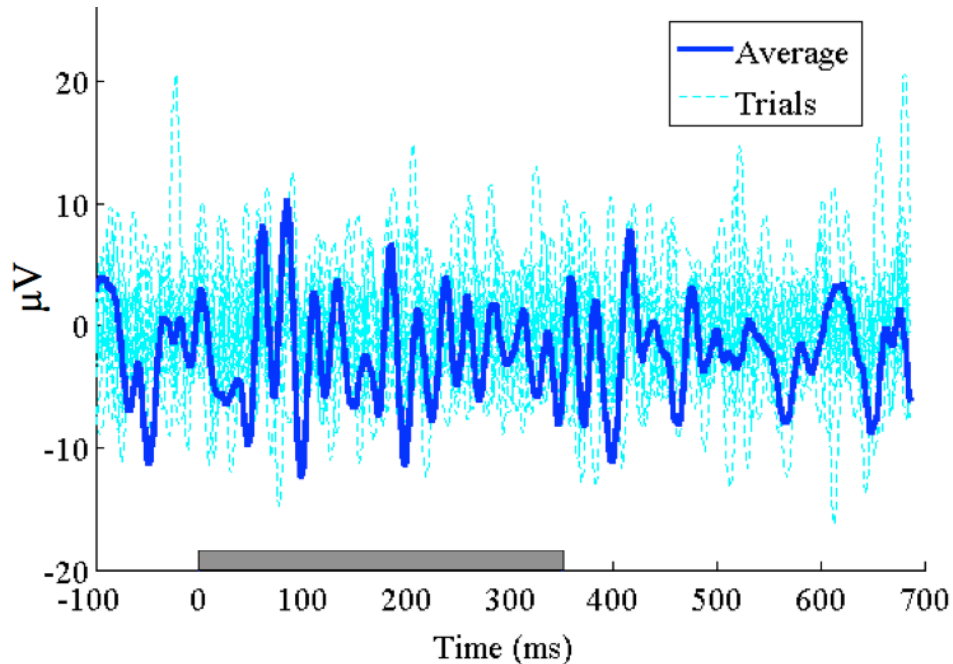


Figure 1: Trial Data for Representative Subject: Individual trials are displayed (cyan) with their scaled average (dark blue). The average response shows a salient 40 Hz component during stimulus presentation, quantified in the next figure. Trial data visualizes the large trial variations, particularly in phase, which is quantified in Figure 3.

3.2 Energy at 40 Hz

The energy output of the Gabor filter at 40 Hz for the trial average is shown in Figure 2, for both the averages over healthy controls and schizophrenic patients. Recall that the Gabor filter has a kernel of 100 ms, smoothing the response, so features at shorter time scales have been smoothed. The response is largely salient only during stimulus presentation, ramping up after stimulus onset and fading after the last click. Additionally, the response is higher for healthy controls for the majority of stimulus presentation, consistent with literature (Kwon et al. 1999, Schnitzler et al. 2005, Light et al. 2006, Krishnan et al. 2009). The difference is statistically significant between 118 and 173 ms (Permutation test, $p < 0.05$). Note that although the stronger response between the two controls oscillates after 450 ms, this is after the stimulus presentation.

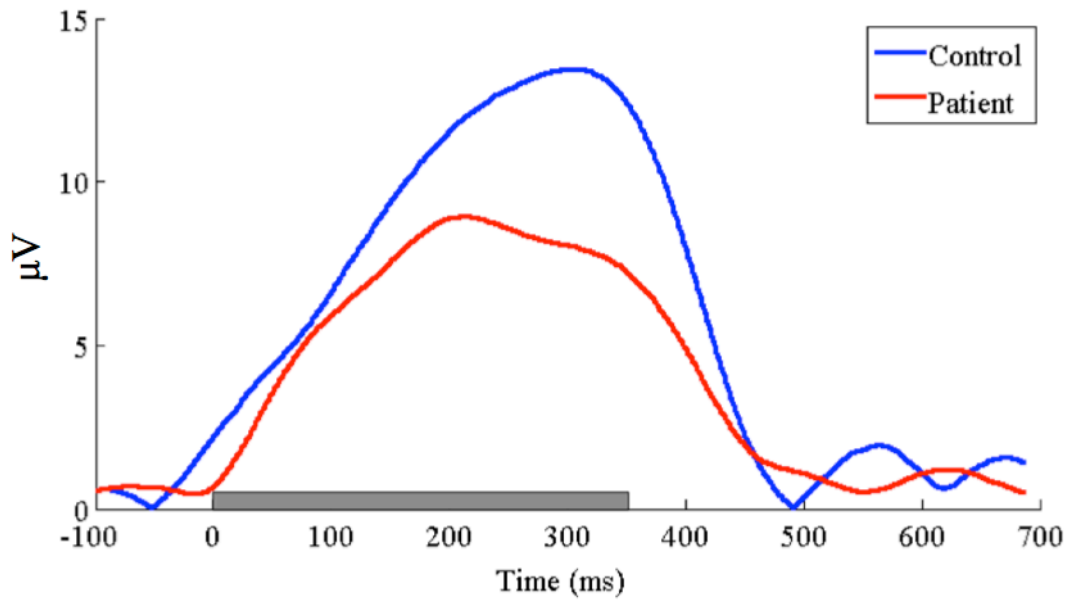


Figure 2: Gabor Filter Energy Output at 40 Hz For Both Group Averages. Energy at 40 Hz is consistently higher during stimulus presentation for the averaged healthy controls. The difference was statistically significant between 118 and 173 ms. Both groups exhibit monotonic increases until a peak is reached.

3.3 ITC at 40 Hz

Inter-trial phase coherence (ITC) at 40 Hz for both groups is shown in Figure 3. ITC for each subject is calculated, and then each group is averaged. As expected, ITC is higher for both groups during stimulus presentation (0 – 350 ms). The difference is statistically significant (Permutation test, $p < 0.05$) between 6 and 49 ms. Higher ITC in controls is consistent with literature (Schnitzler et al. 2005, Light et al. 2006, Krishnan et al. 2009).

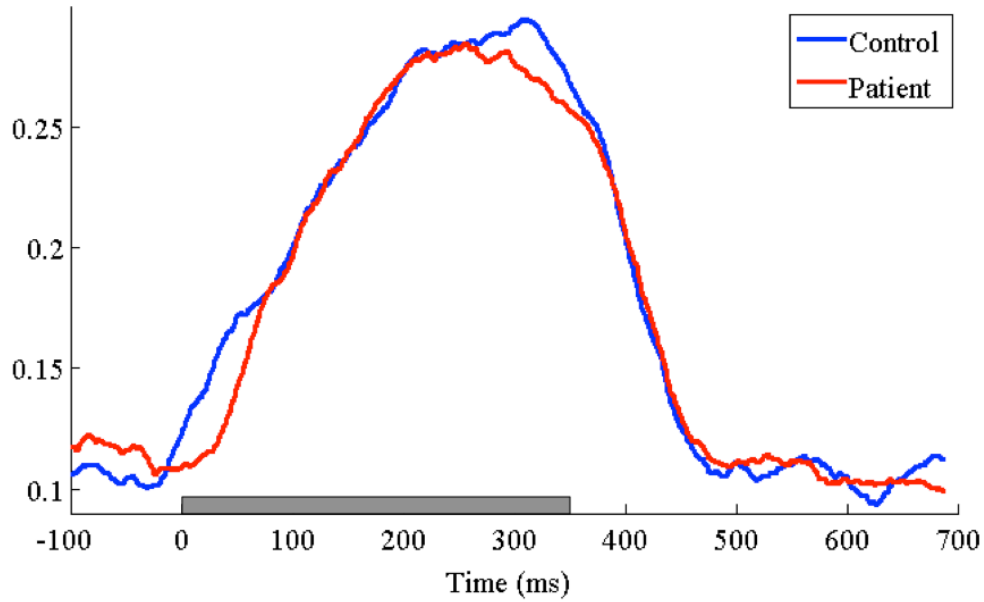


Figure 3: Inter-Trial Phase Coherence at 40 Hz for Both Group Averages. ITC is significantly (Permutation test, $p < 0.05$) higher for the averaged healthy controls near stimulus onset. Similar to energy (Fig. 1), both groups exhibit a near-monotonic increases until a peak is reached.

3.4 ISC at 40 Hz

Inter-Subject Phase Coherence (ISC) at 40 Hz for both groups is shown in Figure 4. ISC within a group is calculated for each trial, and then all trials are averaged within a group. As expected, ISC is notably higher in both groups during stimulus presentation. However, the ISC is higher overall for patients, with a statistically significant difference (Permutation test, $p < 0.05$) between 57 and 107 ms, and a strongly significant difference ($p < 0.01$) between 66 and 93 ms. This is in stark contrast to energy (Fig. 2) and ITC (Fig. 3), which illustrate higher metrics for controls. We believe this is the first reported result of ISC. The intervals of significance are approximately between the second and fourth clicks. Within this interval, patients exhibit a 40 Hz phase that is significantly more aligned with each other.

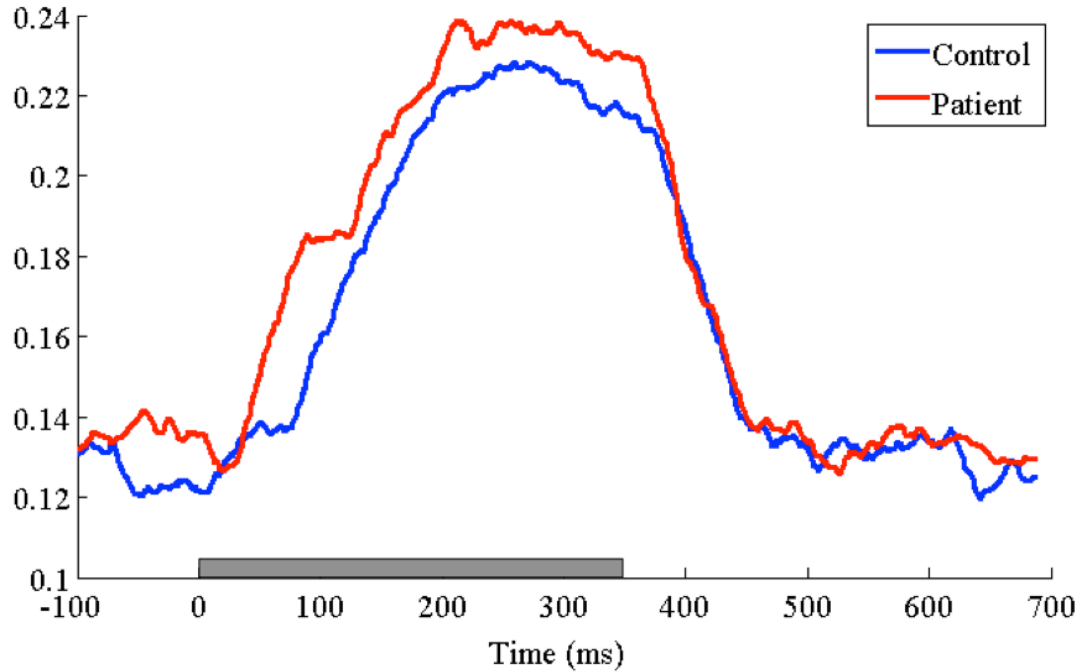


Figure 4: Inter-Subject Phase Coherence at 40 Hz for Both Group Averages: ISC is significantly (Permutation test, $p < 0.05$) lower for the averaged healthy controls shortly after stimulus onset.

This is in contrast to energy (Fig. 1) and ITC (Fig. 2), which both showed higher metrics for controls. Both groups exhibit near-monotonic increases until a peak is reached.

3.5 Summary of Experimental Results

The displayed metrics of energy (Fig. 2), ITC (Fig. 3) and ISC (Fig. 4) exhibited similar overall trends over time, with an overall increase during stimulus presentation and a gradual increase for approximately the first 200 ms. Energy and ITC at 40 Hz are lower in schizophrenic patients, however ISC is higher. We believe this is the first time that higher ISC in schizophrenic patients has been reported. A phenomenological model is proposed in the next section, with results in the subsequent section. Afterwards, we discuss possible explanations of the observed phenomena.

4. Simulation Methods

In the second part of this thesis, a phenomenological model is proposed to explain the experimental observations. The overall observations were that schizophrenic patients exhibit 1) lower power, 2) lower ITC, and 3) higher ISC at 40 Hz. We began with a generalized observed signal $y(t)$, the sum of the desired auditory signal $s(t)$ at the same f_0 frequency of the stimulus, and unrelated noise $n(t)$. Constants c_n^{sig} and c_n^{noise} scale the underlying signal, and the noise, respectively, included in the model to vary signal-to-noise ratio (SNR). The phase φ is the sum of two components, a part φ_i that varies with the i^{th} trial, and a part n that varies with the n^{th} subject.

General Model

$$\begin{aligned}
 s(t) &= c_n^{sig} \sin(2\pi f_0 t + \varphi) && \text{Signal at } f_0 \\
 y(t) &= s(t) + c_n^{noise} n(t) && \text{Observed signal with noise} \\
 \varphi &= \varphi_i + \varphi_n && \text{Phase of } f_0 \text{ signal for } n^{\text{th}} \text{ subject, } i^{\text{th}} \text{ trial}
 \end{aligned}$$

Modeling Group Differences

$$\begin{aligned}
 \varphi_i &\sim VM(0, \kappa_n) && \text{Trial phase concentration depends on subject} \\
 \kappa_n &= \begin{cases} \kappa_{cont}, & n \in \text{Control} \\ \kappa_{pat} < \kappa_{cont}, & n \in \text{Patient} \end{cases} && \text{Trial phase is less concentrated in patients} \\
 \frac{c_n^{sig}}{c_n^{noise}} &= \begin{cases} \alpha_{cont}, & n \in \text{Control} \\ \alpha_{pat} < \alpha_{cont}, & n \in \text{Patient} \end{cases} && \text{Signal to noise ratio is higher in controls} \\
 \varphi_n &\sim VM(0, \beta_n) && \text{Subject phase concentration depends on subject} \\
 \beta_n &= \begin{cases} \beta_{cont}, & n \in \text{Control} \\ \beta_{pat} > \beta_{cont}, & n \in \text{Patient} \end{cases} && \text{Subject phase is more concentrated in patients}
 \end{aligned}$$

All random variables are modeled with a von Mises distribution, which is a close approximation to the wrapped normal distribution (Fisher 1993). The distribution $VM(\mu, \kappa)$ is determined by two parameters. The first parameter μ is the mean, which is set to 0 in all cases here. The second parameter κ is the concentration, analogous to $1/\sigma^2$ in a normal distribution. More information on the von Mises distribution can be found in the Appendix.

To model group differences in ITC, trial phase φ_i is distributed with a higher variance for patients and constant within each respective group. In simulation, κ_n is set to 1 for controls and 0.5 for patients. To model group differences in SNR, observed signals from controls have a higher c_n^{sig}/c_n^{noise} ratio, and ratios are constant within each respective group. In simulation, c_n^{sig}/c_n^{noise} is scaled by 1.5 for controls, or ~ 1.76 dB. To model group differences in ISC, subject phase φ_n is distributed with a lower variance for patients and constant within each respective group. In simulation, β_n is set to 1.5 for patients. For controls, β_n is set to 0, which replicates a uniform distribution. Noise is a mixture of scaled white noise and sinusoidal components that have random variation in AM and FM. Noise is generated identically for all subjects, and is generated for every trial and subject. Specific information on noise generation can be found in the Appendix. As in the experiment, 50 subjects were modeled for each group, each with 75 trials.

5. Simulation Results

The same analysis performed on the experimental data was performed on the simulated data. The results are summarized in Figure 5, where Figure 5a corresponds to Figure 2, Figure 5b corresponds to Figure 3, and Figure 5c corresponds to Figure 4.

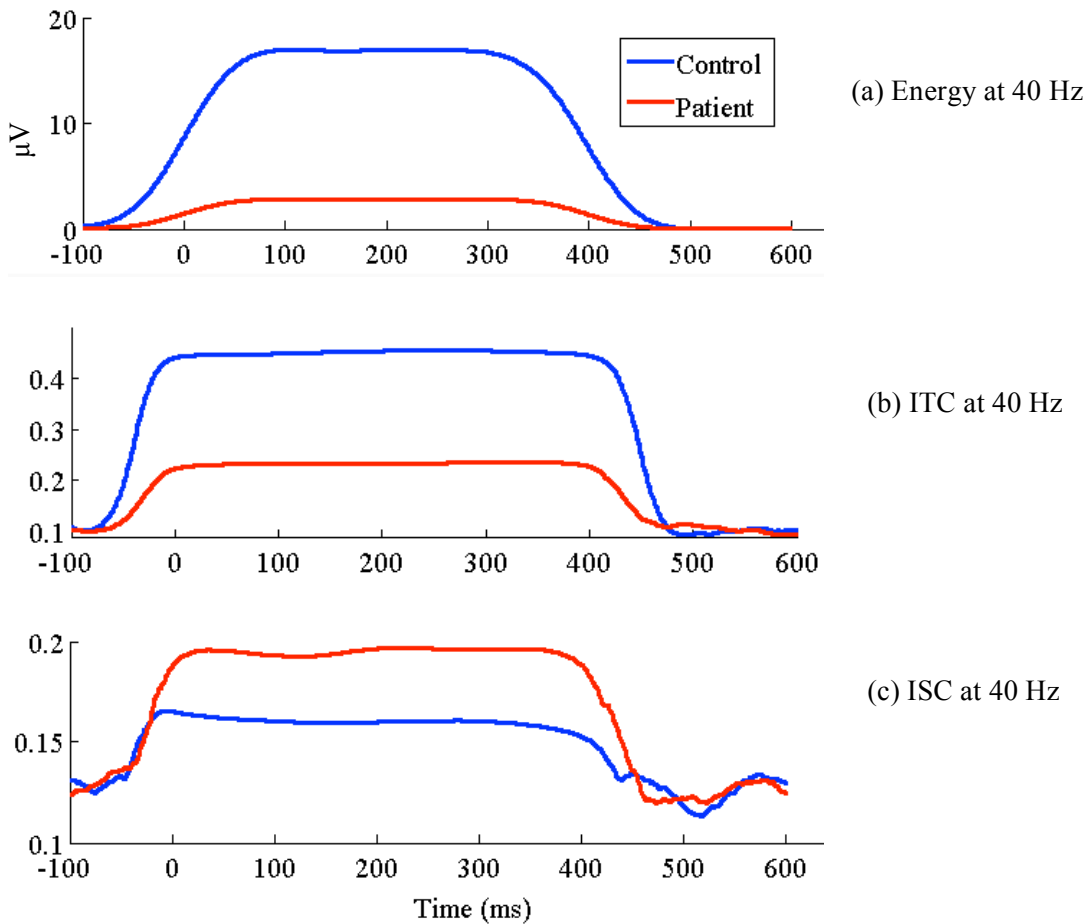


Figure 5: Repeating Analysis for Simulation. The same analysis is performed on the simulation results. The energy output from the Gabor filter at 40 Hz (a) is higher for controls. The ITC (b) is higher for controls. The ISC (c) is higher for patients. The overall relationship between the two groups regarding these analysis results was the same in the model and observation.

Note that the model was designed to explain the overall relationship between the groups regarding this analysis, not model the precise temporal dynamics, e.g. the regions of significant difference. Overall, the energy and ITC are higher in simulated controls, while the ISC is higher in simulated patients. Energy and coherences are computed at 40 Hz, the same frequency of the modeled underlying signal. The overall relationship between the two groups in simulation is consistent with the experimental observations.

6. Discussion

The most surprising result of the data analysis is the higher overall ISC of schizophrenic patients. Analysis showed higher overall power at 40 Hz during all of stimulus presentation, shown in Figure 2. Additionally, ITC is higher overall in controls, as shown in Figure 3. These two results are consistent with literature (Kwon et al. 1999, Schnitzler et al. 2005, Light et al. 2006, Krishnan et al. 2009) but would not suggest that ISC would be higher for patients. Generally speaking, for one group to have a higher ISC but lower ITC, this means that while phase differs between trials, the group is more likely to have the same phase. Conversely, for one group to have a lower ISC but higher ITC, this means that while phase differs between subjects, the group is more likely to have consistent phase between trials.

Examining the converse, this scenario is plausible concerning the second group (healthy controls). In particular, auditory EEG experiments testing near-threshold gaps in solely frequency-modulated (FM) stimuli (Henry and Obleser 2012), as well as stimuli both AM and FM (Henry et al. 2014) found individual performance was strongly correlated with FM stimulus phase, but that the specific phase was not consistent across subjects. Figure 6 shows individual subjects' results of gap-detection performance as a

function of FM stimulus phase. Despite the strong modulation, there qualitatively appears to be large subject variability in the optimal phase. A similar effect has also been observed in the visual system. In flash-lag visual experiments, while performance is highly correlated with phase, the phase is the “preferred” phase, which again varies from subject to subject (Chakravarthi & VanRullen 2012).

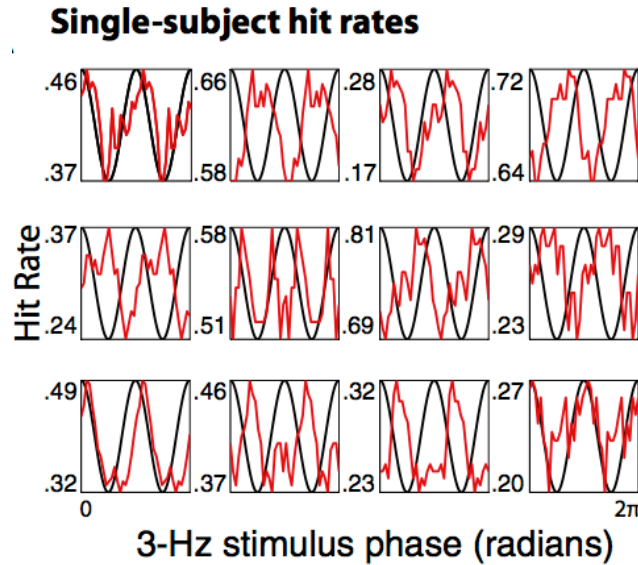


Figure 6: Subject variability in optimal phase (Henry and Obleser 2012). Individual subject performance (hit rate) is plotted as a function of FM stimulus phase. Performance follows a sinusoidal function at the FM rate, but with different phases across subjects. For instance the individual results in the top left exhibit an approximate phase of 0, while the individual results displayed to the right exhibit an approximate phase of $\pi/2$. Across listeners there was no significant correlation between FM stimulus phase and performance.

Therefore, one possible suggestion for lower ISC in controls is the difference in preferred phase. A healthy control could develop a particular preferred phase over time, which enhances their perception performance. Henry and Obleser (2012) found no significant correlation between FM stimulus phase and performance across listeners, who were non-schizophrenic subjects with normal hearing. This suggests that it is the development of the tuning to the phase, not the phase itself, which is important. If this

development was hindered in schizophrenia, then the phases would be similar to each other; primarily driven, for example, by the stimulus. Yet an externally-driven phase does not appear to be optimal, giving rise to lower energy and ITC. Hence, the apparent lack of an internal phase optimization could be an underlying deficit in gamma band auditory processing in schizophrenia.

7. Conclusions

This thesis aimed to introduce novel analysis that would add to the established differences in gamma band auditory responses of schizophrenic patients. Reduced energy and ITC in auditory responses of patients was found, consistent with previous literature. Additionally, ISC was analyzed and found to be higher overall in patients. We believe this is the first time that higher ISC in schizophrenic patients has been reported. A possible explanation has been proposed, where patients exhibit phase that is more stimulus-driven, while controls develop a preferred phase that performs better overall, but is not consistent across subjects. We presented a phenomenological, computational model that exhibits the same overall results of higher energy and ITC but lower ISC for controls.

Future work should focus on further investigating ISC differences in schizophrenia, including a novel experiment to test the proposed hypothesis. As it is not a commonly used metric, an extensive study of responses to different frequencies within the gamma band would be informative, with side-by-side comparisons to ITC. Furthermore, an active experiment should be devised, where performance could be compared to phase, and any preferred phase would become evident in an auditory task. When comparing results, it will be important to consider that selective attention enhances ITC in 40 Hz aSSR (Skosnik et al. 2007). Additionally, special considerations will have

to be made to make a task that elicits a full distribution of performance, but is not too frustrating for patients. Future work can also expand on the phenomenological model. Biophysical, computational models of the auditory cortex have been proposed (Vierling-Classen et al. 2008) to characterize schizophrenia, which provided results consistent with responses to 40 Hz click-trains recorded with MEG. The analysis did not include phase coherence, however. A future study could enhance the proposed model by incorporating elements of the biophysical model, or incorporate phase coherence analysis to the established biophysical model. The results from these experiments and hybrid model would hopefully validate the results reported in this thesis, and firmly suggest a more specific neurobiological basis for the auditory processing deficits in schizophrenia.

Appendix

A.1 Stimulus Information

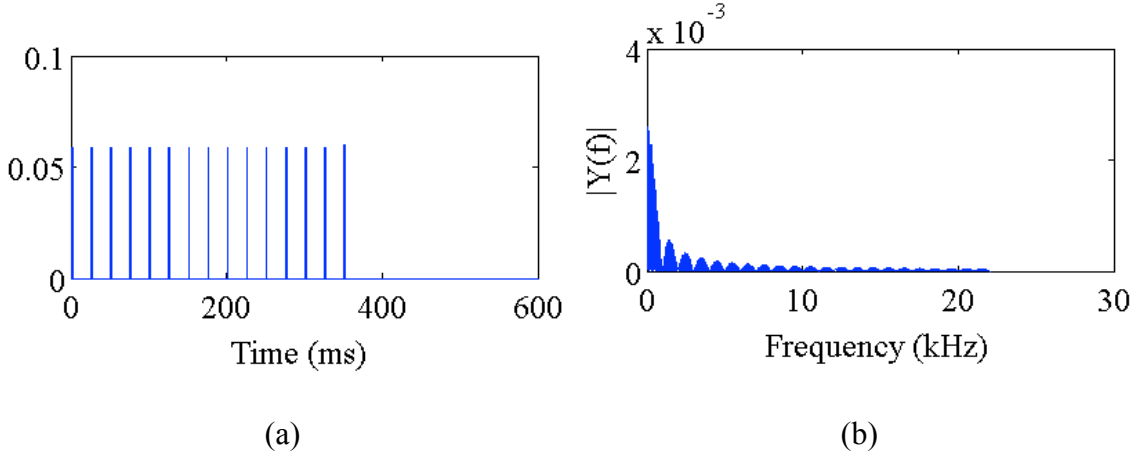


Figure A1: The .wav file is shown in (a), displaying the waveform of a single trial of 15 clicks at 40 Hz. Each click is present for 1 ms. The frequency content is shown in (b), displaying the absolute value of a sinc function, with lobes at multiples of 1kHz and local peaks at multiples of 40 Hz (too small to see at this scale).

A.2 von Mises Distribution

The probability density function of a von Mises (VM) distribution (Fisher 1993) is the following:

$$f(x|\mu, \kappa) = \frac{e^{\kappa \cos(x-\mu)}}{2\pi I_0(\kappa)},$$

where $I_0(\kappa)$ is the modified Bessel function of order 0. The VM distribution is a close approximation to the wrapped normal distribution, where μ is the mean and κ is analogous to $1/\sigma^2$. The support is $[-\pi, \pi]$ with $\mu = 0$. For $\kappa = 0$, VM is a uniform distribution, and as $\kappa \rightarrow \infty$, $VM(\mu, \kappa) \rightarrow N(\mu, 1/\kappa)$.

A.3 Modeled Noise Parameters

Noise is modeled as the sum of white noise $N_1(t)$ and a complex sinusoid $N_2(t)$ with random AM and FM.

$$N(t) = N_1(t) + N_2(t)$$

$$N_1(t) \sim N(0,1)$$

$$N_2(t) = \sin(2\pi f_1 + \theta) \sin(2\pi f_2 \sin(2\pi f_3 t) t)$$

The parameters θ , f_1 , f_2 , and f_3 are all random variables, which are generated for every trial and subject.

$$\theta \sim U[-\pi, \pi)$$

$$f_1(t) \sim N(19, 2)$$

$$f_2(t) \sim N(9, 2)$$

$$f_3(t) \sim N(13, 2)$$

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