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Investigation of the Dependence of Brain Auditory Steady-State Responses on Stimulation Type

DOCTORAL DISSERTATION

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Smegenų elektrinių klausos nuostovių atsakų priklausomybės nuo stimuliavimo pobūdžio tyrimai

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Contents

ABBREVIATIONS

ABR	Auditory brainstem response
AEP	Auditory evoked potential
ALLR	Auditory late latency response
AM	Amplitude modulated
AMFR	amplitude modulation following response
AMLR	Auditory middle latency response
ANOVA	Analysis of variance
ASSR	Auditory steady-state response
BCI	Brain-computer interface
CLAD	Continuous loop averaging deconvolution
Click	White noise bursts
EA	Evoked amplitude
EEG	Electroencephalography
EFR	Envelope following response
EOG	Electrooculography
EP	Evoked potential
ERP	Event-related potential
ERSP	Event-related spectral perturbation
FAM	Flutter amplitude-modulated
FFR	Frequency following response
FFT	Fast Fourier transformation
FM	Frequency modulated
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid

GBR	Gamma-band responses
GFS	Global field synchronization
ICA	Independent component analysis
IGF	Individual gamma frequency
ISI	Inter-stimulus interval
ITP	Inter-trial period
ITPC	Inter-trial phase coherence
LCR	Last click response
MEG	Magnetoencephalography
MM	Mixed modulated
NMWF	Non-negative multi-way factorization
MSAD	Multi-rate steady-state average deconvolution
PANSS	Positive and negative syndrome scale
PET	Positron emission tomography
rCBF	Regional cerebral blood flow
RSG	Repeated sequence gated
SPL	Sound pressure level
SSER	Steady-state evoked response
SSR	Steady-state response
SSSEP	Steady-state somatosensory evoked potential
SSVEP	Steady-state visual evoked potential
SNR	Signal to noise ratio
TF	Time-frequency analysis
TMS	Transcranial magnetic stimulation

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Chapter 1

INTRODUCTION

In the resent years, a tremendous interest and a great need for easily assessable brain signatures that can be used to diagnose or predict the outcome of psychiatric disorders or can be implemented in neuro-technological applications has emerged. Electroencephalography (EEG), being cheap and non-invasive technique, has been widely utilized for this purpose.

The participation of cortical regions in cognitive processes translates into synchronization of rhythmic neural activity in gamma range (30–50 Hz) frequencies (Lachaux et al. 2008a) that can be registered from the scalp using EEG. The auditory steady-state response (ASSR) is one of the most widely investigated responses with respect to gamma band neural oscillations.

ASSRs are evoked electrical oscillatory responses of the brain that are entrained to the frequency and phase of temporally modulated stimuli (Galambos et al. 1981; Picton et al. 2003). Apart from being a widely used diagnostical tool in audiology (Rance et al. 1995; Van Eeckhoutte et al. 2016), ASSRs are frequently employed in other brain research areas: in BCI applications ASSR are utilized as a sensitive-to-attention-level tool for the device control (Kim et al. 2011); in the clinics, ASSRs are used to test levels of consciousness (Binder et al. 2017; Plourde 2006) and constitute a promising biomarker for neuropsychiatric disorders (Kwon et al. 1999; O'Donnell et al. 2013).

ASSRs can be elicited by the variety of periodically repeated sound stimuli — tone bursts (Korczak et al. 2012), square waves (Albrecht et al. 2013), amplitude or frequency modulated (AM/FM) tones (Ross et al. 2005a), amplitude modulated

speech-like (Keitel et al. 2013) and music-like stimuli (Lamminmäki et al. 2014). The type of stimulation used could affect the perception of the stimuli, the observed EEG responses, and change expected physiological effects. The stimulation should ideally produce well defined ASSRs, be convenient for the study participant and be modulated according to the needs of application area.

For example, when ASSRs are utilized in BCI, it is important to verify that responses evoked by different stimulation types are modulated by the tasks given to the subjects during the recording session. However, results on modulation of ASSRs by attention are inconclusive (Brenner et al. 2009a; Mahajan et al. 2014; Müller et al. 2009; Saupe et al. 2009; Skosnik et al. 2007) and limited to the evaluation of small amount of EEG channels. As attentional processes are related to the activity within the large-scale distributed neural systems (Raz and Buhle 2006; Vossel et al. 2014) evaluation of local (one EEG channel) and global (all EEG channels) effects of task-related modulation on ASSRs might give more insights. Moreover, Matsumoto et al. suggested that ASSRs sensitivity to the task-modulation may differ depending on stimulation type (Matsumoto et al. 2012). White noise burst (Click) stimulation is known to produce the largest (Hamm et al. 2012a; O'Donnell et al. 2013) and most reliable (McFadden et al. 2014) responses, most consistently show response enhancement with attention paid to stimulation (Yokota and Naruse 2015), and response attenuation with distraction (Griškova-Bulanova et al. 2011); meanwhile results with AM stimuli are mixed (Brenner et al. 2009a; Lazzouni et al. 2010a; Ross et al. 2004; Skosnik et al. 2007).

40 Hz ASSRs to Click stimulation are the most commonly used in research of neuropsychiatric disorders to test the ability of local cortical networks to generate gamma frequency activity (Light et al. 2006; Tada et al. 2014). The sensitivity of click-elicited ASSRs to attentional demands may be regarded as a disadvantage of the method, as attention is highly challenging to control in psychiatric patients (Nishiguchi et al. 2016; Yu et al. 2015). Moreover, as suggested by subjective reports of participants (although not studied consistently previously), Click stimulation is not pleasant, meanwhile patients with psychiatric disorders often exhibit increased perceptual sensitivity to auditory stimuli that contributes to the functional alterations of auditory stimulus encoding and discrimination of noisy sounds (Freedman and Chapman 1973; Landon et al. 2016). According to Thuné et al.

careful consideration of experimental parameters can optimize the ASSRs elicitation that is particularly important for ASSR use in clinical populations (Thuné et al. 2016). Brenner (Brenner et al. 2009a) and Hamm (Hamm et al. 2011) suggested that different stimulations are likely to influence the response on patients. Thus, there is a need for further research on the more convenient stimulation types for ASSR elicitation.

Both the strength of EEG response and the perceived pleasantness of the auditory stimuli depend on the sound envelope shape, the sound-to-pause ratio and the carrier frequency. The stronger EEG responses but less pleasantly perceived stimulation are related to steeper and more rapid sound onsets/offsets, the shorter sound burst durations/longer pauses between sounds and higher frequencies of sound carriers (Kuwano and Namba 2002). Contrarily, low carrier frequency stimuli with shallow envelopes, long sound parts and short pauses evoke less defined EEG responses (John et al. 2002; Van Canneyt et al. 2019), though may be perceived as more pleasant.

In search for better stimulation type we adopted flutter amplitude-modulated (FAM) stimuli, that was first proposed by Matsumoto et al. in BCI settings (Matsumoto et al. 2012). FAM stimuli are defined by a low frequency 440 Hz carrier (that is pitch standard — the most frequent note in Western music) and equal pause and tone durations. The effect of surprising sound as in Click stimulation is present in FAM, but the transitions from silence to a louder auditory sensation are smoother, less sharp than in Clicks; thus, stimulation is expected to be more pleasant but still produce clear EEG response.

1.1 Aim and objectives

The aim of this work was to investigate the properties of 40 Hz auditory steady-state responses induced by flutter amplitude-modulated tones, and compare them to classical click-induced 40 Hz ASSRs.

The objectives were as follows:

- To estimate subjective pleasantness of flutter amplitude-modulated (FAM) and white noise burst (Click) stimuli.

- To compare effect of different levels of attention paid to stimulation on FAM-elicited 40 Hz ASSRs and on classical click-induced 40 Hz ASSRs by measuring response strength and the local and global phase-locking.
- To compare a potential of FAM-elicited 40 Hz ASSRs and classical click-induced 40 Hz ASSRs to highlight gamma-range abnormalities in patients with schizophrenia.

1.2 Scientific novelty

- This is the first time the subjective pleasantness of auditory stimuli — clicks and flutter amplitude modulated 440 Hz tones — used to elicit 40 Hz ASSRs was evaluated.
- This is the first time both local and global effects of attention manipulation were assessed in response to click and FAM stimulation.
- This is the first time the effect of different stimulation settings in groups of healthy controls and patients with schizophrenia was evaluated simultaneously.

1.3 Practical implications

- FAM stimulation can be used in clinical settings where control of attentional demands is highly challenging as it can elicit ASSRs that are less sensitive to attentional manipulations when compared to classical Click stimulation.
- FAM stimulation can be used in the studies of schizophrenic patients as FAM-evoked ASSRs highlight the specific late-latency entrainment deficits similarly to classical Click stimulation.
- FAM stimulation can be used in studies of populations experiencing increased perceptual sensitivity to auditory stimuli as it is perceived neutrally arousing and neutrally pleasant.

1.4 Statements to be defended

1. Flutter amplitude-modulated tones (FAMs) are perceived as neutrally pleasant and arousing, and more pleasant/less arousing than white noise bursts (Clicks).

2. 40 Hz ASSRs to FAM stimulation are not sensitive to attentional demands, whereas ASSRs to white noise bursts are — EEG response power and local and global phase-locking decrease with distraction and increase with attention.

3. The attentional manipulation has significant effects on EEG power and local and global phase-locking in response to 40 Hz click stimulation, but not FAM stimulation.

4. 40 Hz ASSR evoked by FAM stimuli reflect changes of EEG power and phase-locking in schizophrenia, similarly to click-evoked ASSRs.

Chapter 2

LITERATURE REVIEW

2.1 Electroencephalography

Surface recordings of electrical human brain activity were introduced as electroencephalography (EEG) by Hans Berger in 1924 (Berger 1929). Today EEG is widely used in clinical and scientific practice to obtain physiological and pathophysiological recordings of brain activity. EEG reflects the summation of excitatory and inhibitory postsynaptic potentials at the dendrites of ensembles of neurons with parallel geometric orientation (pyramidal cells organized along cortical columns). EEG is most sensitive to sources orientated radially to the skull. Sources orientated tangentially and localized deeper in the cortex contribute less to the EEG signal (Figure 2.1). It has been estimated that $\sim$ 50 000 neurons compose the EEG signal (Ahlfors et al. 2010; Jackson and Bolger 2014; Murakami and Okada 2006; Scherg 1990).

Electroencephalography has many advantages for studying sensory and neurocognitive processes. Most importantly it is non-invasive measurement that directly measures neural activity at meso- and macro-scale (Varela et al. 2001). EEG is a multidimensional measurement comprising time, space, frequency, power and phase of the activity. It has high temporal resolution (usually from 128 up to $\sim$ 20 000 measurements per second) which allows to capture fast dynamic processes. EEG devices are compact portable and not so expensive compared to alternative brain research tools like magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). Device portability

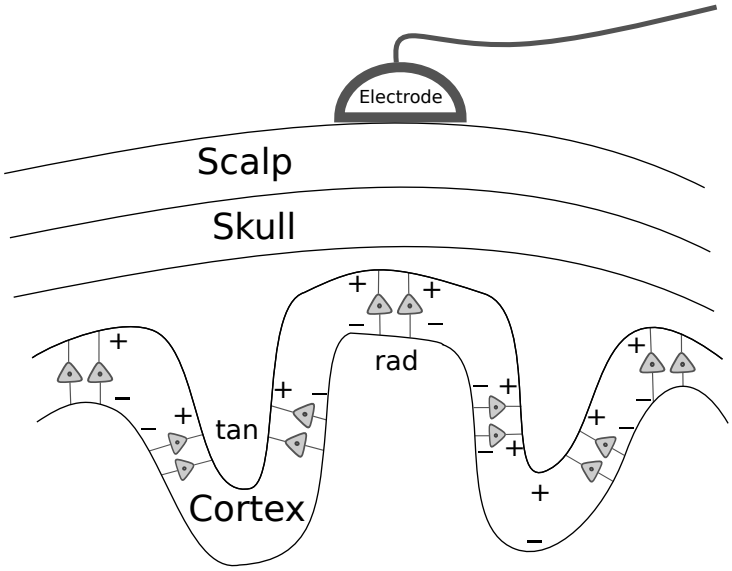


Figure 2.1: **Schematic diagram of brain electrical activity sources comprising EEG.**
Large cortical pyramidal nerve cells are organized in macro-assemblies with their dendrites oriented to the local cortical surface. This spatial arrangement and the simultaneous activation of a large population of these cells contribute to the current flow that generates detectable EEG signals; rad — radially orientated sources, tan — tangentially orientated sources (Baillet et al. 2001; Scherg 1990).

enables more realistic experiment setups for brain-computer interface (BCI) or neurofeedback applications. Depending on task at hand various electrode placement strategies can be used. For BCI and clinical applications few pre-selected electrodes are usually placed on the scalp to minimize setup time and discomfort, while for exploratory research in order to increase spatial resolution high-density arrays placed according to international 10–20 system can contain up to 256 electrodes (Lopez-Gordo et al. 2014).

The unit of measurement of EEG is volts (typical adult human EEG signal is from 10 μV to 100 μV). Microvolt is a relative value — change in the measured electrical potential between recording electrode and a reference electrode. The representation of EEG channels with selected reference strategy is referred to as

montage. The most common montages are referential montage, where each channel represents the difference between a certain electrode and a designated reference electrode (the most common references are nose, ears, mastoids or center electrode Cz) and average reference montage, where averaged signal of all electrodes is used as the common reference for each channel. During post processing it is possible to switch between montages and because EEG amplitude results vary greatly between different montage setups it is best to transform data to reference free representation (Hagemann et al. 2001; Kayser and Tenke 2015; Nunez and Srinivasan 2006).

2.2 Evoked potentials

Evoked potentials (EPs) are electrical potentials generated by the brain that are related to specific internal or external events (stimuli, responses, decisions etc..) (Luck 2014). EPs are too small to be detected in the ongoing highly variable EEG signal. To achieve better signal to noise ratio (SNR) events are repeated and might be presented from 40 up to 1000 times depending on the effect size. Every stimulus onset is precisely marked in EEG recording. The continuous data are cut into segments surrounding stimuli marking (epoch) and averaged to get EP (Figure 2.2). Long pauses between stimuli (inter-stimulus interval (ISI)) or stimulation trials/stimuli onset (inter-trail period (ITP)) of variable duration are made to evade response overlapping or stimulus anticipation effects (Nunez and Srinivasan 2006). Evoked potentials (EP) consist of positive and negative polarity wave deflections that are highly reproducible EP components (N1, N2, P1, P2, P300, I, II etc. — noting positive/negative wave and/or peak number or latency in milliseconds) (Coles and Rugg 1996; Luck 2014; Picton et al. 1974). EPs are simple and fast to compute and require few analysis assumptions or parameters, have high temporal precision, accuracy and decades-long literature of EP findings (Cohen 2014).

EPs to auditory stimuli are called auditory evoked potentials (AEPs) and can be classified into transient and steady-state responses depending on the time course of auditory stimulation (Paulraj et al. 2015; Plourde 2006). When a brief auditory stimulus is presented at a low rate avoiding response overlap corresponding evoked potentials are called transient auditory evoked potentials. Transient AEPs

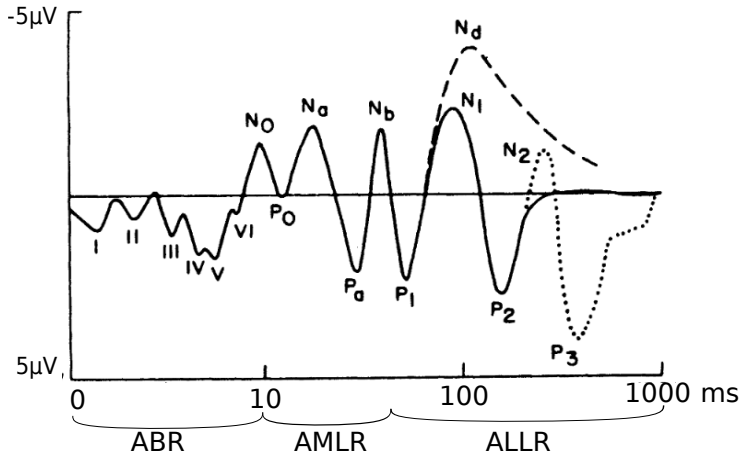


Figure 2.2: **Auditory event-related potential to brief sound.**
In order to extract sound related brain activity EEG is averaged over many stimulus presentation to get better signal to noise ratio. Presented auditory evoked potential (EP) with early brainstem responses (Waves I-VI) (ABR), middle latency components (N_o, P_o, N_a, P_a, N_b) (AMLR) and late latency components (ALLR) (Coles and Rugg 1996; Picton et al. 1974).

components are grouped into categories according to their latency (Figure 2.2). Early auditory brainstem response (ABR) components marked as I, II, III, IV, V, VI are evoked in the time range from 0 to 10 ms. Middle latency auditory response (AMLR) follows ABR from 10–80 ms and is comprised of P_0, N_a, P_a, N_b components originating in thalamus and cortex. Late latency responses (>80ms) are highly dependent on experiment parameters often overlap and are categorized into exogenous (P1, N2, P2) and endogenous (Nd, N2, P300; originating due to some level of cognitive processing) responses (Coles and Rugg 1996; Kraus and Nicol 2009). When stimulus presentation rate is fast enough to cause overlap of responses auditory steady-state evoked potential (ASSR) is generated.

2.3 Steady-state response

Steady-state responses (SSRs) are evoked electrical oscillatory responses of the brain that are entrained to the frequency and phase of temporally modulated stimuli

(Plourde 2006; Thuné et al. 2016). The response is sometimes referred to as steady-state evoked potential, steady-state response, frequency tagging, flicker effect. It can be evoked by sensory stimuli of different modalities:

- Steady-state visual evoked potential (SSVEP) — evoked by rhythmical stimulation of visual system by flickering light source (Regan 1966; Vialatte et al. 2010).
- Steady-state somatosensory evoked potential (SSSEP) — evoked by repetitive modulated vibrations or electric stimulation applied to a part of the body (Franzen and Offenloch 1969; Nangini et al. 2006).
- Auditory steady state response (ASSR) — evoked by rhythmic stimulation of the auditory pathway (Galambos et al. 1981).

2.4 Auditory steady-state response

First report of ASSR response was done by Sem-Jacobsen and colleagues (Sem-Jacobsen et al. 1956) in the recording from the auditory cortex with intracerebral electrodes using click stimuli with repetition rate of up to 200 Hz. However the first detailed description of the steady-state response was done by Galambos and colleagues (Galambos et al. 1981). Galambos and colleagues recorded brain responses to tone bursts of several frequencies presented at various rates and sound levels and demonstrated that the maximum amplitude of the response occurred at 40 Hz and named this response the 40 Hz event-related potential. Since then a variety of terms are used in addition to the 40 Hz auditory steady-state response (40 Hz ASSR) to describe the auditory response: amplitude modulation following response (AMFR), envelope following response (EFR), steady-state evoked response (SSER) or steady-state response (SSR) and steady-state evoked potential (SSEP). Responses modulated at higher rates are often called frequency following responses (FFR). Auditory steady-state responses most easily can be detected noninvasively using EEG and MEG recordings.

At the beginning ASSR research was mostly focused on hearing threshold testing — audiometry. Rickard and colleagues first described pure tones ASSR for hearing testing (Rickards and Clark 1982) and in 1990 the first commercial ASSR systems

appeared. Lately ASSR is increasingly used as a marker of brain function and dysfunction in various neuropsychiatric disorders (Kwon et al. 1999; O'Donnell et al. 2004), and to predict level of consciousness during anesthesia (Plourde 2006). Effects of selective auditory attention on ASSR give rise to development of brain computer interfaces controlled with ASSR (Kim et al. 2011; Lopez et al. 2009).

2.4.1 Auditory steady-state response morphology

The ASSR time course can be divided into four distinct intervals (Ross et al. 2005b):

- During the first 100 ms transient response P1-N1-P2 complex (best seen in low pass filtered ASSR (figure 2.3 p. 12 middle)) and transient gamma band response (tGBR) (best seen in band-pass filtered ASSR (figure 2.3 p. 12 bottom)) appears, similarly to the response that is elicited with the tone burst.
- From 100 ms after tone onset the amplitude of ASSR oscillations develops and increases almost linearly until it reaches its maximum at 200 ms.
- The constant 40 Hz ASSR amplitude between 200 ms and the end of the AM sound at 500 ms indicates a steady-state response that is riding on sustained potential (SP) (Figure 2.3 p. 12).
- After stimulus offset the ASSR decays within 50–100 ms.

The first ASSR time course interval, usually reffered to as "onset" or early-latency gamma, differ from later intervals (late-latency gamma) — reflects different processes and is generated by different networks (Griškova-Bulanova et al. 2016a; Ross et al. 2005b).

2.4.2 ASSR analysis

Although the 40 Hz ASSR is of clinical interest there is no decided best method to analyse it. Analysis of amplitude and latency of various components present in the response (as in figure 2.3 p. 12) frequently utilized in ERP analysis are not common in ASSR research. Variuos deconvolution methods are developed to extract early auditory brainstem response components from high rate ASSR

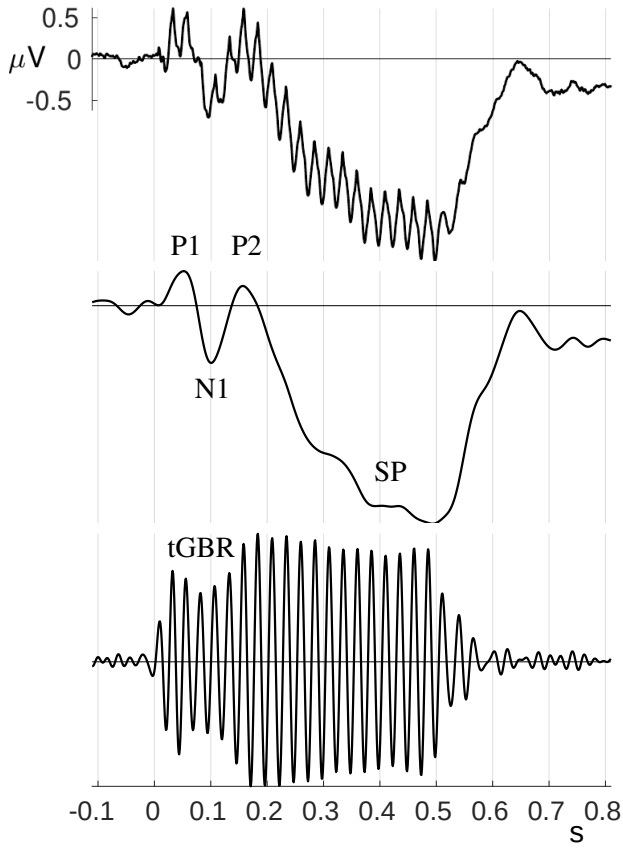


Figure 2.3: **ASSR morphology.**
40 Hz ASSR elicited with 500 ms duration Click stimuli. (Top) Unfiltered ASSR response. (Middle) Transient response P1-N1-P2 complex (onset) and sustained potential (SP) best seen in a low pass (<24 Hz) filtered ASSR. (Bottom) Transient gamma band response (tGBR) followed by steady state best seen in a band-pass (32–60 Hz) filtered ASSR.

would allow faster hearing diagnoses in comparison to traditional auditory transient responses (Özdamar et al. 2007).

Primary techniques used to analyze the ASSR require conversion of temporal ASSR waveform into the frequency domain. Fast Fourier transformation (FFT) is the most common way to transform EEG data to frequency domain. ASSR power and amplitude extracted through Fast Fourier transformation (FFT) has a peak not present during resting state at the stimulus rate and its harmonics (Figure 2.4 p. 13). The mean and maximum values of these peaks are the most commonly reported measures of ASSR.

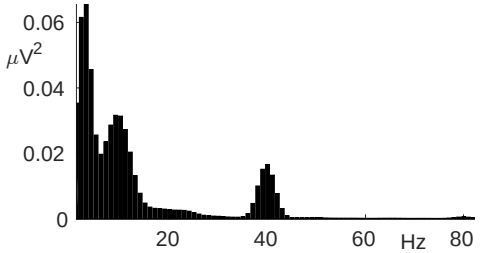


Figure 2.4: **ASSR power spectrum.**
FFT extracted power spectrum of the 40 Hz ASSR elicited by Click stimuli.

The spectrum obtained by Fourier transformation of the time-domain signal is extracted from the entire time duration of the signal and there is no information on the temporal characteristics of the signal. Time-frequency analysis study a signal in both the time and frequency domains simultaneously. Temporal resolution allows to evaluate and separate variation of different frequency activities present in EEG and ASSR, analyse shifts of morphological ASSR parts. The most often used time-frequency transformation techniques are short-time Fourier and wavelet transformations (Cohen 2014; Lachaux et al. 1999).

Event-related spectral perturbation (ERSP), evoked amplitude (EA) and inter-trial phase coherence (ITPC) are the most common measures of time-frequency transformed ASSR. Evoked spectral perturbation (ERSP) (sometimes called total power) is the average oscillations power over epochs. It comprises evoked and induced oscillatory activity. Evoked amplitude (EA) is time-frequency transformed evoked potential (ERP power) and is used to evaluate phase-locked (sometimes

called evoked) activity that is phase-aligned with the onset of the event. Inter-trial phase coherence (ITPC) (sometimes called: phase-locking index/value, inter-trial phase clustering, phase resetting) measures the phase consistency over epochs (Mørup et al. 2007).

Since the energy at low frequencies is higher than the energy at higher frequencies ASSR power results are often normalized dividing by a baseline activity. Contrary, ITPC measure (Figure 2.5 p. 14) evaluates all frequencies equally, it varies between 0 and 1 and is least affected by noisy epochs since all epochs are given the same weight and contribute as every other epoch to the ITPC (McFadden et al. 2014; Mørup et al. 2007).

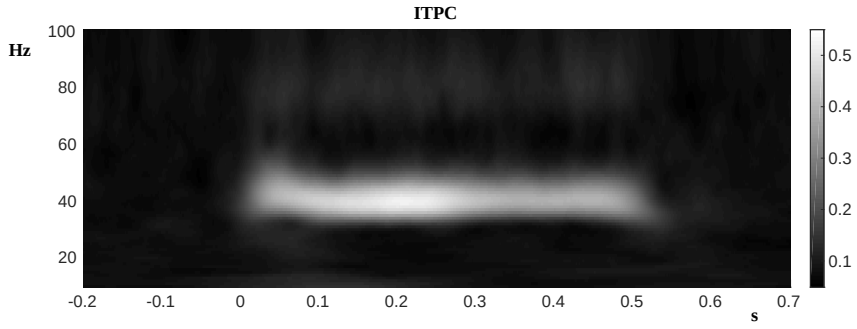


Figure 2.5: **ASSR inter-trial phase coherence (ITPC).**
ASSR evoked with 0.5 sec duration 40 Hz Click stimulus.

2.4.3 ASSR sources

In general ASSRs are larger in the hemisphere contralateral to the stimulated ear and larger in the right hemisphere then in the left (Ross et al. 2005a). MEG studies locate the generators of the 40 Hz ASSR in medial areas of the primary auditory cortex, distinct from those underlying transient auditory components (Gutschalk et al. 1999) with frequency specific organization of neural activity tonotopic representation (Hari et al. 1989; Su et al. 2014). Subcortical origins of the ASSR at the thalamus and brainstem suggested by scalp EEG and intracranial recordings.

Herdman and colleagues (Herdman et al. 2002) modeled the ASSR responses evoked by 1000 Hz tone modulated at 12, 39 and 88 Hz with dipoles localized in

brainstem and cortex. At 88 Hz the largest activity occurred in the brainstem and subsequent cortical activity was minor, at 39 Hz the initial brainstem component remained and significant activity also occurred in the cortical sources. The 12-Hz responses were small and combined activation from brainstem and cortical sources. It was shown that the whole auditory nervous system is activated by modulated tones with the cortex being more sensitive to slower modulation frequencies. A general idea is that the responses to the higher rates mediated by lower stations of the auditory system. Thus, responses modulated by frequencies > 80 Hz are generated mainly in the brainstem (mostly composed of ABR), the responses at modulation frequencies <80 Hz are generated in both brainstem and cortex (composed of AMLR and ABR) (Picton 2010; Plourde 2006).

Auditory path and generators involved in ABR, AMLR and ALLR presented in figure 2.6 p. 16. ABR consists of seven positive waves occurring in the first 10 ms after the stimuli. Waves I ($\approx$ 1.7 ms after the stimuli) and II ($\approx$ 2.8 ms) are generated in extracranial and intracranial portions of the VIIIth nerve. Wave III ($\approx$ 3.9 ms) is derived from the cochlear nucleus; wave IV ($\approx$ 5.1 ms) is generated in the superior olivary complex, wave V ($\approx$ 5.7 ms) is generated in the regions of the lateral leminiscus, wave VI ($\approx$ 8 ms) originate from the inferior colliculus and wave VII ($\approx$ 10 ms) from medial geniculate nucleus (Jewett and Williston 1971; Wilkinson and Jiang 2006). Waves comprising ALLR and AMLR are generated in auditory cortex and thalamus. Waves P0, Na ($\approx$ 22 ms) are generated at the tip of the Heschl gyrus (Liegeois-Chauvel et al. 1991). Wave Pa ($\approx$ 30 ms) is generated in medial part of Heschl gyrus, P1 ($\approx$ 55 ms) — intermediate part of Heschl gyrus, N1 ($\approx$ 100 ms) — lateral part of Heschl gyrus and P2 ($\approx$ 200 ms) — planum temporale (Godey et al. 2001).

Tichko and colleagues (Tichko and Skoe 2017) constructed the model with multiple generators from different locations and latencies — cochlea (0ms), cochlear nucleus (1.25ms), superior olive (3.7ms), inferior colliculus (5ms), primary and non-primary auditory cortical structures (13 and 25ms). The model produced responses with local maxima at 44, 87, 208 and 415 Hz and local minimums at 62, 110, 311 and 448 Hz. Study concluded that frequency following response is a composite response and at any given frequency can reflect activity from multiple generators.

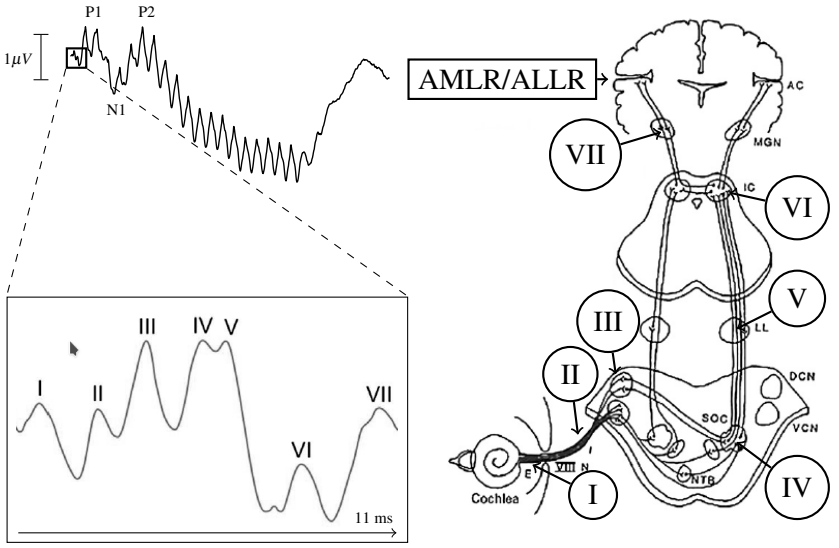


Figure 2.6: **Neural origin of the auditory steady state response (ASSR).** Cochlea (I); Cochlea VIII nerve (II); Cochlear nuclei (III), Dorsal cochlear nuclei (DCN), Ventral cochearl nuclei (VCN); Superior olivary complex (IV; SOC); Lateral lemniscus (V; LL); Inferior colliculi (VI; IC); Medial geniculate nucleus (VII; MGN); Auditory cortex (AC; AMLR and ALLR); Trapezoid body (NTB); (Figure based on Godey et al. 2001; Jewett and Williston 1971; Wilkinson and Jiang 2006).

2.4.4 Mechanisms of ASSR generation

The generation mechanism of the auditory steady-state response is still not well understood. The first hypothesis of ASSR generation mechanisms was proposed by Galambos and colleagues (Galambos et al. 1981) who described ASSR as a superimposition of transient responses. They synthesized a 40 Hz ASSR from middle latency responses (MLR) evoked by short tone pulses presented at 10 Hz rate (Figure 2.7 p. 18) and showed that mainly P_a component composes the response. Other studies also showed good correlation between observed and predicted responses at various rates using different type stimulus (Hari et al. 1989). However later more detailed studies using computer simulations found that predicted ASSRs were not very accurate, usually larger than recorded ones (Azzena et al. 1995; Santarelli et al. 1995). A phenomenon of over-prediction in peak-to-peak amplitudes occurred at rates higher than 40 Hz and under-prediction at rates lower than 40 Hz (Azzena

et al. 1995). Also in subjects under anesthesia the 40 Hz ASSR was much more attenuated than predicted with the superposition of the MLR waves (Plourde and Villemure 1996) as well as for subjects in the sleep state compared to waking state (Suzuki et al. 1994). Research in animal models also found insufficient accuracy for synthesized ASSRs using data directly from rat temporal cortex (Conti et al. 1999).

Prediction mismatch may be due to the unavailability of correct templates for transient responses. First studies used transient responses obtained from brief stimuli presented at low rates (<10Hz). Prediction was improved by using various methods to extract transient response from high rate stimulations close to the modeled ASSRs. In the classical ASSR paradigm the transient responses to individual stimuli cannot be obtained mathematically from overlapped steady-state responses. Transient response extracted from last click responses (mLCR) of a click train presented at the rate of modeled ASSRs improved prediction and indicated the adaptation effect of the neural system to presented click rate (Santarelli et al. 1995). McNeer and colleagues (McNeer et al. 2009) found wave Pa decline with increasing stimulus rate and wave Pb resonance at 40 Hz using continuous loop averaging deconvolution (CLAD) method that uses an irregular stimulus with variable jittered sequence mimicking the classical ASSR (Bohórquez et al. 2007; Özdamar et al. 2007).

Tan and colleagues (Tan et al. 2017) used multi-rate steady-state average deconvolution (MSAD) method which estimates transient responses from the classical ASSR paradigm but with multiple stimulus sequences at different stimulus rates (Wang et al. 2013). CLAD and MSAD comparison revealed significant differences between synthetic transient AEP components (Transient AEP N_bP_b complex appeared to be sensitive to the sequencing scheme) as well as morphological differences in estimated ASSR. Results indicated that both stimulation rate and sequencing factor affect transient AEP reconstructions from steady-state stimulation protocols (Tan et al. 2017). Furthermore, in a comparison of ASSR reconstructed from transient AEPs obtained from CLAD (cAEP), MSAD (mAEP) and classical low rate stimulation (tAEP) different weights calculated for all wave components in all methods (Bohórquez and Ozdamar 2008; Holt and Özdamar 2016; Tan et al. 2017).

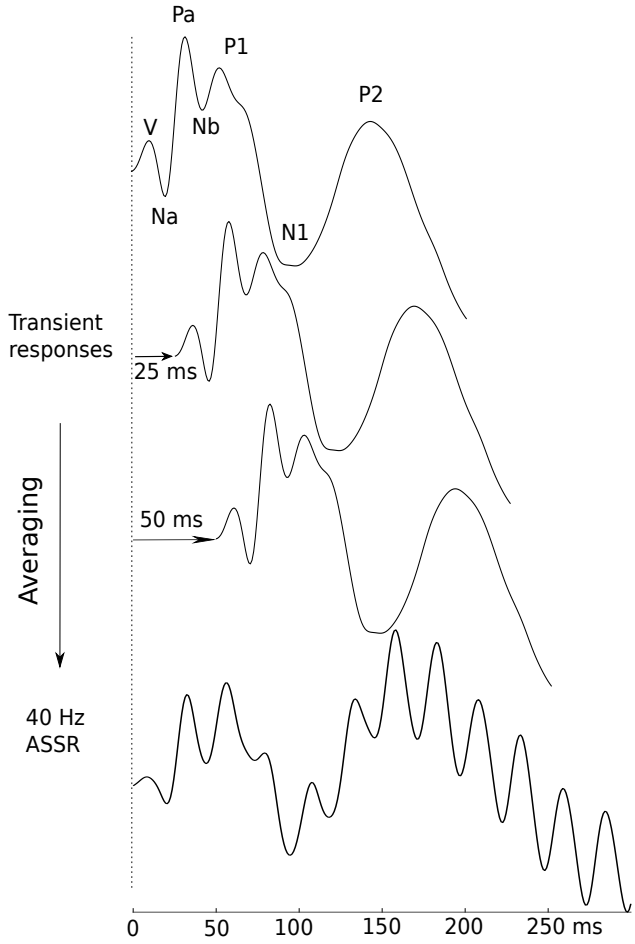


Figure 2.7: **Theoretical diagram illustrating ASSR generation by superposition.**
Generation of the 40 Hz ASSR under superposition hypothesis from transient AEP. Stimulus sequence consists of a series of impulses spaced at T=25 ms. The responses are superposed to generate the 40 Hz ASSR (Galambos et al. 1981; Tan et al. 2015).

While superposition of responses cannot be excluded additional mechanisms explaining ASSR generation appeared. An alternative theory for the generation of ASSRs involves the neuronal gamma-band responses (GBR) and the phase synchronization of the brain waves and considers ASSRs to be induced potentials rather than evoked (Başar et al. 1987; Lütkenhöner and Patterson 2015; Ross et al. 2005a; Tanaka et al. 2013; Thut et al. 2011). The superposition theory was challenged using special stimulation protocol which contained a 40 Hz amplitude modulated regular sound and a separate channel of brief burst serving as a perturbing stimulus. Regular ASSR attenuation caused by the burst could not be explained by the linear superposition theory (Ross et al. 2005a). The study concluded that the response to the extra click presented the half way between two consecutive clicks of regular series of 20–60 Hz and the steady-state response are not governed by the same rules and there is presence of nonlinear mechanisms in the generation of ASSR (Lütkenhöner and Patterson 2015).

Imaging techniques more sensitive to distal generators have described subcortical and cerebellar contributions to ASSR. In a study using regional cerebral blood flow (rCBF) and positron emission tomography (PET) was observed an increase in cortical synaptic activity with 40 Hz stimulation in the auditory cortex, posterior superior temporal gyrus (STG) and superior temporal sulcus (STS) and bilateral activation of the cerebellar hemispheres (Pastor et al. 2002). Later work with transcranial magnetic stimulation (TMS) showed that repetitive magnetic stimulation to the cerebellar hemisphere contralateral to the stimulated ear significantly reduces the amplitude of the steady-state responses to 40 Hz click trains. This cortical effect caused by disruption of cerebellar auditory output implicates the cerebellum as part of distributed network involved in the regulation of frequency specific auditory driven cortical oscillations (Pastor et al. 2006). Finally using fMRI technique and auditory stimulation with 40, 12 and 26 Hz click trains it was shown that input from auditory cortex to the cerebellar hemisphere through cerebro-pontine pathways is conveyed preferentially at gamma band frequencies (Pastor et al. 2008).

2.5 Stimuli for ASSR production

2.5.1 Stimuli types

ASSRs are elicited by periodically repeated sound stimuli. ASSR inducing stimuli are categorized in many ways. They can be separated into categories by their spectral properties as frequency-specific stimuli and broadband stimuli or by sound envelope modulation technique as amplitude-modulated (AM), frequency-modulated (FM), mixed modulation (MM) and repeated sequence gated (RSG) signals (Beck et al. 2007; Korczak et al. 2012).

Amplitude-modulated (AM) stimuli are tones that change in amplitude over time. AM stimuli are formed when some kind of primary (carrier) signal is modulated with usually lower frequency sinusoid. The sinusoidal-amplitude-modulated (SAM) tone is the most common type of stimuli used to evoke ASSR (Picton et al. 2003). SAM ($s_1(t)$) is obtained as:

$$s_1(t) = a\sin(2\pi f_c t)(1 + m_a \cos(2\pi f_m t)), \tag{2.1}$$

where t is a time-course, a is amplitude of signal, m_a is modulation depth, f_c is a carrier tone frequency, and the f_m is an envelope modulation frequency. SAM stimuli as 500 ms duration 1000 Hz tone 100% amplitude-modulated at 40 Hz is displayed in figure 2.8 p. 21.

A frequency modulated (FM) tone is a stimulus where the frequency content of the stimulus changes over the duration of the tone. FM stimuli are formed when tone central frequency is modulated at some rate in a specific range defined by modulation index. FM stimuli as 100 ms duration 1000 Hz tone frequency modulated at 40 Hz with modulation index 10 is displayed in figure 2.9 p. 21.

Mixed modulation (MM) stimuli combine amplitude-modulation and frequency modulation. MM stimuli can be formed as amplitude modulated FM stimuli or as AM stimuli with interchanging frequencies every cycle as in figure 2.10 p. 22. MM evokes a response that is almost as large as the sum of AM and FM stimuli separately (Cohen et al. 1991). MM stimuli displayed in figure 2.10 p. 22 consists of 1000 Hz and 700 Hz interchanging tones 100% amplitude-modulated with 40 Hz sinusoid for 1000 ms.

Repeating sequence gated (RSG) stimuli include many various stimuli that

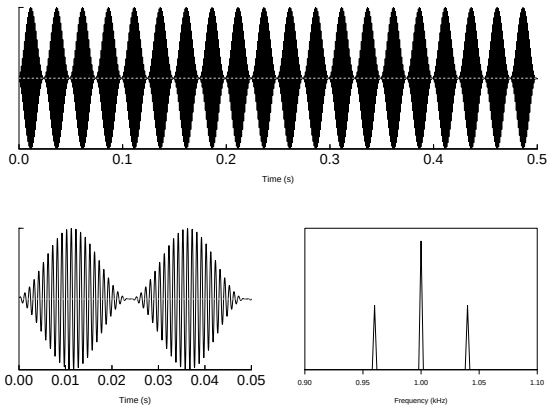


Figure 2.8: **Sinusoidal amplitude-modulated tone.**
1000 Hz tone 100% amplitude modulated at 40 Hz (Top row). Tone dynamics close-up (Bottom left). The power spectrum of stimuli (Bottom right).

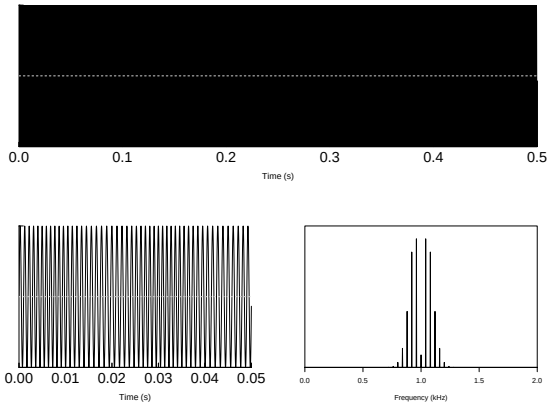


Figure 2.9: **Frequency modulated tone.**
1000 Hz tone frequency modulated at 40 Hz with modulation index 10 (Top row). Tone dynamics close-up (Bottom left). The spectrum of FM stimuli (Bottom right).

have a regular repeating pattern. Repeated short noise bursts or short square stimuli (Clicks; Figure 2.11 p. 22) are the most popular stimuli in this category.

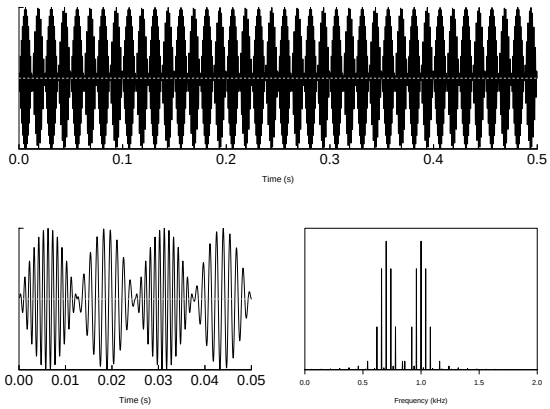


Figure 2.10: **Mixed modulation stimuli.**
Time series of MM stimulus consisting of 1000 Hz and 700 Hz interchanging tones 100% amplitude-modulated with 40 Hz sinusoid (top). Close-up time series dynamics (bottom left). The spectrum of MM stimuli (bottom right).

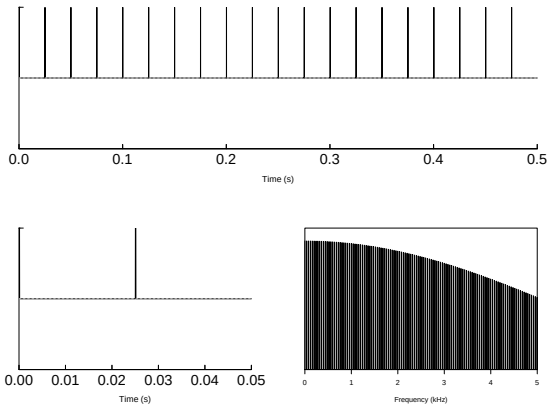


Figure 2.11: **Short square wave (click) stimuli.**
Identical 100 μs duration square waves (clicks) presented at 40 Hz (top row). Close-up time series dynamics (bottom left). The power spectrum of square wave clicks (bottom right).

2.5.2 Carrier frequency

SAM is the most frequency specific stimuli, the power spectrum of SAM has energy at the central carrier frequency (f_c; equation 2.1 p. 20) and two sidebands of energy at $f_c - f_m$ and $f_c + f_m$ (Figure 2.8 p. 21 bottom right; $f_c = 1000$ Hz and $f_m = 40$ Hz). RSG stimuli like clicks (Figure 2.11, p. 22) or amplitude-modulated noise have broadest power spectrum.

It was shown that broadband stimuli activate wider range of the auditory cortex compared to single frequency stimulus (Bilecen et al. 1998; Rauschecker 1998; Saenz and Langers 2014). Larger ASSR responses are achieved when noise rather than a tone is used as the carrier (Picton et al. 2003). Also the stimuli that include high-frequency content show higher detection rates and lower detection times (Santos et al. 2016).

Phase delay of 4.5 ms found between carrier frequencies of 750 and 6000 Hz for EEG AASR (John and Picton 2000). Delays are associated with the difference in arrival time of the traveling waves on the basilar membrane as well as the delays involved in upper levels. Optimized chirp stimuli (Dau chirp) designed to produce simultaneous displacement maxima along the basilar membrane by compensating for frequency dependent traveling time differences in click stimuli (Dau et al. 2000).

In first studies it was shown that ASSR amplitude decreased by a factor of 3 when carrier frequency increased from 250 to 4000 Hz at a modulation rate of 40 Hz (Roß et al. 2000; Ross et al. 2003). Later in a study using stimuli between 440–990Hz it was found that the amplitude of the ASSR was invariant with tone frequencies when the level of sound pressure was adjusted along an equal-loudness curve (Kuriki et al. 2013).

2.5.3 Intensity

Response amplitude is dependent on sound intensity (signal amplitude). A 10dB SPL minimum sound intensity threshold is required to generate ASSR (Vander Werff and Brown 2005). The amplitude of ASSR increases linearly with logarithm of db of stimulus intensity (Roß et al. 2000).

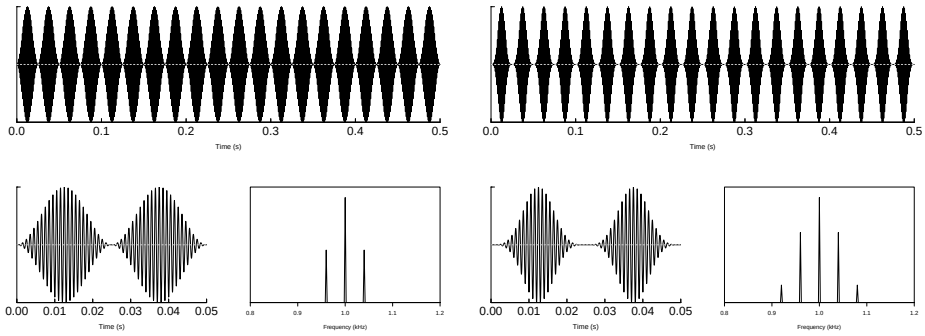
2.5.4 Modulation depth

The carrier frequency (f_c in equation 2.1 p. 20) can be amplitude modulated (m_a in equation 2.1 p. 20) at varying depths. Maximum amplitude modulation is 100 percent as shown in figure 2.8 p. 21. At the other extreme, 0 percent AM of a carrier tone results in a simple sinusoid or pure tone. The SSR amplitude decreases linearly when stimulus modulation depth is decreased in logarithmic steps (Roß et al. 2000) while the phase delay of ASSR does not change with modulation depth (Kuwada et al. 1986).

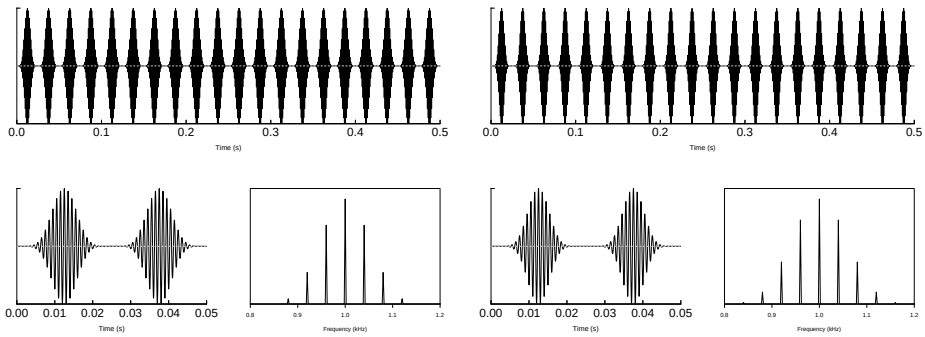
2.5.5 Rise and fall times

Sound envelope can be described by the parameters: amplitude, duration, rise time, and fall time. The rise time reflects how quickly the amplitude reaches a steady-state level whereas the fall time reflects how fast the amplitude decays from one level to another. In general, steeper slopes, greater changes in slope over time or decreasing rise-fall time and short stimuli envelope duration produce larger and earlier responses but also decrease the frequency specificity of the stimuli (Lu et al. 2016; Mo and Stapells 2008). Moreover, envelope pattern has effect on the impression of sound quality, pleasantness and the duration of the sound on the impression of sharpness and articulation (Kuwano and Namba 2002). SAM stimuli (Figure 2.8 p. 21) envelope is continuous with smooth edges — long rise and fall times while click stimuli (Figure 2.11 p. 22) have sharp edges — short rise and fall times and pauses between sounds. Matsumoto developed flutter amplitude modulation with an intermediate duration rise and fall times with symmetric pause and sound burst durations (Matsumoto et al. 2012). Similarly, John and colleagues (John et al. 2002) searched for a compromise between stimuli that are sufficiently frequency-specific (used for estimation of pure-tone thresholds or determination of individual gamma frequency) and stimuli that have sufficiently rapid onsets to evoke easily recognizable responses. They tested a series of AM stimuli (Figure 2.12 p. 25) that differed in amplitude modulation exponent and carrier frequency (N; N=1 gives ordinary SAM). Increasing the value of N caused: a) decrease in the stimulus rise and decay times b) increase in the rise- and decay-slope and c) increase in the periods of silence that occurred between the peaks of the modulation envelope d)

increase in sidebands in power spectrum with the power of the exponent appearing at $f_c + -Kf_m$ for K = 1 to N. The amplitude of the responses increased with increasing N. The "U" shape increase favored low- and high- frequency regions suggesting that different brain areas depending on the shape of the rise function contribute to response (John et al. 2002).



(a) N = 1 (b) N = 2



(c) N = 3 (d) N = 4

Figure 2.12: **Sinusoidal amplitude modulated signals with exponential envelopes.**
Time waveforms and spectra of the 1000 Hz 500 ms duration tone modulated at 40 Hz. Increasing amplitude modulation exponent (N) decreased the stimulus rise and fall times, increased rise and fall slopes, increased the periods of silence that occurred between the peaks of the modulation envelope and the time spectra sidebands increased with the power of the exponent (John et al. 2002).

2.5.6 Modulation frequency

ASSR amplitudes not only vary depending on intensity or sensor position but most importantly show frequency specificity regarding the modulation frequency with highest amplitudes between 40 and 60 Hz (Zaehle et al. 2010). The modulation frequency that elicits the largest ASSR amplitude identifies the characteristic frequency of the neuronal oscillations in the auditory cortex — the individual gamma frequency (IGF). Comparison of IGFs between individuals and within individuals reveals a high inter subject variability but high intra-subject test-retest reliability (Baltus and Herrmann 2015).

2.5.7 Natural sounds

Naturally occurring sounds vary with time in amplitude and in frequency or spectral composition (Heil 1997). Pure simple stimuli utilized in the studies are different from real life sounds therefore new studies emerge using different sounds closer to real life environment and more comfortable for humans like amplitude modulated speech-spectrum noise, speech or music (Keitel et al. 2013; Tan et al. 2017). Lamminmaki and colleagues (Lamminmäki et al. 2014) compared binaural tones, speech and music amplitude modulated at 41 Hz at four different depths (25, 50, 75 and 100%) and showed that AM tones and similarly modulated music and speech stimuli, with tolerable quality and intelligibility elicited reliable responses when the amplitude modulation was deep enough.

2.6 Subject-related variability of ASSRs

ASSRs are affected by various subject-relate factors that can influence results of the experiments like age, arousal, attention or illness.

2.6.1 Age

ASSR responses can be obtained in individuals of all ages. Originally during the first ASSR audiometry studies it was reported that ASSRs cannot be reliably recorded in infants using low modulation frequency of 40 Hz or less (Rickards et al. 1994). Several studies noticed that 80-Hz stimulation is less age-dependent and

ASSRs can be reliably obtained on infants, children, and adults when modulating frequency is greater than 80 Hz (Luts et al. 2006; Perez-Abalo et al. 2001). It might be the case that 40 Hz ASSR was absent in infants because of the immature auditory cortices and due to infants being asleep during the recordings (Korczak et al. 2012). For infants below 1 year of age, the amplitude of the 40 Hz ASSR is approximately the same as the amplitude of the 80 Hz response. By 13 year of age, the amplitude of the 40 Hz ASSR is almost twice as large (Pethe et al. 2004).

There are different reports on aging effects on ASSRs in adult subjects. In some cases no effect was reported (Boettcher et al. 2001; Picton et al. 2005). Boettcher and colleagues (Boettcher et al. 2001) suggested that the normal aging process does not significantly affect the 40 Hz ASSR. In their study comparing the amplitudes of the 40 Hz ASSRs in three different adult groups (10 adults age 22–29 years, 7 adults aged 60–65 years, and 6 adults aged 66–72 years) they found no significant differences in 40 Hz ASSR amplitude or phase across the different age groups for either low (520 Hz) or high (4000 Hz) carrier frequency.

Others reported increase of response measures with age (Herdman 2011a; Poulsen et al. 2006). Poulsen and colleagues (Poulsen et al. 2006) elicited ASSR with 40 Hz modulated tone and amplitude modulated white noise with a sweep from 10 to 100 Hz. ASSRs became larger, less variable with age (subjects from 19 to 45 years) and resonant peak frequency (Individual gamma response) increased from 38 Hz at 19 years to 46 Hz at 45 years.

Others reported decrease of response measures with age. Griškova and colleagues (Griškova-Bulanova et al. 2013) found that phase-locking and evoked aplitudes of 40 Hz ASSR elicited with 500 ms white noise bursts were diminishing with age in the linear manner (46 healthy male subjects, 20–58 years old, during eyes open condition).

2.6.2 Gender

The gender effect on ASSR is unclear. Picton and colleagues (Picton et al. 2009) explored effects of intensity, ear, handedness and gender on ASSR evoked by multiple amplitude modulated (80–101 Hz) tones (500, 1000, 2000, 4000 Hz) and found no consistent effects of gender or handedness (56 adults, 27 female). In a similar study Zakaria and colleagues (Zakaria et al. 2016) explored ASSR elicited

by 40 Hz and 90 Hz AM tones (500, 1000, 2000, 4000 Hz) and found the gender effect was significant for 500 Hz tone amplitude modulated at 40 Hz (28 subj. 14 females). Melynyte and colleagues (Mėlynytė et al. 2018) reported lower phase-locking during 40 Hz ASSR stimulation (white noise bursts) in left-handed females as compared to left-handed males while there was no difference in right-handed subjects.

In addition, evidence exists that the ability to entrain to 40 Hz stimulation depends on the phase of menstrual cycle. Female sex steroid hormones affect the GABAergic transmission which is important for ASSR generation and the ASSR amplitude increases with an increase of estrogen level (Griškova-Bulanova et al. 2014).

2.6.3 Arousal

ASSRs are sensitive to subjects' state of arousal that can be modulated by sleep, anesthesia, or brain trauma. Amplitude of the 40 Hz ASSR is reduced by approximately 50% when transitioning from wakefulness to natural sleep (Galambos et al. 1981; Picton et al. 2003; Tlumak et al. 2012). In contrast, ASSRs evoked with 80-Hz and higher m_f are not affected by sleep and responses obtained from stimulation lower than 10 Hz m_f are enhanced during sleep (Tlumak et al. 2012).

The 40 Hz ASSR is attenuated in a concentration-dependent manner by various anesthetics and is an excellent predictor of the level of consciousness (Plourde 2006). ASSR can be indicator of the level of dysfunction of the central nervous system in disorders of consciousness. Binder et al., measured ASSR evoked by 40 Hz click trains in patients with disorder of consciousness (N=15) and found reduced phase-locking and evoked amplitude compared to healthy control participants (N=24). In addition positive correlation of phase-locking with behavioral scales used for disorders of consciousness assessment of the patient state were observed in the 200–500 ms time window after stimulus onset (Binder et al. 2017).

2.6.4 Attention

Attention effect to auditory stimuli is well known. Selective attention to target auditory stimuli elicits alterations in ERPs such as enhanced N100 and P300 components (Skosnik et al. 2007). However, attentional effects causing modulation of

ASSR are inconclusive. Differences between subject groups, stimuli and analysis methods might influence the response and contribute to the inconclusive results (Brenner et al. 2009b). First study on attentional impact on the amplitude of the ASSR found no effect (stimulus rates 500 Hz tone amplitude modulated at 37–41 Hz, 10 subjects (5 females)) (Linden et al. 1987). Ross and colleagues (Ross et al. 2004) were first to report evidence for attentional modulation of the ASSR in a MEG study. Participants (17 subjects) counted infrequent 500 Hz tones amplitude modulated at 30 Hz among standard 40 Hz AM tones; response was compared to control condition in which subjects counted visual targets. ASSR amplitude enhancement by attention was observed in the left hemisphere, contra-lateral to the auditory stimulation, 200 to 500 ms following sound onset. Saupe and colleagues (Saupe et al. 2009) replicated these results with EEG. Bidet-Caulet and colleagues (Bidet-Caulet et al. 2007) recorded intracranial EEG in epilepsy patients during selective attention task with competing auditory streams (21 and 29 Hz stimulation) and found an enhancement of the ASSR elicited by the attended stream and a reduction for the ignored stream in the left hemisphere. Similarly Lazzouni and colleagues (Lazzouni et al. 2010a) found no effect of attention on ASSR power but increased ASSR amplitude (15 subjects (8 females), 1000 tone amplitude modulated at Hz 39 and 41 Hz).

Skosnik and colleagues (Skosnik et al. 2007) suggested that attentional effects may be to some extent dependent on the AM frequency. They reported strongest effect on response power and phase-locking around 40 Hz in the right ipsilateral hemisphere (15 subjects ASSR elicited with 20 Hz and 40 Hz click stimuli). Bhardwaj and colleagues (Bharadwaj et al. 2014) found ASSR increment for attended frequencies in a study (10 subjects 2 females) using real life vowel sounds modulated at 35 and 45 Hz. Some researchers found no effect of attention for 40 Hz modulated stimuli but power of the responses power measurements where enhanced during 20 Hz stimulation (Mahajan et al. 2014; Müller et al. 2009). In contrast Gander and colleagues (Gander et al. 2010b) suggested that attention modulation of human primary auditory cortex is modality-specific but not frequency-specific.

2.6.5 Psychopathological factors

2.6.5.1 Bipolar disorder

Deficits in the generation and maintenance of ASSR are present in bipolar disorder, implicating disturbances in auditory pathways (Isomura et al. 2016; O'Donnell et al. 2004; Rass et al. 2010). O'Donnell and colleagues (O'Donnell et al. 2004) measured ASSR in unmedicated patients (N=19) during manic or mixed episodes of bipolar disorder and found reduced EEG signal power at stimulation frequencies of 20, 30, 40, and 50 Hz click trains and reduced EEG phase synchronization at 20, 40, and 50 Hz click trains compared to control participants (N=32). Similarly Rass and colleagues (Rass et al. 2010) compared patients with bipolar disorder (N=68) and control participants (N=77); ASSR evoked by click trains presented at 20, 30, 40, and 50 Hz. Patients with bipolar disorder showed reduced mean trial power and phase-locking compared to control participants at 40 and 50 Hz. In addition bipolar disorder patients taking psychotropic medications had decreased ITPC relative to patients withdrawn from medications that implied ASSR sensitivity to medication status.

2.6.5.2 Schizophrenia

Schizophrenia is a mental disorder affecting 1% of population. It is associated with psychotic symptoms, such as hallucinations, delusions (positive symptoms), social deficits, impoverished speech (negative symptoms) and deficits in attention, working memory and executive functions (cognitive deficits) (Saha et al. 2005). The neurobiological mechanisms which produce symptoms of schizophrenia remain poorly understood. The range of cognitive deficits suggests broad alteration in cognitive control affecting integration and connectivity of several brain regions (Lewis et al. 2012).

Gamma-band reflects high frequency (30–80 Hz) synchronized neuronal activity that arises from GABAergic interneurons inducing inhibitory postsynaptic potentials on excitatory pyramidal neurons. This process play an important role of coordination between specific populations of neurons in early sensory processing and higher cognitive functions (Gandal et al. 2012; Lewis et al. 2012). Associations were reported between cognitive, negative and positive symptoms and gamma-band

deficits in schizophrenic patients compared to healthy individuals. The task-related increase in gamma power is smaller in schizophrenic patients compared to healthy subjects (Tregellas 2014).

Auditory processing deficits are one of the most characteristic features of schizophrenia. ASSR has received considerable interest as a biomarker for schizophrenia (O'Donnell et al. 2013, Thuné et al. 2016). Kwon and colleagues (Kwon et al. 1999) were first to report reduced 40 Hz ASSR power and phase synchronization at 40 Hz in schizophrenic patients (N=15) compared to control subjects (N=15). Thune and colleagues (Thuné et al. 2016) summarized 20 studies on schizophrenia (in total 590 healthy controls and 606 patients with schizophrenia), 17 reported significant reductions in 40 Hz ASSR spectral power and phase-locking in patients with schizophrenia compared with healthy controls. Authors concluded, that though the impairment of 40 Hz ASSR in schizophrenia is overall a consistent finding, a careful consideration of experimental parameters for optimization is necessary.

However many important factors modulating ASSR parameters in schizophrenic patients compared to healthy subjects are still not well researched and inconsistent among studies. Results are substantially influenced by physical stimulus properties (Hamm et al. 2012b) such as stimulus frequency (Hayrynen et al. 2016) or stimulus length (Hamm et al. 2015) as well as subjects state such as arousal (Cohen et al. 1991; Griškova et al. 2007b) or attentional demands (Ross et al. 2004; Skosnik et al. 2007). Additionally, reductions of auditory responses in schizophrenia depend on experiment stimulation setup parameters such as inter-stimulus-intervals (ISI). N100 is more consistently reduced in studies using ISIs longer then one second than in studies using shorter ISI (Rosburg et al. 2008).

Furthermore test-retest reliability of the ASSR is impacted by stimulus parameters and analysis methods employed. McFadden and colleagues (McFadden et al. 2014) found that measures of phase-locking (e.g. inter-trial phase coherence) may be more reliable between sessions than measures of evoked power and click train stimuli produce more consistent responses than AM modulated white noise stimuli.

Chapter 3

Methods

3.1 Subjects

The study consisted of three phases. The main goals were to estimate subjective perception of 40 Hz FAM and Click stimuli and evaluate task and psychopathology effects on responses evoked by these stimuli. Healthy without prior psychiatric history, non-smoking right-handed volunteers participated in task effect evaluation related part. Schizophrenic patients form Republican Vilnius Psychiatric Hospital and similar age healthy controls participated in psychopathology effect evaluation part. Demographic characteristics of participants are presented in Table 3.1 p. 33. Subjects were asked not to consume caffeine or other psychoactive stimulant substances one hour before the experiment. The hearing thresholds of all subjects evaluated using audiometer AS608 (Interacoustics A/S, Denmark) were within the norm range (<25 dB HL from 250–8000 Hz). Electrophysiological measurements were performed in males only to exclude potential influence of hormonal fluctuations (Griškova-Bulanova et al. 2014).

Patients were diagnosed with paranoid schizophrenia (F20.0 according to ICD-10, mean illness duration 17 years, SD 12 years) and interviewed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987). PANSS is a medical scale used for measuring symptom severity of patients with schizophrenia. The patients are rated on different symptoms (positive, negative, neuromotor, depressive) as well as reports of family members, caregivers and clinical observations. Of the 30 items, seven items are scored on the positive scale (minimum score = 7,

Table 3.1: Demographic characteristics of participants of subjective stimuli experience, TASK effect and PSYCHOPATHOLOGY effect on 40 Hz ASSRs.

Experimental design	Number of subjects	Mean age (SD)
Subjective evaluation	30 (15 females)	22.3 (2.4)
TASK effect		
Local	22 (0 females)	22.6 (2.2)
Global	27 (0 females)	23.2 (2.4)
PSYCHOPATHOLOGY effect		
Patients	26 (0 females)	42 (11)
Controls	20 (0 females)	38 (14)

maximum score = 49) which describe distortion of normal functions (e.g., hallucinations and delusions). Negative scale represents a loss of normal functions such as ability to tell fantasies from reality or express emotions (7 items, minimum score = 7, maximum score = 49). And general psychopathology scale scores 16 items (minimum score = 16, maximum score = 112) such as depression, disorientation, social avoidance, motor retardation etc. Finally total PANSS score combines all scores from positive, negative and general scale (minimum = 30 and maximum = 210) (Opler et al. 2017). The mean positive symptom score was 21.77 (SD 5.87); the mean negative symptom score was 28.77 (SD 5.56); the mean general symptom score was 49.54, (SD 12.07); and the mean total score was 99.88 (SD 21.27). The treatment at the time of recruitment was based on antipsychotic medication, which was typically a combination of haloperidol with atypical neuroleptics (mean chlorpromazine equivalent 692.23 mg, SD 310.38) and diazepam. Subjects with a history of organic illnesses, head trauma, and alcohol/substance abuse (except tobacco) were excluded.

The study was approved by the Lithuanian Bioethics Committee as a apart of the larger research and by the local committee from Bioethics of Republican Vilnius Psychiatric Hospital. All participants gave their written informed consent.

3.2 Stimulation

Two types of auditory stimuli were presented. Click stimulation consisted of 1.5 milliseconds duration white noise burst (Figure 3.1, p. 34) repeated at 40 Hz for 500 milliseconds. Flutter amplitude modulated tone stimuli (FAM) (Figure 3.2, p. 35) were adopted from Matsumoto et al. 2012:

$$s(t) = \begin{cases} sin(2\pi f_c t)\sin(2\pi f_m t) & \sin(2\pi f_m t) > 0 \\ 0 & \text{otherwise} \end{cases} \tag{3.1}$$

where sinusoid with frequency $f_c = 440$ Hz (center frequency; pitch standard note A) was modulated with $f_m = 40$ Hz frequency sinusoid for 500 milliseconds.

Sound stimuli were created using Matlab software (MATLAB 2010) at a sampling rate of 44100 Hz in the waveform audio file format (*.wav) and presented binaurally at 60 dbA (adjusted with DVM 401 digital environment meter).

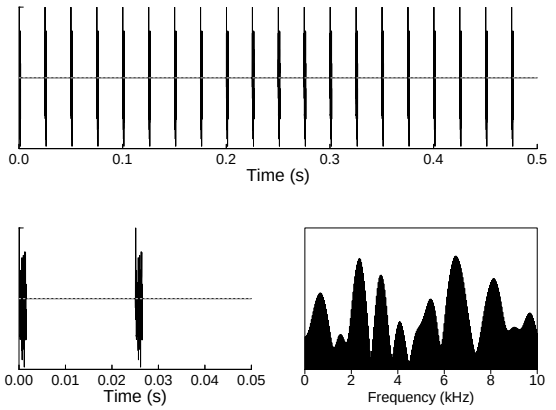


Figure 3.1: **Schematic representation of Click stimuli.**
Stimulus consisted of short (1.5 ms) white noise bursts presented at 40 Hz for 500 milliseconds (top). White noise bursts were separated by pauses and had short rise and fall times (bottom left). Power spectrum of Click stimuli (bottom right).

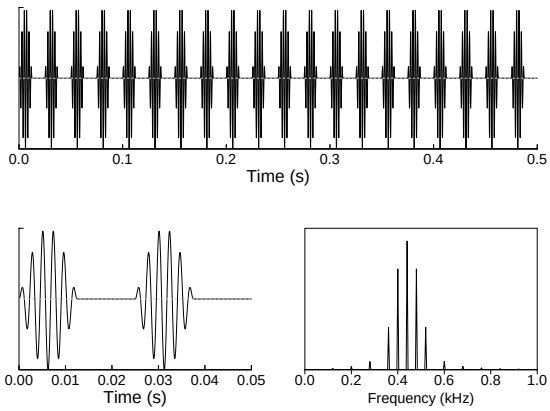


Figure 3.2: **Schematic representation of FAM stimuli.**
Stimulus consisted of 440 Hz tone flutter amplitude modulated (FAM) at 40 Hz for 500 ms (top). FAM stimulus has short pauses between sounds and long rise and fall times (bottom left). The power spectrum of FAM stimuli (bottom right).

3.3 Subjective evaluation of the stimuli

To evaluate subjective perception of the stimuli self-assessment manikin (SAM) method was adopted (Bradley and Lang 1994). Arousal (measuring how arousing the sound was) and valence (measuring how pleasant the sound was) were evaluated by asking the subject to score each sound. Scale from 1 as "not arousing/very unpleasant" to 9 as "very arousing/very pleasant" was used. Click and FAM stimuli were presented in a random order (Table 3.2 p. 37). After presentation of the stimulus for 500 milliseconds SAM manikin icon (Figure 3.3, p. 36) appeared and the subject scored for emotional arousal and valence via keyboard press. Sounds were presented and responses were collected using Psychopy software (Peirce 2008).

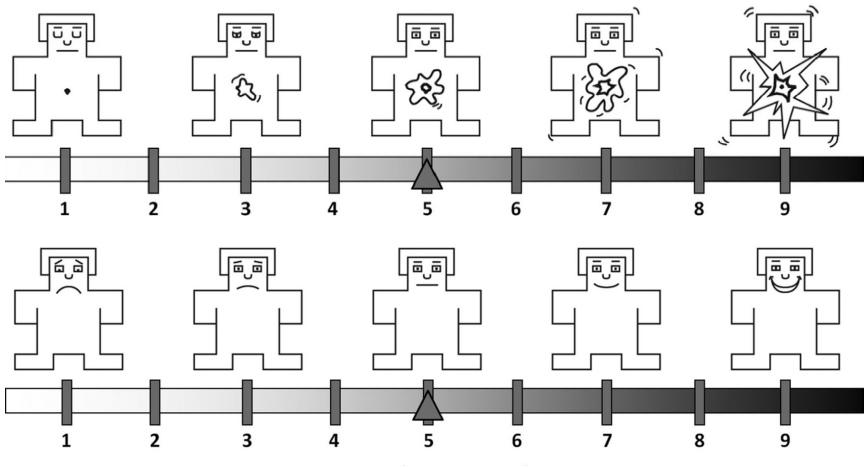


Figure 3.3: **Self-assessment manikin (SAM).**
Arousal scale (top) ranging from 1 (calm) to 9 (aroused) and valence scale (bottom) ranging from 1 (unhappy) to 9 (very happy).

3.4 Electrophysiological evaluation

The TASK effect was evaluated by manipulation subjects' attention paid to stimulation. Three experimental tasks were used:

- Counting (COUNT) — subjects were asked to count sound stimuli and to keep their gaze on the fixation cross. To control for attention subjects reported stimuli count.
- Reading (READ) — subjects were asked to silently read an easily readable catching text presented on the computer screen and to ignore presented sounds. After the stimulation run, subjects were asked to briefly report the content of the reading material to control for their attention.
- Resting (REST) — subjects were asked to close their eyes and let their mind wonder while staying awake.

During electrophysiological evaluation of PSYCHOPATHOLOGY effect on ASSR participants were instructed to watch a silent documentary movie on a screen in front of them and to ignore auditory stimulation.

Click and FAM stimuli were presented in separate runs and the order of runs was randomized for each participant (Table 3.2 p. 37).

Table 3.2: Stimulation parameters for each experimental design.

	Subjective	Task effect	Psychopathology effect
Stimuli	Mixed FAM/Click	FAM/Click presented separately	
Total duration	3 min	20 min	10 min
Trials	20	120	150
Headphones	Sennheiser HD 280 PRO		Beyerdynamic DT-1350

3.5 EEG recordings

For evaluation of TASK effect on 40 Hz ASSR EEG was recorded using ANT device (ANT Neuro, The Netherlands) and 64 channels WaveGuard EEG cap (Figure 3.4 p. 38). Mastoids were used as a reference. Impedance was kept below 20 $k\Omega$ and the sampling rate was set at 1024 Hz. Vertical and horizontal electro-occulograms (VEOG and HEOG) were recorded from above and below the left eye and from right and left outer canthi. A Cedrus StimTracker (Cedrus Corporation, San Pedro, CA) was used to ensure minimal delay between stimulus presentation to participant and the marking of the stimulus in the data.

During evaluation of psychopathology effect on 40 Hz ASSRs, EEG was recorded with a Galileo Mizar Sirius computerized electroencephalogram system (EBNeuro, Italy). Earlobe electrodes served as a recording reference. The ground electrode was attached at the Fpz location. Impedance was kept below 20 $k\Omega$, and the sampling rate was set at 512 Hz. EEG was recorded from nine (Figure 3.4 p. 38) Ag/AgCl electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4).

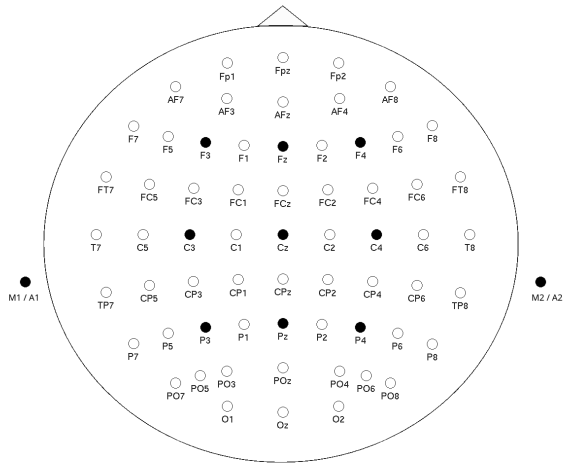


Figure 3.4: **Schematic representation of EEG electrode placement.**
During evaluation of TASK effect on ASSR 64 channels were placed as presented and average mastoids (M1, M2) were used as a reference. During evaluation of psychopathology effect on ASSR 9 channels colored in black were used and average earlobe electrodes (A1, A2) were used as a reference.

3.6 Data analysis

The off-line data preprocessing and analysis was performed using custom written scripts for MATLAB (MATLAB 2010) with the use of functions from EEGLAB (Delorme and Makeig 2004), FieldTrip (Oostenveld et al. 2011), ERPWAVELAB (Mørup et al. 2007). Statistical evaluation was performed in SPSSv20 (SPSS Inc., Chicago, Illinois, USA). Summary of data analysis flow is presented in figure 3.5 p. 43.

3.6.1 EEG pre-processing

Data were filtered from 1 Hz to 100 Hz (FIR filter). The power-line noise was removed (at 50, 100, 150 Hz) using multi-tapering and Thomas F-statistics implemented in CleanLine plug-in for EEGLAB (http://www.nitrc.org/projects/cleanline), which extends functionality from the open source Chronux toolbox (Mitra 2007). Flat channels or channels with high noise were rejected manually. An independent component analysis (ICA, EEGlab "runica"

implementation with default settings) was performed and components related to eye blinks and heart beats were rejected. Data were divided into segments based on stimulus onset. Epochs of 700 milliseconds (100 ms prior to the stimulus onset and 600 ms post-stimulus) were created. Baseline correction was applied and epochs were manually inspected for remaining artifacts. Removed channels were reconstructed using spherical spline method (Perrin et al. 1989).

3.6.2 Signal analysis

The artifact free EEG data subjected to wavelet transformation. The complex Morlet wavelet was used as a mother wavelet $\varphi(t)$:

$$\varphi(t) = Ae^{\frac{-t^2}{2s^2}} e^{i2\pi ft} \tag{3.2}$$

$$A = \frac{1}{\sqrt{s\sqrt{\pi}}} \tag{3.3}$$

$$s = \frac{n}{2\pi f} \tag{3.4}$$

where A is a frequency band-specific scaling factor, t is time, n refers to the number of wavelet cycles and f is a peak frequency of the wavelet. Wavelet transformation was performed in the frequency range of 1–150 Hz in 1 Hz intervals between each frequency. The number of wavelet cycles was 7 for all frequencies.

Wavelet transformed data was normalized and classical measures for oscillatory activity analysis of event related potentials were computed. The following measures were evaluated: inter-trial phase coherence (ITPC), also known as phase-locking index (PLI), that reflects EEG phase consistency over response epochs, highlighting brain ability to consistently follow the stimulation (equation 3.5); evoked amplitude (EA), representing time-frequency transformed evoked potential and measuring only phase-locked (evoked) activity strength that is phase-aligned with the onset of the event (equation 3.6); event-related spectral perturbation (ERSP), also called total power and measuring the average power of oscillations over epochs, highlighting total response strength by catching evoked and induced

oscillatory activity (equation 3.7).

$$ITPC(c,f,t) = \frac{1}{N}\sum_{n}^{N}\frac{X(c,f,t,n)}{|X(c,f,t,n)|} \tag{3.5}$$

$$EA(c,f,t) = \frac{1}{N}\sum_{n}^{N}X(c,f,t,n) \tag{3.6}$$

$$ERSP(c,f,t) = \frac{1}{N}\sum_{n}^{N}|X(c,f,t,n)|^2 \tag{3.7}$$

For evaluation of TASK effect on 40 Hz ASSRs on the local level, the peak (maximal measures of ITPC and EA were extracted) and the mean values were calculated. For the peak estimation (peak ITPC/EA), the ITPC and EA measures were decomposed using non-negative multi-way factorization (NMWF) method as implemented in ERPWAVELAB (Mørup et al. 2007) in 30–50 Hz frequency window (maximal ASSR response) and 200–500 ms time window (entrainment-related part of ASSR referred to as the late-latency gamma) yielding the most consistent activity across all subjects and conditions during ASSR stimulation (Griškova-Bulanova et al. 2011; Korostenskaja et al. 2016).

Alternatively mean value of ITPC and EA for each subject and condition in 200–500 ms time window and 30–50 Hz frequency window were calculated in maximum response channels.

For evaluation of TASK effect on 40 Hz ASSRs on the global level, global field synchronization (GFS) — a multivariate connectivity measurement involving interactions between all brain regions/electrodes — was computed. GFS assesses how well the signals are aligned in time across all channels and does not require prior knowledge on the active brain areas as it assumes that activity of each neural network may be reflected in all electrodes. It is suited to study general functional binding between extended neural networks (Koenig et al. 2001). GFS was calculated from wavelet transformed data in a frequency window from 30 Hz to 50 Hz using all channels as:

$$GFS(f,t) = \frac{|E(f,t)_1 - E(f,t)_2|}{E(f,t)_1 - E(f,t)_2} \tag{3.8}$$

where $E(f,t)_1$ and $E(f,t)_2$ are the eigenvalues 1 and 2 obtained from the principal component analysis (PCA) at frequency f and time point t (Koenig et al. 2001). Mean GFS values were extracted focusing on the 38–42 Hz frequency window for the baseline (-400 to 0 ms) and stimulation period (100–500 ms), corresponding to the late-latency gamma response excluding stimulus onset (Griškova-Bulanova et al. 2016b; Ross et al. 2005a). GFS reactivity was calculated as a difference between mean GFS values during the stimulation period (100 to 500 ms) and the baseline period (-400 to 0 ms) (Koenig et al. 2012).

For evaluation of PSYCHOPATHOLOGY effect on 40 Hz ASSRs, ITPC, EA and ERSP measures were averaged for evaluation of late (late-latency gamma) part of ASSR over the strongest response electrodes (F3, Fz, F4, C3, Cz, C4), then averaged in a frequency window near stimulation frequency (38Hz to 42Hz) and in a time window (200–500 ms) of late part of ASSR (Griškova-Bulanova et al. 2011; Korostenskaja et al. 2016).

3.6.3 Statistical analysis

Data were normally distributed as indicated by Shapiro-Wilk test. Valence and arousal of the stimuli were evaluated in repeated-measures ANOVA with STIMULUS TYPE as a within-subjects factor and GENDER as a between-subjects factor.

Mean and peak ITPC/EA values were analyzed with ANOVA separately for each stimulation type. Means of GFS values were analyzed separately for Click and FAM stimuli with repeated measures ANOVA (rmANOVA) with factors TIME (baseline vs stimulation) and TASK (closed eyes vs reading vs counting). Also a separate rmANOVA on the GFS reactivity was conducted to evaluate the effect of TASK (closed eyes vs reading vs counting).

In evaluation of psychopathology effect late-latency ITPC, EA, and ERSP values were analyzed with independent sample T-tests to assess group difference for each stimulation type. For correlation analyses among ASSR parameters (late-latency ITPC, EA and ERSP) in response to FAMs and Clicks, Pearson's correlation coefficients and corresponding p values were calculated. Similarly, Pearson's correlation was used for correlation analyses among ASSR parameters (late-latency ITPC, EA and ERSP) and clinical variables (the mean positive symptom score, the mean negative symptom score, the mean total score, the mean

general symptom score and medication). Post-hoc comparisons were performed using Bonferroni method.

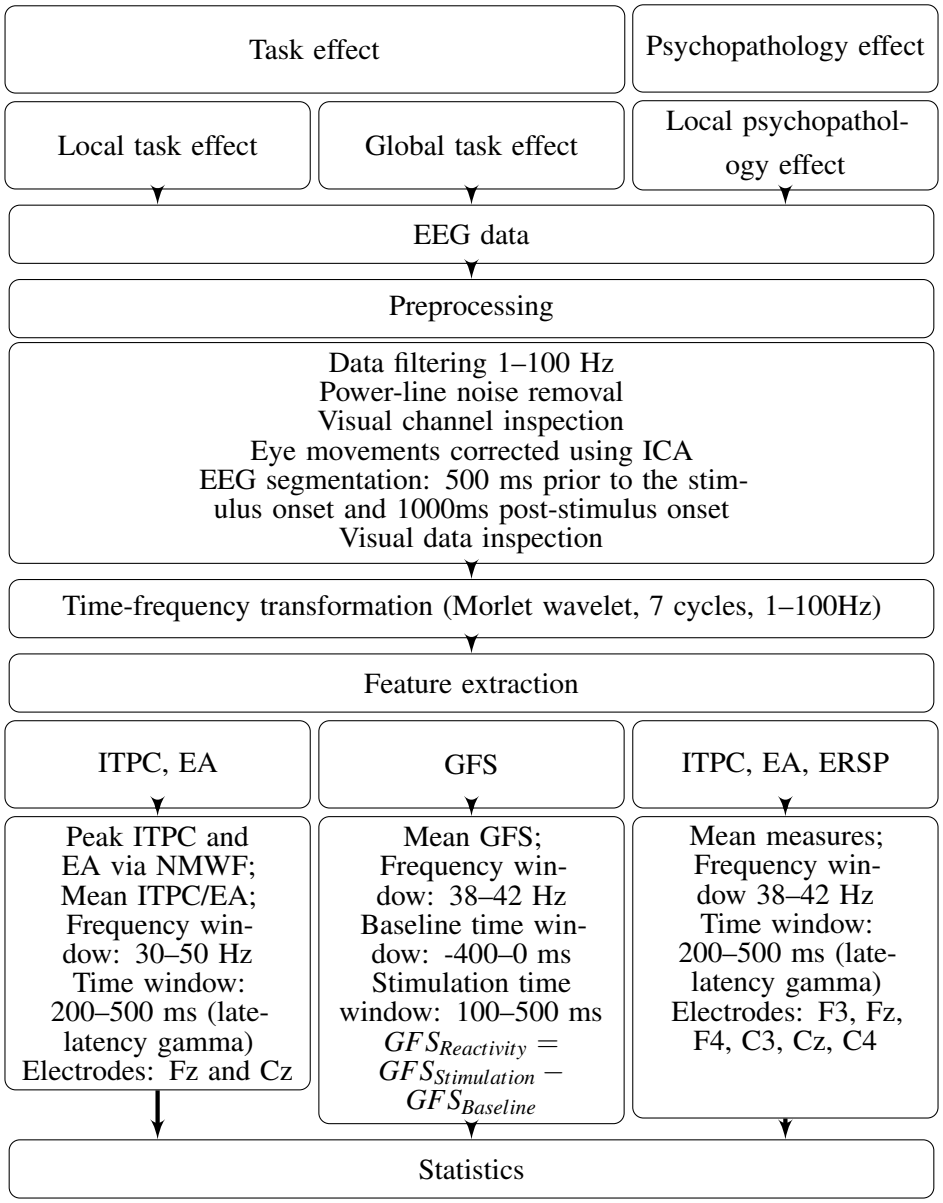


Figure 3.5: **Summary of data analysis.**
ICA — Independent Component analysis, GFS — global field synchronization, ITPC — inter-trial phase coherence, EA — evoked amplitude, ERSP — event related spectral perturbation, NMWF — non-negative multi-way factorization.

Chapter 4

Results

4.1 Subjective evaluation

Subjective evaluation results as means and standard deviations are presented in Table 4.1 p. 44. Participants evaluated Clicks as more arousing ($F_{1,28} = 47.661, p < 0.001$, partial $\eta^2 = 0.63$) and less pleasant ($F_{1,28} = 36.987, p < 0.001$, partial $\eta^2 = 0.57$) than FAM stimuli (Figure 4.1 p. 43). There was no significant effect of GENDER (for arousal: $F_{1,28} = 1.87, p = 0.182$, partial $\eta^2 = 0.06$; for valence: $F_{1,28} = 0.085, p = 0.77$, partial $\eta^2 = 0$) and no interaction between GENDER and STIMULUS TYPE (for arousal: $F_{1,28} = 0.06, p = 0.81$, partial $\eta^2 = 0.0$; for valence: $F_{1,28} = 1.679, p = 0.21$, partial $\eta^2 = 0.06$).

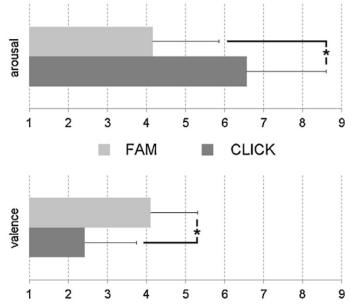


Figure 4.1: **Comparison of emotional response to FAM and Click stimuli.** Means and standard deviations of valence and arousal scores. FAM stimuli was more pleasant and less arousing compared to Click stimuli (*p<0.05).

Table 4.1: Means and standard deviations of arousal and valence scores for FAM and Click stimuli.

	Men		Women		Total	
	Arousal	Valence	Arousal	Valence	Arousal	Valence
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Click	6.13 (2.05)	2.66 (1.54)	7.01 (2.00)	2.19 (1.04)	6.57 (2.04)	2.43 (1.32)
FAM	3.81 (1.89)	3.98 (1.38)	4.52 (1.47)	4.23 (1.03)	4.17 (1.70)	4.11 (1.20)

4.2 Task effect

4.2.1 Local task effect

Means and standard deviations of mean and peak ITPC and EA measures are presented in Table 4.2 p. 45. Grand averaged time-frequency plots of ITPCs during COUNT, READ and REST conditions are presented in figure 4.3 p. 46.

NMWF decomposition resulted in the observation of the most consistent responses to both stimulation types over the fronto-central electrodes (Cz for Click and Fz for FAM stimuli (Figure 4.3 p. 46)). The peak entrainment was observed during 250–350 ms post stimulus time window at around 40 Hz for all subjects. Mean values correspondingly were calculated in the same time window over Cz for Click and Fz for FAM stimuli.

The TASK effect on FAM elicited ASSRs was not significant for all measures (mean ITPC: $F_{2,20} = 0.741, p = 0.49$, partial $\eta^2 = 0.07$; mean EA: $F_{2,20} = 1.706, p = 0.21$, partial $\eta^2 = 0.15$; peak ITPC: $F_{2,20} = 1.454, p = 0.26$, partial $\eta^2 = 0.13$; peak EA: $F_{2,20} = 2.629, p = 0.1$, partial $\eta^2 = 0.21$) (Figure 4.2 p. 45).

The TASK had effect on ITPC in response to Click stimulation (mean ITPC: $F_{2,20} = 3.697, p = 0.04$, partial $\eta^2 = 0.27$; peak ITPC: $F_{2,20} = 6.574, p = 0.01$, partial $\eta^2 = 0.4$): peak and mean ITPCs were higher during counting task compared to reading task ($p<0.03$). Mean EA was not affected by the TASK (mean

Table 4.2: Means and standard deviations of mean and peak ITPC and EA measures during counting, reading and closed eyes conditions.

		ITPC					
		Rest	(SD)	Read	(SD)	Count	(SD)
Peak	Click	0.52	(0.17)	0.45	(0.13)	0.53	(0.16)
	FAM	0.46	(0.18)	0.42	(0.14)	0.44	(0.16)
Mean	Click	0.43	(0.17)	0.41	(0.15)	0.46	(0.15)
	FAM	0.39	(0.18)	0.36	(0.15)	0.34	(0.17)
		EA					
Peak	Click	0.78	(0.35)	0.66	(0.23)	0.77	(0.29)
	FAM	0.67	(0.34)	0.61	(0.22)	0.65	(0.28)
Mean	Click	0.62	(0.31)	0.58	(0.25)	0.66	(0.28)
	FAM	0.56	(0.32)	0.50	(0.24)	0.52	(0.29)

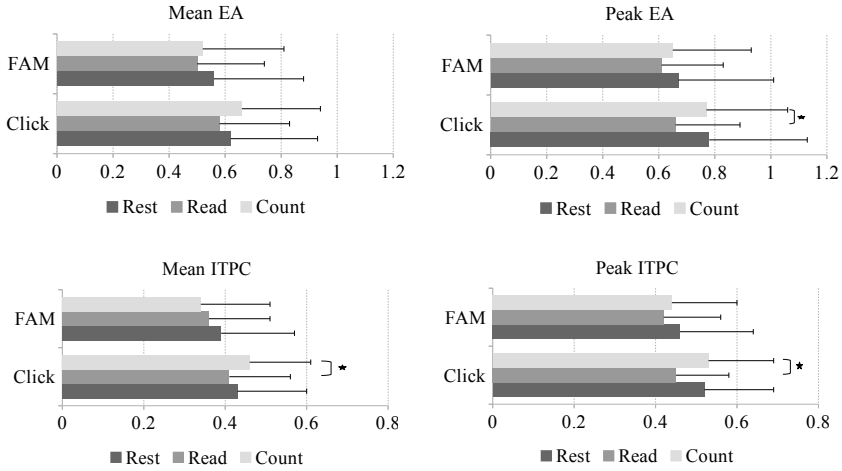


Figure 4.2: **Means and SDs of peak and mean ITPC/EA during counting, reading and resting tasks.**
Peak ITPC, mean ITPC and peak EA were higher during counting task compared to reading task in response to Click stimulation. The TASK effect on FAM elicited ASSRs was not significant for all measures. *p<0.05.

EA: $F_{2,20} = 3.1, p = 0.07$, partial $\eta^2 = 0.24$) and peak EA depended on the TASK (peak EA: $F_{2,20} = 5.053, p = 0.02$, partial $\eta^2 = 0.34$): measurements were lower during reading task compared to stimuli counting task (p = 0.01) (Figure 4.2 p. 45).

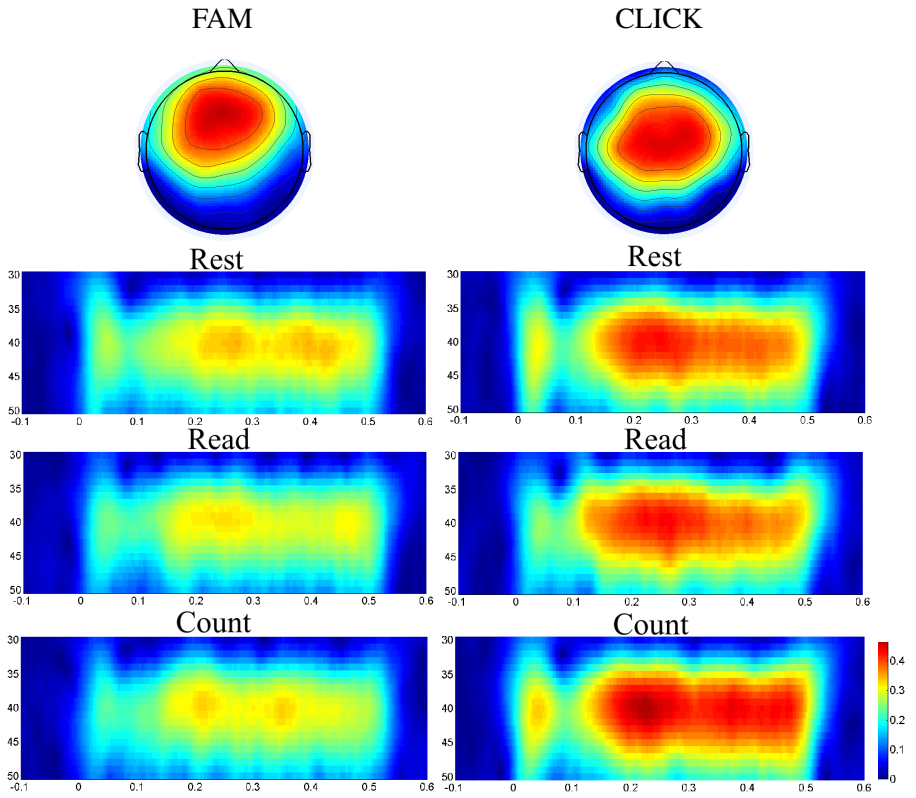


Figure 4.3: **Topographies and time-frequency plots of ITPC measure.** Topographies of 40 Hz ASSR in response to Clicks and FAMs at the time point of maximal entrainment; Grand-averaged time-frequency plots of ITPC in response to Clicks (from Cz electrode) and FAMs (from Fz electrode) during count, read and rest conditions.

4.2.2 Global task effect

Means and standard deviations of GFS reactivity and GFS values during baseline and stimulation period in all three experimental tasks for Click and FAM stimuli are presented in Table 4.3 p. 49. The maximal global synchronization was reached within the time window of 200–350 ms at around 40 Hz (Figure 4.4 47).

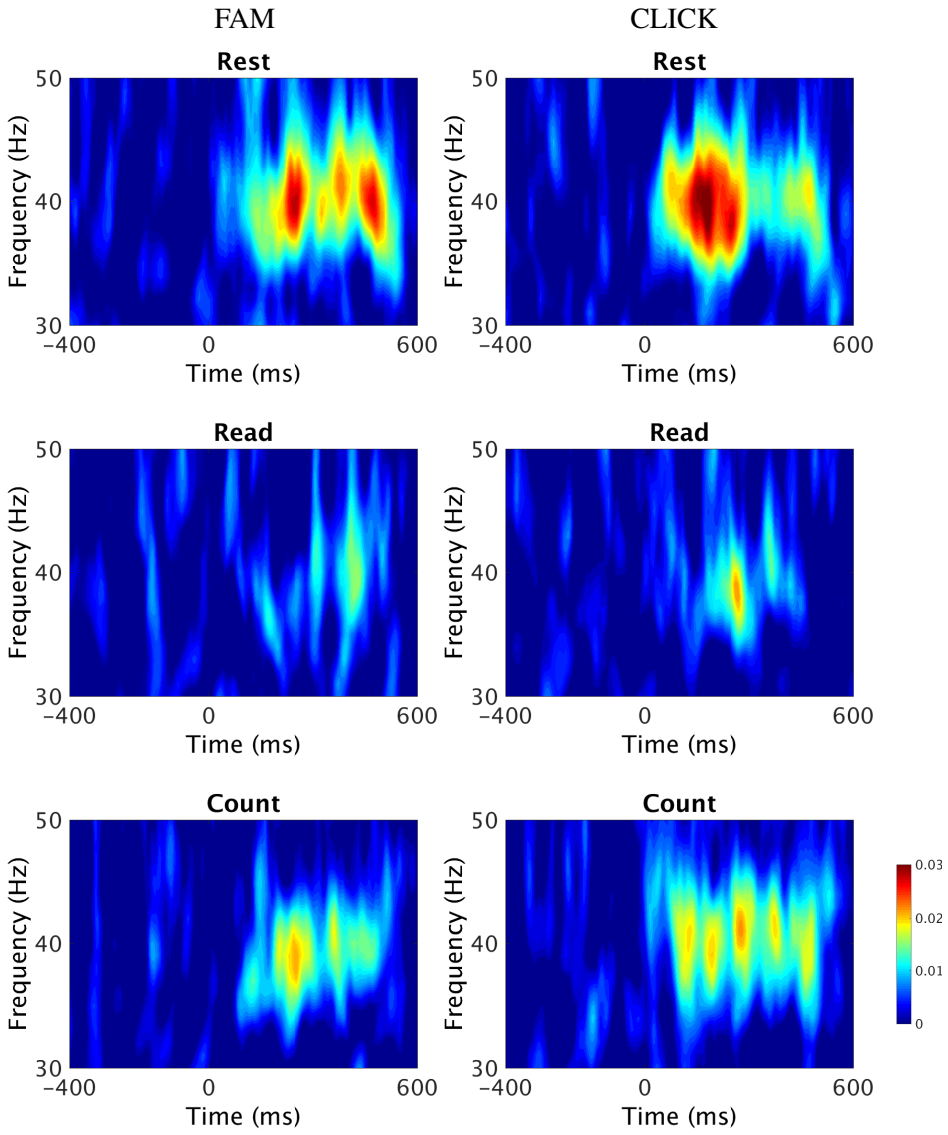


Figure 4.4: **GFS reactivity plots for all conditions and stimuli types.** Time-frequency plots of GFS reactivity in three experimental conditions during FAM (left) and Click (right) stimuli.

For both stimuli higher values were obtained during stimulation than at the baseline during all tasks. The effect of TIME was significant for FAM stimuli $F_{2,26} = 12.147, p < 0.001$, partial $\eta^2 = 0.323$ and for Click stimuli $F_{1,26} =$

19.007, $p < 0.001$, partial $\eta^2 = 0.42$. The effect of TASK was not significant for both stimuli during baseline and stimulus periods (Click: $F_{2,52} = 0.834, p = 0.44$, partial $\eta^2 = 0.03$, FAM: $F_{2,52} = 0.618, p = 0.5$, partial $\eta^2 = 0.023$). For Click stimuli there was a significant interaction between TIME and TASK factors ($F_{2,52} = 7.94, p < 0.001$, partial $\eta^2 = 0.23$). Post-hoc comparisons revealed that at the baseline and during the stimulation lower GFS estimates were observed during reading (distraction from stimulation) than during closed eyes (p = 0.02 at the baseline and p < 0.001 during the 40 Hz stimulation) and while counting (p = 0.01 at the baseline and p < 0.001 during the 40 Hz stimulation).

A significant effect of TASK was revealed for the Click stimuli GFS reactivity estimates ($F_{2,52} = 7.94, p < 0.001$, partial $\eta^2 = 0.23$). Post-hoc comparison indicated significantly larger stimulation-baseline difference in the closed eyes condition as compared to reading (p < 0.001); no difference between the closed eyes condition and the counting condition was observed (p = 0.17) and reactivity during counting did not differ from that during reading (p = 0.14). There was no effect of TASK for FAM stimuli ($F_{2,52} = 2.22, p = 0.14$, partial $\eta^2 = 0.08$)(Figure 4.5, p. 48).

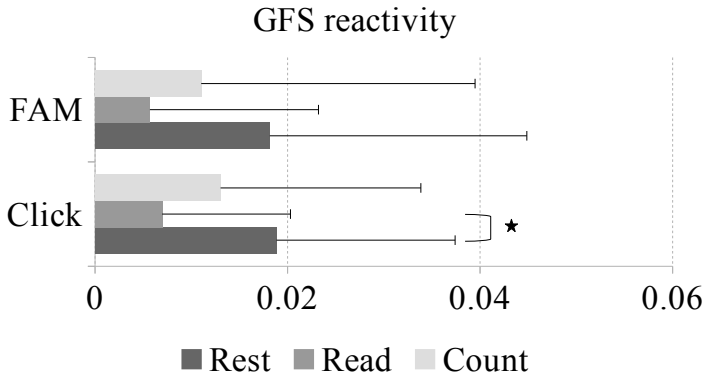


Figure 4.5: **Means and standard deviations of GFS reactivity values during counting, reading and resting task.**
GFS reactivity was higher during resting task compared to reading task during Click stimulation. The TASK effect on FAM elicited ASSRs was not significant. *p<0.05.

Table 4.3: Means and standard deviations of GFS reactivity and GFS during baseline and stimulation period during resting, counting and reading tasks.

	Rest					
	baseline GFS		stimulation GFS		reactivity	
	mean	(SD)	mean	(SD)	mean	(SD)
FAM	0.39	(0.06)	0.41	(0.06)	0.02	(0.03)
Click	0.38	(0.05)	0.40	(0.05)	0.02	(0.02)
	Read					
FAM	0.38	(0.04)	0.39	(0.04)	0.01	(0.01)
Click	0.38	(0.05)	0.38	(0.05)	0.01	(0.01)
	Count					
FAM	0.39	(0.05)	0.40	(0.05)	0.01	(0.03)
Click	0.38	(0.05)	0.40	(0.05)	0.01	(0.02)

4.3 Psychopathology effect

Means and standard deviations of mean ITPC, EA and ERSP values of late-latency gamma presented in Table 4.4 p. 51 and grand-averaged time-frequency plots for both stimulus types in the patient group and healthy controls plotted in figure 4.6 p.50.

Independent sample T-tests were performed to evaluate responses to each stimulus type separately and to compare between experimental groups. Results of independent sample T-tests presented in Table 4.4 p. 51.

The late-latency measures were lower in patients for both Click and FAM stimulation (Figure 4.7 p. 52). All measures of late-latency ASSR response to Click and FAM stimuli correlated in the healthy group. In the patient group only ERSP measure correlated (Table 4.4 p. 51). There were no relationships between late-latency gamma measures of Click-elicited ($0.07 \leq p \leq 0.97$) and FAM-elicited ($0.10 \leq p \leq 0.95$) 40 Hz ASSRs and clinical symptoms.

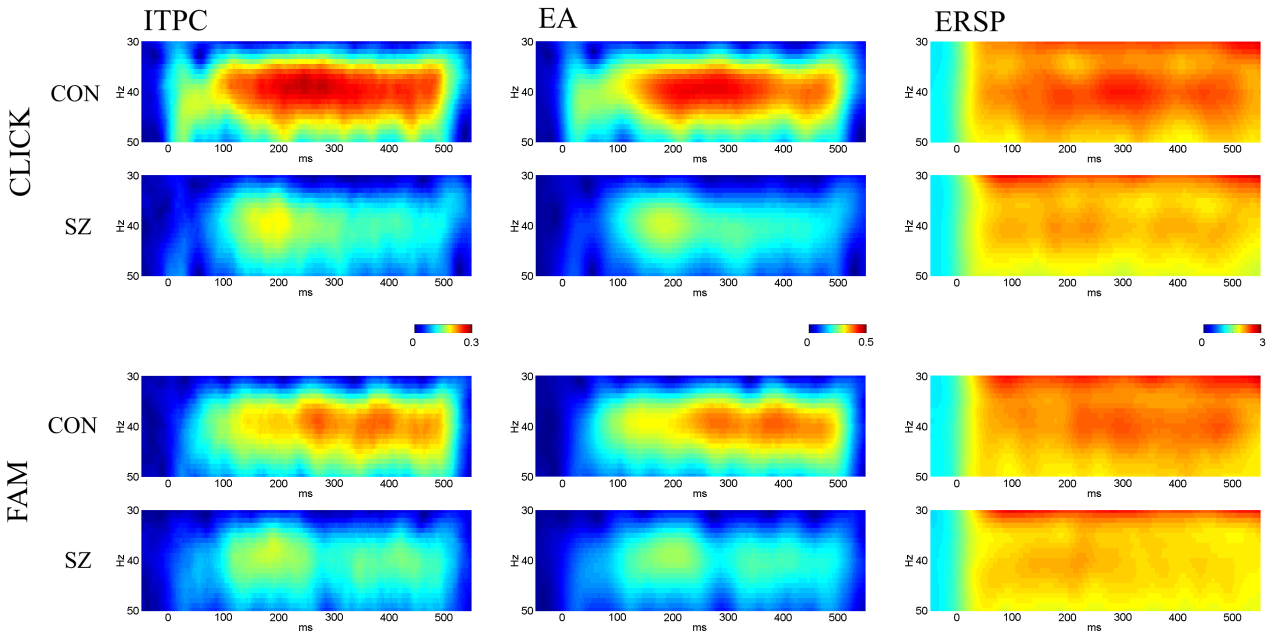


Figure 4.6: **FAM and Click stimuli induced ASSR responses in healthy controls and subjects with schizophrenia.** Grand average time frequency plots of ITPC, EA and ERSP in healthy controls (CON) and subjects with schizophrenia (SZ) to Click stimulation and flutter-amplitude modulated tones (FAMs).

Table 4.4: Means (SDs) of inter-trial phase coherence (ITPC), evoked amplitude (EA), event-related spectral perturbation (ERSP) for Clicks and FAMs, t and p values of independent sample T-tests and Pearson's correlation coefficients (r) and corresponding p values. CON – healthy controls; SZ – schizophrenia patients. P < 0.05 are marked in Bold.

	ITPC				EA				ERSP			
	CON	SZ	t	p	CON	SZ	t	p	CON	SZ	t	p
Late-latency gamma												
Click	0.28 (0.12)	0.18 (0.09)	**3.29**	**0.02**	0.44 (0.19)	0.27 (0.13)	**3.538**	**0.001**	2.37 (0.31)	2.07 (0.28)	3.412	0.001
FAM	0.25 (0.12)	0.18 (0.09)	**2.302**	**0.026**	0.39 (0.2)	0.27 (0.13)	**2.509**	**0.016**	2.29 (0.28)	2.03 (0.3)	**2.991**	**0.005**
r	**0.76**	0.19			**0.77**	0.16			**0.77**	**0.54**		
p	**<0.001**	0.34			**<0.001**	0.43			**<0.001**	**<0.01**		

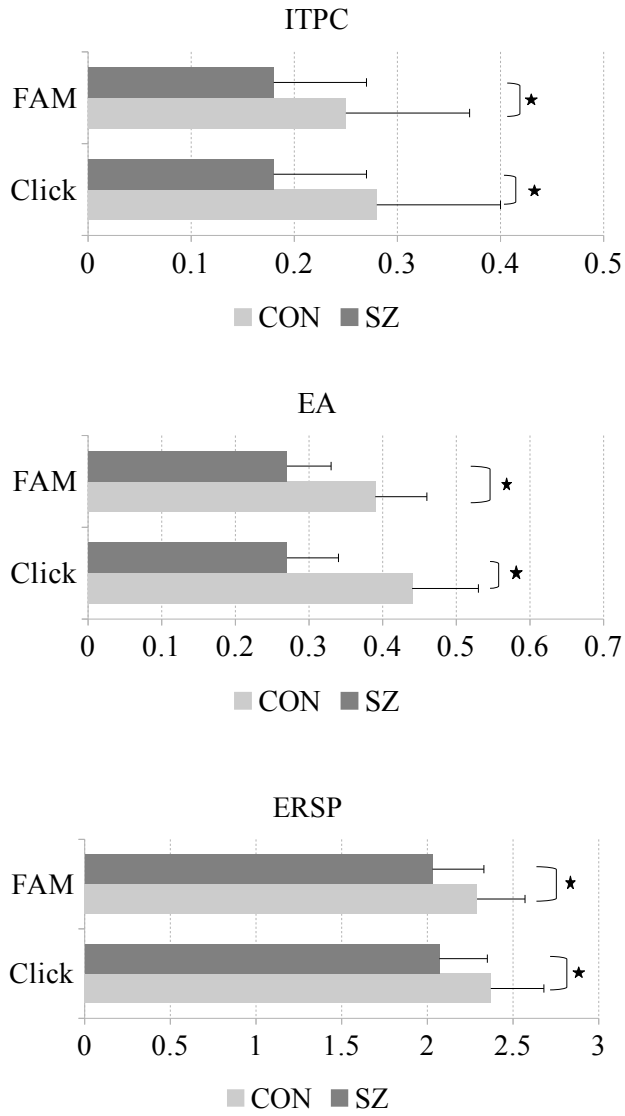


Figure 4.7: **PSYCHOPATHOLOGY effect on FAM and Click stimuli induced 40 Hz ASSR.**
Means end standard deviations of mean ITPC, EA and ERSP values for late-latency gamma responses in healthy controls (CON) and subjects with schizophrenia (SZ) to Click stimulation (Click) and flutter-amplitude modulated tones (FAMs). * $p < 0.05$.

Chapter 5

Discussion

The aim of this study was to investigate subjective pleasantness of 40 Hz Flutter-amplitude modulated (FAM) stimuli and evaluate attentional and psychopathology effects on FAM-elicited 40-Hz ASSR, comparing it to the classical white noise burst (Click) stimulation. For the research and clinical application of ASSRs it is valuable to find the set up where subjects feel comfortable and ASSRs are clearly expressed. FAMs were compared to Clicks and were evaluated as being more pleasant, and thus potentially being suitable in clinical situations where subjects have high noise sensitivity (Freedman and Chapman 1973; Landon et al. 2016). However, it is also important to assure that more comfortable sounds (in this case FAMs) produce detectable EEG responses that are subjected to physiological modulation similarly to conventional stimulation. Both FAM and Click stimuli produced auditory steady-state responses characterized by the peak entrainment at around 250–350 ms and fronto-central topography as evident in attentional modulation experiment and psychopathology modulation experiment. Steeper rise- and fall-slopes and shorter duration of sound part produce stronger activations in auditory cortices (Heil 1997; Lu et al. 2016; Mo and Stapells 2008). Accordingly, as it was expected FAMs resulted in weaker EEG responses in groups of healthy subjects and patients with schizophrenia.

5.1 Subjective evaluation

Flutter-amplitude modulated tones were evaluated as more pleasant and less arousing stimuli in comparison with standard white noise burst stimuli (Table: 4.1, p. 44). The pleasantness of the sound is defined by the sound envelope pattern, the sound-burst duration and the carrier frequency (Kuwano and Namba 2002). The FAM stimuli are somewhat intermediate between conventional AM and Click stimuli. The envelope of AM stimuli is continuous without pauses between sound-bursts. The rise and fall times with conventional AM modulation are long and the transitions are smooth. Contrary, the Click stimuli have long pauses between short duration rapid onset noise bursts. The FAM stimuli as used in this work are characterized by the same durations of sound burst and silent pause within the sound cycle, with shorter rise-fall times than in conventional AM sounds (John et al. 2002; Matsumoto et al. 2012; Van Canneyt et al. 2019). The effect of surprising sound as in click stimulation is present in FAMs, but the transitions from silence to a louder auditory sensation are smoother, less sharp and thus being more pleasant than clicks (Kuwano and Namba 2002; Matsumoto et al. 2012). Additionally FAM stimuli have narrow band spectrum centered around the carriers frequency while spectrum of the Click stimuli is broad. In our study we used 440 Hz carrier for FAMs that is pitch standard note A — the most often-heard pitch in Western music (ISO 1975). And the carrier of Click stimuli was 10–10000 Hz, corresponding to a white noise. This is compatible with earlier works showing that tones with lower carrier frequencies (around 400–500 Hz) are perceived as more pleasant (Bilecen et al. 1998; Müller et al. 2009; Weisz et al. 2012).

5.2 Attentional modulation

Flutter-amplitude modulated (FAM) and white-noise burst (Click) stimuli were presented during several attention-level modulating conditions to investigate potential attention effect on the processing of auditory stimuli. The previously used approach (Griškova-Bulanova et al. 2011; Roth et al. 2013) was elaborated — the general attention to the stimulation was achieved by asking subjects to count the presented trains of periodic sounds, and the general distraction was achieved by engaging subjects in a distractive task — reading. The modulation of responses

was evaluated on the local and global levels to cover both potential interpretations of 40 Hz ASSRs as can be found in the literature: some authors argue that these responses reflect the integrity of auditory circuits (i.e. local networks) (Brenner et al. 2009b; Hamm et al. 2011; Spencer et al. 2009; Teale et al. 2003), while others interpret ASSRs in terms of global synchronization of neural activity with the external environment (i.e. global networks) (Koenig et al. 2012; Light et al. 2006; Tada et al. 2016). All the existing studies evaluating attentional effects on ASSRs used the amplitude/power or inter-trial phase coherence, that measure the local activation. The measures are normally obtained from the single EEG channel with maximal response, or from a group of channels/sensors around the area of the strongest response (Griškova-Bulanova et al. 2011; Skosnik et al. 2007; Yokota and Naruse 2015). Thus the observable changes in ITPC and ERSP, as induced by the varying attentional demands to stimulation, are attributed to the alterations of the activity within these local networks. However, attentional processes per se are related to the activity within the large-scale distributed neural systems (Raz and Buhle 2006; Vossel et al. 2014). Thus the evaluation of large-scale effects of task-related modulation on ASSRs might give better estimation of the induced changes. For the evaluation of the net synchrony/connectivity of electroencephalographic responses, various methods can be employed (Mulert et al. 2011). However only the coherence between brain areas following 40 Hz periodic auditory stimulation was used before: Mulert et al. (Mulert et al. 2011) applied the coherence as a connectivity measure in patients with schizophrenia and Yamasaki et al. (Yamasaki et al. 2005) employed the coherence measure in healthy controls to assess the rapid temporal processing in the auditory cortex (Bowyer 2016; Huang et al. 2017). The GFS as applied in this study assesses how well the signals are aligned in time across all channels. Based on the existing literature, the differences in ASSRs between focused-on-the-stimulus task (counting) and a distraction task (reading) was expected: many authors using click stimulation reported increase of locally assessed response amplitude and phase-locking while direct attention was paid to the stimulation (Dalal et al. 2009; Skosnik et al. 2007). Attentional effect on responses to Click stimuli — stronger responses with attention paid to stimulation — was similar to previously reported studies that also used Click stimulation: 40 Hz ASSR increased with attention paid to stimulation and decreased with a distraction from

stimulation (Albrecht et al. 2013; Griškova-Bulanova et al. 2011; Roth et al. 2013; Skosnik et al. 2007; Yokota and Naruse 2015). This could be explained by the assumption that a strong attentional focus required by demanding visual tasks (like reading) does not allow subjects to process the irrelevant auditory input equally (Muller-Gass et al. 2006), presumably being more inhibitory when the distracting task is more engaging (Griškova-Bulanova et al. 2011) as the 40 Hz ASSRs are sensitive to the concurring task load (Yokota and Naruse 2015).

The similar result was observed on the global level — the GFS values were larger when attention was paid to stimulation. However, the GFS results also showed that the level of synchronization per se (regardless the presence of auditory stimulation) is sensitive to the task being performed — during the engaging reading, the level of synchronization was lower than during unfocused attention with closed eyes and focused attention on the auditory stimulation while counting stimuli. The gamma 'deactivation' was previously observed during high-order processing of complex visual objects (Lachaux et al. 2005) and during reading (Dalal et al. 2009; Goto et al. 2011; Lachaux et al. 2008b); moreover, it was proposed to be global (Lachaux et al. 2008b). As pointed out by Koenig et al. 2012, GFS can be treated as a measure of the global synchronicity that is mediated by a network of cortico-cortical connections and is suited to study a hypothesized general functional binding between extended neural networks. Thus, our observation of lower GFS during distraction from auditory stimulation is compatible with the earlier interpretation of lower phase-locking index and evoked power measures as a result of sensory cortical inhibition of task-unrelated sensory information (Griškova-Bulanova et al. 2011). Overall, this observation fits within the recently proposed model, suggesting that the entrainment of neuronal oscillations might function as a global mechanism used by the brain to optimize attention and stimulus perception (Escoffier et al. 2015).

Importantly, the FAM-elicited ASSR was not modulated by the experimental tasks — this was true both for the local and global measures. This result supports the notion that attentional modulation of AM-evoked ASSRs is not so consistent: several earlier studies reported no effect of attentional modulation on 40 Hz AM-evoked ASSRs (de Jong et al. 2010; Linden et al. 1987; Mahajan et al. 2014; Müller et al. 2009), others reported enhancement of the response with attention

to stimulation (Gander et al. 2010a; Herdman 2011b; Lazzouni et al. 2010b; Paul et al. 2014; Ross et al. 2004; Saupe et al. 2009).

This discrepancy between FAMs and Clicks could potentially be due to the differences in the carrier frequencies of the sounds. Broad-band stimuli (as Clicks in this study) are known to activate wider range of auditory cortex (Bilecen et al. 1998; Rauschecker 1998; Saenz and Langers 2014) including the posterior parts that were previously shown to be involved during attention requiring conditions with auditory stimulation (Alho et al. 2014; Jäncke et al. 1999; Johnson and Zatorre 2005). This notion is supported by the slight differences in the observed topographies in response to FAMs and Clicks — Click stimuli showed central-distribution with maximum at Cz electrode and FAM stimuli resulted in fronto-central distribution with maximum at FCz electrode (Figure 4.3 p. 46). As proposed by Michel et al. 1999 the differences in the topographies indicate the differences in the underlying source configuration. This is further supported by the fact that Clicks produced stronger responses than FAMs on the local level, the effect being due to the shorter rise- and fall-times and shorter envelope in Click stimulation that are causing activating slightly different brain areas dependent on the shape of the rise function (John et al. 2002; Penagos 2004). However, as can be seen from the GFS estimates, FAMs resulted in a global synchronization that was very compatible to Clicks — with auditory stimulation at 40 Hz, global field synchronization increases with both FAMs and Clicks and the GFS values during auditory stimulation were higher than during the silent baseline period. FAM-induced values, nevertheless, were more variable, and the potential absence of significant effect might be attributed to this variability.

It is important to mention, that both local and global measures in response to both FAMs and Clicks during the resting with closed eyes were closer to those in counting condition. This finding is congruent with the previous studies showing that phase-locking is higher in closed eyes condition as compared to distraction and comparable to focused attention condition (Griškova-Bulanova et al. 2011; Griškova et al. 2007a; Voicikas et al. 2016). This could be attributable to effects of involuntary shifts of attention during the closed eyes condition could have occurred and influenced the result. The assumption could be substantiated by the fact that the measures did not differ between counting and resting with closed eyes

conditions. However, Landau et al. 2007 have shown that involuntary attention does not augment gamma band activity as contrasted to voluntary attention; moreover, no difference between the GFS reactivity in the distracting reading condition and focused attention condition where the level of focused attention to stimulation was different were observed. Finally, during the condition in which subjects were not required to perform any specific task, their attention might have been focused on internal thoughts (instead of re-directed to the to-be ignored auditory stimuli) (Muller-Gass et al. 2006).

5.3 Psychopathology

The sensitivity of 40Hz ASSRs to different stimulation types in a group of medicated schizophrenia patients was evaluated. 40 Hz ASSRs to Clicks and FAMs in a sample of male patients with schizophrenia and a group of healthy subjects were assessed for the first time. The potential effects of different stimulus types (clicks or amplitude-modulated tones) on ASSRs have been previously discussed in several studies (Brenner et al. 2009b; Hamm et al. 2012a) but no direct comparison was performed before. The 40Hz ASSRs to both Clicks and FAMs were reduced and less synchronized (evident from the reduced ERSPs, EAs and ITPCs at 200–500 ms) in schizophrenia patients compared with healthy controls that is in line with previous reports (Thuné et al. 2016). The impairment of gamma activity in schizophrenia is interpreted in terms of dysfunction within the glutamate (specifically, its N-methyl-D-aspartate receptors [NMDA]) and gamma-aminobutyric acid (GABA) neurotransmitter systems (Thuné et al. 2016). The data of the current study indirectly suggest that this imbalance, reflected in the reduced evoked amplitude and phase-locking index of the entrained EEG responses at 40 Hz, can be revealed by 40 Hz ASSRs using different stimulation settings.

In contrast to healthy control group, the ITPCs, EAs and ERSPs measures in response to Clicks and FAMs were not correlated in schizophrenia patients. The absence of correlation between the ASSR measures in patient group can be explained by the different pathophysiology revealed by two stimulation types (broad band stimulation in case of clicks and narrow band stimulation in case of FAM tones). Notably, Hamm and colleagues proposed that narrow band and broad band

stimulation may cause activation of different GABA-ergic subsystems (Hamm et al. 2012a), such as GABA-A and GABA-B respectively, both being impaired in schizophrenia (Beneyto et al. 2011; Duncan et al. 2010; Farzan et al. 2009). Whereas the GABA-A subsystem is controlling the spike rate and synchrony in local circuits (Gonzalez-Burgos and Lewis 2008), the GABA-B activity modulates the patterning of activity and not the spike rate, thus producing the net effect of inhibiting gamma oscillations (Brown et al. 2007; Paladini and Tepper 1999; Vertkin et al. 2015). Therefore, as suggested by Hamm, it is possible to speculate that the narrow band FAM stimulation utilized in the current study allowed to evaluate the GABA-A receptor-mediated inhibition from relatively locally distributed GABA-A receptors. At the same time, the broadband click stimulation may have resulted in GABA-A and an additional activation of GABA-B receptors (Kohl and Paulsen 2010; Oswald et al. 2009) that have broader distribution (Bowery et al. 1987). In this way, the ASSRs to Clicks reflected impairment of both GABA-A and GABA-B subsystems and the ASSR to FAMs reflected mainly the specific impairment of GABA-A subsystem only. This is supported by somewhat stronger effect size (reduction of parameters in patients as compared to controls, Fig. 4.6) with click stimulation than FAMs: if patients had impaired both GABA-A and GABA-B subsystems, then cumulative result of the dysfunction should be stronger (as in case of Clicks) than partial result (as in case of FAMs). This assumption is in line with the notion of partly distinct cortical networks, participating in the response to Clicks and FAMs and is further supported by the differences in attentional sensitivity of ASSRs evoked by click and AM stimulation (Griškova-Bulanova et al. 2011; Linden et al. 1987; Roth et al. 2013; Voicikas et al. 2016; Yokota and Naruse 2015).

Similarly to previous reports (Kirihara et al. 2012; Light et al. 2006; Tsuchimoto et al. 2011), the deficits in gamma responses in patient group were not associated with clinical variables. The failure to identify significant associations between the ASSR measures and clinical symptoms were previously explained by the insufficient engagement of neural networks associated with higher cognitive functions (Kirihara et al. 2012; Light et al. 2006), as the ASSR paradigm is passive and does not require higher order processing. It also should be noted that patients in our group received mixed treatment with antipsychotic medication (a combination of haloperidol with atypical neuroleptics) and benzodiazepines. The potential effects

of antipsychotic medication on ASSRs have not been investigated consistently before, and the results in the existing literature are controversial: for example Hong et al. 2004 reported an increase of ASSR with the use of atypical antipsychotics, whereas Light et al. 2006, Spencer et al. 2009, Tsuchimoto et al. 2011, Tada et al. 2016, Parker et al. 2019 did not find the effect of antipsychotic treatment in patients with schizophrenia. However, while it is possible that medication affects gamma-band responses, ASSRs in the current study were obtained in the same patient during the same recording session, and thus should not influence the comparison of ASSRs to both stimulation types - Clicks and flutter amplitude-modulated tones.

Chapter 6

Conclusions

1. Flutter amplitude modulated (FAM) stimuli were perceived neutrally pleasant and neutrally arousing and were rated as less unpleasant and less arousing than click stimuli.

2. 40 Hz auditory steady-state responses (ASSRs) to FAM stimulation were not modulated by attentional demands; click-elicited 40Hz ASSRs were reduced and less synchronized at the local and global level during distractive task as compared to the state of focused attention to stimulation.

3. The amplitudes and the phase-locking of 40 Hz ASSRs evoked by FAM stimuli were reduced in schizophrenic patients in comparison to healthy controls, similarly to reduced parameters of click-evoked ASSRs.

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- Griškova-Bulanova I, Pipinis E, **Voicikas A**, Koenig T (2018) Global field synchronization of 40 Hz auditory steady-state response: Does it change with attentional demands? Neurosci Lett 674:127–131.

- Griškova-Bulanova I, Dapšys K, Melynytė S, **Voicikas A**, Mačiulis V, Andruškevičius S, Korostenskaja M (2018) 40 Hz auditory steady-state response in schizophrenia: Sensitivity to stimulation type (clicks versus flutter amplitude-modulated tones). Neurosci Lett 662:152–157.

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- **Voicikas A**, Niciūtė I, Rukšėnas O, Griškova-Bulanova I. In search for optimal auditory steady state eliciting stimuli: clicks and flutter amplitude modulated tones. EBO — Entrainment of Brain Oscillations; Delmenhorst, Germany; 17–18 09 2015; p. 28.

- Griškova-Bulanova I, Melynytė S,**Voicikas A**, Siurkute A, Dapšys K. Auditory Steady-State Response in Schizophrenia:Is It Sensitive to Recording Condition? International Conference on Basic and Clinical Multimodal Imaging. Utrecht, Netherlands; 1–5 09 2015; p. 75.

- Dapšys K, Melynytė S, **Voicikas A**, Mačiulis V, Griškova-Bulanova I. Modulation of auditory steady-state responses in schizophrenia: eyes closed vs eyes open. 5th European Conference on Schizophrenia Research: Bridging Gaps — Improving Outcomes; Berlin, Germany; 24–26 09 2015; p. 127.

- **Voicikas A**, Niciūtė I, Rukšėnas O, Griškova-Bulanova I. Auditory steady-state response induced with chirp stimuli: read, count or relax? IV International Conference Aspects of Neuroscience; Warsaw, Poland; 14–16 11 2014;

Other publications

- Pipinis E, **Voicikas A**, Griškova-Bulanova I (2018) Low and high gamma auditory steady-states in response to 440 Hz carrier chirp-modulated tones show no signs of attentional modulation. Neurosci Lett 678.

- Melynytė S, Pipinis E, Genyte V, **Voicikas A**, Rihs T, Griškova-Bulanova I (2017) 40 Hz Auditory Steady-State Response: The Impact of Handedness and Gender. Brain Topogr 31:1–11.

- Griškova-Bulanova I, Grikšienė R, **Voicikas A**, Rukšėnas O (2016) Go and NoGo: modulation of electrophysiological correlates by female sex steroid hormones. Psychopharmacology (Berl) 233:2607–2615.

- Rimgailė-Voicik R, Naujalis JR, **Voicikas A** (2015) Organization of club moss gametophytes and juvenile sporophyte populations in pine forests. Polish J Ecol 63:467–480.

Other conferences

- Pacoret C, **Voicikas A**, Herrmann C. S, Griškova-Bulanova I. Neurophysiological synchronous spiking in the auditory steady-state: an EEG study. Alpine Brain Imaging Meeting 2017. Geneve, Switzerland; 08–12.01.2017.
- Griškova-Bulanova I, **Voicikas A**, Pacoret C. Implication of synchronous spiking to the auditory steady-state response interpretation: An EEG study. Neuroscience 2017. Washington DC, USA; 11–15.11.2017.
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- Parčiauskaite V, **Voicikas A**, Griškova-Bulanova I. Auditory steady-state responses to stimulation of different duration. VI International Conference Aspects of Neuroscience.Warsaw, Poland; 25–27 10 2016; p. 69.

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- Griškova-Bulanova I, **Voicikas A**, Melynytė S, Rukšėnas O, Rihs T, Genyte V. Is Handedness Important for 40Hz Auditory SteadyState Responses? Human Brain Mapping 2016; Geneva, Switzerland; 26–30 06 2016; p. 56.

- **Voicikas A**, Niciūtė I, Rukšėnas O, Griškova-Bulanova I. Chirp stimuli for entrainment: chirp up, chirp down and task effects. The Second Workshop and Lecture Series on: "Cognitive neuroscience of auditory and cross-modal perception"; Kosice, Slovakia; 20–24 04 2015; p. 14.

- Griškova-Bulanova I, **Voicikas A**, Arnfred SMH. Real examples of PARAFAC application for wavelet transformed EEG data. Cutting EEG 2014; Berlin, Germany; 19–21 02 2014

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Aleksandras Voicikas ***Curriculum vitae***

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RESEARCH INTERESTS

Electroencephalography (EEG), BCI, steady state response (ASSR, VSSR, SSSR), event-related potentials (ERP), resting state, microstates, experiment setup and optimization, biosignals preprocessing and analysis.

EDUCATION

PhD studies, VU, Life Sciences Center, 2014 to present
- Biophysics
- Thesis topic: *Brain steady-state response dependence on stimulation type*
- Supervisor: dr. Inga Griškova-Bulanova

Master studies, VU, Faculty of Natural Sciences, 2013
- Biophysics
- Thesis topic: *EEG phase coherence during presentation of emotional stimuli*
- Supervisor: Prof. dr. Osvaldas Rukšėnas

Bachelor studies , VU, Faculty of Physics , 2008
- Computing Physics
- Thesis topic: *Statistical simulations: Sinai's billiard and resistor networks*
- Supervisor: Prof. dr. Egidijus Anisimovas

Secondary education, Žemynos gymnasium, 2004

PARTICIPATION IN PROJECTS

- 2014-2016. Research project "Treatment-resistant schizophrenia: identification of electrophysiological markers" MIP-009/2014 form the Research Council of Lithuania within the collaboration programme with USA scientists; researcher
- 2014-2019. PhD project "Brain steady-state response dependence on stimulation type"
- 2016. Institutional partnership project "State-dependent information processing: implementation of electrical neu-

roimaging approach in Lithuania" in collaboration with University of Geneva and University Hospital of Psychiatry Bern, CH-3-ŠMM-02/03 from the Research Council of Lithuania within the Lithuanian-Swiss programme "Research and development"

AWARDS

- LMT (Research Council of Lithuania) scholarship for academic results (2017)

QUALIFICATION IMPROVEMENT

Internship:

- 2016.06.02-07.01 Functional Brain Mapping Laboratory at the University of Geneva (Prof. Christoph Michel, Geneva (Switzerland))

Courses Attended:

- "General competency skills training"; Vilnius, Lithuania; 17-21 10 2016
- "Neuroimaging and fMRI data analysis – clinical and research applications"; Vilnius, Lithuania; 5-9 09 2016
- "London SPM Courses 2016" London, UK; 16-19 04 2016
- "EEG/ERP Topography"; Vilnius, Lithuania; 20-23 03 2016
- "3rd Baltic-Nordic Summer School on Neuroinformatics"; Tartu , Estonia; 15-18 06 2015
- "Cognitive neurosciecne of auditory and cross-modal perception"; Kosice, Slovakia; 20-24 04 2015
- "Practical data analysis and modeling in cognitive and clinical neuroscience"; Ghent, Belguim; 14-18 03 2014
- "Nervous system analysis methods: EEG and ERP"; Vilnius, Lithuania;26-28 09 2013;
- "1st Baltic-Nordic Summer School on Neuroinformatics"; Kaunas, Lithuania; 29-31 05 2013

HARDWARE AND SOFTWARE SKILLS

Computer Programming:

- MATLAB , Python, R, C, Java

Experiment Setup:

- E-Prime, Experiment Builder, PsychoPy

Productivity Applications:

- Git, Microsoft Office, Libre Office, TEX (LATEX, BIBTEX)

Operating Systems:

- Microsoft Windows, Linux

Analog and Digital Electronics:

- Arduino UNO/DUE, Raspbery PI

LANGUAGES

- Lithuanian - mother tongue
- English -(CERF - understanding C1 , speaking B2, writing B2)
- Russian -(CERF - understanding B2 , speaking B2, writing A1)

PROFESSIONAL MEMBERSHIPS

- Lithuanian Neuroscience Association (2012 to present)
- The International Society for Brain Electromagenetic Topography (ISBET) (2016 to present)
- Organisation of Human Brain Mapping (OHBM) (2016 to present)

SCIENCE POPULARIZING

- "10th Conference of Lithuanian Neuroscience Association (LNA)"; Vilnius. Lithuania; 30-1 11-12 2018
- "Nervous system analysis methods: EEG and ERP"; Vilnius, Lithuania; 5-6 02 2016
- "Brain Awareness Week 2015" Vilnius, Lithuania;16 – 22 03 2015
- "School 2013"; Litexpo ;Vilnius, Lithuania 6-8 12 2016
- "Spaceship Earth"; Kaunas, Lithuania; 13 09 2013

OTHER INFORMATION

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