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VILNIUS UNIVERSITY

Evaldas
PIPINIS

Evaluation of electrical brain responses to linear chirp-modulated tones: effect of task and changes in neuropsychiatric disorders

DOCTORAL DISSERTATION

Natural Sciences,
Biophysics (N011)

VILNIUS 2020

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VILNIAUS UNIVERSITETAS

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Galvos smegenų elektrinių atsakų į tonus, kurių amplitudė moduliuota tiesiniu čirpu, įvertinimas: užduoties įtaka ir pokyčiai neuropsichiatrinių sutrikimų metu

DAKTARO DISERTACIJA

Gamtos mokslai,
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CONTENTS

LIST OF ABBREVIATIONS

AM	Amplitude modulated
ANOVA	Analysis of variance
ASSR	Auditory steady-state response
CRS-R	Coma Recovery Scale-Revised
DOC	Disorder of consciousness
EA	Evoked amplitude
EEG	Electroencephalography
EP	Evoked potential
FAM	Flutter amplitude-modulated
FFT	Fast Fourier transformation
FM	Frequency modulated
ICA	Independent component analysis
IGF	Individual gamma frequency
MCS	Minimally conscious state
MEG	Magnetoencephalography
MM	Mixed modulated
N	Sample size
PANSS	Positive and Negative Syndrome Scale
PLI	Phase-locking index
RSG	Repeating sequence gated
SD	Standard deviation
stFFT	Short Time Fast Fourier transformation
SZ	Schizophrenia
TF	Time-frequency
tGBR	Transient gamma band response
TMS	Transcranial magnetic stimulation
VS / UWS	Vegetative state / Unresponsive Wakefulness Syndrome

INTRODUCTION

In the recent years, a great need for objective neurophysiological biomarkers that could be used in diagnostics and monitoring of neuropsychiatric disorders emerged. Electroencephalography (EEG) due to its profound advantages - non-invasiveness, simplicity of use, high time resolution in the milliseconds range and low price tag - has been widely utilized for this purpose.

EEG activity represents rhythmic neural activation as a result of compound action of postsynaptic potentials and can be separated according to the frequency of oscillations into delta (2-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (15-30 Hz), lower (30-80 Hz) and higher (80-150 Hz) gamma frequency ranges (Cohen, 2014). These can be assessed when EEG is collected during the rest. However, a more efficient and increasingly used approach to actively test the ability of the brain to generate particular frequencies is the assessment of responses to presented periodic stimulation, most frequently of auditory modality (Hamm et al., 2012; Mahajan et al., 2014; Puvvada et al., 2018) utilizing the basic property of the nervous system to "follow" periodic input (Picton et al., 2003a). This approach developed into the method of auditory steady-state responses (ASSRs), and ASSRs at the gamma range received most attention and have been proposed to serve as a biomarker of schizophrenia (Thuné et al., 2016). Importantly, promising results were also obtained in other neuropsychiatric (Isomura et al., 2016; Oda et al., 2012; Parker et al., 2019) and developmental disorders (Khaleghi et al., 2019; Wilson et al., 2007), as well as altered consciousness states such as sleep (Górska and Binder, 2019; Picton et al., 2003b), anaesthesia induced loss of consciousness (Plourde, 2006; Plourde et al., 2008) and disorder of consciousness patients (DOC) (Binder et al., 2017). Moreover, ASSRs were reported to be age-dependent (Griskova-Bulanova et al., 2013a; Poulsen et al., 2009) and showed profound signs of modulation by the attention level paid to stimulation (Griskova-Bulanova et al., 2011; Manting et al., 2019; Ross et al., 2004). These all make ASSR-based approach of testing brain functioning in norm and pathological conditions encouraging.

However, ASSR changes in clinical population are not restricted to the low gamma range: altered responses in lower (< 30Hz) (Edgar et al., 2018; Hamm et al., 2011; Puvvada et al., 2018) and higher (>50Hz) frequencies (Hamm et al., 2011; Parker et al., 2019; Tsuchimoto et al., 2011) were

observed and changes were related to the clinical manifestations in patients (Hamm et al., 2011; Tsuchimoto et al., 2011). These results emphasize the need for testing of wider frequency ranges in clinically-oriented research.

However, testing broad frequency windows utilizing single frequency stimuli requires long recording times and is challenging to the subjects. As a solution, to overcome the long duration of the assessment procedure, the stimulation with changing sound modulation frequencies - chirps - was proposed, allowing testing of brain responses at a wide range of frequencies with one stimulus (Artieda et al., 2004; Purcell et al., 2004). Artieda et al. (2004) reported that high carrier amplitude-modulated by a sine wave tones with changing modulation frequencies between 1 and 120 Hz elicit responses with two profound peaks in EEG at the low (30-65 Hz) and high (80-120 Hz) gamma ranges. Recently, employing chirp stimulation, attenuated low (30-50 Hz) and high (90-100 Hz) gamma responses in patients with schizophrenia (Alegre et al., 2017), and high beta/low gamma (27-39 Hz) impairment in autism spectrum disorder and low gamma (30-58 Hz) in fragile X syndrome were reported (De Stefano et al., 2019; Ethridge et al., 2017). Moreover, chirp-evoked responses in the gamma range where shown to be dependent on subjects' age (Poulsen et al., 2009), attention level paid to stimulation (Alegre et al., 2008) and consciousness state, such as sleep (Artieda et al., 2004). The abovementioned suggest that responses to chirp-modulated tones highlight similar aspects of brain functioning as captured by classical ASSRs.

Nevertheless, studies using chirp-based stimulation are still rare and greatly differ in stimulation protocols, subject groups tested, and response evaluation approaches. The shortest chirps used so far were 1600 ms in duration (Alegre et al., 2017; Artieda et al., 2004), still resulting in relatively long recording times. Moreover, all previous studies used high-frequency carriers that are perceived by humans as unpleasant (Västfjäll, 2012; Vitz, 1972). As many neuropsychiatric patients are known to have increased sensitivity to sounds (Bunney et al., 1999; Landon et al., 2016), the utilization of more pleasant low frequency carriers (Patchett, 1979) would be highly advantageous. In order to expand the knowledge and practical application of chirp-evoked responses, a chirp stimulus with the following features was created: 1) frequency of the carrier tone was reduced to 440 Hz, as lower frequencies are known to be more pleasant for the human subjects (Patchett, 1979) but elicit reliable and strong ASSRs (Ross et al., 2003; Voicikas et al., 2016); 2) stimulus duration was shortened to 500 ms which allowed to decrease total stimulation time to several minutes.

Three studies were conducted with the proposed auditory stimulation settings. In Study I (attentional modulation of chirp-evoked responses) two tasks requiring different levels of attention to auditory stimuli were used to assess attentional modulation of chirp-evoked response. It was expected to observe both low (30–50 Hz) and high (80–100 Hz) gamma components in EEG, similar to those as reported previously (Alegre et al., 2008; Artieda et al., 2004). The sensitivity of only low gamma response to attentional manipulations was anticipated based on earlier works (Griskova-Bulanova et al., 2011; Linden et al., 1987; Voicikas et al., 2016). In Study II (chirp-evoked responses in schizophrenia) chirp-evoked responses were compared between patients with schizophrenia and healthy controls. It was hypothesized that brief low carrier frequency chirp modulated stimulation will evoke responses that will capture impaired low frequency, low gamma and high gamma activity in patients with schizophrenia as shown by previous works using discrete single-frequency stimulation settings (Hamm et al., 2011; Puvvada et al., 2018; Thuné et al., 2016; Tsuchimoto et al., 2011). In Study III (responses to chirp in disorder of consciousness) chirp-evoked responses were evaluated in a sample of patients with disorder of consciousness. It was anticipated that in concordance with the previous study (Binder et al., 2017), the response in the low gamma range (30-50 Hz) would show a correlation with the state of DOC patients, whereas high gamma range (80-120 Hz) response would not.

1.1 Aim and objectives

The aim of this work was to evaluate electroencephalographic responses to brief low frequency carrier chirp-modulated tones and test their potential application in neuropsychiatric conditions.

The following objectives were formulated to achieve the aim:

- To assess subjective perception of brief low frequency carrier chirp-modulated tones;
- To evaluate effect of stimulation direction and attentional modulation on chirp-evoked responses;
- To evaluate chirp-evoked synchronization and amplitude in patients with schizophrenia and healthy controls and to relate chirp-evoked responses to the clinical manifestations in patients;

- To evaluate chirp-evoked synchronization in a sample of patients with disorder of consciousness and relate it to the clinical manifestations.

1.2 Scientific novelty

- For the first time the EEG response to brief low frequency carrier chirp-modulated tones was assessed.
- For the first time the effect of attentional demands on responses to brief low frequency carrier chirp-modulated tones was evaluated.
- For the first time comparison of the EEG response to brief low frequency carrier chirp-modulated tones was performed in patients with schizophrenia and healthy controls.
- For the first time the EEG response to brief low frequency carrier chirp-modulated tones was assessed in a clinical sample of patients with disorder of consciousness.

1.3 Practical implication

- Brief low frequency carrier chirp-modulated tone stimulation can be used in clinical settings to obtain brain responses in conditions where control of attention is difficult.
- Brief low frequency carrier chirp-modulated tones can be used to obtain brain responses in schizophrenia where alterations in theta-beta (4-18 Hz), low (30-60 Hz) and high gamma (95-120 Hz) are captured similarly to classical auditory steady-state responses.
- Brief low frequency carrier chirp-modulated tone stimulation can be used in DOC research, as chirp-evoked response highlights deficient low gamma (36-46 Hz) activity similarly to classical auditory steady-state stimulation.

1.4 Defended statements

1. Chirp-evoked response to brief low frequency carrier chirp-modulated tone stimulation is not sensitive to attentional demand – phase-locking

index and evoked amplitude of responses in low (30-60 Hz) and high (90-110 Hz) gamma ranges do not differ between attention focused on stimuli and distraction conditions.

2. Chirp-evoked response to brief low frequency carrier chirp-modulated tone stimulation highlights impaired ability to synchronize at theta-beta (4-18 Hz) and high gamma (95-120 Hz) ranges, and slower low gamma frequencies in patients with schizophrenia. These alterations are related to the manifestation of clinical symptoms.

3. Chirp-evoked response to brief low frequency carrier chirp-modulated tone stimulation highlights impaired synchronization in the low gamma range (30-60 Hz) in patents with disorders of consciousness. Response is positively associated with the Coma Recovery Scale-revised total scores and scores in auditory and visual subscales.

LITERATURE REVIEW

2. Electroencephalography

Almost one hundred years passed from the first human electrical brain activity recording made by German psychiatrist Hans Berger in 1924 (Berger, 1929). Since then electroencephalography has become one of the mostly used neurophysiological tool in a wide variety of clinical and research fields, such as diagnostics of neuropsychiatric disorders, practical applications in brain computer interface, neurolinguistics, and studies on cognitive functioning.

While a variety of brain activity imaging methods exists, EEG remains a widely-used technique due to its advantages: simplicity of use, inexpensiveness, adaptability, and high time resolution. EEG offers the possibility to sample brain activity data up to 20 kHz allowing to track extremely fast processes. The spatial resolution of the method can be increase by using high density EEG recording systems which records from over 256 electrodes or by combining EEG with other neuroimaging techniques (Meyer et al., 2020; Robinson et al., 2017).

The actual EEG signal source is excitatory and inhibitory postsynaptic potentials of pyramidal neurons orientated radially to the scalp surface Figure 2.1 since these potentials overlap in time and are generated by strictly parallelly arranged neuronal structure - cortical columns (Jackson and Bolger, 2014; Murakami and Okada, 2006).

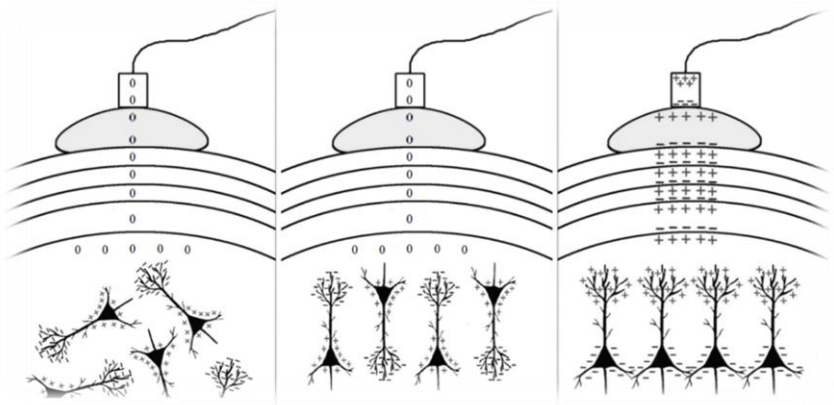

Figure 2.1 EEG signal path from neuron population to the electrode. Lines represent insulating layers with conductive volumes (dura layers, skull layers,

electrode gel, electrode) in between. First two schemes from the left represents no clear dipole neuron arrangement structure and parallel but partly inverted neuron structure (resulting in no measurable electrical EEG activity on the scalp surface). The right scheme represents strictly parallelly radially arranged neuronal structure and EEG signal propagation towards an electrode. (Figure adopted from (Jackson and Bolger, 2014)).

2.1 Evoked potentials

Evoked potential in response to auditory stimuli is called auditory evoked potential (AEP). AEP derived from slow frequency stimulation to which single responses do not overlap in time are called transient AEP (tAEP) (Paulraj et al., 2015). Stimulating with frequencies up till the 5 Hz gives electrical potentials that are subdivided according to time into three periods presented in Figure 2.2.

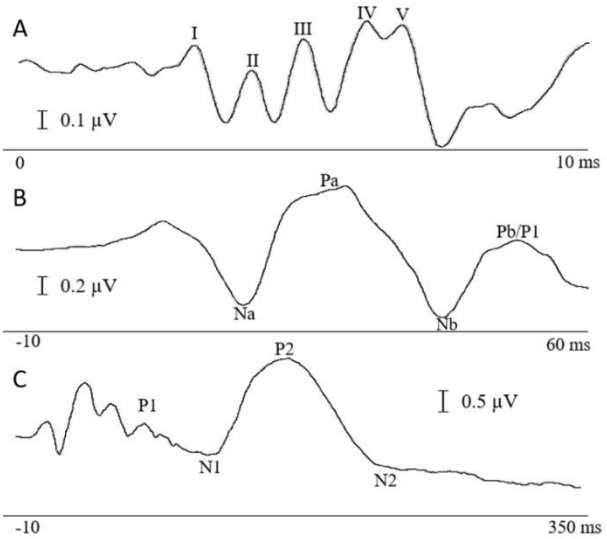

Figure 2.2: A. Early-latency auditory evoked potentials or the auditory brainstem response (ABR). **B.** Middle-latency auditory (MLR) evoked potentials. **C.** Late-latency auditory (LLR) evoked potentials (exogenous responses). (Binder et al., 2009)

Auditory brainstem response (ABR) occurs during first 10 ms after the stimulus (Boston, 1981; Jewett et al., 1970) and represents the electrical activity related to the signal propagation through auditory nerve, cochlear nucleus, superior olivary nucleus and lateral lemniscus to the inferior colliculus. ABR is followed by the middle latency response (MLR) which is

characterized by four peaks - first negative (Na 15-22 ms), first positive (Pa 24-34ms), second negative (Nb 35-50ms) and second positive (Pb later than 50ms) - and represents thalamus and cortex activity (Musiek and Nagle, 2018). Late latency responses (LLR) emerge after the MLR and are of cortical origin. LLR components (P1, partially N2, P2) are affected by the physical properties (intensity, duration, frequency) of the stimulus are called exogenous. In contrast, endogenous components (N100, P300, N400) depend on the subject's attention, stimulus evaluation or categorization (Bruno et al., 2016; Picton, 1988).

2.2 Auditory steady-state responses

Auditory steady state response (ASSR) is a steady state evoked potential to the repetitive (frequency higher than for tAEP) auditory stimulation. ASSR is considered to have an infinitely stable frequency, amplitude and phase (Regan, 1989). While being infinite, ASSR can be analyzed in a shorter periods of time in which response parameters follow or are driven by the characteristics of the external stimulation (Picton et al., 2003a).

Brain ability to entrain to the external stimulation has been demonstrated in 1934 by Adrian and Matthews who reported increase in alpha amplitude in response to flashing light stimuli (Compston, 2010). This response is known as visual steady state response and led to the hypothesis that similar response could be detected in auditory system. Indeed Galambos et al. (1981) showed that auditory steady state response can be elicited by stimulation with frequency of 40 Hz (Galambos et al., 1981). Many of the following research focused on ASSR showed that ASSR is strongest at this frequency (Lindens et al., 1985; Makeig and Galambos, 1989; Picton et al., 2003a; Stapells et al., 1984).

2.2.1 ASSR generation theories

Two main theories (superposition and entrainment) are proposed to explain the origin of ASSRs.

Superposition theory is based on the fact that time period between auditory stimuli required for generation of ASSR is shorter than the length of single tAEP. Therefore, ASSR recorded by EEG represents a summation of successive tAEPs shifted in time. This theory is mainly supported by analyses which generate synthetic ASSR from the tAEP modeled for the high frequency stimuli. Principle of superposition theory and example of

ASSR synthesis is presented in Figure 2.3. As can be seen from the tAEP in Figure 2.2, time difference between Pa and Pb peaks is around 25 ms which would give a perfect overlapping of these peaks at 40 Hz stimulation. However, first works have shown the discrepancies in amplitude and phase between real ASSR (rASSR) and synthetic ASSR (sASSR). This could be explained by the observation that tAEP depends on the frequency of the stimulation and thus low frequency tAEP is unsuitable for the synthesis of 40 Hz ASSR. For example, Pb peak shows maximum response at 40 Hz while Pa decreases with increasing stimulation frequency suggesting that strongest 40 Hz ASSR is derived from increase in Pb peak (Özdamar et al., 2007). However, modeling on tAEP derived from higher frequency jittered stimulus showed that even though rASSR amplitude can be predicted accurately both Nb-Pb and Na-Pa waves contribute to 40 Hz sASSR equally (around 45 % each) while remaining waves contributes 10 % (Bohórquez and Özdamar, 2008). Despite this promising result, sASSR is phase shifted (Bohórquez and Özdamar, 2008). Better estimation of rASSR was observed from novel multi-rate steady-state average deconvolution method used by Tan (2017) which led to the sASSR that was similar to rASSR both in amplitude and phase (Tan et al., 2017).

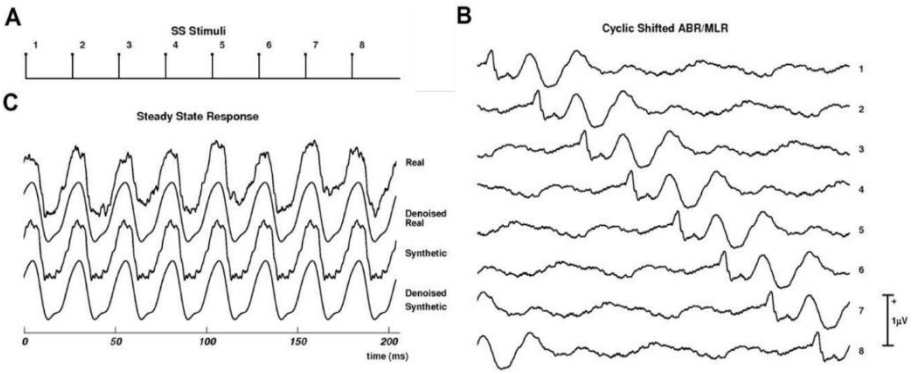

Figure 2.3: A. Sequence of click stimuli. **B.** Cyclic time-shifted deconvolved EP responses. **C.** The first two rows show separately acquired ASSR (raw) and its spectral filtered version (denoised). The bottom two rows show the summated response (synthetic) obtained by adding all the eight shifted responses shown in (B) and its filtered version (denoised synthetic). Picture presents single subject's data from Bohórquez and Özdamar study (Bohórquez and Özdamar, 2008).

On the other hand, results from studies on ASSR sources, ASSR propagation in time, effects of medication and behavioral significance of resonant frequency led to the alternative entrainment theory of ASSR generation. This theory suggests that SSR is generated by naturally existing

brain oscillators that synchronize their activity in response to external stimuli. Simplified phase-locking entrainment model is presented in Figure 2.4.

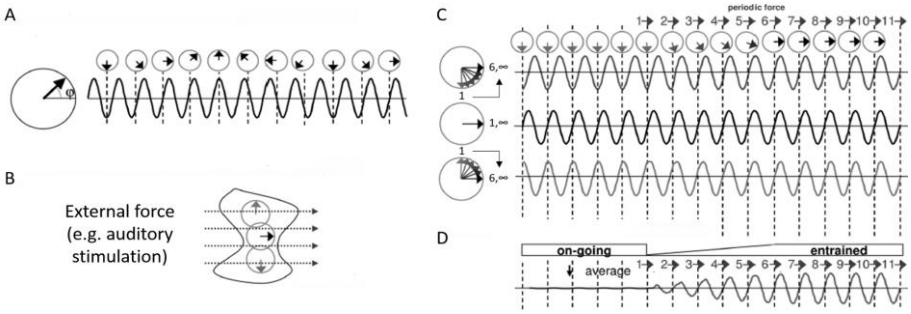

Figure 2.4: A. Single phase oscillator model and its oscillations over time **B.** 3 same frequency but not phase aligned oscillators in a single population. Short arrows represent oscillator's phase, long arrows represent external force direction. **C.** Oscillator's phase shift in response to external periodic force. Phase alignment is already present in one oscillator (middle) at the beginning of periodic force and is reached in other two after the 6th application of external force. **D.** Averaged activity over oscillators during 3 stages: counter phased (until 1) – no amplitude; during phase alignment (from 1 to 6) – increasing amplitude of oscillation, phase aligned (from 6 to the end of external force) – stable amplitude and phase oscillation. (Figure adopted from (Thut et al., 2011)).

As can be seen from the model, some time is required for the entrainment to reach a stable phase (Thut et al., 2011). Indeed, Ross et al. (2002) showed that transient gamma band response (tGBR) appears in a first 100 ms of the stimulation, but the stable amplitude of the oscillation and phase relationship with the stimulus builds up in a time window of 80 to 250 ms (Ross et al., 2002). Furthermore, by combining monaural amplitude modulated 40 Hz stimulation with contralateral noise stimuli Ross et al. (2002) showed that SSR diminishes in amplitude in response to noise burst. This result could not be explained by changes in AEP generated by 40 Hz stimulus (since tAEP elicited by AM stimuli should not change). Moreover, the gap or phase shift in a stimulus causes SSR to be rebuild in a time window of 200 ms, thus implying that ASSR is not an evoked potential (EP) but rather the induced brain response (Ross et al., 2005). Further support for the ASSR entrainment theory comes from Pastor et al. (2006) who showed that although synaptic activity in the temporal cortex increases in response to different stimulation frequencies, only 40 Hz stimulation is associated with bilateral activation of cerebellar hemispheres. Exclusiveness of 40 Hz response has been confirmed by the transcranial magnetic stimulation (TMS) study which

showed that modulation of cerebellar activity specifically reduces only 40 Hz ASSR, showing that neural networks activated during ASSR have frequency specific preferences and should be downregulated in resonant frequency of 40 Hz (Pastor et al., 2006, 2002). Other line of reasoning comes from the notion that if brain ability to synchronize at a specific frequency is an outcome of the inbuilt oscillator properties and not from the superposition of tAEP there should be a behavioral significant outcome of such system. Indeed, importance of specific entrainment frequency has been shown by associations of individual gamma frequency (IGF) with the auditory temporal accuracy where the higher IGF are related to the better perceptual time resolution (Baltus and Herrmann, 2015). These results confirms the behavioral significance of ASSR and further supports the entrainment hypothesis (Baltus et al., 2018).

2.2.2 Stimulation types used for ASSR

Variety of stimuli - amplitude modulation (AM), frequency modulation (FM), frequency-amplitude modulation (MM), repeating sequence gated (RSG) - are used to elicit ASSR. These stimulation types can be classified into two main groups: frequency specific and frequency unspecific. The specific ones have power concentrated in a narrow band of frequencies and include filtered clicks, band-limited chirps, tone bursts, narrow band noise, frequency-modulated pure tones. On the contrary, unspecific stimuli are described by broad band of frequencies and include clicks, noises, amplitude modulated noise, chirps (Beck et al., 2007; Korczak et al., 2012).

Amplitude modulated stimuli are formed by modulating the amplitude of a primary (carrier) sound. The most common AM stimuli is a pure tone modulated by the sine wave of lower frequency (modulation frequency, MF) (Picton et al., 2003a). Main characteristics of AM stimuli are description of a carrier (for e.g. pure tone frequency, language stream etc.), MF, and depth of the modulation. Modulation depth is expressed in a percent of carrier amplitude decrease where 100% stands for the strongest possible modulation (Korczak et al., 2012).

Frequency modulated stimuli are formed by modulating frequency of a carrier tone but leaving the amplitude unchanged. Modulation depth is expressed in a percent of modulation frequency range to that of the original carrier. For example, 1000 Hz carrier modulated in 25 % results in FM stimuli with the frequencies changing from 875 to 1125 Hz (John et al., 2001).

Mixed modulation is a combination of both AM and FM stimuli and is derived by amplitude modulating carrier which is already modulated in frequency. Compared to the single frequency carrier AM stimuli, MM stimuli have wider frequency range and are described by carrier, amplitude and frequency modulation depths (Korczak et al., 2012).

Repeating sequence gated stimuli are derived by presenting various type of tones in a repeating pattern. The pattern is calculated according to the MF and represents time between two consequent peaks of tones. RSG stimuli are described according to the tone (the most commonly used is a short noise burst) and a MF. For example, MF of 40 Hz would result in noise burst presented with 25 ms inter burst intervals (Korczak et al., 2012).

2.2.3 Analysis of ASSR

Compared to the ongoing general EEG activity ASSR is relatively small in amplitude but is phase-locked to the stimulus, therefore SNR is improved by averaging over multiple responses. By analysing ASSR in different frequency bands Ross et al (2002) showed that response can be separated into four components (Ross et al., 2002). Transient response (P1-N1-P2 complex) appears in first 100 ms after the stimulus onset and is followed by a slow negative wave called sustained potential (SP) which lasts until the end of stimulation. These components are best seen in a low pass (to 24 Hz) filtered data. Band pass filtering in gamma range allows to clearly see transient gamma (early gamma response in first 100 ms) and steady-state (late gamma response) components (Griskova-Bulanova et al., 2016; Ross et al., 2005). 40 Hz ASSR and four separate components are depicted in Figure 2.6.

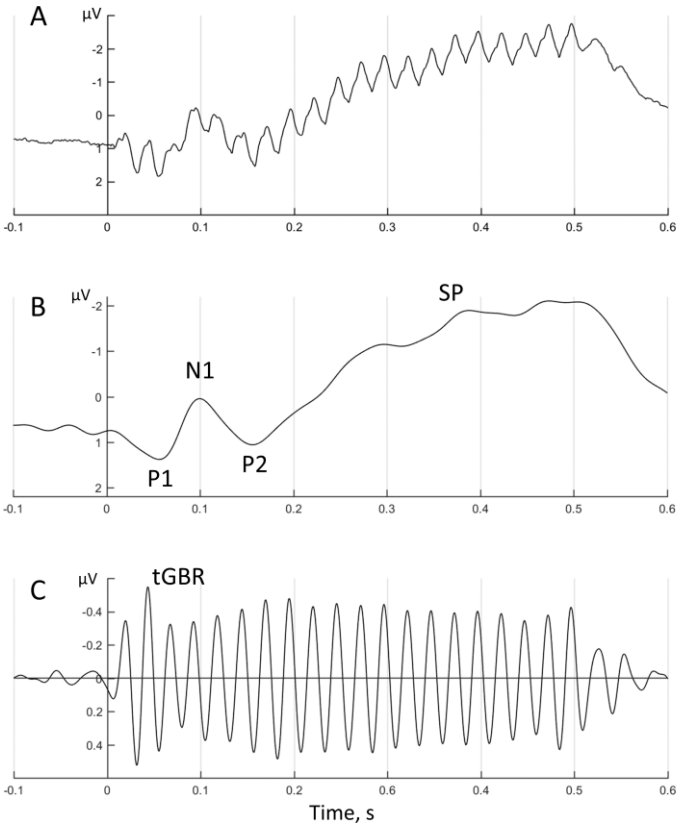

Figure 2.6: ASSR elicited by 500 ms length 40 Hz steady-state stimulation. **A.** Unfiltered response. **B.** Response filtered to 1-24 Hz frequency range. **C.** Response filtered to 30-60 Hz frequency range.

Most ASSR studies nowadays use frequency or time-frequency transformations. Fast furrier transformation (FFT) is used for frequency transformation and results in power spectra of ASSR which usually shows peak at the stimulation frequency and smaller peaks at its harmonics. FFT requires relatively long time window of analysis and is used for the whole or selectively chosen ASSR (e.g. late gamma response) time window. Commonly reported measures are power of single frequency or frequency range. However, since ASSR develops during the stimulation time (Ross et al., 2005), time-frequency transformation is considered to be more suitable for the ASSR analysis (Cohen, 2019). The most frequently used time-frequency (TF) analysis methods are short time FFT (stFFT) and wavelet transformation (Cohen, 2014). There are many different wavelet types that could be used in TF analysis, however, the most commonly used is the

application of complex Morlet wavelets. This results in easily interpretable TF plots and offers easily adaptable time/frequency resolution trade-off. For these reasons TF analysis by complex Morlet wavelets are implemented in most EEG analysis toolboxes (Cohen, 2014).

TF deconvolution of ASSRs with complex Morlet wavelets or stFFT results in amplitude and phase angle time series as outcome measures that allow further calculation of phase-locking index (PLI), global field synchronization (GFS), evoked amplitude (EA), and event related spectral perturbation (ERSP) measurements (Koenig et al., 2001; Mørup et al., 2007).

PLI also known as inter-trial phase coherence – is a measurement of phase consistency over the epochs. During PLI calculation each epoch is weighted equally which reduces noisy data influence on the results. PLI is the most power independent measure; however, since oscillation cycles at high frequencies are short, precise timing of stimulation is crucial for this measurement (Mørup et al., 2007).

ERSP – corresponds to power of each epoch averaged. ERSP includes both: induced and evoked power (Mørup et al., 2007).

EA – corresponds to the wavelet-transformed evoked potential and represents phase-aligned amplitude measure (Mørup et al., 2007).

Induced power – corresponds to power which is not phase-locked to the stimulation and is calculated as a difference between ERSP and evoked power (Mørup et al., 2007).

GFS – corresponds to phase consistency between all electrodes at a given time point, and reflects functional connectivity of brain processes (Koenig et al., 2001).

EEG power in high frequencies is smaller than in low. Thus, in order to better visualize TF composition, ASSRs are normalized to the mean of pre-stimulus activity. There are several normalization methods used:

Subtraction – mean baseline activity is subtracted from each value within the epoch.

Division – each value in epoch is divided by the mean of the baseline. Division could be combined with logarithmic transformation, then result is expressed in bels (typically multiplication is used to convert scale from bel to decibel).

Percent change – result of normalization by subtraction is divided by the mean of the baseline and then multiplied by 100.

Z-score – result of normalization by subtraction is divided by the standard deviation (SD) in the baseline period. This results in measurement scaled to standard deviation units relative to the measurement during the baseline period. (Cohen, 2014; Roach and Mathalon, 2008)

2.2.4 Chirp-based stimuli

An additional way to test brain ability to generate responses at particular frequencies is to use chirp-based stimulation. Chirp represents a stimulus type where the changing modulation frequency is used. Wide stimulation frequency range can be covered (Purcell et al., 2004). Responses to this stimulation type are called chirp-evoked responses or as envelope following responses (Artieda et al., 2004; Purcell et al., 2004).

Chirp stimuli are described by the frequency modulation range, modulation direction (increasing/decreasing), modulation depth and duration. The most common type of chirps used is an AM-chirp derived from carrier tone modulation with sine wave of changing frequency (Artieda et al., 2004; Lehongre et al., 2011; Pérez-Alcázar et al., 2008). To illustrate, the composition of stimuli, response and analysis approach reported by Artieda et al. (2004) are presented in Figure 2.5.

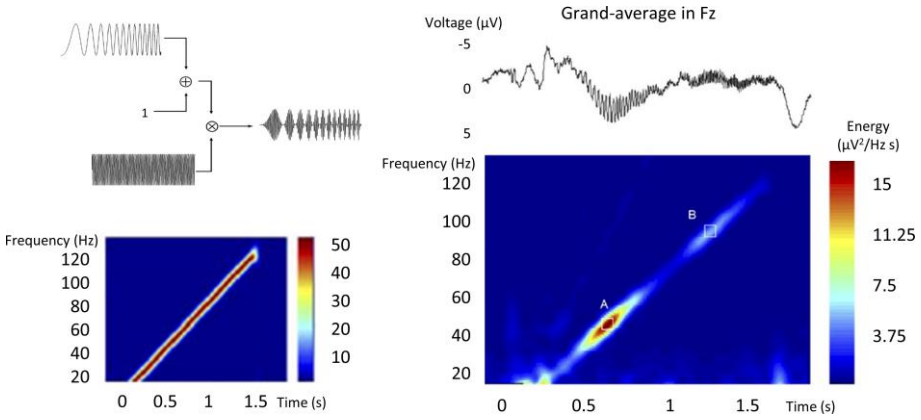

Figure 2.5: top left. Chirp stimulus composition from carrier tone (1200 Hz) amplitude modulated by sine wave with changing frequency (from 1 to 120 Hz). Modulation depth – 1 (corresponding to 100%). **Bottom left.** Chirp stimulus time-frequency power spectra. **Top right.** Grand average of the potentials evoked by chirp. **Bottom right.** Grand average of time-frequency transform of the potentials with colour scale representing absolute power; Both grand averaged plots are obtained from 10 subjects data at Fz electrode. (Figure adopted form Artieda et al. 2004 (Artieda et al., 2004)).

Chirp-evoked response also can be elicited by binaural and acoustic beat stimuli. Single frequency ASSR is produced by presenting two tones (together or separately for each ear) with slightly different frequencies, while chirp response is elicited by modulating difference between the two tones frequencies (Ross et al., 2014).

Over the last decades, chirp-based stimulation has been used in magnetoencephalography (MEG) and EEG research; however, studies differ in stimulation protocol, analysis approach and populations tested. Previous studies discuss the results obtained with chirp-stimulation as comparable to single-frequency ASSRs. The summary of available reports using chirp stimulation is given in Table 2.1.

Table 2.1 A summary of currently available studies assessing chirp-evoked response

Study	Subjects	Chirp stimuli description	Main results
(Purcell et al., 2004)	Human: Healthy	Type: increasing-decreasing Carrier: white noise or 1 kHz tone Modulation depth: 20/50/100 % Length: 30.72s Modulation range: 35-100, 20-100, 70-200 and 100-600 Hz	Responses could be measured up to 485 Hz in younger and up to 235 Hz in older population. White noise carrier chirps elicited stronger response than pure tone chirps. Higher modulation frequency chirps elicited stronger response
(Artieda et al., 2004)	Human: Healthy	Type: increasing Carrier: 1.2 kHz tone Modulation depth: 100 % Length: 1.61s Modulation range: 1-120 Hz	Chirps elicited a diagonal band of energy corresponding to the frequency of modulation at each time instant. Two (30–60 Hz) and (80-120 Hz) peaks in chirp-evoked response were apparent.
(Purcell et al., 2006)	Human: Healthy	Type: increasing-decreasing Beat stimulus: tone1: 900 and 1800Hz tone2: 732 – 752 Hz and 1630 to 1650 Hz Length: 30.72s Modulation range: 150 - 170 Hz	Stimulus frequency had a significant effect on response latency - it was shorter for 1800 Hz. There was no significant effect of stimulus frequency on the magnitude of the elicited response.
(Poulsen et al., 2007)	Human: Healthy	Type: increasing-decreasing Carrier: white noise Modulation depth: 100 % Length: 30.72s	Frequency of the peak response increased with age and was in 25-55 Hz range for adults.

		Modulation range: 10-100 Hz	
(Alegre et al., 2008)	Human: Healthy	Type: increasing Carrier: 1.2 kHz tone Modulation depth: 90 % Length: 1.61s Modulation range: 1-120 Hz	No attention effect on PLIs in 30-50 Hz and 80-120 Hz range and response energy in 30-50 Hz range. Lower response energy in 80-120 Hz range in the reading (distraction from stimuli) condition.
(Pérez-Alcázar et al., 2008)	Rat: Healthy	Type: increasing Carrier: 5 kHz tone Modulation depth: 100 % Length: 3.1 s Modulation range: 1-250 Hz	Response amplitude in awake animals decreased progressively with increasing modulation rate. Lower response amplitude and PLI for frequencies under 100 Hz and higher PLI for frequencies over 200 Hz under the ketamine/xylazine anesthesia.
(Poulsen et al., 2009)	Human: Healthy	Type: increasing-decreasing Carrier: white noise Modulation depth: 100 % Length: 30.72s Modulation range: 10-100 Hz	Frequency of the peak response was in 25-52 Hz range for 10 years old and in 27-55 Hz range in 11.5 years old children. Frequency of the peak response increased with age. Response peak amplitude did not differ between adults and children of 10 and 11,5 years of age.
(Purcell and John, 2010)	Human: Healthy	Type: increasing-decreasing Carrier: 0.5 and 2 kHz tone Length: 30.74s Modulation range: 66 -102 Hz and 86 – 121 Hz	Response amplitude in two separate recordings highly correlated between sessions.
(Pérez-Alcázar et al., 2010)	Rat: Healthy, Parkinson	Type: increasing Carrier: 5 kHz tone Modulation depth: 100 %	Frequency of the peak response in 40-60 Hz range was reduced in Parkinson's disease model rats and was normalized after apomorphine injection.

	's disease model	Length: 3.1 s Modulation range: 1-250 Hz	
(Lehongre et al., 2011)	Human: Normal, Dyslexic	Type: increasing Carrier: white noise Modulation depth: 100 % Length: 5.2s Modulation range: 10-80 Hz	Controls showed a left hemisphere response dominance in 25–35 Hz range and a right dominance above 55 Hz. Left dominance was absent in dyslexics. Enhanced cortical entrainment at rates beyond 40 Hz in dyslexics was associated with a verbal memory deficit.
(Prado-Gutierrez et al., 2012)	Rat: Healthy	Type: increasing-decreasing Carrier: broadband noise, 8 and 4 kHz Modulation depth: 100 % Length: 30.77s Modulation range: 20-200 Hz, 30-210 Hz and 10-190 Hz	Frequency of the peak response was at 122 Hz. Beyond maximum Response amplitude above 122 Hz decreased continuously. Frequency of the peak response did not depend on the stimulus intensity. During maturation, frequency of the peak response and peak amplitude to the tone carrier chirp increased.
(Miyazaki et al., 2013)	Human: Healthy	Type: increasing-decreasing Acoustic beet: tone 1 (498.5–470 Hz) tone 2 (501.5–530 Hz) Length: 16s Modulation range: 3-60 Hz	Response amplitude trajectory follow the rate of the stimulus beat between 3 and 60 Hz, with maximum amplitudes at 3-5 Hz and 40 Hz and minimum amplitudes at 7-10 Hz and 20 Hz. PLI results similar to amplitude results. Responses at frequencies equal to multiples of the beat rates, mostly pronounced in 35-50 Hz gamma range.
(Ross et al., 2014)	Human: Healthy	Type: increasing-decreasing Binaural and acoustic beet: Tone 1 (498.5–470 Hz) Tone 2 (501.5–530 Hz) Length: 16s Modulation range: 3-60 Hz	Acoustic beat response showed phase coherence maximums at ≤ 3 and 12 Hz with the largest maximum at 40 Hz and minimums at 8 and 20 Hz. Response to binaural beat showed highest phase coherence in 30-60 Hz range. Response amplitudes to the acoustic beat were balanced between

			hemispheres below 20 Hz and right lateralized in the gamma-band. Response amplitudes to the binaural beat were left lateralized around 6 Hz and right lateralized around 15 Hz.
(Alegre et al., 2017)	Human: Healthy, Patients	Type: increasing Carrier: 1.2 kHz tone Modulation depth: 90 % Length: 1.61s Modulation range: 1-120 Hz	Response amplitude was reduced in 30-50 Hz and 90-100 Hz range and PLI was reduced in 30-50 Hz range in drug naive schizophrenia patients. There was no difference of response amplitude and PLI in 30-50 Hz range between medicated SZ patients and healthy controls. Response amplitude in 90–100 Hz range was reduced in medicated SZ patients.
(Ethridge et al., 2017)	Human: Healthy, Patients	Type: increasing Carrier: 1 kHz tone Modulation depth: 100 % Length: 2s Modulation range: 0-100 Hz	Fragile X syndrome patients showed decreased gamma phase-locking in 30–58 Hz range and decreased gamma phase-locking in 47–58 Hz range for harmonics.
(Lovelace et al., 2018)	Mice: Healthy, Fragile X syndrome model	Type: increasing and decreasing Carrier: broadband noise Modulation depth: 100 % Length: 2s Modulation range: 1-100 Hz	PLI was reduced in 13–50 Hz and in 70–100 Hz range compared to wild type mice in auditory cortex. PLI was reduced in 30–100 Hz compared to wild type mice in frontal cortex. Response patterns for chirp up and down were similar.
(De Stefano et al., 2019)	Human: Healthy, Patients	Type: increasing Carrier: 1 kHz tone Modulation depth: 100 % Length: 2s Modulation range: 0-100 Hz	PLI was reduced in 27-39 Hz range for older autism spectrum disorder patients. No difference in PLI between younger autism spectrum disorder patients and healthy controls.

2.3 Attention and ASSR

The first study of attention effect by Linden et al. (1987) showed no changes in auditory steady-state responses (Linden et al., 1987); however, over years the question remained open largely because of conflicting results reported in many studies. To illustrate, no attention effect was found on 40 Hz ASSR comparing attend to audio or visual target conditions (de Jong et al., 2010) or to chirp-evoked and flutter amplitude-modulated (FAM) 40 Hz ASSRs between distraction and active listening conditions (Alegre et al., 2008; Voicikas et al., 2016). Similarly, no effect on ASSR power was found in MEG study between attend to sound and ignore sound conditions (Lazzouni et al., 2010). However, Keitel et al. (2013) showed that although ASSR amplitude remains unchanged when comparing attend to both visual and auditory stimulation and attend to auditory only condition, response amplitude attenuates when attention is shifted to only visual stimuli (Keitel et al., 2013). Similarly, background (constant steady-state stimulation presented during other attentional task) ASSR amplitude is reduced by the presentation of task related to auditory but not to visual stimuli (Rohrbaugh et al., 1990) and in addition this attenuation is associated with the response required from subject: no attenuation in silent counting versus attenuation in active button pressing condition (Rockstroh et al., 1996). Contrary to the above mentioned, Ross et al. (2004) showed that attention directed to visual task attenuated amplitude of 40 Hz ASSR (Ross et al., 2004). This result goes in line with the observations that 40 Hz ASSR power, phase locking and source strength increase with attention paid to stimulation (Albrecht et al., 2013; Okamoto et al., 2011; Skosnik et al., 2007). In addition reduced evoked amplitude and phase consistency during the distraction task were shown for 40 Hz response elicited by both 40 and 20 Hz stimulations (Griskova-Bulanova et al., 2011; Griskova et al., 2009, 2007). This attenuation depends on the level of distraction: higher level of distraction results in a stronger attenuation (Roth et al., 2013).

Attention effect on other ASSR frequencies is also ambiguous. Mahajan, et al. (2014) reported that 16 and 23.5 Hz ASSR are enhanced with selective attention to stimulation (Mahajan et al., 2014) which goes in line with results of Müller et al (2009) where same effect for 20 Hz ASSR was shown (Müller et al., 2009) but opposes Skosnik et al. (2007) who reported that selective attention did not changed 20 Hz ASSR power (Skosnik et al., 2007). However, in agreement with Skosnik et al. (2007) are available

results that distraction from the 20 Hz stimuli is not associated with the attenuation of the response (Griskova-Bulanova et al., 2011; Griskova et al., 2009).

It has been suggested that interaction between attention and frequency of ASSR contributes to the ambiguity of reported effects of attention (Skosnik et al., 2007). Voicikas et al. (2016) reported attention effect on ASSR elicited by RSG but not on FAM-elicited 40Hz ASSRs, suggesting that stimulation type can also attribute to the discrepancy of results (Voicikas et al., 2016). Influence of stimulation type on ASSRs is also reported in brain-computer interface studies where attention detection from ASSR signal is influenced by the type of stimuli (AM, FM, RSG) and the carrier sound (natural sounds, music, pure sine wave) used in stimuli generation (Heo et al., 2017; Matsumoto et al., 2012). In addition, it has been argued that conflicting results might be partly explained by inconsistencies in methodologies of studies - brain activity measurement technique, attention modulation modality (whether it is modulated within single or multiple senses) and attention modulation strength (Keitel et al., 2013; Roth et al., 2013).

Similarly to ASSR, ambiguous attention effect on chirp-evoked responses was reported by Alegre et al. (2008) - distraction from the chirp stimulus attenuated high (80-120 Hz) but not low (30-50 Hz) gamma response energy and no effect on PLI was observed (Alegre et al., 2008).

2.4 ASSRs in schizophrenia

Schizophrenia is a heterogeneous behavioural and cognitive syndrome characterized by positive symptoms (delusions and hallucinations), negative symptoms (impaired motivation, reduction in spontaneous speech, social withdrawal) and core cognitive features of impaired attention, working memory and executive functioning (Biedermann and Fleischhacker, 2016; Bowie and Harvey, 2006). Over 1 million people were diagnosed with SZ in 2017, and the prevalence of SZ was 20 million cases globally (James and Abate, 2018). However, diagnosis remains challenging as it is often biased and cognitive changes are non-specific to schizophrenia.

It has been shown that SZ is associated with the dysfunction of parvalbumin γ-aminobutyric acid (GABA) interneurons and N-methyl-D-aspartate (NMDA) receptors resulting in impaired inhibition/excitation balance which leads to observed cognitive impairment and abnormal gamma rhythm-generation (Gao and Penzes, 2015; Lewis et al., 2012; Uhlhaas and

Singer, 2015). Moreover since cognitive deficits are detectable several years before the onset of psychosis, disturbed excitatory/inhibitory balance is a potential target for SZ biomarker research (Hong et al., 2004; O'Donnell, 2007). One of the methods to evaluate brain ability to generate gamma band oscillations noninvasively is a steady-state stimulation in the gamma range.

First study of ASSRs in SZ by Kwon et al. (1999) reported that patients show reduced 40 Hz response power. Kwon et al. (1999) also noted that compared to the healthy controls patients have changed phase-locking to stimulus, suggesting that both power and phase measurements could be beneficial in diagnostics (Kwon et al., 1999). In 2016 Thune et al. (2016) summarised findings in a meta-analysis and showed that SZ patients have reduced power and phase locking in response to 40 Hz auditory steady-state stimulation (Thuné et al., 2016). This effect has been confirmed by analysing 14 phase and 15 power studies with the combined sample size of 606 SZ patients and 590 control subjects. Recent study by Koshiyama et al. (2018) showed that ASSR power is reduced not only in early stage patients (Tada et al., 2016) but also in a high-risk group (HRG). Phase measurement was less distinctive and did not differed between control and HRG groups (Koshiyama et al., 2018). However, Wang et al. (2018) reported that while both steady-state power and PLI are reduced during eyes open state during the first episode schizophrenia, only PLI is state independent (Wang et al., 2018). In contrary Lepock et al. (2019) did not find reduced EA or PLI in HRG, however showed that ASSR strength negatively correlated with the amplitude of mismatch negativity (MMN) which in turn correlated with the reduction of N400, suggesting, that ASSR strength could be related to the attention-dependant cognition (Lepock et al., 2019). Higher ASSR power in SZ patients is also associated with pour metacognition (Leonhardt et al., 2019) and disrupted in verbal fluency (Kim et al., 2019),while increased PLI in 40 Hz ASSR is associated with better performance in logical reasoning and problem solving (Sun et al., 2018). Griskova-Bulanova et al. (2016) reported that early latency ASSR measures correlate with negative symptom scores on Positive and Negative Syndrome Scale (PANSS) and Spencer et al. (2009) showed that changes in 40 Hz ASSR are related to hallucinations (Griskova-Bulanova et al., 2016; Spencer et al., 2009).

Although attenuated ASSR is usually observed in SZ patients or HRG some studies showed no difference in late gamma response (Griskova-Bulanova et al., 2016) or even an enhanced ASSR (Hamm et al., 2012; Kim et al., 2019). These inconsistencies could be attributed to a variety of factors that might influence ASSR in both clinical and healthy populations. It has been shown that ASSR in SZ patients depend on the eyes closed or eyes

open status (Griskova-Bulanova et al., 2013b, 2016) and Wang et al. (2018) reported that this difference is present only in a subgroup of medicated patients (Wang et al., 2018). Atypical antipsychotics were found to normalize ASSRs in the low gamma range (Alegre et al., 2017) while single dose of memantine (NMDA receptor antagonist) combined with different antipsychotics increased 40 Hz ASSR (Light et al., 2017). Hong et al. (2004) reported that 40 Hz ASSR strength in SZ group was higher than in controls, but only for the subsample of patients taking second generation antipsychotics (Hong et al., 2004). Indeed, this could explain results of Hamm et al. (2012) (enhanced ASSR response in SZ patients) since 13 out of 17 subjects were treated with the second generation antipsychotics (Hamm et al., 2012). However, in contrast to these reports Teale et al. (2008) reported attenuated 40 Hz ASSR in patients treated with atypical antipsychotics (Teale et al., 2008). It is also known that ASSR depends on the stimulation type used to elicit response. Griskova-Bulanova et al. (2018) reported that ASSR to RGS and flutter amplitude modulated tones are reduced in SZ patients; however, ASSR measurements do not correlate between different stimulation types, thus suggesting that these responses reflect impairments in different GABA-energic subsystems (Griskova-Bulanova et al., 2018). Finally, it has been proposed that some contradiction of the results could be attributed to the different length of inter-stimulus intervals (ISI) used in SZ research. Kim et al. (2019) reported enhanced 40 Hz ASSR in SZ patients while using 3050-3500 ms ISI, however attenuated response was found in a subsample when 500 ms ISI was used (Kim et al., 2019). This result goes in line with the above mentioned study by Hamm et al. (2012) where 3000 ms ISI was used and enhanced ASSR in SZ patients was reported (Hamm et al., 2012).

Although most research is focused on gamma-range ASSRs, several authors evaluated larger diapason of frequencies. Hamm et al. (2011) tested ASSRs to 5, 20, 40, 80 and 160 Hz stimulations and reported that SZ is associated with lower PLI values to 5 and 80 Hz stimulations (Hamm et al., 2011). Similar results of reduced power and PLI in theta-alpha and 4-16 Hz ranges were shown by sub-harmonic stimulations (Edgar et al., 2018; Hamm et al., 2012). In a larger sample (N=128 SZ and 108 H controls) the reduced phase-locking and power of ASSRs to 2.5, 5 and 10 Hz stimulations was replicated by Puvvada et al. (2018). In addition the reduction in delta band was found to be associated with auditory perceptual abnormality and reduced verbal working memory (Puvvada et al., 2018).

In 2019 Parker et al. (2019) reported reduced 80 Hz ASSR phase and power in patients with psychosis (Parker et al., 2019). This result goes in line

with the previous MEG study in which reduction of 80 Hz ASSR power was found in SZ patients (Tsuchimoto et al., 2011). Tsuchimoto et al. (2011) also noted that severity of hallucinations is related to greater reduction of 80 Hz ASSR. The importance of high gamma ASSR is further emphasized by Hamm et al. (2011) study where attenuation of ASSR was found to be associated with the severity of negative symptoms (Hamm et al., 2011). Overall these studies point to the importance of evaluation of wider frequency ranges in SZ studies.

ASSRs of different frequencies are generated by different brain sources. ASSRs within 4-20 Hz range originate in spatially distributed neural networks including thalamo-cortical pathways, deep cortical and sensory cortical structures (Herdman et al., 2002; Lehongre et al., 2011; Millman et al., 2010), while ASSRs at 30-50 Hz or low gamma are generated in local superficial networks (Plourde, 2006). High gamma responses are thought to predominantly originate in brainstem sources (Tichko and Skoe, 2017). As schizophrenia is associated with the ASSR abnormalities visible in a wide range of frequencies, chirp stimuli designed to elicit responses at a wide frequency range could be of particular use in SZ research.

Artieda et al. (2004) presented chirp stimuli designed to elicit response at frequency range from 1 to 120 Hz. Chirp-evoked response in TF plot was described as a diagonal band of energy corresponding to the frequency of modulation with two main peaks at low (30-60 Hz) and high (80-120 Hz) gamma (Artieda et al., 2004). Potential of this chirp in SZ research was confirmed by Alegre et al. (2017) who reported that drug naïve patients have reduced power and phase synchrony in 30-50 Hz range and reduced power in 90-100 Hz range. It was also noted that medications normalized chirp-evoked response in a low gamma range while high gamma response remained impaired, thus hinting to both complex effects of SZ and the importance of wide frequency range testing (Alegre et al., 2017).

2.5 ASSRs in Disorder of Consciousness

Disorder of consciousness is a medical condition with inhibited consciousness level (Bernat, 2006). Following the injury until patient regains full awareness he usually progresses through the comma, vegetative (VS) and minimally conscious (MCS) states. However, in cases where DOC state exceeds one month the prolonged disorder of consciousness state is diagnosed and full patient recovery might never be reached (Giacino et al., 2014). Etiology in a DOC group varies and may include subcortical,

extensive cortical injuries as well as focal brainstem lesions (Owen, 2013). Patients that retain wakefulness but do not reveal any external signs of conscious awareness are considered to be in a VS alternatively named as unresponsive wakefulness syndrome (UWS) while those who inconsistently but clearly show behavioural evidence of consciousness (show more than reflex motor behaviour but at the same time do not show functional communication or object use) are consider to be in the MCS (Giacino et al., 2002; Laureys et al., 2010). However, since diagnosis is mainly based on assessing awareness behaviourally, it is summarised by Owen et al (2013) that misdiagnosis in a VS might be up to 43%.

As is highlighted by Owen and Coleman (2007) neurophysiological biomarkers are of great need in a field of DOC diagnostics (Owen and Coleman, 2007). Kotchoubey et al. (2005) showed that auditory system remains relatively robust to the nervous system lesions in DOC patients thus suggesting that methods addressing its responsivity would provide a valuable option for DOC studies (Kotchoubey et al., 2005).

Promise of ASSRs in the field of DOC research is highlighted by the knowledge that ASSRs are sensitive to the altered brain functioning states such as sleep (Górska and Binder, 2019; Picton et al., 2003b), brain injury especially in predicting outcome of coma or diagnosing brain death (Firsching, 1989; Harada et al., 1994; Serafmi et al., 1994), anaesthesia (Plourde, 2006; Plourde et al., 2008) and mental disorders such as SZ (Thuné et al., 2016). Serafmi et al. (1994) reported that patients who had 40 Hz ASSR present after the head trauma survived, while absence or sudden disappearance of ASSR predicted patient death (Serafmi et al., 1994). Recently, Chen et al. (2020) reported that several different 40 Hz stimulations elicited ASSR in comatose patients who later had a favourable outcome (severe disability, moderate disability or good recovery). There was only a few ASSR responses in some patients who had an unfavourable outcome (Chen et al., 2020). Binder et al. (2017) showed attenuated EA and PLI in patient group that was associated with CRS-R scores. Furthermore, PLI in patient group positively correlated with CRS-R Auditory and Visual subscales and with the total score of CRS-R, thus confirming the potential of ASSR use in DOC patients diagnostics (Binder et al., 2017). While this study was able to confirm ASSR sensitivity in DOC patients the use of 40 Hz stimulation has limited analysis frequency range and the use of wide frequency stimulation delivered at a same or similar length procedure could be of benefit in DOC patients as is shown in SZ patients (Alegre et al., 2017).

METHODS

Dissertation includes results of three separate Studies: 1) Evaluation of attentional effects on chirp-evoked responses (Study I); 2) Study of chirp-evoked responses in schizophrenia (Study II); 3) Study of chirp-evoked responses in disorder of consciousness (Study III).

3.1 Stimulation

Stimuli were designed in Matlab 2014 environment (The MathWorks, Inc.). Sinusoid carrier of 440 Hz (A4 / note La) was linearly amplitude-modulated in the frequency window from 1 to 120 Hz. Two modulation directions of frequency changes were used: chirp-up (increasing from 1 Hz to 120 Hz) and chirp-down (decreasing from 120 Hz to 1 Hz). Duration of the stimuli was 500 ms and inter-stimulus period was set randomly at 700-1000 ms interval. In order to avoid clicking sounds at the beginning and the end of the stimuli, 15ms onset/offset linear ramps were introduced. The schematic presentation of chirp-down stimulus is depicted in Figure 3.1.

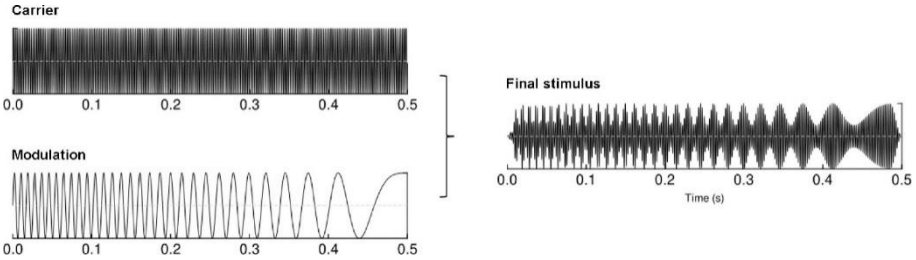

Figure 3.1: A schematic representation of chirp-down stimulus. Carrier - sine wave of 440 Hz; modulation - sinusoid wave with a changing frequency (starting at 120 Hz and ending at 1 Hz). Final stimulus – amplitude-modulated carrier with additional 15ms onset/offset ramps (Binder et al., 2020).

3.2 Subjects

A summary of demographical characteristics of participants from the electrophysiological assessment studies is presented in Table 3.1. Participants were asked not to consume caffeine containing drinks or other psychoactive substances 1 hour prior to the EEG experiment. History of organic illnesses, head trauma and alcohol or substance abuse (except tobacco) were set as exclusion criteria in Studies I and II, where only male

subjects were included to exclude potential influence of hormonal fluctuations (Griškova-Bulanova et al. 2014).

In Study I, non-smoking right-handed healthy males were tested. In Study II, inpatients diagnosed with paranoid schizophrenia (SZ, according to ICD-10) from the Republican Vilnius Psychiatric Hospital and age-matched healthy controls (H) were enrolled. Hearing thresholds of participants were tested with audiometer AS608 (Interacoustics A/S, Denmark) and were within the normal range (<25 dB HL).

In Study III, patients with disorder of consciousness from the hospice „Światło" in Torun were tested. Two groups were created according to the diagnosis: vegetative state (VS; 9 patients (2 females)) and minimally conscious state (MCS; 6 patients (2 females)) groups. Patients were assessed by otoacustic emissions audiological testing according TEOAE protocol (Kemp, 1978) with otoReadTM (Interacoustics, Middlefart, DK). Passing criterion was set at signal to noise ratio (SNR) of 4 dB at minimum 3 out of 6 used frequencies (ranging from 0.5 to 4 kHz).

To evaluate subjective perception of the chirp stimuli, 30 volunteers (15 females and 15 males, mean age = 22.3 and SD = 2.4) were tested. The hearing thresholds of all participants were within the normal range (<25 dB HL). The same group was studied in earlier research (Voicikas et al., 2016).

3.2.1 Ethical statement

All studies were conducted in accordance with the Declaration of Helsinki and approved by Lithuanian Bioethics Committee as a part of a larger project (Study I), the Bioethics Committee of Vilnius Republican Psychiatric Hospital (Study II) and the local review board at the Institute of Psychology, Jagiellonian University (Study III). Subjects or legal surrogates of the patients gave their informed consent.

3.3 Clinical scales

The summarized results of clinical assessment with Positive and Negative Syndrome Scale in schizophrenia patients and Coma Recovery Scale - revised in disorder of consciousness patients are presented at Table 3.1.

3.3.1 Positive and Negative Syndrome Scale

Positive and Negative Syndrome Scale was filled-in by experienced psychiatrists to assess clinical symptoms in SZ patients group. The PANSS

scale scores are derived from the interview, health care staff and family member reports. PANSS is a 30-item scale in which each item might be rated from 1- absent to 7- extreme level of psychopathology (Kay et al., 1987). PANSS includes positive, negative, and general psychopathology subscales. 7 items positive subscale is used to evaluate excess or distortion of normal functions (e.g. delusions, grandiosity, hallucinations). Minimum score of positive subscale is 7, maximum score is 49. 7 items negative subscale (minimum = 7, maximum = 49) represents loss of normal functions (e.g. blunted affect, emotional withdrawal, difficulty in abstract thinking). 16 items general psychopathology subscale (minimum score = 16, maximum score = 112) refers to depression, anxiety, guilt etc. Total PANSS combines all subscales (minimum score = 30, maximum score = 210) (Lindenmayer et al., 2007).

3.3.2 Coma Recovery Scale-revised

Coma Recovery Scale-revised adapted to Polish (Binder et al., 2018) was used by experienced psychologists to evaluate the state of the patients with DOC (Giacino and Kalmar, 2006). Summarized CRS-R results are presented in a Table 3.1. CRS-R scale consists of 23 items grouped into 6 subscales (auditory, visual, motor, verbal, communication, and arousal). Lowest scores indicate reflexive responses (score of 0 indicates response absence) while highest scores show involvement of cognitive processing (Giacino et al., 2004).

Table 3.1: Demographic characteristics of participants and scores of clinical scales (where applicable) from the electrophysiological assessment Studies. Means and standard deviations are provided.

	Study I Attention modulation	Study II Schizophrenia		Study III Disorder of consciousness	
	H	H	SZ	VS	MCS
Subjects (Number of Females)	20 (0)	18 (0)	18 (0)	9 (2)	6 (2)
Age (years)	21.8 (2.3)	42 (13)	38 (14)	46.0 (16)	44.8 (16)
Duration of illness (years)	-	-	13 (10)	3.2 (2.6)	1.9 (2.0)
Medication (Chlorpromazine, mg)	-	-	584 (217)	-	-
PANSS:					
Total	-	-	95 (17)	-	-
Positive scale	-	-	20 (4.4)	-	-
Negative scale	-	-	28.5 (5.2)	-	-
General psychopathology	-	-	46.6 (10.5)	-	-
Hallucinations subscale	-	-	2.5 (1.3)	-	-
CRS-R:					
Total CRS-R	-	-	-	4.1 (1.5)	15 (3.8)
Auditory subscale	-	-	-	1.1 (0.3)	3.2 (0.8)
Visual subscale	-	-	-	0.2 (0.4)	4.7 (0.8)
Motor subscale	-	-	-	1.2 (0.8)	2.8 (1.3)
Verbal subscale	-	-	-	0.2 (0.4)	1.0 (0.6)
Communication subscale	-	-	-	0 (0)	1.2 (0.8)
Arousal subscale	-	-	-	1.3 (0.5)	2.2 (0.8)

H – healthy subjects, SZ – schizophrenia patients (F20.0 ICD-10), VS – vegetative state patients, MCS – minimally conscious state patients. PANSS - Positive and Negative Syndrome Scale, CRS-R - Coma Recovery Scale-Revised

3.4 Experimental tasks

Experimental procedures and stimulation details of all three studies are summarized in Table 3.2.

Two tasks requiring different levels of attention to auditory stimuli were used in Study I: 1) Counting task (focused attention condition) – subjects were asked to keep their gaze at a fixation cross presented on a computer screen in front of them and silently count presented stimuli. Result of the counting had to be reported at the end of the recording session; 2) Reading task (distraction condition) – subjects were asked to ignore the sounds and silently read a text which was presented on a computer screen in front of them. Brief report of the text content was obtained after the recording. Experimental task and stimulation type order was randomized across the group.

In Study II, in order to control for the level of attention, a passive condition was used where subjects watched a silent documentary movie played on a screen in front of them (Griskova-Bulanova et al., 2018).

In Study III, in order to ensure awake state in DOC patients, all recordings were conducted with subject's eyes open while patients were seated in their beds or in a wheelchair.

Table 3.2 Stimulation and experiment details

	Study I Attention modulation	Study II Schizophrenia	Study III Disorder of consciousness
Condition	Active - counting / reading	Passive - watching movie	Passive - eyes open
Stimuli	Chirp-up / Chirp-down	Chirp-up	Chirp-down
Trials	120	450	300
Stimulation type	binaurally	binaurally	binaurally
Stimulation level	60 dBA	60 dBA	54 dBA
Earphones	Sennheiser HD 280 PRO	Beyer dynamic DT-1350	Sennheiser MX 475

Sound pressure level adjusted with a DVM 401 dB meter (Velleman, USA)

For the subjective evaluation of chirp stimuli, self-assessment manikin method (Bradley and Lang, 1994) was used. 20 chirp-up and chirp-down stimuli were presented to the subjects in randomized order. After each stimulus presentation participants evaluated sound via a keyboard in scores from 1 (not arousing/very unpleasant) to 9 (very arousing/very pleasant).

3.5 EEG registration

In Study I, data were collected using ANT device (ANT Neuro, The Netherlands) with 64 channels WaveGuard EEG cap (Figure 3.2). Average M1 and M2 (mastoid) electrodes were used as a recording reference. Sampling rate was set at 1024 Hz and impedance was kept below 20 kΩ. Electro-occulograms (VEOG- vertical and HEOG- horizontal) were recorded from below and above left eye and from left and right outer canthi. A Cedrus StimTracker (Cedrus Corporation, San Pedro, CA) was used to track time of stimulus presentation.

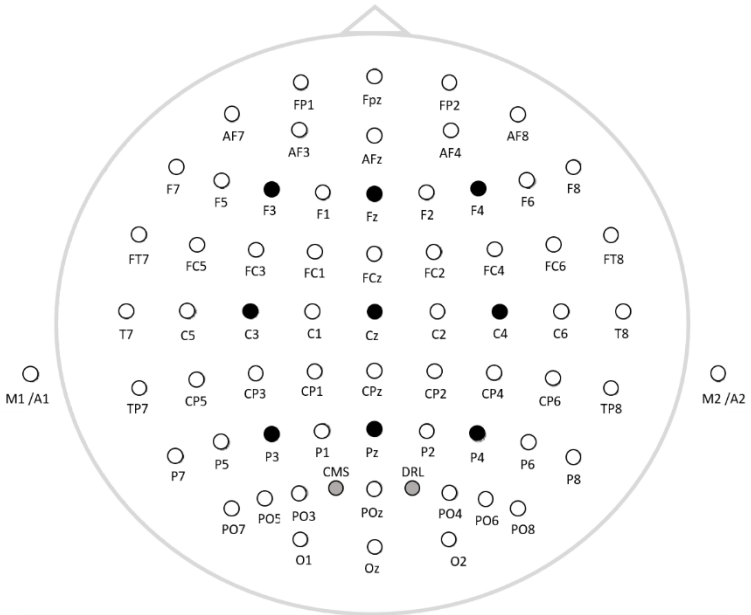

Figure 3.2: Electrode placement during three experiments: 1) 64 electrodes used in Study I (white and black) with M1 and M2 as a reference. 2) 9 electrodes used in Study II (black) with A1 and A2 as a reference. 3) 64 electrodes used in Study III (white and black) with M1, M2, and CMS, DRL as a reference.

In Study II, Galileo Mizar Sirius computerized electroencephalogram system (EBNeuro, Florence, Italy) was used. Nine Ag/AgCl electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) were placed according to 10-20 EEG recording system with the ground electrode attached at Fpz. Earlobe (A1 and A2) electrodes served as a recording reference. Impedance was kept below 20 kΩ and sampling rate was set at 512 Hz.

Collection of data in Study III was performed with Active Two system (BioSemi, Amsterdam, NL) 64 channels. Electrode placement at the standard locations was ensured by using 10-20 systems head cap. Passive Driven Right Leg (DRL) electrode was placed between PO4 and POz while active Common Mode Sense (CMS) electrode positioned in between POz and PO3. Two additional reference electrodes were placed on mastoids and recorded in parallel. Electro-occulograms (VEOG- vertical and HEOG-horizontal) were recorded from below and above right eye and from left and right outer canthi. Sampling rate of the recording was set to 1024 Hz. Stimulus presentation was managed by Presentation software (Neurobehavioral Systems, Berkeley, USA).

3.6 Data analysis

The off-line pre-processing of EEG recordings and data analysis was carried out using custom written scripts for MATLAB (MATLAB R2010a The Math-Works Inc., Natick, Massachusetts, USA). Functions from EEGLAB (Delorme and Makeig, 2004), ERPWAVELAB (Mørup et al., 2007) and FieldTrip (Oostenveld et al., 2011) were used in scripts. SPSSv20 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. Summary of experiments, data pre-processing and analysis steps are presented in Figure 3.3.

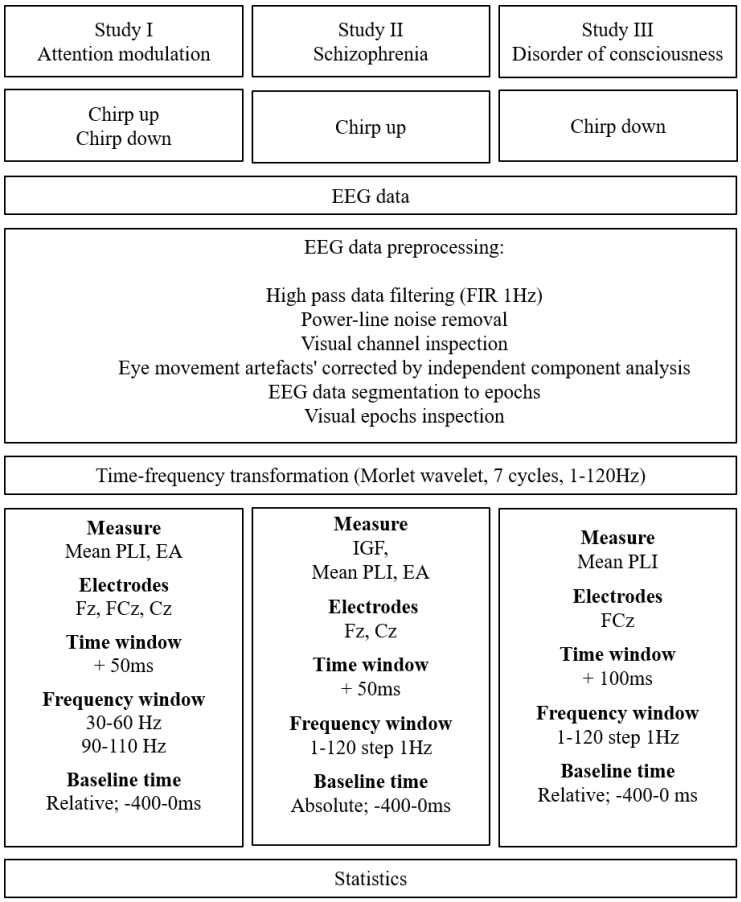

Figure 3.3: Summary of the pre-processing and analysis in Study I, II and III. PLI – phase locking index; EA – evoked amplitude; IGF – Individual gamma frequency (frequency with the strongest response).

3.6.1 EEG pre-processing

EEG data was high-pass filtered at 1 Hz using FIR filter implemented in EEGLAB. Multi-tapering and Thomas F-statistics as implemented in a CleanLine plugin for EEGLAB (*NITRC: CleanLine: Tool*) was used for power-line noise removal. Substantially noisy throughout the recording channels were removed and independent component analysis (ICA) was performed on the remaining data (EEGLAB ICA implementation was used with the default settings). ICA components corresponding to the eye movements were excluded. EEG data was segmented based on the stimulus occurrence time: total length of the epoch was 1500 ms, epoch starting 500 ms before and ending 1000 ms after the stimulus onset. Baseline correction

was performed during the segmentation. Visual inspection of epochs was carried out in order to remove the remaining artefacts if any. Channels removed at the beginning of pre-processing were reconstructed by the spherical spline method (Perrin et al., 1989). Data was re-referenced to average reference.

For pre-processing of data in Study III, data were resampled to 512 Hz and outer edge electrodes were excluded from processing before ICA, leaving 41 EEG channels ('AF3', 'AFz', 'AF4', 'F6', 'F4', 'F2', 'Fz', 'F1', 'F3', 'F5', 'FC5', 'FC3', 'FC1', 'FCz', 'FC2', 'FC4', 'FC6', 'C6', 'C4', 'C2', 'Cz', 'C1', 'C3', 'C5', 'CP5', 'CP3', 'CP1', 'CPz', 'CP2', 'CP4', 'CP6', 'P6', 'P4', 'P2', 'Pz', 'P1', 'P3', 'P5', 'PO3', 'POz', 'PO4') in total.

3.6.2 Signal analysis

Time-frequency transformation of the cleaned EEG data was performed using complex Morlet wavelets with 7 cycles from Matlab© Wavelet Toolbox. Frequencies from 1 to 120 Hz in a step of 1 Hz were covered.

3.6.2.1. Measures

Brain activity in response to chirp stimulation was evaluated using two measures representing oscillation phase and power. Phase locking index which is a measure of phase consistency between epochs, also known as an inter-trial phase consistency (ITPC), was used. Response power was evaluated as an evoked amplitude (EA, represents amplitude which is time locked to stimulus), calculated from the time-frequency transformed evoked potential (averaged across all epochs) (Mørup et al., 2007).

3.6.2.2. Baseline correction

PLI and EA measures were calculated for each electrode and then baseline corrected to the pre-stimulus period lasting from -400 ms to 0 ms. Two types of baseline correction were used: 1) the signal was divided by the mean baseline value (relative baseline correction) in Studies I and III; 2) mean baseline activity was subtracted from the signal (absolute baseline correction) in Study II.

3.6.2.3 Analysis windows

The electrode selection and time-frequency window for the analysis was defined based on the strongest activity observed on the grand averaged (averaged across all subjects) TF data.

In Study I, activity was averaged within low (30-60 Hz) and high (90-110 Hz) gamma ranges resulting in two measures per recording per subject per stimulation type. In Studies II and III, PLI and EA curves were extracted by averaging the response in the time window of +50 ms (Studies I and II) or +100 ms (Study III) separately for each frequency point starting from 2 to 120 Hz in 1 Hz step. Example of procedure is presented in Figure 3.4. Additionally, the individual maximal frequency of the response between 30 and 60 Hz for PLIs was extracted in Study II.

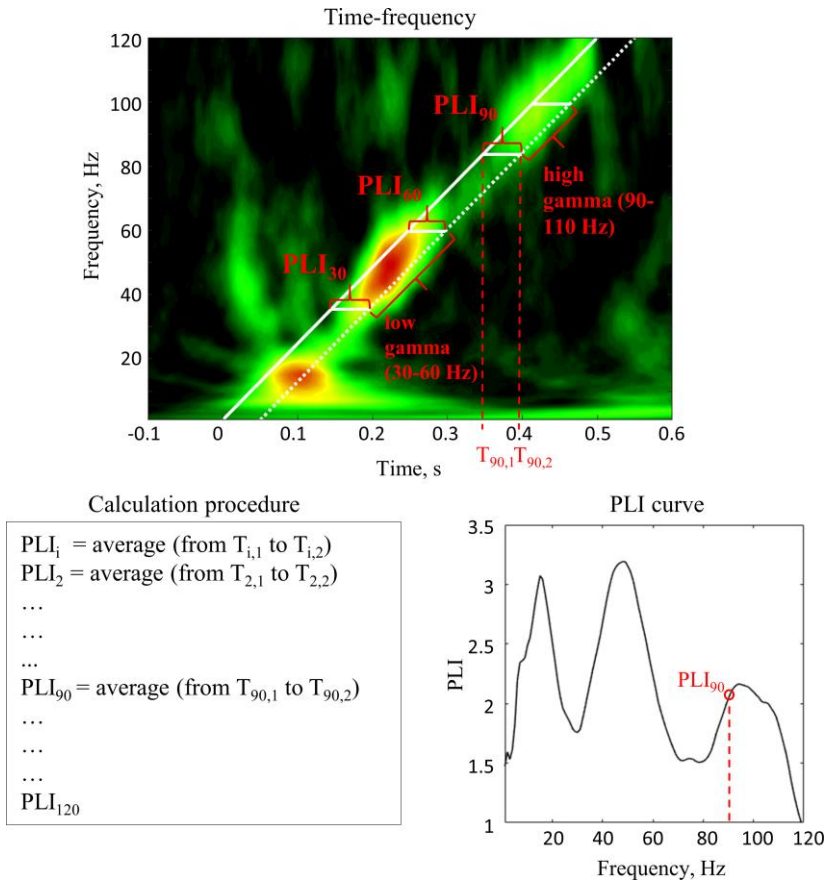

Figure 3.4: Top - Time-frequency plot of phase locking index (PLI) from reading condition in Study I. Diagonal white bold line represents time course of stimulation and dashed white line shows +50 ms averaging window for all

frequencies. Red brackets and white horizontal lines represent low and high gamma frequency range. Red dashed lines and corresponding letters represent beginning and end time points used in averaging response at 90 Hz (PLI_{90}), 60Hz (PLI_{60}) and 30Hz (PLI_{30}). **Bottom left** - details on the averaging procedure for each frequency starting from 2 Hz and ending at 120 Hz in a step of 1 Hz. **Bottom right** - PLI curve derived from averaging in the time window (response at 90 Hz is marked in red).

3.6.3 Statistical analysis

Two separate two-way repeated measures ANOVAs were performed for the low and high gamma band measures in Study I. STIMULATION factor with two levels (chirp direction: down or up) and two-level TASK factor (reading or counting) were tested. Pairwise comparisons followed ANOVAs, with Bonferroni adjustment for the multiple comparisons. Correlation analysis was performed by calculating Pearson's correlation coefficients for the measurements derived from chirp-up and chirp-down stimulation and for the different gamma bands. P values below 0.05 were regarded as significant.

In Studies II and III, the extracted PLI/EA curves were subjected to bootstrap T-test (1000 iterations, $p < 0.05$) to perform a point-to-point comparison between study groups (Oostenveld et al., 2011). Bootstrapping approach is more suitable for the analysis with large amounts of repetitive testing since it is less conservative than Bonferroni correction but still accounts for multiple comparison error effect.

Additionally, in study II, Pearson's correlation was assessed between PLI and EA curves and subjects' age and positive, negative, total PANSS and hallucination subscale scores. 95% bootstrapped confidence intervals were used to assess significance. Independent sample T-test was used to compare IGFs between SZ and H groups.

In Study III, Pearson's correlation was calculated for all CRS-R subscales and total scores and PLI values, separately. Samples that survived the initial test (the uncorrected p-value below 0.005) were clustered based on the spectral proximity. Cluster-level statistics were obtained by summing the frequency sample statistics within each cluster. The maximum of these was used to test the significance of our results against a randomization distribution. Randomization distribution was obtained by randomly permuting original data and calculating maximum cluster-level statistic (this step was repeated 20000 times). The probability of obtaining a statistic from randomization distribution larger than the actual cluster statistic was tested at p level set less than 0.05.

Scores of subjective evaluation of arousal and valence were subjected to two separate ANOVAs with two levels of STIMULATION factor (chirp direction: down or up).

RESULTS

4.1 Subjective evaluation

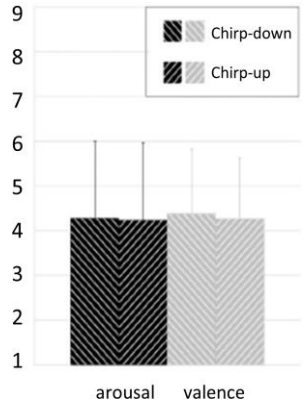

Figure 4.1: The means and standard deviations of arousal and valence scores in chirp-down and chirp-up stimuli subjective evaluation. (N=30, 15 males and 15 females).

Self-assessment manikin (Bradley and Lang, 1994) was used to evaluate subjective perception of the stimuli. No difference in subjective evaluation between two chirp types was observed: $F(1, 29) = 0.191$, $p = 0.67$, partial $\eta^2 = 0.007$ for arousal and $F(1,29) = 1.460$, $p = 0.24$, partial $\eta^2 = 0.048$ for valence. Both chirp stimuli were moderately arousing and neutral. Mean assessment scores and standard deviations are presented in Figure 4.1.

4.2. Study I: attentional modulation of chirp-evoked responses

To evaluate attention modulation of chirp-evoked responses two tasks requiring different levels of attention to auditory stimuli were used (reading task or attention distraction condition; counting task or attention concentration condition). PLI and EA values were averaged in the low and high gamma frequency ranges and compared in separate two-way repeated measures ANOVAs with two-level TASK factor (reading or counting) and two-level STIMULATION factor (chirp direction: down or up).

Mean PLI and EA values with standard errors are presented in Table 4.1 separately for each attention condition (reading and counting) and chirp type (up and down) for low (30-60 Hz) and high (90-110 Hz) gamma frequency ranges. Grand averaged TF plots for both conditions and chirp types are presented in Figure 4.2 for PLI and in Figure 4.3 for EA.

Table 4.1: Mean Phase locking index (PLI) and evoked amplitude (EA) values with standard errors separately for each attention condition (reading and counting) and chirp type (up and down) in low and high gamma frequency ranges.

		PLI		EA	
		Reading	Counting	Reading	Counting
Low (30-60 Hz)	Up	2.62±0.19	2.73±0.23	8.77±1.39	10.65±1.84
	Down	2.84±0.26	2.74±0.24	10.51±1.9	10.54±2.33
High (90-110 Hz)	Up	2.04±0.22	2.06±0.25	5.23±1.07	6.04±1.57
	Down	2.19±0.26	2.04±0.25	6.47±1.54	6.14±1.43

No effect of experimental task on responses at low gamma band as measured by phase locking ($F(1, 19) = 0.001$, $p = 0.98$ partial $\eta^2 < 0.001$) or evoked amplitude ($F(1, 19) = 0.89$, $p = 0.36$, partial $\eta^2 = 0.05$) was observed. Responses did not differ between stimulation types: $F(1, 19) = 0.60$, $p = 0.45$, partial $\eta^2 = 0.03$ for PLI and $F(1, 19) = 0.37$, $p = 0.55$, partial $\eta^2 = 0.02$ for EA. No evidence of interaction between stimulus type and experimental condition was found for PLI ($F(1, 19) = 0.83$, $p = 0.37$, partial $\eta^2 = 0.04$) or EA ($F(1,19) = 0.86$, $p = 0.37$, partial $\eta^2 = 0.04$).

No effect of the experimental task was evident on response at high gamma band as measured by PLI ($F(1, 19) = 0.20$, $p = 0.66$ partial $\eta^2 = 0.01$) or EA ($F(1, 19) = 0.11$, $p = 0.74$, partial $\eta^2 = 0.01$). Responses did not differ between chirp types: $F(1, 19) = 0.25$, $p = 0.63$, partial $\eta^2 = 0.01$ for PLI and $F(1, 19) = 0.73$, $p = 0.40$, partial $\eta^2 = 0.04$ for EA. No evidence of interaction between stimulus type and experimental condition interaction was found for PLI ($F(1, 19) = 0.77$, $p = 0.39$, partial $\eta^2 = 0.04$) and for EA ($F(1, 19) = 1.00$, $p = 0.33$, partial $\eta^2 = 0.05$).

Summary:

Brief (500 ms) low-carrier tones (440 Hz) amplitude modulated by chirp at 1-120 Hz elicited clear response with two (low and high gamma) peaks that did not depend on the attention level and stimulation type.

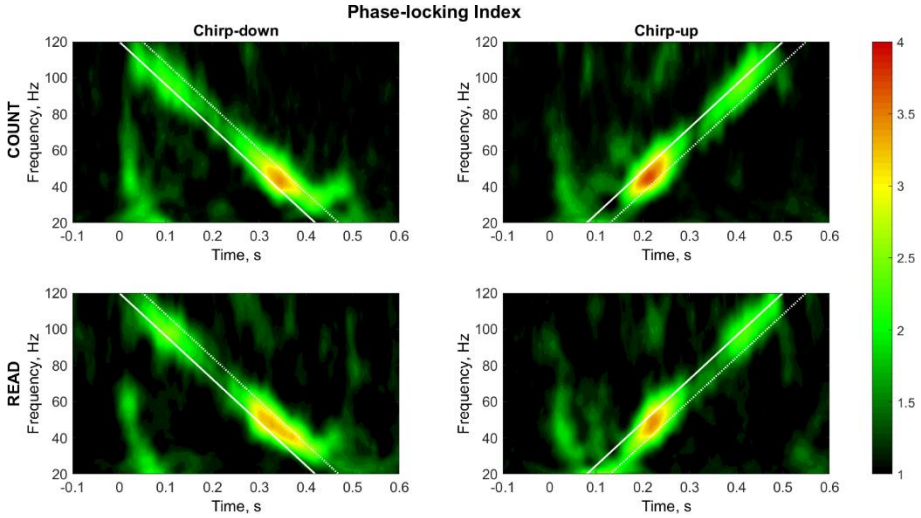

Figure 4.2: Time frequency plots of PLI averaged across Fz, FCz, Cz electrodes and grand averaged across all subjects (N = 20) separately for each chirp type (up and down) and each attention condition (reading and counting). White line represents time of the stimulation, dashed white line represents +50 ms analysis window.

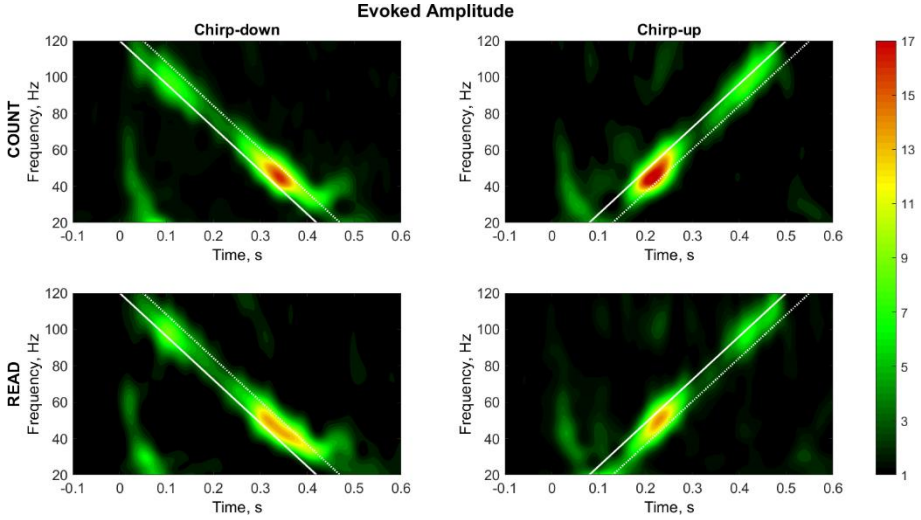

Figure 4.3: Time frequency plots of EA averaged across Fz, FCz, Cz electrodes and Grand averaged across all subjects (N = 20) separately for each chirp type (up and down) and each attention condition (reading and counting). White line represents time of the stimulation, dashed white line represents +50 ms analysis window.

4.2.1 Correlation between responses to two types chirp stimuli

To assess the relationship between responses to different direction of modulation, correlation between PLIs and EAs were calculated. Pearson's correlation coefficients and p values are presented in Table 4.2. Corresponding PLI and EA data points and regression lines are depicted in Figure 4.4.

Table 4.2: Pearson's r with p values for Phase locking index (PLI) and evoked amplitude (EA) separately for each attention condition (reading and counting) in low and high gamma frequency ranges.

		PLI	EA
Low (30-60 Hz)	Counting	0.66 (p = 0.002)	0.58 (p = 0.008)
	Reading	0.74 (p < 0.001)	0.72 (p < 0.001)
High (90-110 Hz)	Counting	0.85 (p < 0.001)	0.84 (p < 0.001)
	Reading	0.76 (p < 0.001)	0.73 (p < 0.001)

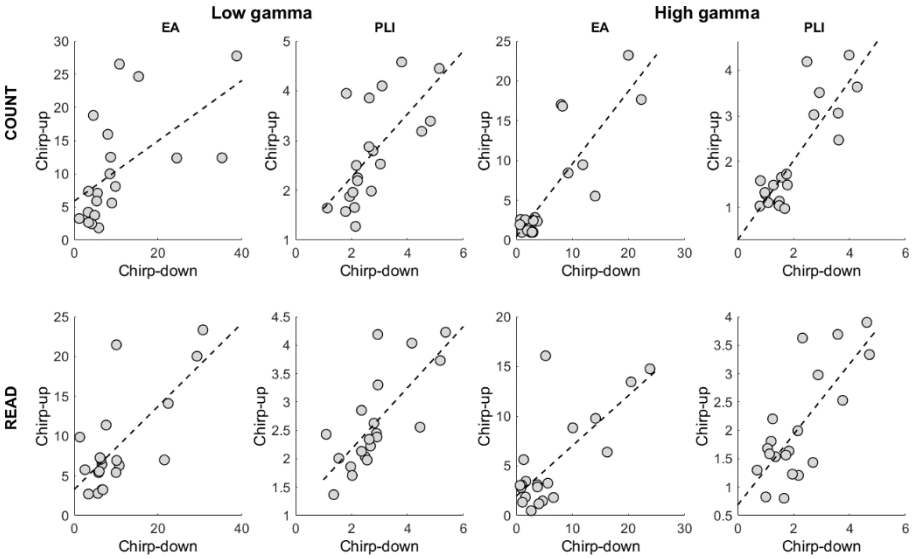

Figure 4.4: Scatterplots of PLI and EA measures and corresponding regression lines (dashed) of both stimulation types in each experimental condition separately for low and high gamma (N = 20).

Summary:

PLI and EA measures were highly correlated for both stimulation methods. This was observed within each of the experimental condition in both low and high gamma bands.

4.3 Study II: chirp-evoked responses in schizophrenia

Chirp-evoked responses were compared between schizophrenia patients (SZ) and healthy controls (H) in order to evaluate a potential of brief chirp stimulation to highlight the impaired patters of brain ability. PLIs and EAs were averaged in time for each frequency separately and the resulting curves were subjected to bootstrap T-test to perform a point-to-point group comparison.

Lower PLI and EA values in schizophrenia patients compared to healthy controls in response to chirps were found in both low and high frequencies: for PLIs, difference was significant at the frequencies ranging from 4 to 18 Hz ($0.001 < p < 0.045$) and from 96 to 119 Hz ($0.009 < p < 0.046$); for EAs, differences were significant from 4 to 13 Hz ($0.003 < p < 0.041$) and from 103 to 117 Hz ($0.001 < p < 0.032$). Grand averaged time-frequency plots of PLI and EA measures for healthy controls and schizophrenia patients are presented in Figure 4.5 A. PLI and EA curves and bootstrapping analysis results in SZ and H groups are depicted in Figure 4.5 B.

Maximum PLI response at the slow gamma range (30-60 Hz) was clearly distinguished for both groups. On average, IGF for the patients was 44 Hz (SD; 7) while for the healthy controls 49 Hz (SD; 8); the difference was significant ($t = 2.096$, $df = 34$, $p = 0.04$).

Summary:

Chirp-modulated stimuli detected impaired brain ability to synchronize at theta-beta and high gamma ranges in schizophrenia patients. The peak frequency at the low gamma range was lower in patients than in controls.

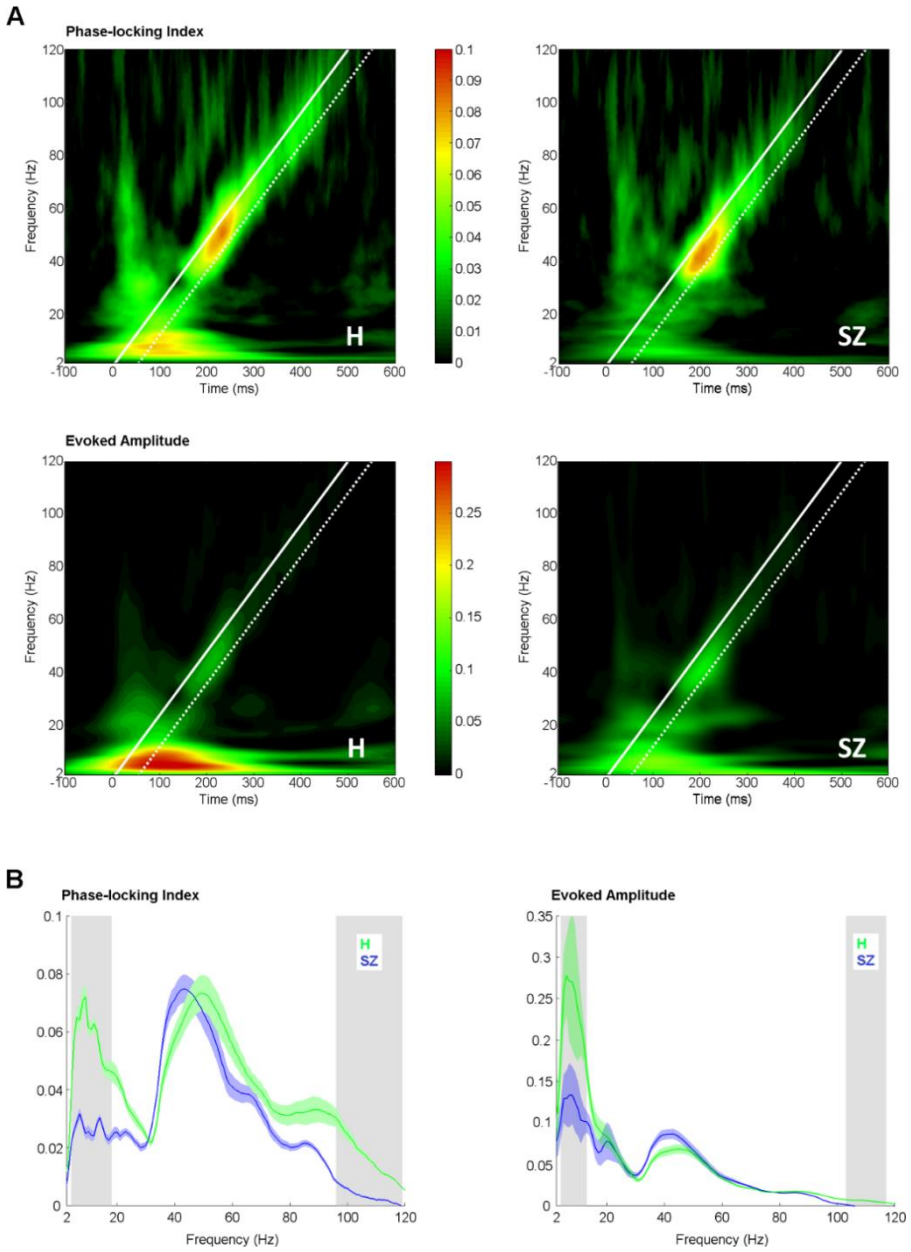

Figure 4.5: A. Phase-locking index and evoked amplitude time-frequency plots averaged across Fz and Cz electrodes and grand averaged across subjects separately for healthy controls (H; N = 18) and patients (SZ; N = 18). White line represents time of the stimulation and dashed line represents +50 ms analysis window. **B.** Grand-averaged PLI and EA curves for healthy controls (H; green) and schizophrenia patients (SZ; blue). The coloured areas around the curves represent standard deviations of PLI and EA. Significantly different frequency windows, as assessed by the bootstrap, are marked by grey shaded areas.

4.3.1 Correlation between response measures and clinical variables

For the patient group associations between PLI/EA and positive, negative, total PANSS and hallucination subscale scores were assessed. Neither positive nor negative PANSS scores were associated with response strength measured by PLI or EA. Total PANSS score correlated with the response strength at the high frequencies: negative association between PLI measure and total PANSS was observed for the frequency range of 91-100 Hz ($0.028 < p < 0.049$, $-0.386 < r < -0.347$) and for EA in the frequency range of 95-101 Hz ($0.030 < p < 0.048$, $-0.378 < r < -0.352$). Hallucination subscale scores positively correlated with PLIs within 32 to 43 Hz window ($0.003 < p < 0.044$, $0.403 < r < 0.636$). The plots showing the course of Pearson r values for association between PLIs and hallucination scores and PLIs and total PANSS scores are depicted in Figure 4.6.

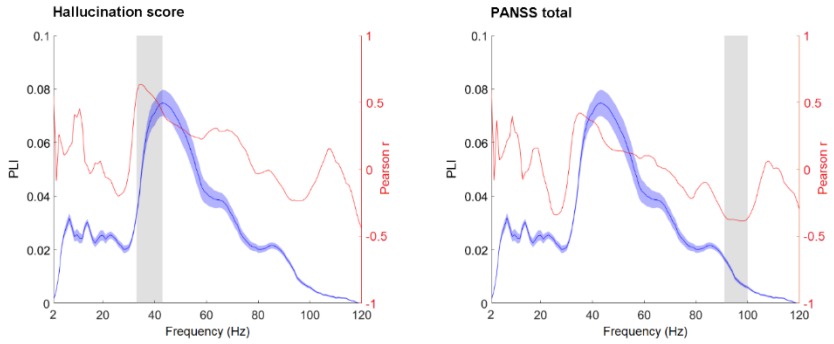

Figure 4.6: PLI curve of SZ group (blue; N = 18) and Pearson's r values (red) for correlation between PLIs and PANSS Hallucination subscale and PANSS Total scores. The blue colored area around the PLI curve represents standard deviation of PLI. The frequency windows where significant correlation was observed, as assessed by the bootstrap, are marked by grey shaded areas.

Summary:

PLIs in the low gamma frequency range of schizophrenia patients were positively associated with the hallucination symptom prevalence. PLIs and EAs in the high gamma range of schizophrenia patients were *negatively associated with the total scores on PANSS.*

4.4 Study III: responses to chirp in disorder of consciousness

PLI values obtained in patients with disorders of consciousness were compared between two subgroups. The topographical representations of responses in minimally conscious patients (MCS) and vegetative state (VS) patients are plotted in Figure 4.7 A. Grand averaged PLI curves for MCS and VS groups are presented in Figure 4.7 C together with grand averaged time-frequency plots in Figure 4.7 B. MCS group displayed higher phase consistency over epochs: non-parametric cluster-based permutation procedure revealed significant difference in the frequency range from 36 to 46 Hz ($p = 0.01$).

Summary:

PLI values in the low gamma frequency range was lower in VS than in MCS patients.

4.4.1 Correlation between response to chirp and CRS-R

In order to relate chirp-evoked responses to the clinical manifestations of DOC patients, Pearson's correlation coefficients were calculated for all CRS-R subscales and total scores and PLI values.

Several positive associations between PLIs in a low gamma frequency range around 40 Hz (from 37 to 44 Hz) and CRS-R scores were found. As shown by non-parametric cluster-based permutation procedure, significant correlation between PLIs in the window from 38 to 43 Hz ($p = 0.014$, $0.70 < r < 0.79$) and Auditory, in the window from 37 to 44 Hz ($p = 0.004$, $0.69 < r < 0.79$) for Visual and in the window from 38 to 43 Hz ($p = 0.014$, $0.69 < r < 0.77$) for total CRS-R scores were obtained. Plots showing course of Pearson's r values for associations between PLI and Auditory, Visual, and Total CRS-R scores are depicted in Figure 4.8 A. Based on the scatterplots of PLI values (averaged in the significant frequency window) against CRS-R scores (Figure 4.8 B), two DOC patient subgroups could be distinguished corresponding to the diagnoses of the patients - MCS and VS respectively.

Summary:

PLIs of DOC patients in the low gamma frequency range were positively associated with the Coma Recovery Scale – revised scores.

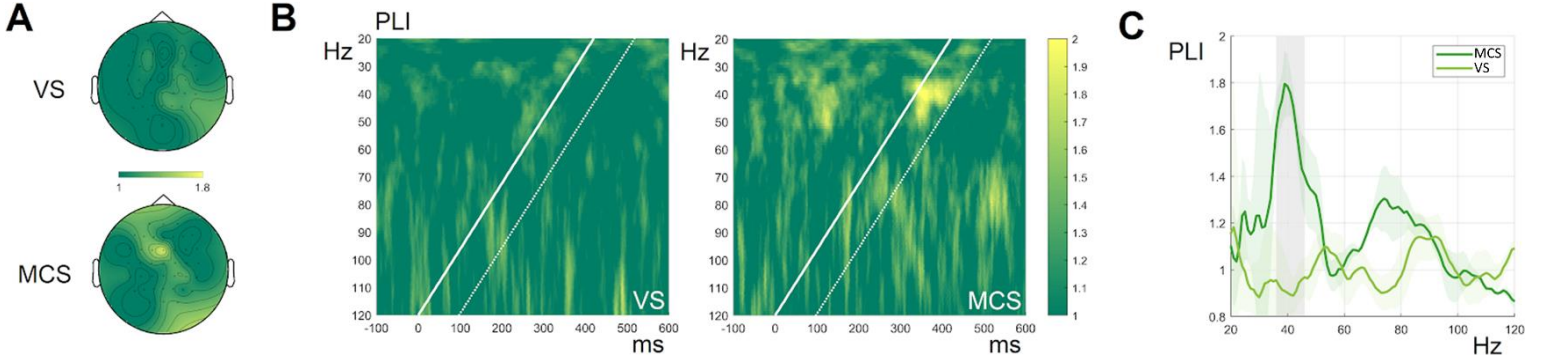

Figure 4.7: A. Grand averaged PLI topographies in the 36-46 Hz frequency window separately for VS (N = 9) and MCS (N = 6) subgroups. **B.** Time-frequency plot of PLI for VS and MCS groups. The white solid line represents time of the stimulation, and dashed line represents +100 ms analysis window. **C.** Grand-averaged PLI curves separately for MCS (dark green) and VS (light green) groups. The green coloured areas around the average PLI curves in each group indicate standard deviations. Grey shaded area marks significantly different frequency window.

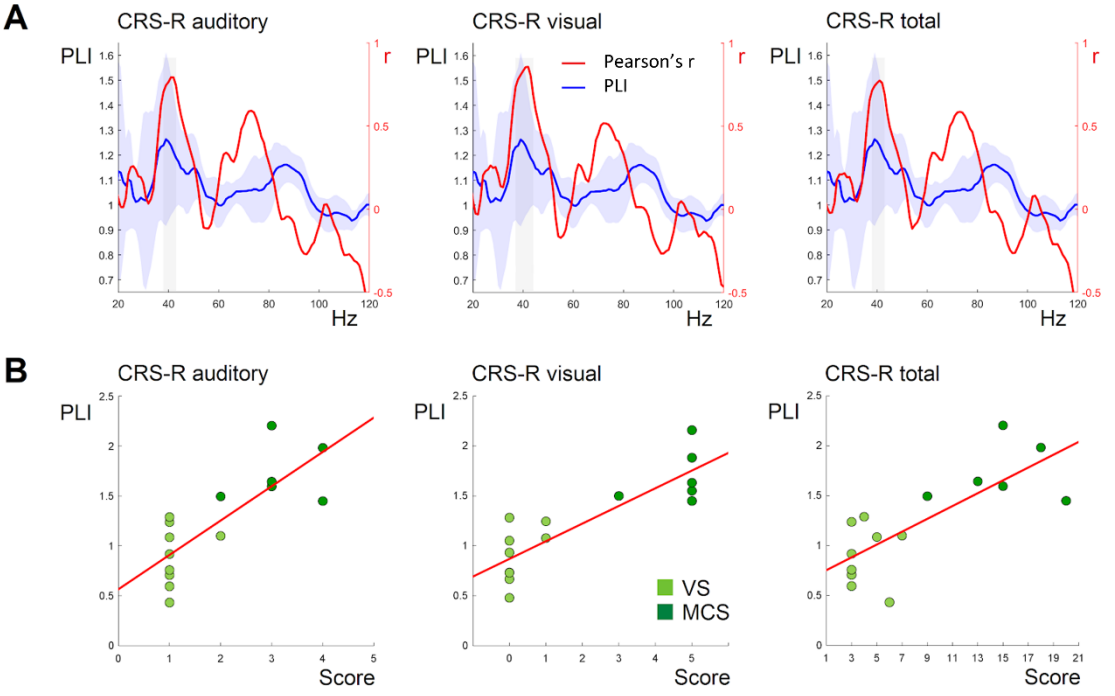

Figure 4.8: A. Phase locking index (PLI) curves (blue) (N = 15) and Pearson's r between PLI and the Auditory, Visual, and total CRS - R scores (red). The blue coloured area around the PLI curve represents standard deviation of PLI. The frequency windows where significant correlation was observed, as assessed by the cluster-based permutation test, are marked by grey shaded areas. **B.** Scatterplots of PLI values averaged in the significant windows (as highlighted above) against individual CRS-R scores and corresponding regression lines (red).

DISCUSSION

It has been shown that brain is able to generate responses at wide range of frequencies (Hamm et al., 2011; Poulsen et al., 2007; Purcell et al., 2004) However, testing multiple frequencies is time demanding. Chirp-modulated sounds were proposed, allowing assessment of multiple frequencies in shorter stimulation run (Artieda et al., 2004; Purcell et al., 2004). However, earlier works used 1.61 - 30.72 s duration chirps, still being to long for use in clinical assessments. Even more, previous work utilize modulation of high frequency carrier that are perceived as unpleasant (Patchett, 1979; Vitz, 1972). Up till now it is not clear if responses to brief low carrier frequency chirp-modulated sounds can capture the same processes under different experimental conditions and in clinical populations. In this study, chirp-modulated 440 Hz stimuli of 500 ms duration were used in three studies: Study I (chirp-evoked response evaluation and investigation of attention effect), Study II (comparison of chirp-evoked responses between healthy controls and schizophrenia patients) and Study III (evaluation of chirp-evoked responses in disorder of consciousness patients).

Two stimulation directions were tested in Study I – ascending (from 1 to 120 Hz) and descending (from 120 Hz to 1 Hz) modulation frequencies. These stimuli elicited clear EEG responses, as can be seen in Figures 4.2 and 4.3. Furthermore, the peak responses were observed in the low (30-60 Hz) and high (90-110 Hz) gamma ranges which is in line with previous reports using chirp stimulation where low and high gamma peaks in responses were observed with different carriers and of different duration (Alegre et al., 2017; Artieda et al., 2004; Poulsen et al., 2007; Purcell et al., 2004). As can be seen from the above-mentioned papers, strongest response to chirp stimulation in low gamma range (30-60 Hz) is centred above the 40 Hz; thus, the result of current work is compatible. This result also goes in line with the notion that resonant gamma frequency varies (is not precisely at 40 Hz) in humans as has been observed with responses to single frequency stimulation (Baltus et al., 2020; Baltus and Herrmann, 2015; Zaehle et al., 2010). Importantly, chirp-evoked response was strongest at fronto-central electrodes in current work, which replicates previous findings of fronto-central activation (Alegre et al., 2017, 2008; Artieda et al., 2004; Poulsen et al., 2007). In addition, no difference in measures between two chirp types was observed and measures were highly correlated. This result confirms and further elaborates the previous observation derived from two subjects

(Artieda et al., 2004), suggesting that responses to stimuli of different modulation direction are stable, reproducible and can be used interchangeably.

Importantly, the subjective evaluation of the sounds showed that both chirp-up and chirp-down modulated tones were perceived as moderately arousing and neutrally pleasant, which is similar to the evaluation of flutter-amplitude modulated tones with a 440 Hz carrier by the same group of subjects in the previous study (FAM: mean arousal score 4.17 (SD 1.70), mean valence score 4.11 (SD 1.20)) (Voicikas et al., 2016).

5.1 Effects of attention level on chirp-evoked responses

The aim of the first study of this thesis was to evaluate attention effect on chirp-evoked responses. Despite numerous researches addressing attention influence on the ASSRs there is no final consensus on the effect of this factor. The proposed brief low-carrier chirp stimuli were tested in the attention-modulation approach. As it is known that sources of low frequency gamma are in the local superficial networks (Plourde, 2006) and high gamma predominantly originates in brainstem sources (Tichko and Skoe, 2017) different effects of attention modulation on these distinct frequency ranges could be predicted. The expectation of attenuated responses in the low gamma range with distraction was based on previous reports where similar attention modulation was found to reduce single frequency 40 Hz ASSR (Griskova-Bulanova et al., 2011; Linden et al., 1987; Voicikas et al., 2016). For the high gamma response, however, no expectations were formed as attention was reported to both enhance and have no effect on high-frequency steady-state responses (Lehmann and Schönwiesner, 2014; Varghese et al., 2015).

Contrary to the expectation, no difference was found in the low gamma between distraction from (reading) and concentration on (counting) the stimulus conditions neither for EA nor for PLI measurements. However, this observation is in accordance with the result by Alegre et al. (2008) who found that reduced attention to stimulation does not result in attenuated phase or energy of 40 Hz response (Alegre et al., 2008). This could be partly due to the auditory stimulation type used (AM), since similar nonsignificant effect of attention has been reported by Mahajan et al. (2014) and by De Jong et al. (2010) using AM stimulation (de Jong et al., 2010; Mahajan et al., 2014), in contrast to significant response enhancement (Skosnik et al., 2007) and attenuated responses with distraction (Griskova-Bulanova et al., 2011;

Roth et al., 2013; Yokota and Naruse, 2015) when click stimuli were used. This explanation is further supported by Voicikas et al. (2016) who show attention effect on ASSR in response to clicks but not to flutter amplitude-modulated stimuli (Voicikas et al., 2016).

High gamma response was centred at around 96 Hz and, even though low and high gamma responses were not compared statistically, high gamma component was visibly weaker as is expected according to the earlier observations (Alegre et al., 2008, 2017; Artieda et al., 2004). Attention effect on high-frequency steady-state responses are not clear since effect of attention was reported in several previous studies (Hairston et al., 2013; Lehmann and Schönwiesner, 2014) but was not found in others (Galbraith and Kane, 1993; Varghese et al., 2015). In the current study, no effect of attention on the high gamma response was detected, which contrasts the results of Alegre et al. (2008), who found that distraction from stimuli attenuates this response (Alegre et al., 2008). However, several differences between stimulation settings and analysis methods could contribute to the difference. Carrier tone as used in the present work was 440 Hz compared to that of 1200 Hz used by Alegre et al. (2008). It has been shown that stronger ASSR is elicited with lower frequency carrier of 250 Hz compared to that of 4000 Hz (Ross et al., 2003) and, while difference between used carrier frequencies (440/1200 Hz) is less dramatic, the potential effect could not be fully discarded. It is also known that with the increasing intensity of the stimulus (60 dBA in current study vs 85 dB in Alegre et al. (2008)) ASSR becomes stronger; however, the stronger modulation depth (100 % in current study vs 90 % in Alegre et al. (2008)) should result in stronger response (Roß et al., 2000). Finally, a longer stimulus duration (1.6 s in Alegre et al. (2008) versus 500 ms in current study) allows longer stimulation with single frequency; together with higher total amount of stimuli presented (500 in Alegre et al. (2008) vs. 120 in current study) this should have resulted in a higher signal to noise ratio in Alegre et al. (2008). To fully address possible differences, it has to be noted that in the current study response strength was averaged over frequency and time, thus giving robust but blunted evaluation of chirp-evoked response strength, while Alegre et al. (2008) compared maximal response values. However, as noted by Alegre et al. (2008), no effect on high gamma response was detected for PLIs (the result which goes directly in line with our observation) and only the small effect was found for power (Alegre et al., 2008), hinting to the relatively week effect of attention on high gamma response and the need for more studies.

5.2 Changes of chirp-evoked responses in schizophrenia

The aim of the second study of this thesis was to evaluate whether brief (500 ms) low-carrier tones (440 Hz) modulated by chirp at 1-120 Hz could highlight dysfunctional processes as observed in patients with schizophrenia at a broad range of frequencies. Chirp-evoked responses in the patient group were attenuated in two frequency ranges - 4-18 Hz (theta-beta) and 95-120 Hz (high gamma) - but were preserved in the low gamma range (around 40 Hz). However, the individual gamma frequency in the patient group was lower compared to that of the healthy controls, and in addition to that chirp-evoked responses at 32-43 Hz range positively correlated with the prevalence of hallucinations. Negative association between measures of chirp-evoked responses and total PANSS scores was found in 91-101 Hz frequency range.

Relatively consistent findings of many studies replicating the first Kwon et al. (1999) report of attenuated 40 Hz ASSR in SZ patients (Kwon et al., 1999; Thuné et al., 2016) led to the expectation of reduced low gamma band response to chirp stimuli. However, as can be seen from Figure 4.4 B low gamma response in the present study was preserved in patients and did not differed from that of the control group. While this result is inconsistent with many studies in schizophrenia where reduced power (Vierling-Claassen et al., 2008; Wilson et al., 2008) and phase (Hirano et al., 2015; Roach et al., 2013; Teale et al., 2008) of 40 Hz ASSR was found, several studies showing unchanged 40 Hz ASSR in SZ should be mentioned (Edgar et al., 2018; Hong et al., 2004) together with those where an increased response in SZ was reported (Hamm et al., 2012; Kim et al., 2019).

Several factors are known that might have contributed to the observed intact response in patients: 1) characteristics of stimuli, 2) recording procedures; 3) age of participants; 4) medication. Firstly, it has been shown that ASSR to click stimuli is strongest and gives a better signal to noise ratio which leads to more power in detecting difference between groups (Voicikas et al., 2016). Secondly, inter-stimulus interval (ISI) length is known to affect the strength of ASSR with longer ISI resulting in a stronger ASSR (Kim et al., 2019). The ISI in our study was set to 700-1000 ms which is directly in between both types used in Kim et al. (2019) who reported attenuated 40 Hz ASSR in SZ group with ISI of 500 ms and enhanced 40 Hz ASSR with 3000 ms. Furthermore, the potential influence of recording condition (subjects watched silent documentary movie) might have had effect in patients, although in the attention modulation part no influence on chirp-evoked

responses was found in H. The exact attentional effect in patients is not known and deserves further detailed evaluation. It is known that ASSR changes with age (Edgar et al., 2018; Griskova-Bulanova et al., 2013a; Poulsen et al., 2007; Purcell et al., 2004) and Thune et al. (2016) reported that difference between SZ and healthy controls tend to be stronger in a younger population (Thuné et al., 2016). Despite that H and SZ groups in the current study were age-matched (the mean age was 38 years) the relatively older age of our subjects might have added to the absence of differences in responses. Finally, it has been suggested that second generation antipsychotics might result in a stronger ASSR (Hong et al., 2004). Alegre et al. (2017) showed that treatment with atypical antipsychotic resulted in a normalised low gamma response to chirp stimuli (Alegre et al., 2017); thus, the medications used in the current study sample might have resulted in a reduced difference between SZ and H groups. It is important to note that although above mentioned factors could influence ASSR, the actual result might depend on interactions of all factors, as it has been shown by Wang et al. (2018) that recording condition (eyes open / eyes closed) effect are dependent on the medication status (Wang et al., 2018).

Spencer et al. (2009) reported positive correlation between hallucination scores and measures of 40 Hz ASSR. Although in the current study no difference in this frequency range between SZ and H groups was observed, a positive association between hallucinations and PLI measurement in patient group was replicated (Spencer et al., 2009). The association between 40 Hz ASSR and hallucination scores, however, is not that consistent: Hirano et al. (2015) and Griskova-Bulanova et al (2016) did not observe any association (Griskova-Bulanova et al., 2016; Hirano et al., 2015).

Chirp stimulation allows evaluation of broad-band responses. In this study IGF in SZ group was lower (on average 44 Hz) compared to the healthy controls (49 Hz) which goes in line with the report of Alegre et al. (2017) who found that treated patients have the lowest IGF (40.8 Hz) as compared to healthy controls (42.3 Hz) or untreated patients (46.4 Hz) (Alegre et al., 2017). Both findings point to the fact that IGF in response to chirp stimulation is of a potential clinical importance. However, little research on IGF obtained with ASSRs and SZ has been done. Nevertheless, studies employing different stimulation procedures supported this notion. Arnfred et al. (2015) employing proprioception task reported that maximum gamma frequency was associated with self-awareness in schizophrenia (Arnfred et al., 2015) and Spencer et al. (2004) reported that visual Gestalt stimuli elicited synchronized gamma oscillations which frequency was lower in SZ (Spencer et al., 2004). Similarly, shift towards lower frequencies and

association with negative symptomatology was reported with 40 Hz ASSR (Griskova-Bulanova et al., 2016) further emphasizing importance of IGF in SZ studies. It is also important to note that IGF in healthy subjects is associated with auditory temporal resolution (Baltus and Herrmann, 2015) and its modulation with auditory transcranial alternating current stimulation results in altered cortical processing (Baltus et al., 2020). The association of IGF with clinical symptoms and the possibility to change IGF with resulting changes in cortical processing suggest that IGF could act as a new potential biomarker.

As of today, only one study by Alegre et al. (2017) used a wide (1-120 Hz) range chirp stimulus in SZ patients and reported impaired response. However, limitation of the study was the use of pre-defined analysis windows within low and high gamma ranges and no analysis of responses to frequencies below 20 Hz. In the current study this problem was solved by performing point-to-point frequency analysis and clustering allowing the unbiased evaluation of a wide frequency range. Impaired responses in theta-beta range were found which goes in line with previous reports of attenuated low frequency ASSRs in SZ (Hamm et al., 2012, 2011; Puvvada et al., 2018). Edgar et al. (2018) reported that low frequency responses compared to the 40 Hz show higher SNR and may be assessed across recording and analyses methods (Edgar et al., 2018). The importance of low frequencies was stressed out by Puvvada et al. (2018) who not only reported the attenuated ASSR in frequencies between 2.5 and 10 Hz with the greater effect on lower frequencies than on 40 Hz ASSR, but also observed the association between working auditory memory and responses at the low frequencies (Puvvada et al., 2018). This effect could potentially stem from the wider affected neural networks tested with the low frequency stimulation, as 4-18 Hz activity originates in the thalamo-cortical networks, sensory and deep cortical structures (Herdman et al., 2002; Lehongre et al., 2011; Millman et al., 2010), while 40 Hz predominantly arise from local superficial networks (Plourde, 2006).

High gamma responses were attenuated in SZ patients in the current work. This result replicates observation by Alegre et al. (2017) that SZ patients show reduced amplitude of ASSR in a range of 95-105 Hz (Alegre et al., 2017). While reduction of evoked amplitude is in line with Alegre et al. (2017), PLI difference was not significant in their study. This discrepancy of results deserves further attention since it has been shown that for SZ patients, PLI measure has a greater test-retest reliability compared to EA, at least for the 40 Hz ASSR (Roach et al., 2019). Further support for affected high gamma response in SZ comes from the classical single frequency ASSR

studies in which reduced power, PLI and time-locked amplitude to 80 Hz stimulation was observed (Hamm et al., 2011; Tsuchimoto et al., 2011). Recent study by Parker et al. (2019) showed that high gamma ASSR is differently affected in SZ and schizoaffective disorder (Parker et al., 2019). Considering the brainstem origin of high gamma oscillations (Tichko and Skoe, 2017), Nopoulos et al. (2001) showed that SZ patients have abnormal midbrain morphology and the severity of changes is associated with greater exposure to neuroleptic medications and psychotic symptoms (Nopoulos et al., 2001). This result goes in line with reports of stronger ASSR attenuation being associated with more negative symptoms (Hamm et al., 2011) and with the severity of hallucinatory experience (Tsuchimoto et al., 2011). In the current work, EA and PLI attenuation in a frequency range of 91-101Hz was negatively associated with total PANSS scores meaning that greater reduction of responses was observed alongside stronger expression of psychopathology. This result goes directly in line with the above-mentioned observations that high gamma response is associated with clinical symptoms of schizophrenia.

5.3 Changes of chirp-evoked responses in disorder of consciousness

The aim of the current study was to evaluate the ability of chirp stimuli to highlight the disruptions in DOC patients at low and high gamma frequency ranges. Binder et al. (2017) observed disrupted low gamma band response to 40 Hz steady-state stimulation in DOC patients and reported positive correlation between ASSR and total, visual and auditory scores of CRS-R (Binder et al., 2017). Based on that report, difference in low gamma responses between DOC subgroups (vegetative and minimally conscious states) together with a positive association between response and CRS scores was expected.

In agreement with Binder et al. (2017) study, MCS patients in the current study had stronger chirp-evoked response in the low gamma range (36-46 Hz) compared to VS group. Overall this finding is in line with earlier works showing gamma range ASSR changes and prognostic value in DOC (Firsching, 1989) (Serafmi et al., 1994). This was further supported by Chen et al. (2020), who evaluated 32 comatose patients of various etiologies and performed multiple 40 Hz stimulation procedures. Authors found that positive outcome was predicted by ASSR in multiple procedures (all favourable outcome patients had an ASSR present); however, 24% of unfavourable outcome patens also exhibited responses to at least a few of the

stimulations (Chen et al., 2020). Additionally, the result of stronger low gamma attenuation in more severe lost consciousness condition is supported by ASSR studies in sleep. The first report that response to chirp is affected by the sleep (awake versus the second sleep stage) was presented by Artieda et al. (2004) who reported the attenuation of 40 Hz chip-evoked response (about 6 times weaker) in two subjects (Artieda et al., 2004). This goes in line with the single frequency steady-state results for lower frequencies (4, 6, 20 Hz), however the effect on 40 Hz was found to be the strongest (Górska and Binder, 2019). While results for the low frequencies lack consistency, the findings of 40 Hz attenuation seem to be constantly replicated (Picton et al., 2003b; Tlumak et al., 2012). Stronger attenuation of low gamma response in VS than MCS patients found in current study is also consistent with effects of anaesthetics. Plourde (2006) reviewed effect of anaesthetics on ASSR and reported that 40 Hz ASSR is attenuated when consciousness is supressed by medication and is restored when subjects regain consciousness. However, it must be noted that not all anaesthetics have the same effect on ASSR for example ketamine was found to strengthen ASSR (Plourde, 2006). It is also possible that stronger reduction of 40 Hz response in VS group could be explained by the differences in the attentional capacities between MCS and VS groups; however, several observations contradict this hypothesis. Firstly, both in this work (Study I), and in work by Alegre et al. (2008) no effect of attention on responses to chirps was found. Secondly, Rosanova et al. (2018) examined UWS patients and healthy controls under awake and sleep conditions and found that responses to TMS stimulations in DOC group are similar to those of sleeping healthy subjects. In addition, they reported the suppression of frequencies higher than 20 Hz and reduced complex brain interaction in UWS patients. Importantly, decrease in suppression of higher frequencies and increase of complex brain interaction were observed in a subject who passed from UWS to MCS and finally to EMCS state (Rosanova et al., 2018). Thus, attenuation of response around 40 Hz appears to be more likely associated with the state of arousal and brain disability to exhibit complex interactions because of changes in excitation/inhibition balance by strengthened inhibition in cortico-cortico pathways, disruptions in ascending activating systems or thalamic hyperpolarization (Meythaler et al., 2001; Rosanova et al., 2018).

The phase-locking in the low gamma activity positively correlated with scores in auditory and visual subscales and with the total CRS-R scores. This means that patients exhibiting stronger response also have higher functional abilities as in CRS-R lower values reflects reflexive behaviour while higher values signify conscious abilities (Giacino et al., 2004). This association

goes directly in line with previous report of single frequency study by Binder et al. (2017) who found same correlation pattern and proposed that ASSR could be beneficial in objective diagnostics in DOC patients (Binder et al., 2017). Bruno et al. (2012) noted that evaluation by CRS-R relies heavily on patient's ability to comprehend language and thus is less sensitive to consciousness in general (Bruno et al., 2012). In further support, Braiman et al. (2018) showed that patients who responded to speech envelope also were able to perform the mental imaginary task (follow command); however, at the same time not all of these patients were able to exhibit behavioural commands following, which is required by CRS-R (Braiman et al., 2018). Cruse et al. (2011) reported that misdiagnosis of command following (disability to behaviourally follow the commands while displaying command following response in EEG) in their patient group was 19%. Thus, disability to follow command might be caused by both inability to comprehend the language (Braiman et al., 2018) or by inability to respond (Cruse et al., 2011). Owen (2013) summarized that total misdiagnosis in DOC patients might be up to 43% and argued for the need of objective physiological biomarkers in diagnosis (Owen, 2013). The fact that low gamma response not only distinguishes between VS and MCS groups but also is associated with CRS-R scores shows the potential of chirp-evoked responses to be used in DOC patients. As chirp-modulated sounds represent non-verbal stimuli they could be easily combined with other methods, potentially allowing for more precise evaluation of command following.

No differences were observed between MCS and VS groups in response at high gamma range, and no associations to CRS-R scores were detected. The high gamma response in H is smaller than low gamma response (Alegre et al., 2008; Artieda et al., 2004). Although differences in low gamma were observed, high gamma response appeared to be very week and almost invisible on the grand averages in both VS and MCS groups (Figure 4.7 B). High electrical muscles activity is prominent in high gamma range and this could have resulted in a decreased signal to noise ratio and inability to observe clear response at 80-120 Hz frequencies.

5.4 Summary

Proposed brief (500 ms) low-carrier tones (440 Hz) amplitude modulated by chirp at 1-120 Hz elicited clear chirp-evoked responses as was expected according to the previous study of Artieda et. al. (2004) (Artieda et al., 2004). These responses were not sensitive to the manipulation of attention

level and did not depend on the modulation direction, being in line with previous reports (Alegre et al., 2008; Artieda et al., 2004). Even more, proposed stimuli were perceived as moderately arousing and pleasant by study participants. In a clinical sample of SZ patients, point by point analysis of chirp-evoked responses revealed impaired brain ability to synchronize at both theta-beta and high gamma ranges. Additionally, while chirp-evoked response in the low gamma range did not differed from healthy controls, the PLI of SZ patients in 32-43 Hz range was associated with the hallucination symptoms. In DOC patients, chirp-evoked responses were associated to CRS-R scores similarly to the previous report of Binder et. al. (2017) on 40 Hz ASSR. Moreover, chirp-evoked responses were able to capture differences at the low gamma range (around 40 Hz) between VS and MCS patients. Taken together all these results advocate the wider use of chirp stimulation in clinical populations where objective, attention-independent and brief evaluation of brain synchronisation properties is of great need (Alegre et al., 2017; Owen, 2013).

CONCLUSIONS

1. Brief low frequency carrier chirp-modulated stimuli of both ascending and descending modulation direction were perceived as moderately arousing and neutrally pleasant.
2. Brief low frequency carrier chirp-modulated stimuli elicited broad band responses with peaks in the low gamma (30-60 Hz) and high gamma (90-110 Hz) ranges that did not depend on the attention level paid to stimulation.
3. Application of brief low frequency carrier chirp-modulated stimuli highlighted deficient synchronization at theta-beta (4-18 Hz) and high gamma (95-120 Hz) ranges in schizophrenia patients compared to controls. Peak of the low gamma responses was lower in patients than controls (44 vs 49 Hz), and phase-locking in this frequency range (32-43 Hz) was positively associated to hallucination prevalence. Response in the high gamma range (91-100 Hz) was negatively associated with the total score on Positive and Negative Syndrome Scale in patients.
4. Phase-locking index of chirp-evoked low gamma range (37-44 Hz) response was positively associated with the severity of disorder of consciousness as measured with Coma Recovery Scale – revised in visual, auditory and total scales. The synchronization in the low gamma range (36-46 Hz) was lower in vegetative than minimally conscious state patients and no differences were observed in the high gamma range.

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LIST OF PUBLICATIONS

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- Pipinis E, Voicikas A, Griskova-Bulanova I. Low and high gamma auditory steady-states in response to 440 Hz carrier chirp-modulated tones show no signs of attentional modulation. Neurosci Lett. (2018) 678:104-109.
- Binder M, Gorska U, Pipinis E, Voicikas A, Griskova-Bulanova I. Auditory steady-state response to chirp-modulated tones: a pilot study in patients with disorders of consciousness. NeuroImage Clin. (2020) doi:10.1016/J.NICL.2020.102261
- Griskova-Bulanova I, Voicikas A, Dapsys K, Melynyte S, Andruskevicius S, Pipinis E. Envelope following response to 440 Hz carrier chirp-modulated tones show clinically relevant changes in schizophrenia. Plos One (under review)

Conferences on the thesis topic

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Other publications:

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